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Charles L. Spurr Piedmont Oncology Fall Symposium

September 30 - October 1, 2016

Marina Inn at Grande Dunes
Myrtle Beach, South Carolina

This activity is sponsored by Wake Forest University School of Medicine.

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September 30 - October 1, 2016

Dear Participant:

We are delighted you have chosen to attend the **Charles L. Spurr Piedmont Oncology Symposium**. An outstanding continuing medical education (CME) activity has been planned for you today. We hope you will enjoy this educational experience.

Agenda/Faculty/Commercial Supporters:
The conference agenda, list of participating faculty, and commercial supporters are enclosed for your review.

Disclosure Statement:
As an accredited CME provider, Wake Forest University Health Sciences/Wake Forest School of Medicine requires that everyone involved with a CME activity comply with the *2004 Updated Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support: Standards to Ensure the Independence of CME Activities*. All planning committee members, staff, and speakers have disclosed the significant financial interests or relationships they have with the manufacturer(s) of any commercial products/services. Their responses are enclosed for your review.

Attendance/Credit Certificates/Evaluation:
Please be sure to sign in at the registration desk. Sign in sheets will be available through the afternoon break.
Your Certificate of Completion will be available online by Wednesday, October 5. To receive your continuing education certificate, you must complete the online program evaluation for this activity. You will be emailed the link to the online evaluation by Wednesday, October 5. We will need your current email address to send you instructions for obtaining your certificate. **Evaluations and certificates will be available online for 2 weeks post activity.**

Once again, we hope you find this course helpful. If there is anything we can do for you while you are here, please do not hesitate to ask any of the faculty or our staff at the registration table. If you have any questions once you leave, please call us using our direct number (336-713-7700).
Thank you for coming.

Credit:
Credit Statement

The Wake Forest School of Medicine designates this live activity for a maximum of **10.0** ***AMA PRA Category 1 Credits*™**. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Accreditation Statement:
The Wake Forest School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

10.0 Continuing Nursing Education (CNE) Contact Hours

Northwest Area Health Education Center (NWAHEC) is an approved provider of continuing nursing education by the North Carolina Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

(#AP006-161001)

10.0 Contact Hours from Northwest AHEC

1.0 CEUs from Wake Forest School of Medicine

Statement of CNE Disclosures

a. Participants must attend the entire activity in order to earn contact hour credit. No partial credit will be awarded. Verification of participation will be noted by learner-signature on the roster and completion of the online evaluation.

b. The objectives for this activity are the following:

- Describe novel treatment strategies for newly diagnosed myeloma.
- Identify potential facilitators and barriers to establishing an integrative oncology program.
- Summarize the antitumor activity and clinical toxicity of melanoma immunotherapies.
- Identify risk factors for burnout.
- Identify ongoing research in thyroid cancer and potentially useful agents in second and third line treatment settings.
- Identify immune checkpoint inhibitors used in the treatment of non-small cell lung cancer, associated immune mediated adverse events and discuss management strategies.
- Discuss novel therapeutics and immune therapies for pancreas cancer.
- Identify clinical challenges in the management of neuroendocrine tumors.
- Describe patient and disease characteristics that influence treatment selection in chronic lymphocytic leukemia.
- Discuss the future of cancer treatment and the role of precision medicine.

c. No commercial support has influenced the planning, implementation, or evaluation of the content of this activity.

Northwest AHEC (NWAHEC) is an approved provider of continuing nursing education by the North Carolina Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

OFFICE OF CONTINUING MEDICAL EDUCATION

LEARNER BILL OF RIGHTS

Wake Forest School of Medicine (WFSM) recognizes that you are a lifelong learner who has chosen to engage in continuing medical education (CME) to identify or fill a gap in knowledge, skill, or performance. As part of WFSM's duty to you as a learner, you have the right that your CME experience with us includes:

- Content that:
  - Promotes improvements or quality of health care;
  - Is valid, reliable, and accurate;
  - Offers balanced presentations that are free of commercial bias for or against a product/service;
  - Is vetted through a process that resolves any conflicts of interest of planners, teachers, or authors;
  - Is driven and based on learning need, not commercial interests;
  - Addresses the stated objectives or purpose; and
  - Is evaluated for its effectiveness in meeting the identified educational needs.

- A learning environment that:
  - Supports learners' ability to meet their individual needs;
  - Respects and attends to any special needs of the learners;
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- Disclosure of:
  - Relevant, financial relationships planners, teachers, and authors have with commercial interests related to the content of the activity; and
  - Commercial support (funding or in-kind resources) of the activity.

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Charles L. Spurr Piedmont Oncology Fall Symposium

Planning Committee, Faculty, & Staff Disclosure

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- *Dr. Kenneth C. Anderson serves as a consultant for Celgene, Millennium, Bristol-Myers Squibb, and Gilead. He has stock shareholder/ownership in Acetylon, Onco Pep, and C4 Therapeutics.*

- *Dr. Farrukh Awan has grant/research support from Pharmacyclics. He serves as a consultant for Gilead and Novartis.*

- *Dr. Eric Liu serves as a consultant for Advanced Accelerator Applications. He serves as a speaker for Ipsen and Novartis.*

- *Dr. Eileen O'Reilly has grant/research support from Abbott Laboratories, Amgen, Bayer, CASI, Celgene, Eli Lilly and Company/Imclone, Exelixis, Genentech, Immunomedics, Incyte, Momenta Pharmaceuticals, Myriad Genetics, Novartis, OncoMed, Pharmaceuticals, Polaris, Pharmaceuticals, Roche, and Vicus Therapeutics. She serves as a consultant for Aduro Biotech, Array, Astellas Pharma US, BioAlliance, Boston Scientifc, Boston Therapeutics, BMS, CASI, Celgene, Cipla, Eli Lilly and Company, EMD Sorono, Gilead, IntegraGen, Medergy, MedImmune, Merrimack, Momenta, Novartis, Onxeo, Pharmacyclics, Sanofi-aventis, Silenseed, Sillajen, and Vicus Therapeutics.*

- *Dr. Dan Shapiro runs a boutique, burnout assessment, and amelioration small business.*

- *Dr. Mark Socinski has grant/research support from Pfizer, Bristol-Myers Squibb, Genentech, Clovis, and Celgene. He serves as a speaker for Celgene, Genentech, Novartis, and Bristol-Myers Squibb.*

- *Dr. Marcia Brose has grant/research support from Bayer, Blueprint MedCorp, Eisai, Genzyme, and Kura Onc, Inc. She serves as a consultant for Eisai and Genzyme.*

Drs. Pasche, Triozzi, Powell, and Lesser have nothing to disclose with regards to this educational activity.
Debbie Olson and Susan Poindexter have nothing to disclose with regards to this educational activity.

Printed 9/23/2016. Any additional disclosures received after this date will be announced.

Charles L. Spurr Piedmont Oncology Symposium
Fall Symposium

AGENDA

Thursday, September 29, 2016

6:00 pm **Reception and Registration for all Attendees and Exhibitors**

Friday, September 30, 2016

7:15 am **Registration, Continental Breakfast, and Exhibits**

General Session

8:00 am **Welcome and Remarks**
Bayard Powell, MD
Professor of Medicine
Section on Hematology and Oncology, Wake Forest School of Medicine

8:10-9:10 am **Multiple Myeloma: Update on Diagnosis and Management**
Kenneth C. Anderson, MD
Kraft Family Professor of Medicine
Director, Jerome Lipper Multiple Myeloma Center
Harvard Medical School, Dana-Farber Cancer Institute

9:10-10:10 am **Integrative Oncology in Clinical Practice**
Gabriel Lopez, MD
Assistant Professor, Department of Palliative, Rehabilitation and Integrative Medicine
Medical Director, Integrative Medicine Center
University of Texas, MD Anderson Cancer Center

10:10-10:30 am **Break and Exhibits**

10:40-11:40 am **Combination Immunotherapy Approaches for Melanoma**
Pierre Triozzi, MD
Professor, Section on Hematology and Oncology
Wake Forest School of Medicine

11:40-12:40 pm	**Hem/Onc Physician and Advance Practice Clinician Burnout and Resilience** **Dan Shapiro, PhD** Vice Dean for Faculty and Administative Affairs Chair, Department of Humanities Garner James Cline Professor of Humanities in Medicine Penn State College of Medicine
12:40 pm	**Lunch**
1:15-2:15 pm	**Lung Cancer 2016** **Mark A. Socinski, MD** Executive Medical Director Florida Hospital Cancer Institute
2:15-2:25 pm	**Stretch Break**
2:25-3:25 pm	**Advanced Thyroid Cancer Update: Successes and New Challenges** **Marcia Brose, MD, PhD** Director, Center for Rare Cancers and Personalized Therapy Associate Professor, Department of Otorhinolaryngology: Head and Neck Surgery Department of Internal Medicine, Division of Hematology and Oncology University of Pennsylvania, Perelman School of Medicine, Abramson Cancer Center
3:25 pm	**Adjourn**
4:00 pm	**Private Reception**

Multiple Myeloma: Update on Diagnosis and Management

Kenneth C. Anderson, MD
Kraft Family Professor of Medicine
Director, Jerome Lipper Multiple Myeloma Center
Harvard Medical School, Dana-Farber Cancer Institute

Multiple Myeloma: Update on Diagnosis and Management

Kenneth C. Anderson, M.D.

Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Harvard Medical School

Criteria for Diagnosis of Multiple Myeloma (MM)

MGUS
- <3 g M spike
  <10% PC

Smoldering MM
- ≥3 g M spike
- OR ≥10% PC

Active MM
- ≥10% PC
- M spike +

AND

No anemia, bone lesions normal calcium and kidney function

AND

Anemia, bone lesions, high calcium or abnormal kidney function

Kyle RA. N Engl J Med 2002; 346: 564

Diagnosis of Active MM In Asymptomatic Patients (IMWG)

Even without CRAB Features, the following define active MM:

Bone marrow plasmacytosis ≥ 60% [1]

Abnormal FLC ratio ≥ 100 (involved kappa) or <0.01 (involved lambda) [2]

Focal bone marrow lesions detected by functional imaging including PET-CT and/or MRI [3, 4]

1. Rajkumar et al N Eng J Med 2011; 365: 474
2. Larsen et al Leukemia 2013; 27: 941
3. Hillengass et al J Clin Oncol 2010; 28: 1606
4. Hillengass et al Leuk Lymph 2013

Rajkumar et al. *Lancet Oncol* 2015; 12:e538-e548

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016 Multiple Myeloma

DEFINITION OF MULTIPLE MYELOMA

Smoldering (Asymptomatic) Myeloma[1,2]

- Serum monoclonal protein
  - IgG or IgA ≥3 g/dL;

Or

- Bence-Jones protein ≥500 mg/24 h

And/Or

- Clonal bone marrow plasma cells 10%–60%

And

- Absence of myeloma defining events or amyloidosis
  - If bone survey negative, assess for bone disease with whole body MRI or PET/CT

[1]The understanding of smoldering (asymptomatic) myeloma is evolving rapidly. Some studies have shown that patients with certain characteristics, including IgG levels of >3 g/dL, IgA of >2 g/dL, or urinary Bence Jones protein of >1 g/24 h (Mateos MV, Hernandez M, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med 2013;369:438-447) or abnormal free light chain ratios (Dispienzeri A, Kyle R, Katzmann J, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. Blood 2008;111:785-789), have an increased risk of progression to active (symptomatic) myeloma. It is also increasingly recognized, that the classical definition of smoldering myeloma using certain tests such as plain x-rays is outdated. Efforts to modify these criteria and reclassify some patients previously classified as "asymptomatic" to having "active disease" are underway.

[2]Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;Vol 15,e538-e548.

MYEL-B

Vaccines Targeting MM Specific Peptides in Smoldering Multiple Myeloma

Goal is to prevent evolution of smoldering to active myeloma

- **Cocktails of immunogenic HLA-A2-specific XBP1, CD138, CS1 peptides to induce MM-specific and HLA-restricted CTL responses**

Clinical trials (LLS TAP Program):

Immune responses to vaccine in all patients including tetramer positive cells and type I cytokines

Lenalidomide with vaccine augments these immune response

Lenalidomide and PDL-1, HDAC 6i 241 with vaccine to induce memory Immune response against myeloma

.

Bae et al, Leukemia 2011; 25:1610-9.
Bae et al, Brit J Hematol 2011; 155: 349-61.
Bae et al, Brit J Hematol 2012; 157: 687-701.
Bae et al, Clin Can Res 2012; 17:4850-60.
Bae et al, Leukemia 2015

Effects of HDACi 241 on MM Specific Cytotoxic T cells (MM CTLs)

Does not affect viability of CD3, CD4, CD8 T cells

Does not induce checkpoint inhibitors on MM CTLs

Increases costimulatory molecules, proliferation, Th-1 cytokine production, and cytotoxicity of MM CTLs

Increases central and effector memory MM CTL cytotoxicity, costimulatory molecules, and proliferation

Decreases regulatory T cells

Integration of Novel Therapy Into Myeloma Management

Bortezomib, lenalidomide, thalidomide, bortezomib/doxorubicin, carfilzomib, pomalidomide, panobinostat, daratumumab, ixazomib, elotuzumab

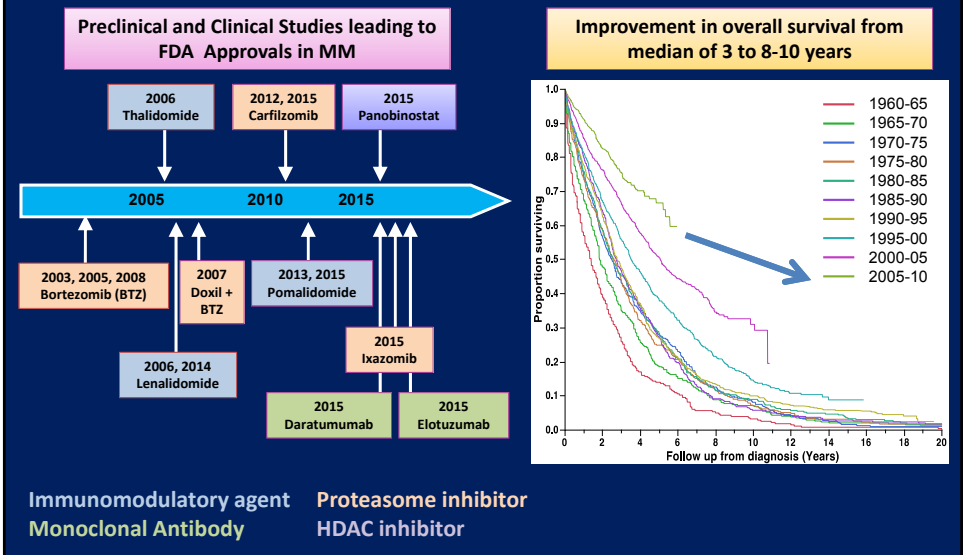
Target MM in the BM microenvironment to overcome conventional drug resistance *in vitro* and *in vivo*

Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy

16 FDA approvals (7 in 2015!) and median patient survival prolonged 3-4 fold

New approaches needed to treat and ultimately prevent relapse

Bench to Bedside Translation of Novel Agents in Myeloma



International Staging System (ISS) for Myeloma

Stage	Criteria	Median Survival (mo)
I	β2m < 3.5 mg/L albumin ≥ 3.5 g/dL	62
II*	Not stage I or III	44
III	β2m > 5.5 mg/L	29

*β2m < 3.5 mg/L and albumin < 3.5 g/dL or
β2m 3.5 - < 5.5 mg/dL, any albumin

Greipp et al. J Clin Oncol 2005; 23: 3412-20

Revised ISS (R-ISS) incorporates LDH and high risk FISH abnormalities

Palumbo et all J Clin Oncol 2015: 33: 2863-9.

Chromosomes and Prognosis in Multiple Myeloma

For conventional low and high dose theapy:

Nonhyperdiploid worse prognosis than hyperdiploid
t(11;14), hyperdiplody -standard risk
t(4;14), t(14;16),t(14;20), del(17p), del(13q14)- high risk

For novel treatments
Bortezomib, but not lenalidomide, can at least partially overcome t(4;14), del(13q14)-

del(17p) p53 remains high risk

Increasing Stringency in Defining Complete Response

- **CR …… Negative Immunofixation & < 5% PC in BM**
- **Stringent CR……Normal FLC & no clonal PC by immunohistochemistry** (Low sensitivity $<10^{-2}$)
- **Outside BM ……..Imaging techniques (MRI & CT-PET).**
- **BM Level……..Immunophenotypic remission** (by multiparametric flow) **Molecular remission** (by sequencing) *

** Pitfalls: 1. Pattern of BM infiltration in MM is not uniform… The possibility of residual MM-PC in another territory cannot be excluded (false negative results).*

2. Extramedullary relapses.

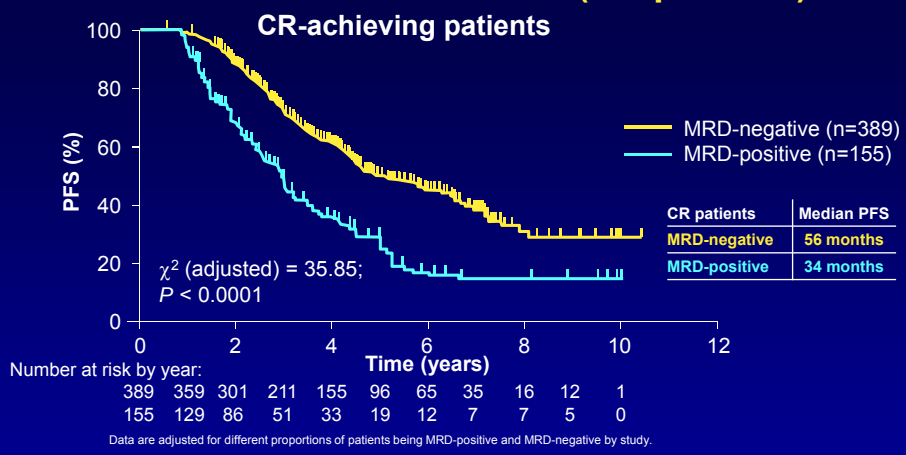
Significant Impact of Minimal Residual Disease (MRD) Status On Survival Outcomes In pts (pts) With Multiple Myeloma (MM) Who Achieve Complete Response (CR): A Meta-Analysis

- A total of 405 published articles with MRD
  - 25 articles recently published articles
- Of these, 21 reported overall survival (OS) or progression-free survival (PFS) results, as well as MRD status
- Overall, 2,208 pts were evaluated for MRD
- Nine publications reported conventional CR at the time of MRD measurement. Six represented unique data sets.

Munshi N et al., JAMA Oncol, in press

13

The effect of MRD status on PFS (CR patients)



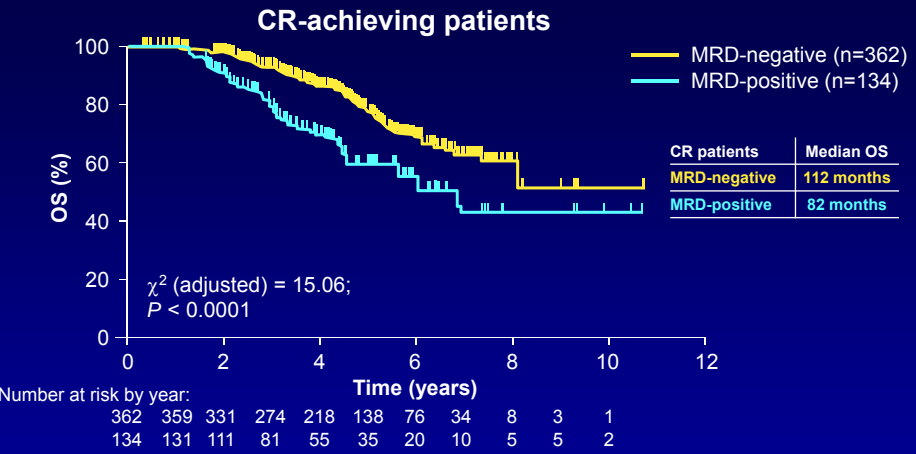
Data are adjusted for different proportions of patients being MRD-positive and MRD-negative by study.

- **3-year PFS: 70% (MRD⁻) vs. 46% (MRD+)**
- **5-year PFS: 48% (MRD⁻) vs. 27% (MRD+)**
- **Majority of MRD-positive patients progressed by 6 years; nearly 50% of MRD-negative patients progression free**

Munshi N et al., JAMA Oncol, in press

14

The effect of MRD status on OS (CR patients)



Data are adjusted for different proportions of patients being MRD-positive and MRD-negative by study.

- **Median OS was not reached for MRD-negative pts versus 82 months for MRD-positive pts)**
- **OS @ 3-years, 94% versus 80% OS @ 7-years, 67% versus 47%**
- **OS @ 5-years, 80% versus 61%**

CR, complete response; MRD, minimal residual disease; NR, not reached; OS, overall survival.

Munshi N, et al. IMW 2015, abstract 0394.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016
Multiple Myeloma

DEFINITION OF MULTIPLE MYELOMA

Active (Symptomatic) Myeloma[2,3]

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma
And
Any one or more of the following myeloma defining events:
- **Calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)**
- **Renal insufficiency (creatinine >2 mg/dL) [>177 µmol/L] or creatinine clearance <40 mL/min**
- **Anemia (hemoglobin <10 g/dL or hemoglobin >2 g/dL below the lower limit of normal)**
- **One or more osteolytic bone lesions on skeletal radiography, CT, or PET-CT**
- **Clonal bone marrow plasma cells ≥60%**
- **Abnormal serum FLC ratio ≥100 (involved kappa) or <0.01 (involved lambda)**
- **>1 focal lesions on MRI studies > 5mm**

[2]Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;Vol 15,e538-e548.
[3]Other examples of active disease include: repeated infections, amyloidosis, or hyperviscosity.

MYEL-B

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016
Multiple Myeloma

MYELOMA THERAPY

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

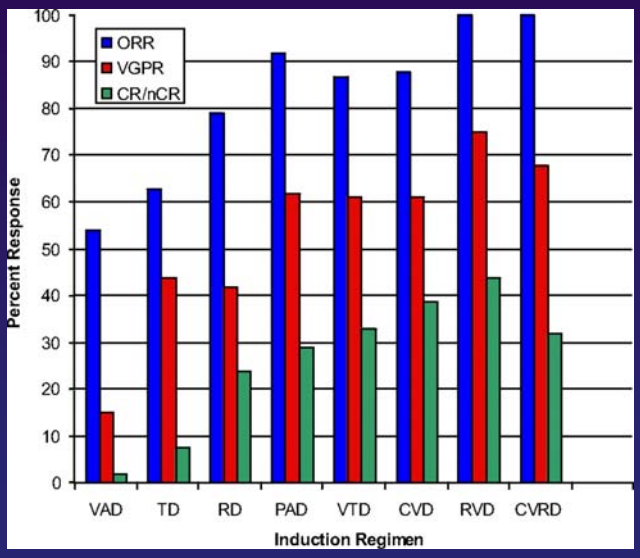
Primary Therapy for Transplant Candidates
(Assess for response after 2 cycles)

Preferred Regimens:
- **Bortezomib/dexamethasone (category 1)**
- **Bortezomib/cyclophosphamide/ dexamethasone**
- **Bortezomib/doxorubicin/dexamethasone (category 1)**
- **Bortezomib/lenalidomide/dexamethasone (category 1)**
- **Bortezomib/thalidomide/dexamethasone (category 1)**
- **Lenalidomide/dexamethasone (category 1)**

Other Regimens:
- **Carfilzomib/lenalidomide/ dexamethasone**
- **Dexamethasone (category 2B)**
- **Ixazomib/lenalidomide/dexamethasone**
- **Liposomal doxorubicin/vincristine/ dexamethasone (DVD) (category 2B)**
- **Thalidomide/dexamethasone (category 2B)**

MYEL-D

Combinations in the Upfront Treatment of MM



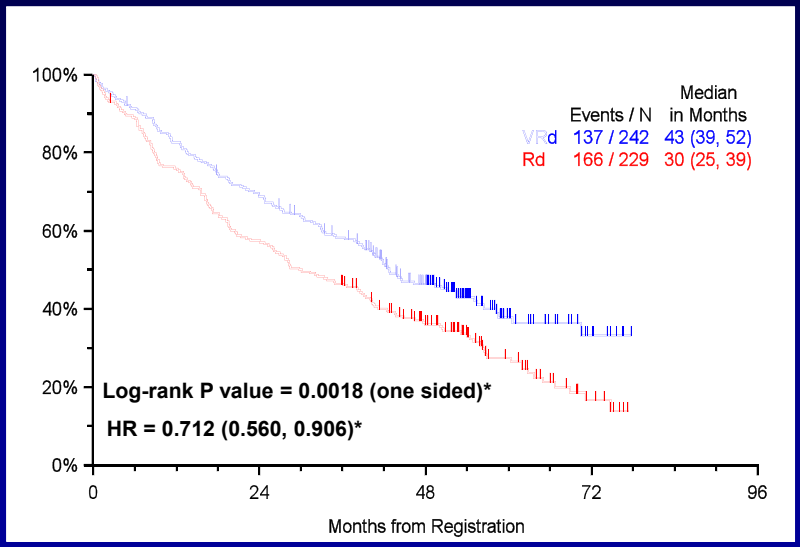
Stewart AK, Richardson PG, San Miguel JF Blood 2009

RVd versus Rd for Newly Diagnosed MM

	RVd	Rd
CR	15.7%	8.4%
VGPR	27.8%	23.4%
PR	38%	39.7%
ORR (PR or better)	81.5%	71.5%
SD	15.7%	24.3%
SD or better	97.2%	95.8%
PD or Death	2.8%	4.2%

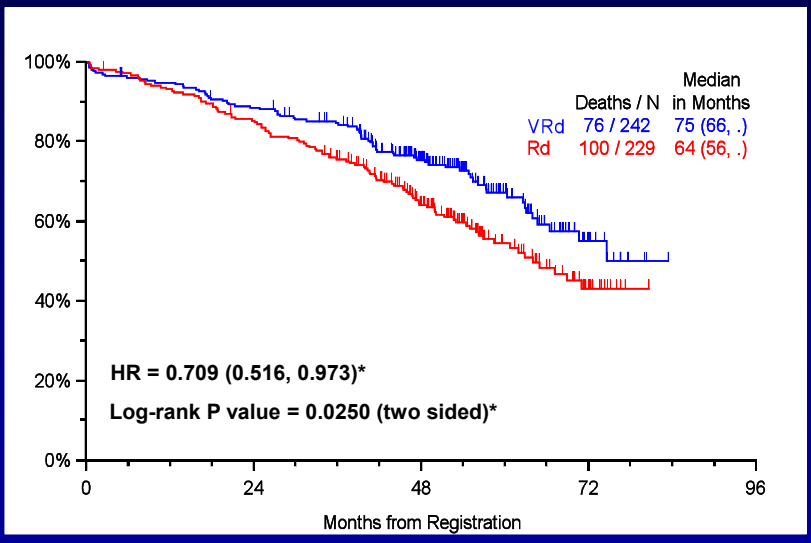
Durie et al, ASH 2015

Bortezomib, lenalidomide and dexamethasone versus Lenalidomide and dexamethasone: Progression Free Survival



Durie et al, ASH 2015

Bortezomib, lenalidomide and dexamethasone versus Lenalidomide and dexamethasone : Overall Survival



Durie et al, ASH 2015

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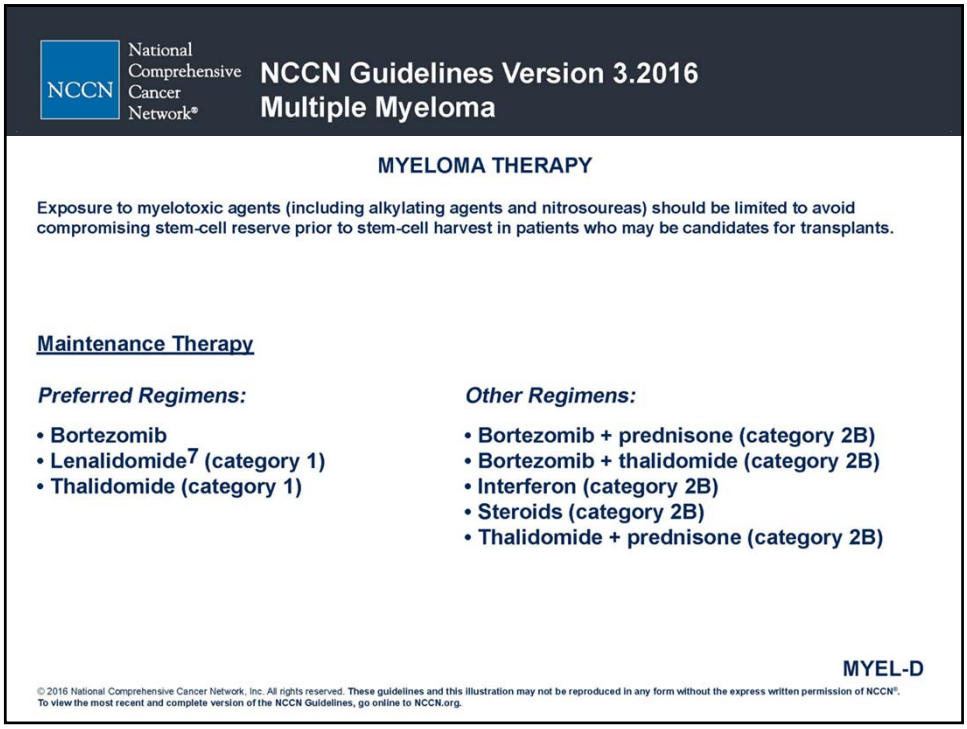
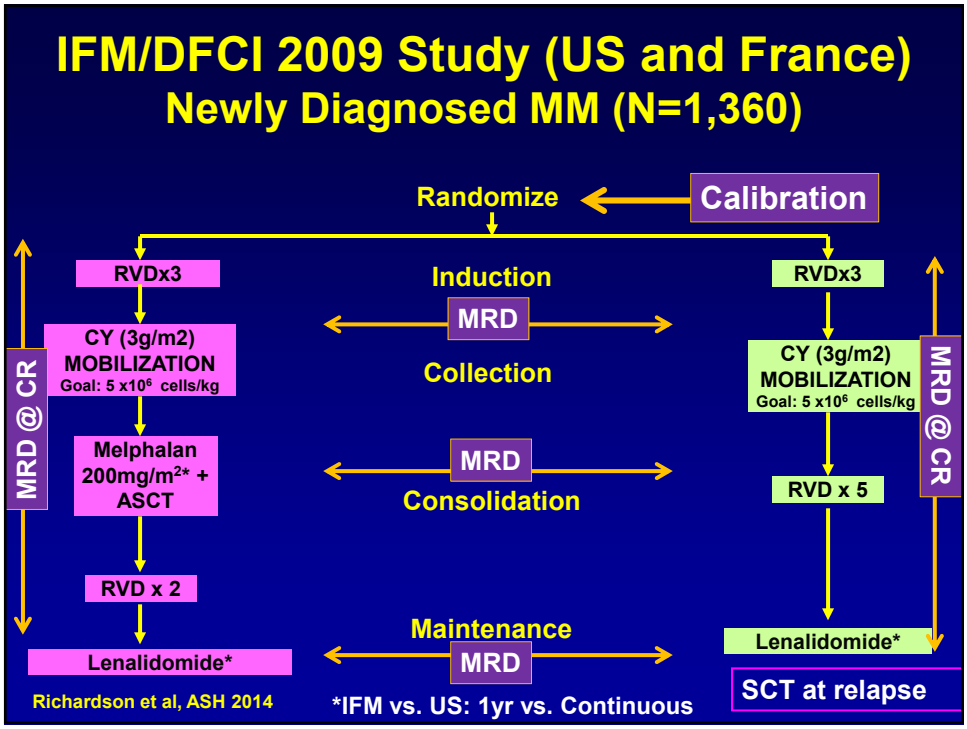


Phase III Maintenance Studies – Transplant Eligible Patients

Trial	N	Regimen	Outcomes
IFM 2005-02[1]	614	Maintenance lenalidomide vs placebo following first or second ASCT	4-yr PFS: 60% vs 33%
CALGB 100104[2]	460	Maintenance lenalidomide vs placebo after ASCT	Median TTP: 46 vs 27 mos
RV-MM-PI-209[3]	402	MPR + maintenance lenalidomide vs MPR vs MEL200 + maintenance lenalidomide vs MEL200	Median PFS (R vs no R): 37 vs 26 mos 5-Yr OS (R vs no R): 75 vs 58 mos
HOVON-65[4]	827	VAD vs PAD followed by HD melphalan and ASCT, then thalidomide or bortezomib as maintenance	Median PFS: 28 vs 35 mos CR/nCR: 15% vs 31%
Nordic MSG 15[5]	370	Bortezomib x 21 wks vs no maintenance	≥ nCR: 45% vs 35%

1. Attal M, et al. N Engl J Med. 2012;366:1782-1791.
2. McCarthy PL, et al. N Engl J Med. 2012;366:1770-1781.
3. Boccadoro M, et al. ASCO 2013, abstr 8509
4. Sonneveld P, et al. *J Clin Oncol.* 2012;30:2946-2955.
5. Mellqvist UH, et al. *Blood.* 2013;121:4647-4654.

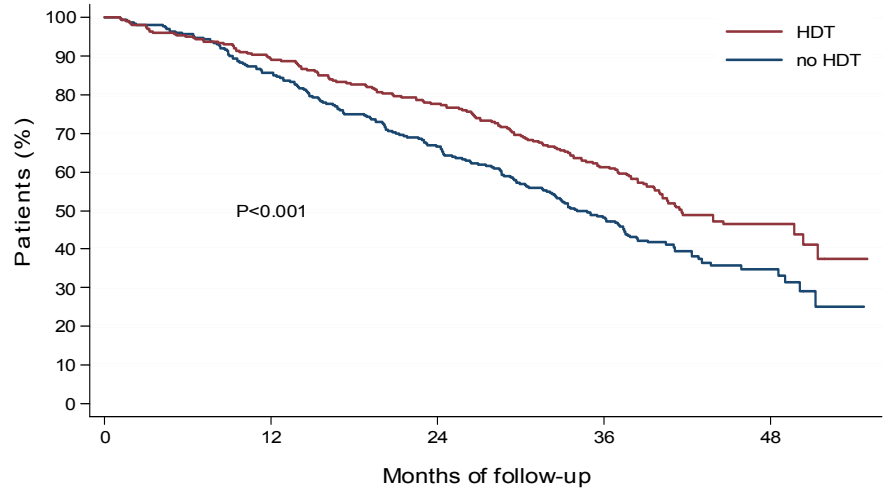


IFM 2009: Best Response

	RVD arm N=350	Transplant arm N=350	p-value
CR	49%	59%	
VGPR	29%	29%	0.02
PR	20%	11%	
<PR	2%	1%	
At least VGPR	78%	88%	0.001
Neg MRD by FCM , n (%)	228 (65%)	280 (80%)	0.001

Attal et al, ASH 2015

ASH 2015: IFM 2009: PFS (9/2015)

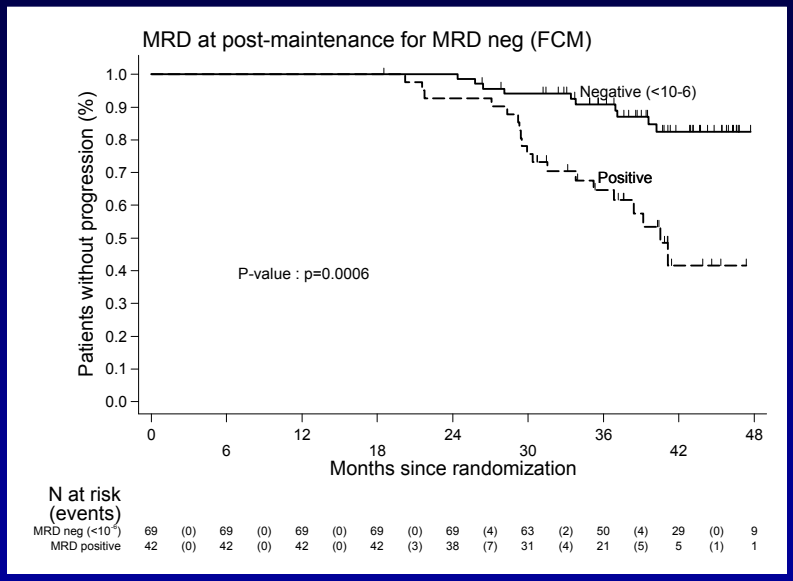


N at risk

HDT	350	309	261	153	27
no HDT	350	296	228	128	24

Attal et al, ASH 2015

Sequencing Distinguishes Outcome in FDM Negative Patients



N at risk (events)

MRD neg (<10^{-6})	69	(0)	69	(0)	69	(0)	69	(0)	69	(4)	63	(2)	50	(4)	29	(0)	9
MRD positive	42	(0)	42	(0)	42	(0)	42	(3)	38	(7)	31	(4)	21	(5)	5	(1)	1

Avet-Loiseau et al, ASH 2015

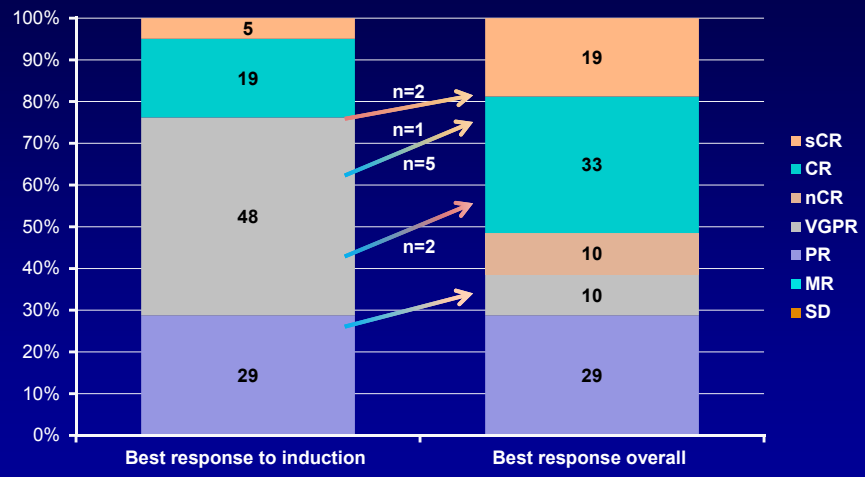
Phase 1/2 Study of Carfilzomib, Lenalidomide, and Dexamethasone (CRd)

		ISS Stage		Cytogenetics		Carfilzomib Dosage		
Response, %	Overall (n=49)	I (n=20)	II/III (n=29)	Normal or Favorable (n=33)	Unfavorable (n=16)	20 mg/m²	27 mg/m²	36 mg/m²
ORR	98	90	97	91	100	100	100	88
VGPR	65	65	66	61	75	100	100	47
sCR, nCR, or CR	53	50	55	52	56	75	85	38

- Generally well tolerated and manageable side effects
- Grade 3/4 adverse events in ≥10% of pts
  - Hematologic: anemia, neutropenia, thrombocytopenia
  - Non-hematologic: hyperglycemia, dyspnea/CHF, HTN, deep vein thrombosis/ pulmonary embolism, renal dysfunction

Jakubowiak AJ et al. Blood 2012; 120: 1801.

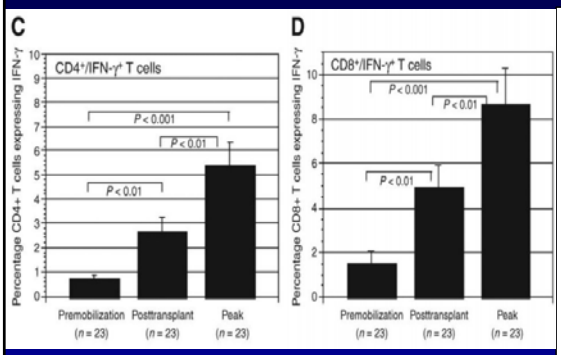
Best Response to Ixazomib Len Dex and Ixazomib maintenance

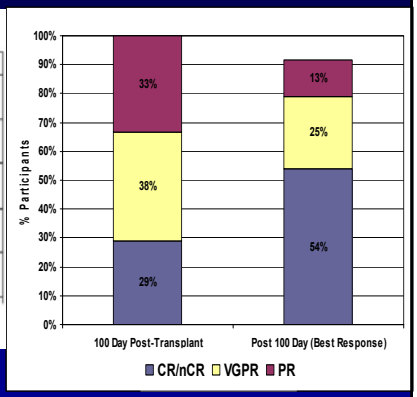


10 (48%) pts improved their response during maintenance:
- 2 VGPR to nCR, 5 VGPR to CR, 1 VGPR to sCR, and 2 CR to sCR

Kumar et al ASH 2014

MM/DC Vaccination following Autologous PBSCT for Myeloma





Rosenblatt et al, CCR 2013; 19: 3640-8.

Ongoing CTN randomized trial of lenalidomide with or without vaccine posttransplant Avigan et al

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016 Multiple Myeloma

MYELOMA THERAPY

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

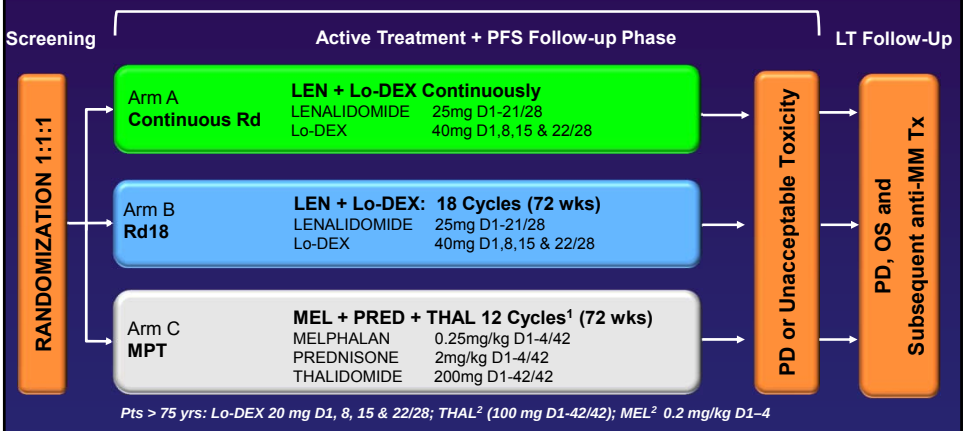
Primary Therapy for Non-Transplant Candidates
(Assess for response after 2 cycles)

Preferred Regimens:
- Bortezomib/dexamethasone
- Bortezomib/cyclophosphamide/ dexamethasone
- Bortezomib/lenalidomide/dexamethasone (category 1)
- Lenalidomide/low-dose dexamethasone (category 1)
- Melphalan/prednisone/bortezomib (MPB) (category 1)
- Melphalan/prednisone/lenalidomide (MPL) (category 1)
- Melphalan/prednisone/thalidomide (MPT) (category 1)

Other Regimens:
- Dexamethasone (category 2B)
- Ixazomib/lenalidomide/dexamethasone
- Liposomal doxorubicin/vincristine/ dexamethasone (DVD) (category 2B)
- Melphalan/prednisone (MP)
- Thalidomide/dexamethasone (category 2B)
- Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)

MYEL-D

FIRST Trial: Len/Dex versus MPT in Newly Diagnosed Non Transplant Candidates



Pts > 75 yrs: Lo-DEX 20 mg D1, 8, 15 & 22/28; THAL[2] (100 mg D1-42/42); MEL[2] 0.2 mg/kg D1–4

- Stratification: age, country and ISS stage

Benhoubker et al, N Engl J Med 2014; 271: 906-17.

FIRST Trial: Conclusions

Continuous Rd significantly extended PFS, with an OS benefit vs. MPT

- **PFS:**
  - **HR= 0.72 (*P*= 0.00006)**
  - **Consistent benefit across most subgroups**
  - **Rd better than Rd18 (HR= 0.70, *P*= 0.00001)**
  - **3 yr PFS: 42% Rd vs. 23% Rd18 and MPT**
- **Planned interim OS: HR= 0.78 (*P*= 0.0168)**
- **Rd was superior to MPT across all other efficacy secondary endpoints**

Safety profile with continuous Rd was manageable

- **Hematological and non-hematological AEs were as expected for Rd and MPT**
- **Incidence of hematological SPM was lower with continuous Rd vs. MPT**

In NDMM transplant-ineligible patients, the FIRST Trial establishes continuous Rd as a new standard of care

Benhoubker et al, N Engl J Med 2014; 271: 906-17.

When to Consider Retreatment

- Differences between biochemical relapse and symptomatic relapse need to be considered
- Patients with asymptomatic rise in M-protein can be observed to determine the rate of rise and nature of the relapse
  - Caveat: patients with known aggressive or high-risk disease should be considered for salvage even in the setting of biochemical relapse
- CRAB criteria are still listed as the indication to treat in the relapsed setting-however, in patients with progression, treatment can avoid CRAB
  - C: Calcium elevation (> 11.5 mg/L or ULN)
    R: Renal dysfunction (serum creatinine > 2 mg/dL)
    A: Anemia (Hb < 10 g/dL or 2 g < normal)
    B: Bone disease (lytic lesions or osteoporosis)

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016
Multiple Myeloma

MYELOMA THERAPY

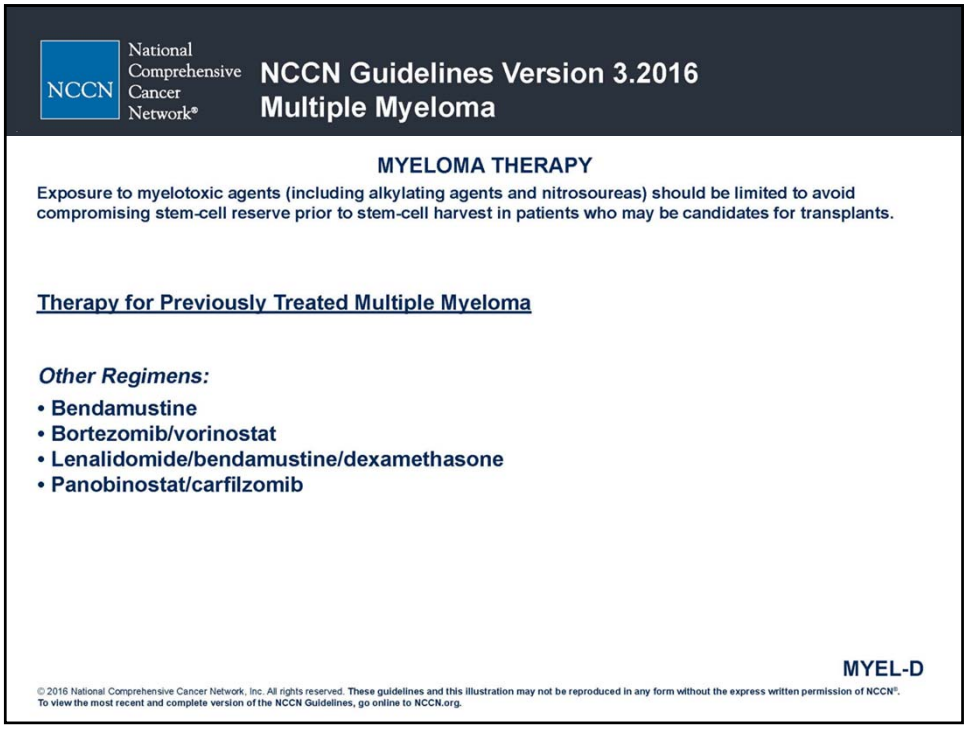
Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

Therapy for Previously Treated Multiple Myeloma

Preferred Regimens:

- Repeat primary induction therapy (if relapse at >6 mo)
- Bortezomib (category 1)
- Bortezomib/dexamethasone
- Bortezomib/cyclophosphamide/dexamethasone
- Bortezomib/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin (category 1)
- Bortezomib/thalidomide/dexamethasone
- Carfilzomib
- Carfilzomib/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone (category 1)
- Cyclophosphamide/lenalidomide/dexamethasone
- Daratumumab
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclo-phosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)
- Elotuzumab/lenalidomide/dexamethasone (category 1)
- Ixazomib
- Ixazomib/dexamethasone
- Ixazomib/lenalidomide/dexamethasone (category 1)
- High-dose cyclophosphamide
- Lenalidomide/dexamethasone (category 1)
- Panobinostat/bortezomib/dexamethasone(category 1)
- Pomalidomide/dexamethasone(category 1)
- Thalidomide/dexamethasone

MYEL-D



Summary and Conclusions

- **Choice of therapy depends on prior treatment and specific factors:**

Initial: Len Dex + bortezomib

1-3 prior therapies:

Pomalidomide/Dex, Carfilzomib (len/dex),

Elotuzumab/len/dex, ixazomib len/ dex

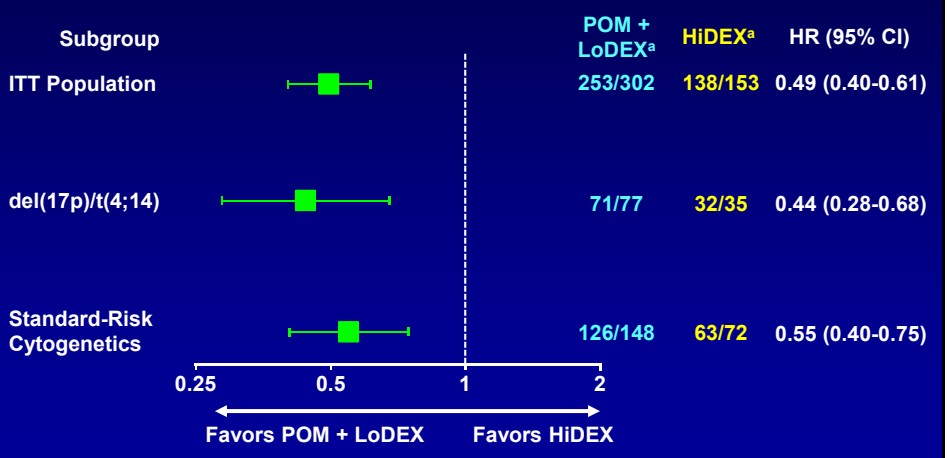
Multiply relapsed: daratumumab, panobinostat/bortezomib, protocols of targetted and immune therapies

Pomalidomide With Low-Dose Dexamethasone Relapsed and Refractory Multiple Myeloma

- POM was effective in heavily pretreated patients who had already received LEN and bortezomib and who progressed on their last line of therapy
- The combination of POM with LoDEX improves the ORR due to synergy between immunomodulatory agents and glucocorticoids
  - POM + LoDEX, 34%; POM alone, 15%
- Response was durable with POM regardless of the addition of LoDEX
  - POM + LoDEX, 8.3 months ; POM alone, 8.8 months
- POM is generally well tolerated, with low rates of discontinuations due to AEs
  - Age had no impact on ORR, DoR, or safety

Richardson et al Blood 2014; 123: 1826-32 .

• POM + LoDEX significantly improved PFS vs HiDEX



San Miguel et al Lancet Oncol 2013; 14: 1055-66.

ASPIRE: Carfilzomib, Lenalidomide, and Dexamethasone (KRd) vs Lenalidomide and Dexamethasone (Rd)

Characteristic	KRd (n=396)	Rd (n=396)
Presence of neuropathy at baseline, %	36.4	34.6
Number of prior regimens, median (range)	2 (1–3)	2 (1–3)
Prior therapies, %		
Transplant	54.8	57.8
Bortezomib	65.9	65.7
Non-responsive to prior bortezomib*	15.2	14.6
Lenalidomide	19.9	19.7
Any IMiD	58.8	57.8
Refractory to prior IMiD in any prior regimen	21.5	22.2
Bortezomib and IMiD	36.9	35.1
Non-responsive to prior bortezomib* and refractory to prior IMiD	6.1	6.8

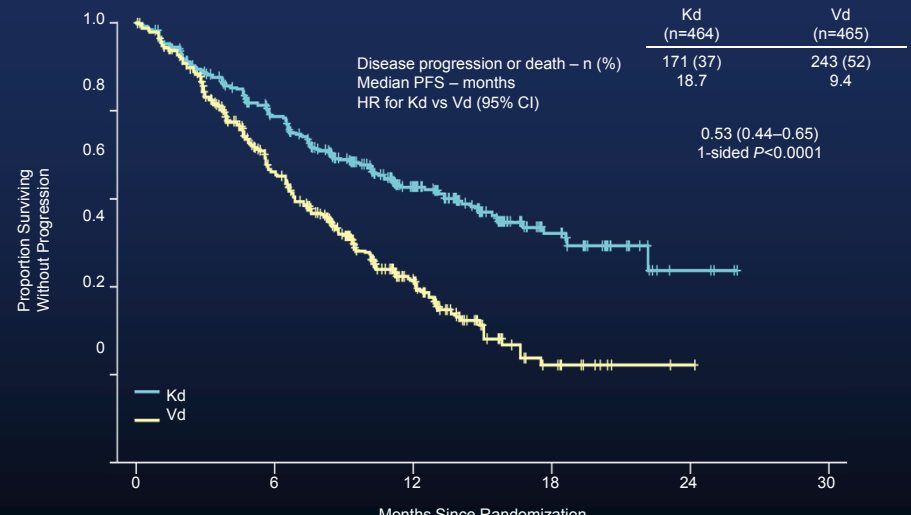
Stewart et al NEJM 2015; 372:142-52.

PFS by Risk Group

	KRd (n=396)		Rd (n=396)			
Risk Group by FISH	N	Median, months	N	Median, months	HR	P-value (one-sided)
High	48	23.1	52	13.9	0.70	0.083
Standard	147	29.6	170	19.5	0.66	0.004

Stewart et al NEJM 2015; 372:142-52.

Primary End Point: Progression-Free Survival
Intent-to-Treat Population (N=929)



- **Median follow-up: 11.2 months**

Dimopoulos et al, ASCO 2015

Carfilzomib Pomalidomide Low dose Dex

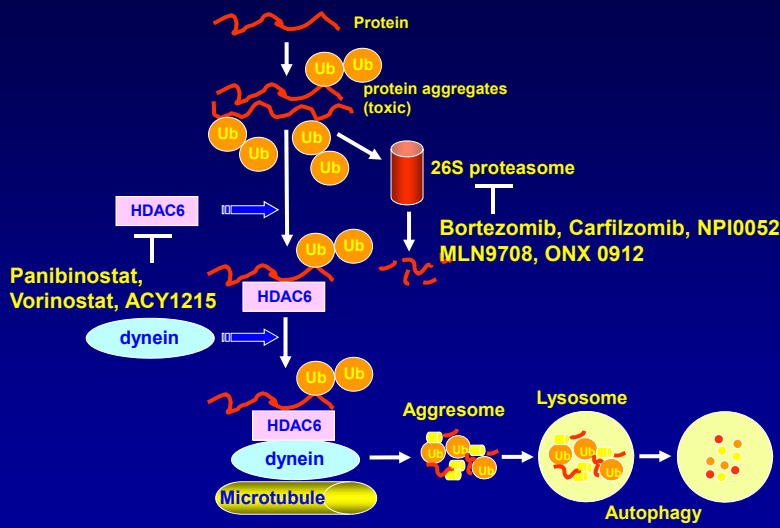
- Median of 5 prior lines of therapy; 49% of patients had high/intermediate risk cytogenetics at baseline

▪ ≥ VGPR	27%
ORR	70%
CBR	83%
▪ DOR (median)	17.7 months
▪ PFS (median)	9.7 months
▪ OS (median)	> 18 months

- Response rates, PFS, and OS were preserved independent of FISH/cytogenetic risk status
- Well tolerated with no unexpected toxicities

Shah et al ASH 2013

Development of Rationally-Based Combination Therapies (HDAC and Proteasome Inhibitors)



Hideshima et al. Clin Cancer Res. 2005;11:8530.Catley et al. Blood. 2006;108:3441-9.

PANORAMA 1: A Randomized, Double-Blind, Phase 3 Study of Panobinostat or Placebo Plus Bortezomib and Dexamethasone in Relapsed or Relapsed and Refractory Multiple Myeloma

Improvement in median PFS of 4 mos w/o difference in ORR or OS

Two-fold increase in nCR/CR rate (28% vs 16%)

Higher rate of Grade 3/4 diarrhea (25.5% vs 8%), fatigue (23.0% vs 11.9%), thrombocytopenia (67.4% vs 31.4%), and leucopenia (34.5% vs 11.4%), discontinuation due to AE (33.6% vs 17.3%).

Confirms PAN-BTZ-Dex in BTZ-refractory pts (PANORAMA 2): ORR: 34.5%; CBR: 52.7%; median PFS: 5.4 mos; median OS: 17.5 mos

FDA approved for relapsed refractory MM exposed to bortezomib and IMiD

Need for less toxic more selective HDACi that can be given with PI to exploit synergistic cytotoxicity.

Richardson PG, et al. Blood. 2013;122:2331-2337
San Miguel J, et al. Lancet Oncol. 2014

Selective Histone Deacetylase 6 Inhibitors Ricolinostat and ACY 241

Synthesized and validated at DFCI

Well tolerated daily oral medication

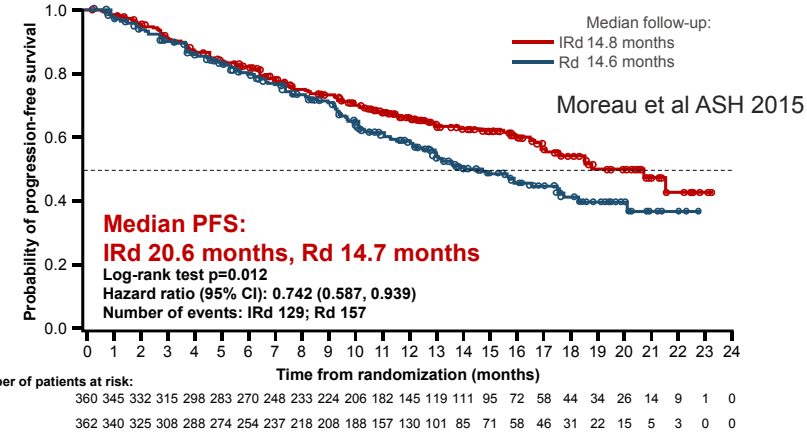
Achieves durable responses when combined with either bortezomib, lenalidomide or pomalidomide in relapsed refractory myeloma

ACY 241 tablet achieves improved PK/PD and durable responses in high risk refractory MM in phase I/II trial, phase III trial soon

Raje et al ASH 2014,2015

Phase 3 study of weekly oral ixazomib plus lenalidomide-dex: final PFS analysis

- **35% improvement in PFS with IRd vs Rd** (data cut-off 30 October 2014)



- A subsequent exploratory analysis of PFS was conducted (median follow-up 23.3 and 22.9 months in the IRd and Rd arms); median PFS 20 vs 15.9 months

Response rates and TTP improved and responses durable with IRd

Response rates, %	IRd (N=360)	Placebo-Rd (N=362)	p-value
Confirmed ORR (≥PR)	78.3	71.5	p=0.035
CR+VGPR	48.1	39.0	p=0.014
Response categories			
CR	11.7	6.6	p=0.019
PR	66.7	64.9	–
VGPR	36.4	32.3	–
Median time to response, mos*	**1.1**	**1.9**	**–**
Median duration of response, mos	**20.5**	**15.0**	**–**

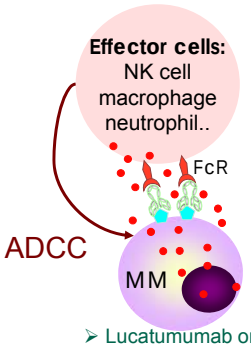
- Significant improvements in different response categories
  - Conservative assessment of best response – derived up until the end of treatment
  - Independently determined by IRC assessment of blinded central laboratory data, rigorously following IMWG 2011 criteria
- PFS benefit confirmed by time to progression (TTP) analysis: median 21.4 months versus 15.7 months with IRd versus Rd, HR 0.712; p=0.007

Moreau et al ASH 2015

visiting committee

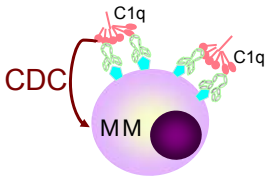
Monoclonal Antibody Based Therapeutic Targeting of Multiple Myeloma

Antibody-dependent Cellular Cytotoxicity (ADCC)



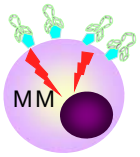
- Lucatumumab or Dacetuzumab (CD40)
- **Elotuzumab (SLAMF7)**
- **Daratumumab (CD38)**
- XmAb®5592 (HM1.24)
- **SAR650984 (CD38)**

Complement-dependent Cytotoxicity (CDC)



- **Daratumumab (CD38)**
- **SAR650984 (CD38)**

Apoptosis/growth arrest via intracellular signaling pathways



- **huN901-DM1* (CD56)**
- **nBT062-maytansinoid /DM4* (CD138)**
- 1339 (IL-6)
- BHQ880 (DKK)
- RAP-011 (activin A)
- **Daratumumab (CD38)**
- **SAR650984 (CD38)**
- **J6M0-MMAF* (BCMA)**

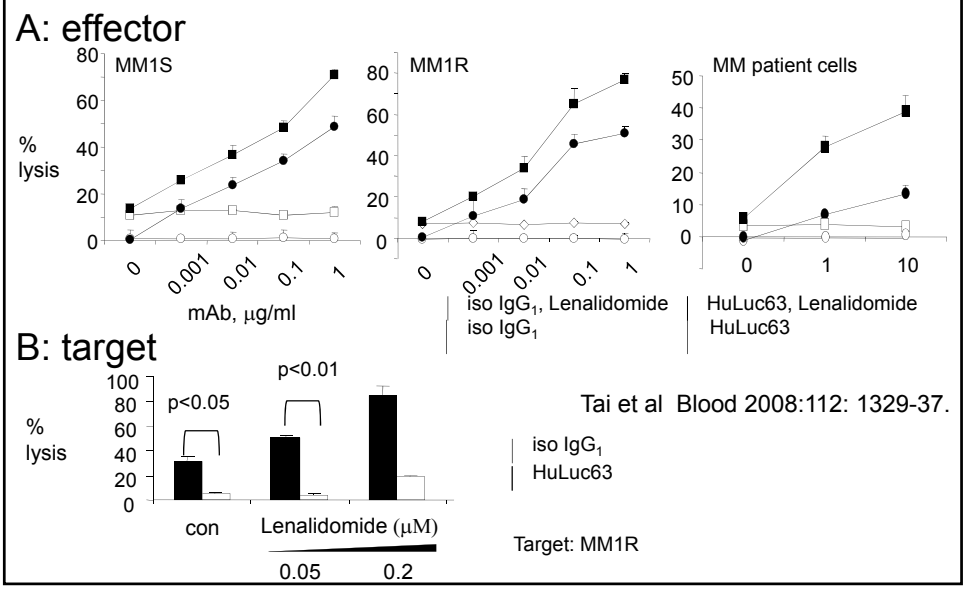
DANA-FARBER CANCER INSTITUTE

The Jimmy Fund®

*** Ab drug conjugate**

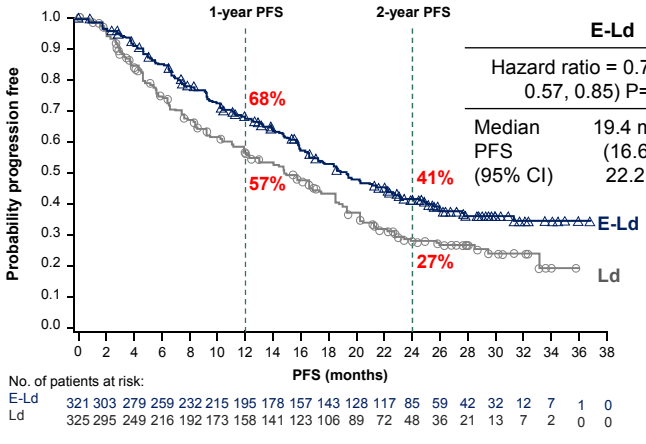
Updated from
Tai & Anderson Bone Marrow Research 2011

Lenalidomide Pretreatment Augments Elotuzumab-Mediated ADCC



Tai et al Blood 2008:112: 1329-37.

