Wake Forest™
School of Medicine

Charles L. Spurr Piedmont Oncology Fall Symposium

September 20-21, 2019

Hyatt Regency
Greenville, South Carolina

Planning Committee

Bayard Powell, MD
Glenn Lesser, MD
Susan Poindexter, RN, BSN, OCN
Debbie Olson

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

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September 20-21, 2019

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 *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 any 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 within 10 business days. 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 within 10 business days. 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 after evaluation link is received.**

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 University 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.

(#AP006-190920)

Participants must attend 90% of the 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.

10.0 Contact Hours from Northwest AHEC

1.0 CEUs from Wake Forest School of Medicine

Learner Objectives:

The objectives for this activity are the following:

- Describe the necessity of opioid medications for pain management in patients with cancer and survivors, and discuss strategies to ensure that patients have access to medications necessary for managing pain.
- Define strategies to maintain patient safety and minimize the risks of opioid misuse and abuse during chronic opioid use.
- Discuss therapeutic targets in difficult-to-treat breast cancer.
- Examine the political landscape impacting healthcare changes.
- Discuss the impact of key healthcare initiatives on oncology care.
- Discuss assessment strategies to predict chemotherapy toxicity in older adults.
- Explore the role of toxicity risk assessment regardless of chronologic age.
- Examine the pathogenesis of testicular cancer.
- Describe testicular cancer treatment considerations.
- Discuss key developments in the treatment of patients with urothelial carcinoma.
- Discuss methods to mitigate cancer-associated anemia.
- Discuss the importance of early ICU transfer for the critically ill cancer patient.
- Discuss treatment strategies for differentiated thyroid cancer.

Charles L. Spurr Piedmont Oncology Fall Symposium

Planning Committee, Faculty, & Staff Disclosure

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- *Dr. Marcia Brose receives grant/research support from Bayer, Blueprint Inc., Eisai, Exelixix, Kura Pharm, Merck, Novartis, and Roche. She serves as a consultant for Bayer and Eisai.*

- *Dr. Patrick J. Loehrer receives grant/research support from Taiho, Eli Lilly, and Walther Cancer Foundation.*

- *Dr. Robert Maki receives grant/research support from Bayer, Karyopharm, Lilly, Pfizer, Springworks, Regeneron, Presage, Sarcoma Alliance for Research through Collaboration (SARC), and Tracon. He serves as a consultant for Bayer, Deciphera, Eisai/Morphotek, Epizyme, GlaxoSmithKline, Immune Design, Janssen/Pharma Mar, Karyopharm, Lilly/Imclone, Novartis, Pfizer, Presage, Sarcoma Alliance for Research through Collaboration (SARC), Springworks, American Board of Internal Medicine, American Society for Clinical Oncology, and UptoDate.*

- *Dr. Guru Sonpavde receives grant/research support from AstraZeneca, Bayer, Amgen, Boehringer-Ingelheim, Janssen, Merck, Sanofi, and Pfizer. He serves as a consultant for Bristol-Myers Squibb, Exelixis, Bayer, Sanofi, Pfizer, Novartis, Eisai, Janssen, Amgen, AstraZeneca, Merck, Genentech, EMD Serono, and Astellas/Agensys. He also serves on steering committees for AstraZeneca, Bristol-Myers Squibb, Astellas, Debiopharm, and Bavarian Nordic.*

- *Dr. Tiffany Traina receives grant/research support from Eisai, Pfizer, Novartis, Innocrin Pharma, AstraZeneca, Astellas, Immunomedics, Genentech/Roche, and Daiichi Sankyo. She serves as a speaker for Roche/Genentech. She also serves as a consultant for Genentech/Roche, Medivation, Pfizer, AstraZeneca, Merck, Astellas Pharma, Puma Biotechnology, Advaxis, Celgene, Innocrin Pharma, Genomic Health, Bristol-Myers Squibb, Samsung, Athenex, Aduro Biotech, and Halozyme.*

Speakers Ms. Shelagh Foster, Dr. Peter Miller, Dr. Heidi Klepin, Dr. Ryan Woods, and Dr. Judith A. Paice have nothing to disclose related to this educational activity. Planning committee members Dr. Bayard Powell, Dr. Glenn Lesser, Susan Poindexter, and Debbie Olson have nothing to disclose related to this educational activity.

Printed 9/16/2019. Any additional disclosures received after this date will be announced.

Charles L. Spurr Piedmont Oncology Symposium
Fall Symposium

Thursday, September 19, 2019

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

Friday, September 20, 2019

7:15 am Continental Breakfast and Exhibits

General Session

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

8:10 am **Cancer Critical Care**
Peter Miller, MD
Assistant Professor, Pulmonary, Critical Care, Allergy and Immunologic Diseases
Medical Director, Medical Oncology Intensive Care Unit
Wake Forest School of Medicine

9:10 am **Updates on the Management of Metastatic Triple Negative Breast Cancer**
Tiffany A. Traina, MD
Clinical Director, Breast Medicine Service Section Head
Memorial Sloan Kettering Cancer Center

10:10 am Break and Exhibits

10:40 am **2019 Legislative Update and What it Means for Oncology**
Shelag Foster, JD
Division Director, Policy & Advocacy
American Society of Clinical Oncology (ASCO)

11:40 am **Testicular Cancer: The Incredible Journey to Cure a Cancer**
Patrick J. Loehrer Sr., MD, FASCO
Director, IU Simon Cancer Center
H.H. Gregg Professor of Oncology
Indiana University School of Medicine

12:40 pm Lunch

1:50 pm	**Urothelial Carcinoma: Current Management and Recent Advances** Guru Sonpavde, MD Director, Bladder Cancer Dana Farber Cancer Institute
2:50 pm	**Anemia in Hematology and Oncology Practice** Ryan Woods, MD Assistant Professor of Medicine, Section on Hemtology and Oncology Wake Forest school of Medicine
3:50 pm	Adjourn
4:00 pm	Private Reception

Cancer Critical Care
Peter Miller, MD
Assistant Professor, Pulmonary, Critical Care, Allergy and Immunologic Diseases
Medical Director, Medical Oncology Intensive Care Unit
Wake Forest School of Medicine

Cancer Critical Care

PJ Miller, MD
Hematology
Critical Care Medicine

Wake Forest School of Medicine

Goals and objectives

- Gain an understanding of what is and isn't a critically ill cancer patient
- Recognition importance of early transfer to an ICU
- Recognize the relationship between organ dysfunction and mortality
- Recognize the vast unknowns
- Discuss the role of evolving goals of care discussions
- Recognize the oncologists important role in an ICU

My Preference

Let's make this an engaging discussion.

I hope to teach and discuss my experience, however, I improve by hearing others' opinions, challenges and successes

Ask questions

If you go get coffee, please bring me some
(black, no cream, no sugar)

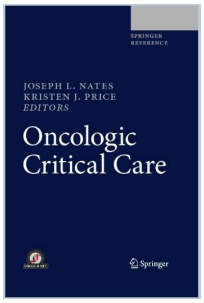
Conflicts of Interest

I have numerous conflicts, none of which are very interesting…

I receive no money or royalties from any pharmaceutical or device manufacturer

In 2012, apparently someone provided me with $13 worth of food that was reportable.

ONCCC-R-NET



Information for this lecture was largely obtained, adapted or referenced directly from the new publication:

Oncologic Critical Care

Growth of a field

- Approximately 1 in 6 deaths globally is due to cancer
- Estimates of 20 % of patients admitted to an ICU have a cancer diagnosis
- Estimates continue to increase
  - Treatment options improve and evolve
  - Targeted therapy reduce multisystem organ failure
  - Less toxic treatments with improved survival
  - More technologically complex equipment available to support organ dysfunction

Chen K., Wallace S.K., Nates J.L. (2019) ICU Utilization. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham
Soares M, Bozza FA, Angus D, et al. Organizational characteristics, outcomes, and resource use in 78 Brazilian intensive care units: The ORCHESTRA study. Intensive Care Med 2015;41:2149-60.
Koch A., Checkley W. Do hospitals need oncological critical care units?. Journal of Thoracic Disease 2017;vol.9

Growth of a field

- 13-22% of all cancer patients estimated to need admission to a general ICU
  - Unbalanced between malignancies
- ~27% **directly linked to cancer**
  - More commonly admitted for concomitant organ dysfunction or illness
- Survival rates continue to improve
- **Urgent recognition of early stage organ failure makes a difference**
- Intricacies and complexities of cancer patients and treatment
  - Organize like-minded physicians and providers

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Growth of a field

- Heterogeneity of malignancy affects mortality
  - Solid tumor
    - ICU mortality – 5-85%
    - Overall hospital mortality 5-77%
  - Heme malignancies
    - ICU mortality – 24-57%
- *Post-operative care most common reason for ICU admission for solid tumors*
- Solid tumor unplanned ICU admissions
  - Hospital survival - 69%
  - 180 day survival - 48%
- Metastatic
  - 1 year survival -12%
  - 2 year survival - 2.4%

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Koch A., Checkley W. Do hospitals need oncological critical care units?. Journal of Thoracic Disease 2017;vol.9

Growth of a field

- Solid tumor:
  - Probability of leaving ICU greater for patients without organ dysfunction
- Stem cell transplant patients admitted to ICU on subsequent admissions – mortality = 67%
- Death rates at 1 year
  - Mechanical ventilation – 87%
  - Pulmonary artery catheterization – 91%
  - Hemodialysis – 94%
- Outcome of heme malignancy patients depends on number of organ system failures

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Koch A., Checkley W. Do hospitals need oncological critical care units?. Journal of Thoracic Disease 2017;vol.9

Growth of a field

- If 3 organ systems failed:
  - Cancer – 75%
  - No cancer – 50%
- Associated with increased mortality
  - SOFA score ≥ 10
  - Acute respiratory failure requiring invasive mechanical ventilation
  - Need for vasopressors
  - Organ failure after transplant

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Growth of a field

- Patients that most benefit (survival) from ICU admission
  - < 3 organ systems failing
  - Recent diagnosis
  - Treatment of oncologic emergencies
    - Tumor lysis, pulmonary leukemic infiltrate or leukostasis
  - Likelihood of cure or control
  - ECOG 0-1
  - Post-operative care
- Admission to an ICU should not be denied to patients solely for a cancer diagnosis

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Soares M, Bozza FA, Angus D, et al. Organizational characteristics, outcomes, and resource use in 78 Brazilian intensive care units: The ORCHESTRA study. Intensive Care Med 2015;41:2149-60.

Growth of a field

- Patients that DO NOT benefit from ICU admission
  - Patient or decision maker do not want aggressive ICU level of care
  - When palliative care is the only treatment option
  - Poor quality of life not expected to improve with treatment
  - Unexpected to recover from acute complication despite aggressive treatment

Chen K., Wallace S.K., Nates J.L. (2019) ICU Utilization. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham

Early ICU admission

- Late admission/never admitted to ICU higher risk of death compared to immediate admission.
- Early intervention of physiologic development best defense
  - ≤ 1.5 hours decreased relative risk of 1 year mortality by 16%
- Early ICU admissions increases survival
  - ≤ 24 hours from admission to transfer

Chen K., Wallace S.K., Nates J.L. (2019) ICU Utilization. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham

Early ICU admission

DEVELOPMENT OF ORGAN FAILURE, RECOGNITION, AND EARLY INTERVENTION IN THE FIRST HOURS OR DAY IS OUR BEST CHANCE TO IMPROVE SURVIVAL

Chemotherapy in the ICU

- Chemotherapy in the ICU should be viewed as a life-support modality
  - Should not use if no expectation to cure/control
- Remember, prognosis is dependent on number of organ systems
  - If chemo is expected to induce organ failure, strong consideration against
- Heme malignancy patients with sepsis or septic shock, chemotherapy not associated with increased risk of death
- Organ failure secondary to heme malignancy
  - Could be INDICATION to give chemotherapy in the ICU
- Can be very challenging to separate what causes what

Chen K., Wallace S.K., Nates J.L. (2019) ICU Utilization. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham

Early ICU admission

- Significant survival improvement, irrespective of hematologic or solid tumor
  - Systematic review: Solid tumor
    - ICU mortality 31.2%
    - Overall hospital mortality: 38.2%

However,

  - Population based observational trial of 118,541 patients
    - ICU mortality 14.1%
    - Overall hospital mortality

- Critical Care Medicine is NOT the same specialty it was 20 years ago!

Chen K., Wallace S.K., Nates J.L. (2019) ICU Utilization. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham

Early ICU admission

- Improvements in critical care management
  - Early use of non-invasive mechanical ventilation
  - Low tidal volume mechanical ventilation
  - Care bundles for sepsis
    - Goal directed therapies
  - Antibiotic stewardships
  - Improved technology for multi-system organ failures

- If majority of cancer patients are admitted for non-direct cancer etiologies, survival should improve similar to non-cancer patients

Chen K., Wallace S.K., Nates J.L. (2019) ICU Utilization. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham

Risk Prediction and Admission

- Cancer = terminal diagnosis = no ICU admission

- Cancer ≠ terminal diagnosis ≠ no ICU admission

- Early identification of at-risk patients is critical
- Open and honest discussions between subspecialties, patients and families
- Nihilism or misplaced optimism may still be present
- Recognition that holistic interventions exist beyond “survival”

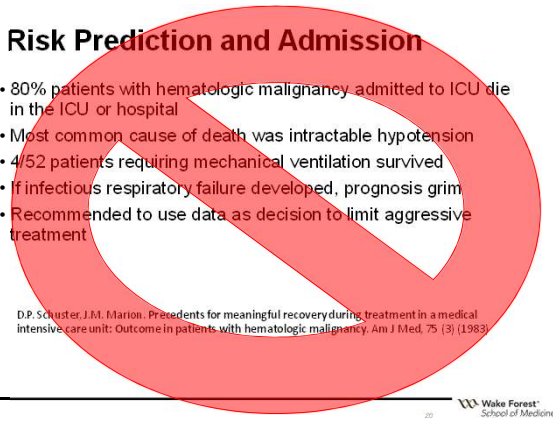
O’Mahony M., Wigmore T. (2019) Patient Risk Prediction Model. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham

Risk Prediction and Admission

- 80% patients with hematologic malignancy admitted to ICU die in the ICU or hospital
- Most common cause of death was intractable hypotension
- 4/52 patients requiring mechanical ventilation survived
- If infectious respiratory failure developed, prognosis grim
- Recommended to use data as decision to limit aggressive treatment

D.P. Schuster, J.M. Marion. **Precedents for meaningful recovery during treatment in a medical intensive care unit: Outcome in patients with hematologic malignancy**. Am J Med, 75 (3) (1983)

Risk Prediction and Admission



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Risk Prediction and Admission

- Increased volume of cancer patients and specialty centers show improved outcomes
- French database
- Cancer patients between 1997-2008
- ICU mortality dropped from 70.4 to 52.5% (relative decrease 25%) then 45%
- Low (<5), medium (5-12) and high volume units (>13)
- Case volume associated strong influence on survival
  - High volume centers with younger patients and heme- malignancies

Zuber et. al. Impact of case volume on survival of septic shock in patients with malignancies. Critical Care Medicine, Jan 2012

Risk Prediction and Admission

- Conundrum
  - Low volume
    - less sick patients, older, lower acuity, less likely to receive transfer
  - High volume
    - Sicker patients, younger, higher acuity, higher likelihood for transfer

The more you treat, the sicker your patients

O'Mahony M., Wigmore T. (2019) Patient Risk Prediction Model. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham

Risk Prediction and Admission

- High volume centers
  - Increased experience in management of critically ill oncologic patients
  - Multi-disciplinary approach
  - Well-established protocols
  - Familiarity in complexity of oncologic patients and treatments
  - Lack of automatic denials for metastatic disease
  - Counterintuitively, admit patients that may look "well"

Why?

- Survival benefit with early intervention!
- 21% of patients died by day 30 that were refused ICU admission for being considered "too well" for the ICU

Risk Prediction and Admission

- Age
  - People are living longer with more comorbidities
  - Half of all cancers after age 70
  - In general, not a poor prognostic factor
  - Recommendation for GOC discussions if numerous comorbidities exist
- Performance status
  - Improved outcomes with ECOG 0-1
  - Higher ECOG due to malignancy ≠ ECOG due to other comorbidities
  - Optimize reversibility to better assess true functional status

O'Mahony M., Wigmore T. (2019) Patient Risk Prediction Model. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham

Risk Prediction and Admission – cancer specific

- Historically outcomes in solid tumor >> heme malignancies
- Organ failure, specifically mechanical ventilation, becomes less of solid tumor vs heme prognosticator
- Although cancer type, stage and remission have little impact on short-term ICU survival, the benefit of aggressive treatment is questionable
- Goal of ICU should be to return patient to physiologic state that can withstand further treatment
  - If not, then this meets the definition for medical futility

O'Mahony M., Wigmore T. (2019) Patient Risk Prediction Model. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham

Risk Prediction and Admission – Acute respiratory failure

- Most common reason for referral to ICU
- 10-50% cancer patients will develop respiratory failure
- Mortality rates could be as high as 67-90%
- Increased hypoxia prior to MV is poor prognostic factor
- Causes include infectious, intravascular volume, ARDS, cardiac, therapeutic pulmonary toxicities, pulmonary involvement of disease
- *NIMV may improve outcomes*
  - ? Does aggressively treating underlying respiratory failure outweigh complications of mechanical ventilation

O'Mahony M., Wigmore T. (2019) Patient Risk Prediction Model. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham

Risk Prediction and Admission – Organ failure

- Increased number = increased mortality
- Gordon et. al (2005): ≥4 organ failures = 100% mortality
- Intensive Care National Audit and Research Centre (ICNARC)
  - 1 organ – 50% mortality
  - 3 organs – 84% mortality
  - 5 organs – 98% mortality
  - Early aggressive management has improved survival
- Renal replacement = 78% mortality
  - Higher when delayed

O'Mahony M., Wigmore T. (2019) Patient Risk Prediction Model. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham

Risk Prediction and Admission- Neutropenia

- Higher risk of death (10%) in critically ill cancer patient
- Neutropenic sepsis/septic shock outcomes continue to improve
- Conflicting data with comparing neutropenic and non-neutropenic patients
- Overall conclusion, chemotherapy-induced neutropenia should not limit ICU level of care

O'Mahony M., Wigmore T. (2019) Patient Risk Prediction Model. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham

Risk Prediction and Admission- Repeated admissions

- Frequent re-admissions associated with worse prognosis
- Repeated admissions conferred 5X higher mortality rate compared to single admission
- Necessitates the need for multidisciplinary approach
  - "What can you offer?"
  - "What is the benefit of what you can do?"
  - "Are we doing things TO or FOR the patient?"

Renton J, Pilcher D, Santamaria J, Stow P, Bailey M, Hart G, Duke G. Factors associated with increased risk of readmission to intensive care in Australia. Intensive Care Med. 2011;37(11):1800–8.