Phase 3 Study of Lenalidomide/Dex with or without Elotuzumab in Relapsed/Refractory MM: PFS



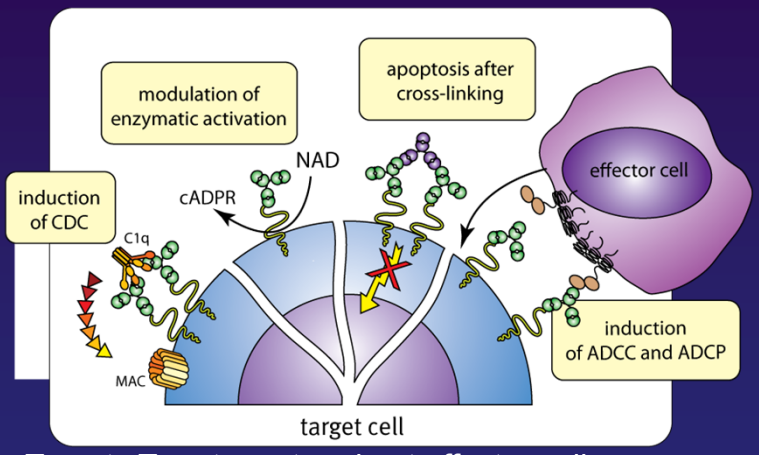
	E-Ld	Ld
Hazard ratio = 0.70 (95% CI: 0.57, 0.85) P=0.0004		
Median PFS (95% CI)	19.4 mo (16.6, 22.2)	14.9 mo (12.1, 17.2)

E-Ld-treated patients had a 30% reduction in the risk of disease progression or death; treatment difference at 1 and 2 years was 11% and 14%, respectively

FDA approved November 2015

Lonial et al, NEnglJMed 2015: 373:621-31

Daratumumab Anti-CD 38 MoAb



Targets Treg to restore host effector cell response

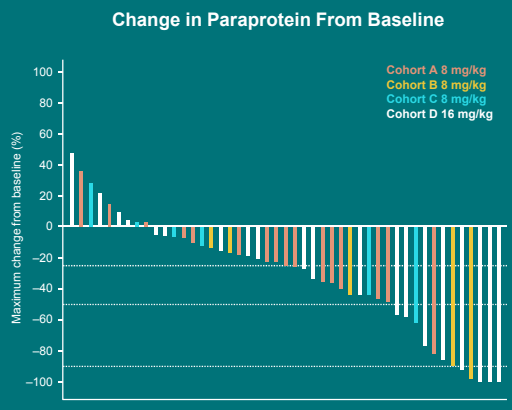
DeWeers et al, J Immunol 2011; 186: 1840 Laubach et al 2014;23:445: Lokhorst et al Blood 2016

Phase I/II Study Daratumumab

No maximum tolerated dose was reached (up to 24 mg/kg)

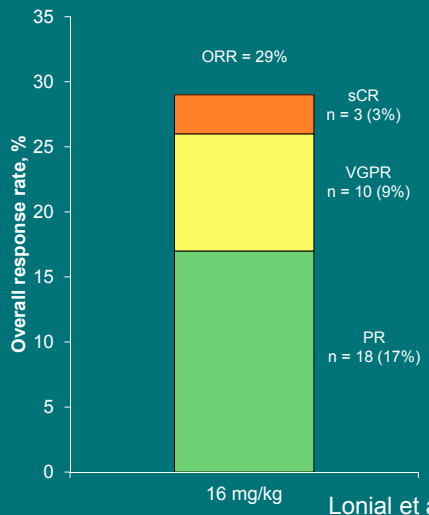
16 mg/kg cohort (42 pts):
ORR 36%
≥PR 15 pts, including 2 CR and 2 VGPR
Median PFS 5.6 months

Led to FDA approval 2015



Lokhorst et al NEnglJMed 2015

Phase 2 Study of Daratumumab (DARA) in Patients with ≥3 Lines of Prior Therapy or Double Refractory Multiple Myeloma: 54767414MMY2002 (Sirius)



- **ORR was 29% (95% CI, 21–39) in patients receiving 16 mg/kg DARA**
- Stringent complete response (sCR) in 3% of patients (95% CI, 0.6–8.0)
- VGPR or better achieved in 12% (95% CI, 7–20) of patients
- Clinical benefit rate (ORR + MR) was 34% (95% CI, 25–44)

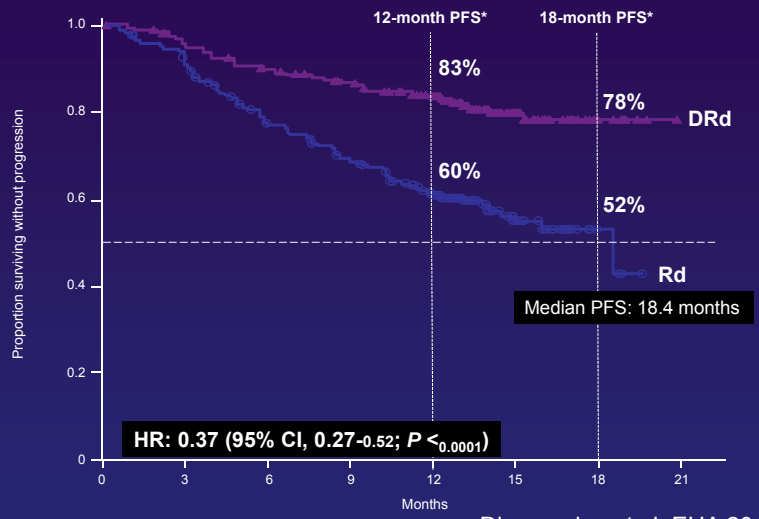
Lonial et al ASCO 2015, Lancet 2016; 387: 1551-60

Dara, Len, and Dex (DRd) Versus Len and Dex (Rd) in RR MM

- **Daratumumab-Rd significantly improved PFS in comparison with Rd alone**
  - **DRd was associated with a 63% reduction in the risk of progression or death**
- **Treatment benefit of DRd versus Rd was consistent across subgroups**
- **DRd doubled CR/sCR rates and quadrupled MRD-negative rates**
- **DRd has a manageable safety profile consistent with the known safety profile of daratumumab or Rd alone**
- **Dimopoulos et al, EHA 2016**

54

Progression-free Survival : Dara Len Dex vs Len Dex



Dimopoulos et al, EHA 2016

63% reduction in the risk of disease progression or death for DRd vs Rd

55

55

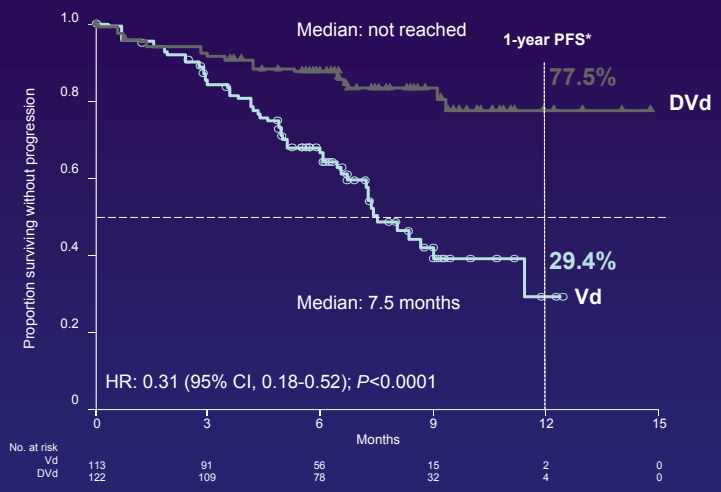
Dara, Bort and Dex (DVd) vs Bort and Dex (Vd) in R/R MM

- Daratumumab-Vd significantly improved PFS, TTP, and ORR in comparison with Vd alone
  - DVd was associated with a 61% reduction in the risk of progression/death
- Treatment benefit of DVd vs Vd was consistent across subgroups
  - Earlier treatment with DVd may be the most beneficial
- Daratumumab-Vd doubled VGPR and CR rates
- Daratumumab-Vd was not associated with any cumulative toxicities

Palumbo et al ASCO 2016

5

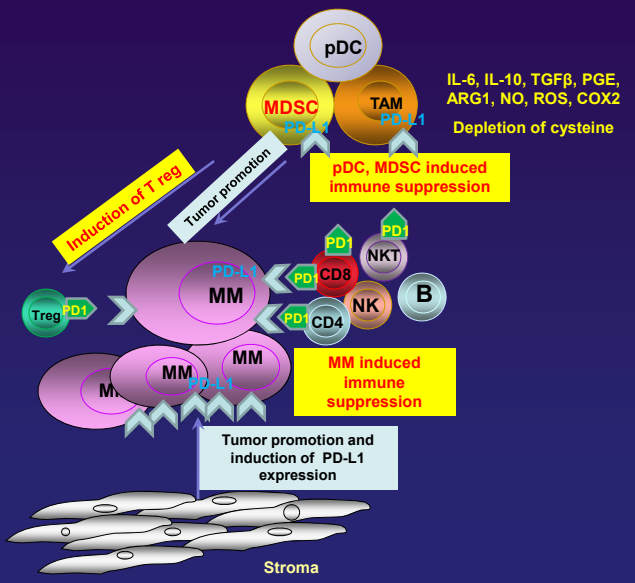
PFS: 1 Prior Line Treatment



69% reduction in the risk of progression or death for DVd vs Vd

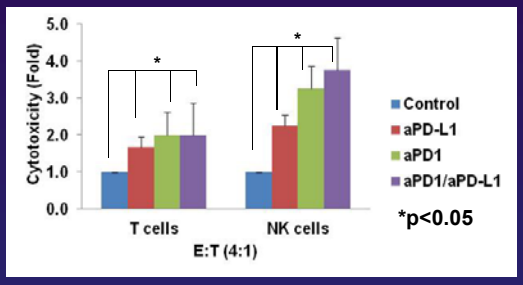
Palumbo et al ASCO 2016

Immune Suppressive Microenvironment in MM



Görgün GT, et al. Blood 2013;121:2975-87

Checkpoint Blockade Induces Effector Cell Mediated MM Cytotoxicity

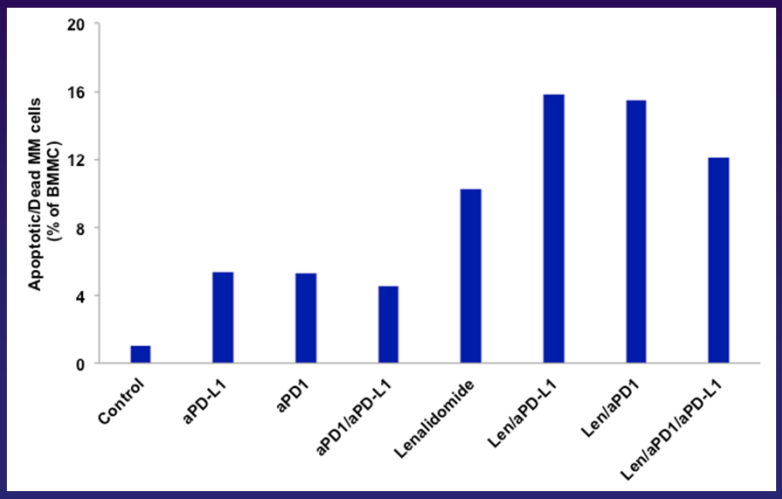


Effector: Autologous effector cells (CD3T cells, NK cells)

Target: CD138+ MM cells from Rel/Ref MM-BM

Görgün G. et al. Clin Cancer Res, in press

Lenalidomide Enhances Checkpoint Blockade Induced Cytotoxicity Against MM cells



Görgün G. et al. Clin Cancer Res, in press

Pembrolizumab With Len/Dex for R/R MM

Best Overall Response n (%)	Efficacy Population† (n = 40)	Len-Refractory (n = 29)
Overall response rate	**20 (50)**	**11 (38)**
Stringent complete response (sCR)	1 (3)	1 (3)
Very good partial response (VGPR)	5 (13)	3 (10)
Partial response (PR)	14 (35)	7 (24)
Stable disease (SD)	19 (48)	17 (59)
Disease control rate (CR+PR+SD)	39 (98)	28 (97)
Progressive disease (PD)	1 (3)	1 (3)

PRESENTED AT: ASCO ANNUAL MEETING '16

Mateos et al, 2016

Data cutoff: April 11, 2016

Immune Effects of HDACi 241 in MM Therapy

Augments PD-L1 expression on MM cells

Augments MM cell line cytotoxicity, which is enhanced with pomalidomide, CD38Ab, and/or PD-1/PD-L1 Abs

Augments and autologous MM cell cytotoxicity, which is enhanced by CD38 Ab and/or PD-1/PD-L1 Abs

Enhances MM cytotoxicity alone and with PD-1/PD-L1Abs, even in the presence of pDCs

Augments NK cell function, alone and with PD-L1 Ab

Myeloma CAR therapy

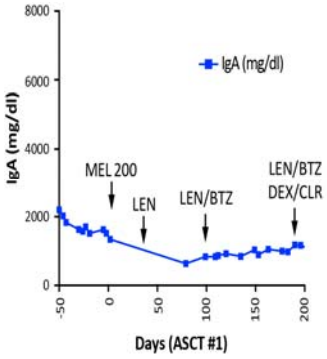
- **Multiple promising targets:**
  - CD19, CD138, CD38, CD56, kappa, Lewis Y, CD44v6, CS1, BCMA
- **Functional CAR T cells can be generated from MM patients**
- **CAR T and NK cells have in vitro and in vivo activity against MM**
- **Clinical trials underway**
  - Anecdotal prolonged responses but no robust efficacy data available yet
- **Many questions remain about CAR design:**
  - optimal co-stimulatory domains
  - optimal vector
  - optimal dose and schedule
  - need for chemotherapy
  - Perhaps 'cocktails' of multiple CARs or CARs + chemotherapy will be required for best outcomes

Stadtmauer et al, 2015

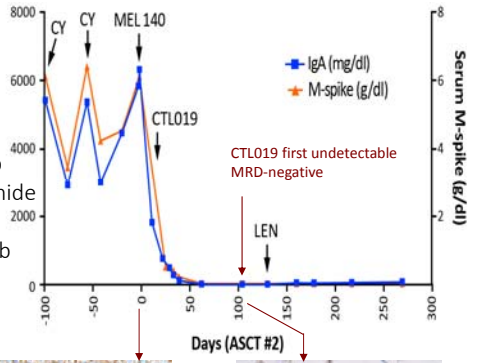
Penn Medicine

the cure is within ABRAMSON CANCER CENTER

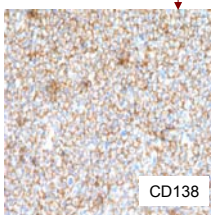
MM Patient #1: Response to CD19 CAR Therapy

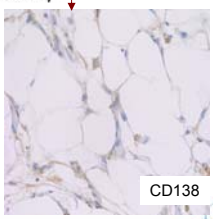


Additional regimens including…
- carfilzomib
- pomalidomide
- vorinostat
- elotuzomab



sCR, MRD neg
Now d +307
TTP after ASCT #1 d190
Remission inversion

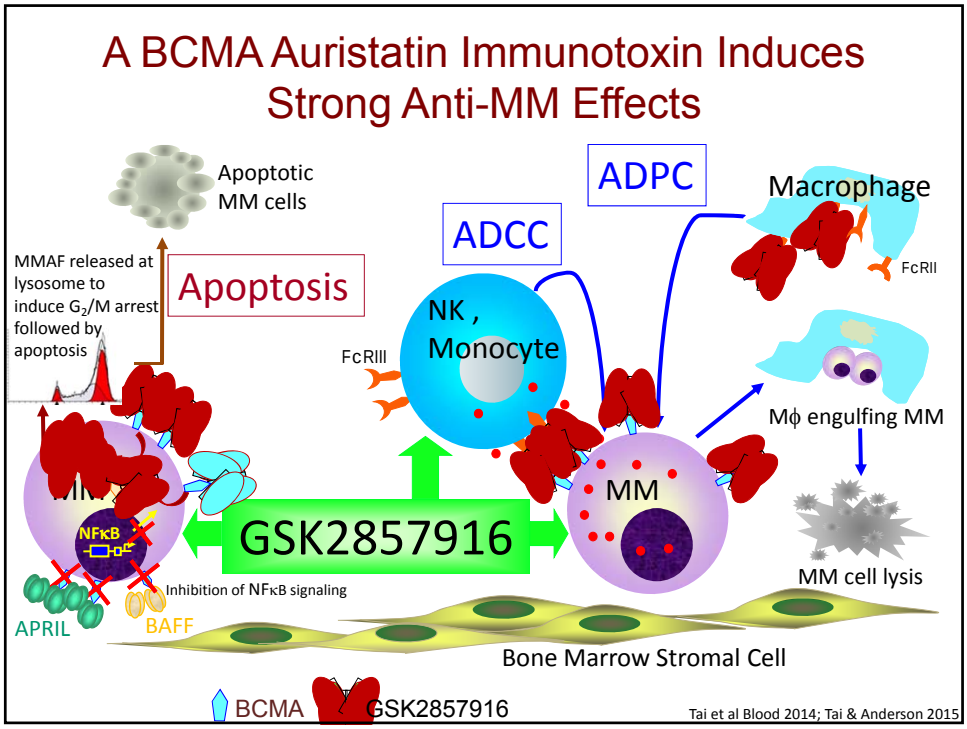


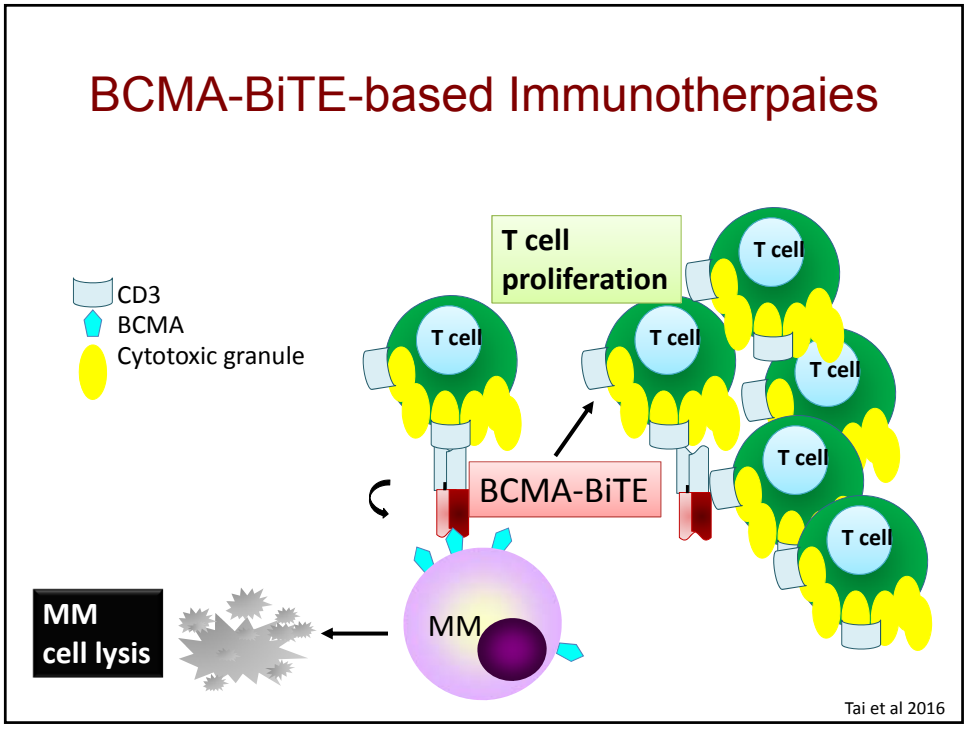


Garfall et al, NEJM 2015; 373: 1040-7

Penn Medicine

the cure is within ABRAMSON CANCER CENTER


A BCMA Auristatin Immunotoxin Induces Strong Anti-MM Effects
Apoptotic MM cells
MMAF released at lysosome to induce G2/M arrest followed by apoptosis
Apoptosis
ADCC
ADPC
Macrophage
FcRII
NK , Monocyte
FcRIII
Mϕ engulfing MM
MM
GSK2857916
NFκB
Inhibition of NFκB signaling
APRIL
BAFF
MM cell lysis
Bone Marrow Stromal Cell
BCMA
GSK2857916
Tai et al Blood 2014; Tai & Anderson 2015


BCMA-BiTE-based Immunotherpaies
CD3
BCMA
Cytotoxic granule
T cell proliferation
T cell
BCMA-BiTE
MM
MM cell lysis
Tai et al 2016

Summary and Conclusions

- Broader population of patients now eligible for therapy: 60% BM plasma cells; kappa:lambda>100; bone disease on MRI or PET/CT
- In newly diagnosed transplant candidates, three drug regimens incorporating immunomodulatory drugs and proteasome inhibitors before and after transplant prolong PFS and OS.
- MRD portends for better patient outcome and is a goal of therapy

Summary and Conclusions

- Relapse therapies now include bortezomib, lenalidomide/dex, bortezomib/pegylated doxorubicin, pomalidomide/dex, carfilzomib, bortezomib/panobinostat, elotuzumab len dex, daratumumab, and ixazomib.
- Novel targeted and immune therapies are showing great promise.
- Incorporation of novel therapies at all stages of disease is further improving patient outcome in MM

Summary and Conclusions

- **Choice of therapy depends on prior treatment and specific factors:**

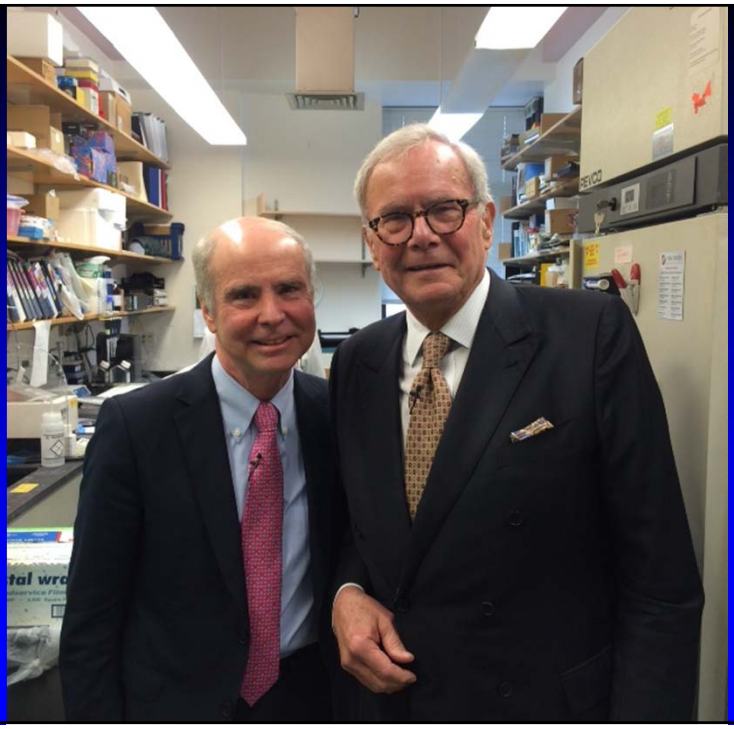
Initial: Len Dex + bortezomib

1-3 prior therapies:

Pomalidomide/Dex, Carfilzomib (len/dex),

Elotuzumab/len/dex, ixazomib len/ dex

Multiply relapsed: daratumumab, panobinostat/bortezomib, protocols of targetted and immune therapies



Integrative Oncology in Clinical Practice

Gabriel Lopez, MD
Assistant Professor, Department of Palliative, Rehabilitation and Integrative Medicine
Medical Director, Integrative Medicine Center
University of Texas, MD Anderson Cancer Center

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®




Integrative oncology in clinical practice

Gabriel Lopez, MD

Assistant Professor
Medical Director, Integrative Medicine Center
Integrative Medicine Program
Department of Palliative, Rehabilitation and Integrative Medicine

Sept 30, 2016

Integrative Medicine in the Media

Objectives

- Background to concepts of *Integrative*, *Complementary* and *Alternative medicine*
- Understand our model of Integrative Oncology Care Delivery
- Review of evidence based integrative approaches for cancer patients

Complementary and Alternative Medicine (CAM)

NIH National Center for Complementary and Integrative Health

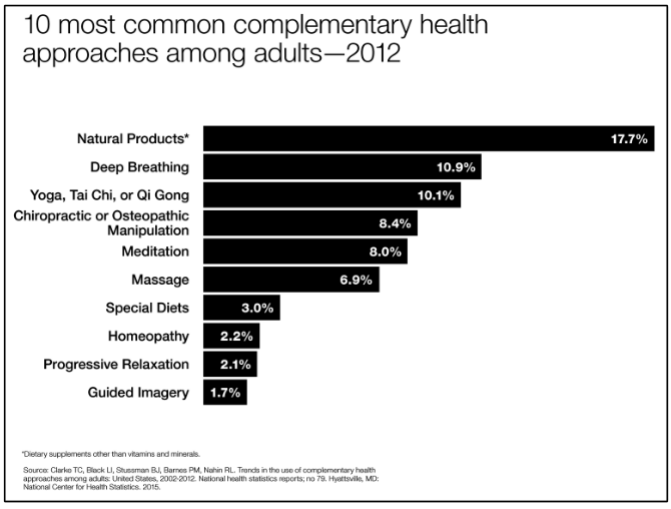
Definition

A group of diverse medical and health care systems, practices, and products that are not presently considered to be part of *conventional* medicine.

* NCCAM prior to December 2014

Complementary Health Approaches	Examples
Natural Products	Dietary Supplements • Herbal medicines (botanicals) • Vitamins • Minerals • Probiotics
Mind and Body Practices	Meditation Yoga Acupuncture Tai chi and Qi gong Massage therapy Relaxation Techniques • Breathing exercises • Guided imagery • Progressive muscle relaxation Movement therapies • Feldenkrais, Pilates Spinal manipulation • Chiropractic, Osteopathic, Physical therapy Energy Therapies • Healing touch, Reiki, Magnet therapy Hypnotherapy
Other Complementary Health Approaches	Whole medical systems • Traditional healers • Ayurvedic medicine • Traditional Chinese Medicine • Homeopathy • Naturopathy

US Adults: Complementary Health Approach Use



Clarke TC, et al. Trends in Complementary Health Approach Use 2010-2012. 2015

CAM Use Among Cancer Patients

- By the General Population (US): **38.3%**
- By Cancer Patients: up to **68%**

Survey Results of 450 patients, majority from outpatient melanoma and breast cancer clinics

Type of CAM	If Heard of CAM, Ever Used (%)	Combined CAM With Conventional Therapy (% of users)	Discussed CAM With Physician (% of users)
CAM overall	83.3	88.0	61.8
CAM overall excluding spiritual/psychotherapy	68.7	75.2	60.7
Spiritual practices	80.5	91.0	36.6
Vitamins/herbs	62.6	76.6	64.1
Movement/physical therapies	59.2	66.9	48.4
Psychotherapy	41.2	58.3	41.1
Mind/body	48.6	79.5	26.3
Special diet	32.3	63.2	41.9
Other therapies	10.5	40.0	15.8

Barnes et al., CDC Advanced Data 2008; Ernst & Cassileth Cancer. 1998; MA Richardson et al. JCO 2000

CAM Use Among *Advanced* Cancer Patients

- Likelihood of CAM use by incurable disease presentation
  - Distant / Metastatic disease
    - **11.6** times (95% CI, 1.5 to 92.8) more likely than those with local disease
    - **4.2** times (95% CI, 1.3 to 13.7) more likely than patients with regional disease.
  - Disease not staged
    - **14.2** times (95% CI, 1.7 to 118.1) than local disease
    - **5.1** times (95% CI, 1.5 to 18.0) more likely than regional disease

Richardson et al. JCO 2000

Complementary, Alternative, and Integrative Medicine

Is there a difference?

Difference Between Alternative, Complementary, and Integrative

- **Alternative medicine** is used in place of conventional medicine.
- **Complementary medicine** is used together with conventional medicine.
- **Integrative medicine** is used together with conventional medicine in a deliberate manner that is personalized, evidence-based, and safe.

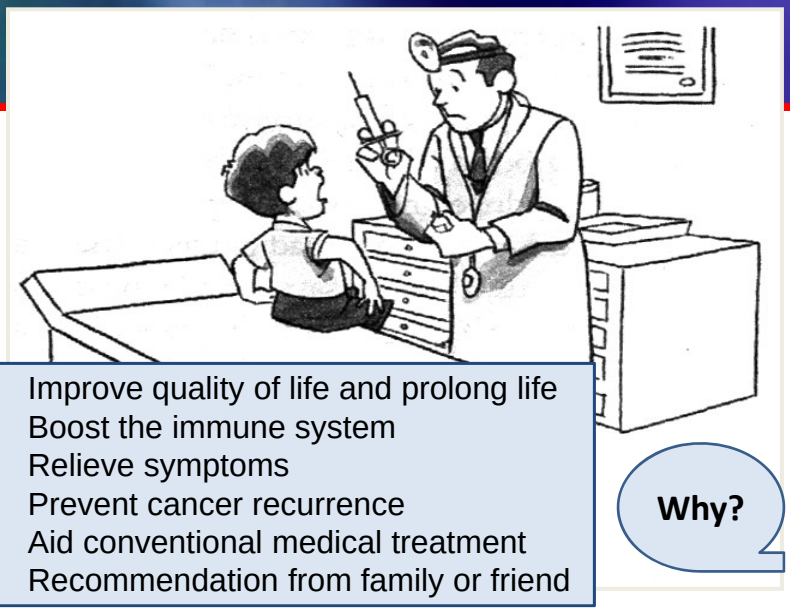
ACADEMIC CONSORTIUM FOR INTEGRATIVE MEDICINE & HEALTH

The practice of medicine that reaffirms the importance of the relationship between practitioner and patient

Focuses on the whole person

Informed by evidence

Makes use of all appropriate therapeutic approaches, providers, and disciplines to achieve optimal health and healing



- Improve quality of life and prolong life
- Boost the immune system
- Relieve symptoms
- Prevent cancer recurrence
- Aid conventional medical treatment
- Recommendation from family or friend

Why?

Objectives

- Background to concepts of Integrative, Complementary and Alternative medicine
- Understand our model of Integrative Oncology Care Delivery
- Review of evidence based integrative approaches for cancer patients

The Integrative Medicine Program at MD Anderson Cancer Center

- **Clinic**
- **Research**
- **Education**

Clinical Program Philosophy

"The Integrative Medicine Center aims to work ***collaboratively*** with the oncology team to build a comprehensive and integrative care plan that is ***personalized***, ***evidence-based***, and ***safe*** with the goal of improving clinical outcomes."

Integrative Medicine Center Model

8 April 1977, Volume 196, Number 4286

SCIENCE

The Need for a New Medical Model: A Challenge for Biomedicine

George L. Engel

"the physician's basic professional knowledge and skills must span the ***social***, ***psychological***, and ***biological***, for his decisions and actions on the patient's behalf involve all three."

Integrative Medicine Center Model*

Physical

- **Exercise**
- **Nutrition**
- **Acupuncture**
- **Oncology Massage**

- Primary Oncology team
- Physical Medicine & Rehabilitation
- Supportive Care
- Cancer Pain

Mind-Body

- **Health Psychology**
- **Meditation**
- **Music Therapy**
- **Tai Chi/Qi Gong**
- **Yoga**

- Psychiatry
- Spiritual Care

Social

- **Group Programs**

- Social Work
- Support Groups

*IMC offerings in bold/boxes

Integrative Oncology Consultation

- Educate
  - Integrative Medicine
  - Herbs & Supplements
  - Nutrition
  - Exercise
  - Acupuncture
  - Oncology Massage
  - Music Therapy
  - Meditation
- Provide personalized therapeutic recommendations
- Interdisciplinary Approach
  - Weekly team meeting to discuss patient cases
- Communication with the primary team

Herbs & Supplements

*** These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.**

Toxicity

Hepatotoxicity from green tea: a review of the literature and two unpublished cases

Gabriela Mazzanti · Francesca Menniti-Ippolito · Paola Angela Moro · Federica Cassetti · Roberto Raschetti · Carmela Santuccio · Sabina Mastrangelo

Abstract
Purpose To review the current literature on suspected green tea-related hepatic reactions and to describe two new cases reported within the framework of the Italian surveillance system of natural health products.
Results A literature search of publication between 1999 and October 2008 retrieved 34 cases of hepatitis. Histological examination of the liver revealed inflammatory reactions, cholestasis, occasional steatosis, and necrosis. A positive dechallenge was reported in 29 cases. There was one reported death. A positive rechallenge occurred in seven cases (20%). In the two new cases, the causality assessment was judged as "possible" according to the RUCAM score.
Conclusions Our analysis of the published case reports suggests a causal association between green tea and liver damage. The hepatotoxicity is probably due to (-)-epigallocatechin gallate or its metabolites which, under particular conditions related to the patient's metabolism, can induce oxidative stress in the liver. In a few cases, toxicity related to concomitant medications could also be involved.

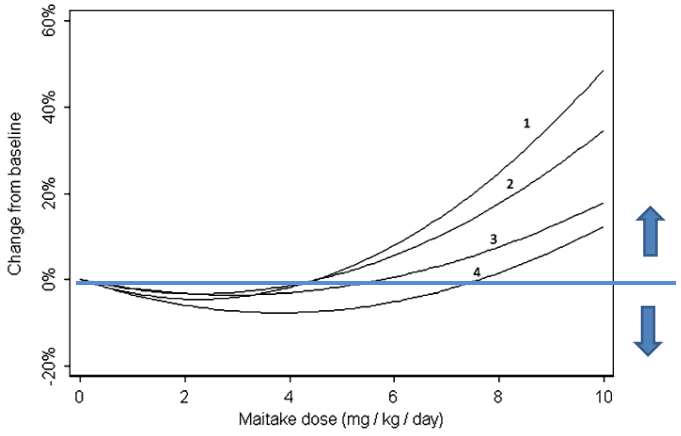
Keywords Green tea · *Camellia sinensis* · Catechins · Epigallocatechin gallate · Hepatotoxicity · Herbal supplements

Introduction

The consumption of tea originated in China and Southeast Asia thousands of years ago and was thereafter introduced progressively all around the world. Historically, green tea has been lauded for various beneficial health effects, and more recently its biological activities have been investigated. Tea is obtained from the leaves of *Camellia sinensis* (L.) Kuntze (Fam. Theaceae). Its composition varies with climate, season, horticultural practices, variety and age of the plant, and manner in which the leaves have been

A phase I/II trial of a polysaccharide extract from *Grifola frondosa* (Maitake mushroom) in breast cancer patients: immunological effects

Gary Deng · Hong Lin · Andrew Seidman · Monica Fornier · Gabriella D'Andrea · Kathleen Wesa · Simon Yeung · Susanna Cunningham-Rundles · Andrew J. Vickers · Barrie Cassileth



Immune Factor Change from Baseline

J Cancer Res Clin Oncol (2009)

Quality

Echinacea and Truth in Labeling

Christine M. Gilroy, MD; John F. Steiner, MD, MPH; Tim Byers, MD, MPH; Howard Shapiro, PhD; William Georgian, MS

Results: Of the samples, 6 (10%) of 59 preparations contained no measurable *Echinacea*. The assayed species content was consistent with labeled content in 31 (52%) of the samples. Of the 21 standardized preparations, 9 (43%) met the quality standard described on the label. Labeled milligrams were weakly associated with measured constituent ($r=0.35$; $P=.02$).

Conclusions: *Echinacea* from retail stores often does not contain the labeled species. A claim of "standardization" does not mean the preparation is accurately labeled, nor does it indicate less variability in concentration of constituents of the herb.

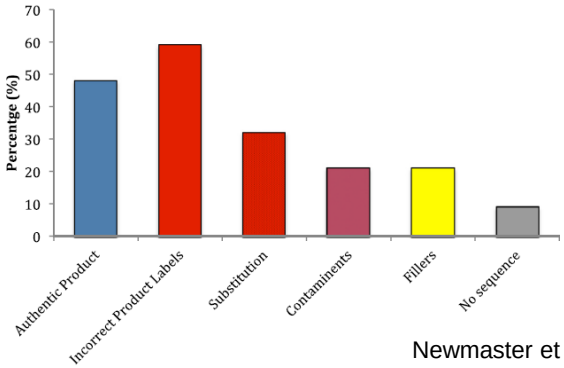
Arch Internal Med 2003

Quality

RESEARCH ARTICLE Open Access

DNA barcoding detects contamination and substitution in North American herbal products

Steven G Newmaster[1*], Meghan Grguric[2], Dhivya Shanmughanandhan[3], Sathishkumar Ramalingam[3] and Subramanyam Ragupathy[1*]



DNA barcode results from blind testing of the **44 herbal products** representing **30 medicinal species** of plants from 12 different companies

Newmaster et al. BMC Medicine 2013

Interactions

MORNINGS

1. *Juvo – Natural Raw Meal, 2 scoops taken with 12 ounces of organic orange juice;*
2. *Udo's Oil 3-6-9 Blend, 2 tablespoons;
3. Mature Multivitamin, 1 tab;
4. Host Defense – 17 Premier Mushrooms, 10 drops;
5. Melatonin, 10 drops;
6. Selenium, 10 drops;
7. Marine Phytoplankton, 10 drops;
8. Mega Green Tea Extract, 3 caps @ 725 mg;
9. Turmeric (Curry), 2 caps @ 527 mg;
10. Turmericforce – 1 sofgel @ 400 mg;
11. *Lycopene, 5 caps @ 10 mg;
12. Folic Acid, 1 cap @ 800 mg;
13. Ginger, 3 caps @ 500 mg;
14. Beta – 1, 3D Glucan, 2 caps @ 500 mg;
15. Echinacea, 2 caps @ 400 mg;
16. Acai, 2 caps @ 400 mg;
17. Resveratrol, 3 caps @ 500 mg;
18. Raw Vitamin C, 3 caps @ 300 mg;
19. *Pycnogenol, 2 tabs @ 50 mg;
20. Vitamin D3, 4 tabs @ 1000 mg;
21. Aged Garlic Extract, 2 caps @ 600 mg;
22. St. Joseph Coated Aspirins, 2 tabs;
23. Oregano Oil, 1 cap a month;
24. ImmPower – Elite Mushrooms, 5 caps;
25. *Host Defense – 17 Premier Mushrooms, 3 caps;
26. IP6 & Inositol Plus Maitake & Cat's Claw, 3 caps @ 130 mg;
27. IP6 & Inositol – Rapid Release Tablets, 1 tabs @ 130 mg;
28. Super B-Complex.

Green Tea

Echinacea

Mushroom extracts (maitake)

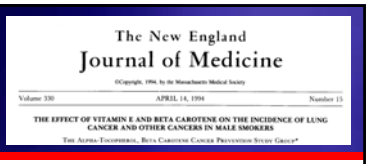
Catharanthus roseus (Periwinkle)
Vinblastine

Taxus brevifolia (Yew Tree)
Paclitaxel

Camptotheca acuminata (Happy Tree)
Irinotecan

Podophyllum pelatum (Mayapple)
Etoposide

ATBC trial

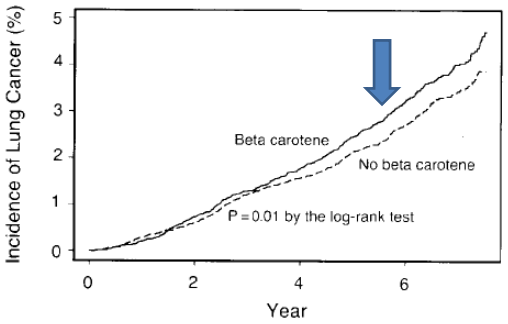

The New England Journal of Medicine

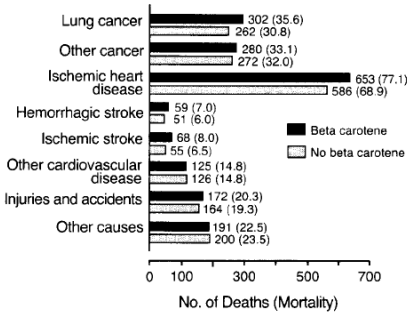
Volume 330 APRIL 14, 1994 Number 15

THE EFFECT OF VITAMIN E AND BETA CAROTENE ON THE INCIDENCE OF LUNG CANCER AND OTHER CANCERS IN MALE SMOKERS

Alpha-tocopherol and Beta-Carotene Trial to Prevent Lung Cancer (ATBC) → 29,000+ smokers randomized to placebo, Vitamin E, Beta-Carotene, or both

Results: Smokers taking beta-carotene supplement had higher incidence of lung cancer





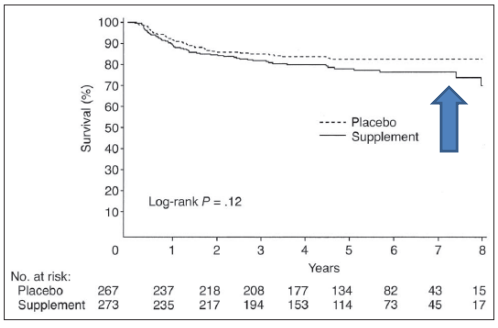
NEJM 1994

Anti-Oxidants During Treatment

Randomized Trial of Antioxidant Vitamins to Prevent Acute Adverse Effects of Radiation Therapy in Head and Neck Cancer Patients

Isabelle Bairati, François Meyer, Michel Gélinas, André Fortin, Abdenour Nabid, François Brochet, Jean-Philippe Mercier, Bernard Têtu, François Harel, Belkacem Abdous, Éric Vigneault, Sylvie Vass, Pierre del Vecchio, and Jean Roy†

- 540 H&N cancer patients treated with radiation
- Randomized to:
  - Vitamin E and Beta-carotene
  - Placebo
- Supplement arm:
  - Decreased acute adverse effects
  - Increased rate local recurrence



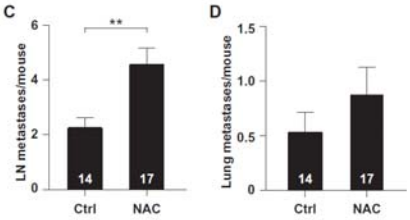
JCO 2005

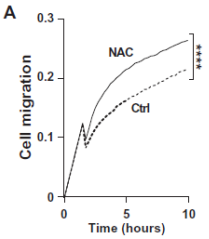
Preclinical study with Anti-Oxidants

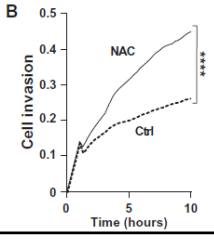
CANCER

Antioxidants can increase melanoma metastasis in mice

Kristell Le Gal,[1,2] Mohamed X. Ibrahim,[1,3] Clotilde Wiel,[1,3] Volkan I. Sayin,[2,4] Murali K. Akula,[1,3] Christin Karlsson,[1,3] Martin G. Dalin,[1,3]* Levent M. Akyürek,[2] Per Lindahl,[2,4] Jonas Nilsson,[1,5] Martin O. Bergo[1,3]†







NAC = n-Acetyl cysteine

www.ScienceTranslationalMedicine.org 7 October 2015

Objectives

- Background to concepts of Integrative, Complementary and Alternative medicine
- Understand our model of Integrative Oncology Care Delivery
- Review of evidence based integrative approaches for cancer patients

Welcome

Consultation: Initial Evaluation

No Pain	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Pain
Not Fatigued/Tired	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Fatigue/Tiredness
Not Nauseated	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Nausea
Not Depressed	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Depression
Not Anxious	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Anxiety
Not Drowsy	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Drowsiness
Best Appetite	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Appetite
Best Feeling or Well Being	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Feeling of Well Being
No Shortness of Breath	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Shortness of Breath
Best Sleep	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Sleep

ESAS

PROMIS 10

MyCAW

Who do we see?

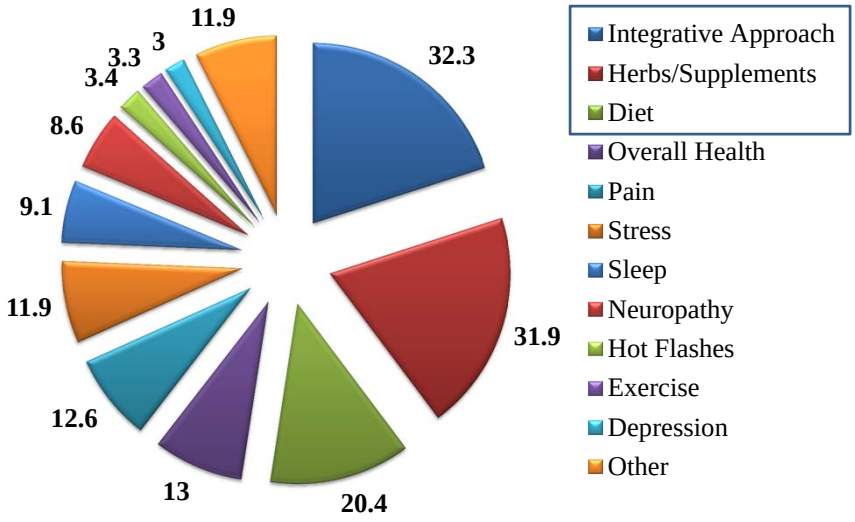
OUTPATIENT:

Cancer Type	(%)
Breast	34%
GU	18%
GI	16%
Skin	10%
Head & Neck	7%
Lung	6%
Hematologic	6%
Other	6%

SEER Staging	(%)
NED	18%
Local	14%
LN Involvement	22%
Metastatic	35%
Unknown	11%

INPATIENT: Top referrals from:
1. Palliative Care
2. Physical Medicine & Rehab
3. Leukemia (3rd most common referral source & most common cancer type)

Reasons for Consultation



Modalities, Interventions and Evidence

Personalized Integrative Oncology Care Plan

Nutrition & Exercise

American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention

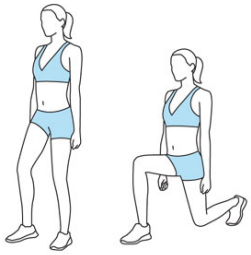
Reducing the Risk of Cancer With Healthy Food Choices and Physical Activity

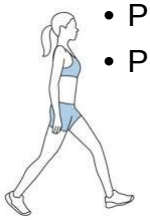
- Healthy body weight (normal BMI)
- Exercise regularly – 150 minutes/week of moderate intensity or 75 minutes of vigorous activity
- 5 servings of fruits and vegetables per day
- Limit processed meat, red meat, and refined grains
- Limit alcohol

McCullough et al. Cancer Epidemiol Biomarkers Prev; 20(6); 1089–97. 2011

Exercise

- Multiple benefits to exercise
  - Improved Mood
  - Decreased Fatigue
- Goal of safe exercise
  - Referral to:
    - Physical Medicine and Rehabilitation
    - Physical Therapy and Occupational Therapy





Nutrition

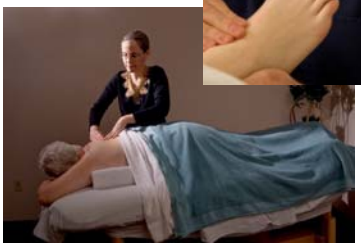
- Emphasize Whole Foods
  - Whole Fruits
  - Whole Vegetables
  - Whole Grains
  - Lean Meats
- Consider Dietician referral

Oncology Massage Therapy

Oncology massage therapists have special training to provide safe and optimal massage through awareness of the unique needs of cancer patients.

How can Oncology Massage help?

- Relieve Anxiety & Stress
- Decrease Pain
- Relieve Constipation
- Relieve Neuropathy



Massage Precautions

- Solid tumor
- Bone metastasis
- Radiation site
- Incision site
- Limb swelling
- Lymphedema risk
- Blood clot
- Blood counts
(platelets, INR, neutrophils)
- Neuropathy
- Medications
(anticoagulants)
- Medical devices
(chemoport, ostomy, IV)

Massage in Supp Cancer Care 2012

Condition	Avoid	But you CAN
• Solid tumor in any area that is accessible to the hands • Known or suspected bone metastasis, including the spine • Swelling or edema, including lymphedema, current or past	• Pressure on the area of the tumor • Pressure on the area • Jostling or moving the joints in the area • Pressure on the area • Positions that put pressure on the area • Positions where gravity increases the swelling	• Touch, hold or stroke with soft hands • Use moderate pressure elsewhere • Touch, hold or stroke with soft hands • Use moderate pressure elsewhere • Massage elsewhere, with patient comfortably positioned
• Tendency toward bruising or bleeding	• Pressure • Aggressive kneading or gliding	• Gentle kneading or light stroking with just the pressure used to apply lotion • "Holding" the body with soft hands
• Fever	• Gliding and kneading strokes with pressure	• Gliding and kneading strokes with just the pressure used to apply lotion • Try resting hands quietly, and imagine coolness coming through your hands
• Any identified risk of lymphedema	• Pressure or rubbing an area at risk of lymphedema	• Use moderate pressure elsewhere
• Radiation site	• Pressure or stretching the skin in the area • If skin is open (e.g., by scratching), avoid any contact with area	• If tolerated, contact with soft, still hands, resting over clothing • Imagine coolness coming through your hands
• Incision site • Recent surgery • Medical devices: IV, chemo port, catheter, oxygen mask, cannula, ostomy	• Pressure, stretching or kneading the area • Positions (e.g., face down) that press or pull on the area • Getting lotion on devices	• Massage elsewhere on the body • Handle any device with clean, dry hands; follow doctor guidelines • Choose positions and pillows that ease discomfort
• Fragile veins or varicose veins • Communicable skin disease • Undiagnosed skin lesions • Removal or radiation of lymph nodes in the armpit, groin, neck or jaw	• Pressure on the area • Contact with the skin • Contact with the skin • Pressure on the limb and the area drained by those lymph nodes	• Touch or hold with soft hands • Ask doctor what touch is possible • Refer to your doctor • Massage with moderate pressure elsewhere on the body • Touch or hold the area with soft hands; no pressure
• Neuropathy • Changes in sensation (e.g., numbness, tingling, weakness) • Easy bruising or bleeding (low platelets, blood thinners, etc.)	• Pressure on the affected area • Pressure and joint movement in the affected area • Pressure anywhere on the body (because of bruising)	• Use moderate pressure elsewhere • Report symptoms to doctor and follow her/his advice • Holding or stroking anywhere with light or no pressure. Ask doctor about best pressure.
• Major problems affecting vital organs (heart, lungs, kidneys, liver, brain)	• Pressure	• Massage without much pressure or moderate pressure, depending upon the patient's tolerance
• Low white blood count (neutropenia) • Fatigue • Risk of blood clot in legs (from cancer or cancer treatment)	• Pressure • Pressure • Contact with thighs, calves, shins or tops of feet, or anywhere blood clots are a risk	• Same as above • Same as above • Massage with moderate pressure on bottoms (soles) of feet if doctor advises it

Massage Pressure levels

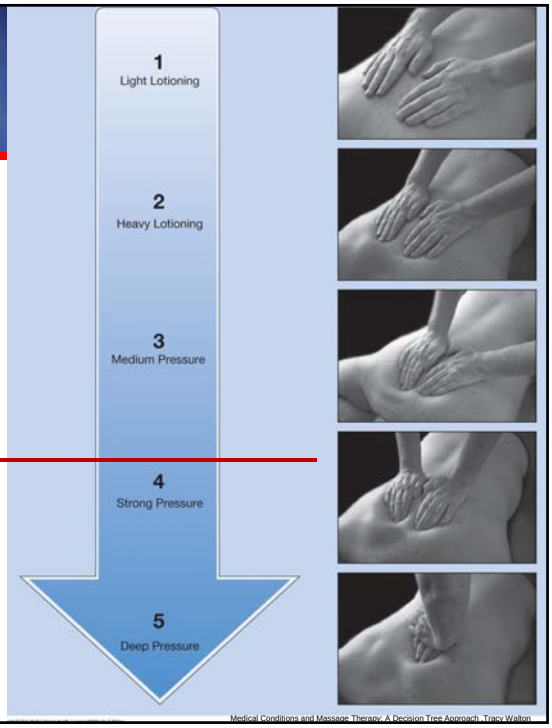
Level 1: slight skin movement

Level 2: slight movement superficial adipose and muscle

Level 3: slight movement medium layer adipose, muscle, & blood vessels

Level 4: move deep layers to fascia, move adjacent joints

Level 5: move deepest layers, engage bone



Medical Conditions and Massage Therapy: A Decision Tree Approach, Tracy Walton

Oncology Massage

Stress and Anxiety

Original Article

Massage Therapy for Symptom Control: Outcome Study at a Major Cancer Center

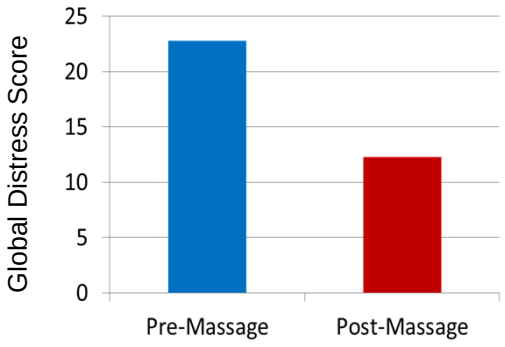
Barrie R. Cassileth, PhD and Andrew J. Vickers, PhD
Integrative Medicine Service (B.R.C., A.J.V.) and Biostatistics Service (A.J.V.), Memorial Sloan-Kettering Cancer Center, New York, New York, USA

Table 2
Improvements in Symptom Scores Following Massage Therapy

Symptom	*n*	Baseline	Post-treatment	Change	Improvement
Presenting[a]	1290	6.6 (2.5)	3.2 (2.7)	3.4 (2.6)	54.1% (34.1)
Pain	1284	3.6 (2.9)	1.9 (2.2)	1.7 (2)	40.2% (40.9)
Fatigue	1263	4.7 (2.9)	2.7 (2.7)	2.1 (2.2)	40.7% (39.1)
Anxiety	1273	4.6 (3.1)	1.8 (2.2)	2.8 (2.5)	52.2% (39.5)
Nausea	1255	1.4 (2.4)	0.7 (1.6)	0.7 (1.6)	21.2% (38.3)
Depression	1254	2.4 (2.8)	1.2 (2)	1.2 (1.9)	30.6% (41.0)
Other	105	6.5 (2.5)	3.4 (2.8)	3.1 (2.8)	46.6% (36.9)

Figures are given as mean (standard deviation).
[a]Defined as the symptom with the highest score at baseline.

Oncology Massage: Our experience



P < 0.0001
n=456
(patient & caregiver)

ESAS Anxiety Score (means)

n= 398
Initial patient visits

Mean difference: 1.33

Pre-Massage	Post-Massage
2.22	0.99

Edmonton Symptom Assessment Scale (ESAS; scale from 0-10, where 10 is most severe). May 2011 – Dec 2013

Acupuncture

Traditional Chinese Medicine practice
Insertion of needles at specific points to help relieve cancer or treatment related symptoms.

How can Acupuncture help?

- Pain
- Nausea
- Dry Mouth
- Hot Flashes
- Fatigue
- Neuropathy

Acupuncture for hot flashes

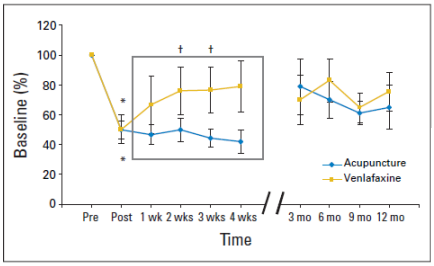


Fig 3. Hot flash frequency (mean ± SE of the mean) as a percentage of baseline for acupuncture and venlafaxine groups at pretreatment (Pre), post-treatment (Post), and follow-up times of 1, 2, 3, and 4 weeks and 3, 6, 9, and 12 months post-treatment. Boxed area highlights the additional analysis of the first 4 weeks post-treatment. (*) $P < .05$, significantly different from Pre; (†) $P < .05$, significantly different from Post.

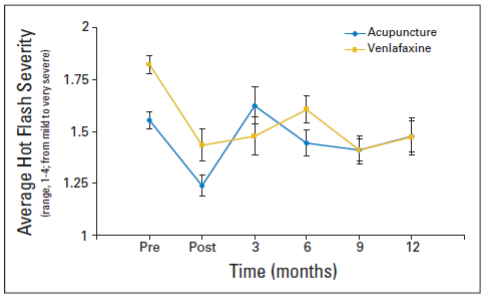


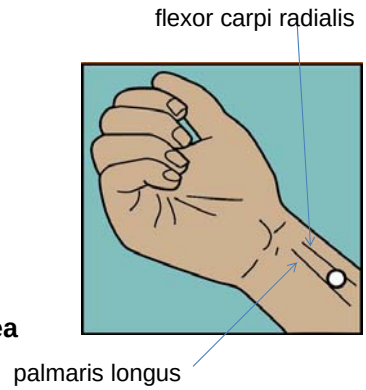
Fig 4. Hot flash severity (mean ± SE of the mean) for acupuncture and venlafaxine groups at pretreatment (Pre), post-treatment (Post); and 3, 6, 9, and 12 months follow-up with significant effect of time, but no group or interaction effects.

Walker 2010

Acupuncture for Emesis

- Acupuncture point, pericardium 6 (P6)
  - Anterior surface of wrist
- Systematic review of 11 trials (JCO 2013)
  - Conclusion:

    Acupuncture as an appropriate adjunctive treatment for **chemotherapy induced nausea and vomiting**



Garcia JCO 2013

Acupuncture for Xerostomia

Symptoms

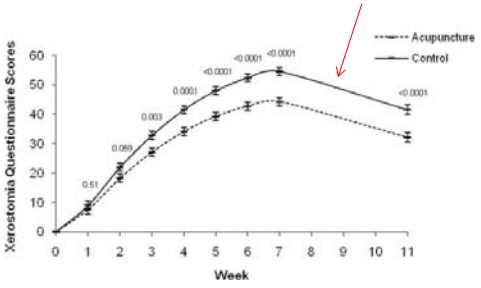


Figure 2. Xerostomia questionnaire mean scores are shown over time. Week 0 is baseline raw mean. Means at weeks 1 through 11 are the least square means adjusted for baseline score. Perpendicular lines at each time point represent standard error.

Saliva Flow

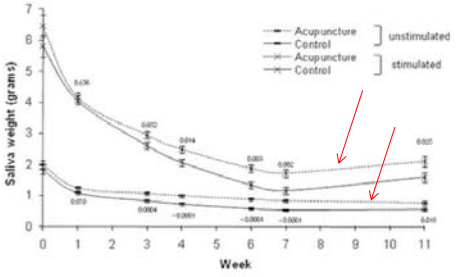


Figure 4. Acupuncture versus control (standard of care) saliva flow outcomes are shown over time. Week 0 is baseline raw mean. Means at weeks 1 through 11 are the least square means adjusted for baseline score. Perpendicular lines at each time point represent standard error.

Cancer (2012)

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015 Adult Cancer Pain

INTEGRATIVE INTERVENTIONS

Consider integrative interventions in conjunction with pharmacologic interventions as needed. Integrative interventions may be especially important in vulnerable populations (eg, frail, elderly, pediatric) in whom standard pharmacologic interventions may be less tolerated or based on patient preference. The utility of integrative interventions underscores the necessity for pain management to be carried out with a team approach that contains a wide range of treatment options.

Pain likely to be relieved or function improved with physical, cognitive, or interventional modalities:

- Physical modalities
  - Bed, bath, and walking supports
  - Positioning instruction
  - Physical therapy
  - Energy conservation, pacing of activities
  - Massage
  - Heat and/or ice
  - Transcutaneous electrical nerve stimulation (TENS)
  - Acupuncture or acupressure
  - Ultrasonic stimulation
- Cognitive modalities
  - Imagery/hypnosis
  - Distraction training
  - Relaxation training
  - Active coping training
  - Graded task assignments, setting goals, pacing, and prioritizing
  - Cognitive behavioral training
- Spiritual care (See NCCN Guidelines for Distress Management)
- See Interventional Strategies (PAIN-M)

Mind-Body Practices

Practices that enhance self-awareness through increased focus on the connection between mind and body using sound, breath, movement, or other approaches.

Yoga

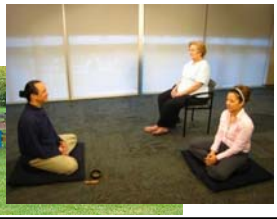
Meditation

Tai Chi

Qi Gong

How can Mind-Body practices help?

- Relieve Anxiety & Stress
- Improve Quality of Life
- Improve Sleep



Meditation: Our experience

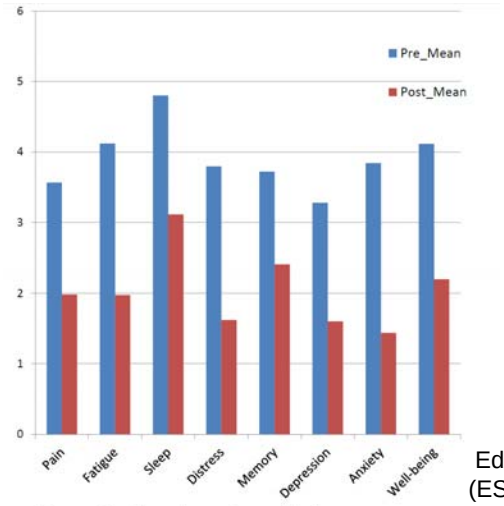


Figure 2 - Pre- to post- meditation mean scores

Reduction in ESAS Score (means) n=121 visits	
Anxiety	-1.9
Fatigue	-1.9
Well Being	-1.6
Sleep	-1.5
Depression	-1.5

Edmonton Symptom Assessment Scale (ESAS; scale from 0-10, where 10 is most severe).

Music Therapy

Music therapists help those affected by cancer learn how to use music (songwriting, listening, etc.) for non-musical goals.

How can Music Therapy help?

- Relieve Anxiety & Stress
- Improve Quality of Life

Music Therapy and Pain, Anxiety

Music Therapy to Reduce Pain and Anxiety in Children With Cancer Undergoing Lumbar Puncture: A Randomized Clinical Trial

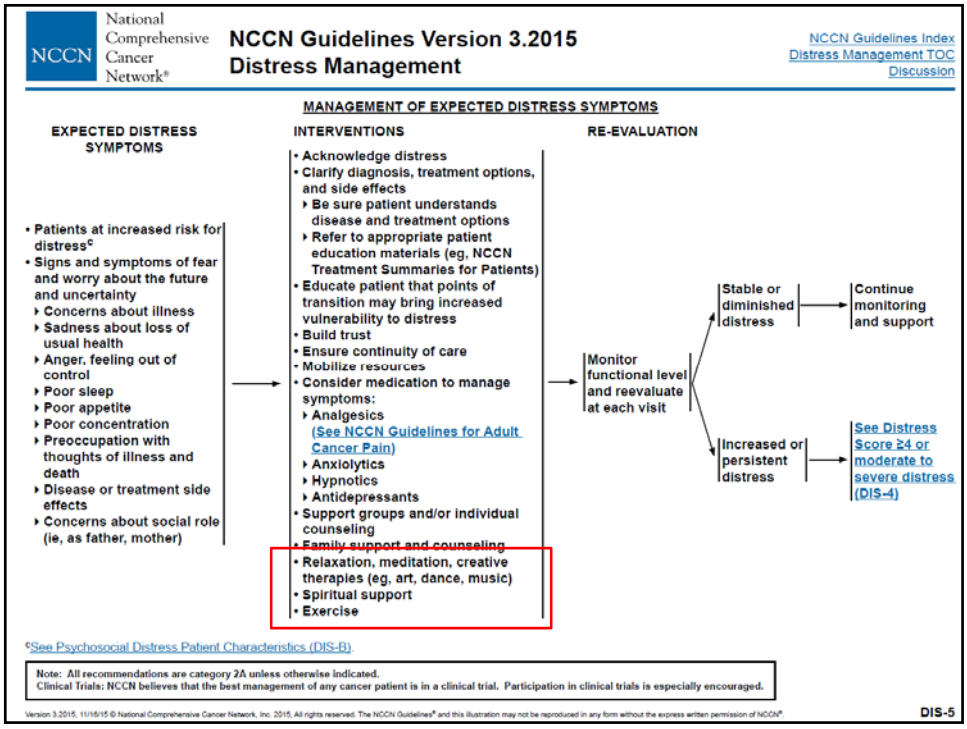
Journal of Pediatric Oncology Nursing
27(3) 146–155

DOI: 10.1177/1043454209355983
http://jopon.sagepub.com
SAGE

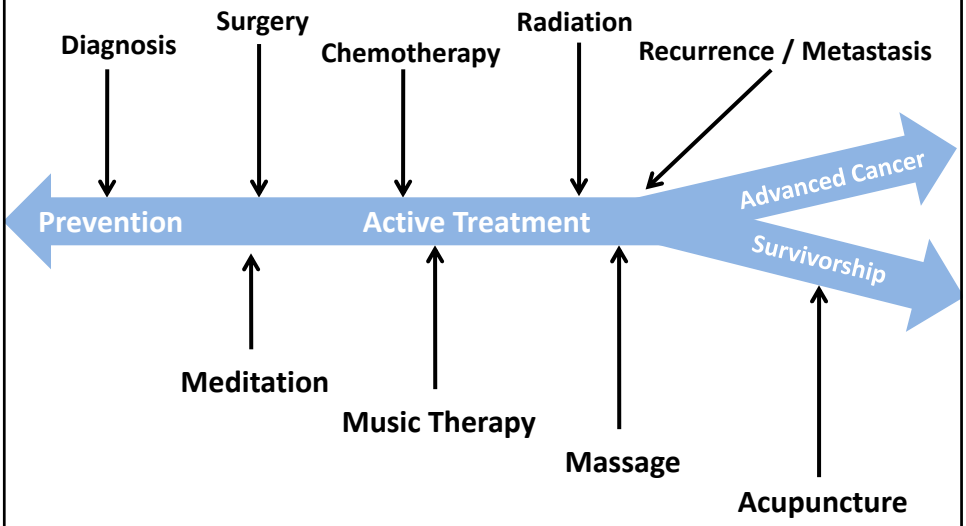
Thanh Nhan Nguyen, RN, MSc,[1] Stefan Nilsson, RN, MSc,[2]
Anna-Lena Hellström, RN, PhD,[2] and Ann Bengtson, RNT, PhD[3]

Table 3. Comparison of Pain Scores and Anxiety Scores Before, During, and After the Procedure

	Pain, Mean (Range, *SD*)			Anxiety, Mean (Range, *SD*)		
	Music (n = 20)	Control (n = 20)	*P* Value	Music (n = 20)	Control (n = 20)	*P* Value
Before	1.2 (0-5, 1.40)	1.75 (0-5, 1.77)	Nonsignificant	8.6 (6-16, 2.78)	13.25 (7-22, 3.73)	<.001
During	2.35 (0-7, 1.90)	5.65 (1-10, 2.50)	<.001			
After	1.2 (0-5, 1.36)	3 (0-7, 2.0)	.003	8.1 (6-13, 2.22)	13.0 (6-21, 4.17)	<.001



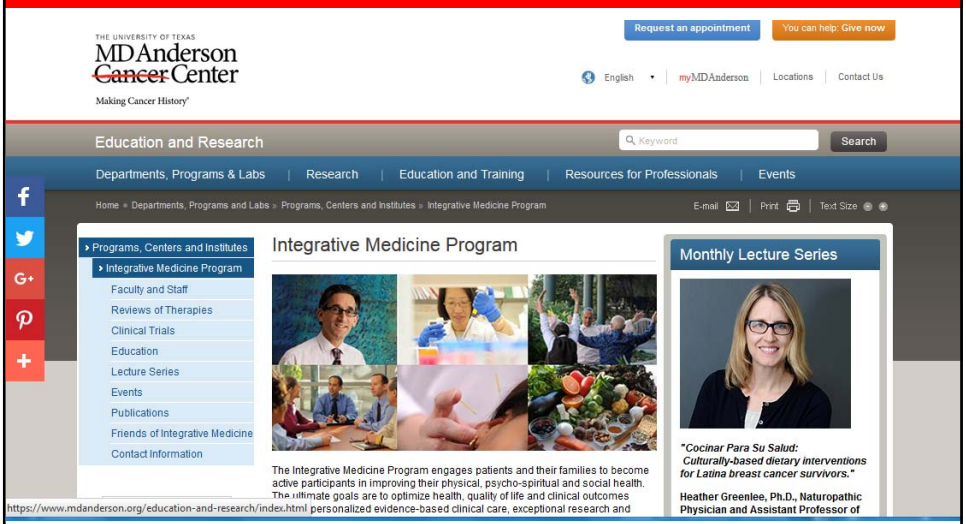
Integrative Medicine, when?
Continuum of Cancer Care



Integrative Medicine Resources

Organization/Web Site	Address/URL
University of Texas MD Anderson Cancer Center Complementary/Integrative Medicine Education Resources	www.mdanderson.org/integrativemed
Memorial Sloan-Kettering Cancer Center Integrative Medicine Service	http://www.mskcc.org/aboutherbs
NIH National Center for Complementary and Integrative Health (NCCIH)	http://nccih.nih.gov/
NCI Office of Cancer Complementary and Alternative Medicine (OCCAM)	http://www.cancer.gov/cam

www.mdanderson.org/integrativemed



Monthly newsletter

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Physical • Mind-Body • Social

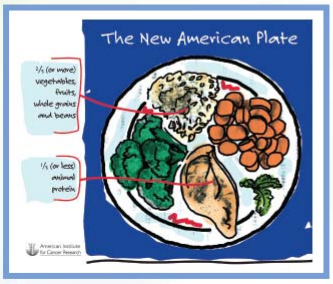
Inside Integrative Medicine

May 2016

See pages 2-3 for information on FREE group classes for patients, caregivers, and anyone touched by cancer.

Optimizing Diet: What You Eat Does Matter to Improve Cancer Outcomes

By: Peiying Yang, Ph.D., Lin Lin Shao, senior clinical dietitian, and Lorenzo Cohen, Ph.D., Integrative Medicine Program



The New American Plate

index (a relative ranking of carbohydrates in foods according to how they affect blood sugar levels).

A whole food, primarily plant-based diet can be easy to achieve if you follow these tips:

1. Fill 2/3 of your plate with mainly colorful vegetables that are low in starch, some whole grains, and some fruit (more vegetables than fruit).
2. Limit intake of processed grains (white flour, pasta, bread, white rice, etc.).
3. Aim for:
   - 5-7 servings* of vegetables per day
   - 2 servings of fruit
   - No more than 6 servings of whole grains

   *A serving of vegetable is ½ cup cooked/chopped or 1 cup leafy greens; a serving of fruit is 1 cup; a serving of grain is ½ cup cooked.
4. Fill 1/3 or less of your plate with protein sources: lean meats such as skinless chicken breast or fish/seafood; and vegetable proteins such as tofu, beans, legumes, and nuts.
5. Limit red meat choices (beef, pork and lamb) and avoid processed meats

Outpatient Group Clinical Services

All Classes are free. Please call **713-794-4700** to sign up.

Physical

Cooking for Optimal Health
The dietitian for the Integrative Medicine Center demonstrates how to prepare dishes meeting the whole foods, plant-based diet recommendations. Participants will also have the chance to enjoy some delicious samples. Recipes will emphasize a different theme each month.

Brief Relaxation Massages
Experience a brief upper body massage for relaxation. These chair massages are generously funded by Angie's Spa.

Get Moving
Recharge and energize with uplifting music and a blend of yoga, dance and martial arts.

Gardening 101
Join expert instructors from Urban Harvest for a lesson on gardening basics. Learn to plan, nurture, and harvest vegetables so that you can experience the benefits of gardening at your own home.

Tai Chi
Find balance and strength through continuous flowing movements that link mind to body

Shape-Up Circuit*
A fitness class designed to improve body composition by increasing muscle strength and burning calories. Led by the Integrative Medicine Physical Therapist, this class will follow a "circuit" format, with different exercises at each station. Suitable for any fitness level. Please bring a water bottle.

Yoga for Fitness
A beginning/intermediate level yoga class that focuses on moving through postures with breath.

Mind-Body

Tibetan Bon Meditation*
Relax and access a deeper awareness through connecting your mind, body and heart through breath, sound and movement practices. Class method rotates weekly (see calendar).

- **Power of Breath**
  Through breath, learn various contemplative stress-relieving methods to use in everyday life.
- **Sacred Sounds**
  Use sound techniques in combination with the breath, that can be helpful to increase memory and cognitive function.
- **Breath & Movement**
  Experience meditation through simple movements & breathing techniques, supportive of better sleep.

Yoga for Health
Features a gentle form of yoga including stretching, breathing, relaxation, and meditation techniques.

Qigong
Experience this ancient Chinese system of self-care using meditation, breath, and movement to balance the body's energy flow.

Social

Laughter for Health
Known in the community as "Laughter Yoga" - a blend of deep breathing, stretching and simulated laughter exercises that may help reduce stress. Please bring a water bottle to class.

Expressive Arts
Classes include: Paint Your Own Pottery, Beading Class, Shibori, Chinese Ink Art, and much more!
Pre-registration is not required.
Underwritten by COLLAGE: The Art of Cancer Network

Support Groups
Professionally-led support groups provide education, and sharing for patients, family and friends.
For a complete list of support groups, please call the Social Work department at (713) 792-6195.
Pre-registration is not required.

P.I.K.N.I.C.
An educational forum for patients, caregivers, and staff who want to learn more about issues relevant to cancer. PIKNIC topics may change, please call 800-345-6324 for the latest schedule.
Pre-registration is not required.

Look Good, Feel Better
Licensed cosmetologists help patients adjust to temporary or permanent changes in their appearance.
MUST pre-register at (888) 227-6333

Activity Level:
= Gentle
= Active
= Very Active

How to schedule an appointment:

- Call Integrative Medicine Center at 713-794-4700 or send a message from myMDA to schedule an appointment.
- Arrive 15 minutes early to check in for group classes
- Following classes do not require pre-registration: Expressive Arts, PIKNIC, and Support Groups

May 2016

MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
2 8:00-12:00 Brief Relaxation Massages 1:00-2:00 Yoga for Health 2:00-4:00 Expressive Arts: Chinese Ink Art – Chrysanthemums	**3** 8:00-12:00 Brief Relaxation Massages 9:30-10:30 Tibetan Bon Meditation: Power of the Breath 11:00-12:30 Gardening 101: Summer Veggies and Herbs 3:30-4:30 Tai Chi	**4** 8:00-5:00 Brief Relaxation Massages 10:30-11:30 Yoga for Health 11:30-12:00 Metastatic Breast Cancer Support Group (Location: ACB2.1049 Side B) 12:00-1:00 Laughter for Health 5:00-7:00 Spine Support Group	**5** 10:30-12:00 Look Good, Feel Better (Must pre-register at 888-227-6333) 12:00-1:00 Caregivers: I've Got Feelings, Too! 12:30-1:30 Shape-Up Circuit 3:30-4:30 Qigong	**6** 11:00-12:00 Yoga for Fitness
9 8:00-12:00 Brief Relaxation Massages	**10** 8:00-12:00 Brief Relaxation Massages 9:30-10:30 Tibetan Bon Meditation: Sacred Sounds 11:15-12:15 Get Moving 3:30-4:30 Tai Chi	**11** 8:00-5:00 Brief Relaxation Massages 10:30-11:30 Yoga for Health 12:00-1:00 Endometrial Cancer Support Group 12:00-1:00 Laughter for Health 6:00-7:30 Ovarian Cancer Support Group	**12** 11:00-12:00 Breast Cancer Support Group 12:00-1:00 Caregivers: I've Got Feelings, Too! 12:30-1:30 Shape-Up Circuit 3:30-4:30 Qigong	**13** 11:00-12:00 Yoga for Fitness
16 8:00-12:00 Brief Relaxation Massages 2:00-4:00 Expressive Arts: Chinese Ink Art – Iris	**17** 8:00-12:00 Brief Relaxation Massages 9:30-11:00 Tibetan Bon Meditation: Breath & Movement 11:15-12:15 Get Moving 3:30-4:30 Tai Chi	**18** 8:00-12:00 Brief Relaxation Massages 10:30-11:30 Yoga for Health 12:00-1:00 Laughter for Health	**19** 12:00-1:00 Caregivers: I've Got Feelings, Too! 12:30-1:30 Shape-Up Circuit 3:30-4:30 Qigong	**20** 11:00-12:00 Yoga for Fitness
23 8:00-12:00 Brief Relaxation Massages 11:00-12:00 Cooking for Optimal Health 1:00-2:00 Yoga for Health 2:00-4:00 Expressive Arts: Chinese Calligraphy – Love and Heart	**24** 9:30-10:30 Tibetan Bon Meditation: Power of the Breath 11:15-12:15 Get Moving 3:30-4:30 Tai Chi	**25** 8:00-5:00 Brief Relaxation Massages 10:30-11:30 Yoga for Health 12:00-1:00 Laughter for Health	**26** 10:30-12:00 Active Surveillance Patient Support Group 12:00-1:00 Caregivers: I've Got Feelings, Too! 12:30-1:30 Shape-Up Circuit 3:30-4:30 Qigong	**27** 11:00-12:00 Yoga for Fitness
30	**31**			

Our Team

Lorenzo Cohen
Peiying Yang
Alejandro Chaoul
Kay Garcia
Jane Williams
Curtiss Beinhorn
Sat-Siri Sumler
Sanober Ajani
Catherine Powers-James
Angela Sue Thompson
Amie Koronczok
Shelby Perez
Mary Jo Cox
Marina Mery
Frank Vazquez
Syd Monroe
Yousra Hashmi

Kathrin Milbury
Michael Spano
Donna Capps
Sarah Prinsloo
Qi Wei
Rosalinda Engle
Smitha Mallaiah
Lisa Connelly
Andrew Cusimano
Stephanie Gabel
Robin Haddad
Anthony Sturm
Duy Trinh
Casey Dutton
Rocio Moguel
Veronica Vasquez
Sharon Mattox

Anne Marie Alcala
Antonio Milland Santiago
Grant Weidler
Robyn Rhea
Jibin Ding
Yan Jiang
Tanier Williams
Yong Pan
Kathryn Moss
Nazli Goktepe
Carol Eddy
Susan Underwood
Eduardo Bruera
Natalie Schuren
Patrick Hwu

Thank you!

Thank You





Combination Immunotherapy Approaches for Melanoma

Pierre Triozzi, MD
Professor, Section on Hematology and Oncology
Wake Forest School of Medicine

Wake Forest School of Medicine

Combination Immunotherapy Approaches for Melanoma

Pierre L. Triozzi, MD
Section of Hematology-Oncology

Off-Label Use Disclosure

I **do not intend** to discuss an off-label use of a product during this activity

Financial Disclosure

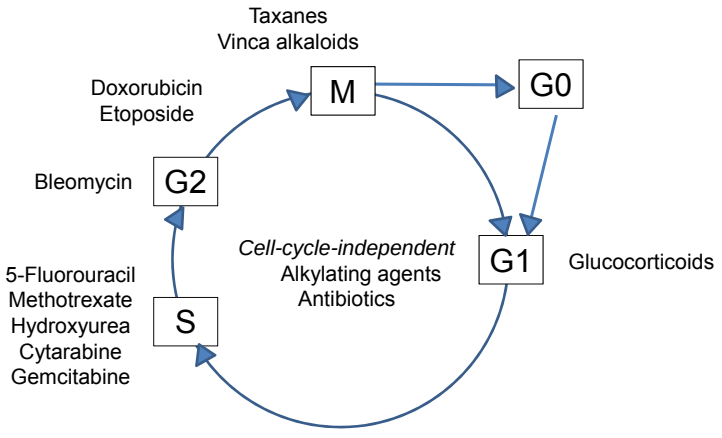
I **have not had** any relevant financial relations during the past 12 months to disclose

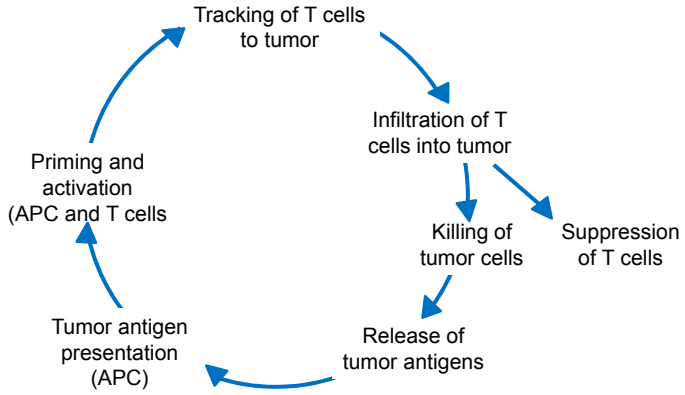
IMMUNOTHERAPY COMBINATIONS

- Dual checkpoint
- Immune agonists
- Targeted
- Chemotherapy
- Radiation
- Surgery

PRINCIPLES OF COMBINATION CHEMOTHERAPY

- Single agent activity
- Different mechanisms of action
  - Additive / synergistic
- Different dose-limiting toxicities
- Optimal dose and schedule
- Different mechanisms of resistance
  - ↓ cross resistance





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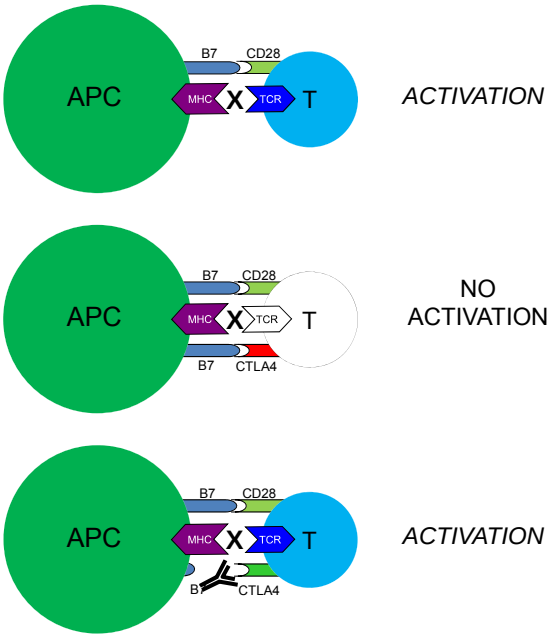

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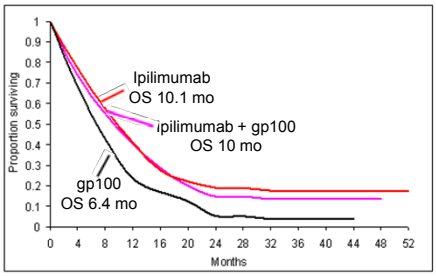
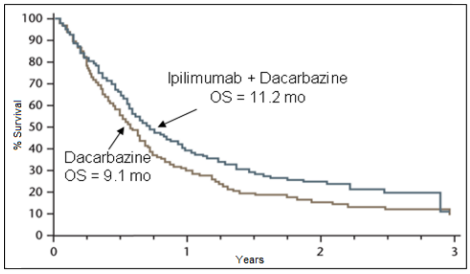
IPILIMUMAB
(Anti-PD-1 mAb)





	n	RR
Ipilimumab	137	11%
gp100	136	2%

	n	RR
Ipilimumab + dacarbazine	250	15%
Dacarbazine	252	10%

Time to response = 13 weeks

Hodi et al. NEJM 2010; Robert et al. NEJM 2011

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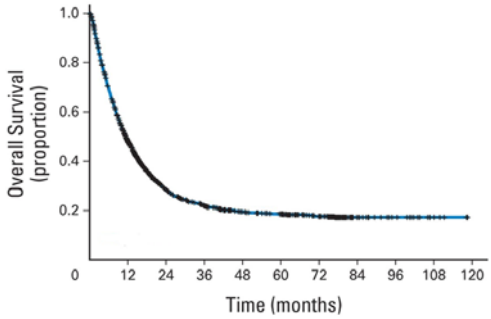
IPILIMUMAB
Survival (Pooled Analysis)

n	1861
mOS	11.4 mo
OS (3y)	22%



Schadendorf et al. J Clin Oncol 2015

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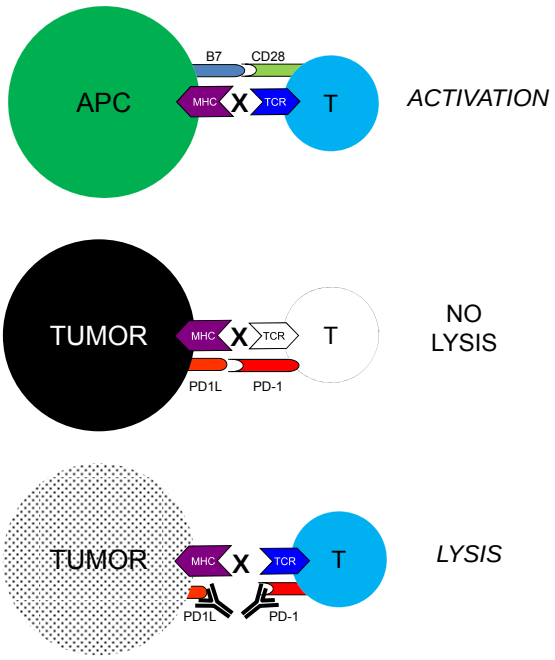

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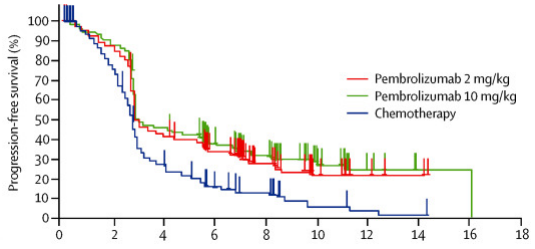
PEMBROLIZUMAB
(Anti-PD-1 mAb)

	Pembrolizumab (2 mg/kg q3w)	Pembrolizumab (10 mg/kg q3w)	Chemotherapy (investigator choice)
n	180	181	179
PFS	3.7 mo	5.4 mo	2.6 mo
RR	21% (CR 2%)	16% (CR 3%)	4% (CR 0%)



Ribas et al. Lancet Oncol 2015

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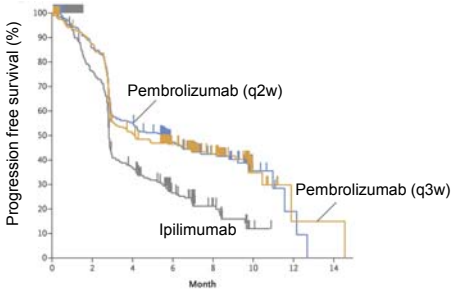
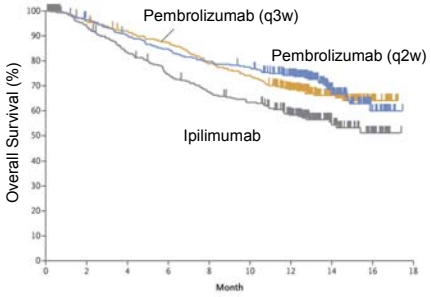
PEMBROLIZUMAB *v.* IPILIMUMAB

	Pembrolizumab (10 mg/kg q2w)	Pembrolizumab (10 mg/kg q3w)	Ipilimumab (3 mg/kg q3w X4)
n	279	277	278
RR	34% (CR 5%)	33% (CR 6%)	12% (CR 2%)
Grade 3/4 AE	13%	10%	20%





Robert et al. N Engl J Med 2015

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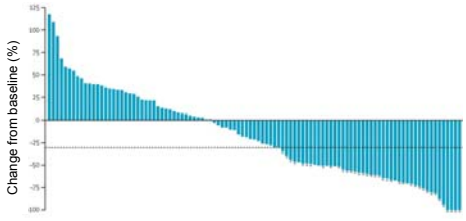
NIVOLUMAB
(Anti-PD-1 mAb)

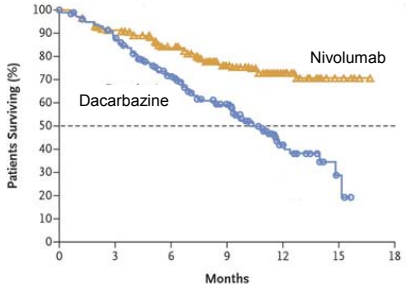
Previously Treated

	Nivolumab	Chemotherapy (Investigator Choice)
n	272	133
RR	32% (CR 3%)	11% (CR 0%)



Previously Untreated

	Nivolumab	Dacarbazine
n	210	208
RR	40% (CR 8%)	14% (CR 1%)



Weber et al. Lancet Oncol 2015; Robert et al. NEJM 2015

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CHECKPOINT INHIBITORS

Target	CTLA-4	PD-1		PD-L1
Drug	Ipilimumab	Nivolumab	Pembrolizumab	Atezolizumab
Formulation	human IgG1	human IgG4	humanized IgG4	engineered humanized IgG1
Administration	3/10 mg/kg q3w x4 (then q12w) IV	3 mg/kg q2w IV	3 mg/kg or 200 mg q3w IV	1200 mg q3w IV
Indication	Melanoma	Melanoma NSCLC RCC Hodgkin's	Melanoma NSCLC HNSCC	Urothelial

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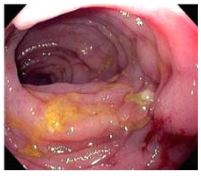
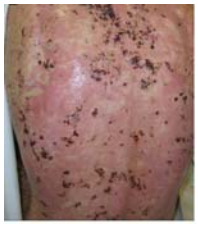
CHECKPOINT BLOCKADE
Adverse Events

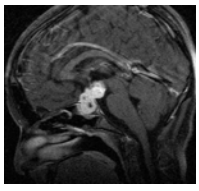
Colitis



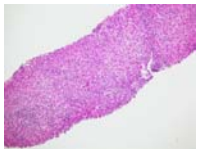
Dermatitis



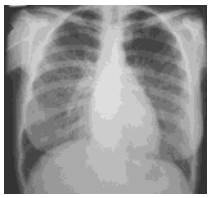
Endocrinopathy
(pituitary, thyroid adrenal)



Hepatitis



Pneumonitis



Eye
Kidney
Pancreas
Nerve
(central / peripheral)
Hematologic

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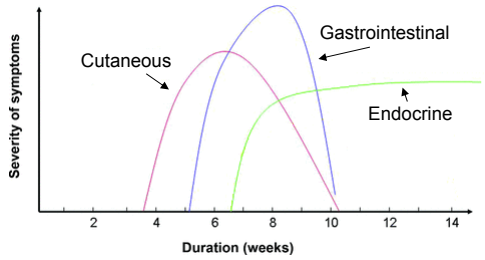
CHECKPOINT BLOCKADE
Time Course of Adverse Events



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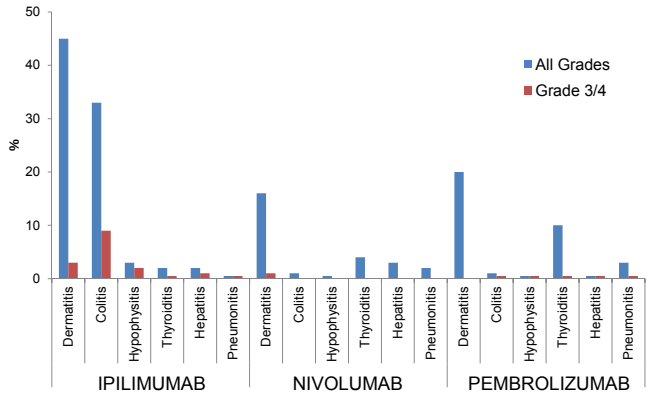
CHECKPOINT BLOCKADE
Adverse Events



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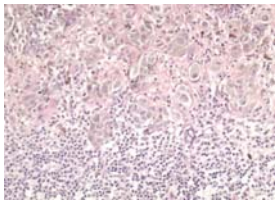
CHECKPOINT BLOCKADE
Response Assessment

- Responses can take months
- Response after treatment suspended
- Prolonged periods of stable disease
- Disease progression prior to response

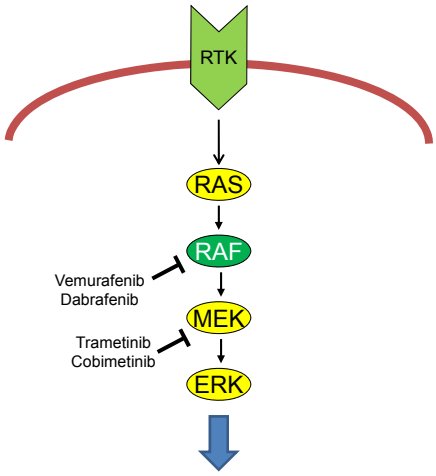
CHECKPOINT BLOCKADE
Pseudoprogression

- Tumor enlargement due to T-cell infiltration and not tumor cell proliferation
- Immune related response criteria
  - PD if tumor burden (all lesions) increases by ≥25%
  - New lesions ≠ PD if tumor burden (all lesions) <25%



Wolchok et al. CCR 2009

MAPK PATHWAY



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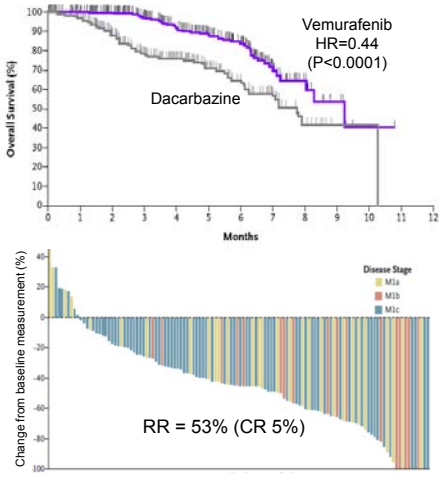
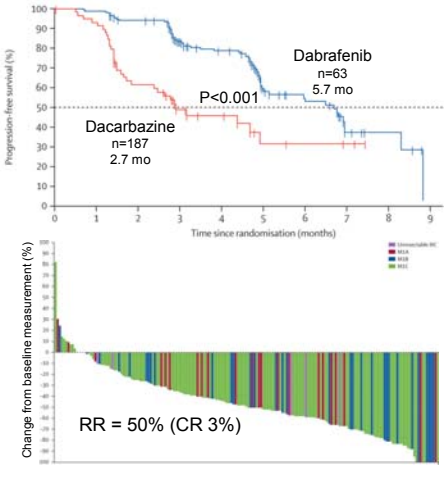
BRAF INHIBITORS

Vemurafenib



Dabrafenib



Chapman et al. NEJM 2011; Sosman et al. NEJM 2012; Hauschild et al. Lancet 2012

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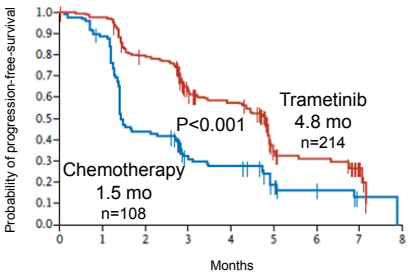
MEK INHIBITOR
Trametinib



RR = 22% (CR 2%)

Flaherty et al. NEJM 2010

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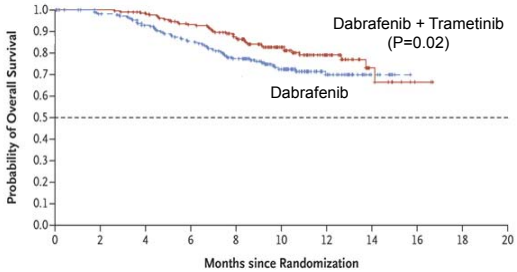
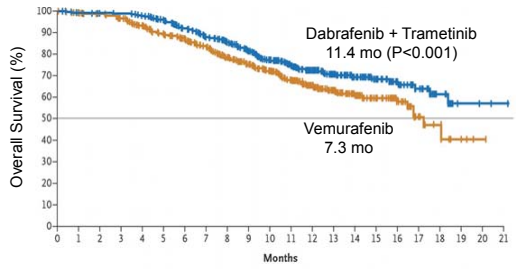
DABRAFENIB + TRAMETINIB
(BRAFi + MEKi)





	Dabrafenib + Trametinib (n=211)	Dabrafenib (n=212)
RR	67%	51%
Grade 3/4AE	32%	34%
CuSCC	2%	9%

	Dabrafenib + Trametinib (n=352)	Vemurafenib (n=352)
RR	64%	51%
Grade 3/4 AE	48%	57%
CuSCC	1%	18%

Long et al. NEJM 2014; Robert et al. NEJM 2015

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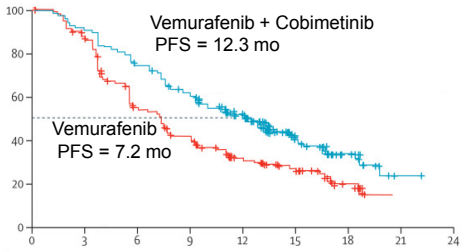
VEMURAFENIB + COBIMETINIB
(BRAFi + MEKi)



TOXICITY

	Vemurafenib + Cobimetinib	Vemurafenib
Grade 3-4	37	28
↑LFTs	15	10
↑CPK	12	1
Fever	2	0

Ascierto et al. Lancet Oncol 2016

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TARGETED THERAPY

	Vemurafenib (BRAFi)	Dabrafenib (BRAFi)	Trametinib (MEKi)	Dabrafenib + Trametinib	Vemurafenib + Cobimetinib
RR	50%	50%	20%	70%	70%
PFS	7 mo	7 mo	5 mo	10 mo	12 mo
OS (1y)	60%	70%	–	80%	
mOS	14 mo	–	–	25 mo	22 mo

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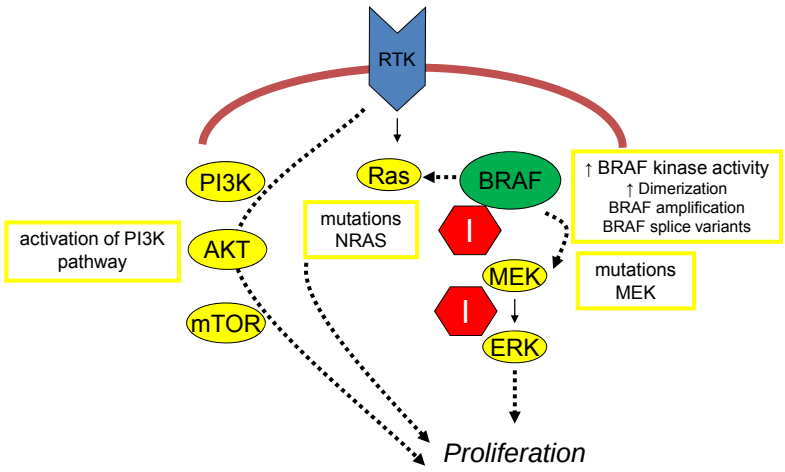
BRAFi
Resistance Mechanisms



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MAPK INHIBITORS
Toxicity

	BRAFi	MEKi	BRAFi + MEKi
Rash	+ (maculopapular)	++ (acneiform)	+ (acneiform)
Photosensitivity	+		
Cutaneous SCC	++ (10-25%)	(0)	+ (<5%)
Arthralgia	+		+
Fever	+		+++
↑ LFTs	+ (vemurafenib)		+
Diarrhea		+	++
Other			*Ocular Cardiac Hemorrhage DVT/PE*

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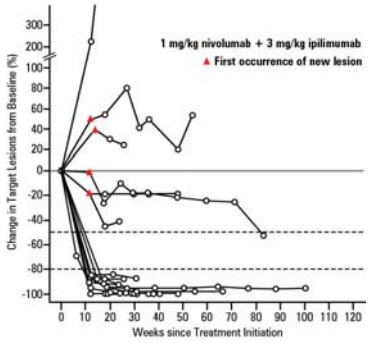
NIVOLUMAB + IPILIMUMAB



Rapid and durable responses

Wolchok et al. NEJM 2013

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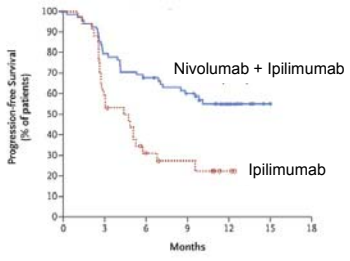
NIVOLUMAB + IPILIMUMAB *v.* IPILIMUMAB

	Nivolumab + Ipilimumab	Ipilimumab
n	95	47
RR	59%	11%
Grade 3/4 AE	54%	24%



Postow et al. NEJM 2015

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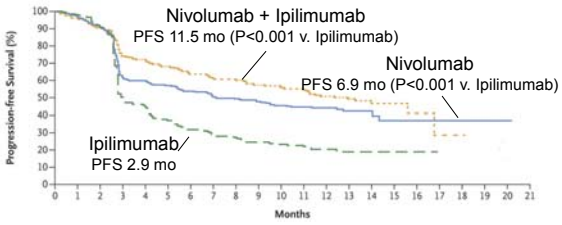
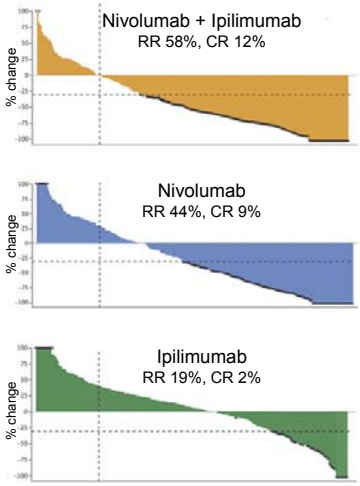
NIVOLUMAB + IPILIMUMAB *v*. NIVOLUMAB *v*. IPILIMUMAB





	Nivolumab + Ipilimumab	Nivolumab	Ipilimumab
n	314	316	315
Grade 3/4 AE	69%	44%	56%
Discontinuation	36%	8%	15%

Larkin et al. N Engl J Med 2015

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IPILIMUMAB + NIVOLUMAB

Indication	Unresectable or metastatic melanoma (Accelerated approval based on PFS)
Dosing	Nivolumab 1 mg/kg, followed by ipilimumab 3 mg/kg on the same day, q3w X4 *then* Nivolumab 3 mg/kg q2w until disease progression or unacceptable toxicity.

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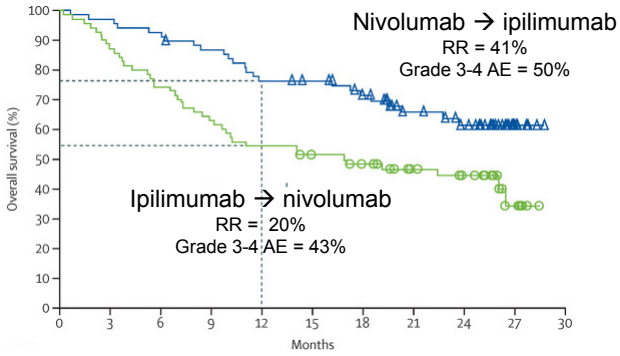
DUAL CHECKPOINT
Melanoma Clinical Trials

Targets	Agents
PD-1 + CTLA-4	Pembrolizumab + ipilimumab
PD-L1 + CTLA-4	Durvalumab + tremelimumab

SEQUENTIAL NIVOLUMB-IPILIMUMAB

Nivolumab 3mg/kg q2w X6 → ipilimumab 3mg/kg q3w x4 → nivolumab 3mg/kg q2w until PD	n=70
Ipilimumab 3mg/kg q3w x4 → nivolumab 3mg/kg q2w X6 → nivolumab 3mg/kg q2w until PD	n=70



Weber et al. Lancet Oncol 2016

NIVOLUMB + IPILIMUMAB
Tumor PD-L1 Expression

	Method	PD-L1 (+)		PD-L1 (−)		Ref.
		Nivolumab + Ipilimumab	Nivolumab	Nivolumab + Ipilimumab	Nivolumab	
Melanoma	IHC ≥5%	PFS 14 mo	PFS 14 mo	PFS 11.2 mo	PFS 5.3 mo	Larkin et al. N Engl J Med 2015

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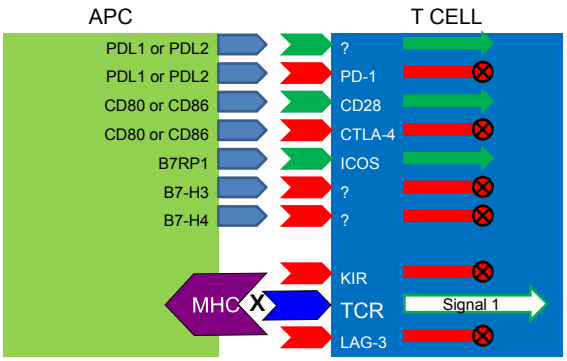
CO-STIMULATORY/INHIBITORY LIGANDS-RECEPTORS



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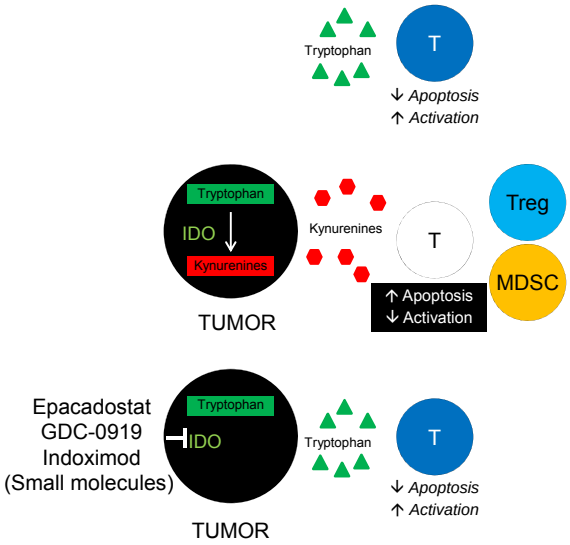
DUAL CHECKPOINT
Clinical Trials

Targets	Agents	Phase	Cancer
KIR CTLA-4	Lirilumab ipilimumab	I	Solid
KIR PD-1	Lirilumab nivolumab	I	NHL, myeloma
LAG-3 PD-1	BMS-986016 Nivolumab	I	Solid

INDOLEAMINE 2,3-DIOXYGENASE
(IDO)



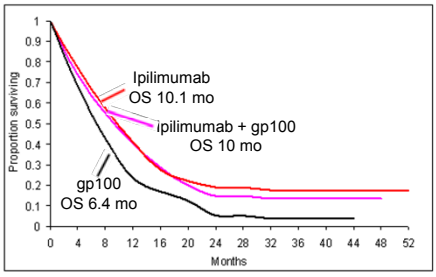
CHECKPOINT + IDOi

Combination	Cancer	Toxicity	Comment	Reference
Epacadostat + Ipilimumab	Melanoma (n=8)	Tolerable	DCR 75%	Puzanov et al. ASCO 2014 (abstr 9029)
Epacadostat + Pembrolizumab	Solid (n=60)	Tolerable	RR 53% (melanoma n = 19)	Hamid et al. SMR 2015

CHECKPOINT + IDOi
Clinical Trials

Targets	Agents	Phase	Cancer
IDO PD-1 PD-L1 CTLA-4	Epacadostat Pembrolizumab/Nivolumab or Durvalumab/Atezolizumab or Ipilimumab	I/II	Melanoma, NSCLC, solid (select)
IDO PD-L1	GDC-0919 Atezolizumab	I	Solid
IDO CTLA-4	Indoximod Ipilimumab	I/II	Melanoma

IPILIMUMAB + VACCINE



	n	RR
Ipilimumab 3 mg/kg	137	11%
gp100	136	2%

Hodi et al. NEJM 2010

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TALIMOGENE LAHERPAREPVEC (T-VEC)

FORMULATION	Attenuated oncolytic herpes virus Expresses GM-CSF
INDICATION	Melanoma (unresectable cutaneous, subcutaneous, and nodal lesions in patients with recurrence after initial surgery)
ADMINISTRATION	Intratumoral

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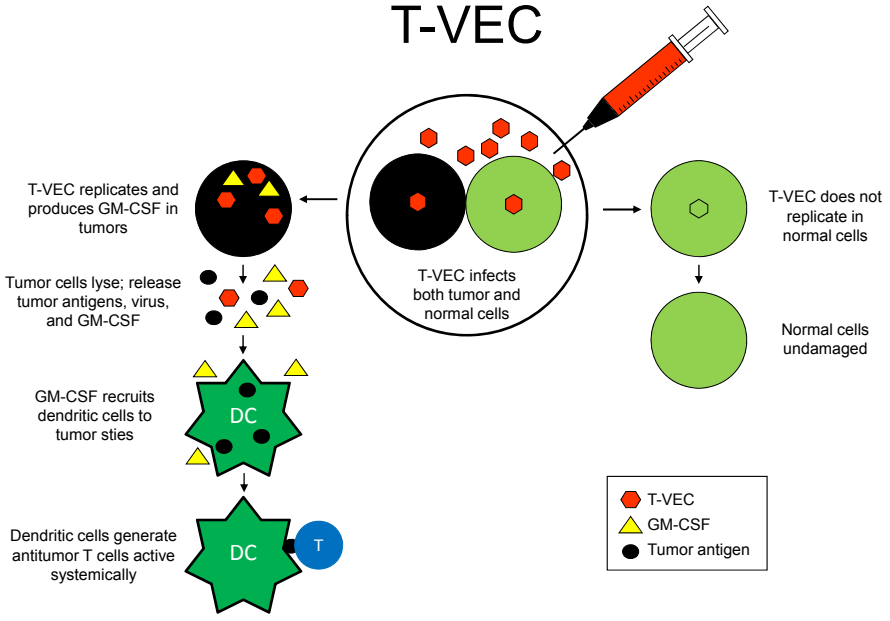
T-VEC



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T-VEC
Melanoma Phase II Trial

Ref.	n	RR	OS
Senzer et al. J Clin Oncol 2009	50	13 (26%); CR 8 (16%) (Regression of injected and uninjected tumors)	1y = 58% 2y = 52%

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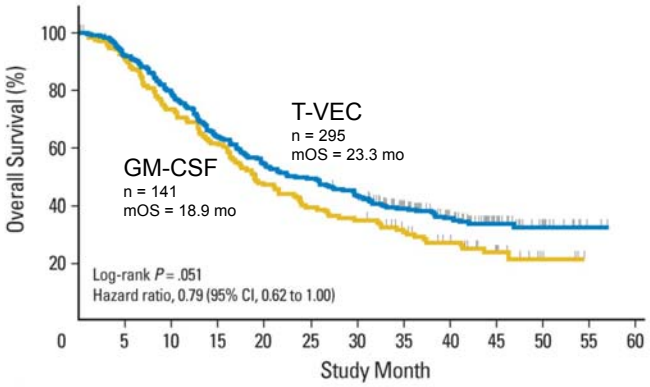
IT T-VEC v. SC GM-CSF
Melanoma



	T-VEC	GM-CSF
RR	26%	6%
Durable (>6 mo) RR	16%	2%

Andtbacka et al. J Clin Oncol 2015

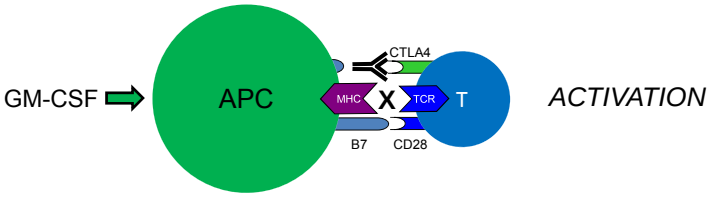
CHECKPOINT + T-VEC
Clinical Trials

Combination	Cancer	Toxicity	Comment	Ref.
Ipilimumab + T-VEC	Melanoma (n=19)	No DLT	RR 41% (CR 24%)	Gibney et al. ASCO 2014
Pembrolizumab + T-VEC	Melanoma (n = 16)	No DLT	RR 56%	Puzanov et al. SMR 2015

Combination	Phase	Cancer
T-VEC Pembolizumab	I, III	Melanoma, HNSCC

T-VEC also being tested in sarcoma, HCC, and breast

GM-CSF



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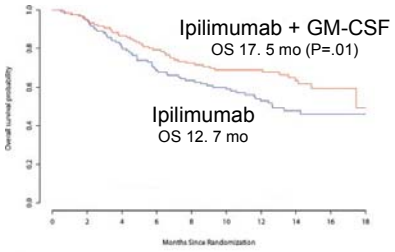
IPILIMUMAB + GM-CSF

Metastatic Melanoma

Ipilimumab	Ipilimumab + GM-CSF
10 mg/kg q3w X4, then q12w	10 mg/kg q3w X4, then q12w + GM-CSF 250 ug/d d1-14 q3w

	Ipilimumab (n=122)	Ipilimumab + GM-CSF (n=123)
RR	15%	16%
PFS	3.1 mo	3.1 mo
Grade 3/4 AE	58%	45% (P=.04)



Hodi et al. JAMA 2014

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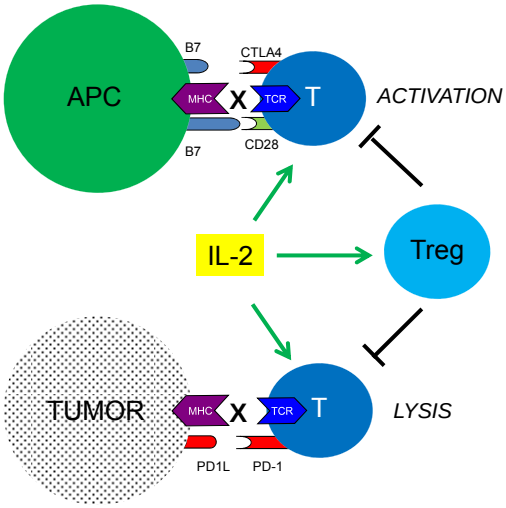
IL-2



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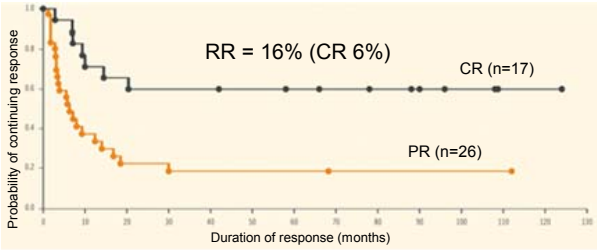
HD IL-2
Response Duration



http://www.proleukin.com/

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CHECKPOINT BLOCKADE + IL-2

Trial	Treatment	Comment
NCT01856023 (PROCLIVITY 02)	Arm 1: HD IL-2 X4 followed by ipilimumab X4 Arm 2: Ipilimumab X4 followed by HD IL-2 X4	*Terminated* (Low accrual)

	Phase	N	RR	Comment	Ref.
IT IL-2 IT ipilimumab	I	12	40%	67% of injected lesions responded	Ray et al. Oncotarget 2016

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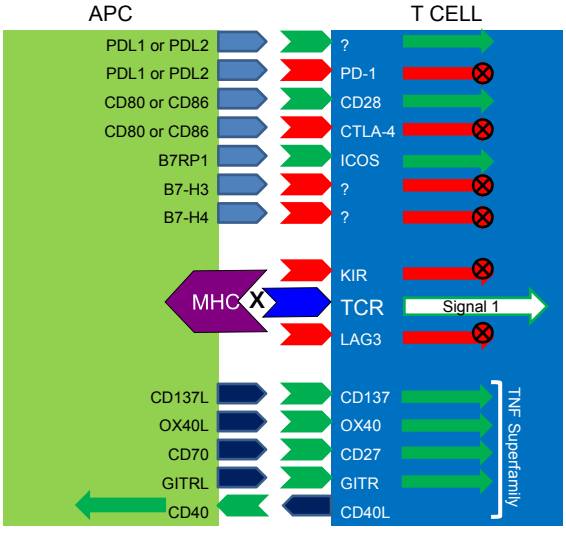
CO-STIMULATORY/INHIBITORY LIGANDS-RECEPTORS



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CHECKPOINT + TNF SUPERFAMILY AGONISTS

Clinical Trials

Targets	Agents	Phase	Cancer
CD40 CTLA-4	CP-870,893 Tremelimumab	I	Melanoma
CD27 PD-1	Varlilumab Nivolumab	I,II	Solid
CD137 PD-1	PF-05082566 Pembrolizumab	I	Solid
GITR PD-1	MK-4166 Pembrolizumab	I	Solid
OX40 CTLA-4/PD-L1 CD20	MEDI6469 Tremelimumab/durvalumab Rituximab	Ib/II	Solid, DLBCL
OX40 PD-L1	MEDI6383 Durvalumab	I	Solid
OX40 PD-L1	MOXR0916 Atezolizumab	I	Solid

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CHECKPOINT + TARGETED

Concurrent vemurafenib and ipilimumab study halted

Tuesday April 9, 2013

A Phase I trial testing Bristol-Myers Squibb's Yervoy and Roche's Zelboraf in melanoma patients was stopped after signs of liver toxicity developed in several patients.

Ribas et al. NEJM 2013

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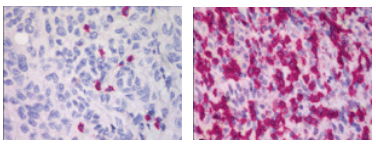
CHECKPOINT + TARGETED

Combination	Cancer	Toxicity	Ref.
Dabrafenib Trametinib Ipilimumab	Melanoma	Problematic (Colitis)	Puzanov et al. ASCO 2014 (abstr 2511)
Dabrafenib Ipilimumab	Melanoma	Tolerable	Puzanov et al. ASCO 2014 (abstr 2511)
Sunitinib Pazopanib Nivolumab	RCC	Manageable (Hepatic and renal)	Amin et al. ASCO 2014 (abstr 5010)

BRAFi
Immune Effects

- ↑ Tumor antigen
- ↑ T-cell infiltration
  - No effect on T cell viability/function
- ↓ Suppressor cells
  - ↓ Treg cells
  - ↓ MDSC

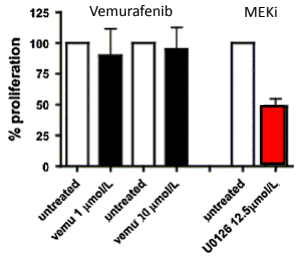


PRE POST

Wilmott et al. Clin Cancer Res 2011

MEKi
Immune Effects

- ↓ Dendritic cells
  - ↓ Viability
  - ↓ T-cell priming capacity
- Vemurafenib – no effect on dendritic cells



Ott et al. Cancer Immunol Immunother 2013

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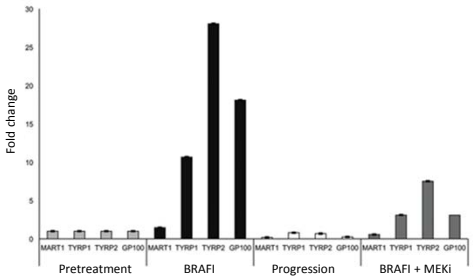
BRAFi + MEKi
Tumor Antigen



Frederick et al. Clin Cancer Res 2013

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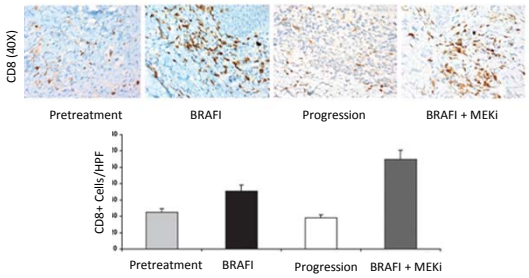
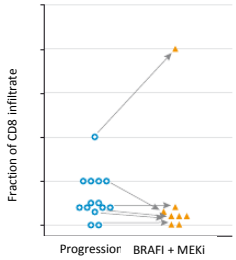
BRAFi + MEKi
CD8 T Cell Infiltration



Frederick et al. Clin Cancer Res 2013



Chen et al. JAMA Oncology 2016

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METASTATIC MELANOMA
Treatment Sequence

- No prospective data
  - Neither whole population nor specific subset
- Choice empirical and clinical
  - Pace of progression
  - Disease-related symptoms
  - Bulk of disease
  - Organ involvement
- Targeted efficacy not influenced by prior immunotherapy
  - Reverse not yet established
- PD often rapid after BRAFi resistance
  - Post-targeted may not be optimal for immunotherapy

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CHECKPOINT + TARGETED
Melanoma Clinical Trials

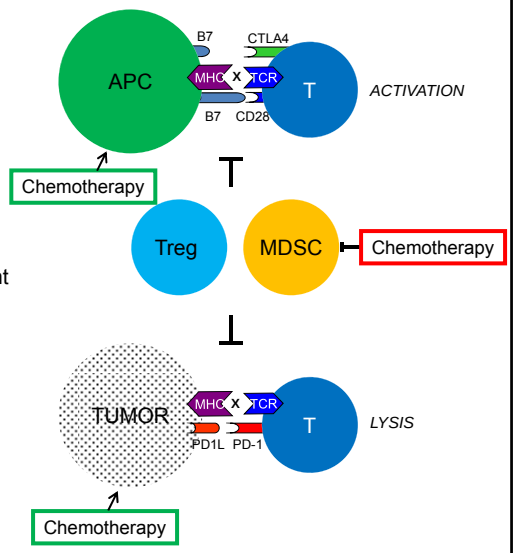
Checkpoint inhibitor	Targeted
Ipilimumab	Vemurafenib
	Dabrafenib
	Dabrafenib + trametinib
Ipilimumab + nivolumab	Dabrafenib
	Dabrafenib + trametinib
Pembrolizumab	Dabrafenib + trametinib
Atezolizumab	Vemurafenib
	Vemurafenib + cobimetinib
Durvalumab	Trametinib
	Dabrafenib + trametinib

CHECKPOINT + TARGETED

	+	–
Concurrent	Synergism	Antagonism ↑ Toxicity
Targeted → Immune	↑ Tumor antigen primes immune response ↓ Tumor immune suppression prior to immunotherapy Toxicity	Immune activation with targeted is transient
Immune → Targeted	↑ Tumor antigen in the presence of an activated immune response ↓ Toxicity	Immune activation may take several months

CHEMOTHERAPY
Immune Effects

- ↑Tumor antigen
  - DNA damage
  - Dying tumor cells
- Activate immune cells
  - Direct effect
  - Lymphodepletion → replenishment
- ↑ Tumor sensitivity to CTL
- ↓ Tumor immune suppression



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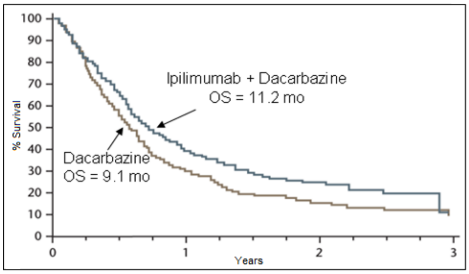
IPILIMUMAB + DACARBAZINE
Melanoma



	n	RR
Ipilimumab 10 mg/kg + Dacarbazine	250	15%
DTIC	252	10%

	Grade 3/4 (%)
Ipilimumab 10 mg/kg + Dacarbazine	56
Dacarbazine	28

	Ipilimumab + Dacarbazine (%)	Ipilimumab (%)
Diarrhea	4	11
Colitis	2	5
Endocrinopathy	0	2
↑ ALT	21	8
↑AST	17	7

Robert et al. NEJM 2011

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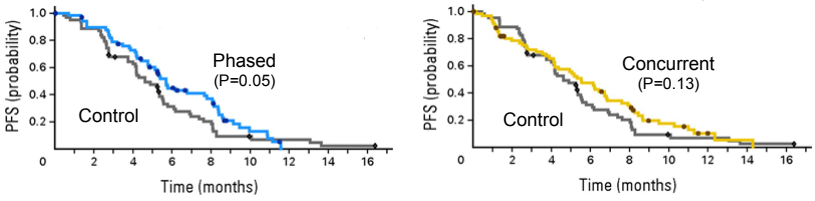
IPILIMUMAB + CHEMOTHERAPY
NSCLC

		Week						
		1	4	7	10	13	16	Grade 3/4 AE
Control (n=66)	Carboplatin	X	X	X	X	X	X	6%
	Paclitaxel	X	X	X	X	X	X	
NSCLC → Concurrent (n=70)	Ipilimumab	X	X	X	X			20%
	Carboplatin	X	X	X	X	X	X	
	Paclitaxel	X	X	X	X	X	X	
Phased (n=68)	Ipilimumab			X	X	X	X	15%
	Carboplatin	X	X	X	X	X	X	
	Paclitaxel	X	X	X	X	X	X	



Lynch et al. J Clin Oncol 2012

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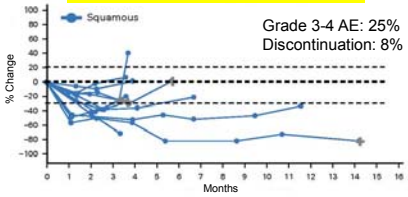
NIVOLUMB + CHEMOTHERAPY
NSCLC

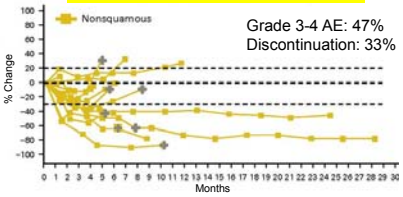
Nivolumab (10mg/kg) + Gem-Cis

Grade 3-4 AE: 25%
Discontinuation: 8%



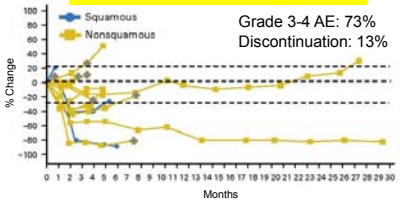
Nivolumab (10mg/kg) + Pem-Cis

Grade 3-4 AE: 47%
Discontinuation: 33%



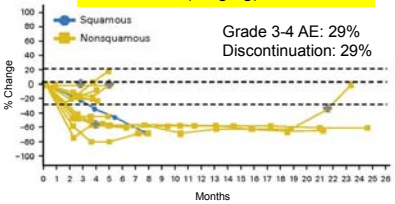
Nivolumab (10mg/kg) + Pac-Carb

Grade 3-4 AE: 73%
Discontinuation: 13%



Nivolumab (5mg/kg) + Pac-Carb

Grade 3-4 AE: 29%
Discontinuation: 29%



Rizvi et al. J Clin Oncol 2016

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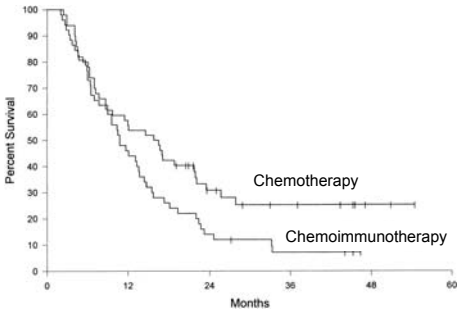
CHEMOIMMUNOTHERAPY
Melanoma

	Chemotherapy	Chemo-immunotherapy
Drugs	Cisplatin Dacarbazine Tamoxifen	Cisplatin Dacarbazine Tamoxifen IFN-alfa-2b IL-2
n	52	50
RR (%)	27	44



Rosenberg et al. J Clin Oncol 1999

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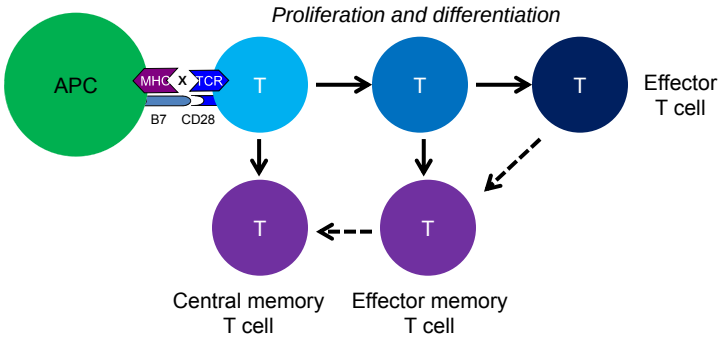
IMMUNOLOGIC MEMORY



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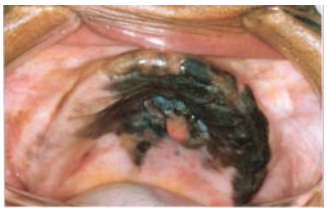
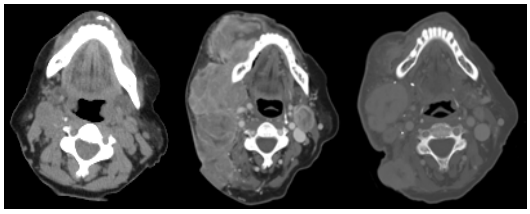
MUCOSAL MELANOMA



	RR
Chemotherapy	10%
Ipilimumab	12%
Imatinib (KIT mutations in 40%)	35%
Nivolumab	23%
Biochemotherapy	40%



Pre-treatment

Ipilimumab X4 → pembrolizumab X3

carboplatin + paclitaxel X2

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CHECKPOINT + CHEMOTHERAPY

- Safety profile consistent with that expected for individual agents
- Treatment discontinuation related to AEs greater with the combination
- Encouraging activity

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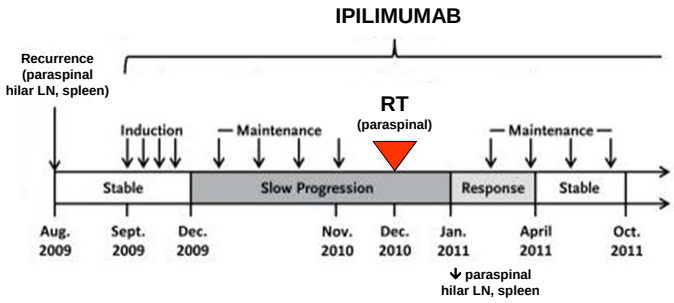
IPILIMUMAB + RADIOTHERAPY



Postow et al. NEJM 2012

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IPILIMUMAB + RADIOTHERAPY
Abscopal Effect

Ref.	No.	Primary site	XRT location	Ipilimumab -XRT interval (mo)	XRT dose (Gy)	Abscopal location	Time to onset after XRT (mo)	Response Duration (mo)
Postow et al. NEJM 2012	1	Upper back	Paraspinal	18	28.5/3	Spleen LN	4	6
Hiniker et al. NEJM 2012	1	Arm	Hepatic	1.5	54/3	Skin	6	6
Stamell et al. Int J Radiation Oncol Biol Phys 2013	1	Scalp	Brain	8	NA	LN	NA	NA
Grimaldi et al. Oncoimmunology 2014	11	NA	CNS 62% Extra-CNS 28%	5 (4–8)	Various	Various	1	2.4
Chandra et al. Oncoimmunology 2015	16	NA	Various	3	26 (8–68)	Various	NA	NA

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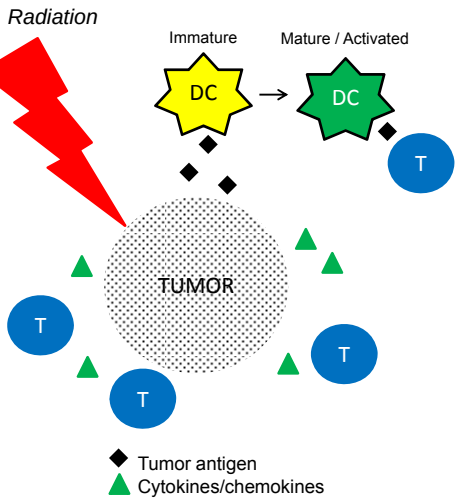
CHECKPOINT + XRT
Abscopal Effect

- ↑ Tumor antigens
  - → APC → systemic response
- ↑ Tumor sensitivity to CTL
- ↑ T cell trafficking into tumor



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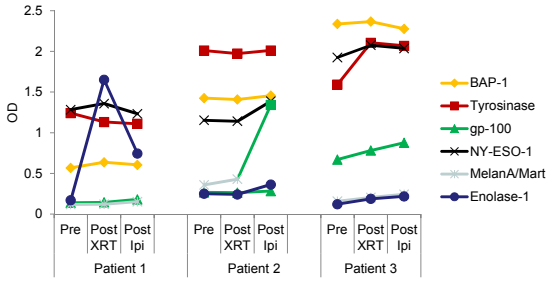
RADIOTHERAPY → IPILIMUMAB
Melanoma Antigen Response



Triozzi et al. Melanoma Res 2015

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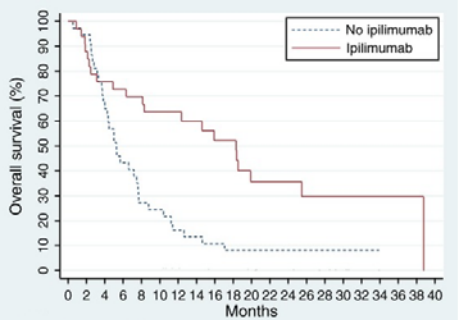
IPILIMUMAB + RADIOTHERPAY
Melanoma Brain Metastasis



	RR
Ipilimumab → XRT	4/10 (40%)
XRT	2/22 (9%)

Silk et al. Cancer Med 2013

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CHECKPOINT + RADIOTHERAPY

- RT may increase depth and duration of responses (not RR)
- Preferred timing, dosing, and volume of RT required to maximize effects?

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CHECKPOINT + RADIOTHERAPY

Checkpoint	Radiotherapy	Phase	Cancer
Ipilimumab	RT	I, I/II, II	Melanoma, NSCLC
	RT + brachytherapy	I	Cervical
	IMRT	Ib	HNSSC
	WBRT	II	Melanoma (brain metastases)
	SART	I, II	Melanoma (brain metastases)
	SBRT	I/II	Melanoma, solid
	Radioembolization	0	Melanoma (liver metastasis)
Pembrolizumab	RT	I, I/II, II	Melanoma, NSCLC, HNSSC, solid
	RT/RFA	II	Colorectal
	HRT	I	Solid
	HFSRT	I	Gliomas
	SABR	I	Breast
	SBRT	II	NSCLC
Nivolumab	RT	I/II, II	NSCLC
Durvalumab	RT	I/II, II	NSCLC
Atezolizumab	SART	I	Solid
Tremelimumab and/or pembrolizumab	SBRT	I	Pancreatic

HRT, hypofractionated; HFSRT, hypofractionated stereotactic; IMRT, intensity modulated; RFA, radiofrequency ablation; RT, conventional external beam; SART, stereotactic ablative; SBRT, stereotactic body; WBRT, whole brain

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TARGETED + RADIOTHERAPY

- BRAF inhibitors can enhance radiosensitivity
  - Synergistic antitumor effect
  - Increase in RT-related side effects
- Increased toxicity with concurrent XRT and BRAFi
  - Skin and visceral
  - Degree (can be severe) and duration are variable
- Radiation recall
  - XRT prior to or subsequent to BRAFi
  - Skin and visceral
  - Severe in some cases
- Hold BRAFi
  - for at least 3 days before and after fractionated RT
  - for at least 1 day before and after stereotactic RT

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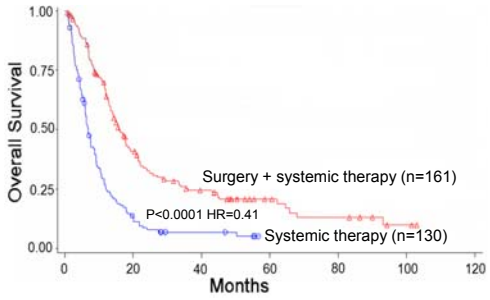
SURGERY
Immune Effects

- ↑ Tumor antigen
  - Tissue trauma
- Immune cell homeostasis
  - Immune suppression → immune recovery
- ↓ Tumor-induced immunosuppression

MELANOMA
Metastasectomy



Howard et al. (MSLT-1) Ann Surg Oncol 2012

IMMUNOTHERAPY + SURGERY

Melanoma Metastatic to Gastrointestinal Tract
(n = 457)

	Survival (months)	HR
Surgery + Immunotherapy*	20	0.54 (P<0.01)
Surgery	13	0.68 (P=0.03)
Immunotherapy	8	
Neither surgery or immunotherapy	5	

*ipilimumab, vaccine, IL-2, interferon

Deutsch et al. Gastrointestinal Cancer Symposium 2015 (abstract)

MELANOMA
Metastasectomy

- Selection bias?
  - More indolent, oligometastatic disease
  - Fit patients who can undergo surgery
- No prospective/randomized clinical data
  - Control group?

IPILIMUMAB
Surgery

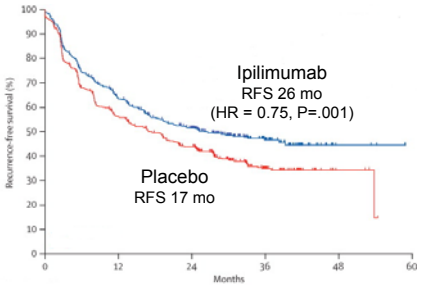
- Retrospective review, n = 23 patients, n = 34 operations
  - Operations 1-123 weeks (median 27) after ipilimumab initiated
- Subcutaneous resections were most frequent, followed by intra-abdominal and nodal procedures
- Grade 1/2 wound complications in 5/23 (22%)
- No Grade 3-5 complications

Gyroki et al. Ann Surg Oncol 2013

EORTC 18071
Adjuvant Ipilimumab *vs* Placebo

Stage IIIA,B,C NED

Ipilimumab 10 mg/kg q3w X 4, then q3m X 3y (n=475)	Placebo q3w X 4, then q3m X 3y (n=476)



FDA approved for melanoma with regional lymph node involvement >1 mm, after complete resection, including total lymphadenectomy

Eggermont et al. Lancet Oncol 2015

EORTC 18071
Adjuvant Ipilimumab *vs* Placebo

Grade 3/4 AE	42% GI 16% Hepatic 11% Endocrine 8%
D/C therapy	52% 39% within first 12w
Deaths	5 (1%)

Eggermont et al. Lancet Oncol 2015

MELANOMA
Adjuvant Therapy

	IFN (*vs* observation)	Ipilimumab (*vs* placebo)
RFS HR	.82	.75
RFS 2y	69 *vs* 59 (10%)	52 *vs* 44 (8%)
RFS 3y	55 *vs* 49 (6%)	46 *vs* 34 (12%)
Grade 3/4 AE	40%	42%
D/C therapy	10%	52%

ECOG 1609
Adjuvant Ipilimumab *v.* Interferon

Stage IIIB-IV NED

Ipilimumab 10 mg/kg (n=500)	Ipilimumab 3 mg/kg (n=500)	Interferon alfa-2b high-dose (n=500)

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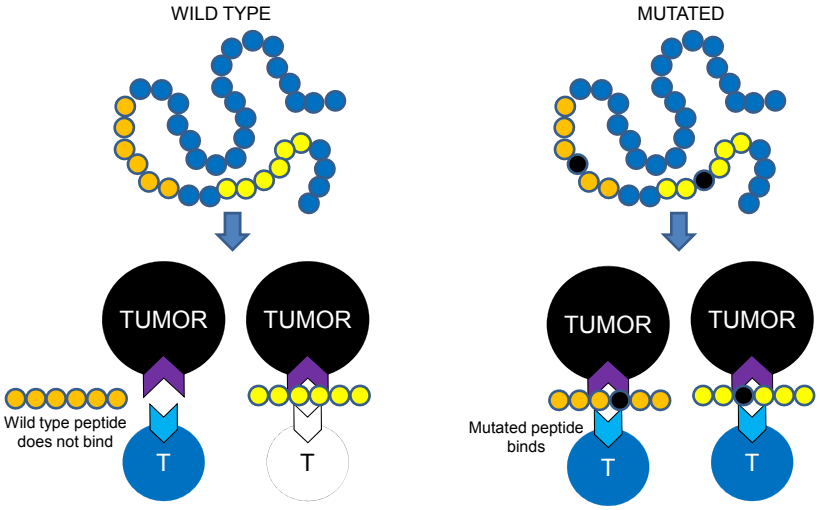
NEOANTIGENS



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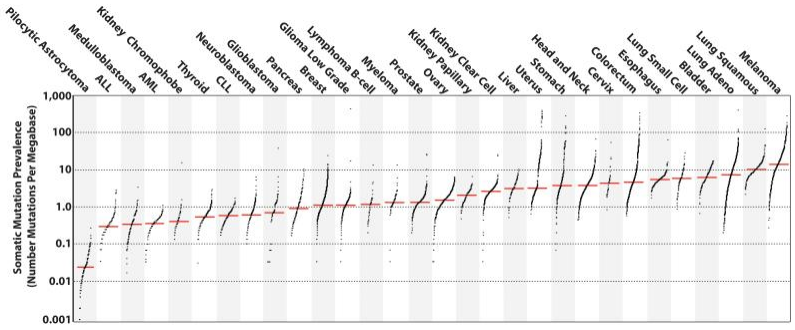
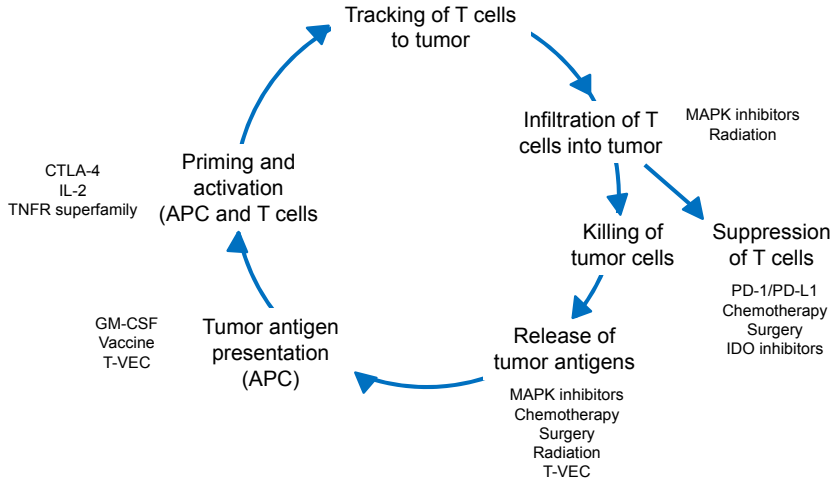
MUTATIONAL BURDEN



Alexandrov et al. Nature 2013



IMMUNOTHERAPY COMBINATIONS
Approaches

Concurrent	Maximize response upfront (↑ toxicity)
Sequential	Overcome resistance in poor responders (↓ toxicity)
Concurrent - Sequential	Overcome resistance after initial response Maintain response

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IMMUNOTHERAPY COMBINATIONS

Dual checkpoint	*FDA approved in melanoma* *Overall survival?* *Toxicity problematic*
Immune agonists	*Under investigation*
Targeted	*Sequential standard of care* *Concurrent under investigation* *Toxicity problematic*
Chemotherapy	*Under investigation* *Overall survival?* *Toxicity problematic*
Radiation	*Frequency of abscopal effect?* *Toxicity not problematic*
Metastatectomy	*Uncertain benefit*

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IMMUNOTHERAPY COMBINATIONS

- Optimize dosing
- Minimize toxicities
- Identify biomarkers
- Efficacy endpoints

Hem/Onc Physician and Advance Practice Clinician Burnout and Resilience

Dan Shapiro, PhD
Vice Dean for Faculty and Administative Affairs
Chair, Department of Humanities
Garner James Cline Professor of Humanities in Medicine
Penn State College of Medicine

Hem/Onc Physician and APC Burnout and Resilience

Dan Shapiro, Ph.D.