Risk Prediction and Admission- Outcome prediction models

- Currently available scoring systems perform poorly due to heterogeneity of cancer patients with conflicting results
  - APACHE, SAPS and MPM UNDERESTIMATE
  - ICU Cancer Mortality model OVERESTIMATES
- Rely on physiologic variables that may be altered at baseline
  - Disease
  - Treatments
- Initial assessment not always reflective of future response to treatment*
  - 54 patients "too unwell for ICU = 26% alive at day 30 and 17% at 6 months.
  - If admitted: 54 % and 32%
  - "Too well for admission" – 21% mortality at day 30

Thiery G, Azoulay E, Darmon M, Ciroldi M, De Miranda S, Le'vy V, Fieux F, Moreau D, Le Gall JR, Schlemmer B. Outcome of cancer patients considered for intensive care unit admission: a hospital-wide prospective study. J Clin Oncol. 2005;23(19):4406–13.

Multidisciplinary care

- Intensive Care is one of the most expensive aspects of healthcare in the US
  - > $108 billion as of 2010
  - ~30% hospital budget
  - Expected to increase as population ages
- Daytime staffing by intensivists improves mortality*
  - 24 hour in-house staffing expensive, limited intensivist pool, no further increase in survival
- If intensivist consultation optional then nighttime intensivist staffing reduced mortality
  - Medical errors caught earlier
- 24h staffing by intensivists (mandatory consult) or closed ICU did not improve ICU patient mortality

Checkley W, Martin GS, Brown SM, Chang SY, Dabbagh O, Fremont RD, Girard TD, Rice TW, Howell MD, Johnson SB, O'Brien J, Park PK, Pastores SM, Patil NT, Pietropaoli AP, Putman M, Rotello L, Siner J, Sajid S, Murphy DJ, Sevransky JE, United States Critical Illness and Injury Trials Group Critical Illness Outcomes Study Investigators. Structure, process, and annual ICU mortality across 69 centers: United States Critical Illness and Injury Trials Group Critical Illness Outcomes Study. Crit Care Med. 2014;42(2):344–56.

Multidisciplinary care

- Co-management (cooperative?!)
  - No consistent definition
  - Leads to inappropriate overlap in medical care
  - Lack of practice boundaries
  - Potential lack of appropriate management
  - Creates an environment of duplicate work
  - Can be a frustrating environment when disagreements arise

Multidisciplinary care

- What do we do at Wake?
- Assisted-management
  - An improvement, rather than type, of co-management
  - Primary management of patient is transferred to ICU team
  - Oncology focuses on a "onco-specifics"
    - No longer focused on organ systems outside of specialty
    - Write orders for oncologic specific medications and labs
    - Do not write orders for anything else
    - Oncology team continues to follow patient daily in ICU
  - ICU team does not write or cancel oncologic specific orders
  - ICU team updates oncology team of patient decline, unexpected results or changes that alter care
  - ICU team involves oncology team for goals of care discussion
  - Minimum of daily face to face interaction between teams

ICU utilization

- Significant variation creates comparison challenges
  - Do patients go to an ICU for life-saving interventions or for increased nursing care?
  - Roughly 10-20% patients receive continuous physician/life support
  - Roughly 20-30% patients in ICU for monitoring and intensive nursing
- Between 2000-2010 ICU beds in non-federal acute care hospitals in the United States has increased from 88,235 to 103,900 (17.8%)
- Ratio of ICU to hospital beds increased from 13.5 to 16.2%
  - > 20% increase
- Reason for transfer to ICU highly variable
  - Physician/provider practice, bed availability, policies, etc.

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ICU utilization

- Cost
  - In 2010, ICU accounted for 13.2% total hospital expenditure, 4.1% national healthcare expenditure, and 0.72% GDP
  - 2000-2010 annual costs increased $56 to $108 billion
  - Hospital stays involving ICU care = 2.5x cost of non-ICU
  - Medicare covers 83% of ICU costs on average
  - Quality improvement and reduction in cost waste should be constantly evaluated

Chen K., Wallace S.K., Nates J.L. (2019) ICU Utilization. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham

ICU utilization – Specialty ICUs

- ORCHESTRA
  - admission to an ICU in cancer centers was not associated with lower ICU mortality, hospital mortality, or better resource utilization
- Although patients were matched for "severity" there were many limitations
  - Study done in Brazil – international disparities known based on global national income
  - Did not evaluate if protocols were actually implemented
  - Did not evaluate discussions between intensivist and oncologist
  - Only 10% patients had hematologic malignancy
    - Makes it underpowered, especially in this group
  - Included both medical and surgical patients

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Koch A, Checkley W. Do hospitals need oncological critical care units? J Thor Dis. 2017;9(3):E304–9.

ICU utilization – Specialty ICUs

- So basically, we still have no idea

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ICU utilization – Optimization

- Benefits to optimization include:
  - Improved patient outcomes
  - Increased bed capacity
  - Improved patient throughput
  - Decreased payment penalties
  - Increased patient satisfaction
- How to optimize
  - Use bundles when available
    - Caution in over-interpretation of results from non-cancer patients
  - Early goals-of-care and end-of-life discussions prior to ICU
  - Establishing and following triage, admission, and discharge criteria
  - Use of intermediate care status/units
  - Multi-disciplinary team involvement
  - ICU physician with increased knowledge of cancer

Chen K., Wallace S.K., Nates J.L. (2019) ICU Utilization. In: Nates J., Price K. (eds) Oncologic Critical Care. Springer, Cham

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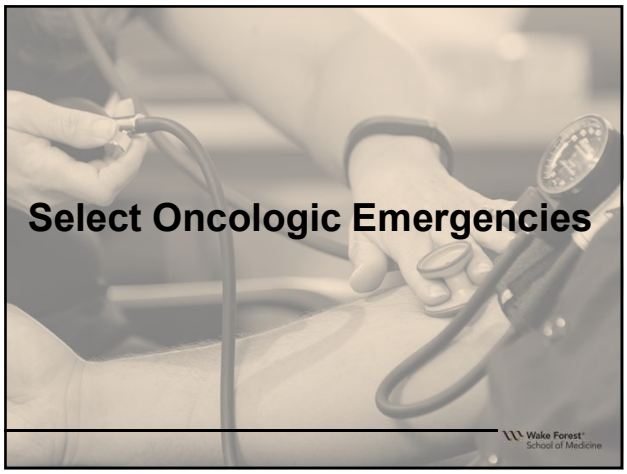

Select Oncologic Emergencies

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Oncologic Emergencies (OE)

- What is the difference between an OE and general critical illness?
  - OE's are directly related to the underlying disease or result of complications of therapy
- We'll go through examples but in general:
  - OE – Spinal cord compression with paralysis due to metastatic disease
  - General critical illness – Influenza pneumonia causing ARDS in immunocompetent patient

Oncologic Emergencies (OE)

- Metabolic
- Hematologic
- Neurologic
- Cardiovascular
- Pulmonary
- Infectious
- Tumor-directed therapy

Halfdanarson TR, Hogan WJ, Madsen BE. Emergencies in hematology and oncology. Mayo Clin Proc. 2017;92(4):609-641

Oncologic Emergencies (OE) - Metabolic

- Hypercalcemia of malignancy
  - Causes:
    - Humoral – tumor production of PTHrP or intact PTH
      - Most common cause
    - Bone destruction/osteolysis
    - Excess production of Vitamin D
  - Presentation:
    - Lethargy, confusion, anorexia, polyuria, polydipsia
    - Can result in cardiac dysrhythmias – bradycardia, shortening of QT, cardiac arrest
    - Physical symptoms as above. Possibly dehydration

Halfdanarson TR, Hogan WJ, Madsen BE. Emergencies in hematology and oncology. Mayo Clin Proc. 2017;92(4):609-641

Oncologic Emergencies (OE) - Metabolic

- Hypercalcemia of malignancy

TABLE 1. Treatment of Hypercalcemia

Intervention	Dosage	Comments
Saline	250-500 mL/h IV until euvolemic and 100-150 mL/h IV after volume repletion is achieved. Can start by giving an 1- to 2-L initial bolus over 1 h if hypovolemic	The rate of infusion should be adjusted for the cardiovascular status of the patient
Pamidronate	60-90 mg IV over 2-4 h	Use with caution in renal insufficiency. Onset of action may take days
Zoledronic acid	4 mg IV over 15 min	Use with caution in renal insufficiency. Onset of action may take days
Calcitonin	4-8 IU/kg SC or IV every 12 h	Rapid onset of action but short-lived
Glucocorticoids	Prednisone, 60 mg/d PO; hydrocortisone, 100 mg every 6 h IV	Useful for hypercalcemia from calcitriol overproduction and in multiple myeloma
Denosumab	120 mg SC weekly for 4 wk, then every 4 wk	Safe in renal insufficiency but doses should be reduced. Can cause severe hypocalcemia
Furosemide	20-40 mg IV	Only for patients with volume overload after volume expansion

IV = intravenously; PO = orally; SC = subcutaneously.

Halfdanarson TR, Hogan WJ, Madsen BE. Emergencies in hematology and oncology. Mayo Clin Proc. 2017;92(4):609-641

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Oncologic Emergencies (OE) - Metabolic

- Tumor Lysis syndrome
  - Rapid cell turnover, cell lysis and release of intracellular contents
  - Nucleic acid catabolism = hyperuricemia → uric acid crystals obstruct renal tubules
  - Release of intracellular phosphate = hyperphosphatemia → HYPOcalcemia
    - Hyperphosphatemia + calcium = calcium phosphate crystals = AKI
  - Hyperkalemia – may be first manifestation
  - Treatment – prevention with hydration*, decrease uric acid production and increase clearance
  - Controversies –
    - How much fluid?
    - What if they develop renal failure and require renal replacement therapy?
    - What if they have heart failure or are near intubation?
      - Remember jump in mortality associated with mechanical ventilation!

Halfdanarson TR, Hogan WJ, Madsen BE. Emergencies in hematology and oncology. Mayo Clin Proc. 2017;92(4):609-641

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Oncologic Emergencies (OE) - Metabolic

- Other metabolic issues:
  - Lactic acidosis
  - Hyponatremia
  - Hypoglycemia
  - Adrenal insufficiency

Halfdanarson TR, Hogan WJ, Madsen BE. Emergencies in hematology and oncology. Mayo Clin Proc. 2017;92(4):609-641

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Oncologic Emergencies (OE) - Hematologic

- Hyperviscosity
  - Intrinsic resistance to the flow of blood secondary to increased production of monoclonal proteins or excessive cellular or acellular elements
  - Waldenstrom macroglobulinemia most common cause – IgM
    - Uncommon if IgM <3g/dL
  - Symptoms – headache, blurry/loss of vision, dizziness, chest pain, shortness of breath, encephalopathy
  - Physical exam – retinal venous engorgement, retinal hemorrhaging, papilledema, bleeding
  - Rouleaux on peripheral smear
  - Treatment: Plasmapheresis or phlebotomy + isotonic fluid replacement

Halfdanarson TR, Hogan WJ, Madsen BE. Emergencies in hematology and oncology. Mayo Clin Proc. 2017;92(4):609-641

Oncologic Emergencies (OE) - Hematologic

- Hyperleukocytosis and leukostasis
  - Exact value less important than clinical picture
  - Results in tissue hypoxia and infarction
  - AML >>> ALL
  - Clinical manifestations similar to hyperviscosity
  - Treatment – Leukapheresis, hydroxyurea, emergent initiation of induction therapy
  - *Monitor closely for development of tumor lysis!

Halfdanarson TR, Hogan WJ, Madsen BE. Emergencies in hematology and oncology. Mayo Clin Proc. 2017;92(4):609-641

Oncologic Emergencies (OE) - Neurologic

- Malignant cord compression
  - Up to 6% cancer patients expected to develop spinal compression
  - Most often implicated
    - Breast, lung, prostate → 2/3 of all cases
    - Multiple Myeloma and non-Hodgkin lymphoma → highest cancer-specific incidence
  - Metastases to vertebral body then erosion is most common
  - Paravertebral tumors can extend through foramina
  - Thoracic spine > lumbar spine > cervical
    - EXAMINE YOUR PATIENT!
  - Corticosteroids and emergent surgical consultation for evaluation

Halfdanarson TR, Hogan WJ, Madsen BE. Emergencies in hematology and oncology. Mayo Clin Proc. 2017;92(4):609-641

Oncologic Emergencies (OE) – Cardiovascular

- Malignant pericardial effusion/tamponade
  - Can be secondary to pericardial metastases, tumor invasion or treatment
  - Rapidly accumulating typically more emergent
    - Decreased ventricular filling, cardiac output → cardiovascular collapse
  - Symptoms – Possible cough, chest pain, hypotension, distant heart sounds, fixed/elevated JVP, pulsus paradoxus, shock
  - EKG – electrical alternans
  - Treatment – large and symptomatic – pericardiocentesis, pericardial drain or window

Halfdanarson TR, Hogan WJ, Madsen BE. Emergencies in hematology and oncology. Mayo Clin Proc. 2017;92(4):609-641

Oncologic Emergencies (OE) – Cardiovascular

- Superior Vena Cava Syndrome
  - Extrinsic compression or occlusion of SVC
    - Thoracic malignancies most common
    - Benign causes – thrombosis of catheters or pacemaker leads
  - Symptoms – dyspnea, orthopnea, cough, facial fullness, headache
    - Chest pain, hemoptysis, hoarseness, syncope
  - Most cases not truly emergent
    - Endovascular stenting
    - Radiation – slow to improve symptoms
    - Elevate head of bed
    - Disease-specific therapy

Halfdanarson TR, Hogan WJ, Madsen BE. Emergencies in hematology and oncology. Mayo Clin Proc. 2017;92(4):609-641

Oncologic Emergencies (OE) – Respiratory

- Superior Vena Cava Syndrome
  - Extrinsic compression or occlusion of SVC
    - Thoracic malignancies most common
    - Benign causes – thrombosis of catheters or pacemaker leads
  - Symptoms – dyspnea, orthopnea, cough, facial fullness, headache
    - Chest pain, hemoptysis, hoarseness, syncope
  - Most cases not truly emergent
    - Endovascular stenting
    - Radiation – slow to improve symptoms
    - Elevate head of bed
    - Disease-specific therapy

Halfdanarson TR, Hogan WJ, Madsen BE. Emergencies in hematology and oncology. Mayo Clin Proc. 2017;92(4):609-641

Oncologic Emergencies (OE) – Respiratory

- Malignant airway obstruction
  - Most commonly lung cancer
    - Anaplastic thyroid, SCC of head and neck, mediastinal lymphoma or germ cell
    - Rarely primary tracheal tumors
  - Dyspnea, coughing, wheezing, stridor
  - CT to diagnose → STABILIZE AIRWAY!
  - Bronchoscopy
    - Restore airway patency
    - Stenting, brachytherapy, laser therapy, etc.
    - Stents can migrate or become infected

Halfdanarson TR, Hogan WJ, Madsen BE. Emergencies in hematology and oncology. Mayo Clin Proc. 2017;92(4):609-641

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Oncologic Emergencies (OE) – Respiratory

- Acute Hemorrhage of airway
  - Tumor erosion
  - Massive hemoptysis definition not standardized
    - ~100-600ml bloody expectorant over 24 hours
  - Respiratory failure symptoms
  - CT angiography to identify bleed → STABILIZE AIRWAY!
  - Local therapy vs therapeutic embolization

Halfdanarson TR, Hogan WJ, Madsen BE. Emergencies in hematology and oncology. Mayo Clin Proc. 2017;92(4):609-641

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Oncologic Emergencies (OE) –

TABLE 12. Emergencies and Other Urgent Adverse Events Related to Targeted Cancer Therapies

Organ system affected	Class of drug	Example
Cardiovascular		
Congestive heart failure	HER2-directed therapy	Trastuzumab, pertuzumab
	Immunotherapy	Ipilimumab, nivolumab, pembrolizumab
Arterial thromboembolism	VEGF-directed therapy	Bevacizumab, aflibercept, ramucirumab
	Kinase inhibitors	Ponatinib, pazopanib
Venous thromboembolism	Immunomodulatory drugs	Thalidomide, lenalidomide
Arrhythmia	Kinase inhibitors	Dasatinib, vandetanib, ibrutinib, lenvatinib
	Antiemetics	Ondansetron, metoclopramide
	Proteasome inhibitors	Bortezomib, carfilzomib
Pulmonary		
Pneumonitis	mTOR inhibitors	Everolimus, temsirolimus
	Kinase inhibitors	Erlotinib, gefitinib, crizotinib, idelalisib
Pleural effusions	Kinase inhibitors	Dasatinib
Gastrointestinal		
Bowel perforation	VEGF inhibitors	Bevacizumab
Diarrhea	Kinase inhibitors	Multiple TKIs
	Immunotherapy	Ipilimumab, nivolumab, pembrolizumab
Acute liver failure	Multiple targeted agents	
Endocrine		
Adrenal insufficiency	Immunotherapy	Ipilimumab, nivolumab, pembrolizumab
Hypophysitis	Immunotherapy	Ipilimumab, nivolumab, pembrolizumab
Hyperglycemia	mTOR inhibitors	Everolimus, temsirolimus
Hematologic		
Hemorrhage	VEGF inhibitors	Bevacizumab, aflibercept, ramucirumab
Neutropenia	Multiple targeted agents	
Thrombocytopenia	Multiple targeted agents	

HER2 = human epidermal growth factor receptor 2; mTOR = mammalian target of rapamycin; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

Halfdanarson TR, Hogan WJ, Madsen BE. Emergencies in hematology and oncology. Mayo Clin Proc. 2017;92(4):609-641

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Questions?

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Information contained likely to be updated prior to Spurr Symposium presentation.

References and works to be fully cited by symposium

Information for this lecture was largely obtained, adapted or referenced directly from the new publication: *Oncologic Critical Care*.

Citations referencing *Oncologic Critical Care* should be cross-referenced for original publications.