Talk organization:

Do a case

Self-Assessment

Data on burnout

Systems contributions to burnout

Personal contributions to burnout

7 life categories to make decisions for

The case study: Underline contributing variables

John X, MD is a 45 YO Hematologist who is well known and well liked in the medical community. His practice, and that of his colleagues, is busy. He is slightly more successful than colleagues at keeping his sickest patients out of the hospital, but his patient satisfaction data is somewhat worse. In the last year, he's received a few complaint letters calling him "disrespectful," but in his defense, he says none of his colleagues set limits with medication seeking or overly somatic patients. He's a self-described "grinder" meaning that he sees more patients than his peers in a typical session, though data reveals that he cancels more clinics than his peers, so his overall RVU's are around the median for his group.

He describes his work this way, "I'm an air-traffic controller, almost all my planes land just fine with a little help, but occasionally, there's a disaster. I spend too much time with my face in the electronic medical record because our EMR sucks. I have a handful of patients who are incredibly draining — some of my sickle cell kids and hemophiliacs whine, are medication seeking, and depressed."

Dr. X drinks half a bottle of wine to one bottle per night (a wine lover, he and his wife typically share a bottle or two) and reports feelings of frustration more days than not, as well as some emotional numbing. He's been taking Ambien to sleep for a few years but doesn't generally feel well rested.

Financially, he reports making good money but "it still doesn't feel like enough." He's had a few recent conflicts with his his partners over plans to refurbish the office and how they should manage a young physician who wants to join the practice.

On a personal note, he's got some mild hypertension, and he was recently sued, which angers him. Otherwise, he says when asked, "I'm good brother. Everyone should have my problems."

Put variables in order, in terms of their power to predict MI's:

Diabetes

Smoking

Hypertension

Plasma Lipoproteins

Obesity

Diet

Physical Activity

Alcohol Consumption

Psychosocial variables

Quick and Dirty Assessment:

Of the following, which is most accurate?

1) I enjoy my work. I have no symptoms of burnout

2) Occasionally I am under stress, and I don't always have as much energy as I once did, but I don't feel burned out

3) I am definitely burning out and have one or more symptoms of burnout, such as physical and emotional exhaustion

4) The symptoms of burnout that I'm experiencing won't go away. I think about frustration at work a lot

5) I feel completely burned out and often wonder if I can go on. I am at the point where I may need some changes or may need to seek some sort of help

Rage?

Letters of complaint?

Physical?

Emotional numbing?

Time thief?

Data on physician burnout

Rates are high

Rates are worsening

Burnout has serious consequences

Specialty breakdown

37% -- Derm to 53% critical care

Oncology = 44%

ETOH meet WHO diagnostic criteria for abuse or dependence

12.9% of males,

21.4% females

Higher ETOH correlated with depression, burnout, suicidal ideation, worsened QOL, lower career satisfaction.

Also related to medical error: recent medical error = increased ETOH!

Burnout increasing: It's getting worse

9% increase in physicians reporting burnout symptoms between 2011 and 2014.

Consequences:

Depression

Suicidal ideation

Reduced safety

Increased rates of malpractice

Canary in the coalmine:

Complaint letters!

Systems observations

More hours = more burnout

Uninterested or disengaged boss = more burnout

Computerized order entry = more burnout

Perceived control over practice environment, call & coverage, overall workload = reduced burnout

Isolation from other docs/nurses = more burnout

Observations from treating physicians: Themes

1. Forget the why
2. Neglect key relationships
3. Hiders
4. Use self-deprecation as a motivating strategy

5. Competing vs connecting

6. Fraud syndrome

7. Stuffing emotions as lifelong pattern

8. Somatic patients

9. Pressure: Overbuy, too many pts, not enough time off

10. Mistakes haunt

11. Celebrate self-denial instead of self-care

12. Over-controlling

13. Exposure to tragedy

14. Self-destructive coping

<u>7 areas of life to make decisions in:</u>

1. Financial

2. Family

    Magic trio: Compliment, be helpful, deeply inquire

3. Physical

4. Intellectual

5. Relationships

6. Clinical

7. Spiritual

******

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Lung Cancer 2016
Mark A. Socinski, MD
Executive Medical Director
Florida Hospital Cancer Institute

Lung Cancer 2016

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Orlando, FL

Advanced NSCLC 2016

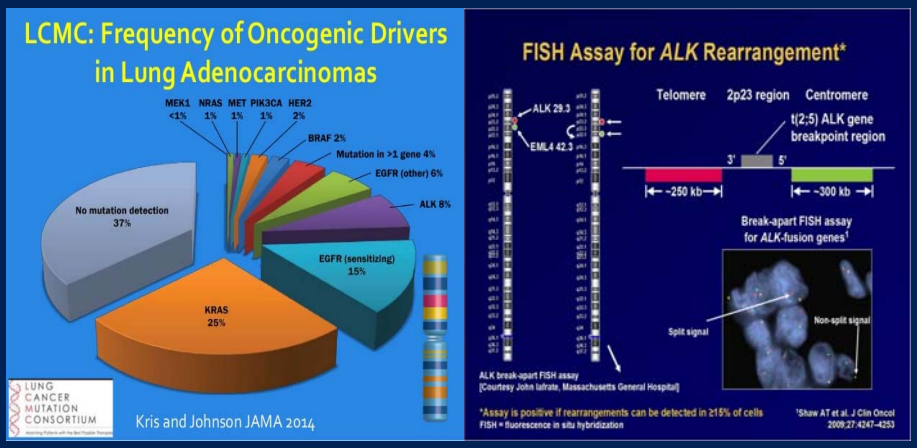
- Accurate histologic and molecular classification paramount in advanced NSCLC
- Histology drives molecular testing strategies and therapeutic choices
- The list of actionable oncogenic drivers continues to grow
- Targeted therapy in targeted patients based on molecular testing now defines the standard of care (EGFR mutations, ALK translocations, others)
- Immunotherapy established as the standard in the 2nd line setting and is moving into 1st line
- PD-L1 testing will be routine, should be reflexive and is still controversial

Advanced NSCLC 2016

Overview

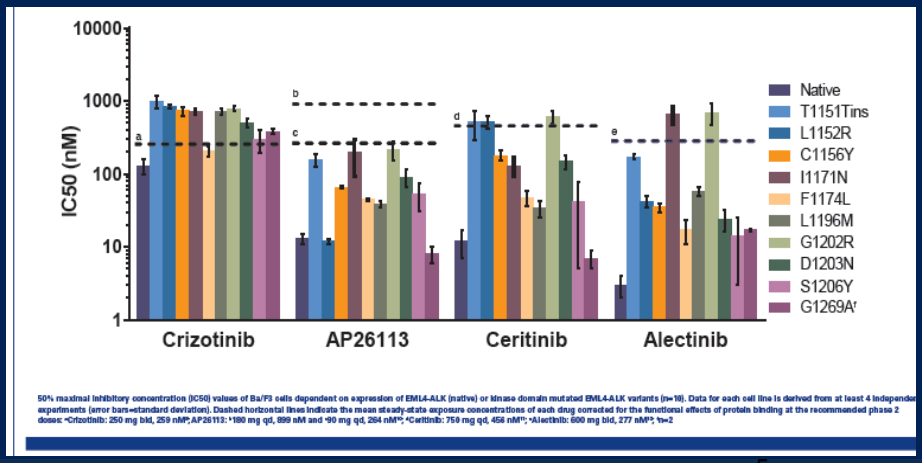
- New agents for ALK+ NSCLC
- BRAF, met, ret alterations
- 3rd generation EGFR inhibitors
- Evolving strategies with immunotherapy in advanced disease

ALK positive NSCLC- A distinct entity



PRESENTED AT: ASCO ANNUAL MEETING '16

Inhibitory Profiles of ALK Inhibitors in Cellular Models



50% maximal inhibitory concentration (IC50) values of Ba/F3 cells dependent on expression of EML4-ALK (native) or kinase domain mutated EML4-ALK variants (n=18). Data for each cell line is derived from at least 4 independent experiments (error bars=standard deviation). Dashed horizontal lines indicate the mean steady-state exposure concentrations of each drug corrected for the functional effects of protein binding at the recommended phase 2 doses: [a]Crizotinib: 250 mg bid, 259 nM; AP26113: [b]180 mg qd, 899 nM and [c]90 mg qd, 284 nM[1]; [d]Ceritinib: 750 mg qd, 458 nM[2]; [e]Alectinib: 600 mg bid, 277 nM[3]; n=2

5

1. Gettinger, et al. Presented at: ESMO. 2014 (abstr 439O). 2. Squillace, et al. Presented at: AACR. 2013 (abstr 5655). 3. Kozuki TJSMO 2015

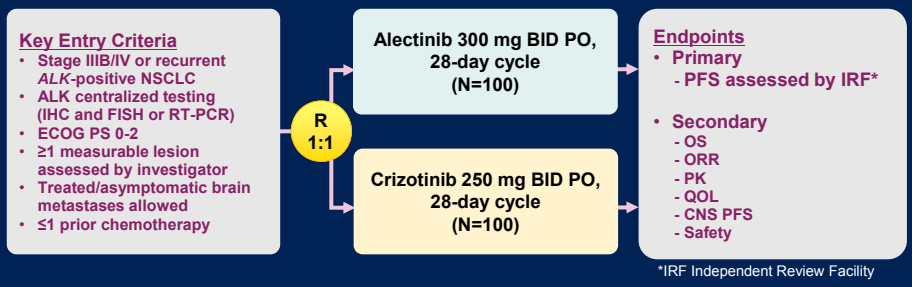
Alectinib versus Crizotinib in ALK Inhibitor Naïve *ALK*-Positive Non-Small Cell Lung Cancer: Primary Results from the J-ALEX Study

Hiroshi Nokihara, Toyoaki Hida, Masashi Kondo, Young Hak Kim, Koichi Azuma, Takashi Seto, Yuichi Takiguchi, Makoto Nishio, Hiroshige Yoshioka, Fumio Imamura, Katsuyuki Hotta, Satoshi Watanabe, Koichi Goto, Kazuhiko Nakagawa, Tetsuya Mitsudomi, Nobuyuki Yamamoto, Hiroshi Kuriki, Ryoichi Asabe, Tomohiro Tanaka, Tomohide Tamura

Abstract 9008

Presented by: Hiroshi Nokihara

J-ALEX Phase III Study Design



*IRF Independent Review Facility

Stratification factors: Clinical stage (IIIB/IV vs. Recurrent)
Prior chemotherapy (0 vs. 1)
ECOG PS (0/1 vs. 2)

JapicCTI-132316

Baseline Characteristics

		Alectinib (N=103)	Crizotinib (N=104)
Sex	Male / Female	41 (39.8%) / 62 (60.2%)	41 (39.4%) / 63 (60.6%)
Median age (range)		61.0 (27-85)	59.5 (25-84)
ECOG PS*	0	54 (52.4%)	48 (46.2%)
	1	47 (45.6%)	54 (51.9%)
	2	2 (1.9%)	2 (1.9%)
Prior chemotherapy*	0	66 (64.1%)	67 (64.4%)
	1	37 (35.9%)	37 (35.6%)
Clinical stage*	Stage IIIB	3 (2.9%)	3 (2.9%)
	Stage IV	76 (73.8%)	75 (72.1%)
	Postoperative recurrence	24 (23.3%)	26 (25.0%)
Histology	Squamous cell carcinoma	2 (1.9%)	0
	Adenocarcinoma	100 (97.1%)	103 (99.0%)
	Other	1 (1.0%)	1 (1.0%)
Brain metastases by IRF	Yes / No	14 (13.6%) / 89 (86.4%)	29 (27.9%) / 75 (72.1%)
Smoking status	Never smoker	56 (54.4%)	61 (58.7%)
	Past or Current smoker	47 (45.6%)	43 (41.3%)
ALK test method	IHC and FISH	96 (93.2%)	94 (90.4%)
	RT-PCR	7 (6.8%)	10 (9.6%)

*Stratification factors

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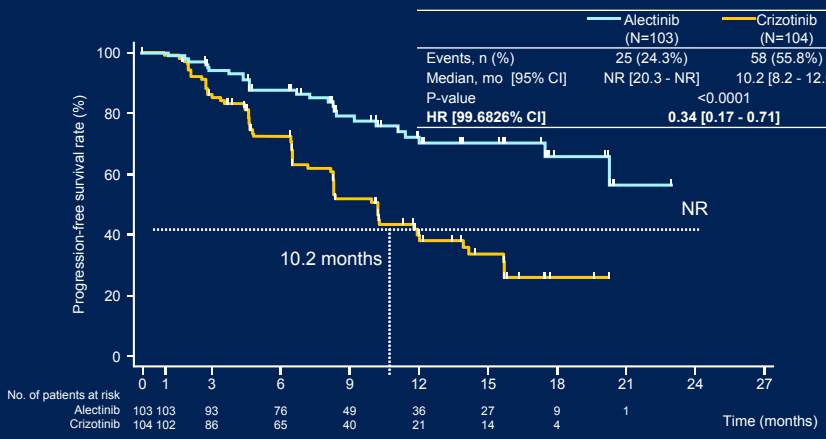
Primary Endpoint: PFS by IRF (ITT Population)



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Objective Tumor Response

ORR assessed by investigator in ITT population

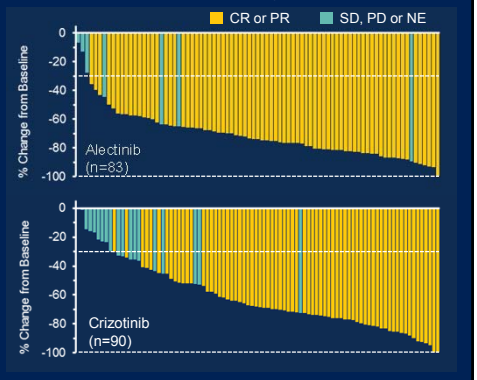
	Alectinib (N=103)	Crizotinib (N=104)
ORR [95%CI]	**85.4% [78.6 - 92.3]**	**70.2% [61.4 - 79.0]**
CR or PR	88	73

ORR* assessed by IRF

	Alectinib (n=83)	Crizotinib (n=90)
ORR [95%CI]	**91.6% [85.6 - 97.5]**	**78.9% [70.5 - 87.3]**
CR or PR	76	71

* In patients with measurable lesion assessed by IRF at baseline

Water fall plot* assessed by IRF



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Common AEs, ≥20% of Patients in Either Arm

	All Grade		Grade 3/4	
	Alectinib (N=103)	Crizotinib (N=104)	Alectinib (N=103)	Crizotinib (N=104)
Constipation	36 (35.0%)	46 (44.2%)	1 (1.0%)	1 (1.0%)
Nausea	11 (10.7%)	77 (74.0%)	0	2 (1.9%)
Diarrhea	9 (8.7%)	76 (73.1%)	0	2 (1.9%)
Vomiting	6 (5.8%)	60 (57.7%)	0	2 (1.9%)
Aspartate aminotransferase increased	11 (10.7%)	32 (30.8%)	1 (1.0%)	5 (4.8%)
Alanine aminotransferase increased	9 (8.7%)	33 (31.7%)	1 (1.0%)	13 (12.5%)
Visual disturbance	1 (1.0%)	57 (54.8%)	0	0
Nasopharyngitis	21 (20.4%)	24 (23.1%)	0	0
Dysgeusia	19 (18.4%)	54 (51.9%)	0	0
Pyrexia	10 (9.7%)	21 (20.2%)	1 (1.0%)	0
Decreased appetite	1 (1.0%)	21 (20.2%)	1 (1.0%)	1 (1.0%)

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Conclusion

- At a pre-planned interim analysis, J-ALEX met the primary endpoint, demonstrating superiority of alectinib compared with crizotinib in ALK inhibitor naïve patients
  - PFS HR of alectinib vs. crizotinib: 0.34
  - Median PFS in alectinib arm was not reached [95% CI:20.3 - NR]
  - Crizotinib behaved as expected, both PFS and ORR
- Alectinib was well-tolerated with a favorable AE profile
  - Less discontinuation or interruption due to AEs than crizotinib
  - No treatment-related deaths in either arm
- Alectinib has the potential to be a new standard first-line therapy for *ALK*-positive NSCLC

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Brigatinib Exhibits a Pan-Inhibitory Preclinical Profile Against ALK Resistance Mutants

- Brigatinib overcomes mechanisms of resistance to first- and second-generation ALK inhibitors in preclinical models[1]
  - Potently inhibited all ALK resistance mutations tested, including G1202R, at clinically achievable levels
  - Significantly prolonged survival and reduced tumor burden in an ALK-dependent orthotopic brain tumor model in mice
- Brigatinib yielded promising clinical activity in crizotinib-treated ALK+ NSCLC patients in a phase 1/2 study[2]

(1) Zhang, et al. *Cancer Res*. 2015;75(15 suppl):abstract 781.
(2) Camidge, et al. *J Clin Oncol*. 2015;33(suppl):abstract 8062.
(3) Katayama, et al. *Clin Cancer Res*. 2015;21:2227-35.
(4) Friboulet, et al. *Cancer Discov*. 2014;4:662-73.

Effective Average Concentration (C_{ave}) in Patients* Exceeds IC_{50} by at Least 2-fold — Yes / No

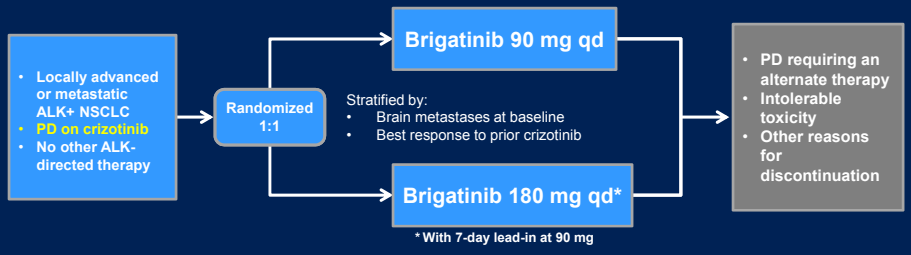
ALK Variant	TKI Activity, IC_{50} (nM)			
	Crizotinib	Ceritinib	Alectinib	Brigatinib
Native	107	37	25	14
T1151Tins	1109†	283	201	114
L1152R	844†	437†	62	11
L1152P	721	451	48	20
C1156Y	529†	195	67	45
I1171N	532†	119	724†	124
F1174C	238	109†	31	58
F1174L	253†	117	44	55
F1174V	257†	121†	46	64
V1180L	170	16	597	11
L1196M	589†	67	133	41
L1198F	17	697	84	82
G1202R	617†	354†	695†	184
D1203N	459†	159	42	79
S1206F	199†	39	34	43
S1206Y	179†	42	19	36
E1210K	240	80	59	107
G1269A	509†	29	56	9

* Effective C_{ave} at steady-state concentrations at approved/recommended phase 2 doses (180 mg for brigatinib) corrected for functional effects of protein binding; †ALK mutations previously associated with clinical resistance[3,4]

Adapted from Zhang, et al. Poster presented at AACR Annual Meeting, April 18–22, 2015, Philadelphia, PA, Abstract 781.

ALTA: Randomized Dose Evaluation of Brigatinib

A phase 2, open-label, multicenter, international study (NCT02094573)



* With 7-day lead-in at 90 mg

Primary Endpoint: Confirmed ORR per RECIST v1.1 (assessed by investigator)

Key Secondary Endpoints: Confirmed ORR (assessed by an IRC), CNS response (IRC-assessed intracranial ORR and PFS in patients with active brain metastases†), duration of response, PFS, OS, safety, and tolerability

Randomized phase 2 design not intended for statistical comparisons between arms; however, post hoc comparisons were performed on PFS and OS to support dose selection

† Active brain metastases were defined as lesions with no prior radiotherapy or those with investigator-assessed progression after prior radiotherapy

Abstract 9007

Demographics and Baseline Characteristics

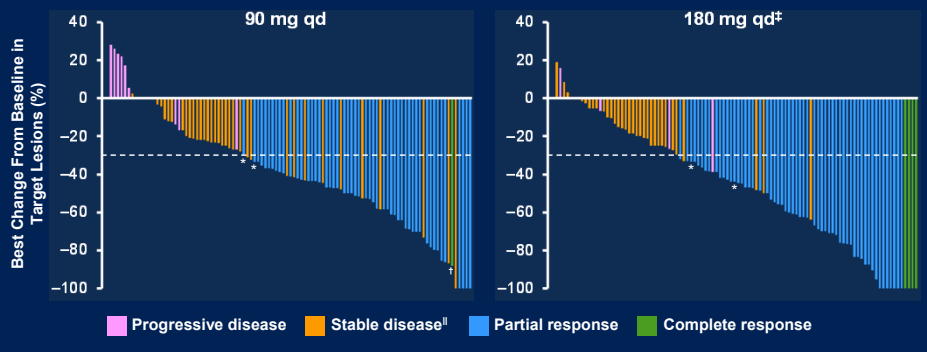
		90 mg qd n=112	180 mg qd* n=110	Total N=222
Median age, y (range)		50.5 (18–82)	56.5 (20–81)	54 (18–82)
Gender, n (%)	Female	62 (55)	64 (58)	126 (57)
Race, n (%)	White	72 (64)	76 (69)	148 (67)
	Asian	39 (35)	30 (27)	69 (31)
	Other	1 (1)	4 (4)	5 (2)
ECOG, n (%)	0/1	105 (94)	101 (92)	206 (93)
	2	7 (6)	9 (8)	16 (7)
Smoking history, n (%)	No	71 (63)	63 (57)	134 (60)
	Yes	40 (36)	47 (43)	87 (39)
	Unknown	1 (1)	0	1 (<1)
Histology, n (%)	Adenocarcinoma	107 (96)	108 (98)	215 (97)
	Other	5 (4)	2 (2)	7 (3)
Prior chemotherapy, n (%)	Yes	83 (74)	81 (74)	164 (74)
Brain metastases at baseline,† n (%)	Present	80 (71)	74 (67)	154 (69)
Best response to prior crizotinib, n (%)	CR or PR	71 (63)	73 (66)	144 (65)
	Other response or unknown	41 (37)	37 (34)	78 (35)

CR = complete response, PR = partial response. * 180 mg qd with 7-day lead-in at 90 mg; † Presence of brain metastases as assessed by the investigator

- Arms balanced for important prognostic factors including gender, ECOG PS (0/1 vs. 2), brain metastases, prior chemotherapy, and prior response to crizotinib

Data as of February 29, 2016

Brigatinib Antitumor Activity by Arm



Confirmed ORR: 45% (90 mg), 54% (180 mg)

Dotted line at –30% indicates threshold for partial response per RECIST v1.1
* Single response awaiting confirmation
† Patient had a lymph node target lesion which resolved to <10 mm shortest diameter (CR per RECIST v1.1)
‡ 180 mg qd with 7-day lead-in at 90 mg
‖ Category includes single responses that were not confirmed

Data as of February 29, 2016

IRC-Assessed Intracranial Response Rates

IRC-Assessed Efficacy Parameter	Patients With Measurable (≥10 mm) Brain Metastases		Patients With Only Nonmeasurable Brain Metastases	
	90 mg qd n=25	180 mg qd* n=18	90 mg qd n=54	180 mg qd* n=54
Confirmed intracranial ORR, n (%) [95% CI]	9 (36) [18–58]	12 (67) [41–87]	3 (6) [1–15]	10 (19) [9–31]
Best overall response, n (%)				
Confirmed intracranial CR	2 (8)	0	3 (6)	10 (19)
Confirmed intracranial PR	7 (28)	12 (67)	NA	NA
Intracranial CR awaiting confirmation	0	0	0	1 (2)
Intracranial PR awaiting confirmation	3 (12)	0	NA	NA
Intracranial disease control rate, n (%) [95% CI]	22 (88) [69–98]	15 (83) [59–96]	39 (72) [58–84]	47 (87) [75–95]

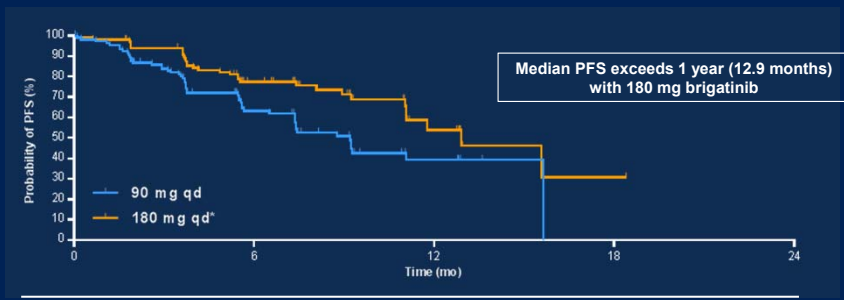
Of 222 randomized patients, 215 had a baseline brain MRI evaluated by the IRC, with 151 identified as having brain metastases at baseline
Intracranial response defined as a ≥30% decrease in measurable lesions or complete disappearance of lesions in patients with only nonmeasurable lesions
NA = not applicable

- Among patients with measurable, active† brain metastases at baseline, IRC-assessed intracranial ORR:
  - 37% (7/19) at 90 mg
  - 73% (11/15) at 180 mg

* 180 mg qd with 7-day lead-in at 90 mg
† Active brain metastases were defined as lesions with no prior radiotherapy or those with investigator-assessed progression after prior radiotherapy

Last scan date: February 17, 2016

PFS by Arm

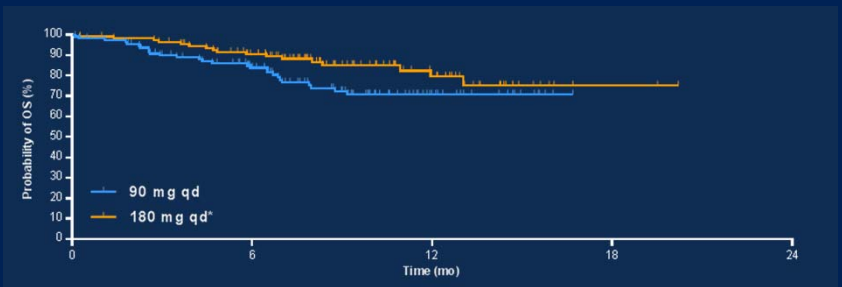


	Events / Total (%)	1-Year PFS Probability, % (95% CI)	Median PFS (95% CI)	Hazard Ratio (95% CI)†
90 mg qd	50/112 (45)	39 (27–52)	9.2 months (7.4–15.6)	0.55 (0.35–0.86)
180 mg qd*	31/110 (28)	54 (37–68)	12.9 months (11.1–not reached)	

* 180 mg qd with 7-day lead-in at 90 mg
† Study was not designed to compare treatment arms statistically; however, post hoc comparisons were performed to support dose selection

Data as of February 29, 2016

Survival by Arm



	Events / Total (%)	1-Year OS Probability, % (95% CI)	Median OS	Hazard Ratio (95% CI)†
90 mg qd	27/112 (24)	71 (60–79)	Not reached	0.57 (0.31–1.05)
180 mg qd*	17/110 (15)	80 (67–88)	Not reached	

* 180 mg qd with 7-day lead-in at 90 mg
† Study was not designed to compare treatment arms statistically; however, post hoc comparisons were performed to support dose selection

Data as of February 29, 2016

Treatment-Emergent Adverse Events

Treatment-Emergent AEs Reported in ≥10% of All Patients	90 mg qd n=109		180 mg qd* n=110	
	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %
Nausea	33	1	40	1
Diarrhea	19	0	38	0
Headache	28	0	27	1
Cough	18	0	34	0
Fatigue	20	1	27	0
Vomiting	24	2	23	0
Dyspnea	21	3	21	2
Increased blood creatine phosphokinase	11	3	30	9
Decreased appetite	22	1	15	1
Constipation	19	1	15	0
Hypertension	11	6	21	6
Muscle spasms	12	0	17	0
Arthralgia	14	1	14	0
Back pain	10	2	15	2
Abdominal pain	17	0	8	0
Rash	7	1	16	3
Increased amylase	8	1	15	1
Increased aspartate aminotransferase	8	0	15	0
Pyrexia	14	0	6	1

* 180 mg qd with 7-day lead-in at 90 mg; median time on treatment was 7.5 months in 90 mg qd arm and 7.8 months in 180 mg qd arm

- Some AEs appear dose-related; the increased rates are mainly in grade 1–2 events

Data as of February 29, 2016

Dose and Safety

Select Safety Parameters	90 mg qd n=109	180 mg qd* n=110
Dose reduction due to any AE, n (%)	8 (7)	22 (20)
Dose interruption ≥3 d (any reason), n (%)	20 (18)	40 (36)
Discontinuation due to any AE, n (%)	3 (3)	9 (8)
Discontinuation due to PD, n (%)	33 (30)	19 (17)
Discontinuation due to death, n (%)	7 (6)	1 (1)
Median dose intensity, mg/d	90	174

* 180 mg qd with 7-day lead-in at 90 mg

- A subset of pulmonary AEs with early onset (median: Day 2; range: Day 1–9) including dyspnea, hypoxia, cough, pneumonia, or pneumonitis occurred in 14 (6%) patients (3% with grade ≥3 events)
- All of these events occurred at 90 mg in both arms; no events with early onset occurred after escalation to 180 mg
- Managed with dose interruption and successful reintroduction (6/14) or continued treatment with resolution (1/14)
- Seven patients discontinued, including 1 patient who died having had such AEs (dyspnea, cough, and pneumonia)
  - Autopsy: lymphangitic carcinomatosis, widespread post-tumor lung scarring, and diffuse alveolar damage; causes of death reported as lung cancer, adhesive pericarditis, and respiratory failure
- Although pathophysiology is unclear, trend toward lower frequency of these AEs with ≥7-day crizotinib washout (4/110), compared with <7-day washout (10/109)
  - Relative risk: 2.52 (95% CI: 0.82–7.80)

Data as of February 29, 2016

Conclusions

- Brigatinib demonstrated substantial efficacy and an acceptable safety profile in both arms
- At 180 mg (with 7-day lead-in at 90 mg):
  - 54% ORR
  - 67% intracranial ORR (for patients with measurable brain metastases)
  - Median PFS >1 year (12.9 months); 80% 1-year OS
- Observed clinical activity at 180 mg with 7-day lead-in at 90 mg was not associated with an increased risk of additional early pulmonary AEs
- A consideration of efficacy outcomes and AEs supports choice of 180 mg regimen
- Brigatinib has the potential to be a promising new treatment option for patients with crizotinib-resistant ALK+ NSCLC
- A randomized, phase 3 study of brigatinib with 180 mg regimen vs crizotinib in ALK inhibitor–naive patients has been initiated (ALTA-1L, NCT02737501)

Second Generation ALK inhibitors

	Ceritinib[1] N= 163	Alectinib[2] N=138	Brigatinib[3] N = 110
Design/ Assessment	Phase I/II Investigator/BIRC	Phase 2 BIRC	Phase 2 Investigator
PS 2	12%	9%	8%
Brain Mets	60%	61%	67%
Previous Rx	56% (≥ 3 prior)	80% (≥ 2 prior)	74% (≥ 2 prior)
ORR	56% (49-64)	50% (41 – 59)	54% (43-65)
CNS Response	36%* N = 28	57% N = 35	67% N = 12
Median PFS	6.9 m (5.6 – 8.7)	8.9 (5.6-11.3)	12.9 (11.1- NR)

* Retrospective Assessment

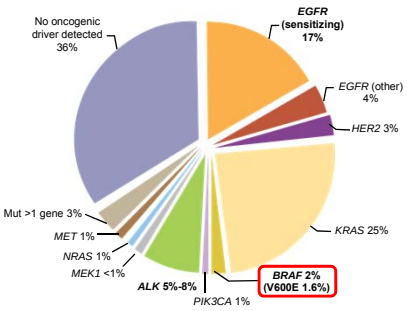
1. Kim,Lancet Oncol,2016
2. Ou, JCO 2016
3. Kim, ASCO 2016

23

PRESENTED AT: ASCO ANNUAL MEETING '16

BRAF Mutations in Non-Small Cell Lung Cancer

- *BRAF* mutations were observed in approximately 2% of patients with lung adenocarcinoma[1]

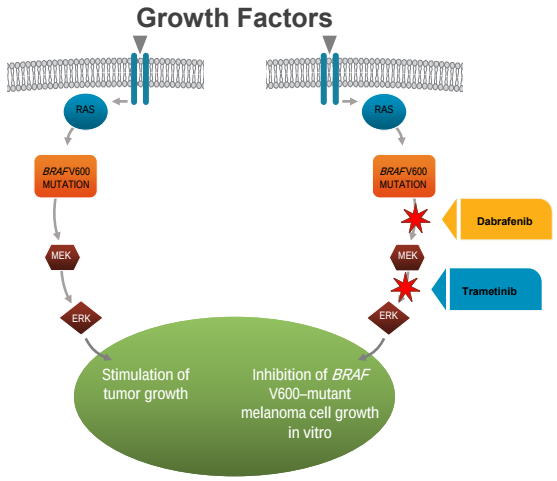


1. Kris MG, Johnson BE, et al. *JAMA*. 2014;311(19):1998-2006; 2. Sholl LM, et al. *J Thorac Oncol*. 2013;8(3):322-328.

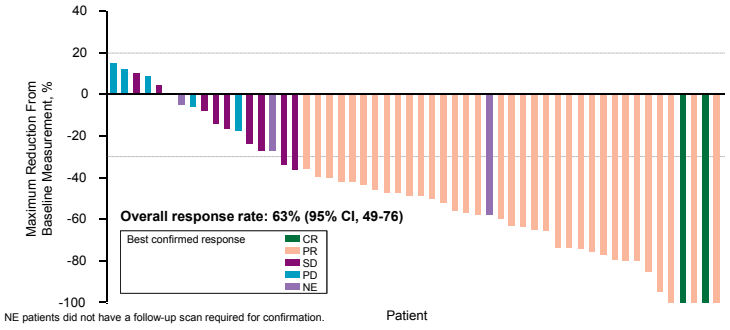
06/2016 M-DAB-1139477

Mechanism of Action for Dual MAPK Pathway Inhibition With Dabrafenib Plus Trametinib

- Dabrafenib is an inhibitor of some mutated forms of BRAF kinases as well as wild-type BRAF and CRAF kinases[1]
- Trametinib is a reversible inhibitor of MEK1 and MEK2 activation and kinase activity[2]
- Dabrafenib and trametinib target 2 different kinases in the RAS/RAF/MEK/ERK pathway[1,2]



BRF113928 Cohort B: Maximum Change in Target Lesion by Best Investigator-Assessed Confirmed Response



NE patients did not have a follow-up scan required for confirmation.

ORR (CR + PR), [95% CI] – 63% [49-76]
Disease control rate (CR + PR + SD), [95% CI] - 75% [62-86]
Median DOR – 9 mos (5.8-17.6)
Median PFS – 8.6 mos (5.2-19.1)

Planchard D, et al. ASCO 2016 [abstract 107].

MET Exon 14-Altered Lung Cancers

- Incidence
  - 3-4% of nonsquamous NSCLCs
  - 20-30% of sarcomatoid lung carcinomas
- Clinicopathologic Features
  - older patients
  - ↓ proportion of never smokers
  - patients should be screened regardless of these clinical features
  - 15-20% with concurrent *MET* amplification

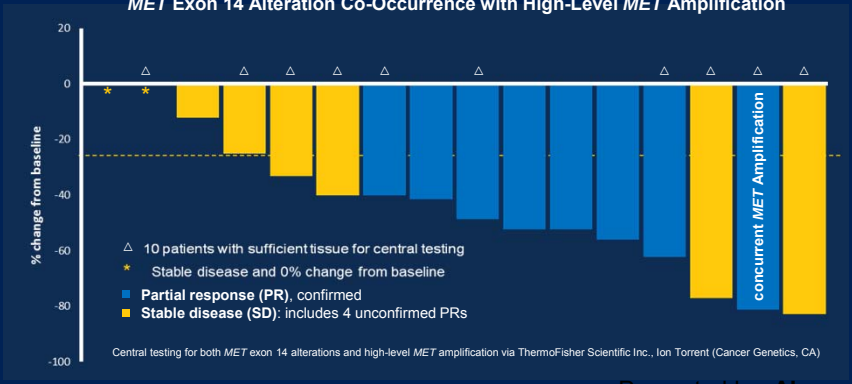
- Diagnosis
  - DNA-based next-generation sequencing
  - RNA sequencing
  - IHC alone is insufficient

Paik PK et al. Cancer Discov 2015;5. Awad MM et al. J Clin Oncol 2016;34. Tong et al. Clin Cancer Res 2016. TCGA Research Network. Nature. 2014;511. Schrock AB et al. ASCO 2016 Abstract 9021.

Antitumor Activity

ORR (95% CI) – 44% (22-69)

***MET* Exon 14 Alteration Co-Occurrence with High-Level *MET* Amplification**

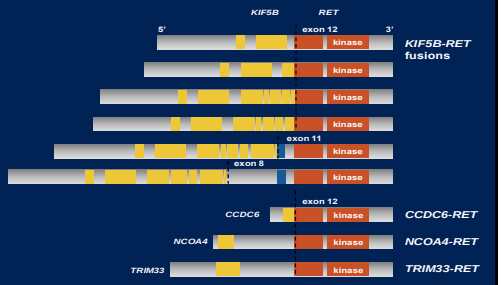


Central testing for both *MET* exon 14 alterations and high-level *MET* amplification via ThermoFisher Scientific Inc., Ion Torrent (Cancer Genetics, CA)

Presented by: **Alexander Drilon MD**

RET Rearrangements

- intact tyrosine kinase domain fused to an upstream gene partner
  - most common: *KIF5B*
  - others: *CCDC6, NCOA4, TRIM33, KIAA1468*
- result in ligand-independent dimerization and downstream growth pathway activation
- oncogenic *in vitro* and *in vivo*
- 1-2% NSCLC



Drilon AD, Cancer Discov 2013;3:630-5, Kohno T, Nat Med 2012;18:375-7, Saito M, Carcinogenesis 2014;35:2452-6
Suehara Y, Nat Med 2012;18;6599-608, Lipson D, Nat Med 2012;18:382-40, Takeuchi K, Nat Med 2012;18:378-81

RET Inhibitors—Efficacy Summary

Agent	*RET* testing	n	ORR (%)	PFS (months)	OS (months)
Cabozantinib (Drilon, ASCO 2015)	FISH/NGS	Stage I, 16	38	7	10
Cabozantinib (Gautschi, ASCO 2016)	FISH/NGS/RT-PCR	13	31	3.6	4.9
Vandetanib (Sato, ASCO 2016)	FISH/RT-PCR	19/17	47/53	4.7	47% 1-year
Vandetanib (Lee, ASCO 2016)	FISH confirmed	18	17	4.5	11.6
Vandetanib (Gautschi, ASCO 2016)	FISH/NGS/RT-PCR	11	18	2.9	10.2
Sunitinib (Gautschi, ASCO 2016)	FISH/NGS/RT-PCR	9	22	2.2	6.8
Any RET inhibitor (Gautschi, ASCO 2016)	FISH/NGS/RT-PCR	41	23	2.9	6.8

Stage IV NSCLC – EGFR mutation +

Management of EGFR mutation-positive advanced NSCLC

- Testing all adenocarcinomas and selected squamous carcinomas is standard (and should be reflexive)
- At least 8 randomized phase III trials show EGFR TKIs to be superior to standard chemotherapy
- Erlotinib, afatinib and gefitinib all FDA-approved
- Dominant mechanism of resistance is development of T790M
- 3rd generation TKIs have activity against T790M
- Re-testing essential to identify patients with T790M
- Oligo-metastatic progression often managed with loco-regional approaches (SBRT, surgery, etc)

Detection of T790M+ progressive disease
TIGER-X: Tissue, Plasma, and Urine *EGFR* Test Platforms

	FFPE tissue	Plasma	Urine
EGFR test platform	Real-Time PCR (*therascreen*®)	Digital PCR + Flow Cytometry (BEAMing)	Mutation Enrichment NGS (trovera)
Company	Qiagen	Sysmex-Inostics	Trovagene
Specimen collection	Mandatory	Mandatory	Optional
Test specimen input	Two 5 μm slides	2 mL	100 mL
EGFR mutations detected	T790M, Ex19del, L858R, G719X, L861Q, S768I, Ex20ins	T790M, Ex19del, L858R, G719X, L861Q	T790M, Ex19del, L858R

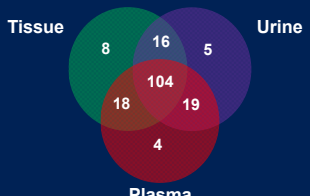
FFPE, formalin-fixed, paraffin-embedded; NGS, next-generation sequencing; PCR, polymerase chain reaction.

3
3

Plasma, Tissue, and Urine Identify Unique and Overlapping Subsets of T790M-Positive Patients

- 181 samples had matched pretreatment T790M results in plasma, tissue, and urine
  - 7 were T790M-negative or inadequate by all 3 sample types (4%)
  - 174 were T790M-positive by at least 1 sample type (96%)

T790M-Positive Cases



Proportion of patients in diagram not to scale.

- Total positive by tissue: 146 of 181
- Total positive by plasma: 145 of 181
- Total positive by urine: 144 of 181

104 (57%) were positive by all 3 sample types

Investigator-Assessed Confirmed Response Rate Is Similar for T790M-Positive Patients Identified by Plasma, Tissue, and Urine Test

Sample Type	n	Objective Response Rate,* % (95% CI)
Tissue	443	**33.9** (29.5–38.5)
Plasma	374	**32.1** (27.4–37.1)
Urine	169	**36.7** (29.4–44.4)

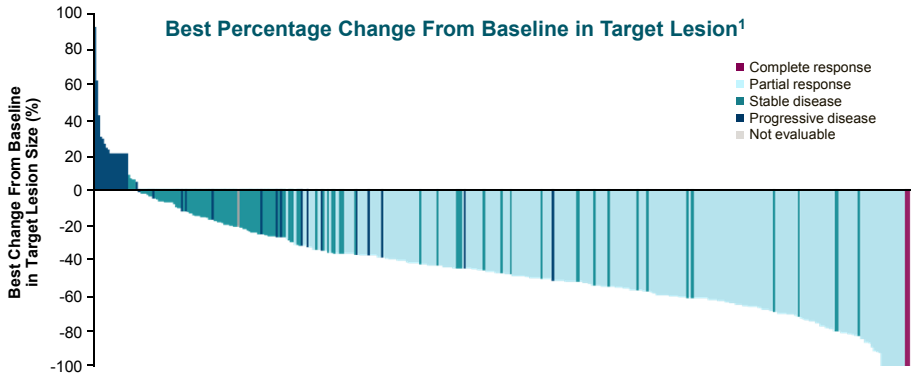
*Investigator-assessed confirmed objective response rate (RECIST v1.1).

Duration of Response and Progression-Free Survival: Results Independent of Sample Type Used to Identify T790M Positivity

Abstract 9001
Presented by: Heather A. Wakelee

LI123

AURA Pooled Phase 2 Studies: Osimertinib Confirmed Response Rates in T790M+ Disease (n=411)*



- Osimertinib was associated with an ORR of 66.1% (95% CI: 61.2, 70.7)[1]
- DCR was ~91% in the AURA Phase 2 studies[2,3]
- Median DoR not yet reached for the pooled Phase 2 analysis[1]
- Median DoR in AURA = 12.4 months (95% CI: 8.3, NC); data maturity = 31%[4]

*By BICR analysis.
1. Goss GD, et al. ECC 2015. Poster P365. **2.** Yang JCH, et al. WCLC 2015; MINI 16.06. **3.** Mitsudomi J, et al. WCLC 2015; MINI 16.08. **4.** Jänne PA, et al. ELCC 2015. Abstract LBA3.

EUROPEAN LUNG CANCER CONFERENCE 2016

Osimertinib (AZD9291) as first-line treatment for EGFR mutation-positive advanced NSCLC: updated efficacy and safety results from two Phase I expansion cohorts

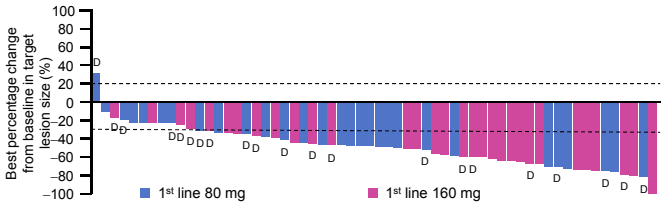
Suresh S Ramalingam,[1] James C-H Yang,[2] Chee Khoon Lee,[3] Takayasu Kurata,[4] Dong-Wan Kim,[5] Thomas John,[6] Naoyuki Nogami,[7] Yuichiro Ohe,[8] Mireille Cantarini,[9] Helen Mann,[9] Yuri Rukazenkov,[9] Serban Ghiorghiu,[10] Pasi A Jänne[11]

[1]Emory School of Medicine, Atlanta, GA, USA; [2]National Taiwan University and National Taiwan University Cancer Center, Taipei, Taiwan; [3]St George Hospital, Sydney, Australia; [4]Kansai Medical University Hirakata Hospital, Osaka, Japan; [5]Seoul National University Hospital, Seoul, Republic of Korea; [6]Olivia Newton-John Cancer Research Institute, Austin Health, Melbourne, Australia; [7]National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; [8]National Cancer Center Hospital East, Kashiwa-City, Japan; [9]AstraZeneca, Macclesfield, UK; [10]AstraZeneca, Cambridge, UK; [11]Dana-Farber Cancer Institute, Boston, MA, USA

Presented by Suresh S Ramalingam at the 6th IASLC/ESMO European Lung Cancer Conference, 13–16 April 2016, Geneva, Switzerland; Abstract LBA1_PR.

esmo.org

Tumour response to osimertinib in EGFRm first-line cohorts (investigator assessed)



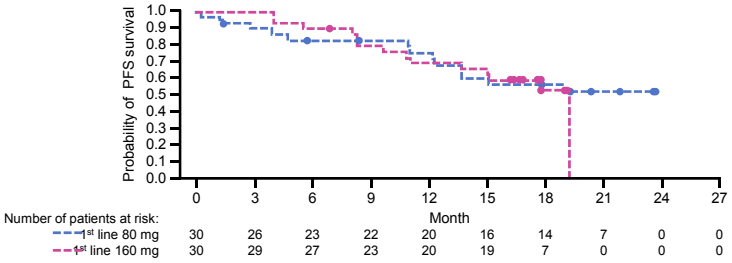
	80 mg n=30	160 mg n=30	Total N=60
Confirmed ORR	67% (95% CI 47, 83)	87% (95% CI 69, 96)	77% (95% CI 64, 87)
Disease control rate*	93% (95% CI 78, 99)	100% (95% CI 88, 100)	98% (95% CI 89, 100)
Best objective response			
Complete response	0	2	2
Partial response	20	24	44
Stable disease ≥6 weeks	8	4	12
Progressive disease	2	0	2

Population: evaluable for response; data cut-off: 4 January 2016 RECIST 1.1, programmatically calculated from investigator-recorded tumour measurement
*Complete response, partial response, stable disease
CI, confidence interval; D, discontinuation; ORR, objective response rate

EUROPEAN LUNG CANCER CONFERENCE 2016

Presented by Suresh S Ramalingam at the 6th IASLC/ESMO European Lung Cancer Conference, 13–16 April 2016, Geneva, Switzerland; Abstract LBA1_PR.

PFS in osimertinib EGFRm first-line cohorts (investigator assessed)



	80 mg n=30	160 mg n=30	Total N=60
Median PFS,* months (95% CI)	NC (12.3, NC)	19.3 (11.1, 19.3)	19.3 (13.7, NC)
Remaining alive and progression-free,† % (95% CI)			
12 months	75 (55, 88)	69 (49, 83)	72 (59, 82)
18 months	57 (36, 73)	53 (32, 70)	55 (41, 67)

Population: safety analysis set; data cut-off: 4 January 2016
Progression events that do not occur within 14 weeks of the last evaluable assessment (or first dose) are censored
Circles on the Kaplan-Meier plot denote censored observations
*Progression-free survival is the time from date of first dosing until the date of objective disease progression or death
†Calculated using the Kaplan-Meier technique

elcc

EUROPEAN LUNG CANCER CONFERENCE 2016
Presented by Suresh S Ramalingam at the 6th IASLC/ESMO European Lung Cancer Conference, 13–16 April 2016, Geneva, Switzerland; Abstract LBA1_PR.

Osimertinib activity in patients with leptomeningeal disease from non-small cell lung cancer: updated results from the BLOOM study

James Chih-Hsin Yang[1], Dong-Wan Kim[2], Sang-We Kim[3], Byoung Chul Cho[4], Jong Seok Lee[5], Xin Ye[6], Xiaolu Yin[6], Zhenfan Yang[6], Haiyi Jiang[6], Myung-Ju Ahn[7]

[1]National Taiwan University Hospital, Taipei, Taiwan;
[2]Seoul National University Hospital, Seoul, Republic of Korea;
[3]Asan Medical Center, Seoul, Republic of Korea;
[4]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea;
[5]Seoul National University, Bundang Hospital, Seongnam, Republic of Korea;
[6]Astrazeneca, Shanghai, China; [7]Samsung Medical Center, Seoul, Republic of Korea

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented by: James Chih-Hsin Yang Abstract 9002

BLOOM study design: osimertinib LM cohort 1

Study cohort objectives – cohort 1: EGFRm NSCLC and LM

To assess the safety and tolerability of osimertinib in patients with LM

First patient dosed: April 14, 2015

Osimertinib LM cohort 1

Advanced or metastatic EGFRm NSCLC and confirmed diagnosis of LM by positive CSF cytology

Key inclusion criteria:

- Primary tumor with EGFR L858R or exon 19 deletion
- Prior EGFR-TKI treatment
- ECOG PS 0–2
- Stable extracranial disease
- At least one LM lesion by MRI scan

Osimertinib 160 mg QD

Data cut-off: March 10, 2016

Assessments

- Adverse events*
- Efficacy assessment:
  - OS
  - Brain MRI and extracranial MRI or CT scan*†
  - CSF cytology
  - Neurological exam*
  - CNS symptoms*
- PK in CSF
- Quantification of EGFRm DNA in CSF

*As assessed by study investigator; †modified RECIST for CNS disease; RECIST 1.1 for extracranial disease. CT/MRI, CSF cytology and neurological exam frequency every 6 weeks. 1 cycle = 21 days of continuous dosing. CSF, cerebrospinal fluid; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group Performance Status MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria In Solid Tumors

NCT02228369

Patient demographics: osimertinib LM cohort 1

- All 21 patients were Asian with adenocarcinoma histology
- Two patients had T790M detected in CSF at study entry; 6 patients had T790M detected in plasma
- Duration of treatment: 1–49 weeks ongoing
- Twenty-one patients dosed; 15 patients are ongoing treatment
  - Safety analysis: n=21
  - Efficacy analysis n=21*

Characteristic, n	N=21
Gender: male / female	6 / 15
Age: median (range), years	59.0 (44–75)
Smoking status: current / former / never	1 / 5 / 15
ECOG PS: 0 / 1 / 2	1 / 11 / 9
Neurological assessment at baseline: normal / abnormal	11 / 10
Prior lines of systemic therapy: median (range)	3.0 (1–8)
Prior whole brain radiotherapy	11
Prior EGFR-TKIs†: gefitinib / erlotinib / dacomitinib / HM61713 (BI 1482694)	16 / 3 / 1 / 1
Prior systemic response to EGFR-TKI: partial response / stable disease / progressive disease	14 / 6 / 1
Tumor tissue EGFRm mutation status (local test)‡: Ex19Del / L858R	9 / 13

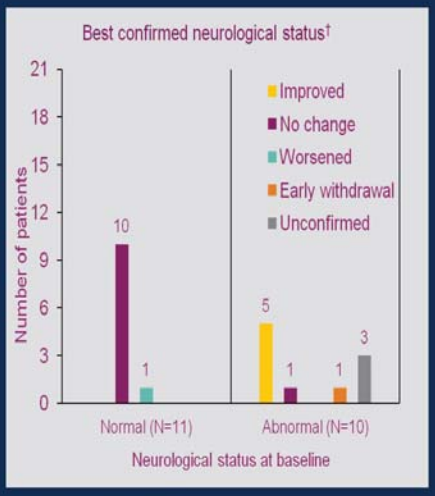
*Efficacy analysis set included all dosed patients; †One patient received two lines of therapy: gefitinib and HM61713; ‡One patient had both Ex19Del and L858R detected at baseline. Ex19del, exon 19 deletion

Osimertinib activity across LM assessments

Efficacy assessments were conducted on 21 patients

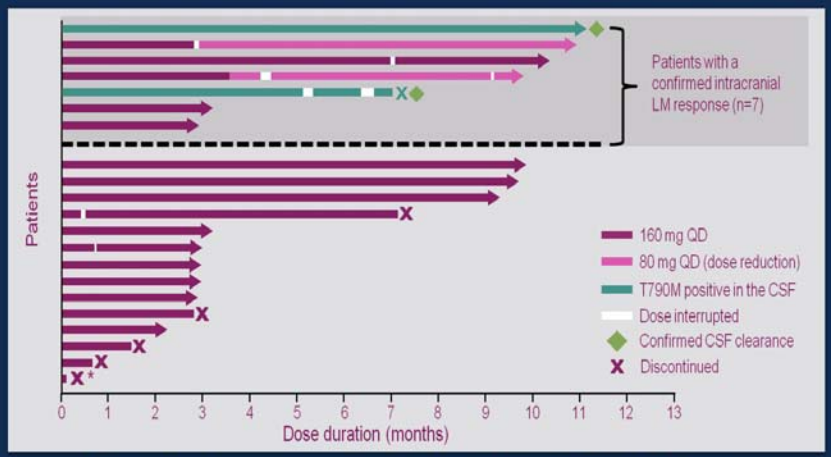
- Seven patients had confirmed* radiological improvement
- Two patients had confirmed* CSF cytology clearance; no tumor cells were detected in two consecutive CSF samples
- Five patients had confirmed* improved neurological function

Best MRI imaging intracranial response, n (%)	N=21	
	Confirmed*	Unconfirmed
Responding	7 (33)	1 (5)
Stable disease	9 (43)	2 (10)
Early withdrawal	2 (10)	



Population: efficacy, n=21 *Response confirmation was done at least 4 weeks after the initial response; †Response assessed by neurological examination

Time on treatment



Fifteen patients are ongoing treatment at time of data cut-off (March 10, 2016)
7 of whom have been on treatment for >9 months

*Patient died due to aspiration pneumonia. Arrows represent observations at the time of data cut-off.
Two patients experienced AEs leading to dose reduction: one patient had skin pruritus and one patient had neutropenia

Conclusions

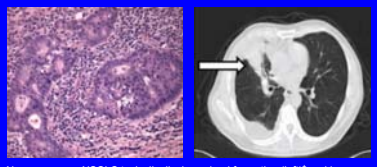
- Preclinical data indicate that osimertinib crosses the BBB
- Osimertinib shows encouraging preliminary safety, tolerability and activity in pre-treated patients with EGFRm advanced NSCLC and LM
  - The AE profile is as expected and manageable
  - Neurological function improved from baseline in 5 patients
  - Radiological improvements in LM were seen in 7 patients
  - Clearance of tumor cells from the CSF occurred in 2 patients at 2 consecutive visits
  - Time on treatment suggests durable clinical benefit, with 15 patients remaining on treatment, 7 of whom have been on treatment for >9 months
- Further evaluation of osimertinib in this setting is warranted
- The BLOOM study is ongoing and a cohort enrolling patients with T790M positive NSCLC and LM is open; T790M status is based on testing of an extracranial tumor or plasma sample

Presented by: James Chih-Hsin Yang

Stage IV NSCLC - Immunotherapies

Comparative Studies of Nivolumab Vs Docetaxel in 2nd Line NSCLC

NON-SQUAMOUS NSCLC*

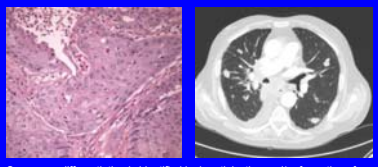


Non-squamous NSCLC typically displays gland formation (left)† and is normally found in the outer parts of the lung (right). Arrow indicates location of disease.‡2,3

CHECKMATE 057[1,6]

Phase 3 study of nivolumab vs docetaxel in patients with metastatic non-squamous NSCLC with progression on or after platinum-based chemotherapy (N=582)

SQUAMOUS NSCLC*



Squamous differentiation is identified by keratinization and/or formation of intercellular bridges (left),† typically occurs in cells that line the inside of the airways in the lungs, and tends to be found in the middle of the lungs (right).§2,4

CHECKMATE 017[1,7]

Phase 3 study of nivolumab vs docetaxel in patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy (N=272)

ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer.

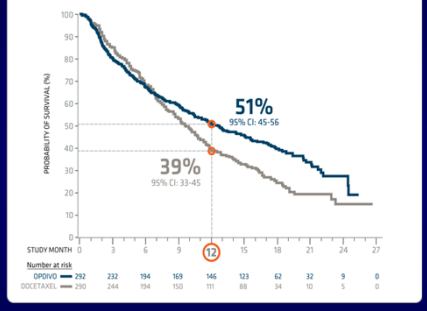
* For each histology, immunohistochemistry (IHC) is shown on the left and computed tomography (CT) is shown on the right.
† Images adapted from: Dubinski W et al. *Pulm Med.* 2012;2012:249082. DOI: 10.1155/2012/249082.
‡ Image adapted from: Bai C et al. *Oncol Lett.* 2013;5(5):1559-1561. DOI: 10.3892/ol.2013.1263.
§ Image adapted from: Cedres S et al. *Case Rep Med.* 2012;2012;947524. DOI: 10.1155/2012/947524.

2

Nivolumab Delivered Superior Overall Survival

NON-SQUAMOUS

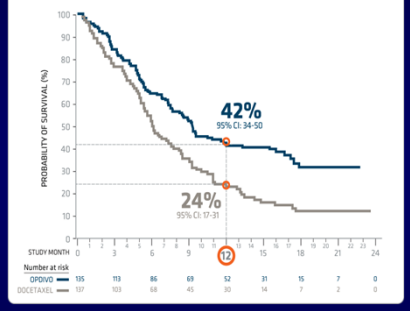
CHECKMATE 057: Overall Survival[1,6]



- Median OS was 12.2 months (95% CI: 9.7–15.0) for Nivo and 9.4 months (95% CI: 8.0–10.7) for docetaxel, HR=0.73 (95% CI: 0.60–0.89, *P*=0.0015)
- CHECKMATE 057 results were based on the prespecified interim analysis when 413 events (93% of the planned number of events for final analysis) were observed

SQUAMOUS

CHECKMATE 017: Overall Survival[1,7]



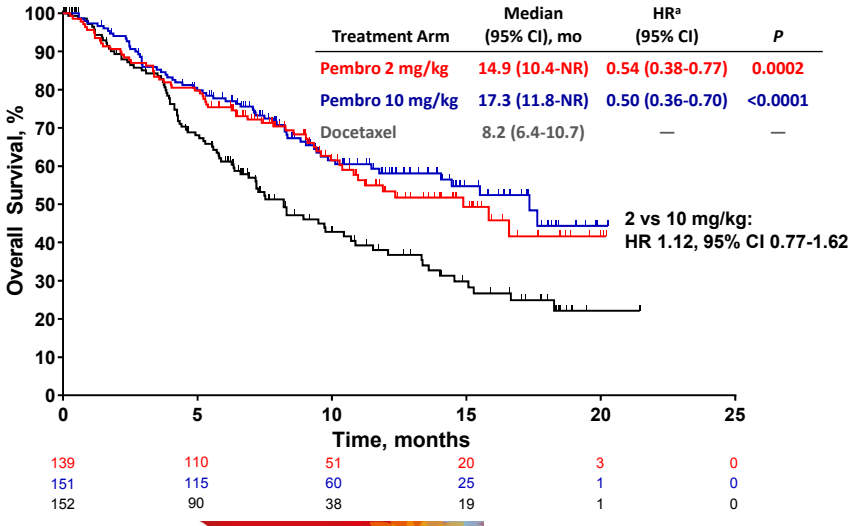
- Median OS was 9.2 months (95% CI: 7.3–13.3) for Nivo and 6 months (95% CI: 5.1–7.3) for docetaxel, HR=0.59 (95% CI: 0.44–0.79, *P*=0.00025)
- CHECKMATE 017 results were based on the prespecified interim analysis when 199 events (86% of the planned number of events for final analysis) were observed

* Vs docetaxel.
CI=confidence interval; HR=hazard ratio; OS=overall survival; PD-L1=programmed death ligand 1.

Please see Important Safety Information throughout this presentation.

30

KEYNOTE-010: OS, PD-L1 TPS ≥50% Stratum



Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	14.9 (10.4-NR)	0.54 (0.38-0.77)	0.0002
Pembro 10 mg/kg	17.3 (11.8-NR)	0.50 (0.36-0.70)	<0.0001
Docetaxel	8.2 (6.4-10.7)	—	—

2 vs 10 mg/kg:
HR 1.12, 95% CI 0.77-1.62

SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

Phase III Study Showed Genentech's Cancer Immunotherapy TECENTRIQ™ (Atezolizumab) Helped People with a Specific Type of Lung Cancer Live Significantly Longer Compared to Chemotherapy

TECENTRIQ showed significant improvement in overall survival for people regardless of their PD-L1 status

Data will be discussed with global health authorities, including the U.S. Food and Drug Administration (FDA)

South San Francisco, CA -- August 31, 2016 --

Keynote – 010 – Abstract 9015

	PD-L1 status			
TPS	1-24%	25-49%	50-74%	75-100%
Prevalence (%)	47	11	15	27
ORR (%)	9	16	23*	33*
PFS HR^	1.08	0.95	0.78	0.52*
OS HR^	0.74*	0.86	0.58*	0.51*

- * p < 0.05, ^ HR relative to the control arm of docetaxel
- Median survival for the TPS 50-74% and 75-100% was 15.8 and 16.6 mos, respectively

Keynote – 010 – Abstract 9015

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PRESENTED AT: ASCO ANNUAL MEETING '16
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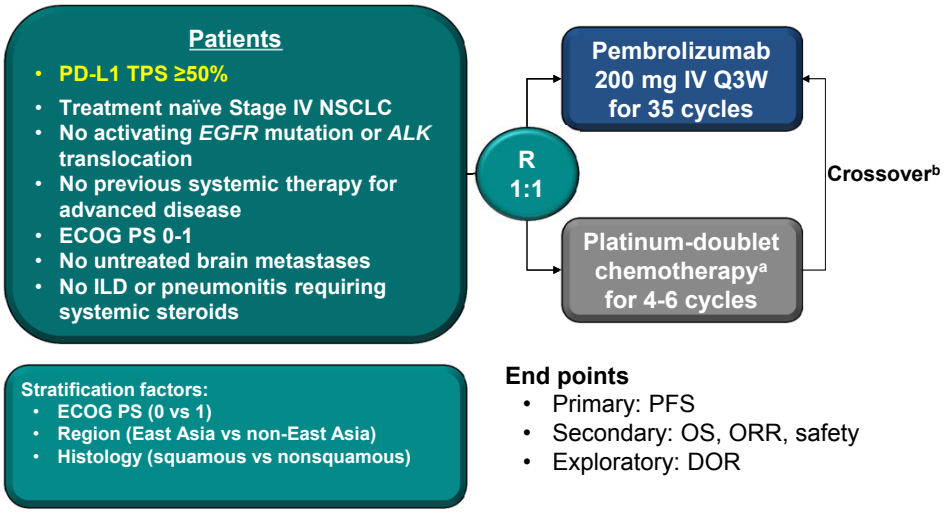
Presented by:

KEYNOTE-024: Study Design in 1st line Treatment of Advanced NSCLC



End points
- Primary: PFS
- Secondary: OS, ORR, safety
- Exploratory: DOR

[a]Investigator's choice of carboplatin or cisplatin + pemetrexed, carboplatin or cisplatin + gemcitabine, or carboplatin + paclitaxel. Pemetrexed-containing regimens permitted only for patients with nonsquamous histology; patients could continue pemetrexed as maintenance therapy.
[b]Crossover from chemotherapy to pembrolizumab was permitted for patients who had disease progression verified by blinded, independent central review and who met safety criteria.
ClinicalTrials.gov identifier NCT02142738.

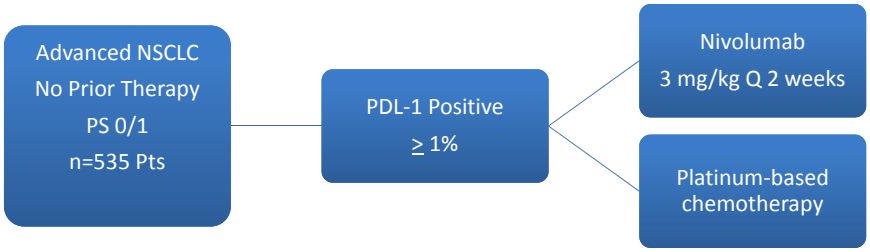
Merck's KEYTRUDA® (pembrolizumab) Demonstrates Superior Progression-Free and Overall Survival Compared to Chemotherapy as First-Line Treatment in Patients with Advanced Non-Small Cell Lung Cancer

KEYNOTE-024 Studied Patients Whose Tumors Expressed High Levels of PD-L1

- Phase III randomized, pivotal trial
- Treatment naïve stage IV NSCLC patients (n=305)
- Pembrolizumab 200 mg q wks vs standard of care platinum-based doublets (bevacizumab not allowed)
- 1^0 endpoint – PFS, 2^0 endpoints – OS, ORR
- Trial demonstrated superior PFS and OS for pembrolizumab

Business Wire, June 16, 2016 06:45 AM Eastern Daylight Time

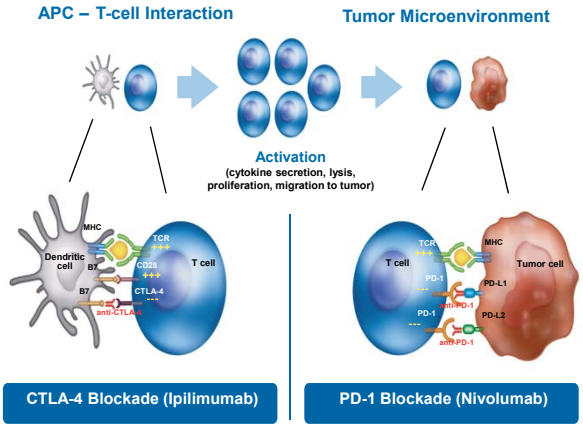
CheckMate 026 Trial



Primary endpoint: PFS

NCT02041533

Ipilimumab and Nivolumab Mechanism of Action



- CTLA4 is expressed on T-cells and inhibits T-cell activation[7]
- Ipilimumab disrupts the CTLA-4 pathway, thus inducing anti-tumor immunity[7]
- PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function. Nivolumab disrupts PD-1 pathway signaling and restores antitumor T-cell function[7-12]

PRESENTED AT: ASCO Annual '15 Meeting

CheckMate 012: Safety and Efficacy of First-line Nivolumab and Ipilimumab in Advanced NSCLC

Matthew D. Hellmann,[1] Scott N. Gettinger,[2] Jonathan Goldman,[3] Julie Brahmer,[4] Hossein Borghaei,[5] Laura Q. Chow,[6] Neal E. Ready,[7] David E. Gerber,[8] Rosalyn Juergens,[9] Frances A. Shepherd,[10] Scott A. Laurie,[11] Tina Young,[12] William J. Geese,[12] Shruti Agrawal,[12] Xuemei Li,[12] Scott J. Antonia[13]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Yale Comprehensive Cancer Center, New Haven, CT, USA; [3]UCLA, Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [4]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [5]Fox Chase Cancer Center, Philadelphia, PA, USA; [6]University of Washington, Seattle, WA, USA; [7]Duke University Medical Center, Durham, NC, USA; [8]UT Southwestern Medical Center, Dallas, TX, USA; [9]Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; [10]Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; [11]Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, ON, Canada; [12]Bristol-Myers Squibb, Princeton, NJ, USA; [13]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

PRESENTED AT: ASCO ANNUAL MEETING '16

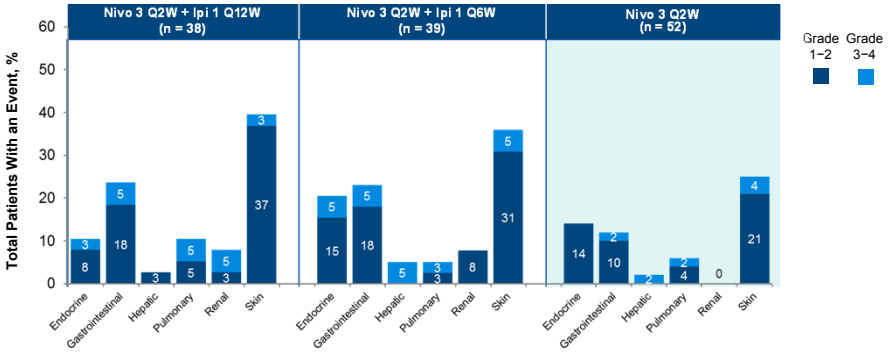
Abstract 3001

Nivolumab Plus Ipilimumab in First-line NSCLC: Baseline Patient Characteristics

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)	Nivo 3 Q2W + Ipi 1 Q6W (n = 39)
Median age, years (range)	68 (50–91)	62 (47–87)
Male, %	45	62
Non-squamous histology, %	82	85
Disease stage, %		
Stage IIIB	11	3
Stage IV	89	97
ECOG PS, %		
0	32	41
1	68	54
Smoking status, %		
Never	5	23
Former/current	95	74
***EGFR* mutation status, %**		
Mutant	11	10
Wildtype	74	67
Unknown	16	23
PD-L1 quantifiable, N (%)	31 (82)	30 (77)
≥1%, n/N (%)	21/31 (68)	23/30 (77)
≥5%, n/N (%)	16/31 (52)	19/30 (63)
≥10%, n/N (%)	13/31 (42)	15/30 (50)
≥25%, n/N (%)	10/31 (32)	8/30 (27)
≥50%, n/N (%)	6/31 (19)	7/30 (23)

5

Nivolumab Plus Ipilimumab in First-line NSCLC: Treatment-related Select AEs



- All treatment-related pulmonary events were pneumonitis
- Grade 1–2 hypersensitivity/infusion reaction occurred in 5% and 6% of patients in the nivo 3 Q2W + ipi 1 Q12W and monotherapy groups, respectively

Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock
Select AEs are those with potential immunologic etiology that require frequent monitoring/intervention

7

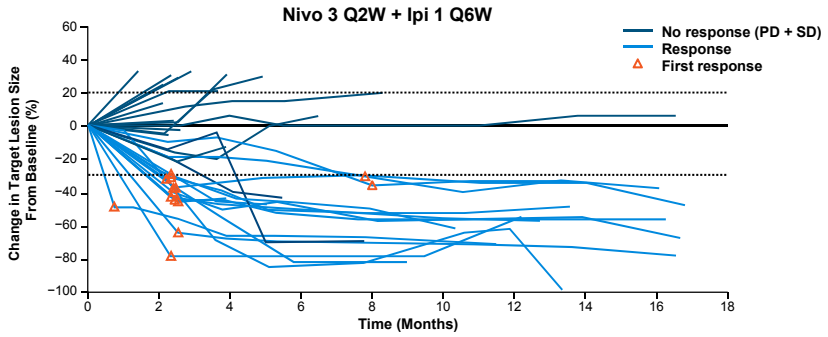
Nivolumab Plus Ipilimumab in First-line NSCLC: Summary of Efficacy

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)	Nivo 3 Q2W + Ipi 1 Q6W (n = 39)	Nivo 3 Q2W (n = 52)
Confirmed ORR, % (95% CI)	**47** (31, 64)	**39** (23, 55)	**23** (13, 37)
Median duration of response, mo (95% CI)	NR (11.3, NR)	NR (8.4, NR)	NR (5.7, NR)
Median length of follow-up, mo (range)	12.9 (0.9–18.0)	11.8 (1.1–18.2)	14.3 (0.2–30.1)
Best overall response, %			
Complete response	0	0	8
Partial response	47	39	15
Stable disease	32	18	27
Progressive disease	13	28	38
Unable to determine	8	15	12
Median PFS, mo (95% CI)	8.1 (5.6, 13.6)	3.9 (2.6, 13.2)	3.6 (2.3, 6.6)
1-year OS rate, % (95% CI)	NC	69 (52, 81)	73 (59, 83)

NC = not calculated (when >25% of patients are censored); NR = not reached
Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock except for OS data, which are based on an August 2015 database lock

8

Nivolumab Plus Ipilimumab in First-line NSCLC: Kinetics of Response

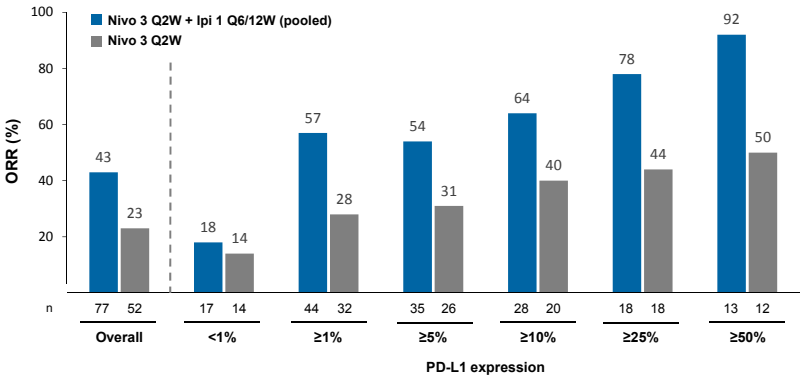


- 12/15 responders (80%) in the Q6W arm and 14/18 responders (78%) in the Q12W arm had a response by time of first scan (week 11)
- 12/15 responders (80%) in the Q6W arm and 12/18 responders (67%) in the Q12W arm had an ongoing response at time of database lock

PD = progressive disease; SD = stable disease
Includes all patients with baseline target lesion and ≥1 post-baseline assessment of target lesion (n = 33)

9

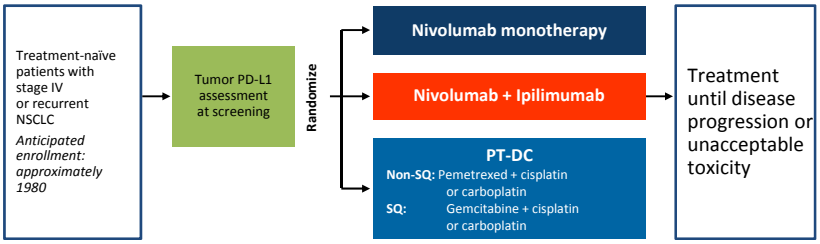
Nivolumab Plus Ipilimumab in First-line NSCLC: Efficacy Across All Tumor PD-L1 Expression Levels



Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock

11

CheckMate 227 (NCT02477826): Study Design



Primary endpoints
- OS
- PFS

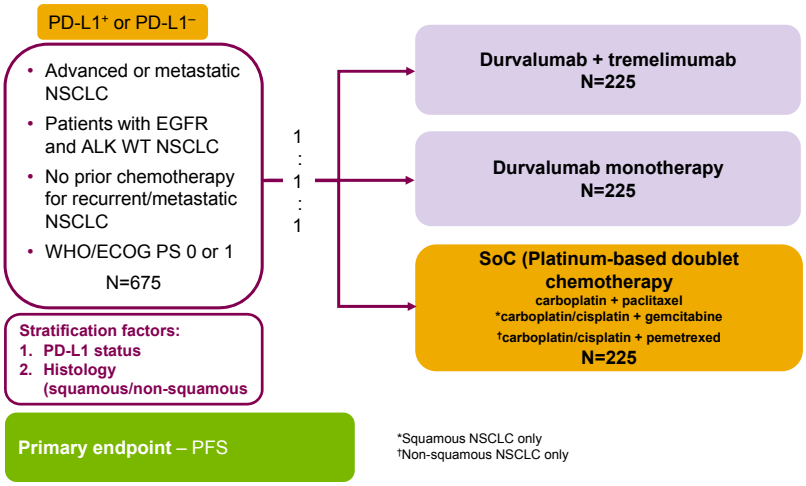
Secondary endpoints
- ORR
- Disease-related symptom improvement (measured using LCSS)

63

MYSTIC: NSCLC

MYSTIC study design

Phase 3, randomised, open-label, global, multicentre first-line study



Primary endpoint – PFS

*Squamous NSCLC only
†Non-squamous NSCLC only

D419AC00001
ClinicalTrials.gov. Available at: http://www.clinicaltrials.gov/ct2/show/NCT02453282
Rizvi N, et al. Poster presented at SiTC 2015. Poster 181

64 MedImmune

See slide notes for additional study details

Durvalumab is an investigational drug and is not approved for use in any country

ARCTIC: NSCLC

ARCTIC study design

Phase 3, randomised, open-label, multicentre third-line study

- EGFR/ALK WT NSCLC patients (Stage IIIb/IV)
- At least two prior systemic treatment regimens
- Disease progression or recurrence after both a platinum-based chemotherapy regimen and at least one additional systemic therapy
- Confirmed PD-L1 status by a specified immunohistochemistry assay on a recent sample (≤3 months), if technically feasible, **AND** an archived tumour tissue block or newly cut unstained slides, if available

N=900

Sub-study A PD-L1+ (1 : 1)
- **SoC** (vinorelbine, gemcitabine, erlotinib)
- **Durvalumab monotherapy**

Sub-study B PD-L1- (3 : 2 : 2 : 1)
- **Durvalumab + tremelimumab combo**
- **SoC** (vinorelbine, gemcitabine, erlotinib)
- **Durvalumab monotherapy**
- **Tremelimumab monotherapy**

Co-primary endpoints – PFS and OS
- Primary comparisons: monotherapy vs SoC and combo vs SoC

See slide notes for additional study details

D4191C00004

ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT02352948

Planchard D, et al. Poster presented at ASCO 2015. Poster TPS8104

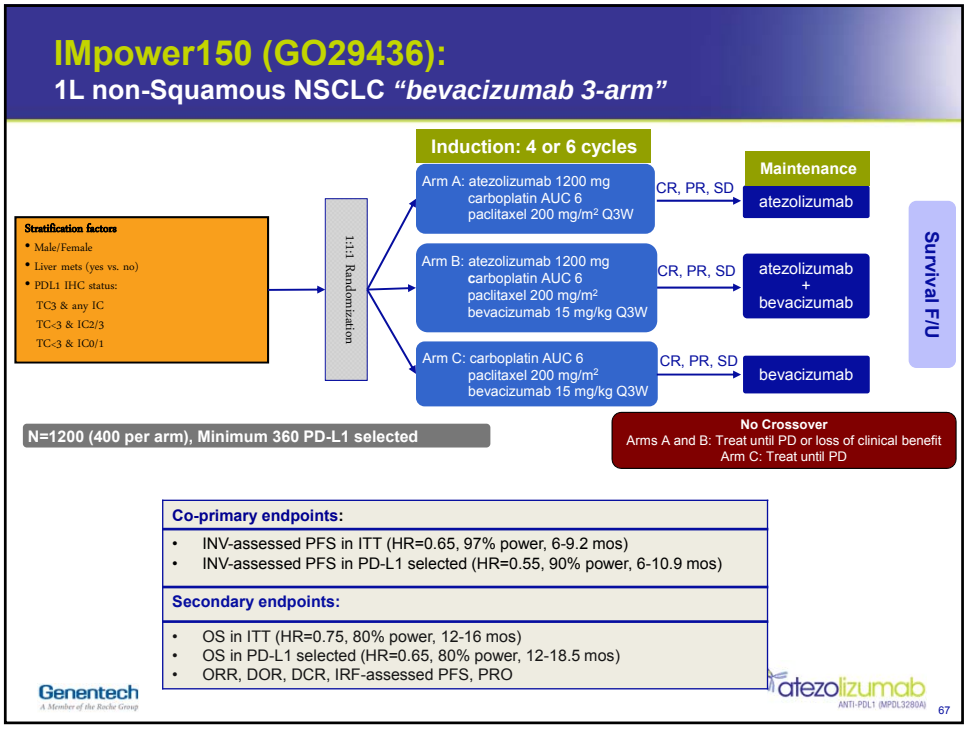
65 MedImmune

Durvalumab is an investigational drug and is not approved for use in any country

1L NSCLC Strategic Context & Clinical Development Plan

- **The 1L and adjuvant CDP was developed in order to:**
  - Confirm the benefit atezolizumab as monotherapy in the PD-L1 selected subset TC3 or IC3
  - Confirm the benefit of atezolizumab when added to chemotherapy in an all comer population

Study #	Histology	Population	Treatment Arms	N	1° EP
Monotherapy					
IMpower110 GO29431	Non-squamous	TC3 or IC3	atezo vs. carbo or cis/pem	400	Inv PFS
IMpower111 GO29432	Squamous	TC3 or IC3	atezo vs. cis/carbo + gem	400	Inv PFS
Chemotherapy Combination					
IMpower150 GO29436	Non-squamous	All Comers (TC3 or IC2/3)	atezo/carbo/pac vs. atezo/carbo/pac/bev vs. carbo/pac/bev	1200	Inv PFS ITT Inv PFS Dx+
IMpower130 GO29537	Non-squamous	All Comers (TC3 or IC2/3)	atezo/carbo/nab-p vs. carbo/nab-p	550	Inv PFS ITT Inv PFS Dx+
IMpower131 GO29437	Squamous	All Comers (TC3 or IC2/3)	atezo/carbo/pac vs. atezo/carbo/nab-p vs. carbo/nab-p	1200	Inv PFS ITT Inv PFS Dx+
IMpower132 GO29438	Non-squamous	All Comers (TC3 or IC2/3)	atezo/pem/carbo or cis vs. pem/carbo or cis	680	Inv PFS ITT Inv PFS Dx+
Adjuvant					
IMpower010 GO29427	All	TC3 or IC3	atezo vs. BSC	845	DFS


IMpower150 (GO29436):
1L non-Squamous NSCLC "bevacizumab 3-arm"
Induction: 4 or 6 cycles
Maintenance
Stratification factors
• Male/Female
• Liver mets (yes vs. no)
• PDL1 IHC status:
TC3 & any IC
TC-3 & IC2/3
TC-3 & IC0/1
1:1:1 Randomization
Arm A: atezolizumab 1200 mg carboplatin AUC 6 paclitaxel 200 mg/m² Q3W
CR, PR, SD
atezolizumab
Arm B: atezolizumab 1200 mg carboplatin AUC 6 paclitaxel 200 mg/m² bevacizumab 15 mg/kg Q3W
CR, PR, SD
atezolizumab + bevacizumab
Arm C: carboplatin AUC 6 paclitaxel 200 mg/m² bevacizumab 15 mg/kg Q3W
CR, PR, SD
bevacizumab
Survival F/U
N=1200 (400 per arm), Minimum 360 PD-L1 selected
No Crossover
Arms A and B: Treat until PD or loss of clinical benefit
Arm C: Treat until PD
Co-primary endpoints:
• INV-assessed PFS in ITT (HR=0.65, 97% power, 6-9.2 mos)
• INV-assessed PFS in PD-L1 selected (HR=0.55, 90% power, 6-10.9 mos)
Secondary endpoints:
• OS in ITT (HR=0.75, 80% power, 12-16 mos)
• OS in PD-L1 selected (HR=0.65, 80% power, 12-18.5 mos)
• ORR, DOR, DCR, IRF-assessed PFS, PRO
Genentech
A Member of the Roche Group
atezolizumab
ANTI-PDL1 (MPDL3280A)
67

Thank you

Advanced Thyroid Cancer Update: Successes and New Challenges

Marcia Brose, MD, PhD
Director, Center for Rare Cancers and Personalized Therapy
Associate Professor, Department of Otorhinolaryngology: Head and Neck Surgery
Department of Internal Medicine, Division of Hematology and Oncology
University of Pennsylvania, Perelman School of Medicine, Abramson Cancer Center

Advanced Thyroid Cancer Update: Successes and New Challenges

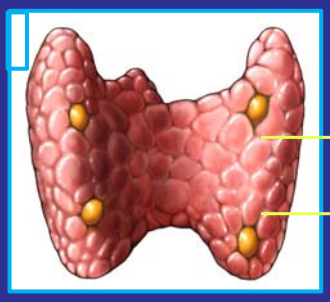
Marcia S. Brose MD PhD
Associate Professor
Director, Thyroid Cancer Therapeutics
Director, Center for Rare Cancers and Personalized Therapy
Associate Professor
Department of Otorhinolaryngology: Head and Neck Cancer
Department of Medicine, Division of Hematology/Oncology
Abramson Cancer Center
The University of Pennsylvania
Philadelphia, PA

Disclosures

- Companies: AstraZeneca, Bayer/Onyx, Eisai, Exelixis, Novartis, Roche/Genentech, Bristol-Myers Squibb
- Relationships: Advisory board consultant, honoraria, research grants, and primary investigator

2

Thyroid cancer: clinical pathology



Follicular cells → Differentiated → Papillary (87%)
Differentiated → Follicular (6%)
Differentiated → Hürthle cell (3%)
Follicular cells → Anaplastic (1%)
Parafollicular cells → Medullary (2%)

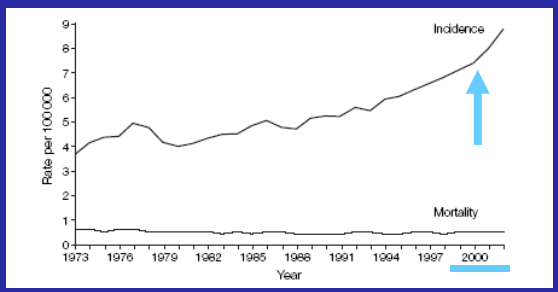
NOTE: Primary Thyroid Lymphoma is most often MALT but can be aggressive and is most often associated with Hashimotos Thyroiditis

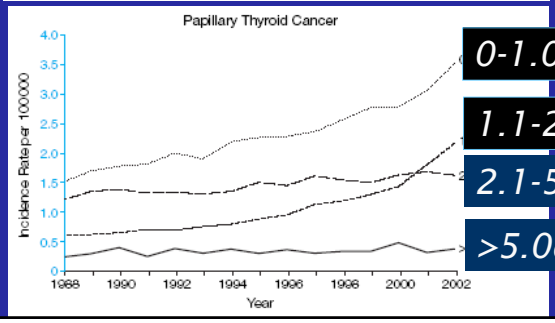
Treatment of Differentiated Thyroid Cancer includes:
- **Surgery – thyroidectomy**
- **Radioactive iodine**
- **Thyroid stimulating hormone (TSH) suppression**

Carling T and Uldesman R. *Cancer of the Endocrine System: Section 2: Thyroid Cancer.* Principles of Clinical Oncology. 7th edition. Lippincott Williams and Wilkins. 2005.

Howlader N et al. SEER Cancer Statistics Review; http://seer.cancer.gov/statfacts/html/thyro.html.

Thyroid cancer in the United States





Davies, JAMA 2006 295:2164

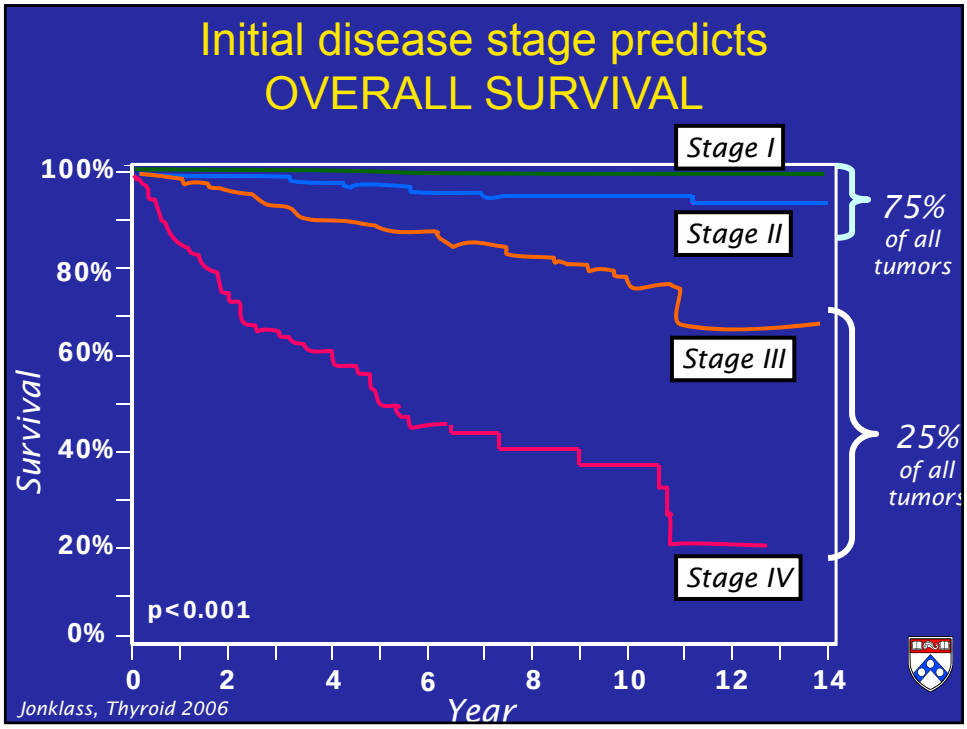
AJCC/TNM 6th edition

- Tumor (primary only)
  - T1 ≤ 2cm
  - T2 2-4cm
  - T3 > 4cm or microextrathyroidal
  - T4 extrathyroidal
- Distant mets
  - M0 none
  - M1 present
- Nodal metastases
  - N0
  - N1a Level VI
  - N1b Levels II-V or VII

MSB
05/09/08

AJCC/TNM

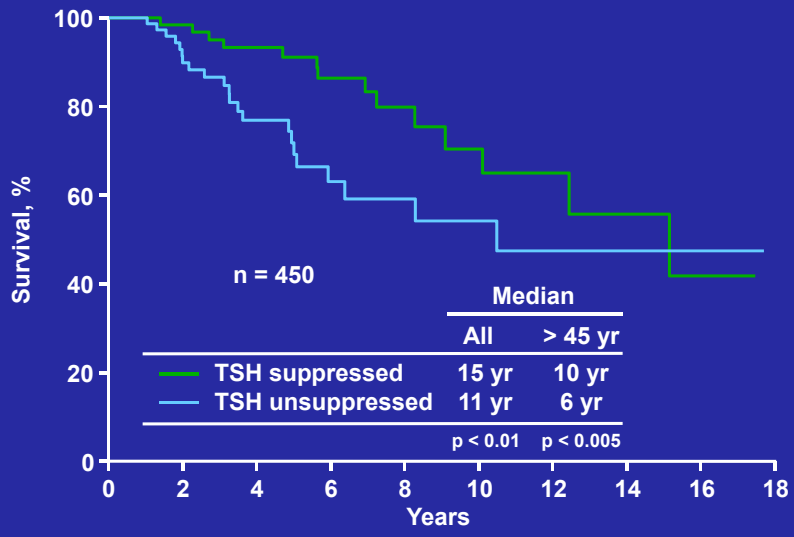
Stage	<45 y.o.	≥ 45 y.o.
I	Any T, any N, M0	T1, N0, M0
II	Any T, any N, M1	T2, N0, M0
III		T3, N0, M0 T1-T3, N1a, M0
IVa		T4a, any N, M0 T1-T3, N1b, M0
IVb		T4b, any N, M0
IVc		Any T, any N, M1



Differentiated Thyroid Cancer: Treatment Strategy

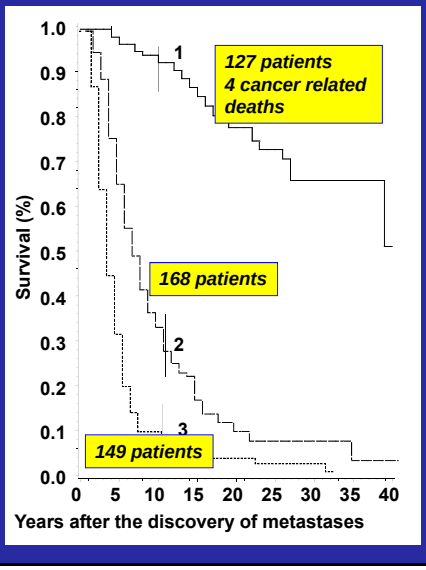
- High Risk: (Age >45, male, metastasis, extrathyroidal extension, >4cm)
  - Total Thyroidectomy
  - **RAI (^{131}I) Ablation**
  - **TSH Suppression Therapy with Thyroid Hormone**
  - Follow Serial Thyroglobulin Levels (Tg)
  - XRT for recurrent local disease/positive margins
  - Surveillance: NeckUS, Tg, Neck MRI, Chest CT, RAI Whole body scan, FDG-PET

TSH Suppression Improves Survival for DTC Patients With Metastases



Jonklaas et al. *Thyroid.* 2006;16:1299-1242.

Survival and Response to Treatment



- Group 1: initial ^{131}I uptake and CR
  - Age < 40 years
  - Well-differentiated cancer
  - Small size of metastases
- Group 2: initial ^{131}I uptake and persistent disease
- Group 3: no initial ^{131}I uptake

Durante et al. *J Clin Endocrinol Metab.* 2006;91:2892-2899.

RAI-Refractory Disease

- 25-50% of Metastatic Thyroid Cancers loose ability to take up Iodine
- This is attributed to down regulation of the Na+/I- Symporter (NIS) and other genes of NaI metabolism
- This results directly in a loss of overall survival

RAI-refractory disease: criteria

- We need to educate oncologists and endocrinologists when to refer patients to oncologists for treatment.
- RAI refractory means that there are **progressing lesions** that **do not take up RAI** (Note: there may still be some that do)
  - RAI uptake scan is negative and CT scan shows nodules
  - RAI uptake scan has uptake but not in some nodules that are progressing
  - Patient has exceeded total lifetime dose of 600 mCi

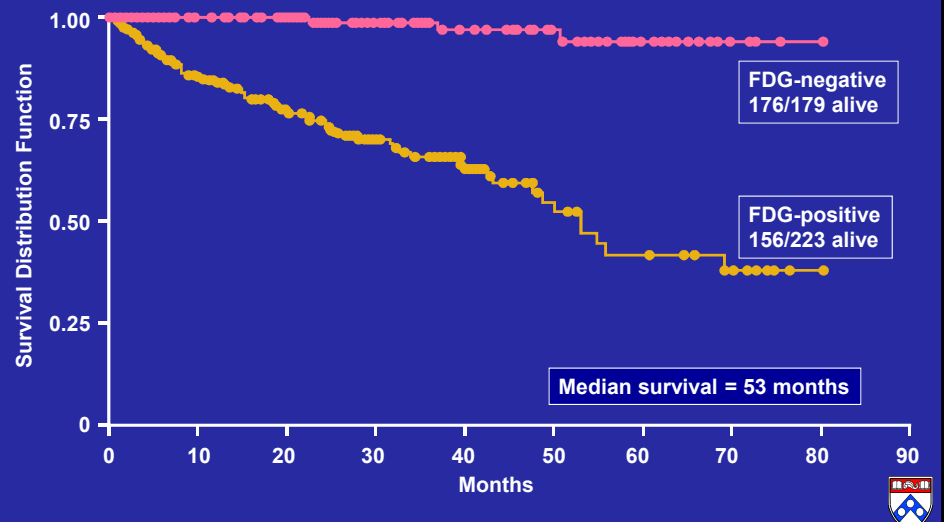
Cooper DS, et al. Thyroid. 2009;9:1[illegible]4.
Hodak SP, Carty SE. Oncology. 2009;23:775-6.
Mehra R, Cohen RB. Hematol Oncol Clin North Am. 2008;22:1279-95,xi.

Radioactive Iodine (RAI)-Refractory Differentiated Thyroid Cancer (DTC)

- It is estimated[1] that in the USA in 2013 there were:
  - >60 000 new cases of thyroid cancer, and
  - 1850 deaths due to thyroid cancer
- **In approximately 5–15% of patients with thyroid cancer, the disease becomes refractory to RAI[2,3]**
- **Median survival for patients with RAI-refractory DTC and distant metastases is estimated to be 2.5–3.5 years[4,5]**
- Patients suffer multiple complications associated with disease progression
- In 2013 the first kinase inhibitor sorafenib was approved for RAI refractory progressive DTC

1. Howlader N et al. SEER Cancer Statistics Review; http://seer.cancer.gov/statfacts/html/thyro.html;
2. Xing M et al. Lancet 2013; 381:1058–69; 3. Pacini F et al. Expert Rev Endocrinol Metab 2012;7:541–54;
4. Durante C et al. J Clin Endocrinol Metab 2006;91:2892–99. 5. Robbins RJ et al. J Clin Endocrinol Metab 2006;91:498–505.

FDG-PET Predicts Survival in Patients With Metastatic Thyroid Cancer

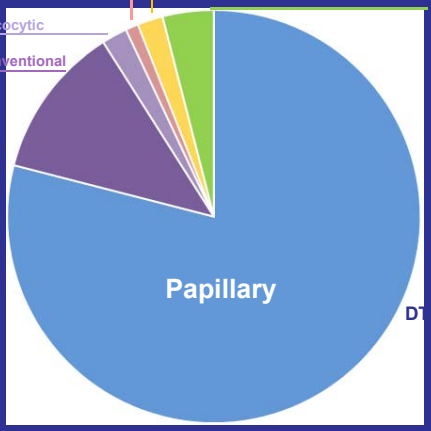


Robbins et al. *J Clin Endocrinol Metab.* 2006;91:498-505.

Genetics of Differentiated Thyroid Cancer: aberrant intracellular signaling

Poorly differentiated
- ***RAS* (25–30%)**
- *TP53* (20–30%)
- *CTNNB1* (10–20%)
- ***BRAF* (10–15%)**

Follicular
Mutations in 70–75%
- ***RAS* (40–50%;** lower in oncocytic)
- *PAX8/PPARγ* (30–35%; lower in oncocytic)
- *TP53* (21%)
- *PTEN* (8%)
- *PIK3CA* (7%)
- ***BRAF* (2%)**

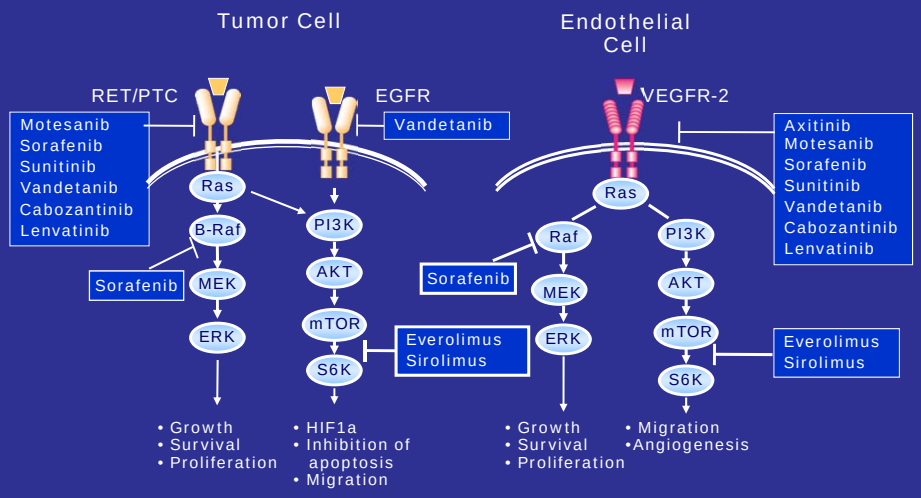


Papillary
Mutations identified in ~70%
- ***BRAF*[a] (40–50%)**
- ***RAS*[b] (7–20%)**
- *RET/PTC* (clonal; 10–20%)
- *EGFR* (5%)
- *TRK* (<5%)
- *PIK3CA* (2%)

Papillary
Follicular - Conventional
Follicular - Oncocytic (Hürthle cell)
Poorly differentiated
Anaplastic
Medullary

[a]***BRAF* mutations** are mostly V600E; 1–2% are K601E and others
[b]***RAS*** includes *N-*, *H-*, and *K-RAS* (predominantly *NRAS* and *HRAS* codon 61)
Nikiforov YE et al. Arch Pathol Lab Med 2011;135:569–77; COSMIC database – Catalog of Somatic Mutations in Cancer (as of February 22, 2013) http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/

Targeting Cell Signaling in Thyroid Cancer



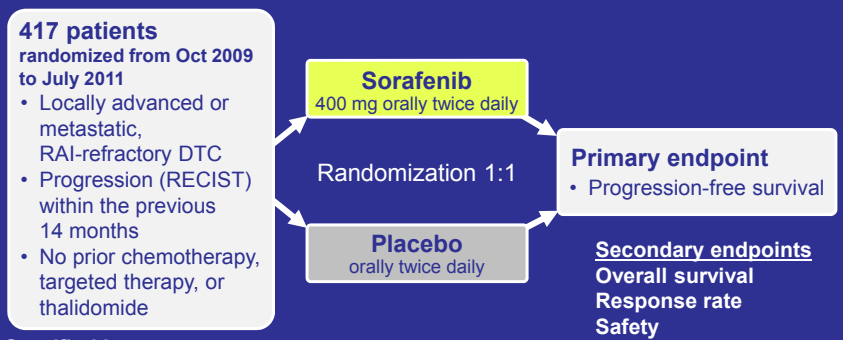
EGFR, epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor.
Graphic adapted from Keefe SM, et al. *Clin Cancer Res*. 2010;16:778-783.

Radioactive Iodine (RAI)-Refractory Disease

- We need to educate oncologists and endocrinologists when to refer patients to oncologists for treatment.
- RAI refractory means that there are **progressing lesions** that **do not take up RAI** (Note: there may still be some that do)
  - RAI uptake scan is negative and CT scan shows nodules
  - RAI uptake scan has uptake but not in some nodules that are progressing
  - Patient has exceeded total lifetime dose of 600 mCi

Cooper DS, et al. Thyroid. 2009;9:1176-214.
Hodak SP, Carty SE. Oncology. 2009;23:775-6.
Mehra R, Cohen RB. Hematol Oncol Clin North Am. 2008;22:1279-95,xi.

DECISION study design (ASCO 2013)

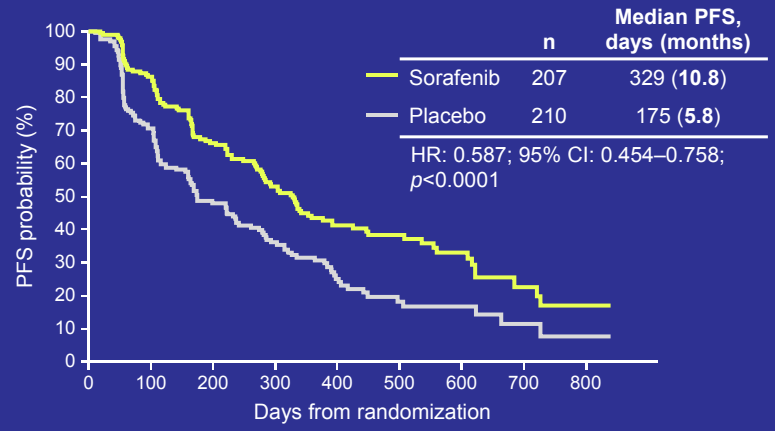


Secondary endpoints
Overall survival
Response rate
Safety
Time to progression
Disease control rate
Duration of response
Sorafenib exposure (AUC_{0-12})

- **Stratified by:**
  - **geographical region (North America or Europe or Asia)**
  - **age (<60 or ≥60 years)**
- Progression assessed by independent central review every 8 weeks
- At progression:
  - patients on placebo allowed to cross over at the investigator's discretion
  - patients on sorafenib allowed to continue on open-label sorafenib at the investigator's discretion

Brose, M.S. et al, *The Lancet*, 14: 60421-9, April 2014

DECISION: Progression-free survival
(by independent central review)



	n	Median PFS, days (months)
Sorafenib	207	329 (**10.8**)
Placebo	210	175 (**5.8**)

HR: 0.587; 95% CI: 0.454–0.758; *p*<0.0001

Overall Survival median PFS has not been reached

Full analysis set.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

ORR and Median TTP Were Significantly Higher in the Sorafenib Group Versus Placebo

	Sorafenib n (%)	Placebo n (%)	HR and *P* Value
Total evaluable patients	196	201	
Disease control rate (CR + PR + SD ≥ 6 months)	106 (54.1)	68 (33.8)	*P* < 0.0001
ORR[a]	24 (12.2)	1 (0.5)	*P* < 0.0001
CR	0	0	—
PR	24 (12.2)	1 (0.5)	—
SD for ≥ 6 months	82 (41.8)	67 (33.2)	—
Median duration of response (PRs), mo (range)	10.2 (95% CI: 7.4-16.6)	NA	—
Median time to progression, mo (range)[b]	11.1 (95% CI: 9.3-14.8)	5.7 (95% CI: 5.3-7.8)	0.56 (95% CI: 0.43-0.72) *P* < 0.001

CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease; TTP, time to progression.
[a]ORR = CR + PR.
[b]Time to progressive disease as defined by RECIST.
Brose MS, et al. *Lancet*. 2014;384(9940):319-328.

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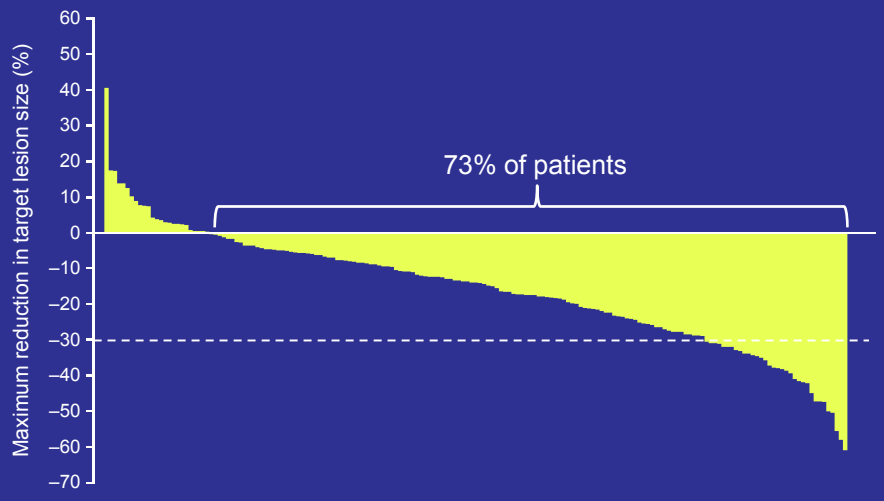
Maximum reduction in target lesion size: sorafenib arm (by independent central review)



Maximum reduction is defined as the difference in the sum of the longest diameter of target lesions from baseline. Negative values refer to maximal reduction and positive values to the minimal increase.

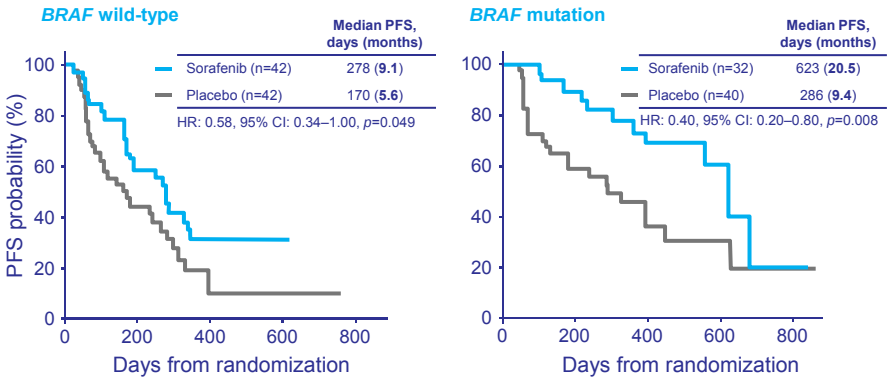
Most common treatment-emergent AEs (double-blind period)

AE*, %	Sorafenib (n=207)		Placebo (n=209)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hand–foot skin reaction	76.3	20.3	9.6	0
Diarrhea	68.6	5.8	15.3	1.0
Alopecia	67.1	0	7.7	0
Rash/desquamation	50.2	4.8	11.5	0
Fatigue	49.8	5.8	25.4	1.4
Weight loss	46.9	5.8	13.9	1.0
Hypertension	40.6	9.7	12.4	2.4
Metabolic – lab (other)	35.7	0	16.7	0
Anorexia	31.9	2.4	4.8	0
Oral mucositis	23.2	1.0	3.3	0
Pruritus	21.3	1.0	10.5	0
Nausea	20.8	0	11.5	0
Hypocalcemia	18.8	9.2	4.8	1.4

*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0

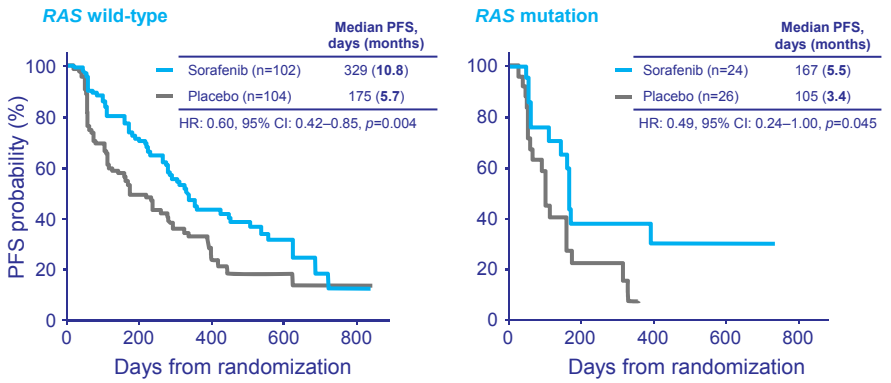
Presented by: Marcia S. Brose MD PhD

Sorafenib benefit by *BRAF* status (PFS) – Papillary histology only



BRAF mutation did not predict PFS benefit from sorafenib (biomarker-treatment interaction p=0.393)

Sorafenib benefit by *RAS* status (PFS)



RAS mutation was not an independent prognostic factor for PFS

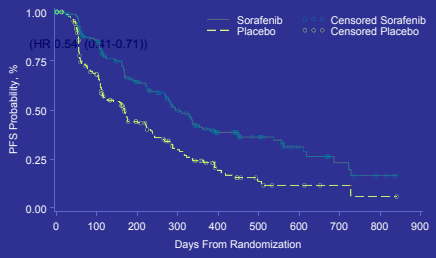
Univariate (placebo arm only): mutant vs wild type *RAS*, HR=1.80; p=0.022

Multivariate (placebo arm only): mutant vs wild type *RAS*, HR=1.56; p=0.154

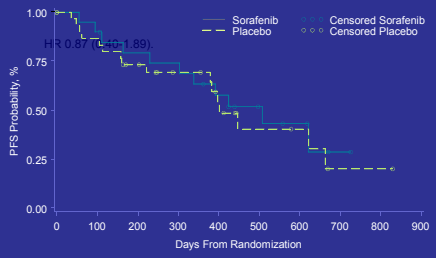
RAS mutation did not predict PFS benefit from sorafenib (biomarker-treatment interaction p=0.422)

DECISION: A Post Hoc Subgroup Analysis by Maximum Tumor Size

Tumor Size ≥ 1.5 cm



Tumor Size < 1.5 cm



- A post hoc subgroup analysis by maximum tumor size showed a treatment effect for PFS in favor of sorafenib over placebo for patients with a maximum tumor size of 1.5 cm or larger (HR = 0.54; 95% CI: 0.41-0.71)[1,2]
- A numerically lower effect was reported in patients with a maximum tumor size < 1.5 cm (HR = 0.87; 95% CI: 0.40-1.89)[1,2]

1. Nexavar Summary of Product Characteristics. Berlin, Germany: Bayer Pharma AG; January 2015. 2. Schlumberger M, et al. Presented at ATA 2014.

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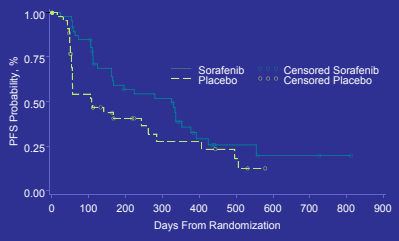
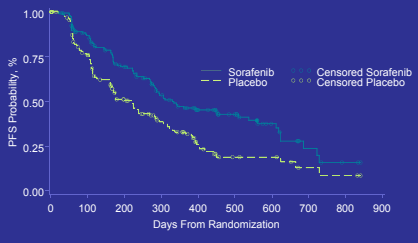
DECISION: A Post Hoc Subgroup Analysis by Thyroid Carcinoma Symptoms at Baseline

Symptomatic at Baseline[a]



Asymptomatic at Baseline[b]



- Analysis by thyroid carcinoma symptoms at baseline showed a treatment effect for PFS in favor of sorafenib over placebo for both symptomatic and asymptomatic patients[1,2]
- The HR for PFS was 0.39 (95% CI: 0.21-0.72) for patients with symptoms at baseline and 0.60 (95% CI: 0.45-0.81) for patients without symptoms at baseline[1,2]

[a]Patients with selected adverse event (AE) or medical history findings: dyspnea, dyspnea exertional, pleural effusion, dysphagia, hemoptysis, chest pain, bone pain, tumor pain, spinal cord compression, cough, obstructive airways disorder, pulmonary embolism. (Global Biostatistics: /by-sasp/patdb/projects/439006/14295/stat/prod_query11/pgms/i-ema-25.sas sbjd 21JAN2014 17:07.)

[b]Patients with absence of selected AE or medical history findings: dyspnea, dyspnea exertional, pleural effusion, dysphagia, hemoptysis, chest pain, bone pain, tumor pain, spinal cord compression, cough, obstructive airways disorder, pulmonary embolism. (Global Biostatistics: /by-sasp/patdb/projects/439006/14295/stat/prod_query11/pgms/i-ema-25b.sas ecjjb 01APR2014 11:41.)

1. Nexavar Summary of Product Characteristics. Berlin, Germany: Bayer Pharma AG; January 2015. 2. Schlumberger M, et al. Presented at ATA 2014.

SELECT: Study Schema

Global, randomized, double-blind, phase 3 trial

Patients with DTC (N = 392)
- IRR evidence of progression within previous 13 months
- ^{131}I-refractory disease
- Measurable disease
- Up to 1 prior VEGF or VEGFR-targeted therapy

Stratification
- Geographic region (Europe, N. America, Other)
- Prior VEGF/VEGFR-targeted therapy (0,1)
- Age (≤ 65 years, > 65 years)

Randomization 2:1

Lenvatinib (n = 261)
24 mg daily PO

Treatment until IRR-verified disease progression (RECIST v1.1)

Placebo (n = 131)
Daily PO

Primary endpoint
- PFS

Secondary endpoints
- ORR
- OS
- Safety

Lenvatinib
(Optional, open-label)

DTC, differentiated thyroid cancer; ^{131}I, radioiodine; IRR, independent radiologic review, ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; RECIST, response evaluation criteria in solid tumors; VEGF/VEGFR, vascular endothelial growth factor/receptor.

Schlumberger M et al., N Engl J Med 372(7): 621-630, February 2015

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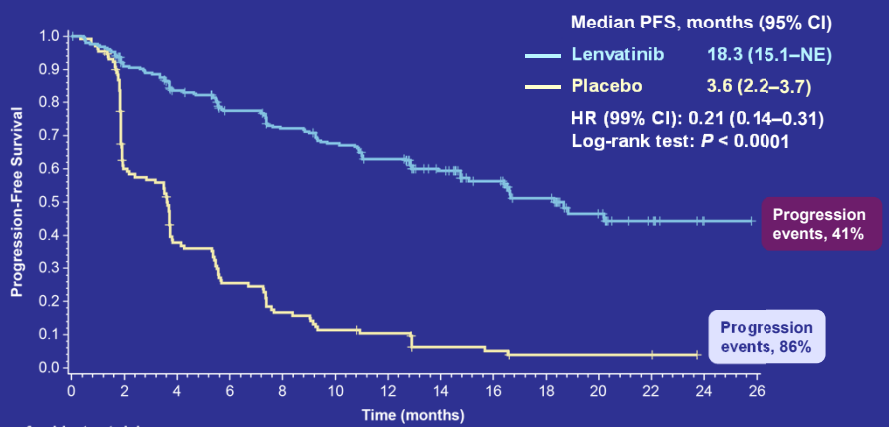
SELECT: Primary Endpoint: Kaplan-Meier Estimate of PFS

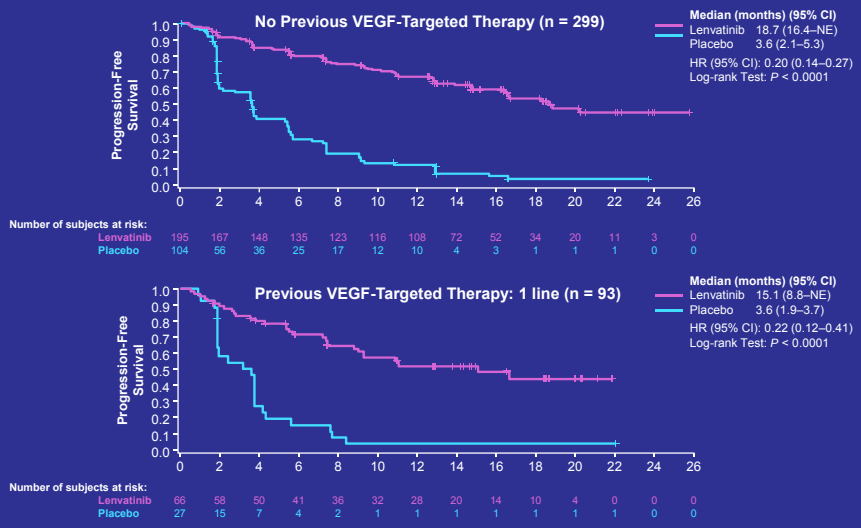


Number of subjects at risk:

Lenvatinib	261	225	198	176	159	148	136	92	66	44	24	11	3	0
Placebo	131	71	43	29	19	13	11	5	4	2	2	2	0	0

CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival.

SELECT: PFS by Previous VEGF-Targeted Therapy



CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival; VEGF, vascular endothelial growth factor.

Select: Response Rates

n (%)	Lenvatinib (n = 261)	Placebo (n = 131)
Overall response rate	169 (65%)	2 (2%)
Complete response	4 (2%)	0
Partial response	165 (63%)	2 (2%)
Stable disease ≥ 23 weeks	40 (15%)	39 (30%)
Progressive disease	18 (7%)	52 (40%)
Duration of response, months, median (95% CI)	NE (16.8–NE)	–

Median time to objective response for lenvatinib[a]: 2.0 months (range, 1.9–3.5 months)

[a] Non-responders were not included in the median time to response assessment.
CI, confidence interval; NE, not estimable.

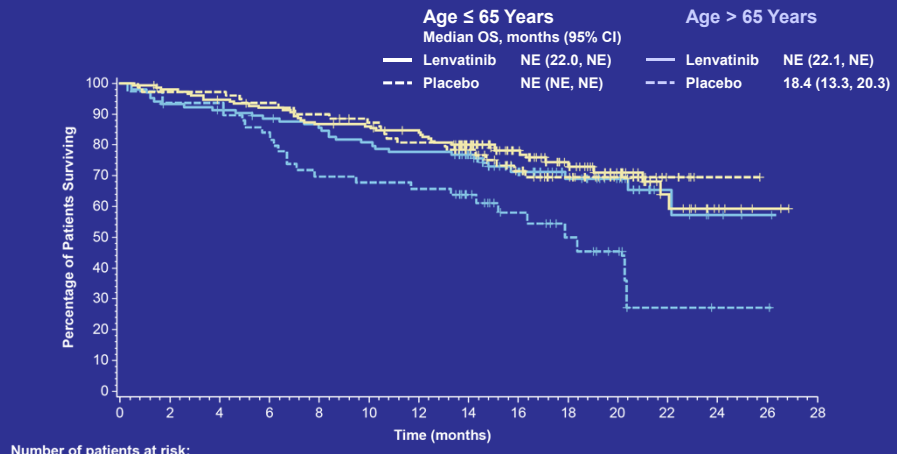
Presented by: Martin Schlumberger, MD

Most Frequent Treatment-related Adverse Events (> 20%)

	Lenvatinib (n = 261)		Placebo (n = 131)	
Adverse Event, %	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Hypertension	68	42	9	2
Diarrhea	60	8	8	0
Fatigue / asthenia	59	9	28	2
Decreased appetite	50	5	12	0
Nausea / vomiting	46	3	15	1
Decreased weight	46	10	9	0
Stomatitis	36	4	4	0
Palmar-plantar erythrodysesthesia syndrome	32	3	1	0
Proteinuria	31	10	2	0
Headache	28	3	6	0
Dysphonia	24	1	3	0

Presented by: Martin Schlumberger, MD

Overall Survival, by Age



Number of patients at risk:

Age Group (years): ≤ 65															
Lenvatinib	155	150	144	139	131	129	124	102	70	47	31	14	6	2	0
Placebo	81	79	79	76	73	69	63	52	37	28	16	6	1	0	0
Age Group (years): > 65															
Lenvatinib	106	98	95	91	88	82	79	67	42	31	24	8	4	1	0
Placebo	50	47	47	42	35	34	33	26	16	11	7	2	1	1	0

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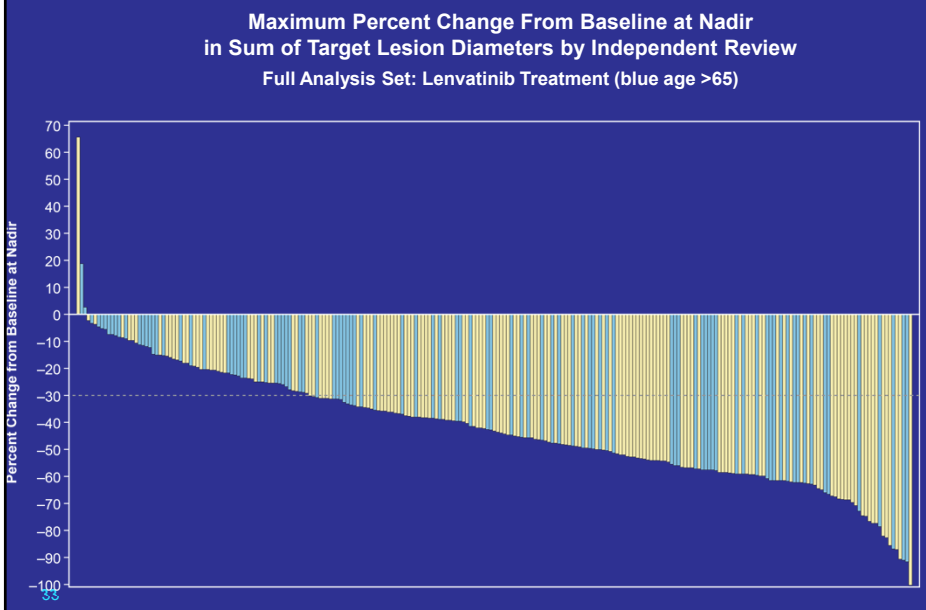
CI, confidence interval; HR, hazard ratio; OS, overall survival; NE, not evaluable.

Lenvatinib Responses



SELECT Summary

- The patients on the lenvatinib study had disease that was more aggressive with a PFS of 3.6 months compared to 5.8 months on the decision study.
- Based on SELECT, Lenvatinib was approved in April 2015 (in the US and EU) for treatment of RAI refractory progressive DTC

NCCN and ATA guidelines for the treatment of differentiated thyroid cancer (DTC)

Initial treatment

- Total thyroidectomy, except in patients with unifocal microcarcinoma (individualized to patient and extent of disease)[1,2]

Postoperative treatment

- Radioactive iodine (^{131}I) (RAI) therapy[1,2]

Follow-up treatment

- Levothyroxine to suppress TSH levels to < 0.1mU/L[1,2]

Recurrent or metastatic disease treatment

- Local therapy (re-operation, external radiation)
- Systemic therapy
  - RAI therapy
  - patients with refractory advanced disease …

NCCN = National Comprehensive Cancer Network.
ATA = American Thyroid Association .

1. NCCN Clinical Practice Guidelines in Oncology. Thyroid Carcinoma V.1.2016.
2. Cooper DS, et al. Thyroid .2009;9:1167-214.

NCCN v 1.2016 Guidelines: Treatment of Metastatic Disease Not Amenable to RAI Therapy

- For progressive and/or symptomatic disease, consider lenvatinib or sorafenib[y]
- While not FDA approved for the treatment of differentiated thyroid cancer, other commercially available small molecular kinase inhibitors can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate.
- Consider resection if distant metastases, and/or EBRT/SBRT/IMRT/other local therapies when available to metastatic lesions if progressive and/or symptomatic.
- Active surveillance may be appropriate in asymptomatic patients with indolent disease.

- [y] The decision of whether to use lenvatinib or sorafenib should be individualized based on likelihood of response and comorbidities.

NCCN = National Comprehensive Cancer Network.
ATA = American Thyroid Association .

1. NCCN Clinical Practice Guidelines in Oncology. Thyroid Carcinoma V.1.2016.
2. Cooper DS, et al. Thyroid .2009;9:1167-214.

Summary: RAI refractory DTC 2016

- Two drugs are now approved to treat RAI refractory DTC: sorafenib and lenvatinib
  - We have data that lenvatinib is active following sorafenib.
  - Await data on the efficacy of sorafenib following lenvatinib
  - Ability to manage toxicities will be key to success with these agents
- New data from SELECT shows an OS survival benefit in patients over 65 with rapidly progression disease.

Summary: RAI refractory DTC 2016

- As all patients will ultimately progress, both agents will be needed and will be used sequentially, as well as additional strategies
- A phase II of the addition of everolimus to sorafenib at the time of progression results in a PFS of 13.9 additional months.
- Other MKIs are also active in this setting including pazopanib and cabozantinib based on phase II evidence can be considered in third line

Thyroid Cancer: Clinical Pathology

Follicular cells → Differentiated → Papillary, Follicular, Hurtle Cell

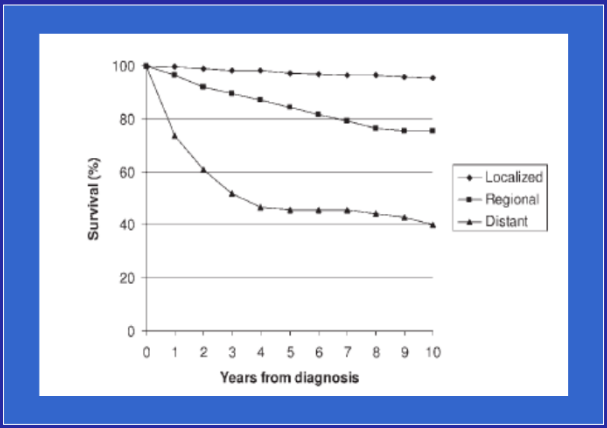
Follicular cells → Anaplastic

Parafollicular cells → Medullary → Sporadic, Familial

Rationale for RET as a Therapeutic Target

- Activated by mutations in ~50% of cases (>60% of progressive cases presenting for clinical trials)
- Somatic mutation of RET associated with poor prognosis
- Limited expression outside the thyroid, potentially high therapeutic index
- Associated with familial MTC and MEN 2B

Patients With Distant Metastasis at Diagnosis Have a Poor Prognosis

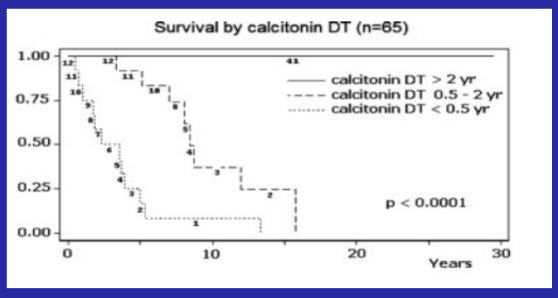


- 10-year overall survival: 40%
- Median overall survival: 3.2 years

Roman et al. 2005.

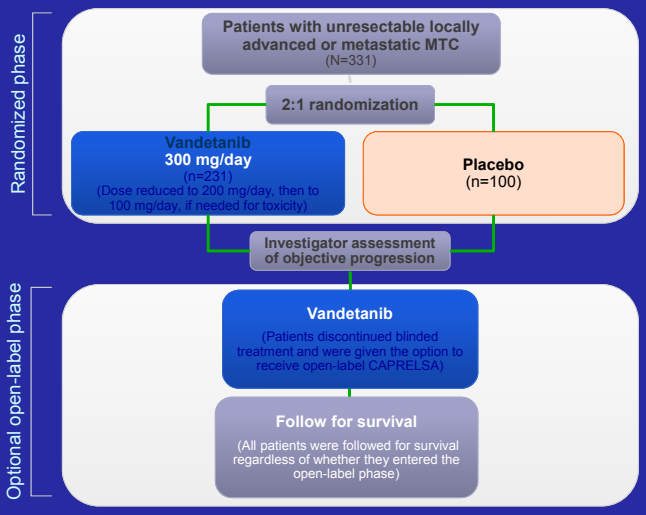
Risk Stratification Using Serum Calcitonin DT

- Calcitonin DT highly predictive of mortality
- Independent predictor in multivariate analysis, controlled for TNM stage
- Rapid DT could identify stage II and III patients at higher risk for death



Barbet. *JCEM.* 2005.

ZETA Study Design[1,2]



1. CAPRELSA® (vandetanib) Tablets [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. **2.** Wells SA Jr et al. *J Clin Oncol*. 2012;30(2):134-141.

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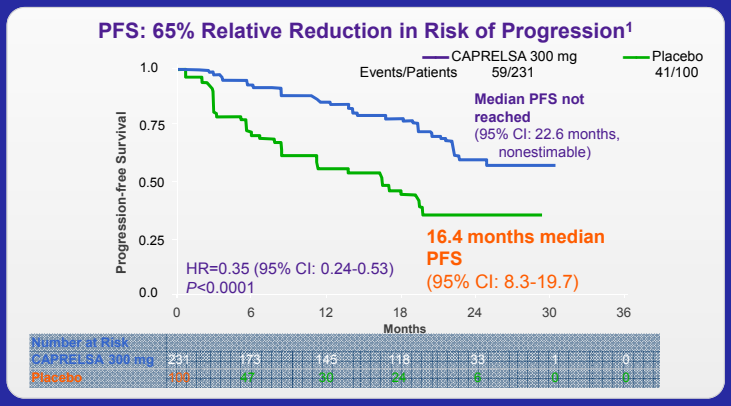
ZETA Study: Vandetanib Significantly Prolonged PFS[a] vs Placebo



CI=confidence interval; HR=hazard ratio.
[a]PFS is defined as time from the date of randomization until the date of objective disease progression based on Response Evaluation Criteria In Solid Tumors (RECIST) assessment or death (by any cause in the absence of progression), provided death was within 3 months from the last evaluable RECIST assessment.[2] Centralized, independent blinded review of the imaging data was used in the assessment of PFS.[1]
1. CAPRELSA® (vandetanib) Tablets [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. **2.** Wells SA Jr et al. *J Clin Oncol*. 2012;30(2):134-141.

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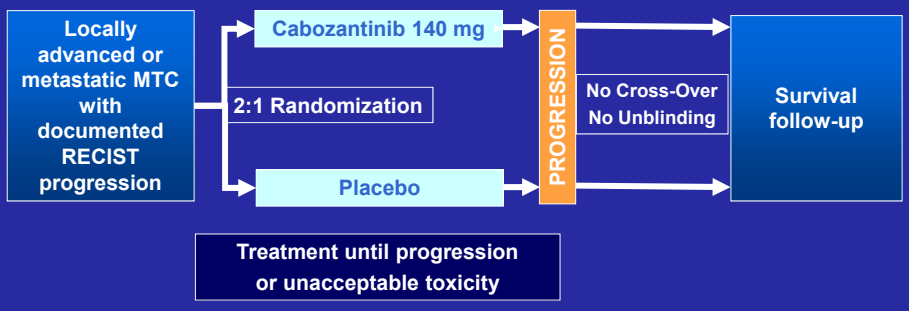
Vandetanib in Patients With Locally Advanced or Metastatic Medullary Thyroid Cancer: A Randomized, Double-Blind Phase III Trial

1. Eligibility did not require progressive disease. Thus many patients enrolled may have had stable disease.
   1. This could have been done by requiring progressive disease by RECIST
   2. No data on Calcitoning doubling time.