Updates on the Management of Metastatic Triple Negative Breast Cancer
Tiffany A. Traina, MD
Clinical Director, Breast Medicine Service Section Head
Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center

Updates on the Management of Metastatic Triple Negative Breast Cancer

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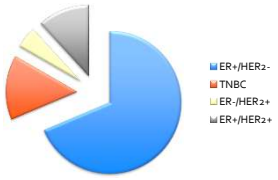
Associate Professor of Medicine
Dept of Medicine; Weill Cornell Medicine
September 2019

Triple Negative Breast Cancer

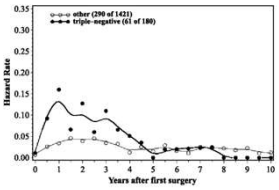
Breast Cancer Subtypes



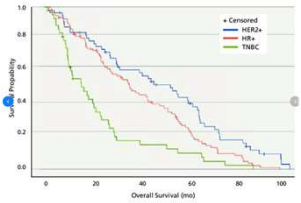
- TNBC represents ~15% of the 266,000 new breast cancer diagnoses in 2018
- Compared with ER+ BC, TNBC is associated with:
  - Younger age
  - Higher rates of distant recurrence
  - Sites of MBC often viscera and brain
  - 6% of pts with TNBC present with de novo MBC

TNBC Recurrence & Survival Patterns

Recurrence in first 1-3 years

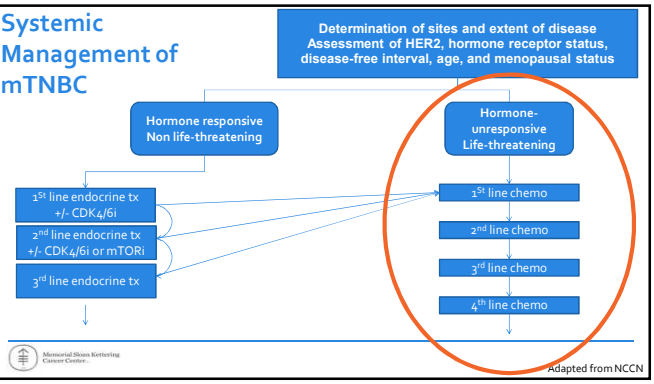


Poor overall survival



Dent et al CCR 2007; Seah et al JNCCN 2014

Systemic Management of mTNBC

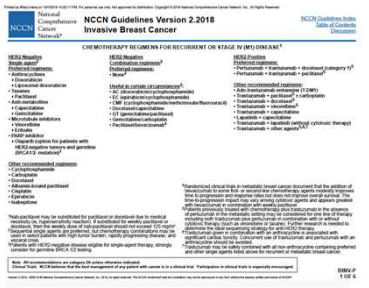


Adapted from NCCN

Chemotherapy has been the Standard of Care

Anthracyclines
Paclitaxel
Capecitabine
Gemcitabine
Vinorelbine
Eribulin
PARPi

Other:
Cyclophosphamide
Platinums
Docetaxel
Nab-paclitaxel
Ixabepilone


NCCN Guidelines Version 2.2018
Invasive Breast Cancer

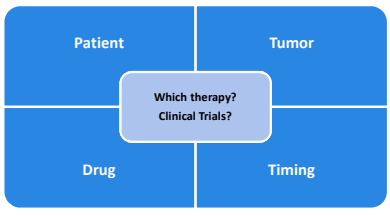
CHEMOTHERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE[1]

Memorial Sloan Kettering Cancer Center

Factors to consider for treatment

KPS
Comorbidities
gBRCA status
Compliance
Convenience
Preference

Prior tx
Activity profile
Toxicity profile
Predictive BM

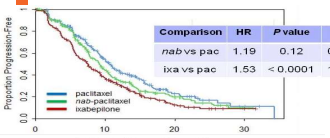


Disease burden
Symptoms
Tempo/DFI
Predictive BM
PDL1 status
Genomics

Life events
Wash out
Trial availability
Sequencing?

Memorial Sloan Kettering Cancer Center

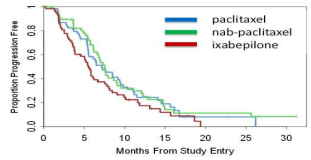
CALGB 40502: taxanes prevail



Comparison	HR	*P* value	95% CI
nab vs pac	1.19	0.12	0.96-1.49
ixa vs pac	1.53	< 0.0001	1.24-1.90

Agent	N	Median PFS
paclitaxel	283	10.6
nab-paclitaxel	271	9.2
ixabepilone	245	7.6

Triple Negative Disease

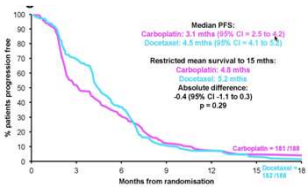


Comparison	HR	P-value	95% CI
nab vs. pac	0.93	0.7354	0.62 – 1.40
ixa vs. pac	1.46	0.0647	0.98 – 2.18

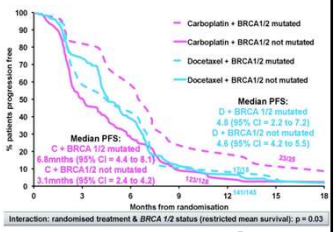
Rugo H et al, JCO June 8, 2015

TNT: Docetaxel vs. Carboplatin

ITT: No difference



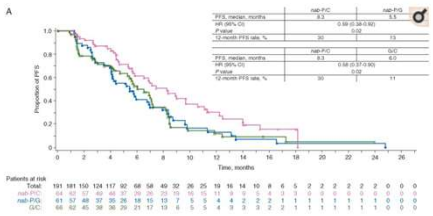
gBRCAm status matters!



Interaction: randomised treatment & *BRCA 1/2* status (restricted mean survival): p = 0.03

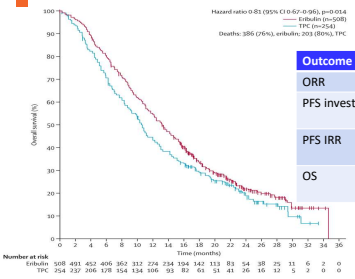
Tutt et al, SABCS 2014 S3-01 and 2018

TnAcity: 1st Line chemotherapy doublets *nab-paclitaxel and carboplatin*



Yardley et al Ann Oncol 2018 Aug

Beyond 1st line?
Eribulin improves OS by ~20% compared to TPC



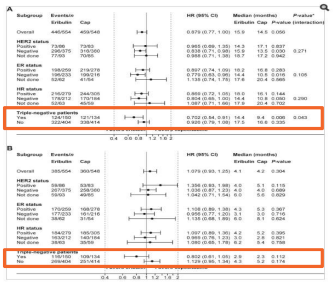
Outcome	Result	P value
ORR	5% vs 12%	0.002
PFS investigator	2.2 vs 3.6 mo; HR 0.76	0.002
PFS IRR	2.2 vs 3.7 mo; HR 0.87	0.137
OS	10.6 vs 13.1 mo; HR 0.81	0.041

Cortes et al, Lancet 2011

Eribulin improves OS by ~30% in patients with metastatic TNBC compared to capecitabine

OS

PFS



Kaufman et al, JCO 2015

Management of TNBC: Rapidly Changing Landscape

Neoadjuvant	Surgery	Adjuvant	1L Therapy	2L +
Benefit to adding a platinum in neoadjuvant? • CALGB 40603 • GeparSixto • BrighTNess • ADAPT		**What is the role of Capecitabine?** • CREATE-X (residual disease) • GEICAM (no residual disease)	**How should we treat gBRCAm patients?** • OLYMPIAD • EMBRACA	**How should we treat on progression?** • ASCENT (IMMU-132)* • Other ADCs? • What about continued IO?
Should IO be added? • Keynote-522* • IMpassion-030*		• OlympiA • Multiple ongoing studies	**Should IO be added?** • IMpassion-130 • Keynote-355*	
What is the best sequence for IO / chemo? • GeparNuevo			**Benefit to adding a platinum in metastatic?** • TNT • TnAcity	
What is best chemo partner for IO? • GeparSepto • ETNA • NEOTRIP*			**Other targeted therapy?** • AKTi • AR	

Study ongoing or data not yet read out

BRCA1/2

Immuno-oncology

Antibody drug conjugates

AKT inhibitors

OlympiAD: Ph III trial of olaparib in gBRCA mutation associated breast cancer

- HER2-negative mBC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious gBRCA mutation
- Prior anthracycline and taxane
- ≤2 prior chemotherapy lines in metastatic setting
- HR+ disease progresses on ≥1 ET, or not suitable for ET
- If prior platinum use:
  - No evidence of progression during treatment in the advanced setting
  - ≥12 mo since (neo)adjuvant treatment

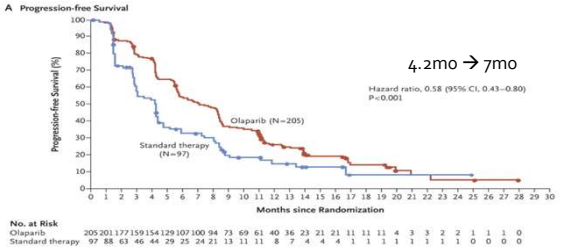
- **Primary endpoint**: PFS by blinded indepe

Olaparib
300mg tablets BID

TPC: Capecitabine
Eribulin
Vinorelbine

Robson et al, NEJM 2017

Olaparib associated with a 42% increase in median PFS as compared to treatment of physician's choice



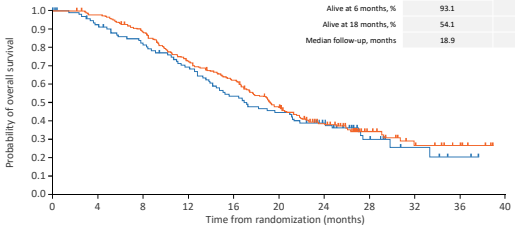
4.2mo → 7mo

Robson et al, NEJM 2017

Olaparib FDA approved based on these data!

Overall survival; ITT

	Olaparib	TPC
Deaths, n (%)	130 (63)	62 (64)
Median OS, months	19.3	17.1
HR 0.90		
95% CI 0.66–1.23; *P*=0.513		
Alive at 6 months, %	93.1	85.8
Alive at 18 months, %	54.1	48.0
Median follow-up, months	18.9	15.5

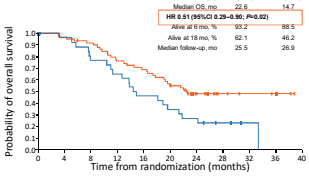


Robson et al AACR 2018

Overall survival in prespecified subgroups

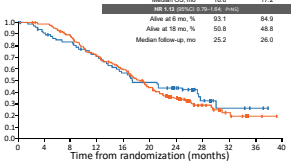
No prior chemotherapy for mBC (1L)

	Olaparib	TPC
Deaths, n (%)	30 (50.8)	21 (75.0)
Median OS, mo	22.6	14.7
HR 0.51 (95%CI 0.29–0.90; P=0.02)		
Alive at 6 mo, %	93.2	88.5
Alive at 18 mo, %	62.1	46.2
Median follow-up, mo	25.5	26.9



Prior chemotherapy for mBC (2/3L)

	Olaparib	TPC
Deaths, n (%)	100 (68.5)	41 (59.4)
Median OS, mo	18.8	17.2
HR 1.13 (95%CI 0.79–1.64, P=NS)		
Alive at 6 mo, %	93.1	84.9
Alive at 18 mo, %	50.8	48.8
Median follow-up, mo	25.2	26.0



Robson et al AACR 2018

EMBRACA: Ph III trial of talazoparib in gBRCA mutation associated BC

Eligibility

- Locally advanced or metastatic HER2-negative breast cancer
- Germline BRCA1 or BRCA2 mutation
- No more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease
- Prior treatment with a taxane and/or anthracycline unless medically contraindicated

2:1

N=431

Talazoparib
1mg daily

TPC: Capecitabine
Eribulin
Vinorelbine
Gemcitabine

Litton et al SABCS 2017

Summary (OlympiAD and EMBRACA)

	OlympiAD	EMBRACA
HR (PFS)	0.58 (0.43-0.80)	0.54 (0.41-0.71)
HR (OS)	0.90 (0.66-1.23)	0.76 (0.54-1.06)
HR (OS) 1st Line setting	0.51 (0.29-0.90)	NR
ORR	59.9% (vs 28.8% TPC)	67.6% (vs 27.2% TPC)
Deterioration HRQoL	0.44 (0.25-0.77)	0.38 (0.26-0.56)
SAE ≥ Grade 3	36.6% (vs 50.5% TPC)	25.5% (v. 25.4% TPC)
Anemia ≥ Grade 3	16.1%	39.2%
Neutropenia ≥ Grade 3	9.3%	20.9%
Thrombocytopenia ≥ Grade 3	2.4%	14.7%
MDS/AML	0	0
Nausea (any grade)	58.0%	48.6%
Alopecia (any grade)	3.4%	25.2%

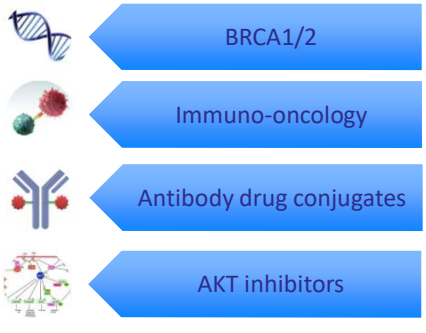
Next steps in PARP inhibition

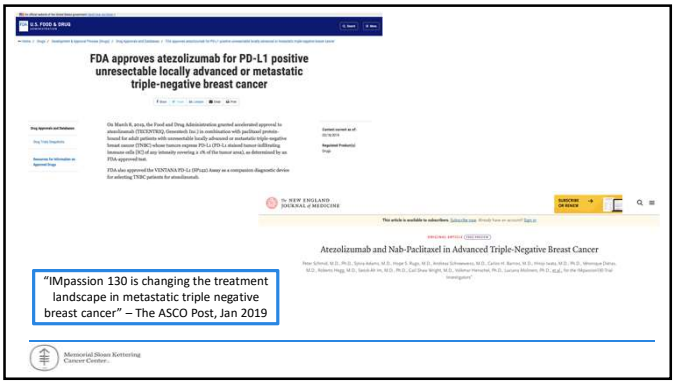
Extending PARPi therapy

- Combinations (conventional cytotoxics)
- Combinations (targeted agents)
  - PIK_3CAi
  - VEGF (e.g. cedirinib)
  - Increase replication stress (ATMi, ATRi)
  - IO (innate immunity?)
- Early stage disease (adjuvant olaparib, neoadjuvant talazoparib)
- Other genes, somatic mutations

Other PARPi in development

- Veliparib
  - BrighTNess: C+P+V vs. C+P vs. P Neoadjuvant TNBC → AC.
    - Addition of V did not inc pCR
  - BROCADE: C+P+V vs. C+P in met g*BRCA*
- Niraparib
  - BRAVO: Niraparib vs. TPC in met g*BRCA*. Closed early and has not reported
- Rucaparib
  - Phase II of rucaparib in patients with metastatic BC with high loss of heterozygosity/HRD





"IMpassion 130 is changing the treatment landscape in metastatic triple negative breast cancer" – The ASCO Post, Jan 2019

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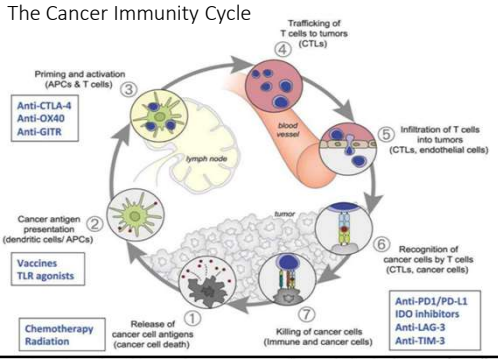
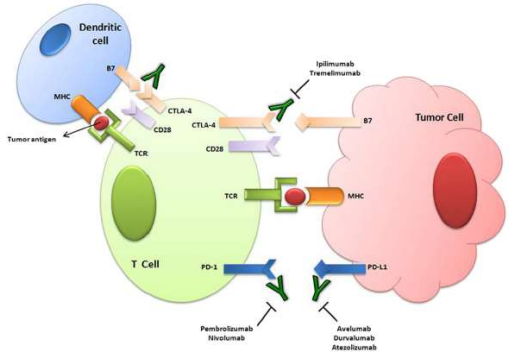
The Cancer Immunity Cycle



Adapted from Chen DS and Mellman, I; Immunity, 2013



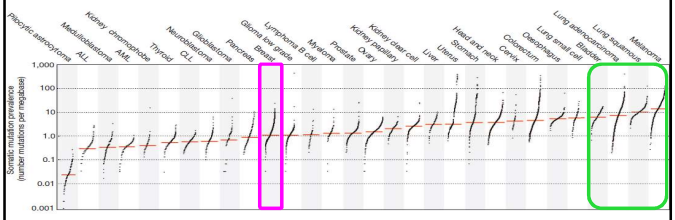
Why is TNBC a target for immunotherapy?

IMMUNOTHERAPY

TNBC

- Limited treatment options
- Increased tumor mutational burden
- Higher TILs
- High PD-L1 expression

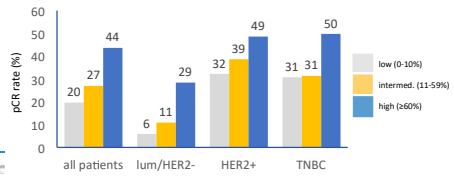
Breast cancer has a relatively modest tumor mutational burden



LB Alexandrov et al.. Nature 2013

TILs as a Predictive and Prognostic Biomarker in Different Subtypes of BC Treated with Neoadjuvant Rx

- **Meta-analysis of 3771 patients (GBG)**
  - **High TILS are more frequent in TNBC (30%) > HER2 (19%) > luminal (13%)**
  - **TILS are linked to increased pCR rates in all subtypes**
  - **High TILS associated with OS for TNBC and HER2; Low TILS associated with OS for luminal**



Denkert et al, Lancet Oncol; 2018

PD-L1 expression in early breast cancer

BC subtype	N (%)	PD-L1 positivity
Lum A	54 (49.5)	5 (9.3)
Lum B	24 (22)	10 (41.7)
HER2+	17 (15.6)	5 (29.4)
TNBC	14 (12.8)	6 (42.9)

PD-L1 IHC expression on	N = 110 (%)
Tumor cells	6 (5.5)
Immune cells	22 (20)
Stromal cells	4 (3.6)
Any cells	26 (23.6)

PD-L1 positivity : ≥1% expression on tumor or immune or stromal cells

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Buisseret et al. Oncoimmunology 2017

Single Agent Checkpoint Inhibitors: Phase Ib Trials

Agent	Subtype	ORR	ORR (PD-L1+)
Pembrolizumab (anti-PD1)			
• Single agent (Keynote-012, n=27)	TNBC	18.5%	18.5%
• Single agent (Keynote-028, n=25)	ER+/HER2-	12.0%	12.0%
Atezolizumab (anti-PD-L1)			
• Single agent (n=21)	TNBC	19.0%	19.0%
Avelumab (anti-PD-L1)			
• Single agent (Javelin, n=168)	All	4.8%	33.3% (n=4/12)
	ER+/HER2-	2.8%	NR
	HER2+	3.8%	NR
	TNBC	8.6%	44.4% (n=4/9)

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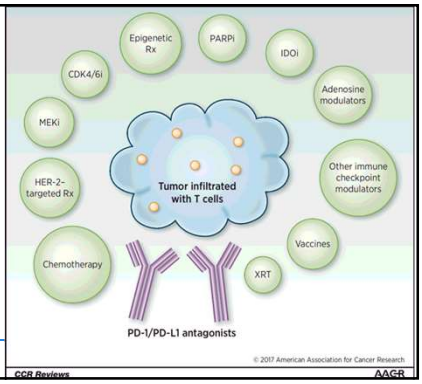
Nanda et al, JCO 2016, Emens et al, AACR 2015, Dirix et al, BCRT 2017, Rugo et al, CCR 2018

Enhancing the Tumor Immune Response



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Emens et al, CCR 2018

CCR Reviews AACR

Key Trials: Checkpoint + Chemotherapy

Drug	Trial	Phase	BC subtype	Disease Setting	Prior Lines of Therapy	Patients N=Evaluable/Enrolled	ORR	mPFS, months	mOS, months
Pembrolizumab	ENHANCE-1 Pembro + Eribulin	Ib/II	TNBC	Metastatic	≤2	n=106/107 PD-L1+ n=49 PD-L1- n=49 1st line n=65 1-2 prior lines n=41	26.4% 30.6% 22.4% 29.2% 22%	4.2	17.7
Atezolizumab	Atezolizumab + nab-paclitaxel	Ib	TNBC	Metastatic	≤2	n=32 1st line n=13	39% 54%	5.5 8.6	14.7 24

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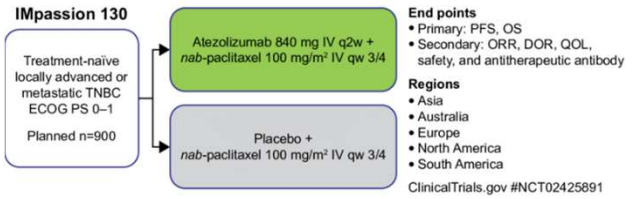
Lyons, Dickler and Comen. Current Oncology Reports.