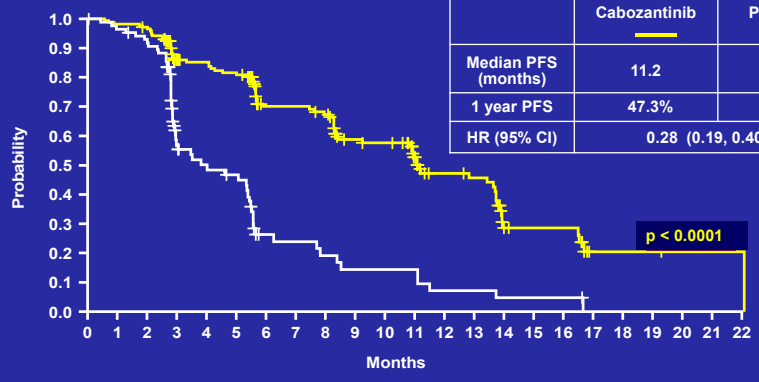
2. No difference in overall survival was observed (data was immature)

3. QT prolongation was observed in 8% of the vandetanib arm, unexplained sudden deaths (4)

Cabozantinib in MTC: Phase 3 Study Rationale and Design (EXAM)



Cabozantinib Phase III in MTC Progression Free Survival by IRC



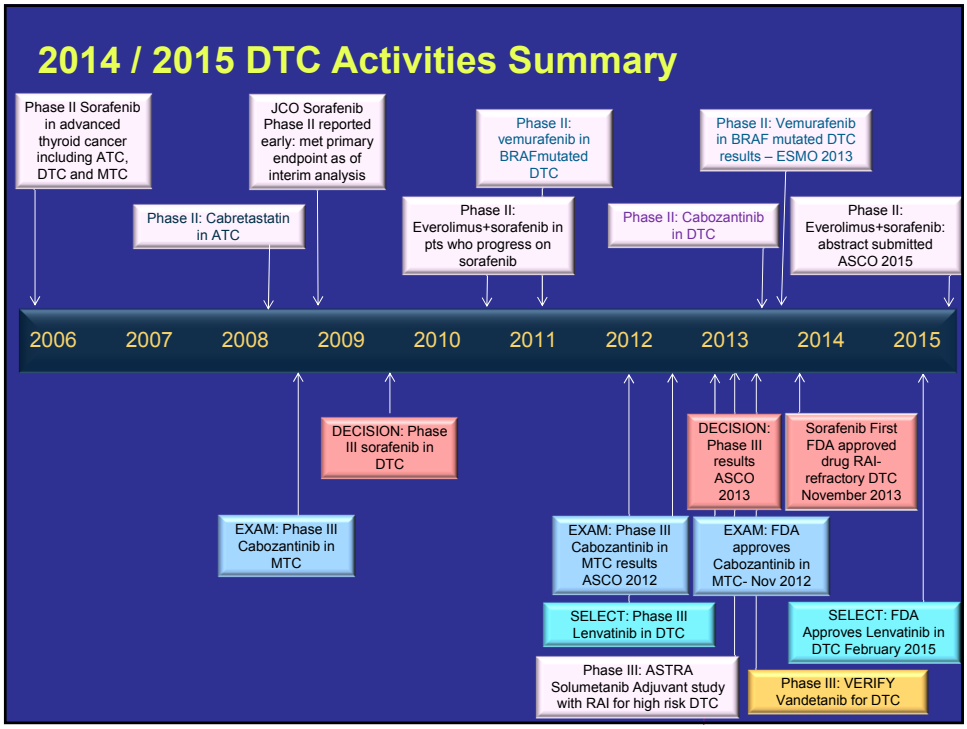
	Cabozantinib	Placebo
Median PFS (months)	11.2	4.0
1 year PFS	47.3%	7.2%
HR (95% CI)	0.28 (0.19, 0.40)	

- **Significant difference in tumor response rate**
  - 28% in cabozantinib vs. 0% placebo; p<0.0001
- **Median duration of response: 14.6 months**

ASCO 2012 oral presentation

Summary Targeted Therapy for MTC

- Currently there are two approved FDA drugs for MTC, vandetanib and cabozantinib
- Vandetanib is associated with QT prolongation. Physicians must complete and comply with the REMS program in prescribing
- Cabozantinb is associated with fistula formation and GI tract perforations and care must be given to assess the risk and monitor treatment appropriately.



University of Pennsylvania Thyroid Cancer Therapeutics Program

- **Brose Translational Research Lab**
  - Mark Yarchoan MD
  - Aaron Cohen MD
  - Christian Squillante MD
  - Waixing Tang, MD
- **Thyroid Cancer Clinical Trials Unit**
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  - Theresa Sabato, RN
  - Carolyn Grande, RN, CRNP
  - Dena Torrente
  - Diane Foglia
  - Jennifer Arrington
  - Tracey McCray
- **Experimental Therapeutics Program**
  - Andrea Troxel, PhD
  - Peter O'Dwyer, MD
- **Pathology/Imaging**
  - Michael Feldman, MD, PhD
  - Laurie Loevner, MD
- **Thyroid Cancer Interest Group**
  - Susan Mandel, MD
  - Ara Chalian, MD
  - Douglas Fraker, MD
  - Robert Lustig, MD
  - Virginia LiVolsi, MD
  - Zubair Baloch, MD
  - Steve Keefe, MD
  - Daniel Pryma MD
- **Marcia Simpson Brose is a Damon Runyon-Siemens Clinical Investigator**

Damon Runyon Cancer Research Foundation

- **Many community endocrinologists who have referred their patients, and the patients who have agreed to participate in our trials**

Review Questions

QUESTION 1:

- A 38 year old female is diagnosed with thyroid cancer and on staging she has a 2cm primary and multiple (approx 10) 1 to 2mm metastatic pulmonary nodules thyroid cancer. Her stage is
-
- A. II
- B. III
- C. IVa
- D. IVb

Review Questions

QUESTION 1:

- A 38 year old female is diagnosed with thyroid cancer and on staging she has a 2cm primary and multiple (approx 10) 1 to 2mm metastatic pulmonary nodules thyroid cancer. Her stage is
-
- A. II
- B. III
- C. IVa
- D. IVb

- Answer is A: stage II. Patients under 45 are at most a stage II due to the overall good prognosis for patients in this age group.

Review Questions

QUESTION 2:

- The patient is treated with total thyroidectomy and radioactive iodine. What additional treatment is indicated at this time?
-
- A. external beam radiation to the neck
- B. chemotherapy with doxorubicin
- C. observation only
- D. TSH suppression therapy

Review Questions

QUESTION 2:

- The patients is treated with total thyroidectomy and radioactive iodine. What additional treatment is indicated at this time?
-
- A. external beam radiation to the neck
- B. chemotherapy with doxorubicin
- C. observation only
- D. TSH suppression therapy

- Answer is D: TSH suppression therapy. At this point in her treatment her disease is likely going to respond to RAI. However as she has residual disease in her lungs she should start out with her TSH suppressed. With time, if the disease responds completely and she has not evidence of disease, this can be liberalize a bit. TSH suppression therapy has shown to have a survival benefit. C might also be considered, but close surveillance to US and Tg is indicated. A and B are not indicated.

Review Questions

QUESTION 3:

- A patient with metastatic RAI refractory differentiated thyroid cancer has tumor nodules that have doubled in size over the prior year. What are your treatment options at this point?
-
- A. observation
- B. start treatment with sorafenib
- C. start treatment with lenvatinib
- D. all of the above

Review Questions

QUESTION 3:

- A patient with metastatic RAI refractory differentiated thyroid cancer has tumor nodules that have doubled in size over the prior year. What are your treatment options at this point?
-
- A. observation
- B. start treatment with sorafenib
- C. start treatment with lenvatinib
- D. all of the above

- Answer is D: all of the above may be correct in different settings. If the tumor burden is very small (only a few lesions), and the largest lesions are less than 1.5 cm, observation may be considered. Both sorafenib and lenvatinib have been approved for treatment in this setting, and the choice of which to use first should be individualized based on patient characteristics, and expected toxicity profiles.

Review Questions

QUESTION 4:

- A patient with newly diagnosed metastatic medullary thyroid cancer in the neck and lungs and a documented RET mutation comes to you for evaluation. He has had a complete thyroidectomy and had positive lymph nodes in the neck which were also removed. On CT scan the patient has approximately 15 lesions from 5mm to 2cm in the lungs. He is asymptomatic. What do you recommend?
-
- A. observation
- B. start treatment with vandetanib
- C. start treatment with cabozantinib
- D. external beam radiation to the neck

References:

1. Gupta-Abramson V, Troxel AB, Nellore A, Puttaswamy K, Redlinger M, Ransone K, Mandel SJ, Flaherty KT, Loevner LA, O'Dwyer, PJ, Brose MS: Phase II Trial of Sorafenib in Advanced Thyroid Cancer. Journal of Clinical Oncology 26(29): 4714-4719, October, e-pub June 9 2008 Notes: Highlighted by an accompaning editorial

2. Smallridge RC, Copland JA, Brose MS, Wadsworth JT, Houvras Y, Menefee ME, Bible KC, Shah MH, Gramza AW, Klopper JP, Marlow LA, Heckman MG, Von Roemeling R.: Efatutazone, an Oral PPAR-γ Agonist, in Combination with Paclitaxel in Anaplastic Thyroid Cancer: Results of a Multicenter Phase 1 Trial. J Clin Endocrinol Metab 98(6): 2392-400, June 2013.

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4. Brose,M.S., Nutting,C.M., Jarzab, B., Elisei, R., Siena, S., Bastholt,L., de la Fouchardiere, C., Pacini, F., Paschke, R., Shong, YK, Sherman, SI, Smit, JWA, Chung, J., Kappeler, C., Pena, C., Molnar, I., Schlumberger, M.J., on behalf of the DECISION Investigators*: Sorafenib in locally advanced or metastatic, radioactive iodine-refractory, differentiated thyroid cancer: a randomized, double-blind, phase III trial. The Lancet 14: 60421-9, April 2014

References:

5. Cabanillas ME, Brose MS, Holland J, Ferguson KC, Sherman SI.: A phase I study of cabozantinib (XL184) in patients with differentiated thyroid cancer. Thyroid 24(10): 1508-1514, October 2014.

6. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu J, Sherman SI.: Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 372(7): 621-630, February 2015.

7. Worden F, Fassnacht M, Shi Y, Hadjieva T, Bonichon F, Gao M, Fugazzola L, Ando, Y, Hasegawa Y, Park do J, Shong YK, Smit JW, Chung J, Kappeler C, Meinhardt G,Schlumberger M, Brose MS. : Safety and tolerability of sorafenib in patients withradioiodine-refractory thyroid cancer. Endocr Relat Cancer 22(6): 877-87, December 2015 Notes: http://erc.endocrinology-journals.org/content/22/6/877.full.

8. Wells, SA, Robinson, BG, Gagel, RF, Henning, D, Fagin, JA, Santoro, M, Baudin, E, Elisei, R., Jarzab, B, Vasselli, JR, Read, J, Langmuir, P, Ryan, AJ, Schlumberger, MJ: Vandetanib in patients with locally advanced or metastatic medullary thyorie cancer: A randomized double-blind Phase III trial. J Clin Oncol 30(2): 134-141.

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9. Brose, M.S., Cabanillas, M.E., Cohen, E.E., Wirth, L.J., Riehl,T., Yue, H., Sherman, S.I., Sherman, E.J. : An open-label, multicentre, phase 2 study of the BRAF inhibitor vemurafenib in patients with metastatic or unresectable papillary thyroid cancer positive for the BRAFV600 mutation and resistant to radioactive iodine. Lancet Oncology In Press 2016.

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11. Brose,M.S. Clary, D.O., Cohen, E.E.W, Schöffski, P., Elisei, R., Schlumberger, M.J., Wirth, L.J., Miles, D., Aftab, D.T., Sherman, S.I.: Correlative Biomarker Analysis in the EXAM Trial, a Phase 3 Study of Cabozantinib in Patients With Progressive Medullary Thyroid Cancer. Cancer in press.

Charles L. Spurr Piedmont Oncology Symposium
Fall Symposium

AGENDA

Saturday, October 1, 2016

7:15 am **Registration, Continental Breakfast, and Exhibits**

General Session

7:50 am **Welcome and Remarks**
Bayard Powell, MD
Professor of Medicine
Section on Hematology and Oncology, Wake Forest School of Medicine

8:00-9:00 am **Pancreas Cancer: Current and Future Directions**
Eileen O'Reilly, MD
Professor
Associate Director, David M. Rubenstein Center for Pancreatic Cancer
Memorial Sloan Kettering Cancer Center

9:00-10:00 am **Neuroendocrine Tumors: A Growing and Unusual Problem**
Eric H. Liu, MD
Co-Director, The Neuroendocrine Institute
Chief Medical Advisor, The Healing NET Foundation
Rocky Mountain Cancer Center

10:00-10:30 am **Break and Exhibits**

10:30-11:30 am **Chronic Lymphocytic Leukemia in the Modern Era**
Farrukh Awan, MD, MS
Associate Professor of Medicine
Division of Hematology
The Ohio State University

11:30-12:30 pm **The Wake Forest Baptist Precision Oncology Initiative**
Boris Pasche, MD, PhD
Charles L. Spurr Professor of Medicine
Chair, Department of Cancer Biology
Director, Wake Forest Baptist Comprehensive Cancer Center

12:30 pm **Adjourn**

Pancreas Cancer: Current and Future Directions

Eileen O'Reilly, MD
Professor
Associate Director, David M. Rubenstein Center for Pancreatic Cancer
Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center

Pancreatic Adenocarcinoma: Current and Future Directions

October 1st, 2016

Eileen M. O'Reilly, M.D.
Associate Director
David M. Rubenstein Center for Pancreatic Cancer
Attending Physician, Member
Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College

Memorial Sloan Kettering Cancer Center

Disclosures

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  - Momenta
  - OncoMed
  - Array Pharmaceuticals
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  - Immunomedics
  - MedImmune
  - Celgene
  - Incyte Pharmaceuticals
  - AbbVie
  - Genentech
  - Polaris
  - BMS
  - EMD-Serono
  - AduroBiotech
  - Halozyme
  - Merrimack
  - NewLink Genetics

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Agenda

- Front-line therapies
- Emerging standards beyond 1st-line
- Novel therapeutics
- Genomic profiling

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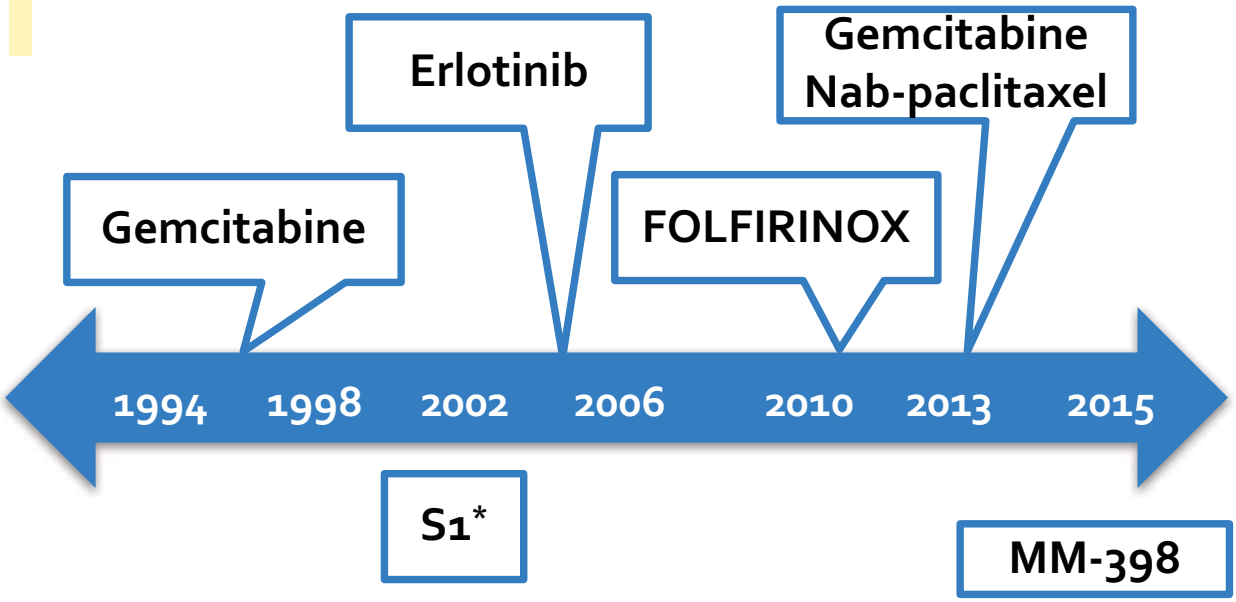
Approved Drugs/Regimens PDAC



*Approved in Japan

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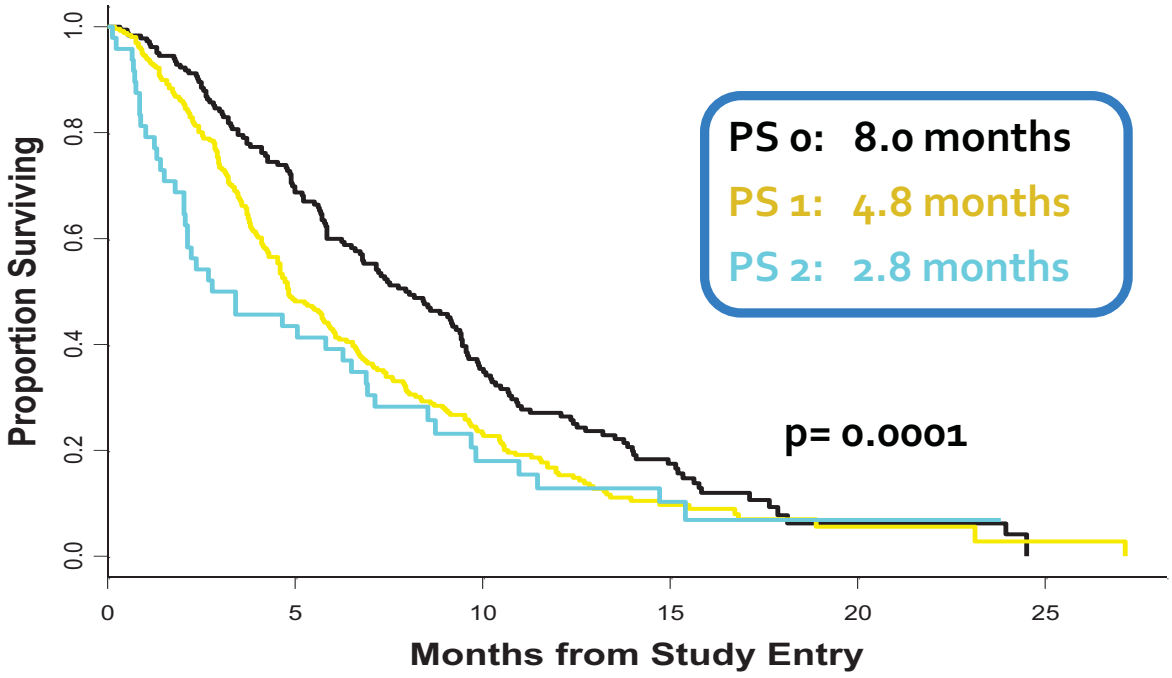
Overall Survival CALGB 80303 by Performance Status (Pooled)



Kindler, H. et al. J Clin Oncol, 2010

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FOLFIRINOX vs Gemcitabine Prodige – ACCORD 11

Untreated
Metastatic Panc
Adenocarcinoma
ECOG 0-1

RANDOMIZE

FOLFIRINOX
N= 167

Gemcitabine
N= 169

Randomization 1: 1
Stratification
- PS: 0 vs 1; Primary tumor location, Center

Primary Endpoint: Overall Survival

Conroy, et al. NEJM, 2011

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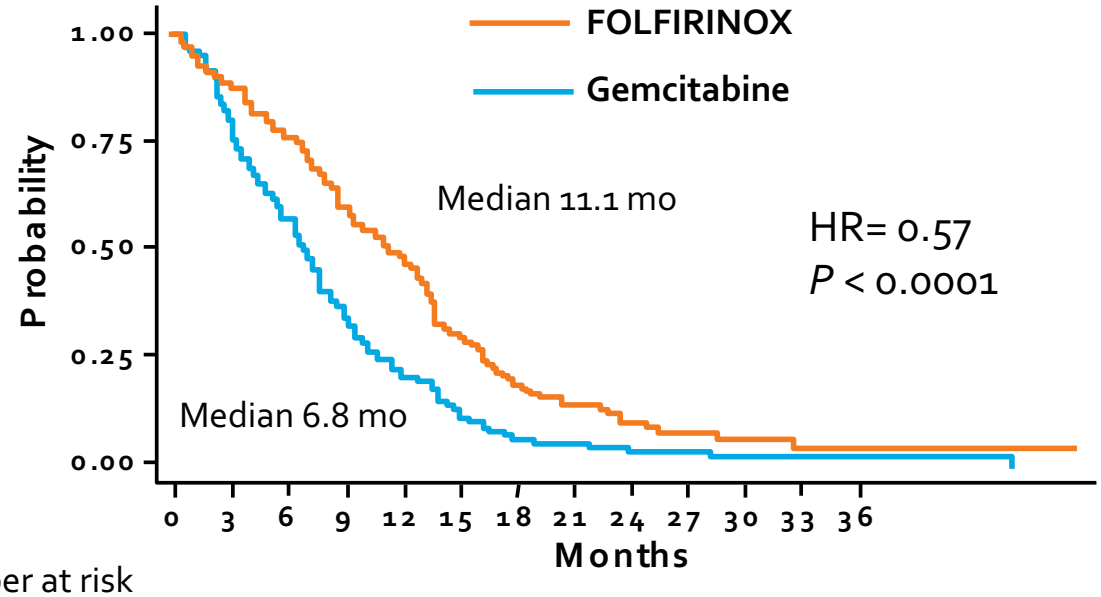
FOLFIRINOX vs Gemcitabine Overall Survival



Number at risk

Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2

Conroy, T. NEJM, 2011

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MPACT: Phase III Nab-Paclitaxel + Gemcitabine vs Gemcitabine

Untreated Metastatic Panc Adenocarcinoma KPS 70- 100%

RANDOMIZE

Nab-Paclitaxel + Gemcitabine N= 431

Gemcitabine N= 430

Randomization 1: 1

Stratification

-Performance status (90-100 vs 70-80)
-Liver metastases (Present vs Absent)
-Region

Primary Endpoint: Overall Survival

Von Hoff, D. NEJM, 2013

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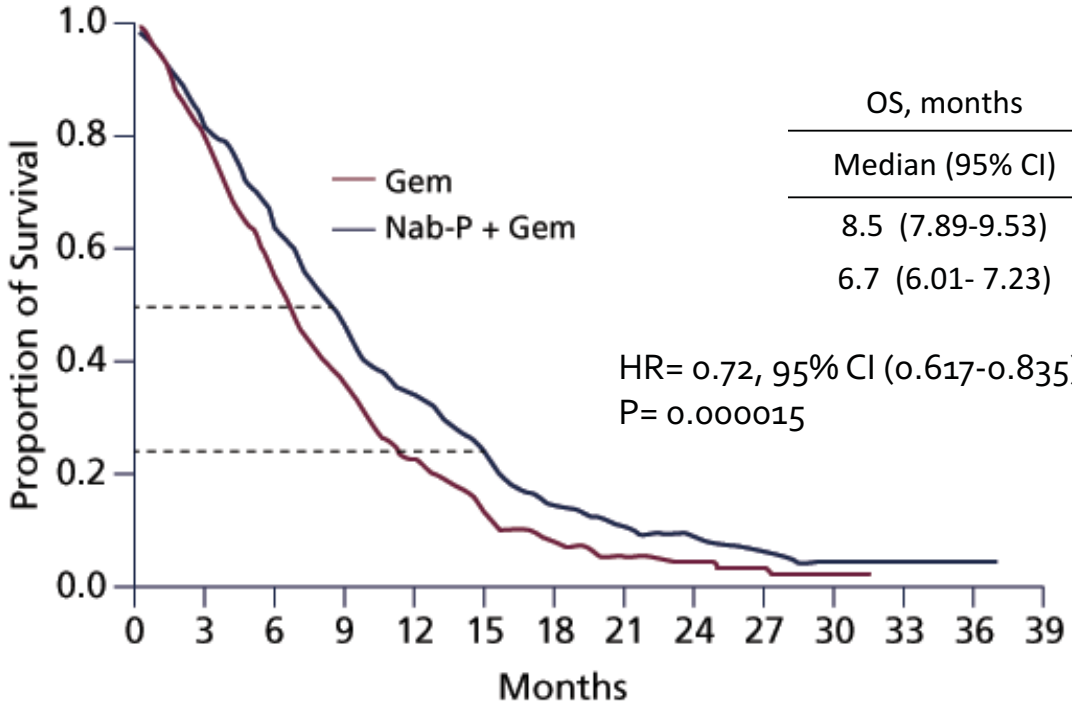
MPACT: Overall Survival



OS, months
Median (95% CI)
8.5 (7.89-9.53)
6.7 (6.01- 7.23)

HR= 0.72, 95% CI (0.617-0.835)
P= 0.000015

Von Hoff, D. N Engl J Med, 2013

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FOLFIRINOX vs Gem + Nab-P

	FOLFIRINOX	Gemcitabine/nab-paclitaxel
Sample size	342	861
Location	France	N America, Europe, Australia
Eligibility, PS	**ECOG 0-1**	**KPS 70-100**
% head/non-head	39%/ 61%	44%/ 56%
Survival, median % at one-year	11.1 months 48%	8.5 months 35%
Toxicity (grade 3/4)	Fatigue 24% Neutropenia 46%	Fatigue 17% Neutropenia 38%
Poorer PS patients?	N/A	Benefit in KPS 70-80 pts
QoL data?	Yes	No
Biomarker data	N/A	SPARC: not predictive

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Which Regimen First For PC?

- No clear data to guide
  - Age, performance status, patient preference
- Nab-paclitaxel and gemcitabine – applicable to broader patient population
  - Older, less robust performance status
  - Easier to add other agents

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Second-Line Therapy in Pancreas Adenocarcinoma

- About 40-50% receive a second-line therapy – impact on survival unclear
- Few patients receive therapy on trial in 2nd-line
- Data to support gemcitabine-based treatment for patients with POD on 5-FU-based regimen
- Data to support 5-FU-based therapy for patients with POD on gem-based therapy

Sultana, A. B J Cancer, 2008. Schrag, D. ASCO, 2009. Pelzer, U. Eur J Cancer, 2011. Xiong, HQ. Cancer, 2008

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Second-Line Treatment Oxaliplatin: Mixed Data in PDAC

	CONKO-003		PANCREOX	
	5-FU/LV	OFF	5-FU/LV	mFOLFOX
Med OS	3.3 m	5.9 m	9.9 m	6.1m
	HR 0.068		HR 1.78	
Med TTP	2 m	2.9 m		
Med PFS			2.9	3.1

Oettle, H. J Clin Oncol. 2014;32:2423-2429. Gill, S. ASCO 2014. Abstract 4022

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NAPOLI-1: Phase III Design Gemcitabine-Pre-treated

Met PDAC
Prior Gemcitabine
KPS 70- 100%
N= 417

RANDOMIZE

- MM-398 100 mg/m² q3 wks (N= 151)
- Infusional 5-FU/LV wkly x 4 q6w (N= 149)
- MM-398 +Inf. 5-FU/LV q2 wks (N= 117)*

Stratification
- Albumin, KPS, Ethnicity

Primary Endpoint: Overall Survival

Secondary Endpoints: PFS, RR, Ca 19-9, Safety, QoL

*Trial amended after N= 63 to include 3rd arm MM-398+5-FU/LV

Wang-Gillam, A. Lancet, 2016

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NAPOLI-1: Prior Therapy

	MM-398+ 5-FU/LV N= 117	5-FU/LV N= 119
Gemcitabine	53 (45%)	55 (46%)
Gem-combination*	64 (55%)	64 (54%)
5-FU-based	50 (43%)	52 (44%)
Irinotecan-based	12 (10%)	17 (14%)
Platinum-based	38 (32%)	41 (34%)

13% Prior gemcitabine/nab-paclitaxel*

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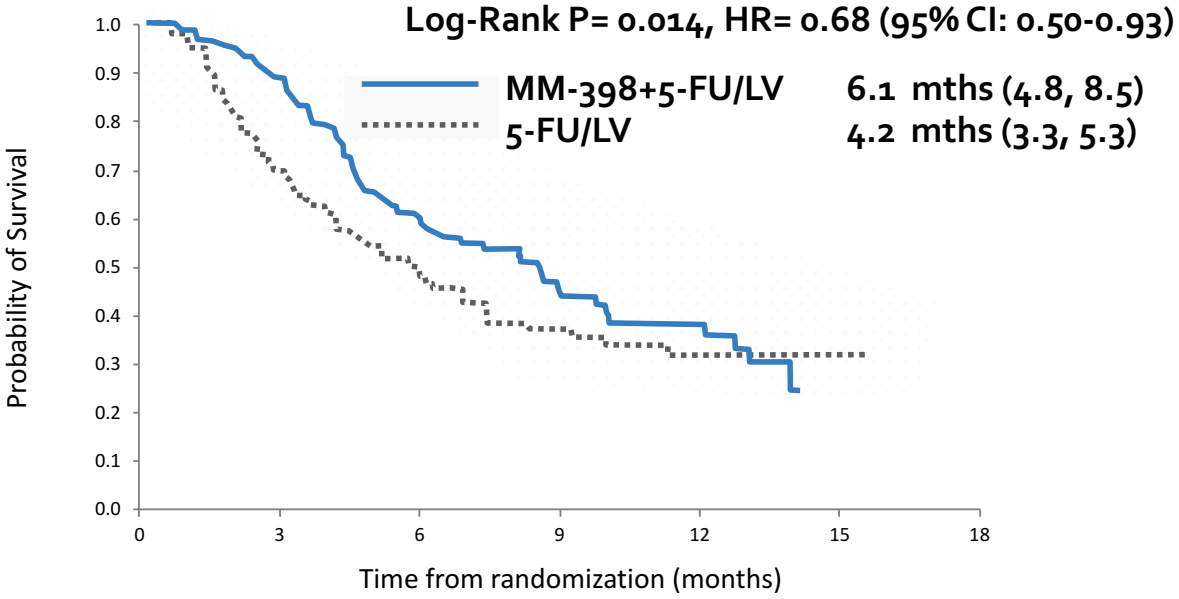
NAPOLI-1 Overall Survival: MM-398/5-FU/LV vs 5-FU/LV



Wang-Gillam, A. Lancet, 2016

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NAPOLI-1: Grade 3-4 Toxicity

Event, n (%)	MM-398+ 5-FU/LV N= 117	5-FU/LV N= 134
Diarrhea	15 (13%)	6 (4%)
Vomiting	13 (11%)	4 (3%)
Nausea	9 (8%)	4 (3%)
Fatigue	16 (14%)	5 (4%)
Neutropenia	32 (27%)	2 (1%)
Anemia	11 (9%)	9 (7%)
Hypokalemia	4 (3%)	3 (2%)

Fatal neutropenic sepsis 0.8% in MM-398 + 5FU/LV

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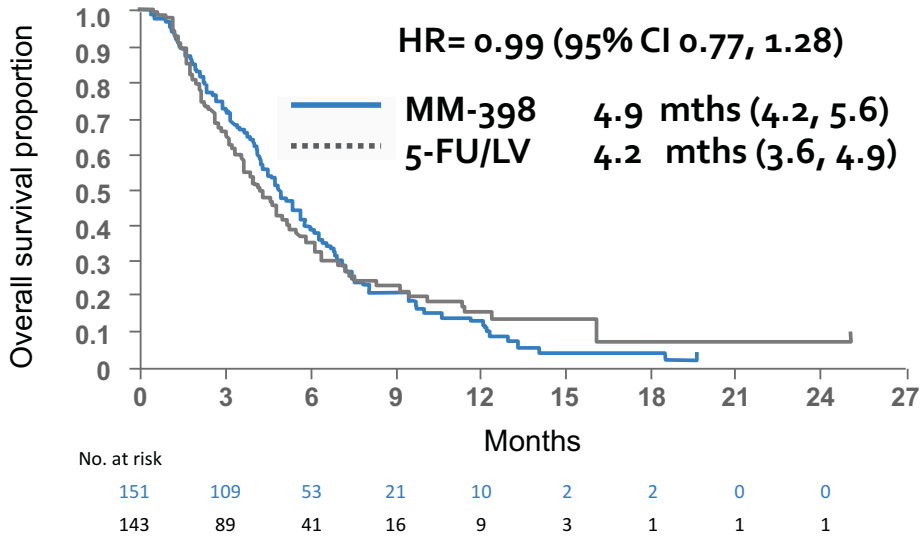
NAPOLI-1: Overall survival MM-398 vs 5-FU/LV



No data to support use of single-agent MM-398

Wang-Gillam, A. Lancet, 2016

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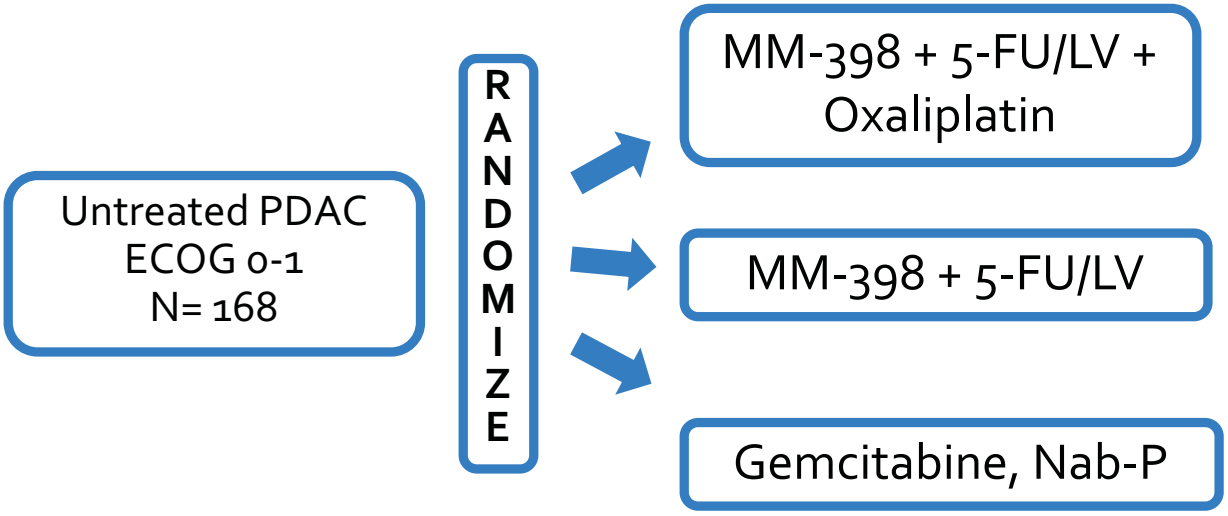
Ongoing Development MM-398 Front-Line



Primary: 24 weeks PFS

Secondary: OS, PFS, RR, Ca 19-9, QoL

NCT02551991

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Conclusions: Second-Line

- Established therapy for beyond gemcitabine-pre-treated
  - Level 1 evidence: MM-398 +5-FU/LV
- Oxaliplatin-based therapy
  - Option, but data mixed
- Continues to be area of unmet need
  - Clinical trials

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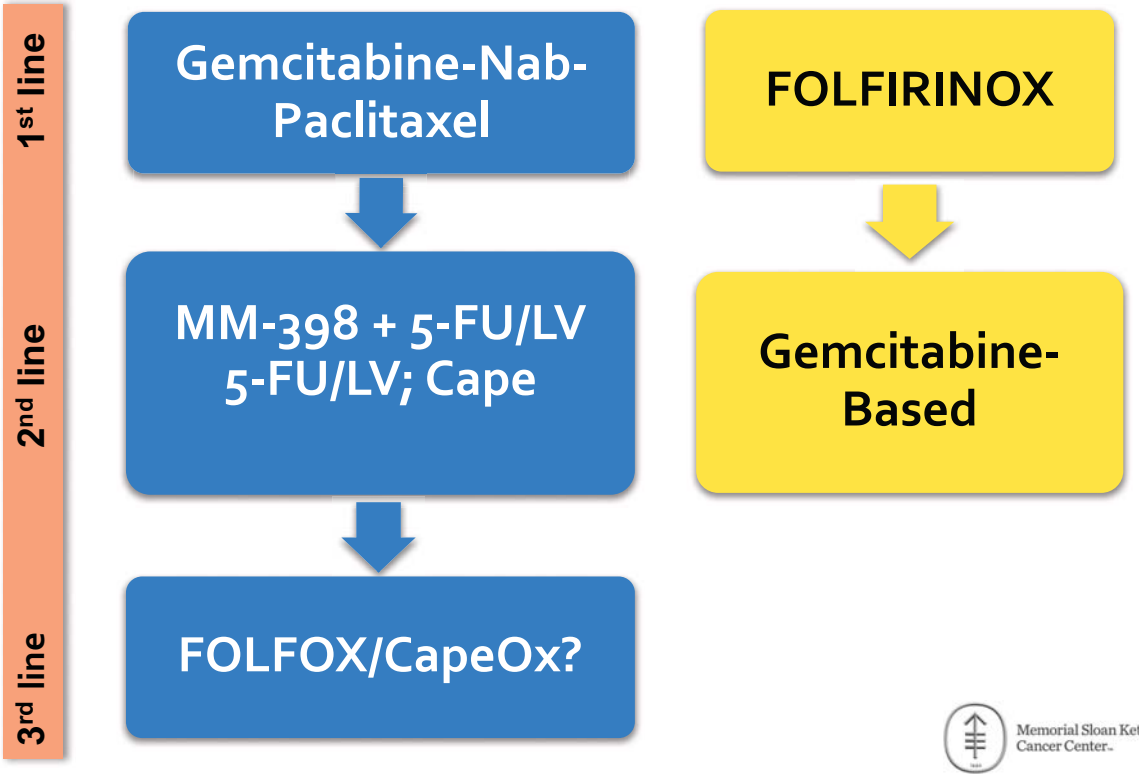
Current Approach to Treatment Sequencing for Advanced PDAC



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Novel Therapeutics

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PDAC: Formidable Tumor Biology Multiple Challenges

- Complex microenvironment/ stroma
- Immunosuppression
- Multiple gene mutations
- Non-druggable tumor suppressor genes
- Drug resistance
- No validated biomarkers

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Genomic Analyses of PDAC

- N= 456 pancreatic ductal adenocarcinomas
  - Whole genome, deep-exome sequencing
  - Copy number, RNA expression profiles
  - 32 recurrently mutated genes
    - KRAS, TP53, SMAD4, CDKN2A
  - 10 pathways
    - KRAS, TGF-b, WNT, NOTCH, ROBO/SLIT signalling, G1/S transition, SWI-SNF, chromatin modification, DNA repair and RNA processing

Bailey, P. et al. Nature, 2016

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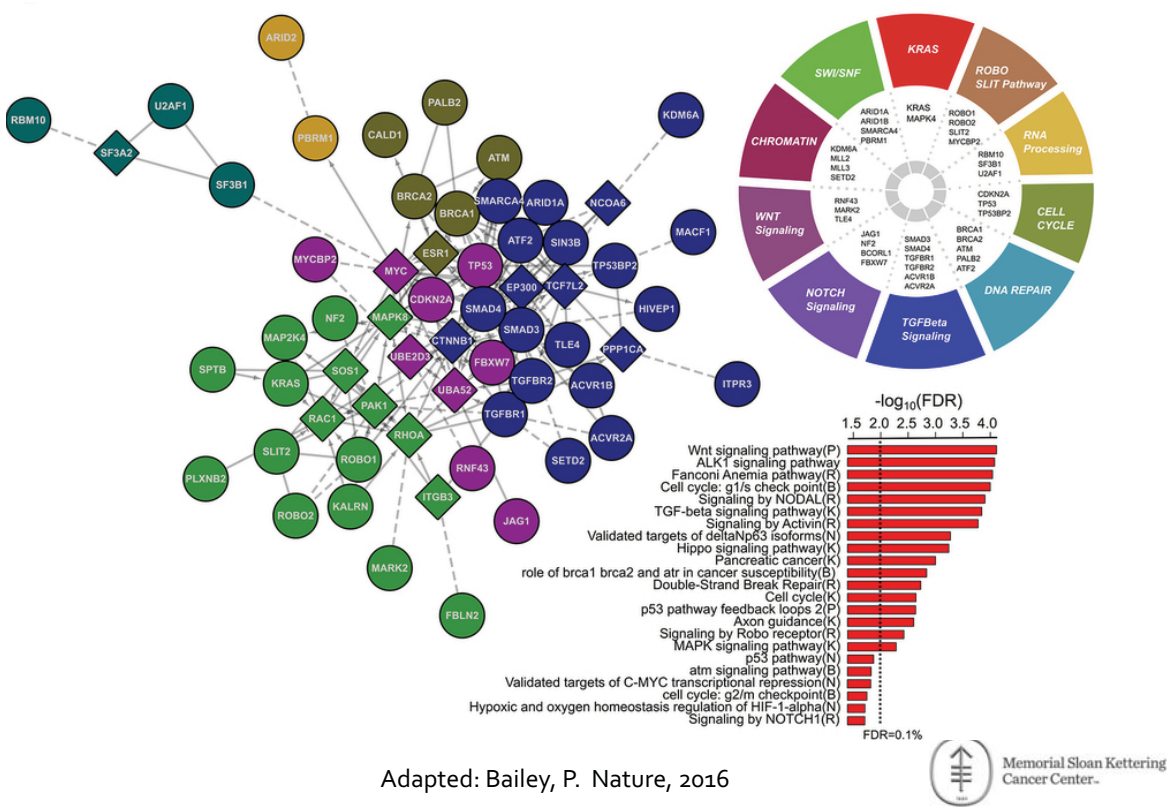
Altered Genes Pathways in PDAC



Adapted: Bailey, P. Nature, 2016

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Therapeutic Opportunities

- Stromal depletion
- Targeting stem cells
- Targeting metabolism
- Targeted therapy for genetic subgroups
- Targeting inhibitors of key signaling pathways
- Immunotherapy
- Radioimmunotherapy

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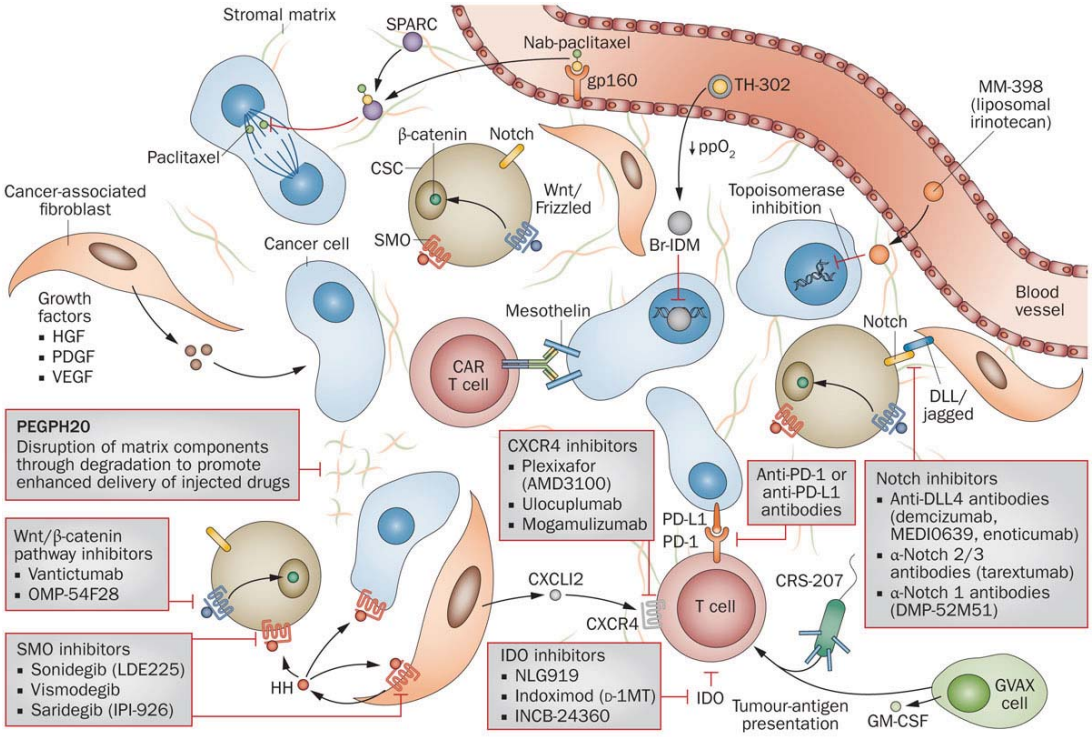
Novel Therapy Approaches



Garrido-Laguna, I, Hildalgo, M. Nat Cancer Reviews, 2015

Targeting Stroma

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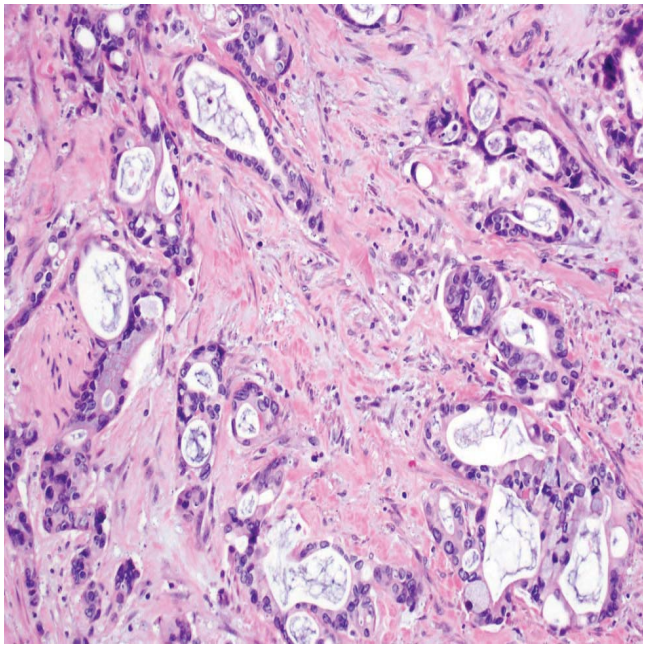
Microenvironment in PDAC

- Hypovascular, hypoxic
- Physical stromal barrier
  - Hyaluronan (HA) glycosaminoglycans
  - Increased EMT, chemoresistance
- PEGPH20 rhuman hyaluronidase
  - Depletes HA in stroma
  - Improves drug delivery



Jaocobetz, et al. Gut, 2013. Provenzano, P. Cancer Cell, 2012. Courtesy: J. Shia (MSKCC)

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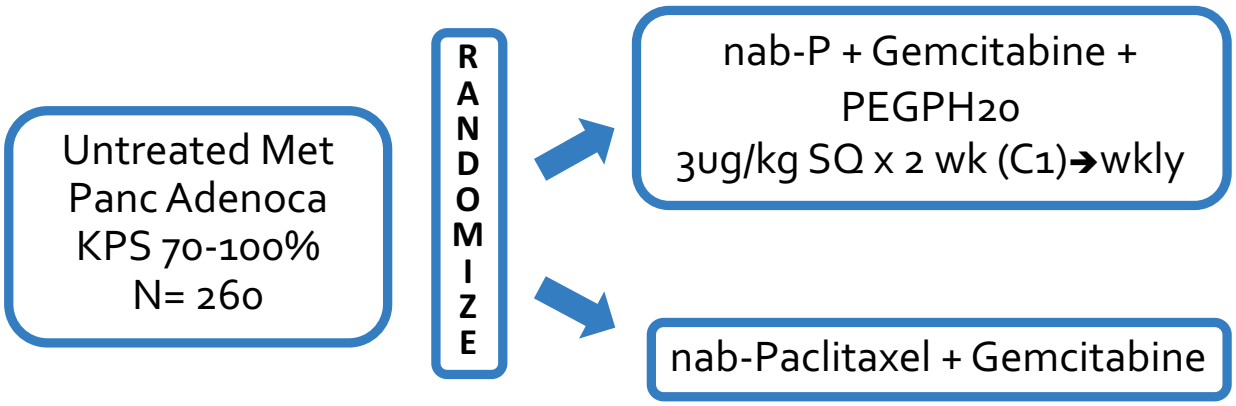
Randomized Phase II nab-P + Gemcitabine +/- PEGHPH20



Primary endpoint: Progression-free survival
Secondary endpoints: PFS by Hyaluronan, ORR, OS, Safety, Correlatives

Hingorani, S. J Clin Oncol 2015;33:4006 [abstr]

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Study Conduct

- Hold April 2014
  - DSMC/ FDA – increased thromboembolic (TE) events
  - Re-opened late 2014
    - Rigorous screening for TE's
    - Primary prophylaxis: enoxaparin
- Data presented early

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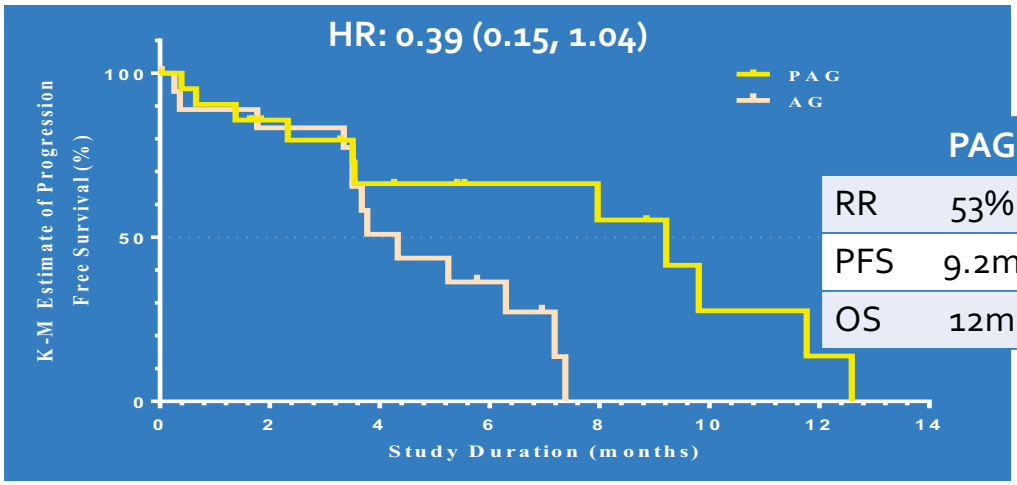
Rand Phase II: PFS In HA-High Pts Treated PEGPH20 + nab-P+Gem (PAG) vs nab-P + Gem (AG)



	PAG	AG
RR	53%	23.8%
PFS	9.2m	4.3m
OS	12m	9m

Subjects At Risk									
	PAG	23	14	10	6	5	2	1	0
	AG	21	14	7	4	0	0	0	0

Hingorani, S. J Clin Oncol 2015;33:4006 [abstr]

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Tumor Microenvironment/ Stroma: PEGPH20

- Randomized phase II trials
  - Nab-P + gemcitabine +/- PEGPH20 (completed)
  - FOLFIRINOX +/- PEGPH20 (SWOG-NCI)

- Phase III trial underway
  - Nab-P + gemcitabine +/- PEGPH20 (HALO-301)
  - Biomarker selected: Hyaluronan-high
  - Primary endpoints: PFS, OS
  - N= 420

NCT02715804

Targeting Genetic Subgroups

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DNA Repair Defects Common in Hereditary PDAC

Syndrome	Mutated Gene	Relative Risk	Reference
Peutz-Jegher	STK11 (19p13)	RR 132 x	Gastro 2000
Hereditary Pancreatitis	PRSSI (7q35) SPINK1 (5q31)	~ 50 x	Pancreat 2001 JNCI 1997
FAMMM	CDKN2A (9p21)	13- 22 x	NEJM 1995
FAP	APC (5q13)	RR 4.5 x	Gastro 2002
Hereditary Breast-Ovarian Syndrome	**BRCA1(17q21)** **BRCA2 (13q12)**	RR 2.2 x RR 3.5 x	JNCI 1999, 2002 BJC, 2012
HNPCC	**MLHI (3p21)** **MSH2 (2p16)**	~ 9	Cancer 1996 JAMA 2009
Ataxia Telangiect	**ATM (11q23)**	Increased	Clin Gen 1999
Breast, Pancreas	**PALB2 (16p12.2)**	Increased	Science 2009

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BRCA and PDAC

- 5-8% of PDAC patients germline BRCA 1 or 2 mutation
  - Ashkenazi Jewish 5-16%
  - Familial PDAC 5-19%
  - Familial breast/ovary cancer 5-10%

- BRCA Founder mutations in AJ descent (2-3%)
  - BRCA 1: 185delAG, 5382insC
  - BRCA 2: 6174delT

Hahn, SA. Gastro, 2003. Murphy, KM. Can Res, 2002. Ozcelik, H. Nat Genetics, 1997. Lal, G. Can Res, 2000. Lucas, AL. CCR, 2013. Ferrone, C. J Clin Oncol, 2009. Stadler, ZK. Can, 2012. Brose, MS. JNCI, 2002

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BRCA Mutations and PC Cont.

- Median age at diagnosis
  - Approx 10 yrs younger than SEER
- Prognostic effect of BRCA
  - Ovary ca: Longer OS for BRCA vs non-BRCA 53.7 vs 37.9 mths, p= 0.002
  - Breast Ca: No clear differences in OS
  - Pancreas Ca: Data suggests BRCA-associated PC better than non-BRCA; Utility to platinum

Howlader, et al. 2012. SEER registry. Golan, T. BJC, 2014. Chetrit, et al. J Clin Oncol, 2008

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Advanced Pancreas Adenoca

- Current strategies
  - FOLFIRINOX
  - Gem + Nab-Paclitaxel
  - Median survival < 1 year
- Novel Targets
  - DNA damage control?

Therapeutic opportunity?

Conroy, T. NEJM, 2011. Von Hoff, D. NEJM, 2013. Jones, S. Science, 2008. Bailey, P. Nature, 2016

Courtesy: Michael Pishvaian, MD

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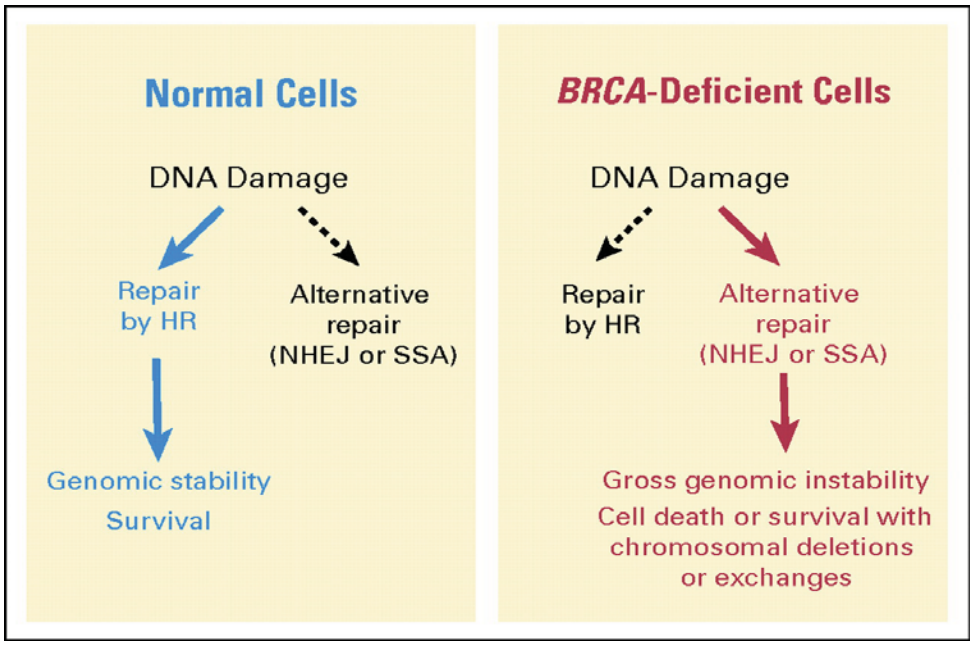
Loss of Functional BRCA-1/2 Affects DNA Double-Strand Break Repair Pathway



Ashworth, et al. J Clin Oncol, 2008

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Phase IB Cisplatin, Gemcitabine + Veliparib Untreated Met PC + Fm Hx or BRCA mut

DL	Veliparib PO BID	N	Dose-Limiting Toxicity	BRCA Subgroup
0	20mg BID, day 1-12	3	-	N= 2: 1 PR, 1 SD
1	40mg BID, day 1-12	3	-	N= 1: 1 PR
2	**80mg BID, day 1-12**	**6**	**-**	**N= 5: 3 PR, 2 SD**
2A	80mg BID, day 1-21	5	2 (grade IV plts, ANC)	N= 1: 1 PR

Recommended phase II dose of veliparib combined with fixed dose cisplatin + gemcitabine is 80 mg PO BID day 1-12, q 3 wks

O'Reilly, EM. NCT01585805. (NCI, Lustgarten Foundation). AACR, 2014; ASCO, 2014

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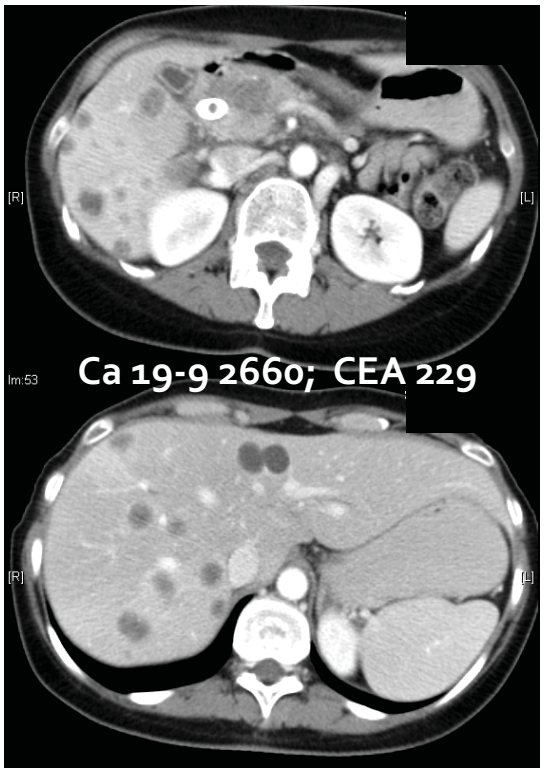
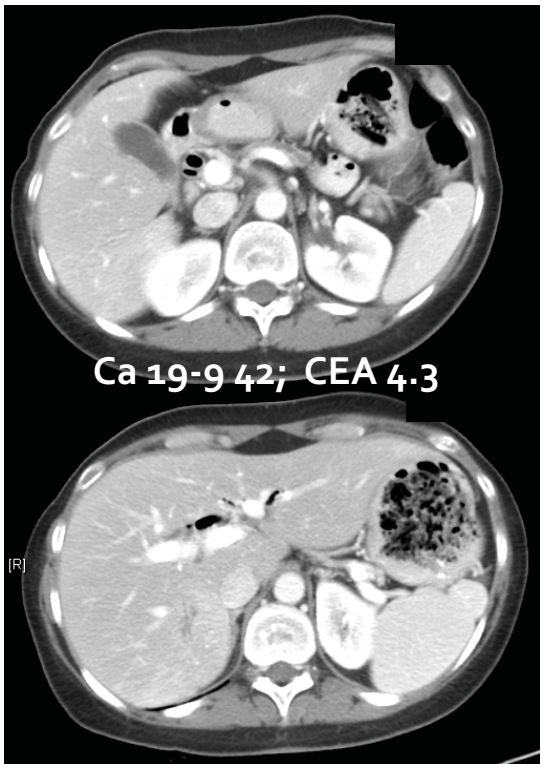
Patient BRCA1 Mutation





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Randomized Phase II
Cisplatin, Gemcitabine +/- Veliparib
Germline BRCA/PALB2

Untreated Stage III- IV PDAC
ECOG 0-1
N= 50- 70

RANDOMIZE

Arm A:
Cisplatin,Gemcitabine + Veliparib

Arm B:
Cisplatin, Gemcitabine

Randomization 1: 1
Primary Endpoint: Response Rate

NCT01585805 O'Reilly, EM, Lowery, M., Kelsen, D

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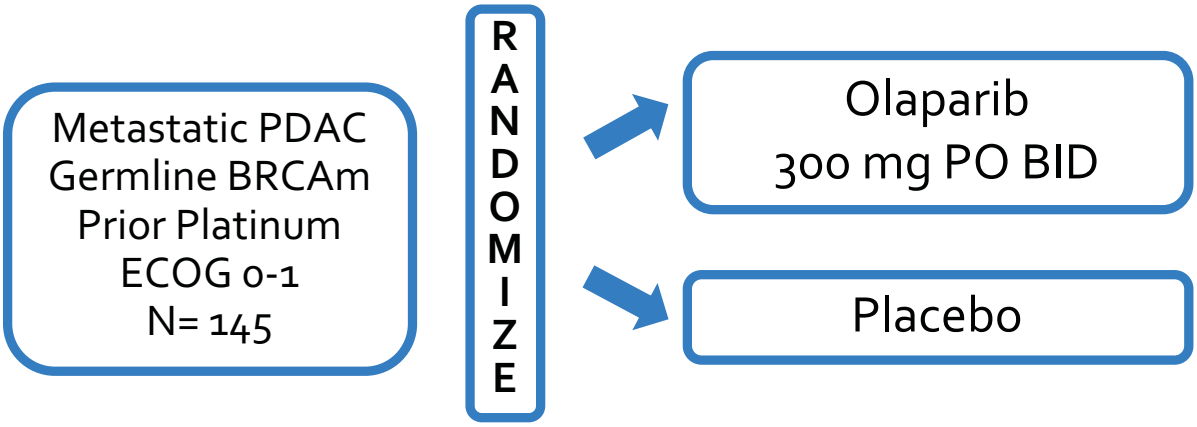
Phase III Trial Maintenance (POLO)
Platinum Therapy → Olaparib/Placebo



Randomization 3: 2
Primary Endpoint: PFS (central review mRECIST 1.1)

NCT02184195 (Astra Zenica, Myriad) Golan, T., Kindler, H

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Other PARPi Studies in PDAC

NCT	Design	N	Sponsor
01489865	FOLFOX + Veliparib: wild-type + germline BRCA Untreated, previously treated (phase I-II)		AbbVie Georgetown
01585805	Cisplatin, Gemcitabine +/- Veliparib Germline BRCA, PALB2 (randomized phase II)	50-70	MSKCC/NCI Lustgarten
01296763	Irinotecan, Cisplatin, Mitomycin C +/- Olaparib Wild-type + germline BRCA (phase I-II): **CLOSED**		John Hopkin's Columbia
02042378	Rucaparib, phase II PDAC Germline, somatic BRCA (previously treated):	100	Clovis
01989546	BMN-673 Germline BRCA + advanced ST; phase I-II		BioMarin
02184195	Platinum: maintenance +/- Olaparib (Phase III) Germline BRCA	145	Astra-Zenica POLO Trial
02677038	Olaparib Phase II Single-arm BRCA-ness Phenotype	48	
Pending	Phase II Gemcitabine, nab-Paclitaxel, Cisplatin Enriched for DDR deficiency	80	

www.clinicaltrials.gov

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Immune Therapy in PDAC

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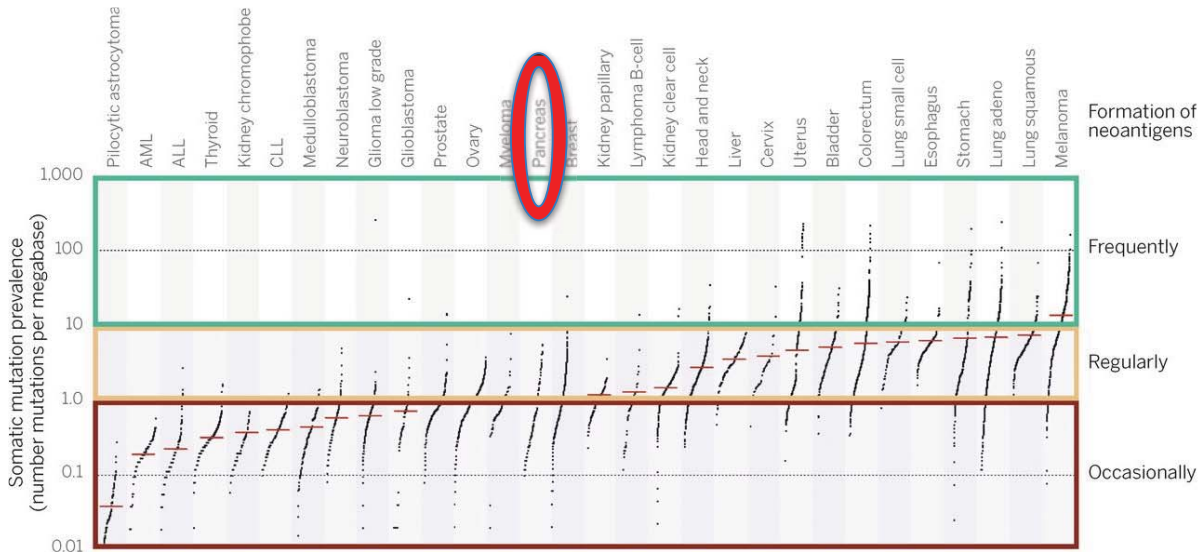
Immunogenicity Potential



Alexandrov, LB. Nature 2013. Schumacher, TN. Science 2015

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Immune Checkpoint Blockade

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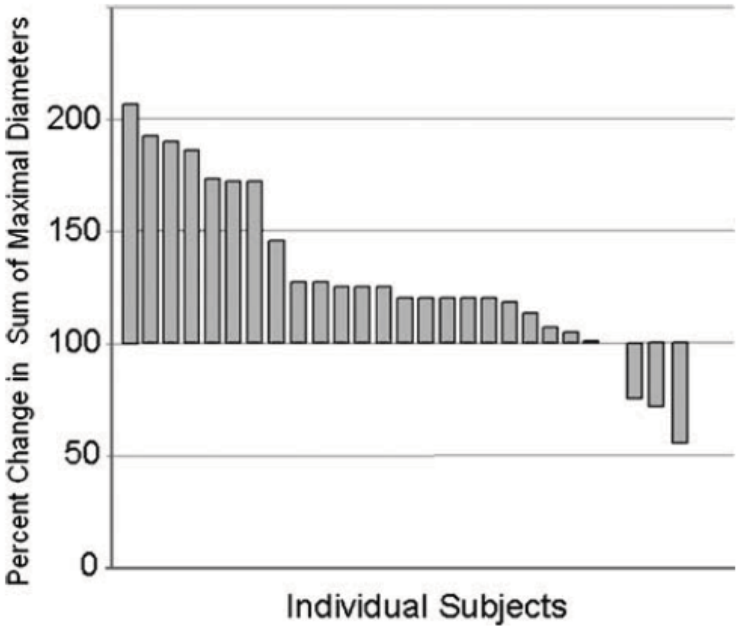
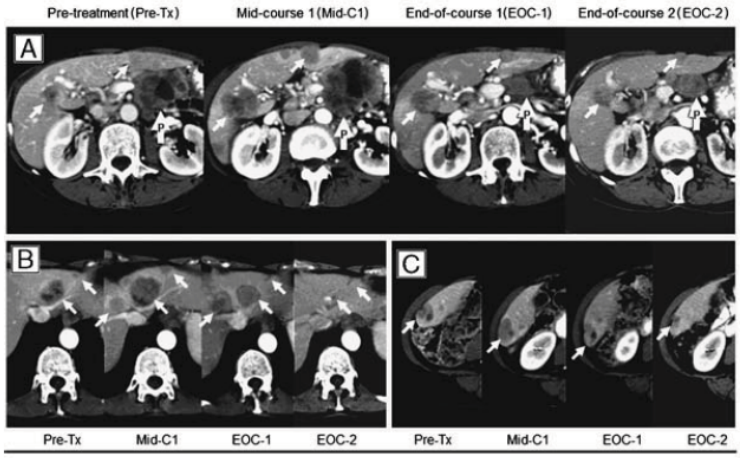
Phase II Ipilumumab PDAC (N= 27)



Royal, et al. J Immunother, 2010

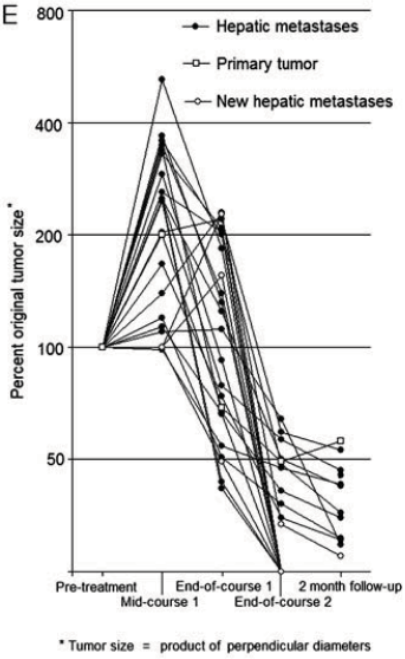
Memorial Sloan Kettering Cancer Center

Ipilumumab 3mg/kg
Delayed Tumor Response (N= 1)



D

Week	Tumor Markers beta-HCG	CEA	CA 19-9	
0	8.6	16.7	174	
3	11.0	76.2	535	
6	8.0	116.8	345	— Mid-course 1
9	5.5	34.4	73	
12	3.5	14.2	66	— End-of-course 1
28	3.9	10.4	28	— End-of-course 2



Royal, et al. J Immunother, 2010

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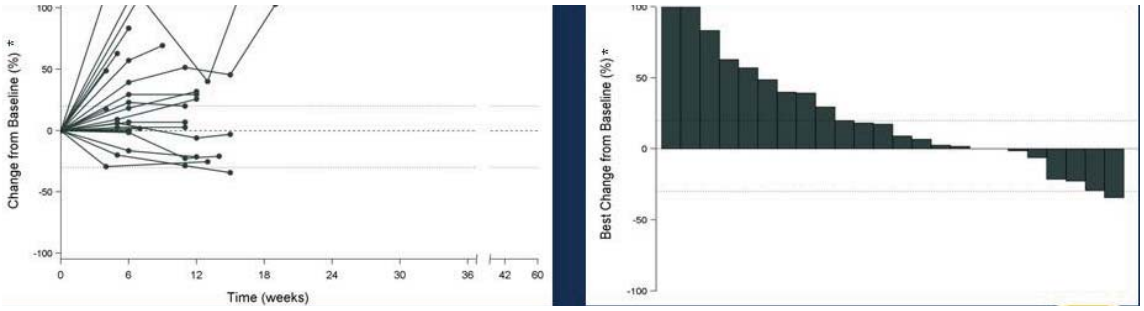
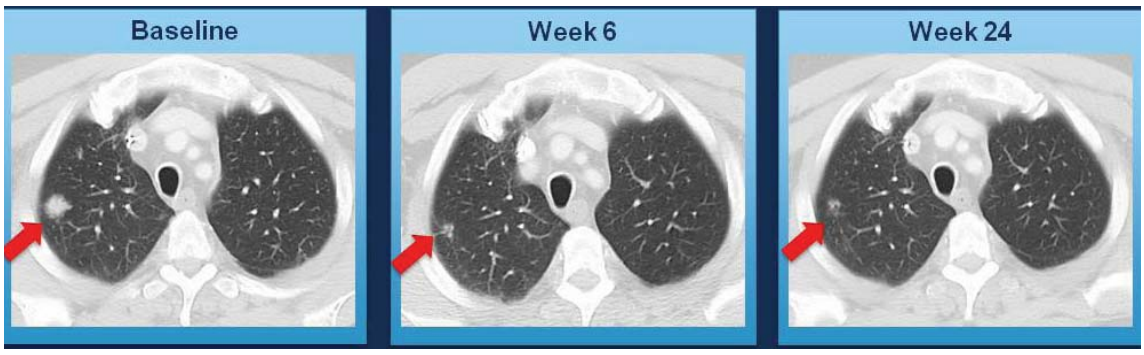
MEDI4736 PDAC Cohort, ASCO 2014
Anti-PD-L1





Segal, N. ASCO, 2014

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Combination Approaches

- Combination PD-1/PD-L1 + anti-CTLA4
- Checkpoint inhibitors + vaccines
- Cytotoxic therapy + immune therapy

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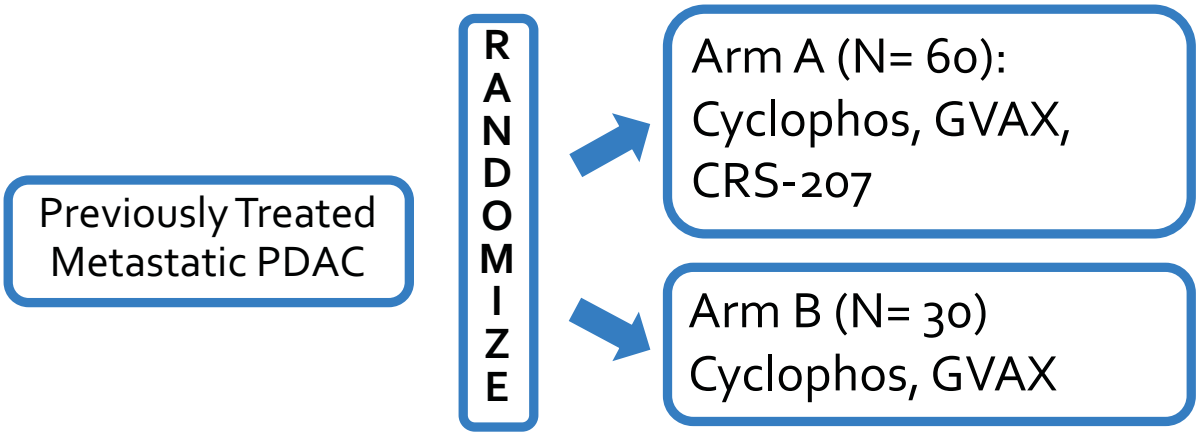
Randomized Phase II Previously Treated PDAC

CRS 207: modified listeria vaccine



Randomization 2: 1
Primary Endpoint: Overall Survival
Secondary Endpoints: Safety, Immunity, Responses

Le, D. J Clin Oncol, 2015

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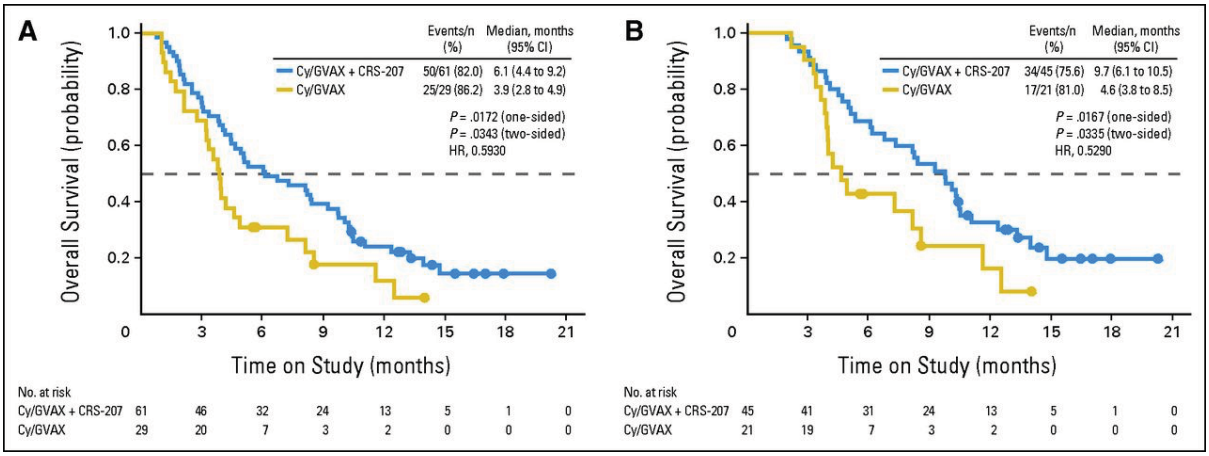
Overall Survival: +/- CRS207

A: All patients
B: Per Protocol Analysis (≥ 3 doses incl. 1 CRS-207)



Le, D. J Clin Oncol, 2015

Memorial Sloan Kettering Cancer Center

Randomized Phase II: ECLIPSE 2nd-3rd Line Met PDAC (accrued)

Previously Treated Metastatic PDAC 2nd, 3rd-Line Stable/POD

RANDOMIZE

- Arm A (N= 30 + 50): Cyclo, GVAX, CRS-207
- Arm B (N= 30 +50) CRS-207 alone
- Arm C (N= 30 + 50) Single agent therapy

Randomization 1: 1: 1
Primary Endpoint: Overall Survival in 3rd-Line
Secondary Endpoints: Safety, Immunity, Responses
Stratify: SD or PD, 2nd vs 3rd Line

NCT02004262

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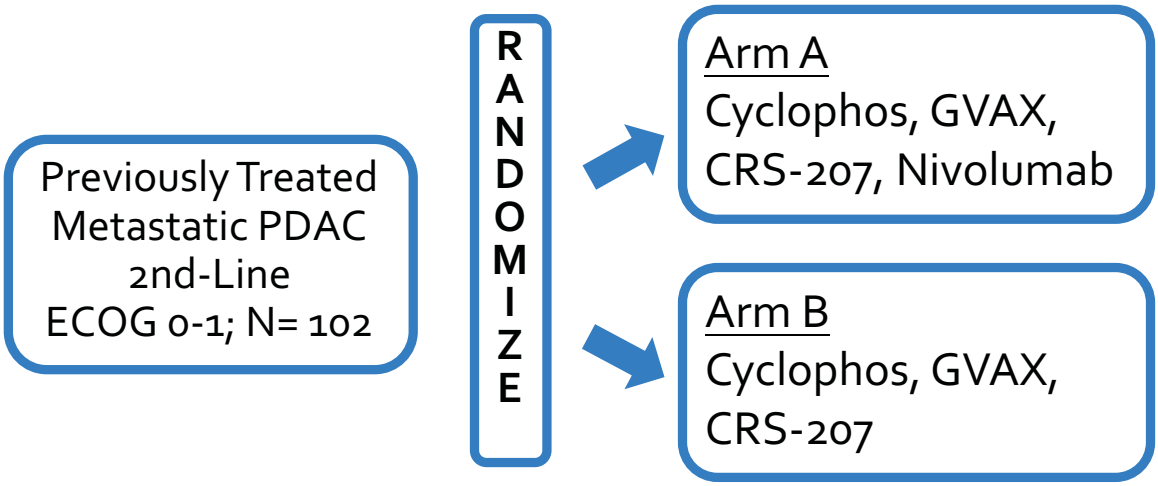
Rand Phase II: STELLAR
2nd Line Met PDAC (ongoing)



Randomization 1: 1
Primary Endpoint: Overall Survival
Secondary Endpoints: Safety, Immunity, Responses

NCT02243371

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Selective Ongoing Immune Therapy Trials in PDAC

NCT	Trial Design	Other
02309177	Nivolumab, Nab-Paclitaxel +/- Gemcitabine 1st L, 2nd L; (panc cohort)	Celgene
02331251	Pembrolizumab + Gemcitabine, Nab-Paclitaxel (panc cohort)	Western Regional Medical Center
02077881	Indoximid (IDO Inhibitor) + Gemcitabine, Nab-Paclitaxel, Phase I-II	NewLink Genetics
02311361	Tremelimumab +/or MEDI4736 + SBRT (Panc cohort)	RADVAX Abramson, U Penn
02472977	Ulocuplumab + Nivolumab 2nd L+, Phase I-II (Panc, Small cell)	BMS
02301130	Mogamulizumab (CCR4 inhibitor) + MEDI4736 or Tremelimumab (panc cohort)	Kyowa Hakko Kirin Pharma
02465983	CAR T cell mesothelin, CD19	U Penn, UCSF

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Other Stromal/Immune Targets

- CCL2 (chemokine)/CCR2 (receptor)
  - Mobilize monocytes, modulates immunity
  - CCR2 inhibitor (PF-04136309)
  - Evaluated with FOLFIRINOX
  - Phase Ib/rand. II gemcitabine/nab-paclitaxel +/- CCR2i
- Ibrutinib (BTK inhibitor)
  - Phase II/III: Gemcitabine, nab-paclitaxel +/- ibrutinib
- MSI-H – early signal identified (1-2% PDAC)

Nywening, T. Lancet Oncology, 2016. NCT0273298. NCT02436668. NCT01876511

Immune Therapy Summary

- PDAC immune privileged
- Immune therapy activity observed in PDAC
- Combination approaches appear key
  - Multiple strategies under evaluation
- Biomarker identification
- Delayed response potential

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Disappointments 2016

- Hypoxia/ stroma
  - Evofosfamide (rand phase III)
  - Necuparanib (rand phase II)

- Targeted strategies
  - Ruxolinib: JAK kinase inhibitor (phase III x 2)
  - Tarextumab: Notch stem cell inhibitor (rand ph II)

- Immune therapeutics
  - Algenpantucel-L (adjuvant phase III)
  - CRS-207 (ECLIPSE, rand phase II)

Molecular Profiling PDAC

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Conclusions PDAC

- Improving front and second-line treatment options

- Novel therapeutics
  - Very active area of research
  - Multiple ongoing randomized phase II trials
  - Intense biomarker evaluation

- Optimism that meaningful progress on the horizon

Neuroendocrine Tumors: A Growing and Unusual Problem

Eric H. Liu, MD
Co-Director, The Neuroendocrine Institute
Chief Medical Advisor, The Healing NET Foundation
Rocky Mountain Cancer Center

NEUROENDOCRINE TUMORS
A Growing and Unusual Problem

Eric Liu, M.D.
Co-Director, The Neuroendocrine Institute, Denver, CO
Chief Medical Advisor, The Healing NET Foundation
October 1, 2016

Conflicts of Interest

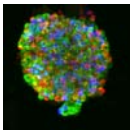
- Novartis – Speaker Bureau
- Ipsen – Speaker Bureau
- AAA – Consulting
- Lexicon - Consulting

Stuff You Need to Know

- Overview of Neuroendocrine
- Diagnostics
- Pathology
- Therapy
- What's new in Neuroendocrine?
- The Neuroendocrine Institute

Basics of Neuroendocrine Cells

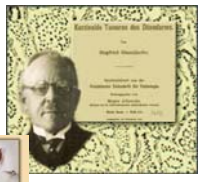
- Found in bronchial, gastroenteropancreatic tract
- Secrete hormones
  - Serotonin
  - Insulin
  - Gastrin
  - Glucagon
  - VIP
  - Somatostatin
  - Histamine
- Express SOMATOSTATIN RECEPTORS



Liu and Oberg, Endo Meta Clin N Am, 39(4):697-71, 2010

Terminology

- "Carcinoid"
- APUDoma
- Islet Cell Tumors
- Neuroendocrine carcinoma



Modlin et al, Hum Pathol 12:1440-51, 2004

Definitions

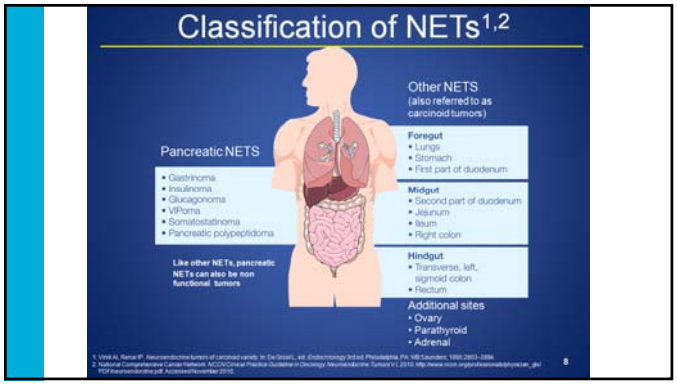

Siegfried Oberndorfer

Cardinoid
slow growing tumor of the GI and bronchial tracts that derives from enterochromaffin cells that frequently secrete serotonin

Neuroendocrine Tumors
tumors derived from GI endocrine cells that can secrete many hormones

Insulin glucagon gastrin VIP

Express somatostatin receptor

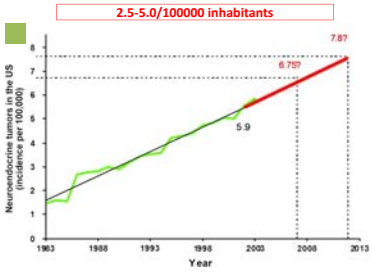


Incidence of neuroendocrine tumors

2.5-5.0/100,000 inhabitants

Modlin, I. M. et al. J. Natl. Cancer Inst. 2008;100:1282-1289; doi:10.1093/jnci/djn275

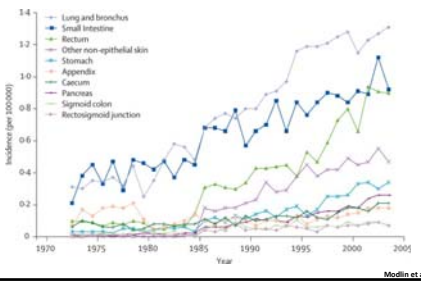
Incidence of neuroendocrine tumors



Modlin, I. M. et al. J. Natl. Cancer Inst. 2008;100:1282-1289; doi:10.1093/jnci/djn275

Incidence of neuroendocrine tumors

Surveillance, Epidemiology and End Results (SEER), US population 1974-2005

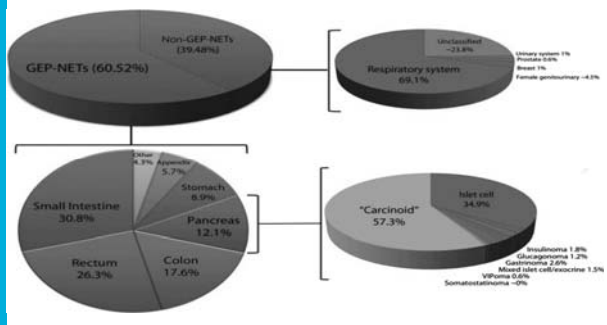


Lung

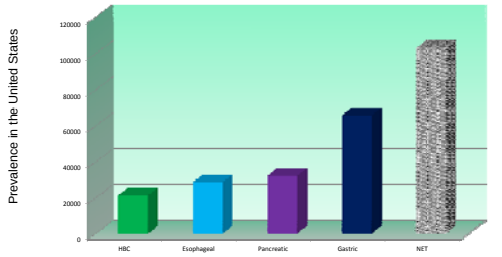
Small intestine
Rectum

GEP-NET
~ 75%

Modlin et al., Lancet Oncol. 2008

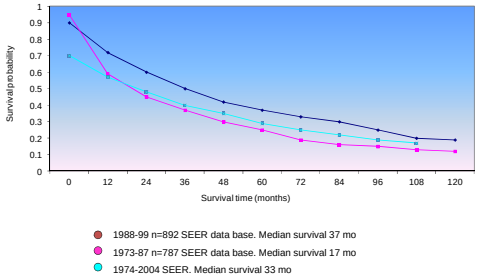


Neuroendocrine Tumors are common compared to other cancers

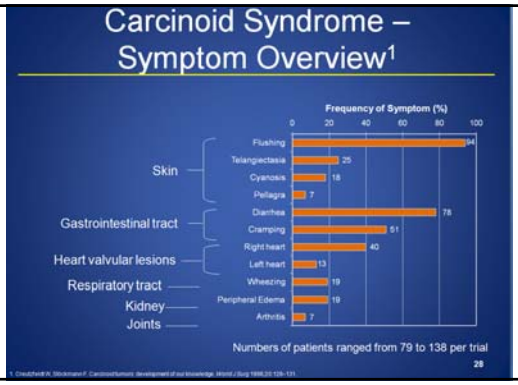


Modlin et al., Lancet Oncol, 2008

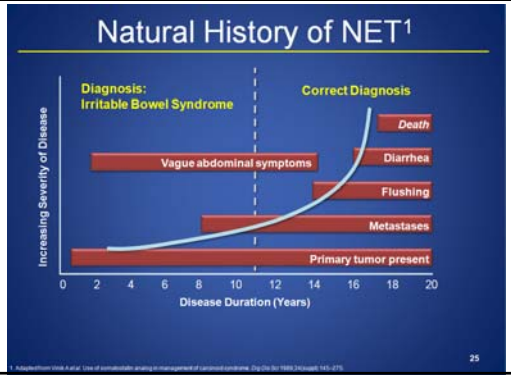
Survival of patients with metastatic carcinoid



Carcinoid Syndrome – Symptom Overview[1]



Natural History of NET[1]



Stuff You Need to Know

- Overview of Neuroendocrine
- Diagnostics
- Pathology
- Therapy
- What's new in Neuroendocrine?
- The Neuroendocrine Institute

Biochemical Testing

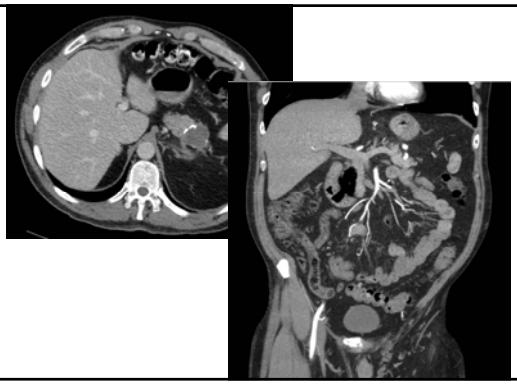
- Hormone levels (serum and urine)
  - 5-HIAA
  - Gastrin
  - Insulin/C-peptide/Proinsulin
  - Glucagon
  - VIP
  - Serotonin
  - And others…

Biochemical Testing

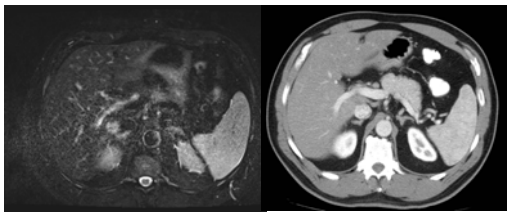
- Biomarkers
  - Chromogranin A
  - Chromogranin B
  - Pancreastatin
  - Neuron specific enolase
  - Ghrelin
  - Pancreatic Polypeptide
  - Substance P
  - And more…

Imaging

- CT
- MRI
- Ultrasound
- Endoscopy



CT vs. MRI



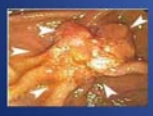
MRI may pick up ~ 20% more lesions

Giesel et al, 2011, Dromain, et al, 2005

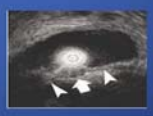
Primary Carcinoid Tumor

Image of a gastric carcinoid tumor

Image of carcinoid tumor in the duodenal bulb



Carcinoid tumor involving the ampulla

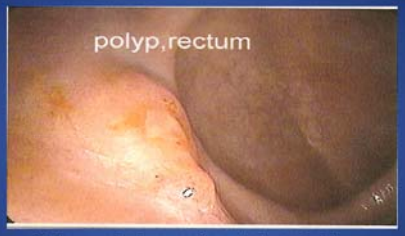


Endosonographic image of hypoechoic submucosal tumor extending through the muscularis propria layer in the duodenal bulb

40

Images provided by Dr Jeffrey Lee (2009).

Colonoscopy

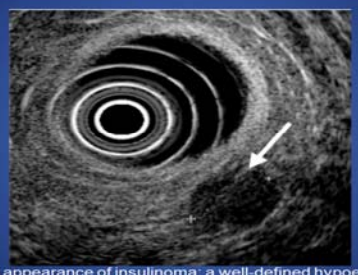


- Colonoscopic image of a rectal carcinoid

58

1. Reproduced from Gastroenterology Associates. http://gieassociateschicago.com/services. Accessed December, 2010.

Endoscopic Ultrasound

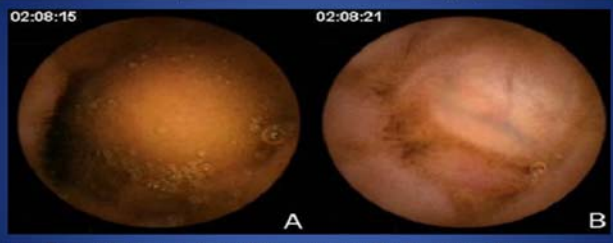


90% sensitive

Typical EUS appearance of insulinoma: a well-defined hypoechoic 1.5 mm mass in the mid body of the pancreas.

41

Capsule Endoscopy



- Two endoscopic images that may show the location of the patient's primary tumor in the submucosa

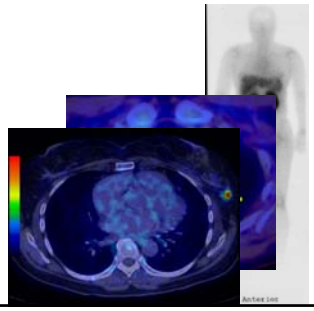
56

The Ideal Imaging Modality

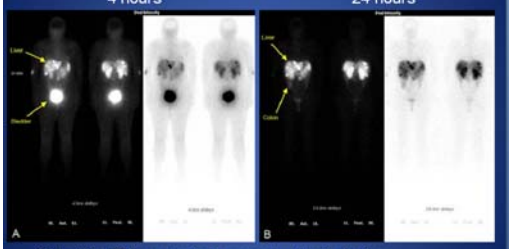
The Ideal Imaging Modality

Nuclear Imaging

- Octreoscan: ^{111}Indium
- FDG
- ^{11}C-HTP
- ^{18}F-DOPA
- ^{68}Ga-octreotate



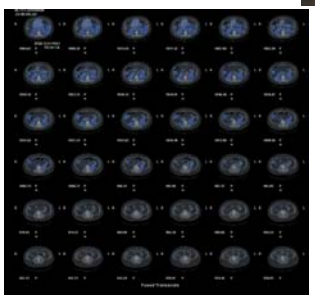
OctreoScan™

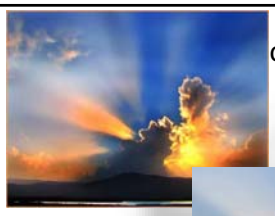


- OctreoScan™ from showing increased uptake in the liver, retroperitoneal lymph nodes, and colon

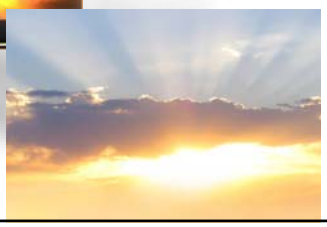
40

Octreoscan





oscan



Stuff You Need to Know

- Overview of Neuroendocrine
- Diagnostics
- Pathology
- Therapy
- What's new in Neuroendocrine?
- The Neuroendocrine Institute

Pathological Classification of NETs

Histological classification	Well-differentiated	Moderately differentiated*	Poorly differentiated
Appearance	Monomorphic population of small, round cells		Cellular pleomorphism
Prognosis	Prolonged survival	Intermediate	Poor
Mitotic rate (mitoses/10 HPF)	<2		>10
Ki-67 (MIB-1) index	<2%		>10%
Necrosis	Absent		Present

Images courtesy of Nasir Anjal, MD, Department of Pathology, H. Lee Moffitt Cancer Center and Research Institute, Tampa.
Reproduced with permission from Strosberg J et al. Gastrointest Cancer Res 2:113–125, © 2008 by International Society of Gastrointestinal Oncology.

*Not well defined in the medical literature.

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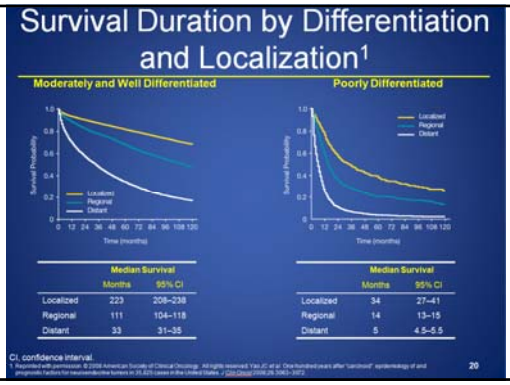
Survival Duration by Differentiation and Localization[1]



Moderately and well Differentiated	Median Survival Months	95% CI
Localized	223	208–238
Regional	111	104–118
Distant	33	31–35

Poorly Differentiated	Median Survival Months	95% CI
Localized	34	27–41
Regional	14	13–15
Distant	5	4.5–5.5

CI, confidence interval.

1. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved. Yao JC et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–3072.

20

Stuff You Need to Know

- Overview of Neuroendocrine
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CUT IT OUT

CUT IT OUT

CUT IT OUT

Surgical Treatment of Midgut NET

- Resection of primary 7.4 vs. 4.0 years; p<0.001
- LN mets resected: 7.9 vs. 6.2 years; p<0.001
- Liver mets: p<0.001
  - (+) 4.9 yrs
  - (-) 10.1 yrs
- Liver mets (-) & LN resection 12.4 yrs vs. ~7.6, p<0.01

Hellman, et al. World J Surg 2002;26:991-7.

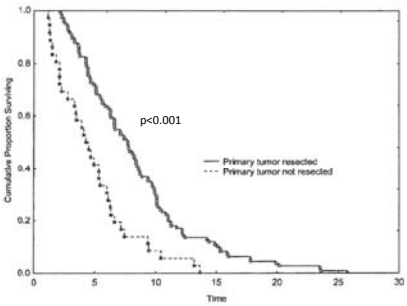
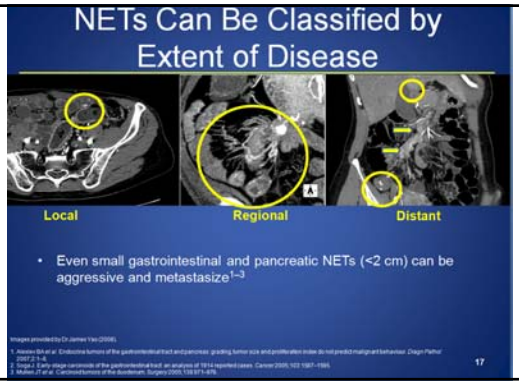
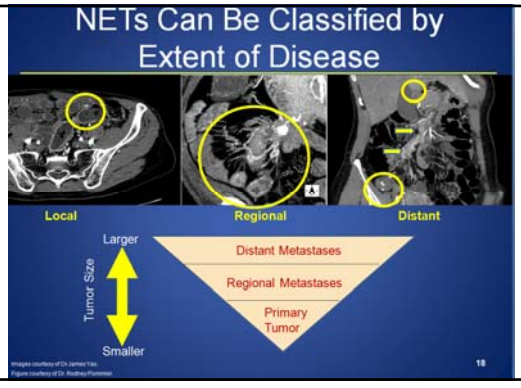


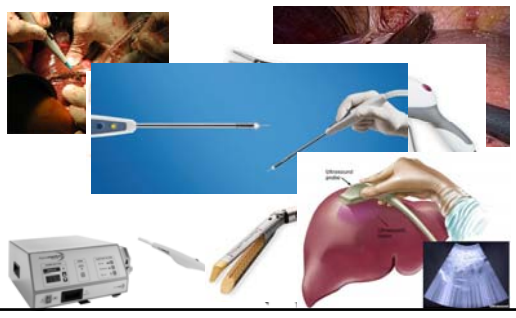
Fig. 3. Survival of patients with and without primary tumor resected.

Hellman, et al. World J Surg 2002;26:991-7.





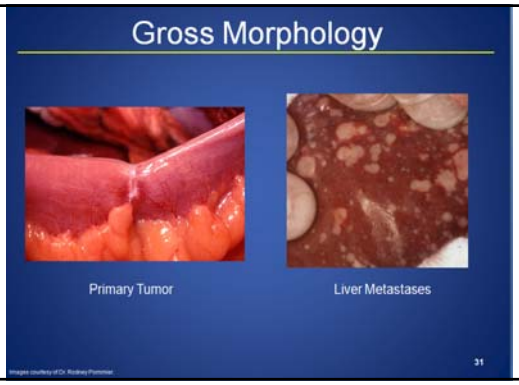
Liver Surgery

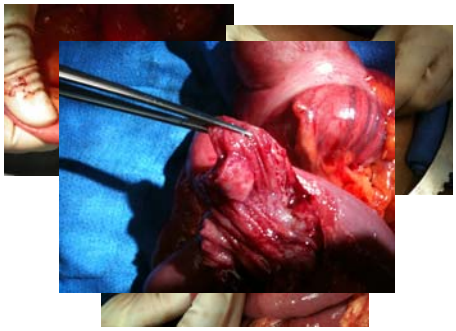


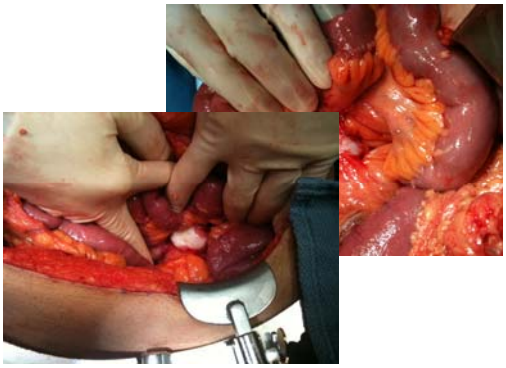
Other ways to treat the liver

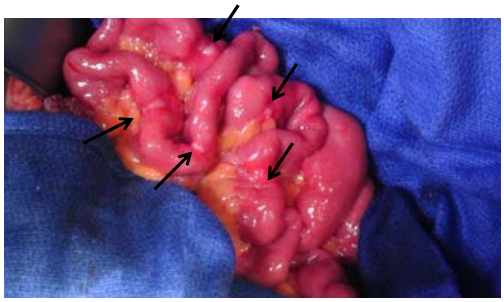
NANOKNIFE

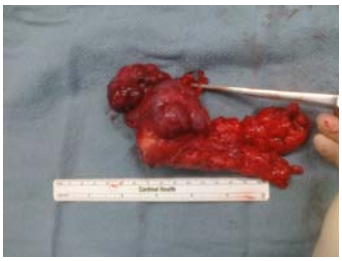
GROSS SURGERY
AND
SQUISHY ORGANS

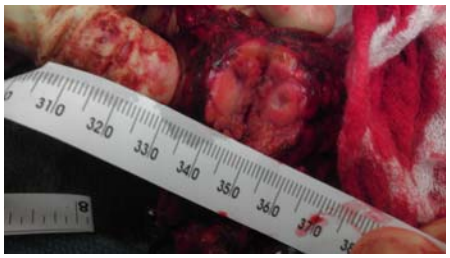


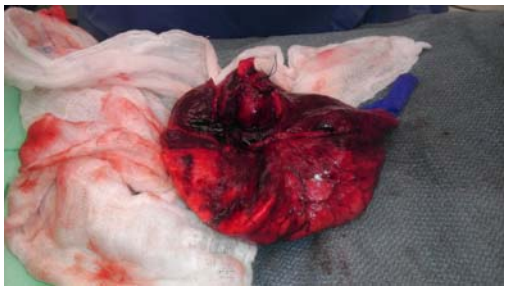




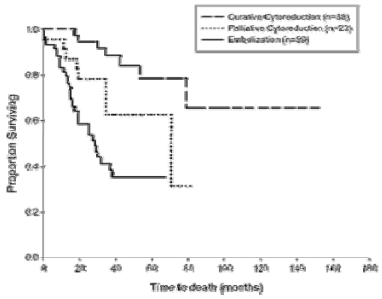






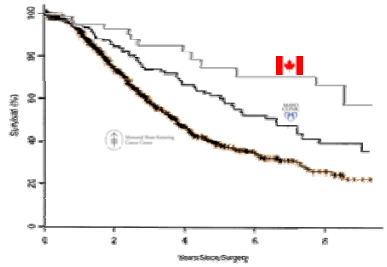


The better the surgery, the better the outcome

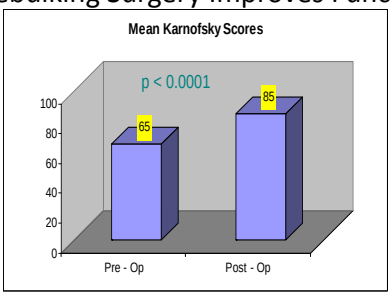


Boudreaux et al, Ann Surg, 2005

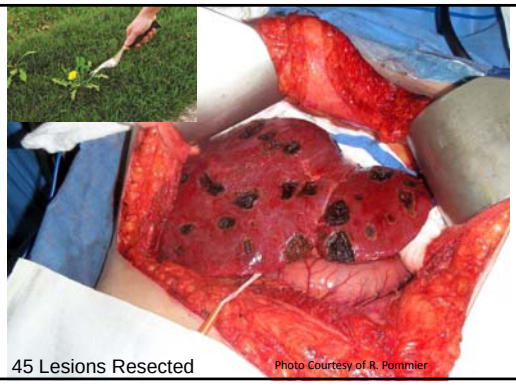
Neuroendocrine is different from Adenocarcinoma



Debulking Surgery Improves Function

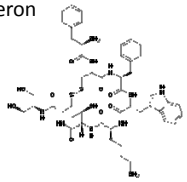


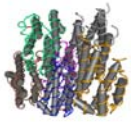
Boudreaux et al, Ann Surg, 2005



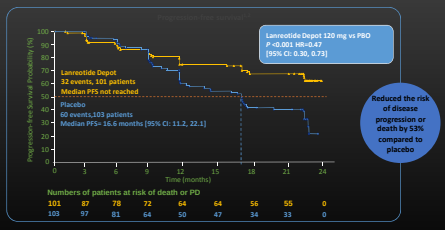
Biotherapy

- Somatostatin Analogues (Fast Acting vs. LAR)
  - Sandostatin LAR – octreotide
  - Somatuline Depot - lanreotide
- Interferon



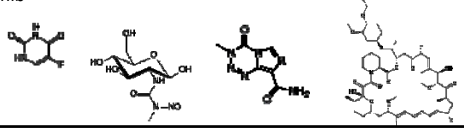


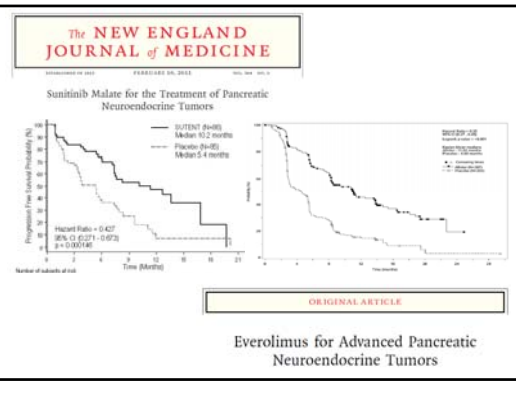
Lanreotide Depot: Significantly Extended PFS



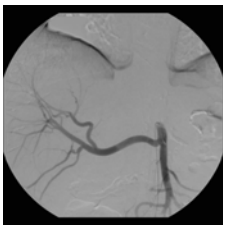
Chemotherapy

- 5-FU
- Streptozotocin
- Temozolomide
- Everolimus
- Bevacizumab
- Sunitinib
- Etoposide
- Doxorubicin
- Platinum
- Dacarbazine
- Taxotere





Embolization



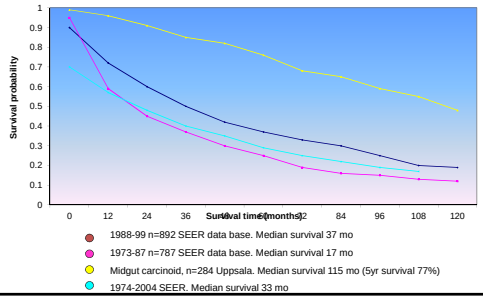
- Bland embolization
- Chemoembolization
- Radioembolization
  85% responded

NCCN Guidelines

Stuff You Need to Know

- Overview of Neuroendocrine
- Diagnostics
- Pathology
- Therapy
- What's new in Neuroendocrine?
- The Neuroendocrine Institute

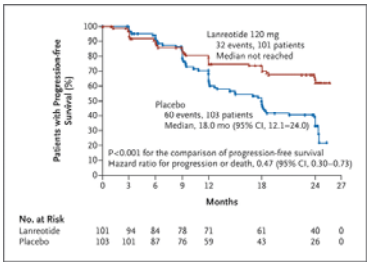
Where can we be?



What's New in Neuroendocrine?

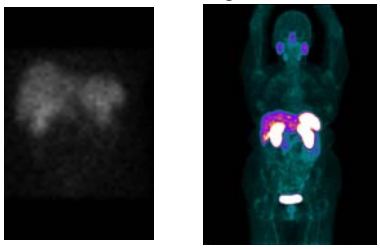
- Somatuline (Lanreotide)
- Gallium Scan
- PRRT
- Afinitor for Lung and GI NETs

Somatuline slows tumor growth



Neuroendocrine Institute

Clinical Program

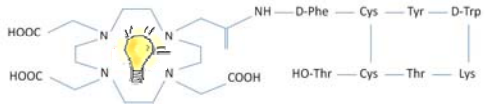


Standard Vanderbilt

Referral Center *for* Referral Centers

67

68Ga-DOTATATE

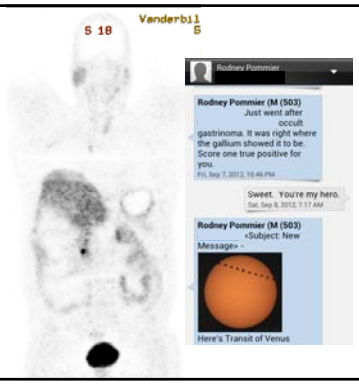


$^{68}Ge/^{68}Ga$ – Generator Comparison

Technical Information Bulletin

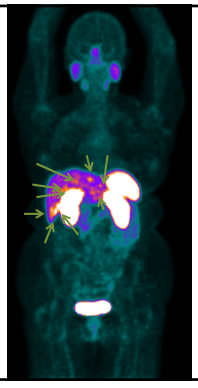
$^{68}Ge/^{68}Ga$-Generator (Obninsk) $^{68}Ge/^{68}Ga$-Generator IGG100

Pommier
Surgery
Gastrin still
elevated



She has three lesions on conventional imaging

She has three lesions on conventional imaging

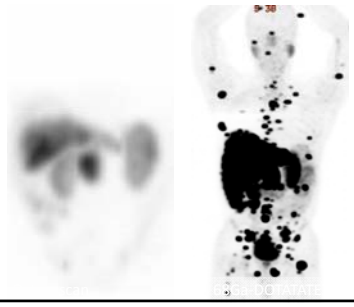


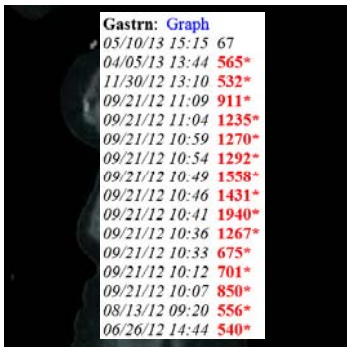
Dennis, he's 45 years old, he has two children, he's a teacher, and he has…

At ANY Other hospital he got this

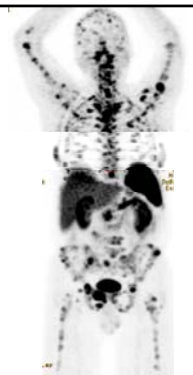
Dennis, he's 45 years old, he has two children, he's a teacher, and he has…

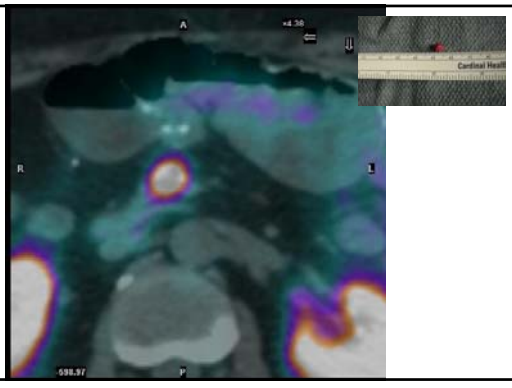
At a NET Center he got this

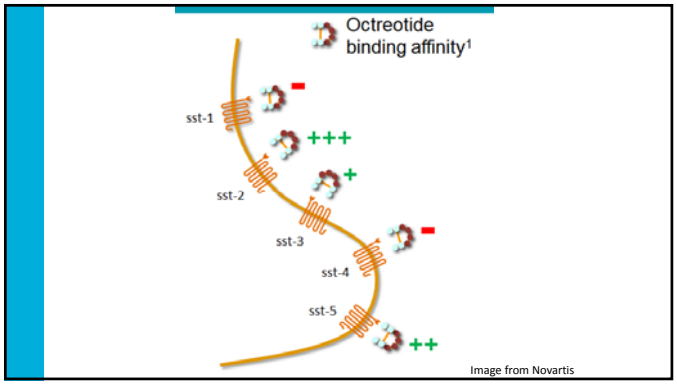


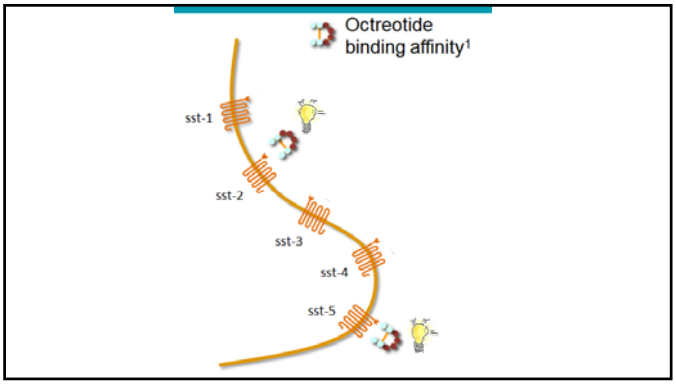


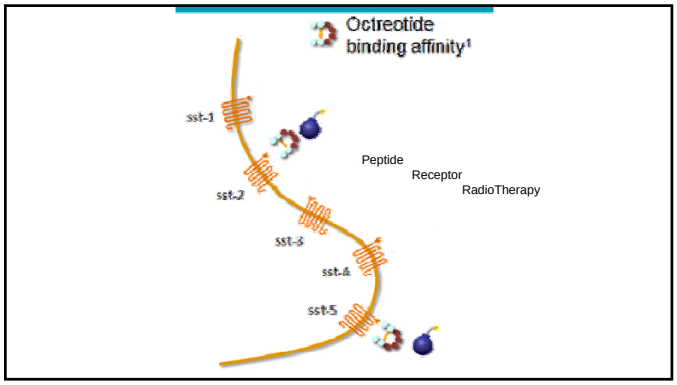
I ALMOST OPERATED ON THIS PERSON…

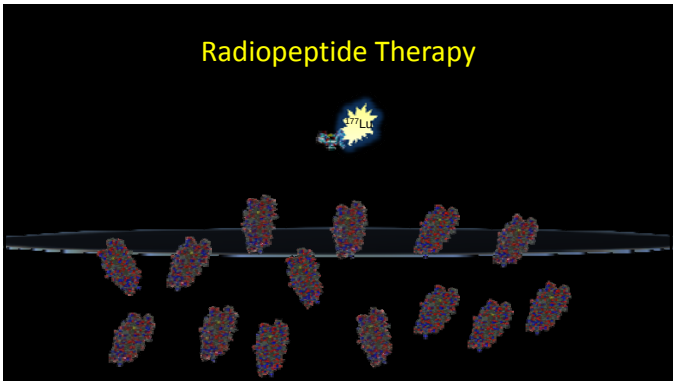


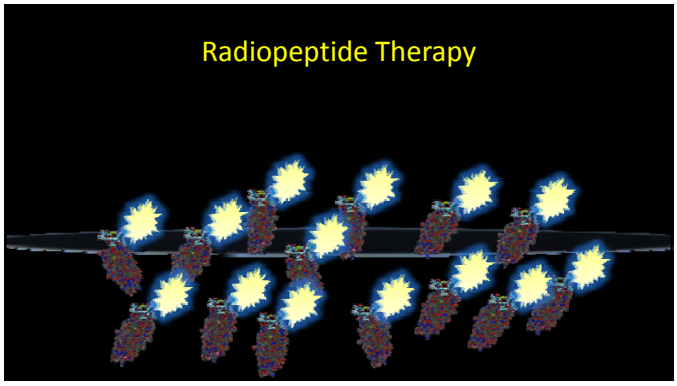


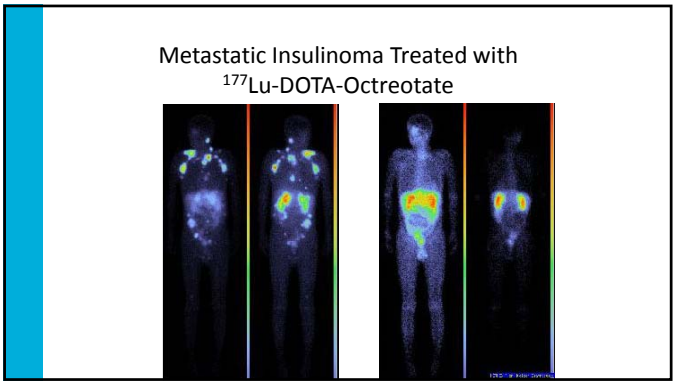

Octreotide
binding affinity¹
sst-1
sst-2
sst-3
sst-4
sst-5
+++
+
++
Image from Novartis


Octreotide
binding affinity¹
sst-1
sst-2
sst-3
sst-4
sst-5

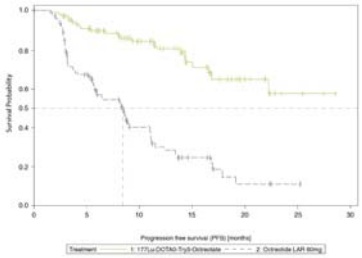

Octreotide
binding affinity¹
sst-1
sst-2
sst-3
sst-4
sst-5
Peptide
Receptor
RadioTherapy


Radiopeptide Therapy
177Lu

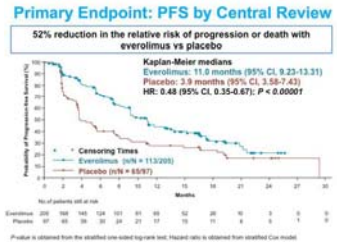

Radiopeptide Therapy

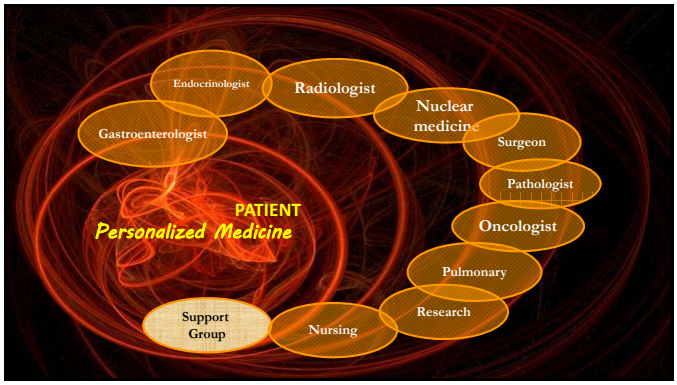

Metastatic Insulinoma Treated with
177Lu-DOTA-Octreotate

Survival With PRRT



Afinitor for Lung & GI NETs

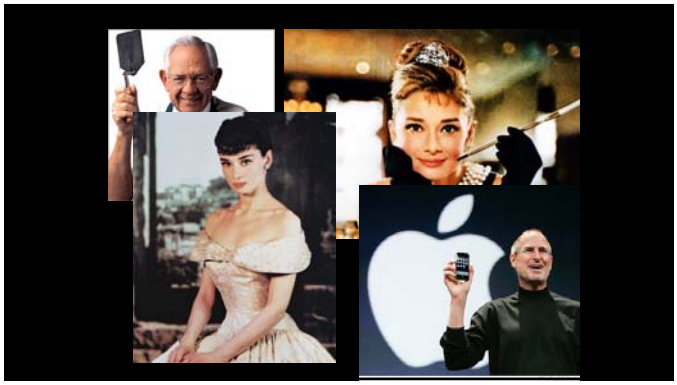




The Neuroendocrine Institute at Rocky Mountain Cancer Centers

Mesenteric Vascular Reconstruction

Images Courtesy of Dr. Nic Yee



The Neuroendocrine Institute at Rocky Mountain Cancer Centers

Thank You

- Allen Cohn
- Charlie Nutting
- Glenn Balasky
- Melissa Coria
- Pam Gaytan
- Laura Devor
- Doni Trujillo
- Nic Yee
- Marc Sarti
- Craig Kornbluth
- Jennifer Kemp
- Garrett Ganuth
- Maureen Tarrant
- Amanda Veit
- Brandon Mencini
- Robert Portwood
- Amanda Peeks
- Cindy Lovelace
- The Healing NET Foundation
- Kjell Oberg
- Carol Word
- Maurine Taylor
- Liz May
- Shalini Chahal
- Maggie Ryan

Chronic Lymphocytic Leukemia in the Modern Era

Farrukh Awan, MD, MS
Associate Professor of Medicine
Division of Hematology
The Ohio State University

CHRONIC LYMPHOCYTIC LEUKEMIA IN THE MODERN ERA

Farrukh Awan, MD, MS
Associate Professor of Medicine
Division of Hematology
The Ohio State University
Oct 2016

The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

cll.osu.edu

Case 1

59-yr-old male with IGHV mutated CLL presents with progressive fatigue, lymphadenopathy and splenomegaly.

His lab evaluation reads:

- WBC count: 195,000 cells/μL
- Hemoglobin: 8.5 mg/dL
- Platelet count: 86,000 cells/μL
- Beta-2 macroglobulin: 1.8
- FISH: del(13q14)

What is the best choice of therapy:

- Chlorambucil
- Fludarabine + rituximab
- Fludarabine, cyclophosphamide, rituximab
- Lenalidomide ± rituximab
- Chlorambucil + obinutuzumab
- Unsure

The James
THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

Case 2

64-yr-old male with IGHV unmutated, 17p deleted CLL presents with progressive fatigue, lymphadenopathy and, splenomegaly.

His lab evaluation reads:

- WBC count: 195,000 cells/μL
- Hemoglobin: 8.5 mg/dL
- Platelet count: 86,000 cells/μL
- FISH: del(17p13)

- What is the best choice of therapy:

- Chlorambucil
- Fludarabine + rituximab
- Fludarabine, cyclophosphamide, rituximab
- Lenalidomide ± rituximab
- Bendamustine + rituximab
- Chlorambucil + obinutuzumab
- Chlorambucil + ofatumomab
- Ibrutinib

INITIAL MANAGEMENT

The James
The Ohio State University
Comprehensive Cancer Center

What do we do at Initial Presentation?

- **All patients undergo**
  - History and Physical
  - CBC with diff
  - CMP
  - Peripheral Blood Flow cytometry

- **Optional**
  - Quantitative Immunoglobulins
  - Direct Anti-Globulin Test
  - Infectious Serology
  - CT scan CAP
  - Bone Marrow Biopsy

Definition of CLL
IWCLL - 2008

- Small, monomorphic, mature B-cells
- Atleast 5,000/ul B-cells
- Co-express CD5 and CD23

What do we do at Initial Presentation?

- **Prognostic Markers**
  - Interphase FISH
  - Conventional karyotyping
  - IGHV mutational analysis
  - Beta-2 microglobulin
  - LDH
  - Lymphocyte doubling time

EARLY TREATMENT

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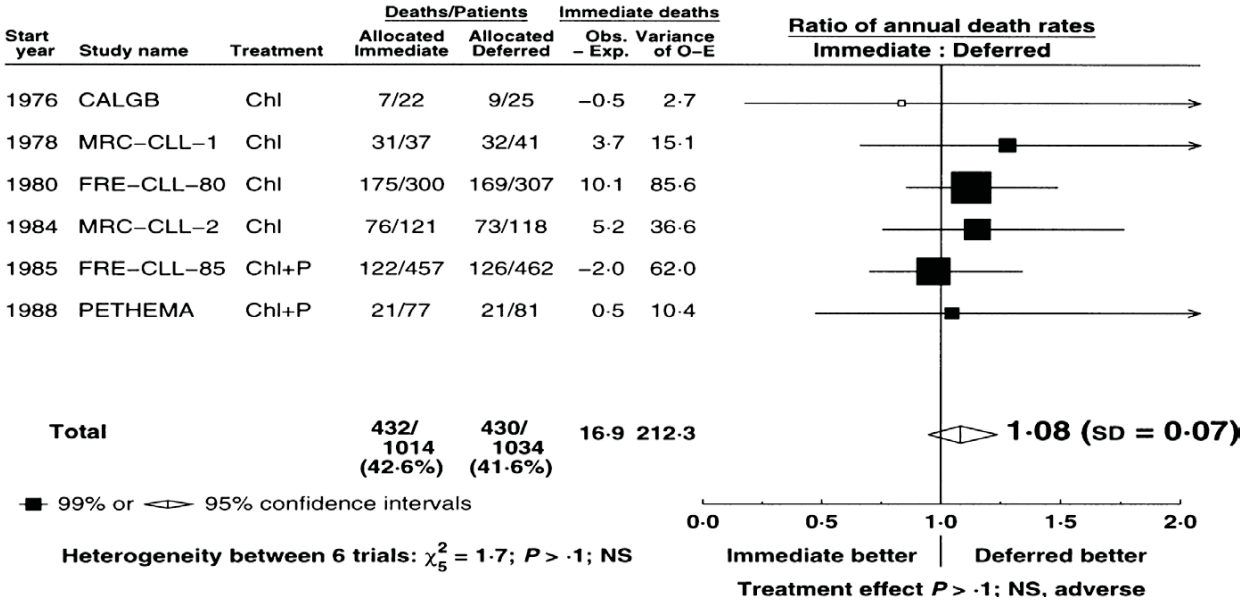
Early Treatment Does not improve Survival



J Natl Cancer Inst, 1999

Early Intervention

- Multiple trials are ongoing with various non-chemotherapeutic agents and combinations
- Patients with high-risk disease should be referred to a CLL center
- OSU-15012 is early intervention trial with ibrutinib in patients with high-risk disease

STAGING

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Staging and Risk Stratification

- Rai/Binet Staging
- Novel Prognostic markers

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Prognostic Markers

- Interphase cytogenetics by FISH
- IGHV Mutational Status
- ZAP-70
- CD38

Prognostic Markers

- Interphase cytogenetics by FISH
- IGHV Mutational Status
- ZAP-70
- CD38

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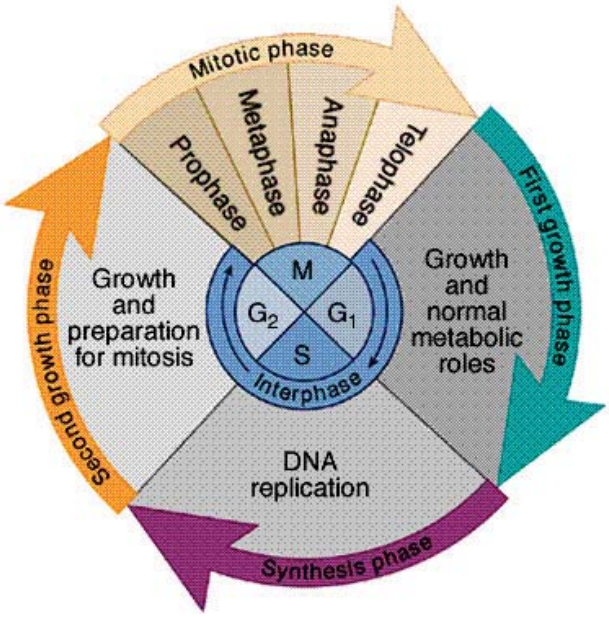
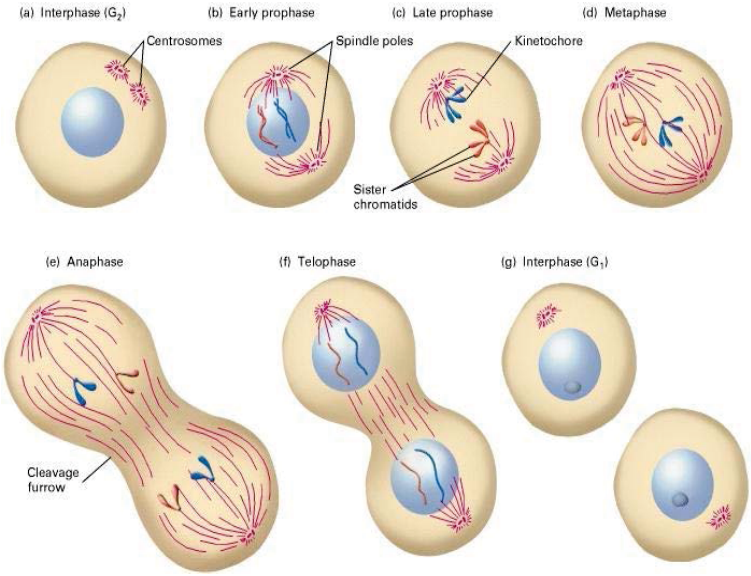
Interphase Cytogenetics by FISH

- Traditional metaphase cytogenetic analysis
  - Requires dividing cells in metaphase
  - CLL cells often have limited number of metaphases
- Interphase cytogenetic analysis by FISH
  - Utilizes specific probes in interphase cells
  - Greater sensitivity in CLL

Phases of Cell Cycle





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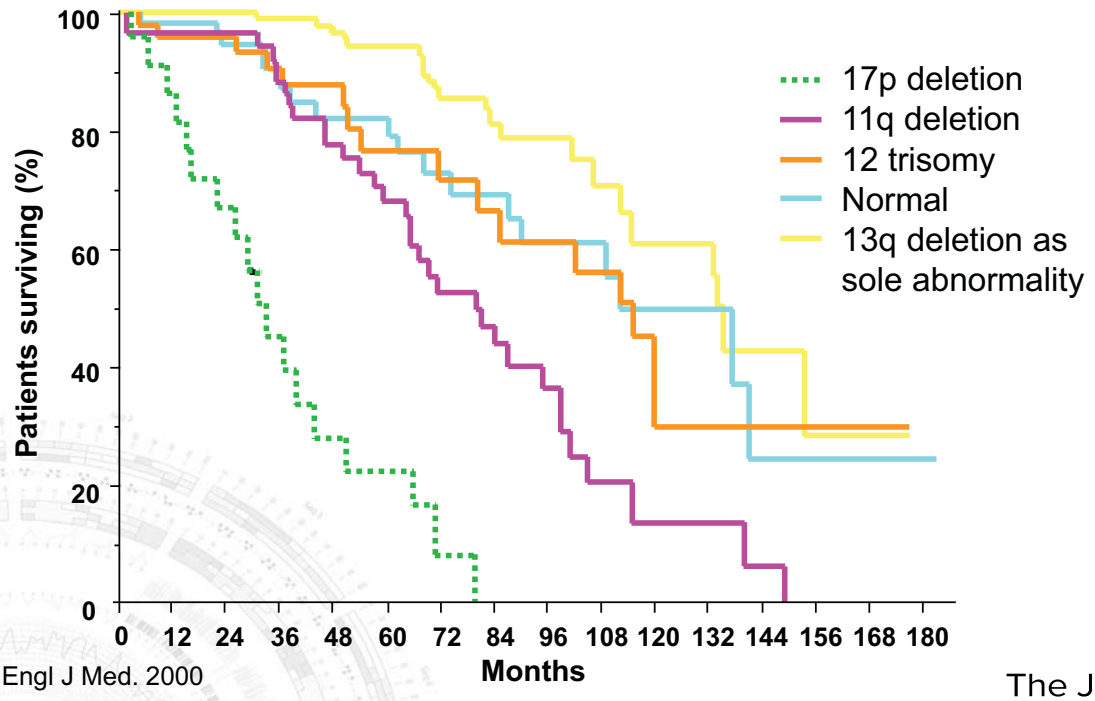
Interphase FISH correlates with Overall Survival



Dohner, et al. N Engl J Med. 2000

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Outcome by Interphase FISH Abnormalities

Abnormality detected by FISH	Median Time to Treatment (months)	Median Overall Survival (months)	Percentage of Patients (%)
Del 17p	9	32	7
Del 11q	13	79	18
Trisomy 12	33	114	16
Del 13q	49	133	55
Normal	92	111	18

Dohner, et al. N Engl J Med. 2000

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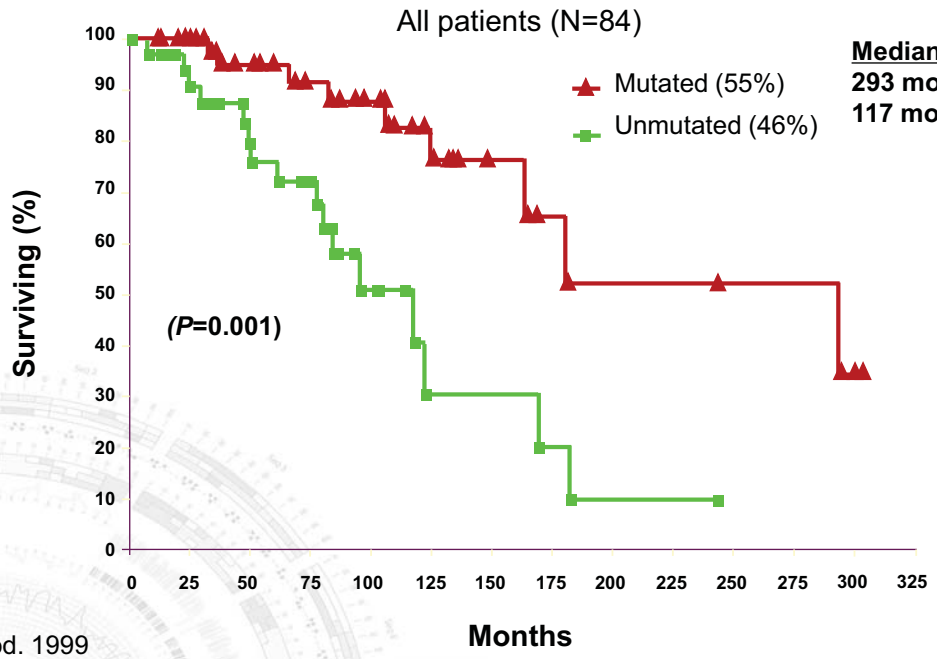
Prognostic Markers

- Interphase cytogenetics by FISH
- IgHV Mutational Status
- ZAP-70
- CD38

Significance of IGHV

- Immunoglobulin heavy chain variable region (IGHV) undergoes hyper-mutation during B-cell development
- Mutational status of IGHV predicts clinical outcome in CLL
- Mutated IGHV is defined as <98% sequence homology to established germline sequence
- Unmutated IGHV predicts earlier therapy, poorer response, inferior survival and risk of transformation

IGHV Mutational Status predicts Survival



Hamblin et al. Blood. 1999

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Prognostic Markers

- Interphase cytogenetics by FISH
- IGHV Mutational Status
- ZAP-70
- CD38

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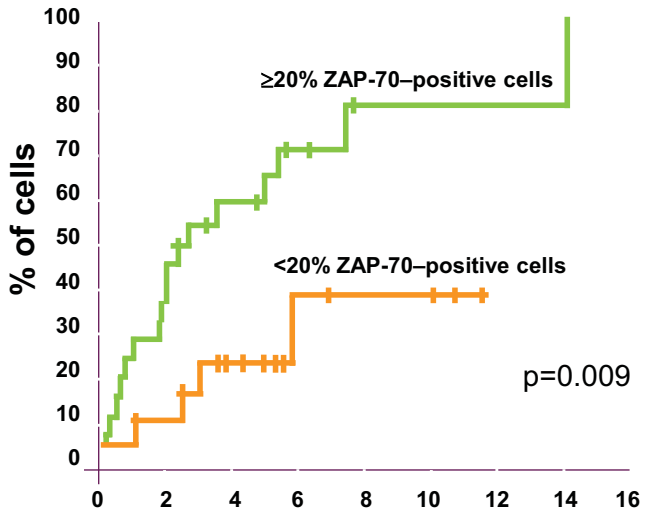
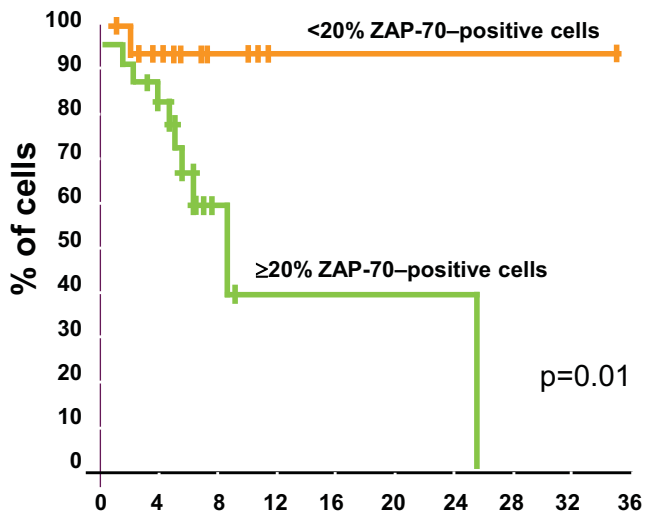
ZAP-70 predicts Progression and Survival in CLL