IMpassion130: Nab-Paclitaxel +/- Atezolizumab



End points
- Primary: PFS, OS
- Secondary: ORR, DOR, QOL, safety, and antitherapeutic antibody

Regions
- Asia
- Australia
- Europe
- North America
- South America

ClinicalTrials.gov #NCT02425891

- Archival tissue collection
- Any PD-L1 status permitted

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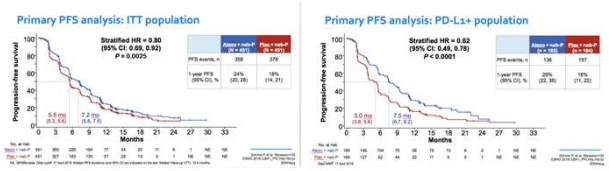
IMpassion130: Baseline Characteristics

Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Median age (range), y	55 (20-82)	56 (26-86)
Female, n (%)	448 (99%)	450 (100%)
Race, n (%)[a]		
White	308 (68%)	301 (67%)
Asian	85 (19%)	76 (17%)
Black/African American	26 (6%)	33 (7%)
Other/multiple	20 (4%)	26 (6%)
ECOG PS, n (%)[b,c]		
0	256 (57%)	270 (60%)
1	193 (43%)	179 (40%)
Prior (neo)adjuvant treatment, n (%)	284 (63%)	286 (63%)
Prior taxane	231 (51%)	230 (51%)
Prior anthracycline	243 (54%)	242 (54%)

Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Metastatic disease, n (%)	404 (90%)	408 (91%)
No. of sites, n (%)[d]		
0-3	332 (74%)	341 (76%)
≥ 4	118 (26%)	108 (24%)
Site of metastatic disease, n (%)		
Lung	226 (50%)	242 (54%)
Bone	145 (32%)	141 (31%)
Liver	126 (28%)	118 (26%)
Brain	30 (7%)	31 (7%)
Lymph node only[d]	33 (7%)	23 (5%)
PD-L1+ (IC), n (%)	185 (41%)	184 (41%)

Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR) http://bit.ly/2DMhayg

Atezolizumab prolongs PFS in PDL1+ TNBC



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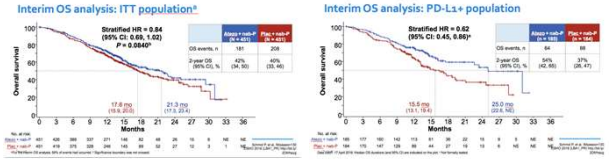
Overall survival data encouraging…



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IMpassion130 OS Update

median follow up ~18 months

	Nab-pac + Atezo	Nab-pac
ITT population (events/pt; %)	**255/451 (57%)**	**279/451 (62%)**
HR (95% CI); p	0.86 (0.72-1.02) P=0.078	-
Median OS, months	21.0 (19.0-22.6)	18.7 (16.9-20.3)
PD-L1+ (events/pt; %)	**94/185 (51%)**	**110/184 (60%)**
HR (95% CI); p	0.71 (0.54-0.93)	-
Median OS, months	25.0 (19.6-30.7)	18.0 (13.6-20.1)

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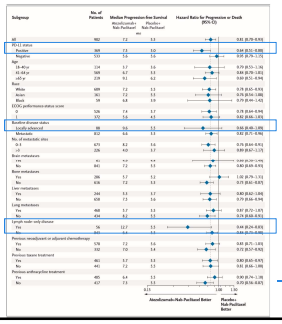
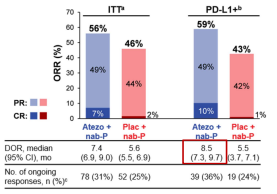
Schmid P, et al. IMpassion130 ASCO 6/4/19

IMpassion 130: PFS Subgroups & ORR



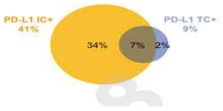


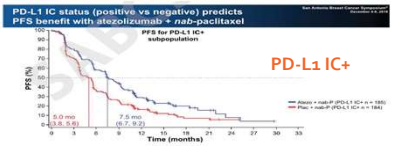
	Atezo + nab-P	Plac + nab-P	Atezo + nab-P	Plac + nab-P
DOR, median (95% CI), mo	7.4 (6.9, 9.0)	5.6 (5.5, 6.9)	8.5 (7.3, 9.7)	5.5 (3.7, 7.1)
No. of ongoing responses, n (%)[a]	78 (31%)	52 (25%)	39 (36%)	19 (24%)

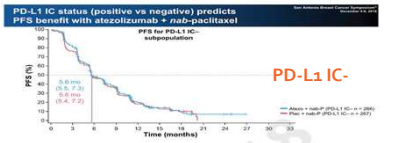
Schmid P, et al – N Engl J Med October 20, 2018 - DOI: 10.1056/NEJMoa1809615

PD-L1 IC status predictive of PFS benefit from atezolizumab

The majority of patients with expression of PD-L1 on TC are included within the PD-L1 IC+ population

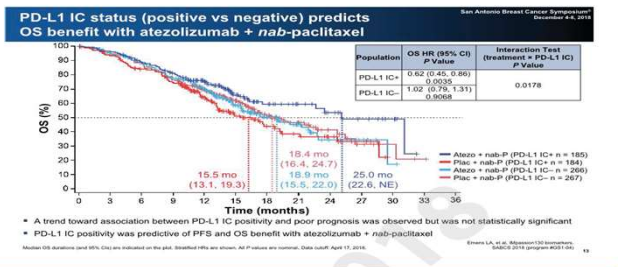






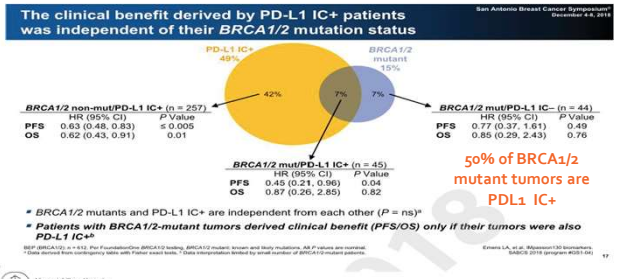
Emens et al SABCS 2018

PD-L1 IC status predictive of OS benefit



Emens et al SABCS 2018

BRCA status is not an independent predictor of atezolizumab benefit



50% of BRCA1/2 mutant tumors are PDL1 IC+

Emens et al SABCS 2018

AESIs suggestive of potential immune-related etiology

AESI, n (%)[a]	Atezo + nab-P (n = 452)		Plac + nab-P (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All	259 (57%)	34 (8%)	183 (42%)	19 (4%)
Important AESIs				
Hepatitis (all)	69 (15%)	23 (5%)	62 (14%)	13 (3%)
Hepatitis (diagnosis)	10 (2%)	6 (1%)	7 (2%)	1 (< 1%)
Hepatitis (lab abnormalities)	62 (14%)	17 (4%)	58 (13%)	12 (3%)
Hypothyroidism	78 (17%)	0	19 (4%)	0
Hyperthyroidism	20 (4%)	1 (< 1%)	6 (1%)	0
Pneumonitis	14 (3%)	1 (< 1%)	1 (< 1%)	0
Meningoencephalitis[b]	5 (1%)	0	2 (< 1%)	0
Colitis	5 (1%)	1 (< 1%)	3 (1%)	1 (< 1%)
Adrenal insufficiency	4 (1%)	1 (< 1%)	0	0
Pancreatitis	2 (< 1%)	1 (< 1%)	0	0
Diabetes mellitus	1 (< 1%)	1 (< 1%)	2 (< 1%)	1 (< 1%)
Nephritis	1 (< 1%)	0	0	0
Other AESIs[c]				
Rash	154 (34%)	4 (1%)	114 (26%)	2 (< 1%)
Infusion-related reactions	5 (1%)	0	5 (1%)	0

AESI, adverse event of special interest. Data cutoff: 17 April 2018. [a] Baskets of preferred terms according to medical concepts. [b] All events of photophobia. [c] Includes all AESIs occurring in ≥ 1% of patients in either arm.

Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR) http://bit.ly/2DMhayg

IMpassion130 Conclusions & Questions

- Atezolizumab improves mPFS when added to nab-pacli in 1L TNBC and shows numerical improvement in OS for patients with PD-L1 IC+
- PD-L1 IC expression ≥1% is the only predictive biomarker of atezolizumab benefit
  - *Will this be true for all checkpoint inhibitors?*
- Co-expression of BRCA1/2 mutation with PD-L1 IC+ is uncommon (~7%)
  - 50% of BRCA1/2 mutations associated with PD-L1 IC+ tumors
  - *Opportunity for concurrent PARPi and checkpoint blockade for these patients?*
- *Are there other chemotherapy partners of benefit? Platinum? Eribulin?*
- *What is optimal approach for patients with shorter DFI?*
- *What is best second line approach upon POD with checkpoint blockade?*

BRCA1/2

Immuno-oncology

Antibody drug conjugates

AKT inhibitors

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Engineering ADCs in TNBC

- The target
  - Selectivity
  - Level of expression
  - ADC internalization
  - Intracellular trafficking
- The linker
  - Cleavable vs. non-cleavable
- The payload
  - Tubulin directed
  - DNA damaging

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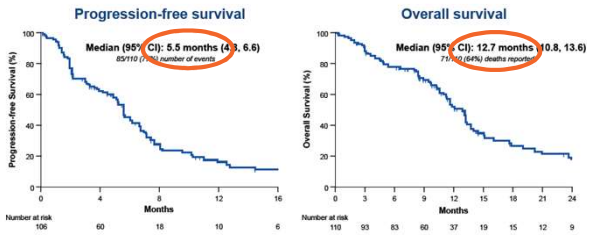
Sacituzumab: TNBC Efficacy

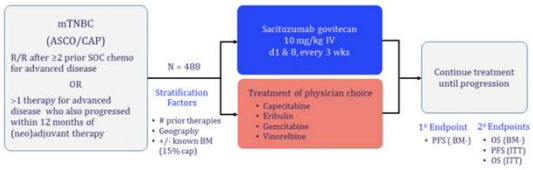
mTNBC, ≥2 priors, s/p taxane. No biomarker selection. N=110



Bardia et al, NEJM 2019

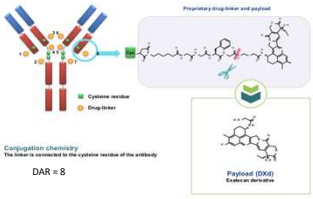
ORR 34%, DoR 7.7mo

ASCENT: Randomized Ph III ongoing

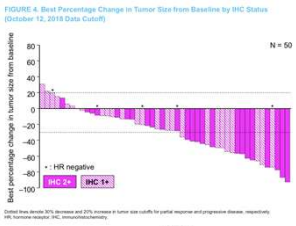


Other ADCs in TNBC…
trastuzumab deruxtecan

Trastuzumab deruxtecan
DS-8201a

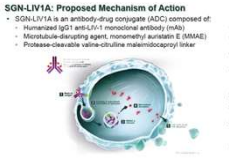


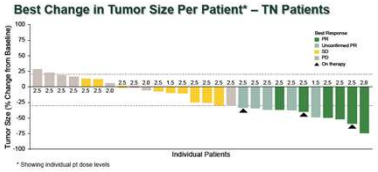
HER2 "low"



Poster # P6-17-02 – San Antonio Breast Cancer Symposium® – December 4–8, 2018

Other ADCs in TNBC…
ladiratuzumab vedotin





- Metastatic TNBC, ≥2 prior chemotherapy
- Results: ORR 25%, mPFS 11 weeks (95% CI, 6-12 weeks)
- Treatment related AEs, all grade: alopecia 41%, neutropenia 25%, neuropathy 20%, vomiting 24%

Forero et al SABCS 2016, Modi et al SABCS 2017

BRCA1/2

Immuno-oncology

Antibody drug conjugates

AKT inhibitors

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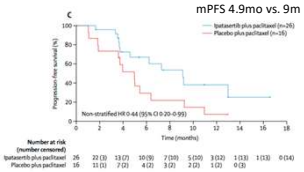
AKT inhibition in 1st line mTNBC

Paclitaxel +/- capivasertib **Ipatasertib**

	PFS	OS
ITT N=138	4.2 vs 5.9 m. HR 0.74 (0.5,1.08) p=0.06	12.6 vs 19.1 m. HR: 0.61 (0.37, 0.99) p=0.02
PIK3CA/AKT1/ PTEN Altered N=28	3.8 vs 9.3 m. HR 0.3 (0.11-0.79) p=0.01	10.4 vs NR. HR 0.37 (0.12-1.12) p=0.61
PIK3CA/AKT1/ PTEN WT N=84	4.4 vs 5.3 m. HR 1.13 (0.7,1.82) p=0.067	13.2 vs 16.6 m. HR 0.84 (0.48,1.49) p=0.56

PIK3CA/AKT/PTEN altered
mPFS 4.9mo vs. 9m



Schmid, et al, ASCO 2018, Kim et al, Lancet Onc 2017

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AR as a target in TNBC

	AR >0%	AR >10%	CBR24	CBR16	mPFS
Bicalutamide[1]	--	12%	19%	--	12 wks
Enzalutamide[2]	79%	*55%	*29%	*35%	*14.7 wks
Abiraterone[3]	--	38%	20%	--	11.2 wks
Seviteronel[4]	Phase I published; Phase II manuscript in preparation				
Bicalutamide + Palbociclib[5]	Phase I completed; Phase II ongoing				
Enzalutamide + taselisib	Phase I complete				

[1]Gucalp et al. CCR. 2013; [2]Traina et al. J Clin Oncol. 2018;
[3]Bonnefoi et al. Annals Oncol. 2016; [4] Gucalp et al ASCO 2017; [5]Gucalp et al SABCS 2017

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Management of TNBC: Rapidly Changing Landscape

Neoadjuvant	Surgery	Adjuvant	1L Therapy	2L +
Benefit to adding a platinum in neoadjuvant? • CALGB 40603 • GeparSixto • BrighTNess • ADAPT		**What is the role of Capecitabine?** • CREATE-X (residual disease) • GEICAM (no residual disease)	**How should we treat gBRCAm patients?** • PARPi • PARPi combinations with IO?	**How should we treat on progression?** • IO post progression on IO? • IMMU-132 in 3L+ • Other ADCs?
Should IO be added? • Keynote-522* • IMpassion* • ISPY		**What is the role of PARPi?** • OlympiA • Multiple ongoing studies	**Should IO be added?** • IMpassion-130 • PD-L1+ TNBC • Keynote-355*	**Other targets?** • AR
What is the best sequence for IO / chemo? • GeparNuevo		**Should IO be added?** • Impassion • SWOG1418	**Other targets?** • AKT inhibitors • AR	
What is best chemo partner for IO? • GeparSepto • ETNA • NEOTRIP*				

*Study ongoing or data not yet read out

Thank You!

Memorial Sloan Kettering Cancer Center

2019 Legislative Update and What it Means for Oncology
Shelag Foster, JD
Division Director, Policy & Advocacy
American Society of Clinical Oncology (ASCO)

2019 Legislative Update and What it Means for Oncology

Shelagh Foster, JD
Division Director, Policy and Advocacy
ASCO

ASCO

ASCO's Policy Vision

All patients should have access to high-quality, high-value cancer care – no matter who they are or where they live

ASCO

Turning Our Vision into Reality: Policy Priorities

Access

Expanding patient access to affordable cancer care and clinical trials

Delivery

Reforming cancer care delivery and reimbursement

Research

Investing in cancer research that saves Americans' lives

ASCO

Policy Priorities

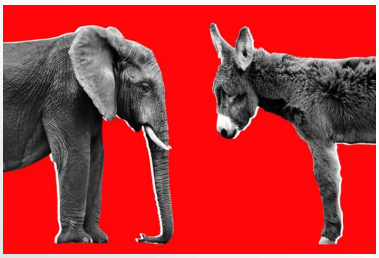
GOAL 1: Pursue access to high quality, affordable care for every patient with cancer

GOAL 2: Advance evidence-based policies and delivery system reform that supports oncology providers in their delivery of high quality, high value cancer care

GOAL 3: Advocate for policies that support a robust federally funded cancer research, prevention, drug development, and clinical trials system

ASCO

Political Reality



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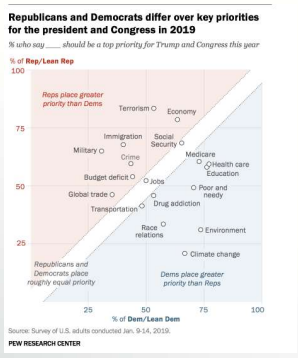

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Political Impact on Policy…is Real

InsideHealthPolicy
An Inside Washington news service

HOME LATEST NEWS TOPICS FDA WEEK INSIDE CMS INSIDE DRUG PRICING HEALTH E

Monday, August 12, 2019

Inside Drug Pricing

Drug Import Realities Kick In; Politics Drove CAR-T Coverage; Novartis In Hot Seat

By John Wilkerson
August 12, 2019 at 11:23 AM

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Major Driver of Change

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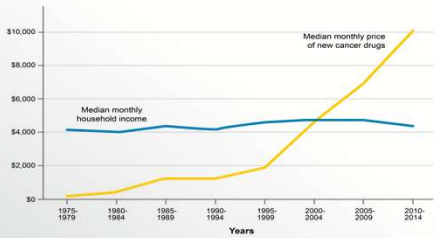
Launch Price of New Cancer Drugs Compared with Household Income, 1975-2014



Source: Ramsey S, Blough D, Kirchhoff A, Kreizenbeck K, et al. Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. *Health Affairs*. June 2013.

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"One of my greatest priorities is to **reduce the price of prescription drugs.**"

PRESIDENT DONALD J. TRUMP

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Drug Pricing Blueprint

HHS has identified four key strategies for reform:

1. **Competition**
   Lower drug prices and increase innovation through more competition
2. **Seniors**
   Give Medicare Part D plans tools to negotiate lower prices for seniors
3. **Incentives**
   Develop incentives for drug makers to lower their list prices
4. **More Options**
   Offer more drug options, which will lower out-of-pocket spending

HHS.GOV/DrugPricing

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- Part B Changes
- Step Therapy
- Preauthorization
- Pharmacy Benefit Managers
- Rebates

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Administrative Action on Drug Pricing

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Congressional Proposals: Positives

- **Price Transparency:** Allowing lawmakers, patients, and providers greater transparency on all aspects of drug pricing (including PBMs!)
- **Pay for delay/evergreening/product hopping:** Preventing drug manufacturers from participating in anti-competitive behaviors
- **Reducing Market Exclusivity**: Reducing the time it takes before a generic/biosimilar can enter the market
- **Patient Out of Pocket Maximums in Part D**

ASCO in Action
News, Advocacy, and Analysis on Cancer Policy

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Congressional Proposals: Concerns

- **ASP Formula:** Including Value of Coupons in the Determination of Average Sales Price for Drugs, Biologicals, and Biosimilars under Part B
- Establishing a Maximum Add-on Payment for Drugs, Biologicals, and Biosimilars
- **More to come?**

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116th Congress: Looking Ahead

- Federal Budget
- Surprise Billing
- Other ASCO Priority Legislation
  - Prior Authorization
  - Step Therapy
  - Clinical Trials Coverage
  - Oral Chemotherapy Parity

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Federal Funding for Cancer Research

FY2020: Budget resolution passed increasing non-defense discretionary spending caps. Congress now working on finalizing spending bills before September 30th.

News

Medical Research Funding Increase Expected With New Budget Deal

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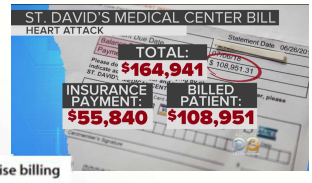
Surprise Billing



Physicians back alternative approach on surprise billing

JULY 2, 2019 AMA

Trump urges Congress to end 'surprise billing' of hospital, ER patients

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Other ASCO Priorities

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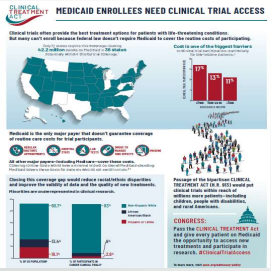
Medicaid Coverage of Clinical Trial Routine Care Costs



The *CLINICAL TREATMENT Act* (H.R. 913)

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Prior Authorization: the *Improving Seniors' Timely Access to Care Act* (H.R. 3107)

Requires Medicare Advantage plans increase transparency on use of prior authorization and real-time approval of some treatments.

Step Therapy: *Restoring the Patient's Voice Act* (HR 2279)

Requires private plans to implement a clear process for step therapy and includes protocol exceptions

Oral Parity: *Cancer Drug Coverage Parity Act* *(HR 1730/S 741)*

Requires private plans to provide cost sharing for oral cancer drugs at a rate that is no less favorable than the cost-sharing for IV cancer drugs

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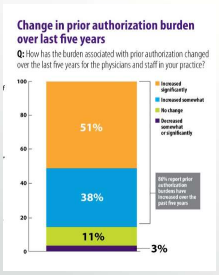

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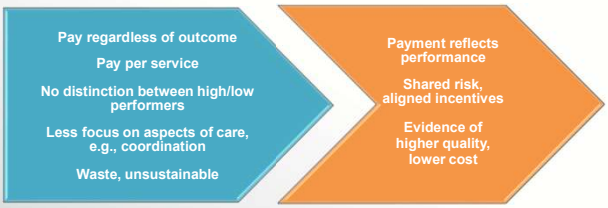
Payment Reform: Move From Volume to Value



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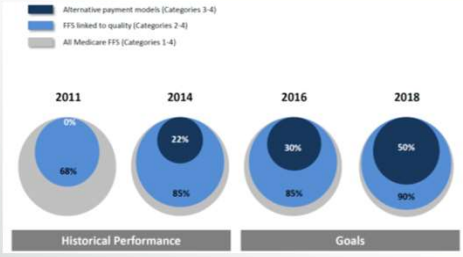
Payments in FFS Linked to Quality and APMs: Aspiration



Kate Goodrich April 2016, PCPI Conference

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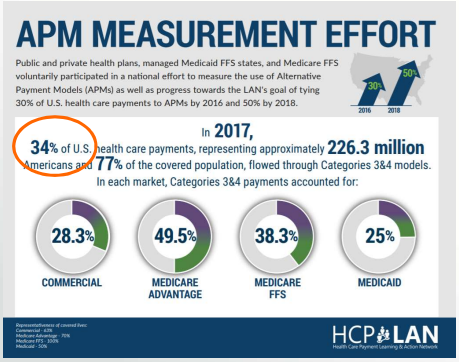

STATUS:

Slow but steady progress toward an ambitious goal

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Highlights from Proposed 2020 Physician Fee Schedule

- Coding, billing changes value time with patient
- Conversion factor ($ per RVU formula) essentially flat
- Streamlined Quality Payment Program (MIPS Value Pathways)
- Relaxing barriers to use of non-physician health providers
- Expansion of opioid use treatment services

Overall impact on oncology = ~0%

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Proposed 2020 Hospital Prospective Payment

A Few Highlights

HOSPITAL OUTPATIENT

- Price transparency for 300 services consumers likely to shop for
- Continue phasing in site-neutral payments for services in off-campus clinics
- Loosened physician supervision, from direct to general

INPATIENT

- **CAR T**
  - ➢ DRG add on payment increase from 50 to 65% of technology cost
  - ➢ Finalized days after rule
    - ✓ No requirement for CED
    - ✓ Must be enrolled in FDA REMS
    - ✓ Must be in approved compendia

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Bottom Line

"Change is possible.

Change is necessary.

And change is coming…"

HHS Secretary Alex Azar
Federation of American Hospitals Policy Conference
March 5, 2018

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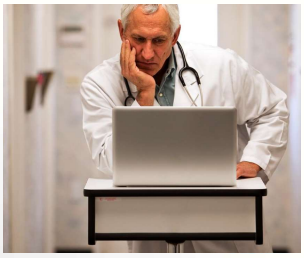
Goal: Sustainable Practice Environment

- NO MANDATORY DEMONSTRATIONS
- Test multiple payment models
- Pathways vs. UM, step therapy
- Relieve administrative burden



Hope in Rare Moments of Bipartisanship

NIH Funding

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Relationships Matter

"…budget of $39 billion this year…world's largest biomedical research agency

[Francis Collins]…has used charm to rally Congress to restore growth to NIH's budget after more than a decade of stagnation.

NIH has largely escaped political interference during his tenure."

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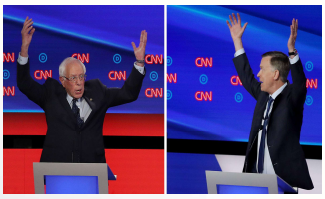
What Comes Next? Fasten Your Seatbelts



ASCO Health Reform Principles

- Access to affordable coverage regardless of income, health status.
- Reforms should not interrupt access to care/coverage
- Timely access to cancer specialists, full range of services
- Cancer prevention and screening without copay
- Access to clinical trials
- Value-based reform should be patient-centered
- Engage patients and providers in reform

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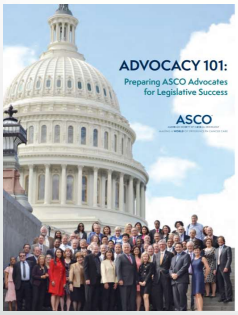

We Need You.

ASCO

You don't have to be in Washington.

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Testicular Cancer: The Incredible Journey to Cure a Cancer

Patrick J. Loehrer Sr., MD, FASCO
Director, IU Simon Cancer Center
H.H. Gregg Professor of Oncology
Indiana University School of Medicine

Testicular Cancer: *The Incredible Journey to Cure a Cancer*

Charles L. Spurr Symposium
September 22, 2019

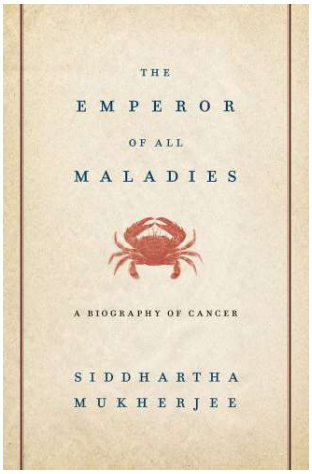
Patrick J. Loehrer Sr., M.D.
Indiana University Melvin and Bren Simon Cancer Center

Disclosures

Grant funding:

- **Novartis**
- **Eli Lilly**

When are we going to find the cure for cancer?



"Diagnosis: a bulging tumor in the breast...like touching a ball of wrappings"
"Treatment: none"

--Egyptian Text: Ca 2500 BC

Cancer: circa 1968

- Acute Lymphoblastic Leukemia was first disease curable with chemotherapy
- Hodgkin Disease treated with MOPP
- The most common cause of cancer death in young men was testicular cancer
- Testicular cancer treated with surgery curing about 50% of patients with early stage disease in a few centers of excellence.
- 95% of all others died of cancer, usually within a year

Importance of Testis Cancer

- Most common carcinoma in men ages 15-35 years
- Value of combined modality therapy
- Model for randomized studies
- New drug discovery
- Goal is cure

Germ Cell Tumors: Primary Sites

- Testis
- Ovaries
- Mediastinum
- Retroperitoneum
- Pineal Gland

Clinical Presentation

- Painless unilateral intrascrotal mass (>50%)
- Back or flank pain (11%)
- Gynecomastia (7%)
- Uncommon:
  - Hemoptysis
  - Dyspnea
  - CNS Symptoms
  - Bone metastasis

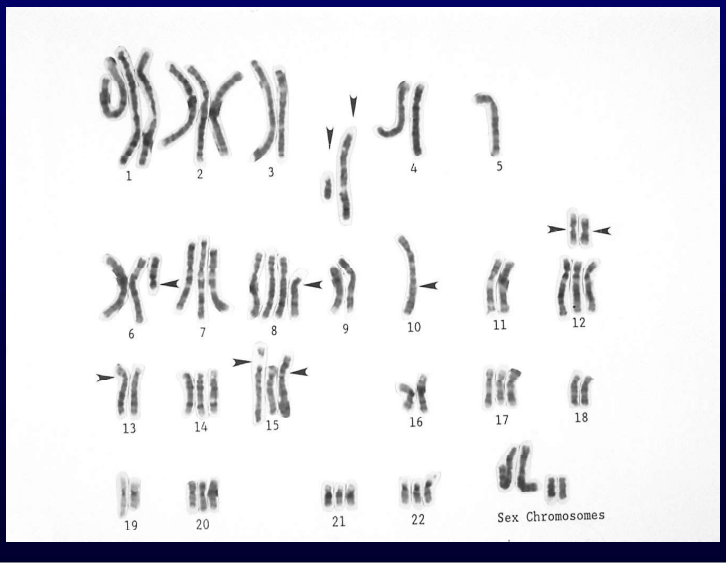
Histology and Serum Markers

	BHCG	AFP
• **Seminoma**	+/-	-
• **Non-Seminoma**		
Teratoma	-	-
Choriocarcinoma	+++	-
Yolk Sac Carcinoma	-	+++
Embryonal Carcinoma	++/-	++/-

Staging

- Stage I – Testicle alone
  - Is – Marker elevation alone after orchiectomy
- Stage II – Retroperitoneal Lymph node involvement
- Stage III – Disseminated disease (lungs, liver, brain, bone) or marker positive disease after RPLND

Isochromosome 12p: i(12p)



Germ Cell Tumors

- Background
- Disseminated Disease
  - Good Risk
  - Intermediate and Poor risk
- Mediastinal GCT
- Clinical Stage I disease

Historical Perspectives

1. Single agent studies with Vinblastine + Bleomycin achieved results similar Actinomycin-D

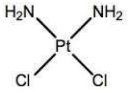
2. Vinblastine + Bleomycin synergistic to preclinical systems; initial studies in testicular cancer produced a 25% cure rate

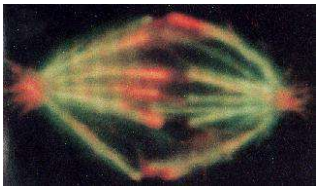
3. Cisplatin produced 3 complete and 3 partial responses in 11 patients with refractory testicular cancer

History Of Platinum

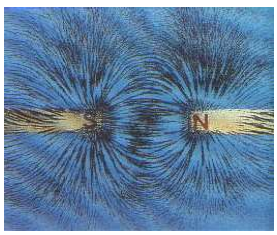
- Barnett Rosenberg discovered the effect of Platinum co-ordination complexes on E-coli cell growth in an electrolysis experiment

Discovery of cisplatin



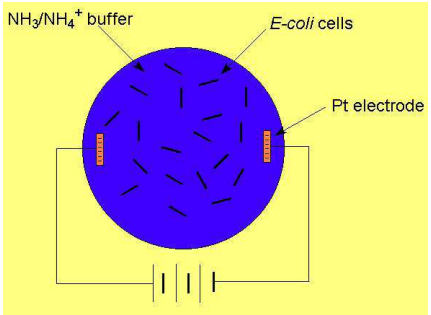


Mitosis



Magnetic field lines

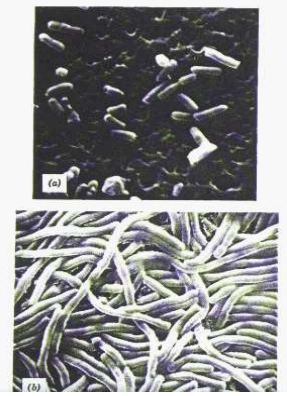
Does electromagnetic radiation play a role in mitosis?



The experiment

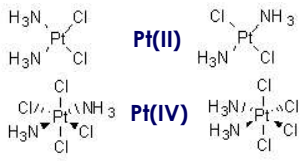
Discovery of cisplatin

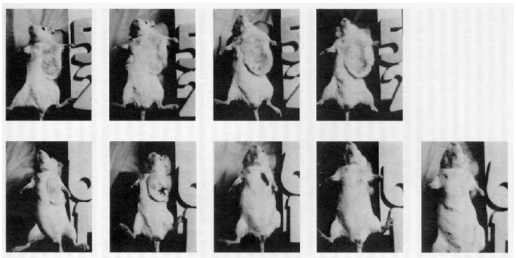
Result:



B. Rosenberg, L. van Camp, T. Krigas, *Nature (London)* **1965**, *205*, 698

Cause:

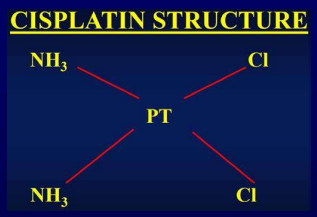


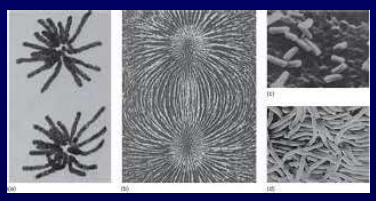


Thomson, *J. Biol. Chem.* **1967**, *242*, 1347

Rosenberg et al. *Nature* 1965,1969; Thomson *et al. J Biol Chem,* 1967

History Of Platinum





- Cis-diamminedichloroplatinum (CDDP) demonstrated a wide spectrum of activity against experimental tumors
- First entered human clinical trials in 1972
- Early toxicity outweighed therapeutic advantage

Historical Perspectives

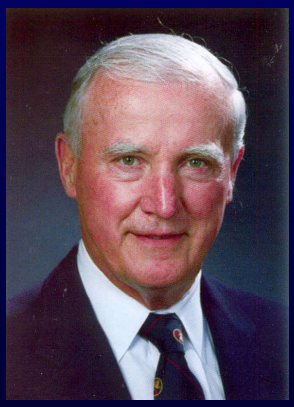
1. Single agent studies with Vinblastine + Bleomycin achieved results similar Actinomycin-D

2. Vinblastine + Bleomycin synergistic to preclinical systems; initial studies in testicular cancer produced a 25% cure rate

3. Cisplatin produced 3 complete and 3 partial responses in 11 patients with refractory testicular cancer

Story of two men

Lawrence H. Einhorn



John P. Donohue

Testicular Cancer: Background Material

- Dose Limiting Side effects:
  - Cisplatin- kidneys
  - Vinblastine- bone marrow
  - Bleomycin- lung
- Synergy
- Combination vs. sequential therapy

Original PVB Regimen

Induction

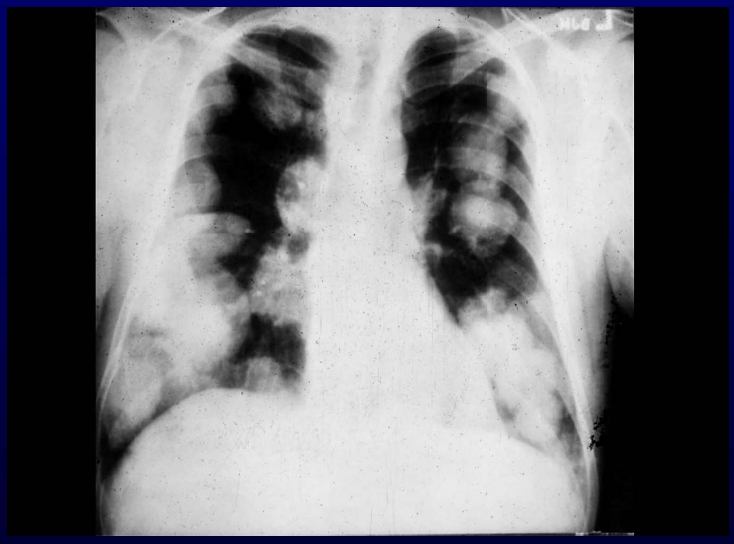
Cisplatin	20 mg/m^2 IV x 5 days	Repeat every 3 wks x 4 courses
Vinblastine	0.2 mg/kg IV x 2 days	
Bleomycin	30 IU IV push weekly	