Risk of disease progression



Likelihood of survival



Crespo, M. et al. N Engl J Med 2003

ZAP-70 Problems

- Not reproducible across laboratories
- This variability is likely due to
  - Different clone of ZAP-70 antibody
  - Condition antibody kept at and how many times is it thawed
  - How CLL cells are processed
  - What is the positive and negative control used
  - What is readout result and how does it relate to literature reports showing this is a valid test
- Outside of clinical trial, ZAP-70 utility is limited

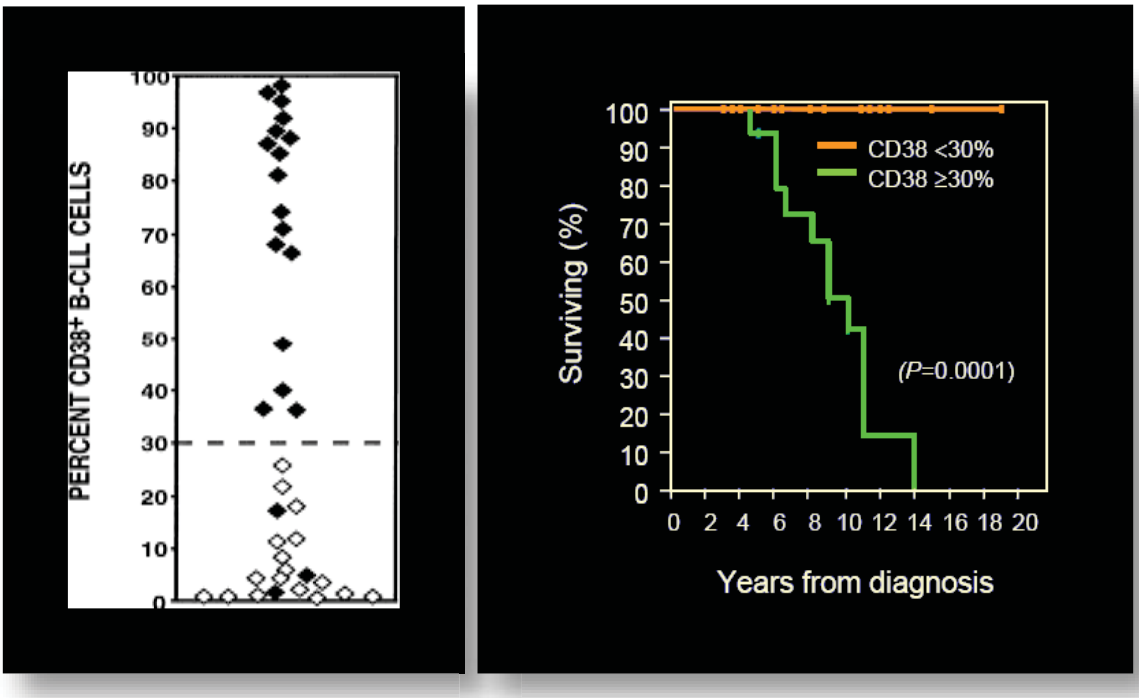
Prognostic Markers

- Interphase cytogenetics by FISH
- IGHV Mutational Status
- ZAP-70
- CD38

CD38 status predicts outcomes

- CD38 is involved in cellular metabolism and lymphocyte proliferation
- Expression of CD38 has been identified as poor prognostic factor
- CD38 expression may change over time
- CD38 positive if >30% cells express CD38
- Unmutated IGHV correlates with CD38 expression

CD38 expression correlates with IGHV mutational status



Damle, et al, Blood, 1999

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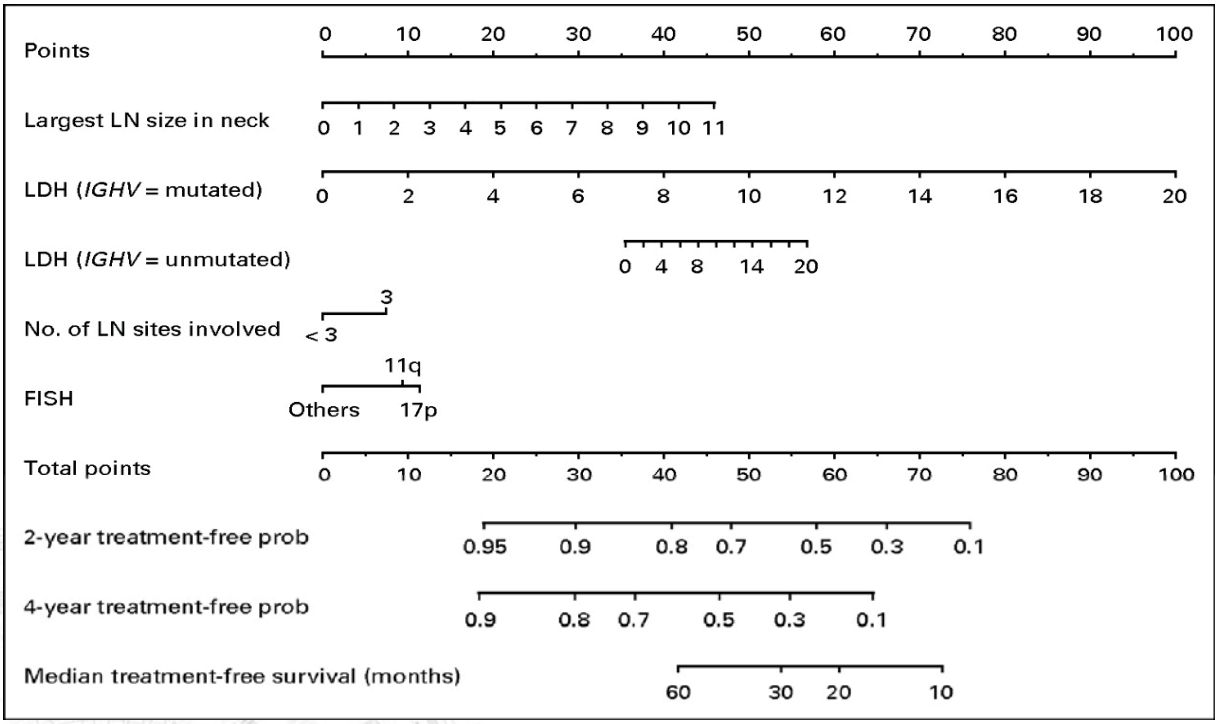
Other Prognostic Markers

	Favorable Outcome	Un-Favorable Outcome
LDH	Low or Normal	Elevated
Lymphocyte Doubling Time	> 12 months	< 12 months
Thymidine Kinase Activity	Low or Normal	Elevated
Beta-2 Microglobulin	Low or Normal	Elevated

Other Prognostic Markers

- NOTCH1 and SF3B1 are the most frequently mutated genes that predict poor prognosis
- MicroRNA expression levels, mir-155
- Global and gene-specific aberrant DNA methylation
- Aberrant methylation has been described for genes that are specifically deregulated in CLL, such as BCL2, TCL1

MDACC NOMOGRAM FOR TIME TO FIRST TREATMENT



William G. Wierda et al. JCO 2011;29:4088-4095

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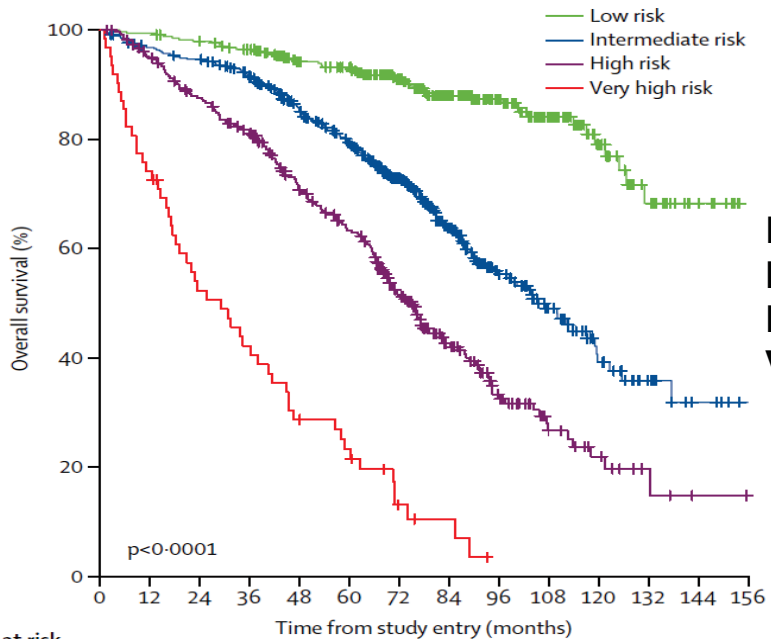
CLL IPI score

- Age (1)
  - ≤65 Years
  - >65 Years
- Binet B/C or Rai I-IV (1)
  - Yes
  - No
- Beta-2 Microglobulin (2)
  - ≤3.5 mg/dL
  - >3.5 mg/dL
- IGHV Unmutated (2)
- Deletion 17p (FISH) and/or TP53 mutation (sequencing) (4)

The International CLL-IPI working group, Lancet Oncol 2016; 17: 779–90

CLL IPI score – predicts survival



Low	**0-1**	**93% 5-yr**
Intermediate	**2-3**	**79% 5-yr**
High	**4-6**	**63% 5-yr**
Very High	**7-10**	**23% 5-yr**

The International CLL-IPI working group, Lancet Oncol 2016; 17: 779–90

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Prognostic factors in CLL: Summary

- Interphase-FISH cytogenetic analysis is standard of care
- Chromosomal abnormalities may change with time
- IGHV status does not change with time
- CD38 and ZAP-70 generally correlates with IGHV

WHEN DO YOU TREAT

Timing of Therapy

- Worsening or steroid resistant anemia and/or thrombocytopenia
- Spleen >6cm below the left costal margin
- Lymph Nodes >10cm
- Lymphocyte doubling time (LDT) of <6 months

NCI-IWCLL recommendations, Blood, 2008

Timing of Therapy

- Constitutional symptoms
  - Unintentional weight loss of >10% within the previous 6 mos
  - significant fatigue (ECOG PS 2 or worse)
  - fevers >100.5°F for >2 wks without other evidence of infection
  - night sweats for >1 month without evidence of infection

NCI-IWCLL recommendations, Blood, 2008

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Don’t Treat

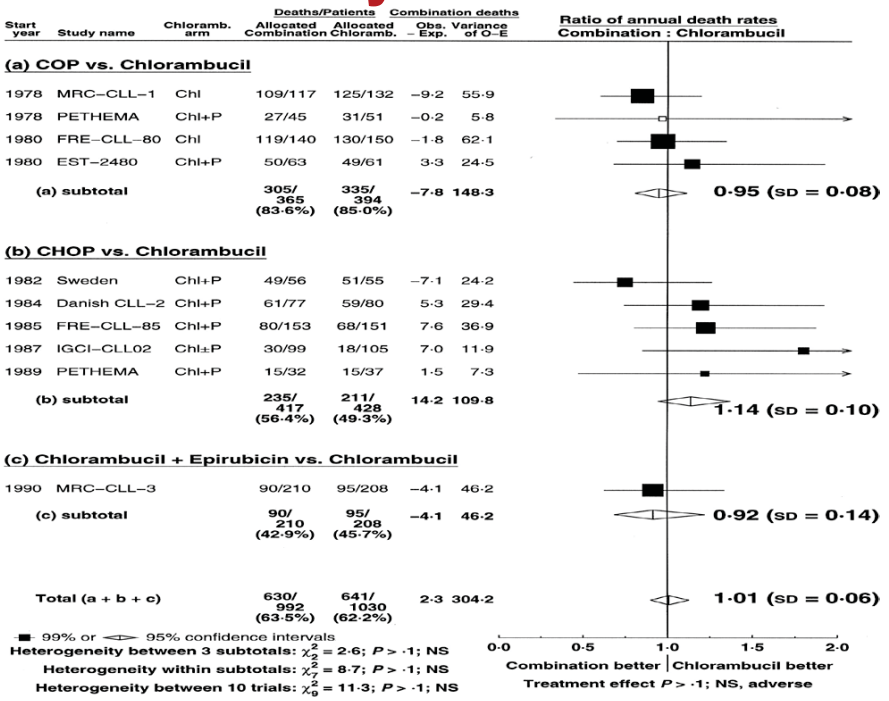
- Hypogammaglobulinemia
- Monoclonal or oligoclonal paraproteinemia
- Elevated leukocyte count

NCI-IWCLL recommendations, Blood, 2008

YOUNG AND FIT PATIENT

INITIAL TREATMENT

High Grade Lymphoma like therapy is not very effective



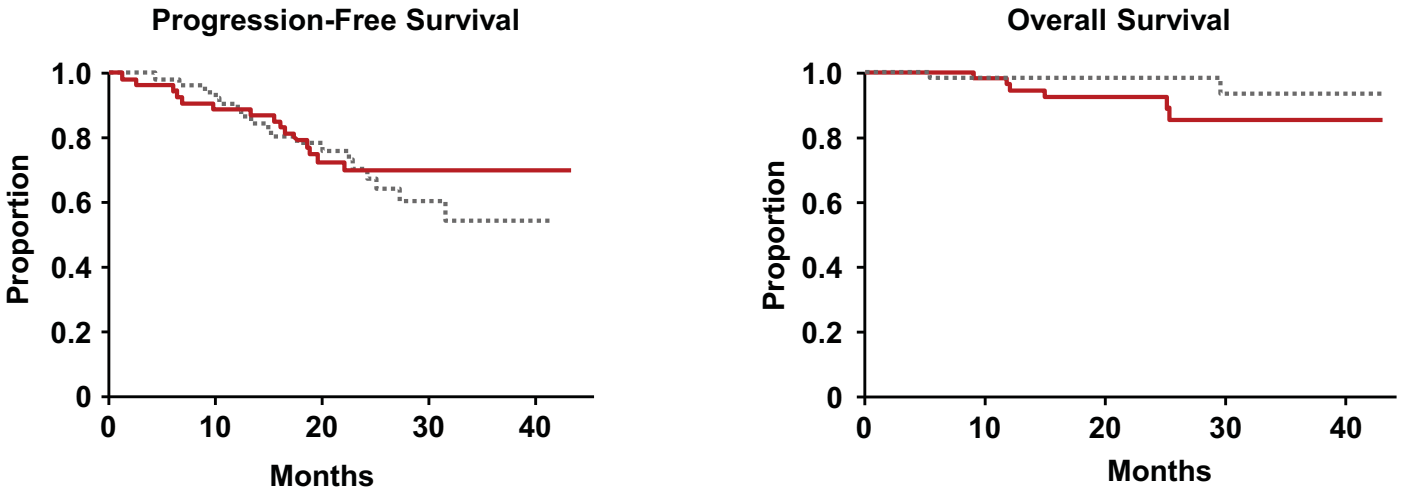
J Natl Cancer Inst, 1999

FCR – Fludarabine, Cyclophosphamide and Rituximab – the MDACC experience

Author	Regimen	No of patients	CR(%)	ORR (%)
Keating	FCR	300	72	95
6-yr OS = 77% 6-yr-FFS = 51%				

Keating, et al. JCO 2005 and Tam, et al. Blood 2008

Does Adding Rituximab to Fludarabine improve outcomes – FR

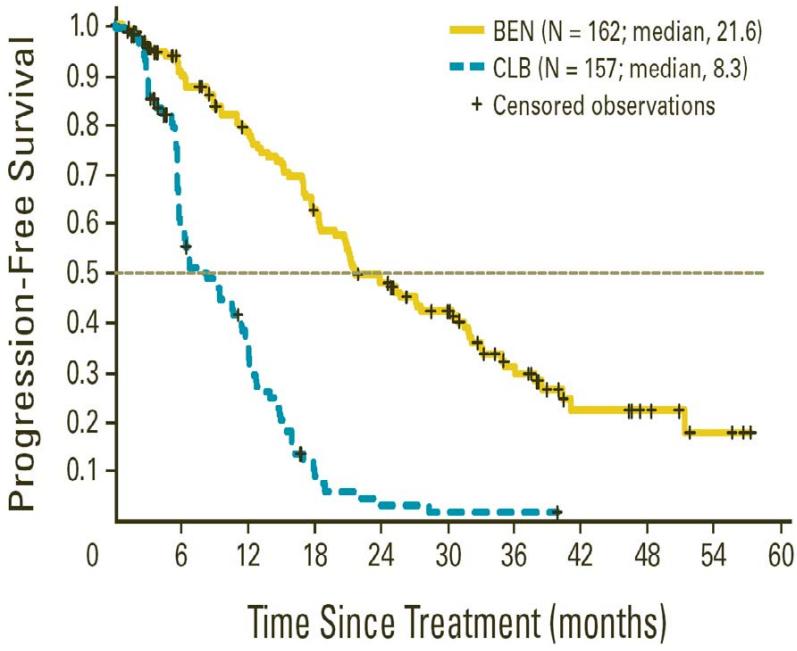


Concurrent FR (n=51) CR=47%, ORR=90%

Sequential F+R (n=53) CR=28%, ORR=77%

Byrd, Blood 2003

Bendamustine – Phase III



	Ben	Clb
ORR (%)	68	31
CR (%)	31	2
Median PFS	21.8m	8m

Phase III

Knauf, et al. JCO 2009

FCR vs. BR – CLL-10 GCLLSG Trial

	FCR	BR
N	274	273
ORR (%)	97	97
CR (%)	47	38*
PFS at 2-yr (%)	85	78*
OS at 2-yr (%)	95	94
Severe Neutropenia (%)	81	56*
Severe Infections (%)	47	26*

Eicchorst, et al. Ash 2013, Lancet Oncology, p928–942, July 2016

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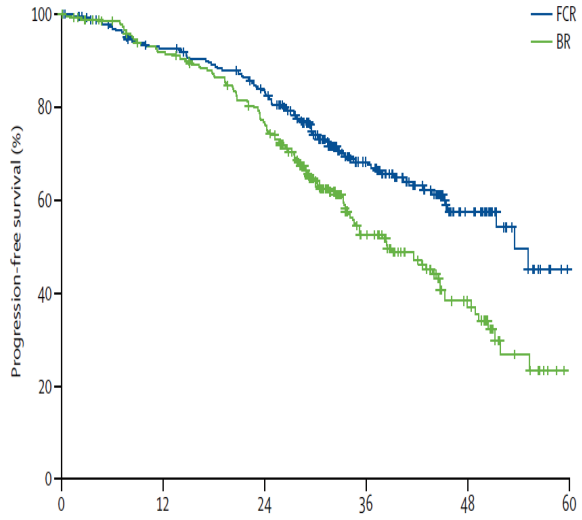
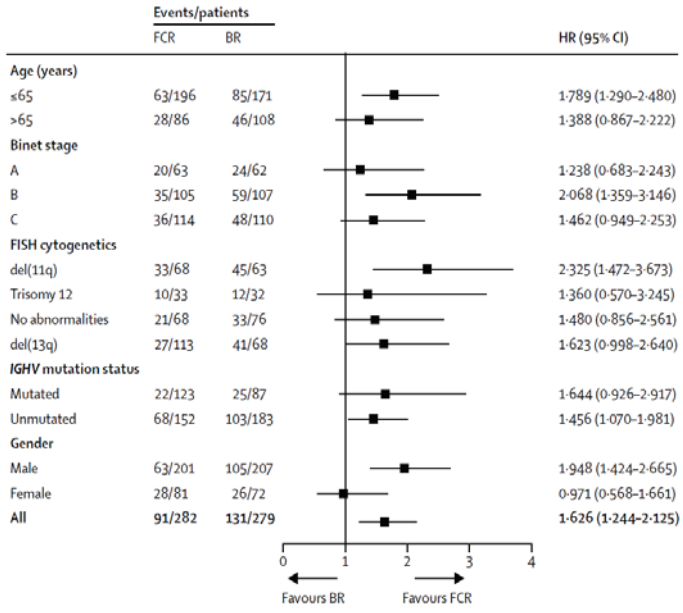
CLL-10 trial – FCR is better than BR





Eicchorst, et al. Ash 2013, Lancet Oncology, p928–942, July 2016

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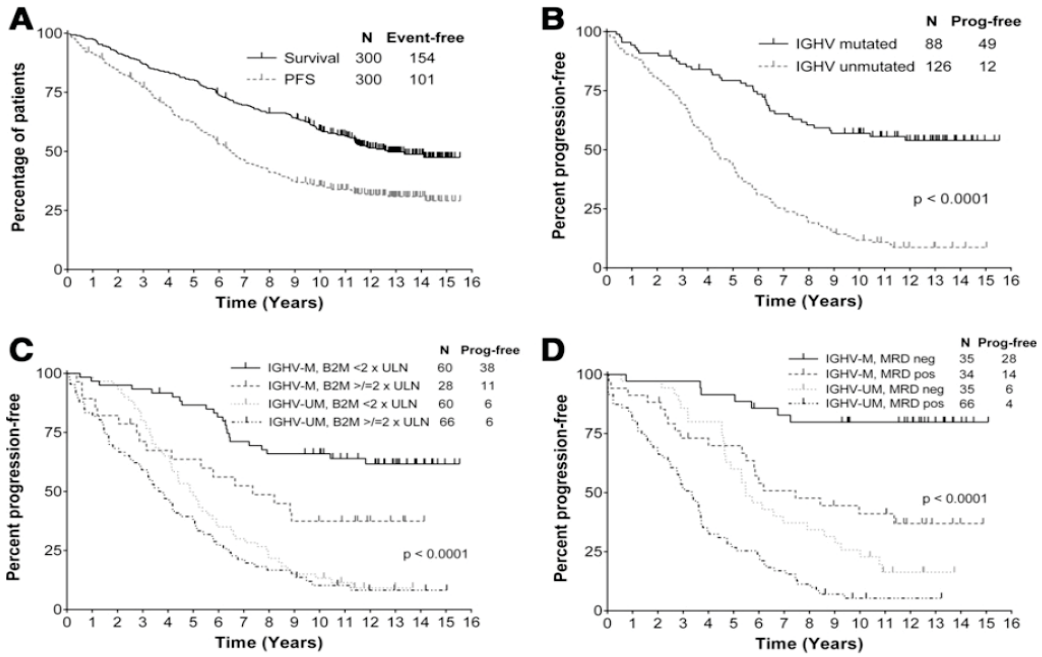
Is FCR really the Best Choice?

	FCR MDACC	FCR CLL-8	FR CALGB 9712	FCR CLL-10	BR CLL-10
ORR (%)	95	90	90	95	96
CR (%)	72	44	47	40	31
PFS	51% (6-yr)	65% (3-yr)	27% (5-yr)	55 mo med	41 mo med
OS	77% (6-yr)	87% (3-yr)	71% (5-yr)	91% (3-yr)	92% (3-yr)

Therapy related myeloid neoplasms FCR~9% vs. FR=0%

Lancet 2010, JCO 2011, Modern Pathology 2012

Long-Term Remissions possible with FCR



Thompson, et al. Blood 2016

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TREATMENT RECOMMENDATION

FIRST LINE THERAPY

YOUNG, HEALTHY PATIENTS

Fludatabine, Cyclophosphamide and Rituximab (FCR)

Bendamustine and Rituximab (BR)

Ibrutinib (approved as first line)

Clinical trial

But the median age of diagnosis for CLL is 72?

What do we do for the elderly (>65/70yrs) and unfit?

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OLDER AND UNFIT PATIENT

INITIAL TREATMENT

Treatment Options in Elderly Populations

- Avoid fludarabine-based regimens
- Bendamustine + rituximab
  - Slightly higher toxicity rate but feasible in this population
- Chlorambucil + rituximab
  - Chlorambucil 10 mg/m^2 on Days 1-7 every month x 6-12
  - Rituximab 375 mg/m^2 Mo 1 and 500 mg/m^2 months 2-6
  - ORR 82% (9% CR, 15% nPR) with median PFS of 23.5 months

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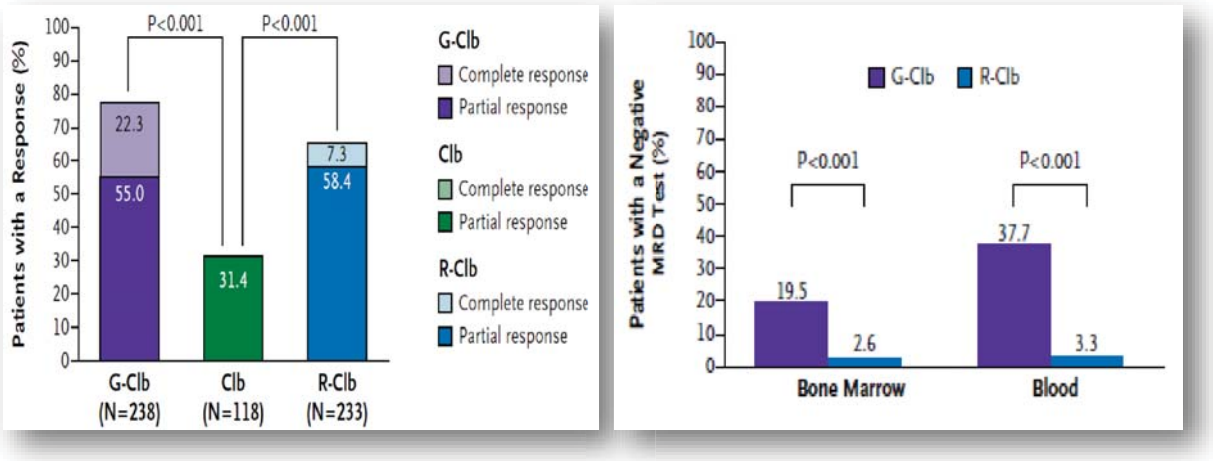
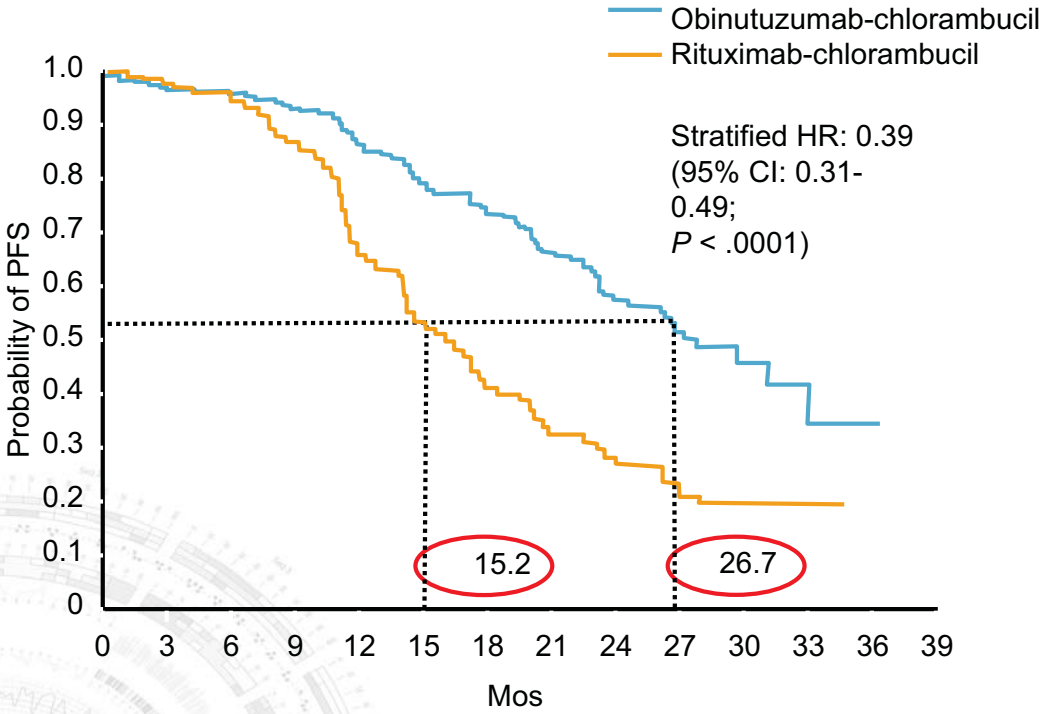
Obinutuzumab plus Chlorambucil



- Well tolerated in patients with co-morbids and median age of 73y
- Improved PFS when compared to R+Clb and Clb alone

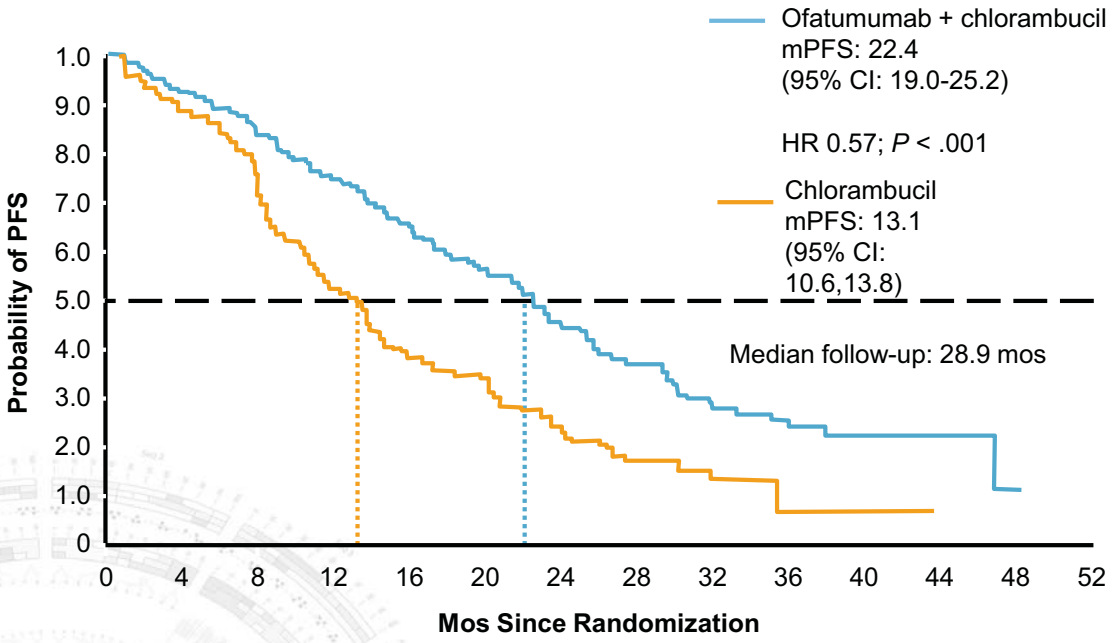
Goede, et al. Nejm 2014

Obinutuzumab plus Chlorambucil



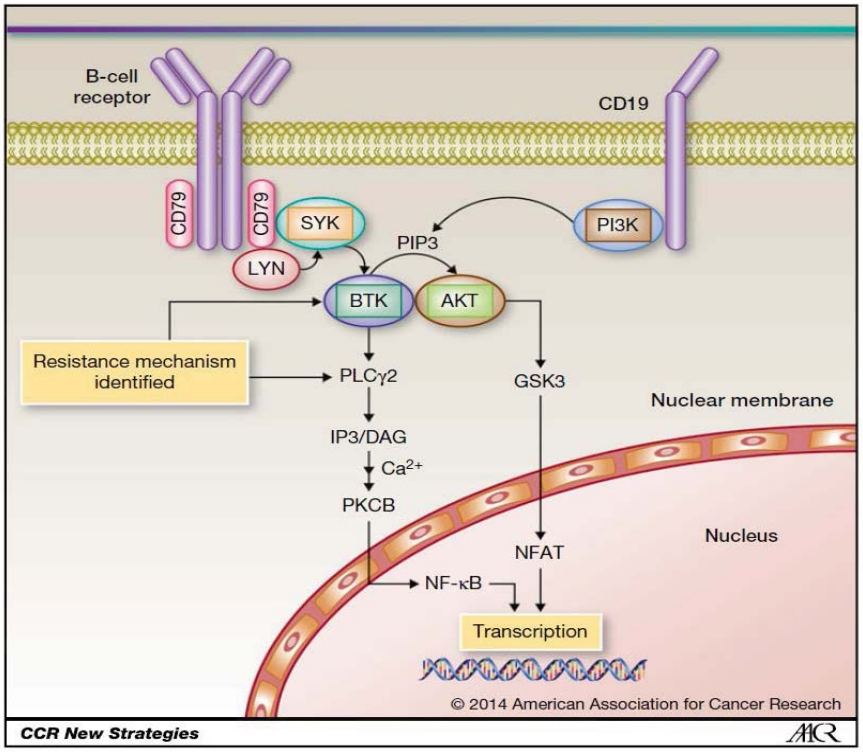
Goede, et al. Nejm 2014

Ofatumumab plus Chlorambucil



Hillmen P, et al. ASH 2013. Abstract 528; Hillmen, et al, Lancet 385, 2015.

Targeting kinases in CLL

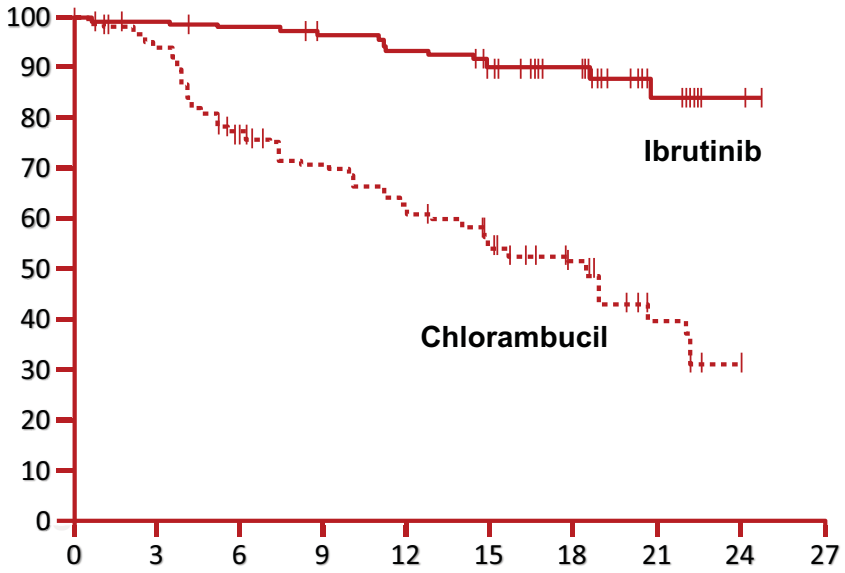


Awan F, et al, CCR 2014

Ibrutinib

- Forms a specific bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC_{50} = 0.5 nM
- Orally administered with once-daily dosing resulting in 24-hr target inhibition
- No cytotoxic effect on T cells or NK cells
- Promotes apoptosis and inhibits migration and adhesion in CLL cells

Ibrutinib vs Chlorambucil (Resonate-2)



- Ibrutinib is better than Chlorambucil in patients older than 65 years of age with previously untreated CLL

TREATMENT RECOMMENDATION

FIRST LINE THERAPY

OLDER, LESS HEALTHY PATIENTS

Ibrutinib (approved as first line)

Obinutuzumab +/- Chlorambucil

Ofatumumab + Chlorambucil

Clinical trial

TREATMENT

Del17p Patients

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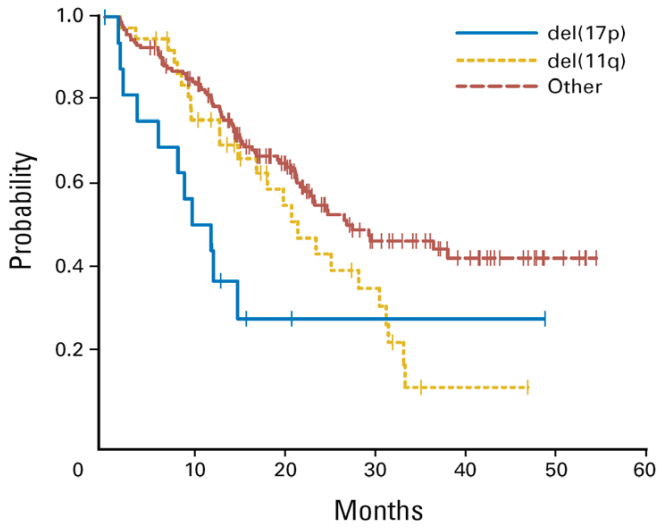
Poor prognosis of Del 17p is not overcome by FC (E2997)

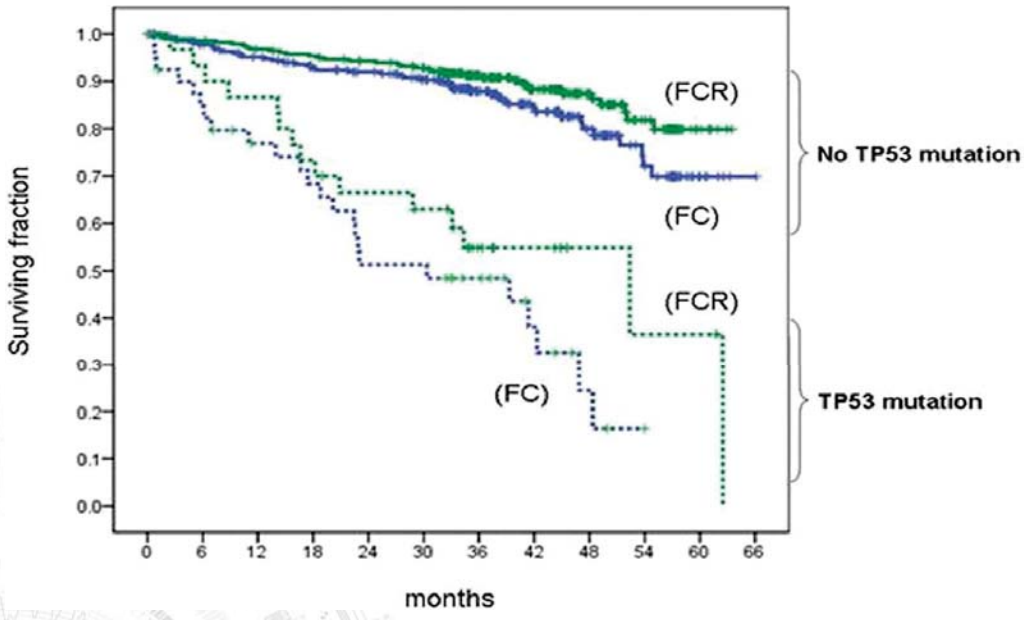


	F	FC
Del 17p	8.9	11.9*
Del 11q	14.9	25.2*
No 17p or p53 del	19.2	99

PFS (months) in E2997

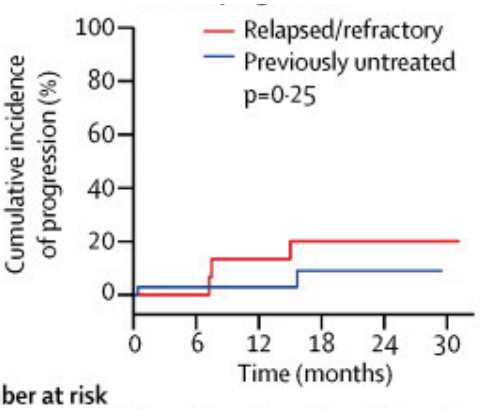
Grever et al, JCO, 2007

FCR does not improve Overall Survival in Del 17p disease

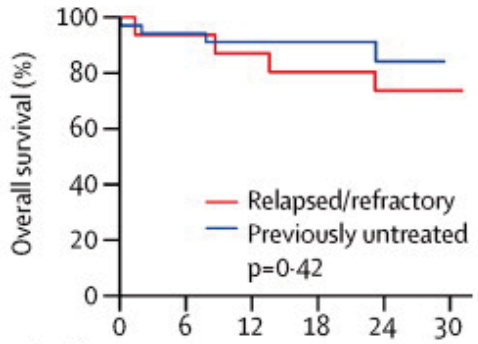


Zenz et al, ASH Abstract 1267, 2009

Ibrutinib PFS and OS in Del17p Disease



Number at risk						
Previously untreated	34	32	25	13	10	0
Relapsed/refractory	16	15	13	12	11	2

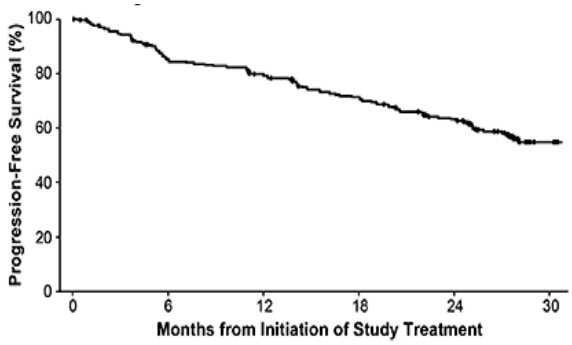


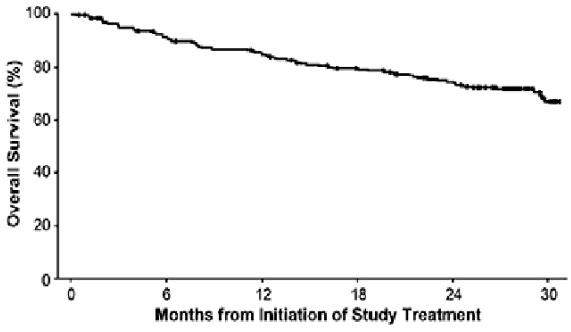
Number at risk						
Previously untreated	34	32	25	13	10	0
Relapsed/refractory	16	15	13	12	11	2

Farooqui, et al. Lancet Oncol. 2015

Ibrutinib PFS and OS in Del17p Disease

243 CLL pts with del17p (241 R/R and 2 TN)





- **ORR (including PR-L) was 84%**
- **Median PFS was 32 mo**
- **30 month OS was 67%**

Jones J. EHA, 2016; 135185

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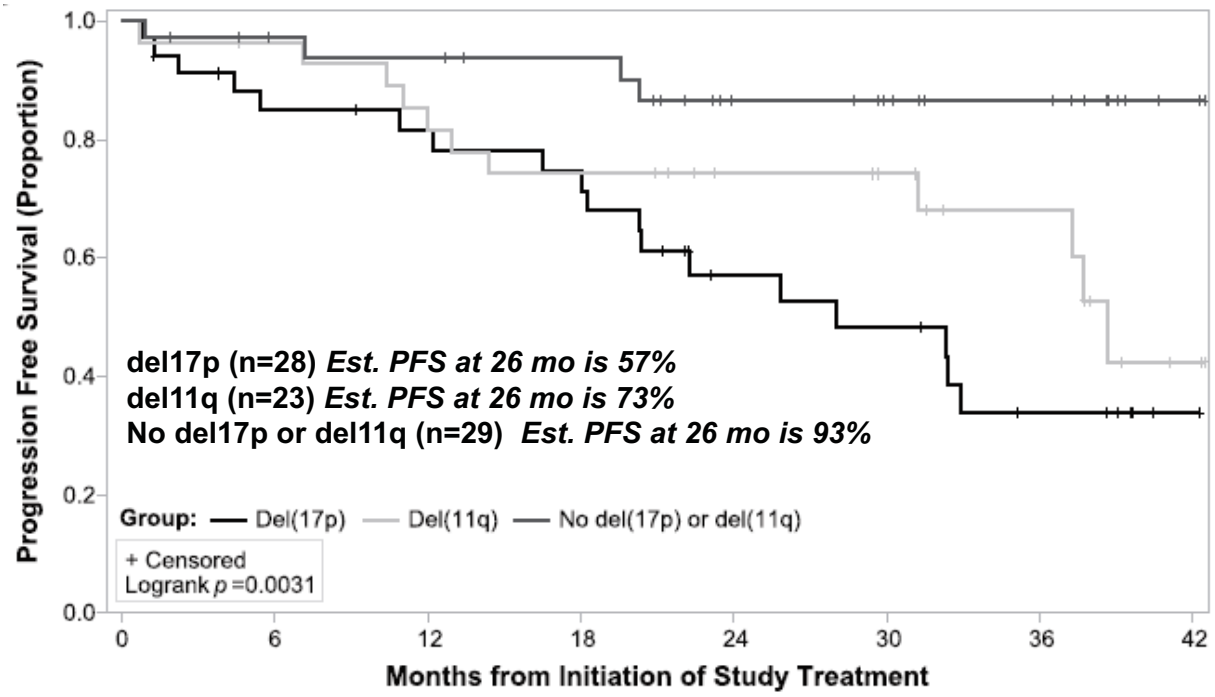
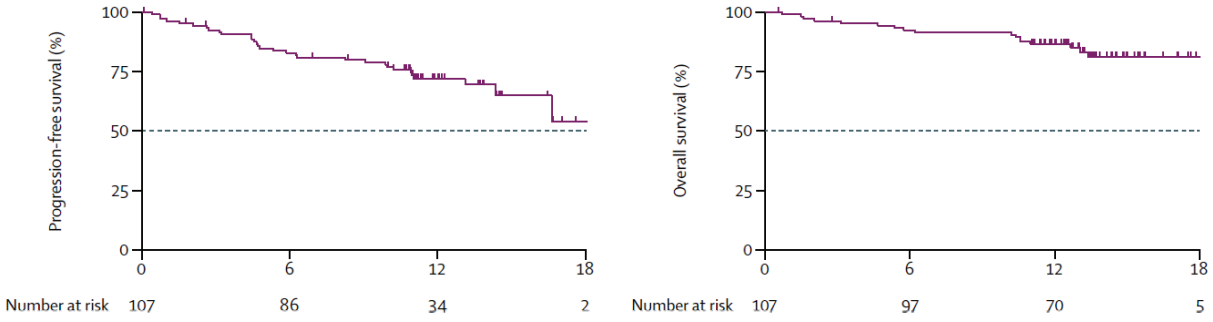
PFS by FISH: Relapse Cohort



Byrd, et al. NEJM 2013, Blood 2015

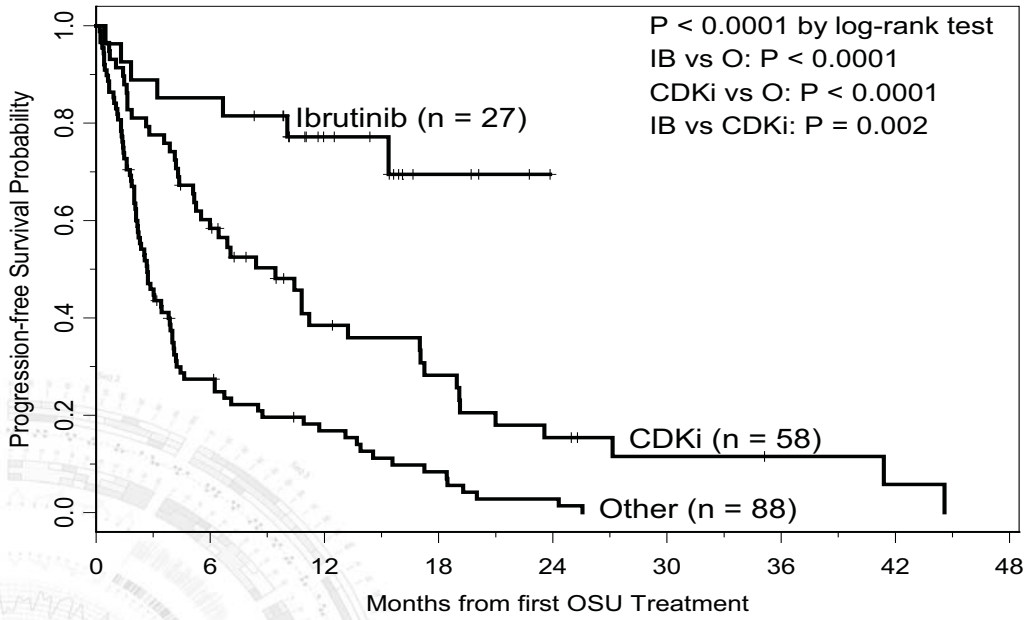
Venetoclax PFS in Del17p Disease



- **ORR (including PR-L) was 79%**
- **12-month PFS was 72%**
- **12-month OS was 87%**

Stilgenbauer, et al. Lancet Oncol 2016; 17: 768–78

Early Results Of Impact: Outcome of Treatment of del(17p13.1) CLL at OSU



Stephens DM, et al. Leukemia. 2014a

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TREATMENT RECOMMENDATION

Del17p Patients

Ibrutinib (approved as first line)

Venetoclax (approved for relapsed setting)

Clinical trial

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TREATMENT

Relapsed Patients

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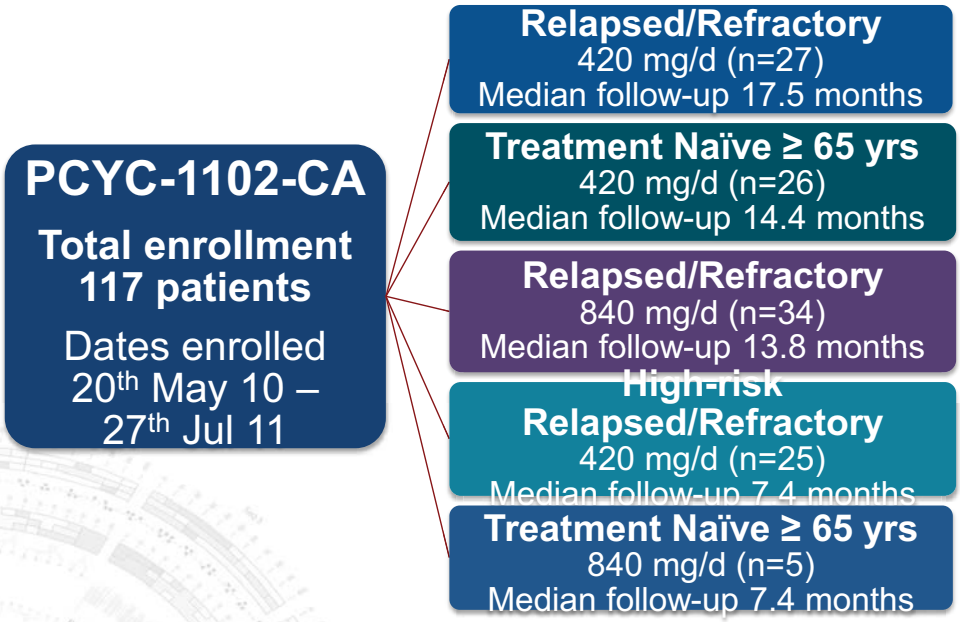
PCYC-1102-CA: Phase IB/II in CLL/SLL



Co-leaders: J Byrd and S O'Brien

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Phase II CLL Patient Characteristics

	TN ≥65 yrs (N=31)	R/R + HR (N=85)
Age, years ≥ 70 years, (%)	74%	35%
ECOG Status 0, 1, 2 Median Prior Therapies	74%, 26%, 0% N	41%, 56%, 2% 4 (1-12)
Rai Stage III/IV at Baseline	48%	65%
Prognostic Markers, % IGHV unmutated del(17p13.1) del(11q22.3)	 55% 7% 3%	 85% 35% 39%

Modest toxicity in phase II study similar to phase I study

NEJM 2013
Lancet Oncology

Ibrutinib in Refractory CLL With 11q Deletion

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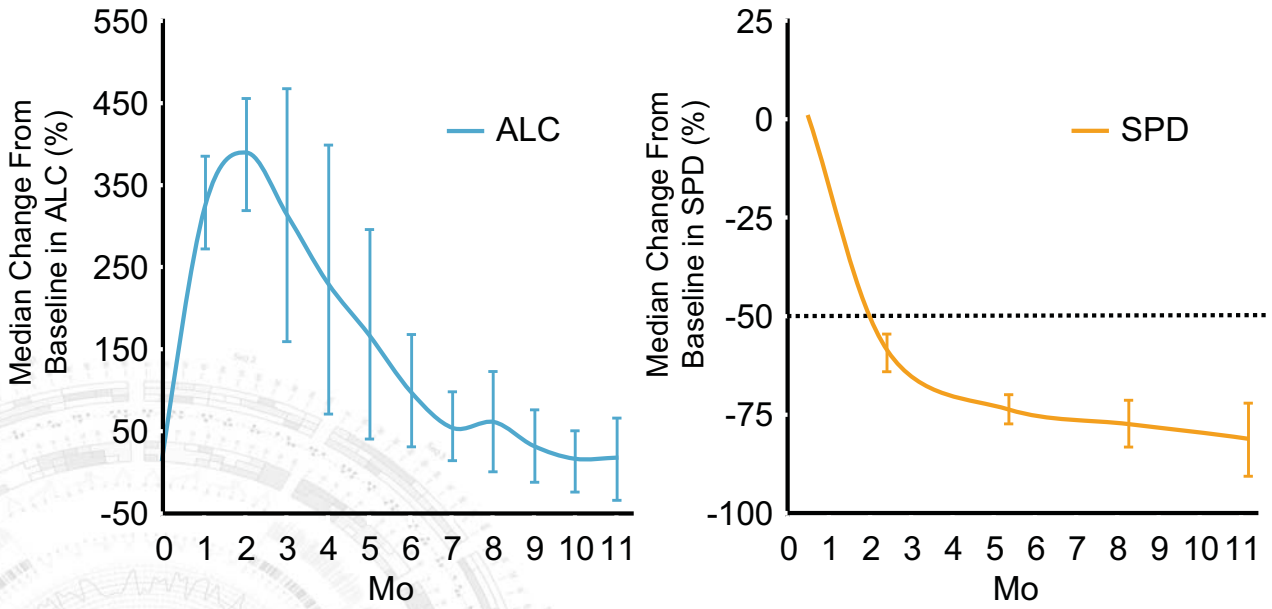
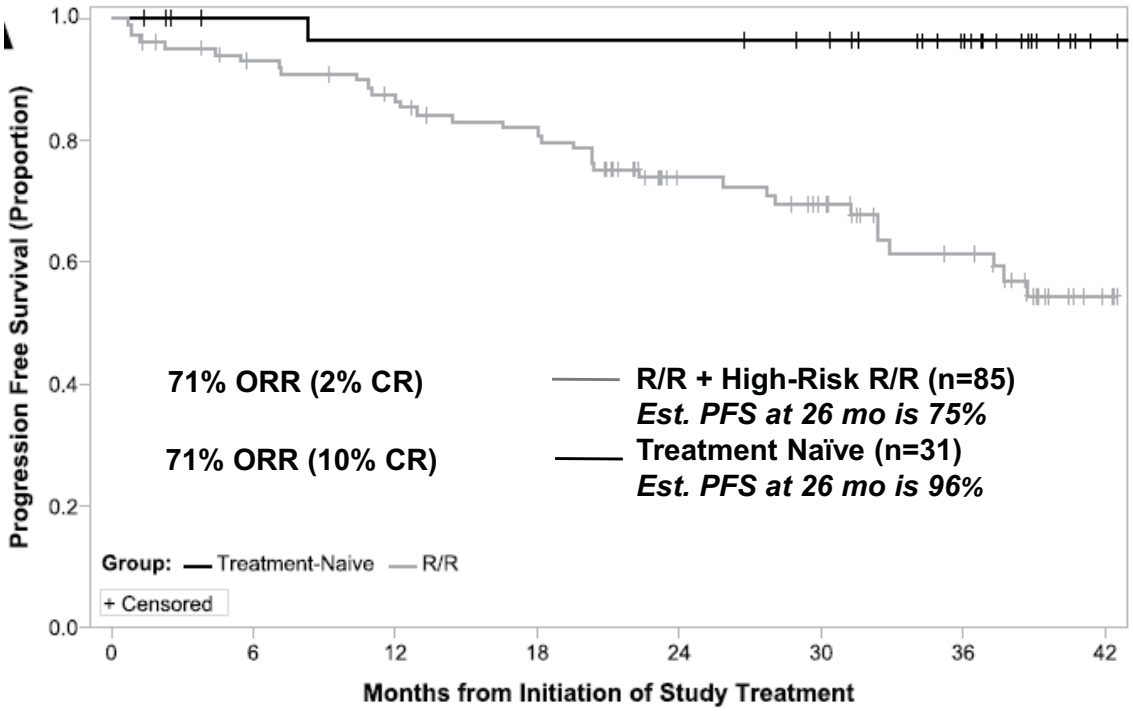
Pattern of Response: Blood Lymphocytes vs Lymph Nodes



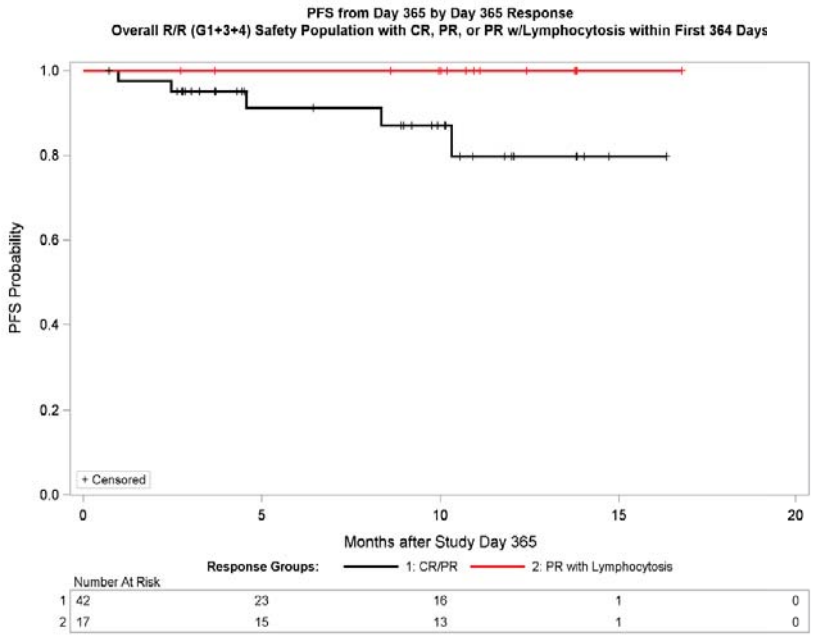
Byrd JC, et al. N Engl J Med. 2013;369:32-42.

Phase II Response and Progression-free Survival



Byrd, et al. NEJM 2013, Blood 2015

PR-L is not associated with inferior PFS compared with PR/CR at 12 months



Woyach J et al: Blood 2014

Can I Use Ibrutinib in Autoimmune Cytopenias?

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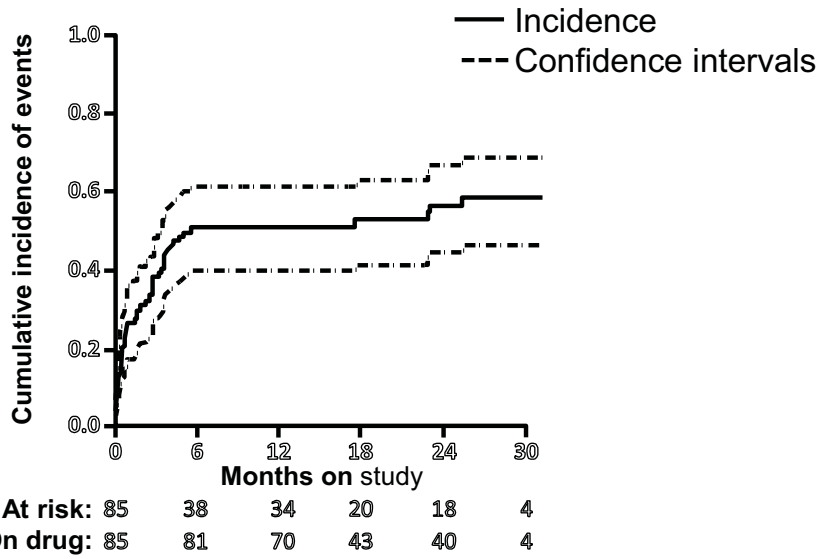
Autoimmune Cytopenias on Ibrutinib

- 6 cases of treatment-emergent AIC in 301 patients treated with ibrutinib at OSU-CCC
- 4/6 had previous history of AIC
- Corresponds to an estimated incidence rate of 13 episodes for every 1000 patient-years of ibrutinib treatment
- Majority of patients on concurrent medications to control AIC at the start of ibrutinib were able to stop it within the first 12 months.

Rogers KA et al. Leukemia. 2015

Issues With Ibrutinib

- Disrupts collagen-induced platelet aggregation
- vWF binding



Lipsky AH et al. Haematologica. 2015;100:1571-1578.

Management of Bleeding Issues With Ibrutinib

- Avoid aspirin, NSAIDs, fish oil
- Avoid warfarin
- Can consider alternate anti-coagulants with caution

Ibrutinib prescribing information. Available at http://www.imbruvica.com

Other Issues With Ibrutinib

- Diarrhea
- Fatigue
- Upper respiratory tract infection
- Rash
- Nausea
- Arthralgia
- Atrial fibrillation
- Cytopenias
- **Treatment discontinuation due to AEs = 6%**
- **No evidence of cumulative toxicity or long-term safety**

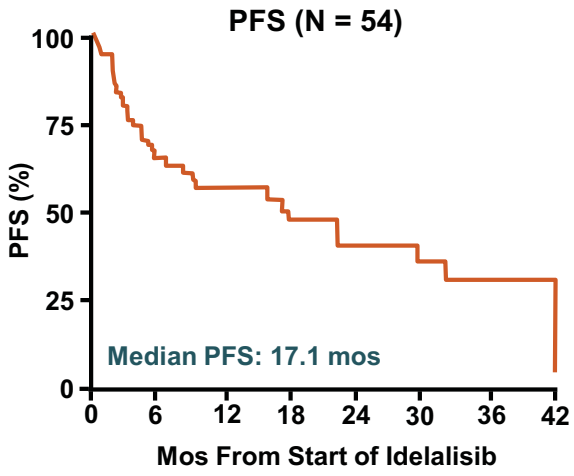
AEs = adverse events.

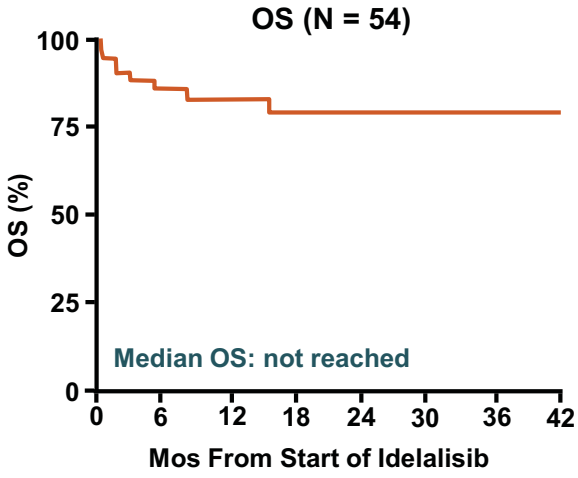
Ibrutinib prescribing information. Available at http://www.imbruvica.com

Ibrutinib—Conclusion

- Promising responses ~90%
- Low incidence of complete responses 2–7%
- Response deepens over time
- Del17p responds, but PFS is shorter.
- Use full dose
- Avoid with anticoagulation
- Follow stopping rules prior to surgical interventions

Idelalisib in relapsed/refractory CLL





Brown JR, et al. Blood. 2014 May 29;123(22):3390-7

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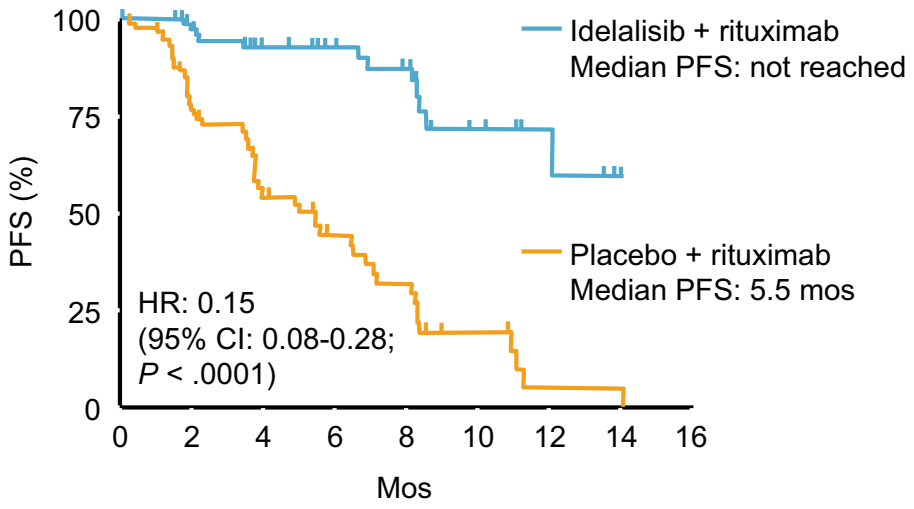
Phase III Idelalisib and Rituximab for Previously Treated Patients With CLL



Furman R, et al. N Engl J Med. 2014

How to Choose Between Ibrutinib and Idelalisib

Ibrutinib	Idelalisib
Patients allergic to rituximab	Patients on anti-coagulation
Inflammatory bowel disease	Atrial fibrillation
Liver problems	Patients on concurrent azoles (CYP3A Inhibitors)
Lung problems	

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Summary Recommendations for Untreated Patients

- Ibrutinib is approved for all indications
- Consider ibrutinib especially for elderly and patients with comorbid conditions
- For frail, elderly patients and patients with comorbid conditions CD20 antibody based options are also available
- BR and FCR are also reasonable options for certain patients
- Need to have a discussion about length of therapy and side effects and long-term results

Summary Recommendations for Relapsed Patients

- Ibrutinib is approved for all indications
- Idelalisib + rituximab is approved for relapsed patients
- Idelalisib is contraindicated in patients with untreated disease
- Venetoclax is approved for patients with del17p
- Chemoimmunotherapy can be considered in a subset of patients with prolonged (>3yrs) initial remission

Case 1

59-yr-old male with IGHV unmutated CLL presents with progressive fatigue, lymphadenopathy and splenomegaly.

His lab evaluation reads:
- WBC count: 195,000 cells/μL
- Hemoglobin: 8.5 mg/dL
- Platelet count: 86,000 cells/μL
- Beta-2 macroglobulin: 1.8
- FISH: del(13q14)

What is the best choice of therapy:

- Chlorambucil
- Fludarabine + rituximab
- Fludarabine, cyclophosphamide, rituximab
- Lenalidomide ± rituximab
- Chlorambucil + obinutuzumab
- Unsure

Case 1

59-yr-old male with IGHV unmutated CLL presents with progressive fatigue, lymphadenopathy and splenomegaly.

His lab evaluation reads:
- WBC count: 195,000 cells/μL
- Hemoglobin: 8.5 mg/dL
- Platelet count: 86,000 cells/μL
- Beta-2 macroglobulin: 1.8
- FISH: del(13q14)

What is the best choice of therapy:

- Fludarabine, cyclophosphamide, rituximab

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Case 2

64-yr-old male with IGHV unmutated, 17p deleted CLL presents with progressive fatigue, lymphadenopathy and, splenomegaly.

His lab evaluation reads:
- WBC count: 195,000 cells/μL
- Hemoglobin: 8.5 mg/dL
- Platelet count: 86,000 cells/μL
- FISH: del(17p13)

- What is the best choice of therapy:

- Chlorambucil
- Fludarabine + rituximab
- Fludarabine, cyclophosphamide, rituximab
- Lenalidomide ± rituximab
- Bendamustine + rituximab
- Chlorambucil + obinutuzumab
- Chlorambucil + ofatumomab
- Ibrutinib

Case 2

64-yr-old male with IGHV unmutated, 17p deleted CLL presents with progressive fatigue, lymphadenopathy and, splenomegaly.

His lab evaluation reads:
- WBC count: 195,000 cells/μL
- Hemoglobin: 8.5 mg/dL
- Platelet count: 86,000 cells/μL
- FISH: del(17p13)

- What is the best choice of therapy:

- **Ibrutinib**

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Thank you!

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