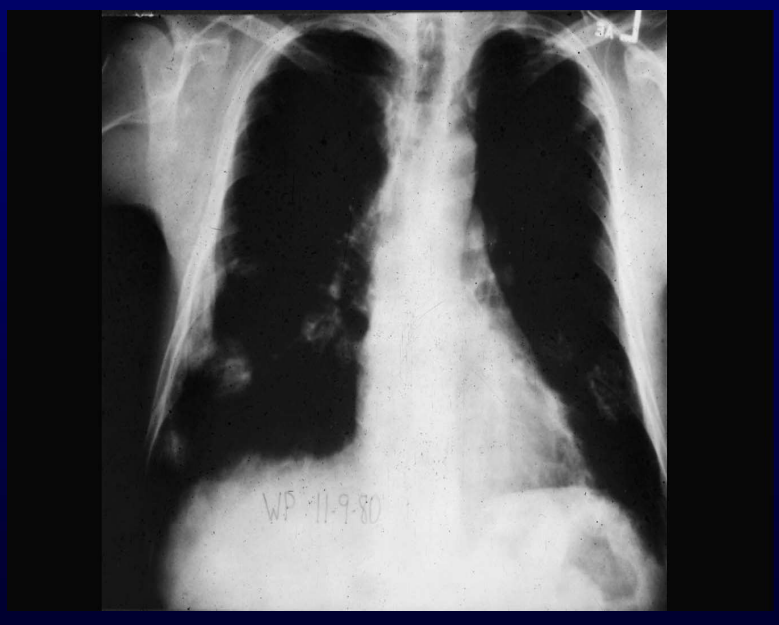
Maintenance

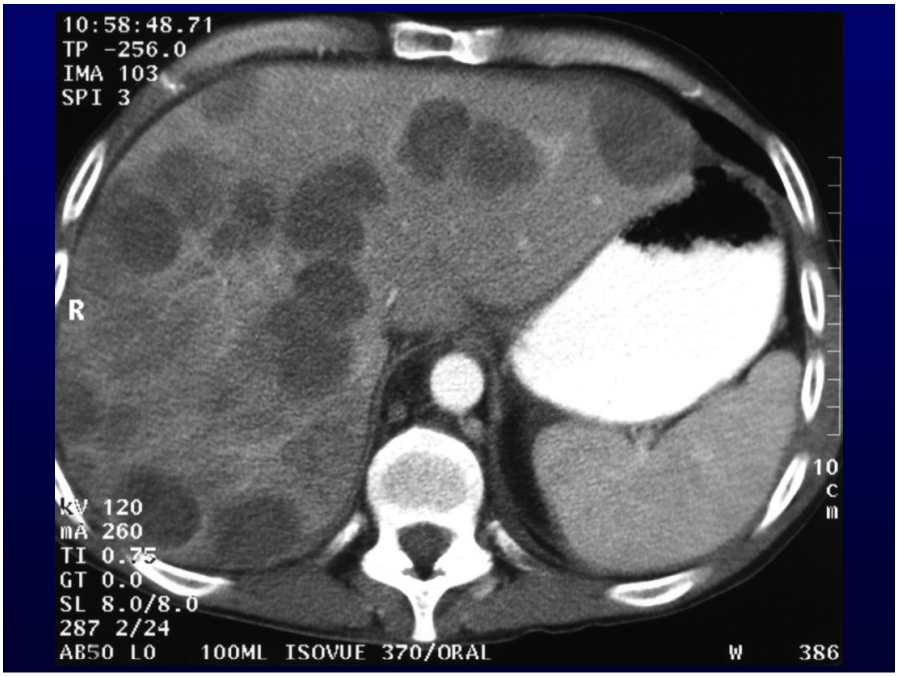
Vinblastine	0.3 mg/kg IV monthly x 21 mos

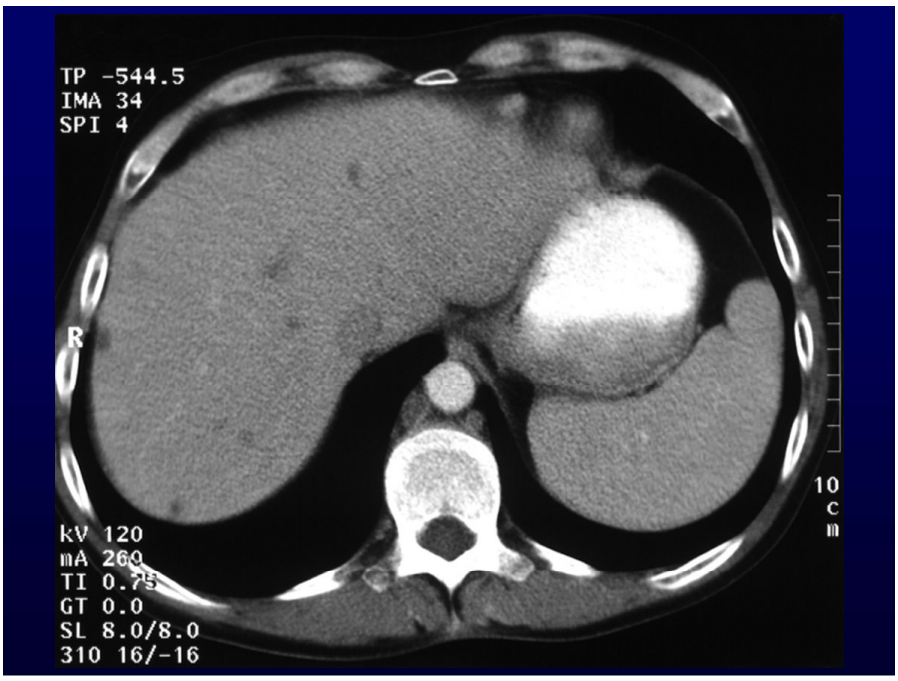
Results: PVB

- In 47 consecutive patients, 33(70%) had a complete remission and 5 more were rendered disease free with surgery.
- At five years 27 (57%) remain disease free
- Primary toxicity was sepsis and neutropenia









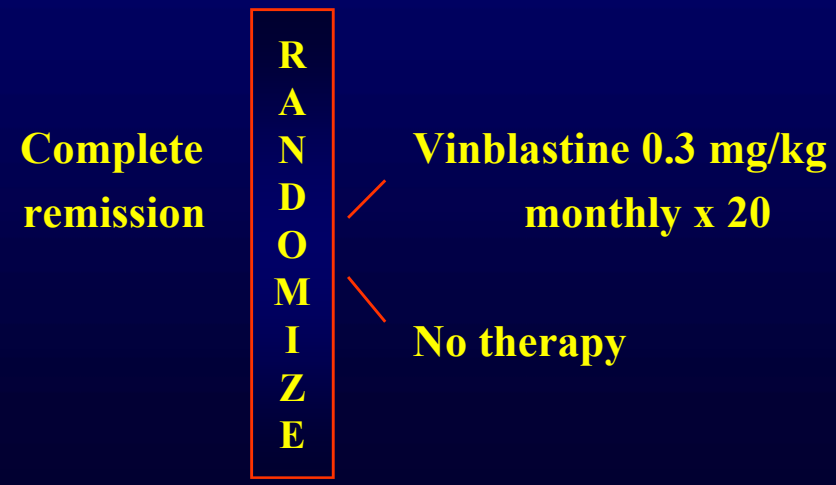
How do you make it “better”?

- Less toxic
- More active
- Improved cure rate

What was done?

- All of the above
  - Decreased dosage of vinblastine (less toxic)
  - Deleted maintenance therapy (less toxic)
  - Improved supportive care (less toxic, improved survival)
  - Segregate populations into good and poor risk (can tailor therapy accordingly)

MAINTENANCE THERAPY



MAINTENANCE VINBLASTINE: RESULTS*

	Vinblastine	No Maintenance
No pts.	57	56
Relapses:	5 (9%)	4 (7%)
Cures:	54 (95%)	53 (95%)

*Einhorn, et al.: NEJM 305:717-731, 1981

From Schabel FM, et al: Cancer Treat Rep 63:1459-1473, 1979

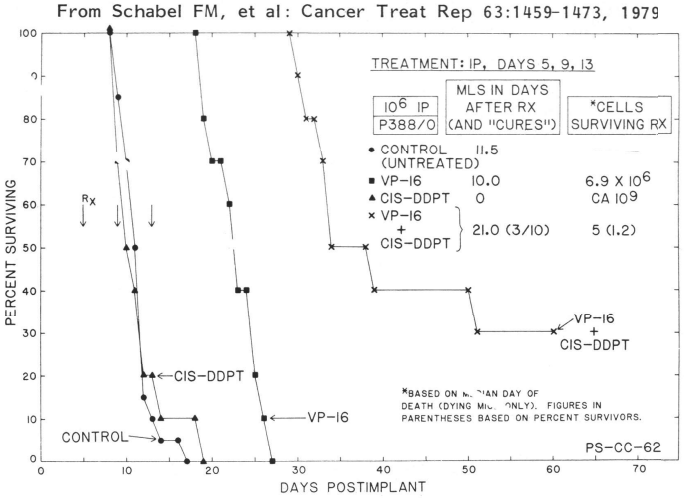


FIGURE 6.—Therapeutic synergism of *cis*-platinum + VP-16-213 against advanced P388/0 leukemia in BDF_1 mice. Cumulative mortality plots of optimal therapeutic responses at ≤ LD10 doses, Days 5, 9, and 13.

SEG GU 332

RANDOMIZE

Cisplatin 20 mg/m^2 X 5
Vinblastine 0.15 mg/kg days 1 & 2
Bleomycin 30 units days 2, 9, 16

Cisplatin 20 mg/m^2 x 5
VP-16 100 mg/m^2 x 5
Bleomycin 30 units days 1, 8, 15

Courses repeated every 3 weeks for 4 courses

International Consensus Classification*

- **"Good Prognosis"**
  60% of all patients;
  91% 5 year survival and 87% PFS
- **"Intermediate Prognosis"**
  26% of all patients;
  79% 5 year survival and 74% PFS
- **"Poor Prognosis"**
  14% of all patients (all with NSGCT)
  48% 5 year and 41% PFS

** JCO 15:594-603, 1997*

IGCTCC Classification: NSGCT

Good Prognosis (56% of NSGCT)

- **All of the following:**
  - AFP < 1,000 ng/ml
  - BHCG < 5,000 IU/L
  - LDH ≤ 1.5 x normal
  - Non-mediastinal primary
  - No non-pulmonary visceral metastasis

* *JCO 15:594-603, 1997*

Carboplatin inferior to Cisplatin in Good Risk Disease

- **PE x 4 versus CE x 4** ***(MSKCC, J. Clin Oncol 11:598, 1993)***
  - 265 patients entered
  - Carboplatin arm inferior with respect to:
    - Event Free (IR or Relapse) Survival (p=0.002)
    - Progression Free Survival (p=0.005)
    - Toxicity (Myelosuppression, GCP fever)
- **BEP x 4 vs. BEC x 4** ***(MRC/EORTC, J Clin Oncol 15:1844, 1997)***
  - 598 patients entered
  - Carboplatin arm inferior with respect to:
    - Complete Response rate (94% vs. 87%; p=0.009)
    - Survival (p=0.003)

EST 4887

RANDOMIZE

Cisplatin 20 mg/m^2 days 1-5
Etoposide 100 mg/m^2 days 1-5
} x 3 cycles

Cisplatin 20 mg/m^2 days 1-5
Etoposide 100 mg/m^2 days 1-5
Bleomycin 30 units/week
} x 3 cycles

Results:	BEP(n=86)	EP (n=86)
Total NED	82 (95%)	78 (90%)
Relapse	8 (9%)	18 (23%)
Dead	3 (3.4%)	7 (8.1%)
Continuously NED	74 (88%)	80 (70%)

Historical Perspective: Good Risk Disease

- BEP superior to PVB
- BEP x 3 is similar to BEP x 4
- Cisplatin is superior to carboplatin
- BEP x 3 is superior to PE x 3
- BEP x 3 is less toxic than PE x 4

"International Germ Cell Consensus"

Advanced (14%)

PMNSGCT or NSGCT with non-pulmonary visceral metastasis

- AFP > 10,000
- HCG > 50,000
- LDH > 10XULN

at start of chemo

Chemotherapy recommended:

BEP x 4 or VIP x 4

Intermediate (26%)

Seminoma with non- pulmonary visceral metastasis

- AFP 1,000 to 10,000
- HCG 5,000 to 50,000
- LDH 1.5 to 10 x ULN

at start of chemo

Chemotherapy recommended:

BEP x 4 or BEP x 3 followed by EP x 1

Historical Perspective: Poor Risk Disease

- BEP superior to PVB
- P_{200}VBE superior to PVB
- BEP_{100} superior to BEP_{200}
- BEP similar to VIP
- BEP superior to BOP/VIP
- BEP x 4 is superior to high dose chemotherapy plus stem cell transplant

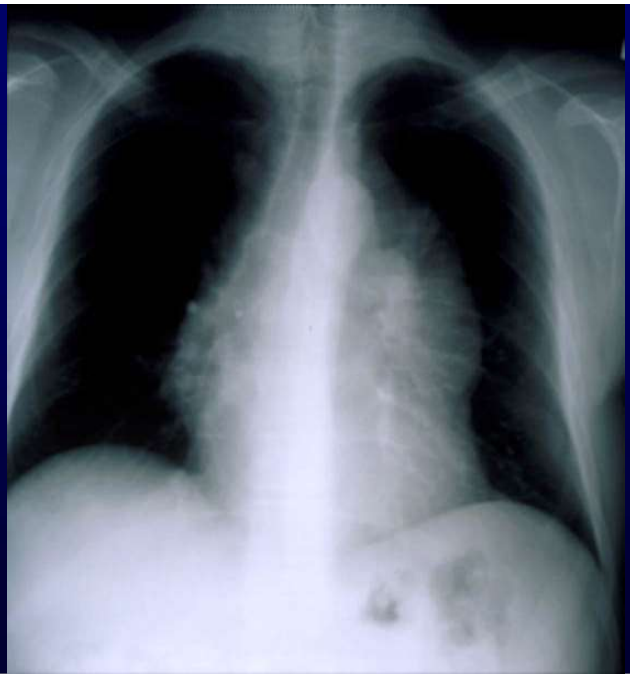
Germ Cell Tumors

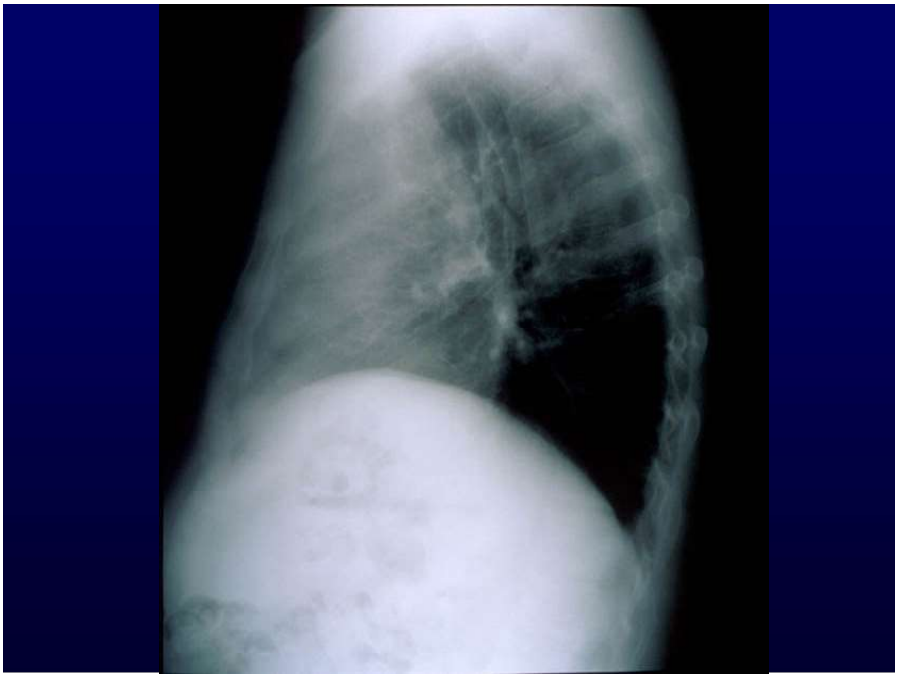
- Background
- Disseminated Disease
  - Good Risk
  - Intermediate and Poor risk
- Mediastinal GCT
- Clinical Stage I disease

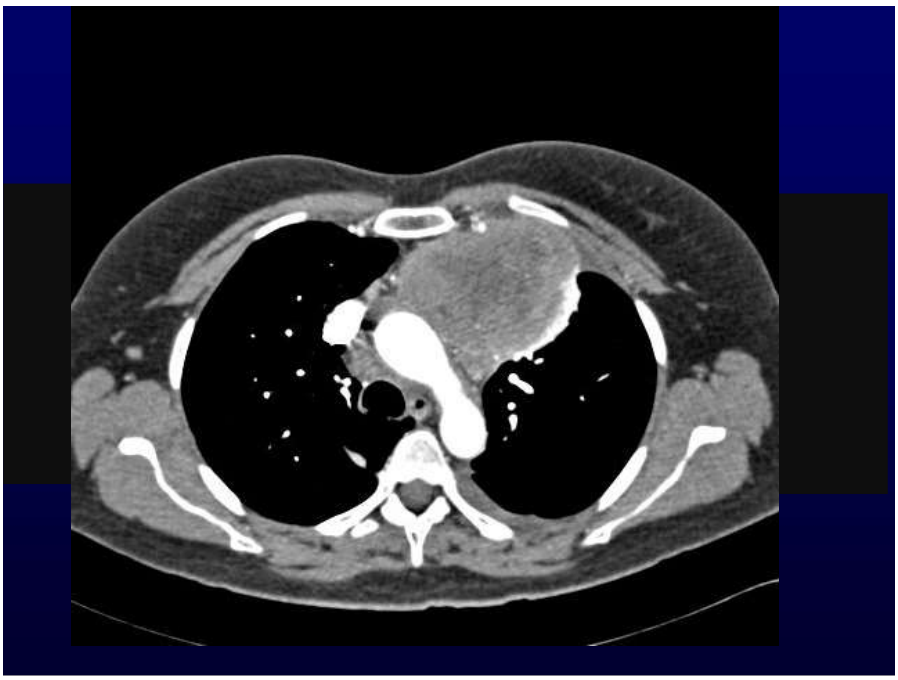
Case Report

• A 31 year old WM presents with cough and chest pain.

• Physical exam reveals a thin, tall man appearing somewhat pale. VS were WNL LN: normal; CV: distant heart sounds; Abd: soft and non-tender; GU: atrophic testis







Differential Diagnosis: Anterior Mediastinal Neoplasms

- Thymoma/ Thymic Carcinoma
- Lymphoma (Hodgkin's and NHL)
- Endocrine (Thyroid and Parathyroid)
- Germ Cell Neoplasms

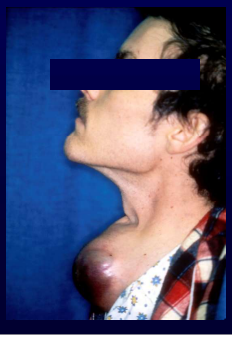
Labs:

- BHCG- 50,000 IU/l
  AFP – 251 ng/ml

- CBC:
  Hg -10.1
  Ht - 29.7
  WBC – 7.4
  Platelet Ct – 74,000

Case Report: (cont'd)

- The patient is begun on BEP and sent to his local physician for second and third courses.
- Nine weeks later he presents with chest wall mass.



- His BHCG is now 32 mIU/L and his AFP is normal.
- CBC has Hb= 9.7, WBC = 3.2 and Platelet count = 23,000/ml

What's going on?

Mediastinal Germ Cell Tumors

- Most common extragonadal site
- Older age onset
- Male preponderance (equal for teratoma)
- Elevated BHCG and/or AFP
- i12p
- Associated Syndromes:
  - Hematologic disorders
  - Non-germ cell malignancies
  - Klinefelter's (younger onset)

Mediastinal NSGCT: Hematologic Malignancies

- Acute megakaryocytic leukemia
- Myelodysplastic syndrome
- Refractory thrombocytopenia
- Refractory Anemia with Excess Blasts
- Malignant histiocytosis
- Systemic mastocytosis

Mediastinal NSGCT: Non-Germ Cell Malignancies

- Rhabdomyosarcoma
- Synovial Cell Sarcoma
- PNET
- Nephroblastoma
- Adenocarcinoma

EGCT: Meta-analysis (cont'd)

Type	N	5 yr. PFS	5 yr. Survival
Mediastinal seminoma	51	88%	89%
Retroperitoneal seminoma	52	77%	88%
Mediastinal NSGCT	287	44%	49%
Retroperitoneal NSGCT	227	45%	63%

Chronic Toxicity of Chemotherapy

- Sterility
- Peripheral neuropathy
- Ototoxicity
- Leukemia
- Cardiovascular: cholesterol, hypertension, or vascular events

Metabolic Syndrome In Long-term Survivors Of Testicular Cancer*

- Scandinavian study of 1,135 patients diagnosed 1980-1994
- Patients receiving > 4 courses of cisplatin combination chemotherapy had increased odds (OR 2.1; 95% C.I. 1.6-4.7) for metabolic syndrome compared with control group
  - Association strengthened after adjusting for testosterone, smoking, and physical activity

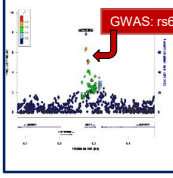
*Haugnes HS, Fossa SD, et al.: Ann Oncol 18:241-248, 2007

Chronic Toxicity of Chemotherapy

	Induction	
Cisplatin	20 mg/m² IV x 5 days	Repeat every
Vinblastine	0.2 mg/kg IV x 2 days	3 wks xfour courses
Bleomycin	30 IU IV push weekly	
	Maintenance	
Vinblastine	0.3 mg/kg IV monthly x 21 mos	

IUSCC: Bedside to Bench to Bedside

WFS1 (Wolfram Syndrome) SNP and Cisplatin-associated Hearing loss



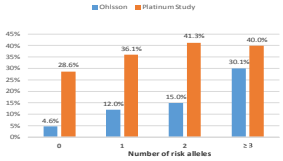
GWAS: rs62283056 – *WFS1* (P = 1 X 10^{-8})*

SNP (MAF, 0.21) in WFS1 associated with cisplatin-associated hearing loss and decreased expression of WFS1

Travis et al J Clin Oncol 8/10/16

R01 CA157823 Travis: PI

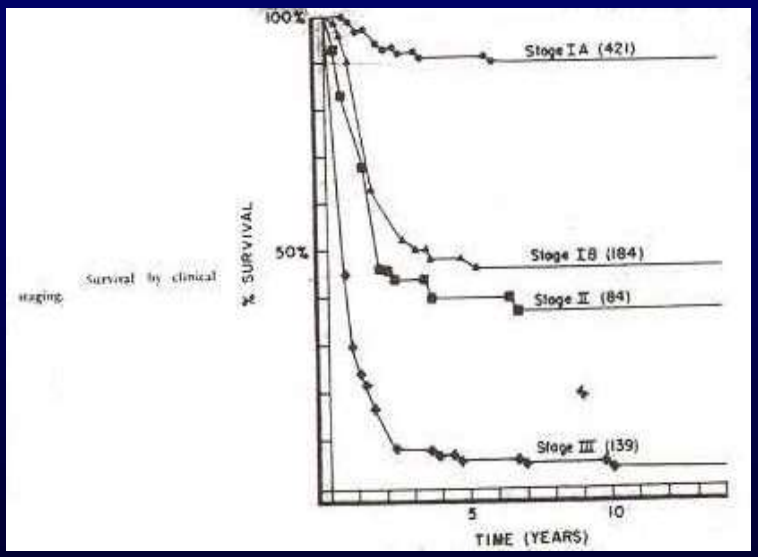
Transdisciplinary Collaboration



Age:

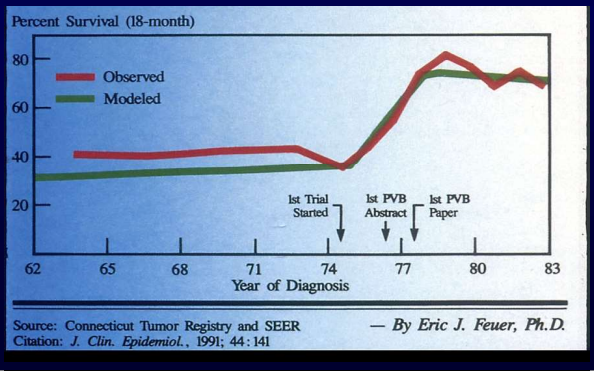
Mean age 61.7 years

Platinum study:
Median age 38 years



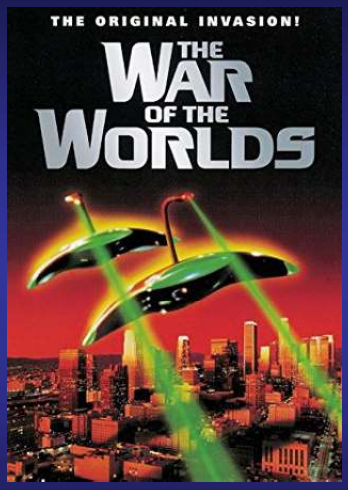
Testicular Cancer: Incidence and Mortality

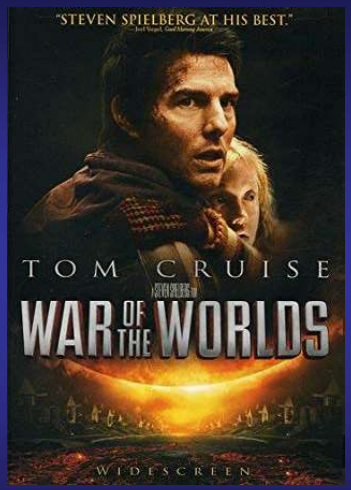
- 8,800 new cases in US annually
- Most common cancer in men between ages of 15-35
- Most curable cancer seen in oncology



Testicular Cancer

	Incidence	Cure Rate
Stage I	40%	100%
Stage II	40%	98%
Stage III	20%	80%
TOTAL		95%





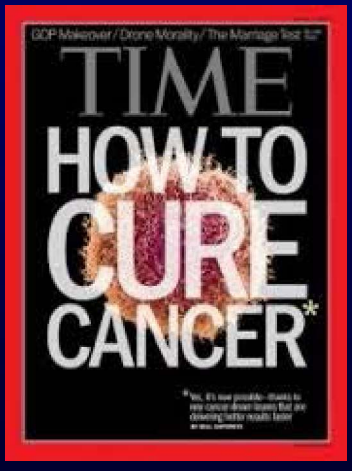
The disease of cancer will be banished from life by calm, unhurrying, persistent men and women, working with every shiver of feeling controlled and suppressed, in hospitals and laboratories, and the motive that will conquer cancer will not be pity nor horror; it will be curiosity to know how and why.

- H.G. Wells

Germ Cell Tumors: A Story of …

- Basic research
- Clinical research
  - Surgery
  - Medical Oncology
  - Radiation Oncology
  - Pathology
- Symptom science
- Team Science

Germ Cell Tumors: A Story of …



Urothelial Carcinoma: Current Management and Recent Advances

Guru Sonpavde, MD
Director, Bladder Cancer
Dana Farber Cancer Institute

Urothelial carcinoma: current management and recent advances

Guru Sonpavde, MD
Director, Bladder Cancer
Dana-Farber Cancer Institute
Harvard Medical School
Boston, MA

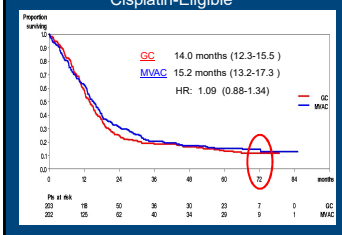
Disclosures

- **Advisory Board:** Merck, BMS, Sanofi, Bayer, Genentech, Novartis, Pfizer, Astellas, Janssen, Amgen, AstraZeneca, Eisai, Exelixis, EMD Serono
- **Research Support to Institution:** Onyx/Amgen, Sanofi, Bayer, Boehringer Ingelheim, Celgene, Merck, Pfizer
- **Steering committee**: Astrazeneca, BMS, Bavarian-Nordic, Astellas, Debiopharm

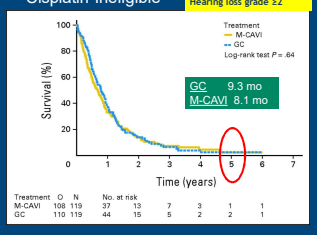
First-Line Chemotherapy for Metastatic Urothelial Carcinoma

ECOG PS=2
CrCl <60 mL/min
Neuropathy grade ≥2
CHF class ≥ 3
Hearing loss grade ≥2

Cisplatin-Eligible[1]



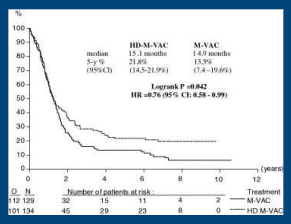
Cisplatin-Ineligible[2]



1. von der Maase H, et al. *J Clin Oncol.* 2005;23(21):4602-4608;
2. De Santis M, et al. *J Clin Oncol.* 2012;30(2):191–199.

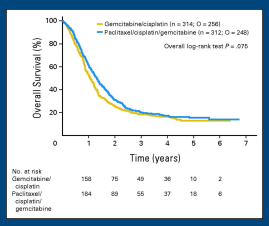
First-line ddMVAC or GC + paclitaxel (cisplatin-eligible)

MVAC vs. "dose dense" MVAC



Sternberg CN. Eur J Can 42:50 (2006)

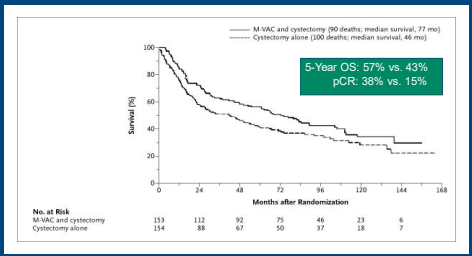
GC vs. GC + Paclitaxel



Bellmunt J. **J Clin Oncol**. 2012 Apr 1;30(10):1107-13.

4

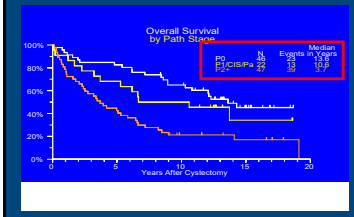
Neoadjuvant MVAC x 3 Improves Survival in Resectable MIBC: SWOG-8710

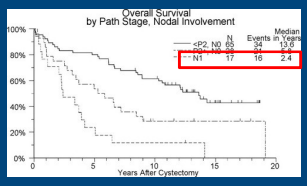


M-VAC, methotrexate, vinblastine, doxorubicin and cisplatin; OS, overall survival; pCR, pathologic complete response.
Grossman HB, et al. *N Engl J Med.* 2003;349(9):859-866.

Grossman HB. NEJM 2003

Impact of pathologic response on OS: S8710





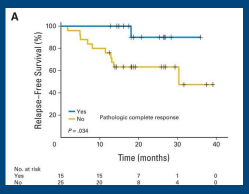
Impact of baseline clinical stage on pCR

- cT2N0 disease, <P2=55% and P0=39%
- T3 - T4N0 disease, <P2=35%, P0=24%

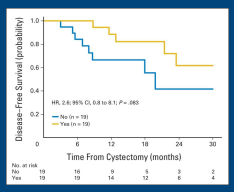
Sonpavde et al, Cancer 115, Issue: 18: 4104-4109, 10 June 2009

- **FDA has accepted pCR as an endpoint for approval in breast cancer**
- **FDA workshop at BCAN 8/8/2019; most participants appeared enthusiastic about pCR as surrogate endpoint in MIBC**
- **Trial level surrogacy of pCR rate remains unproven**

DD-MVAC x 3-4 cycles as neoadjuvant therapy: Relapse-free survival by pT0 rate



Elizabeth R. Plimack et al. JCO 2014;32:1895-1901



Toni K. Choueiri et al. JCO 2014;32:1889-1894

- pCR 26-38%
- Some N1 patients were allowed
- Time from diagnosis to RC was shorter

JOURNAL OF CLINICAL ONCOLOGY ASCO

S1314: Descriptive data on pathologic response by treatment arm in evaluable subjects

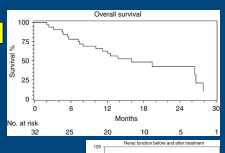
N=167	GC (N=82)	ddMVAC (N=85)
Chemotherapy Response		
CR (pT0)	28 (35%)	27 (32%)
PR (downstaged to ≤T1)	12 (15%)	20 (24%)
CR + PR	*40 (50%)*	*47 (56%)*
Non-responders	42 (50%)	38 (44%)

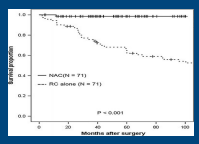
COXEN disappointing to predict pCR to specific regimens

Flaig T, et al. ASCO 2019

Fractionated weekly split dose gemcitabine + cisplatin or gemcitabine + carboplatin for patients ineligible for conventional day 1 cisplatin

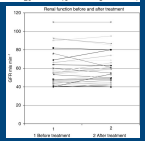
GC-SD

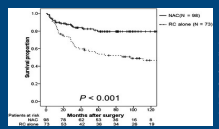




N=32
N=19 with Cr Cl 40-60

pCR was similar to standard GC across datasets





GCa

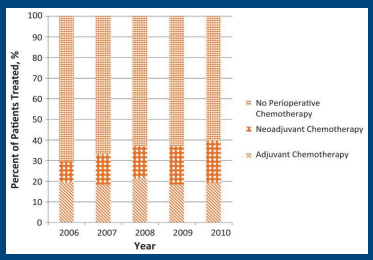
- Nonrandomized and retrospective studies (n=41-98) report feasibility
- Potential modest OS, PFS benefit from delivering neoadjuvant GCa compared to cystectomy alone in propensity score matched analysis
- pCR rates have been 16-30.3%
- suggestion of improved PFS.

Hussain S, BJC 2004

Koie T. Med Oncol 31:949, 2014; Murasawa H. Int J Clin Oncol 22:159-165, 2017; Koie T. Int J Clin Oncol 18:724-30, 2013; Mertens LS. 188: 1108. J Urol 2012

Trends in use of perioperative chemotherapy

Reardon Z,…Cookson M. Eur Urol 2015 (n=5692 from NCDB)



Neoadjuvant chemotherapy increased from 10.1% in 2006 to 20.8% in 2010 (p = 0.005).
Adjuvant chemotherapy remained stable between 18.1% and 21.3% (p = 0.68).

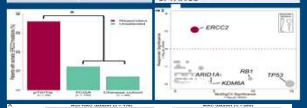
Is precision medicine possible with neoadjuvant cisplatin-based chemotherapy?

Gene	P value
ATM	0.001542
RB1	0.001542
FANCC	0.050980

	Residual Disease	Complete Response (pT0)
No Variants	22	1
Variant in ATM, Rb1 or FANCC	0	13

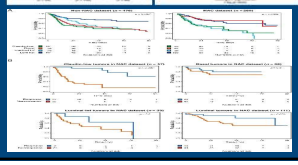
Plimack E. Eur Urol 2015

→ **DNA repair gene** variants associated with pCR



Van Allen EM…Rosenberg. J: GU-ASCO 2015, Cancer Discov 2014; Liu D. JAMA Oncol 2016

→ **ERCC2 mutations** associated with pCR → Bladder sparing approach for those with somatic ERCC2 mutations planned to be prospectively investigated



Seiler R; Eur Urol 2017

→ **Basal gene expression** subtype showed most improvement in OS with NAC

Daniel Geynisman, Fox Chase Cancer Center

Major Inclusion Criteria:
- cT2-T3 N0M0
- ECOG 0-1
- Urothelial Predominant Histology

- **MFS is defined as the absence of a recurrence of urothelial carcinoma that is >cN1 (more than one clinically suspicious pelvic lymph node) or surgically unresectable local recurrence (e.g., >cT4a) or M1 disease.**

TURBT #1 → AMVAC x 3 → TURBT #2

Sequencing (Caris)
Mutation positive defined as any alterations in:
- ATM
- RB1
- FANCC
- ERCC2

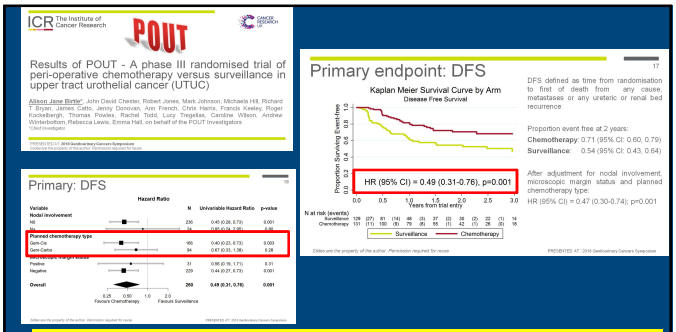
No residual tumor/cT0 AND Mutation Pos (+)		Active Surveillance
cTa or cTis or cT1 or Pos (+) cytology or cT0 mutation Neg (-)	Patient & Physician Choose	Intravesicle Tx OR Chemo-RT OR Cystectomy
cT2	Patient & Physician Choose	Chemo-RT OR Cystectomy
≥cT3		Cystectomy

Primary Endpoint: Metastasis-free survival (MFS) at 2 years.
Non-inferiority design with a 14% margin between risk-adapted design (MFS=78%) and standard-of-care (MFS=64%).
Sample size=70 with an 82% power, Type I error=0.045

Adjuvant Chemotherapy: Randomized Bladder Trials Not Definitive

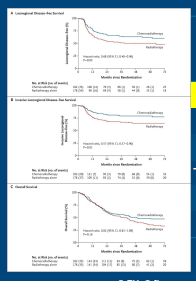
Retrospective Studies and Meta-analyses Are Supportive

	Regimen	Benefit: Progression	Benefit: Survival
Skinner ('88)	CISCA	Yes	No
Stockle ('92)	M-VA(E)C	Yes	Not evaluated
Studer ('94)	Cisplatin	Not evaluated	No
Freiha ('96)	CMV	Yes	No
Bono ('89)	Cisplatin-MTX	No	No
Stadler - p53+ (2009)	MVAC	No	No
Cognetti - ASCO 2008	GC	No	No - Incomplete accrual
Paz-Ares - ASCO 2010	PGC	Yes	Yes - Incomplete accrual
Sternberg (*Lancet Oncol.*)	GC/MVAC/DD-MVAC	Yes	No -Incomplete accrual



- POUT2: Chemotherapy with or without immunotherapy following nephro-ureterectomy for upper tract urothelial cancer
  - Chief Investigator: Dr Alison Birtle from Institute of Cancer Research (ICR-CTSU), London

ChemoRT for Locally Advanced Bladder Cancer: 5-FU + Mitomycin-C

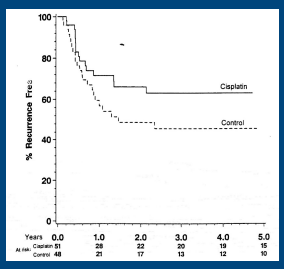


	XRT (N=178)	XRT + 5FU/MMC (N=182)	HR, *P* Value
2-Y Locoregional DFS	54%	67%	0.68, 0.03
EFS	58%	71%	NA
5-Y OS	33%	48%	.82, 0.16
Toxicities			
Acute Grade 3-5	27.5%	36.0%	0.07
Late Grade 3-4	15.7%	8.3%	0.07

5-FU, 5-fluorouracil; DFS, disease-free survival; EFS, event-free survival; XRT, external radiation therapy; MMC, mitomycin-c; NA, not available; Y, year.

James ND, et al; BC2001 Investigators. *N Engl J Med.* 2012;366(16):1477-1488.

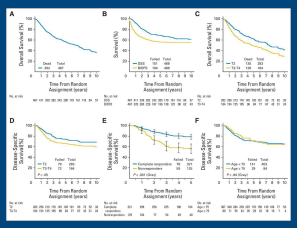
RT +/- Cisplatin



Coppin CM et al. J Clin Oncol. 1996

Cisplatin-based chemotherapy + XRT

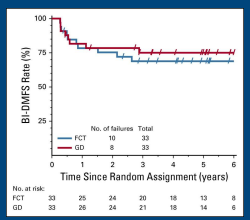
RTOG pooled experience



- N=348
- Complete response: 69%
- Trials evolved to exclude hydronephrosis, multifocal disease, CIS
- 5- year OS rate 57%

Raymond H. Mak,.. Anthony L. Zietman; *JCO* **2014,** 32, 3801-3809.

Cisplatin+5FU + XRT BID vs. Gemcitabine + XRT once daily



Both regimens → DMF3 >75%.

Fewer toxicities with GD

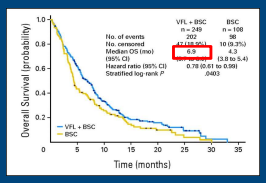
No single optimal chemo regimen (Other studies have used cisplatin alone, paclitaxel alone, cisplatin+paclitaxel, carboplatin-paclitaxel)

Bladder-intact distant metastasis–free survival (BI-DMFS).
FCT, fluorouracil plus cisplatin and radiation twice a day;
GD, gemcitabine and once daily radiation.

John J. Coen,..William U. Shipley; *Journal of Clinical Oncology* 2019 3744-51.

Post-Platinum Chemotherapy for UC

Vinflunine + BSC vs BSC Phase III[1]
- Survival longer in eligible population (n = 357)
- Required 1 prior platinum-based line for metastatic disease
- PS 0-1



Taxanes
- Nonrandomized phase II trials[2-4]

Drug	N	RR %	Median PFS (mo)	Median OS (mo)
Paclitaxel[2]	31	10	2.2	7.2
Paclitaxel[3]	45	9	3.0	7.0
Docetaxel[4]	30	13	-	3.6

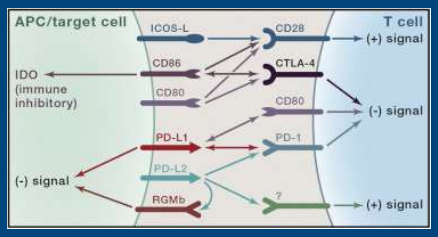
BSC, best supportive care; PFS, progression-free survival; RR, response rate.

1. Bellmunt J, et al. *J Clin Oncol*. 2009:27(27):4454-4461; 2. Vaughn DJ, et al. *J Clin Oncol*. 2002:20:937-940; 3. Joly F, et al. Clin Genitourin Cancer. 2009:7(2):E28-33; 4. McCaffrey JA, et al. *J Clin Oncol*. 1997:15(5):1853-1857.

The era of immune checkpoint inhibitors (ICIs) is here!

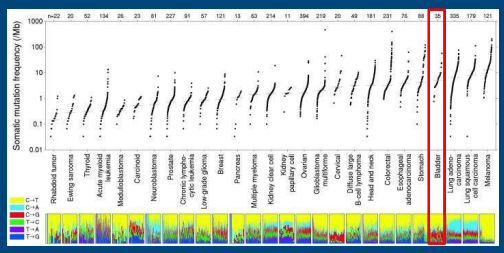
How effective are PD-1/PD-L1 inhibitors for UC?
- Post-platinum
- First line
- Neoadjuvant
- Switch maintenance

Immune Checkpoint Blockade approach to Cancer Therapy



Topalian SL, Drake CG, Pardoll DM. Cancer Cell 2015

High Somatic Mutation Burden in UC



Lawrence MS, et al; Nature. 2013;499(7457):214-218.

Checkpoint Inhibitor Approvals: Previously Treated Disease

May 2016 — Feb 2017 — May 2017

Atezolizumab — Nivolumab — Durvalumab — Avelumab — Pembrolizumab

Above agents are indicated in patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with (platinum-containing) chemotherapy.

Phase III KEYNOTE-045: Study Design

Key Eligibility Criteria
- Urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
- Transitional cell predominant
- PD after 1-2 lines of platinum-based chemo or recurrence within 12 mo of perioperative platinum-based therapy
- ECOG PS 0-2
- Provision of tumor sample for biomarker assessment

Stratification Factors
- ECOG PS (0/1 vs 2)
- Hemoglobin level (<10 vs ≥10 g/dL)
- Liver metastases (yes vs no)
- Time from last chemotherapy dose (<3 vs ≥3 mo)

R (1:1)
N = 542

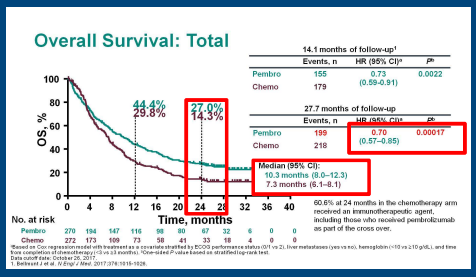
N = 270 — Pembrolizumab 200 mg IV Q3W for 2 years

N = 272 — Paclitaxel 175 mg/m² Q3W OR Docetaxel 75 mg/m² Q3W OR Vinflunine 320 mg/m² Q3W

Key Endpoints:
Primary: OS and PFS in total and PD-L1 CPS ≥10% populations
Secondary: ORR and DOR in total and PD-L1 CPS ≥10% populations; safety in total population

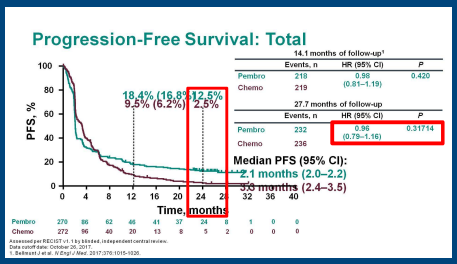
Bellmunt J, et al. SITC 2016; Abstract 470.; NEJM 2017

Phase III KEYNOTE-045 ASCO GU 2018 UPDATE:
Pembrolizumab vs Chemotherapy as Salvage



Bellmunt J, et al. 2018 ASCO GU. Abstract 410; Bellmunt J, et al for the KEYNOTE-045 Investigators. N Engl J Med. 2017;376(11):1015–1026.

Phase III KEYNOTE-045 ASCO GU 2018 UPDATE:
Pembrolizumab vs Taxane/Vinflunine as Salvage



Bellmunt J, et al. 2018 ASCO GU. Abstract 410; Bellmunt J, et al for the KEYNOTE-045 Investigators. N Engl J Med. 2017;376(11):1015–1026.

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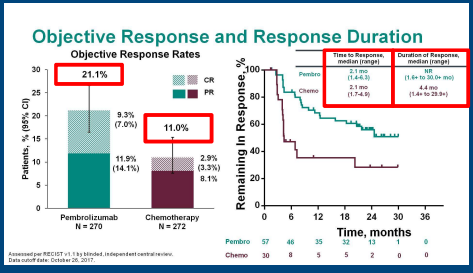
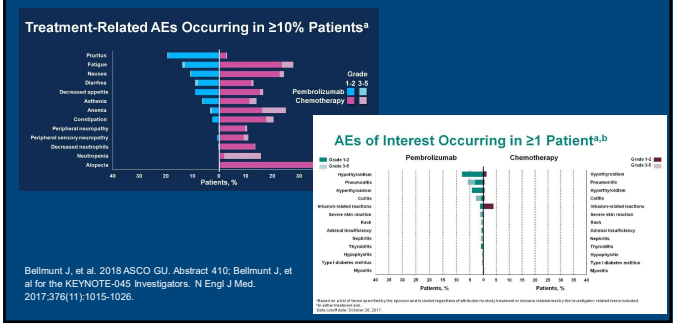
Pembrolizumab vs Taxane/Vinflunine as Salvage



Bellmunt J, et al. 2018 ASCO GU. Abstract 410; Bellmunt J, et al for the KEYNOTE-045 Investigators. N Engl J Med. 2017;376(11):1015–1026.

Phase III KEYNOTE-045 ASCO GU 2018 UPDATE: Toxicities Pembrolizumab vs Taxane/Vinflunine as Salvage



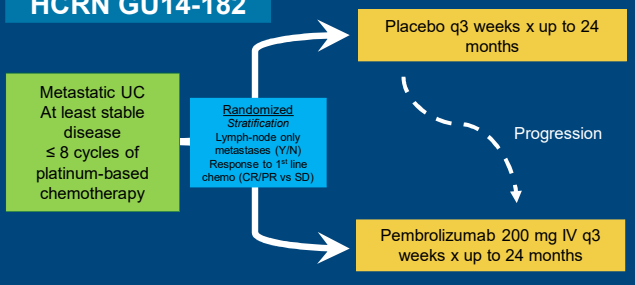
Bellmunt J, et al. 2018 ASCO GU. Abstract 410; Bellmunt J, et al for the KEYNOTE-045 Investigators. N Engl J Med. 2017;376(11):1015-1026.

Immune Checkpoint Inhibitors in Platinum-Refractory Setting

	Atezolizumab[1]	Nivolumab[2]	Durvalumab[3]	Avelumab[4]	Pembro[5]
Phase	III	II – Single arm	I/II	I	III
No. patients	459 atezo	265	191	249	266 pembro
Dosing	1200 mg q3w	3 mg/kg q2w	10 mg/kg q2w	10 mg/kg q2w	200 mg q3w
ORR	13.4%	19.6%	17.8%	17%	21.1%
DOR	63% ongoing at 17.3 mo	77% ongoing at 7 mo	77% ongoing at 5.8 mo	82% ongoing at 9.9 mo	Median NR at 27.7 mo
Median OS	11.1 mo (NS)	8.7 mo	18.2 mo	6.5 mo	10.3 mo
Median PFS	2.1 mo	2.0 mo	1.5 mo	1.5 mo (6.3 w)	2.1 mo
Grade ≥3 trAE	20%	18%	6.8%	8%	15%

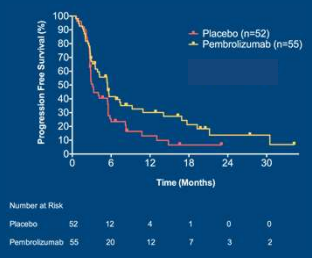
1. Powles T, et al. Lancet. 2018;391:748-757; 2. Sharma P, et al Lancet Oncol. 2017;18:312-322; 3. Powles T, et al. JAMA Oncol. 2017;3:e172411; 4. Patel MR, et al. Lancet Oncol. 2018;19:51-64; 5. Bellmunt J et al. N Engl J Med. 2017;376:1015-1026.

HCRN GU14-182



ASCO 2019 Abstract 4504 Galsky et al.

Progression-free Survival with switch maintenance pembrolizumab: HCRN GU14-182



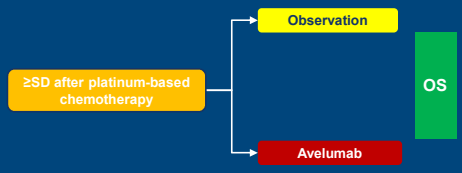
Median PFS and 95% CI
Placebo: 3.2 (2.8, 5.5)
Pembrolizumab: 5.4 (3.6, 9.2)

Hazard Ratio: 0.64 (0.41, 0.98)

Log rank $p = 0.038$

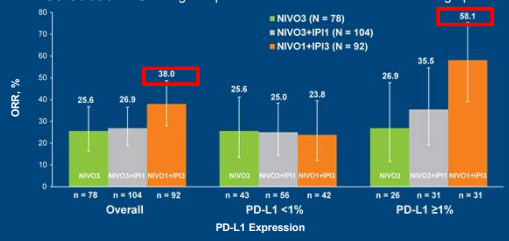
ASCO 2019 Abstract 4504 Galsky et al. 31

Second-Line Switch Maintenance: Avelumab Undergoing Evaluation in Phase III JAVELIN Bladder 100 Trial



NCT02603432

CheckMate 032: Nivolumab Alone or in Combination with Ipilimumab in Platinum-Pretreated mUC High response rate with combination in PD-L1 high patients

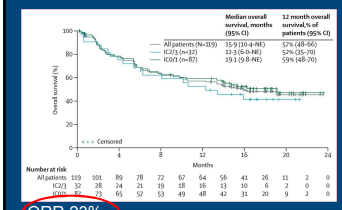


Overall cohort	NIVO3	NIVO3 + IPI1	NIVO1 + IPI3
Responders, N	20	28	35
Duration of response, median	30.5 mo	22.3 mo	22.9 mo

Rosenberg JE et al. *Proc ESMO* 2018;Abstract LBA32.

First-Line PD-1/PD-L1 Inhibitors for Cisplatin-Ineligible UC

Atezolizumab (N=119)[1]



ORR 23%

Median PFS 2.7 mo

Pembrolizumab (N=370)[2,3]

	Total Population N = 370		
	n	%	95% CI
ORR	108	29	25-34
CR	27	7	5-10
PR	81	22	18-27
SD	67	18	14-22
PD	155	42	37-47

1. Balar AV, et al; for the IMvigor210 Study Group. Lancet. 2017;389(10064):67-76; 2. O'Donnell PH, et al. 2017 ASCO. Abstract 4502; 3. Balar AV; et al. Lancet Oncol. 2017;18:1483-1492.

Ongoing First-Line Phase III Trials Incorporating IO for Advanced UC: Including Cisplatin-Eligible and -Ineligible Patients in the Same Trial!

Trial	Strategy	Experimental Arm(s)	Standard Arm
IMvigor130	PD-L1 + Chemo	Atezo OR Atezo + Gem-Plat	Placebo + Gem-Plat
KEYNOTE-361	PD-1 + Chemo	Pembro OR Pembro + Gem-Plat	Gem-Platinum
DANUBE	PD-L1 +/- CTLA-4	Durvalumab OR Durva + Treme	Gem-Platinum
NCT03036098 CM-901	PD-1 + CTLA-4	Nivo + Ipi*	Gem-Platinum
NILE	PD-L1 +/- CTLA-4 (+ Chemo)	Durvalumab +Gem-Plat OR Durva + Treme + Gem-Plat	Gem-Platinum

Use PD-L1 expression to select therapy for the first-line therapy of cisplatin-ineligible patients

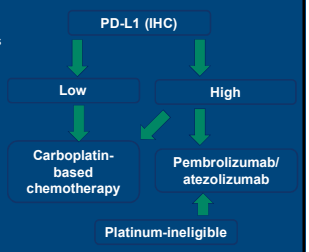
5/18/2018

FDA Alert

- In two ongoing clinical trials (KEYNOTE-361 and IMVIGOR-130), the Data Monitoring Committees' (DMC) found patients in the **monotherapy arms of both trials with PD-L1 low status had decreased survival compared to patients who received cisplatin- or carboplatin-based chemotherapy.**

- **Approval labels changed to: those who not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10 for KN-361, ≥5% for IMVIGOR130], or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status**

- **Platinum-ineligible patients remain ill-defined** (?both ECOG-PS=2 + Cr Cl <60, ECOG-PS=3, Cr Cl <30, comorbidities)



Atezolizumab + Platinum-based chemo met PFS endpoint

Sunday, Aug 4, 2019

Genentech's Tecentriq® (Atezolizumab) Plus Platinum-Based Chemotherapy Reduced the Risk of Disease Worsening or Death in People With Previously Untreated Advanced Bladder Cancer

IMvigor130 is the first positive Phase III study of a cancer immunotherapy combination in previously untreated advanced bladder cancer

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

South San Francisco, CA -- August 4, 2019 --

Genentech, a member of the Roche Group (SIX: RO, ROG; OTCQX: RHHBY), today announced that the Phase III IMvigor130 study met its co-primary endpoint of investigator-assessed progression-free survival (PFS). The combination of Tecentriq® (atezolizumab) plus platinum-based chemotherapy showed a statistically significant reduction in the risk of disease worsening or death in people with previously untreated locally advanced or metastatic urothelial carcinoma (mUC) compared with chemotherapy alone. Encouraging overall survival (OS) results were observed at this interim analysis, however these data are not yet mature and follow-up will continue until the next planned analysis.

Adjuvant PD-1/PD-L1 Inhibitor Phase III Trials

PI	Population	Control Arm	Experimental Arm	Primary Endpoint
Industry	All-comers MIUC Prior NAC- ≥pT2 No AC ≥pT3	No therapy	Atezolizumab	PFS
Industry	All-comers MIUC Prior NAC- ≥pT2 No AC ≥pT3	Placebo	Nivolumab	PFS
Intergroup[a]	All-comers MIUC Prior NAC- ≥pT2 No AC ≥pT3	No therapy	Pembrolizumab	PFS/OS
UK-CRU (POUT-2)	Upper tract Urothelial carcinoma	Gem-platinum	Gem-platinum + IO	PFS

Neoadjuvant Checkpoint Inhibition in Bladder Cancer: Early Results of Phase II Trials

	Necchi #4507 **Pembrolizumab (n=43)**	Powles #4506 **Atezolizumab (n=68)**
Eligibility	T2-T3b, N1 allowed (5%) T4b not allowed	T2-T3b N+ not allowed T4b allowed (7%)
% patients cisplatin ineligible	0%	100%
% who also got neoadj. chemo	12%	0%
Duration of neoadjuvant therapy	3 cycles (9 weeks)	2 cycles (6 weeks)
Safe?	Yes	Yes
Pathologic complete response rate (pT0)	40%	29%
Biomarker data presented	Yes	Yes

pT0 rates with chemo

Gem Cis 15-26%

DDMVAC 26-43%

A Phase 1b/2 Study of Neoadjuvant Pembrolizumab and Chemotherapy for Locally Advanced Urothelial Cancer

Characteristic	Pembrolizumab + Gem – Cis (n=36)
Time to surgery	From the onset of chemo: 18.8 weeks (11.5, 26.6) From the end of chemo: 5.7 weeks (3, 13.6)
Pathologic Stage	
≤ ypT1N0 (%, 95% CI)	22 (61.1%)
P0	16 (44.4%)
P1/CIS/Pa	5
P2+	15
LN status positive	5
LN removed, >10	28
Clinical T and ypPathology	
cT2 → <P2	18
cT3-4 → <P2	4
cT2 → P2+	11
cT3-4 → P2+	3

pCR not associated with PD-L1

Christopher J. Hoimes, ESMO 2018

Merck's KEYTRUDA® (pembrolizumab) in Combination with Chemotherapy Met Primary Endpoint of Pathological Complete Response (pCR) in Pivotal Phase 3 KEYNOTE-522 Trial in Patients with Triple-Negative Breast Cancer (TNBC)

JULY 29, 2019

KEYTRUDA is the First Anti-PD-1 Therapy to Demonstrate a Statistically Significant Improvement in pCR Rates as Neoadjuvant Therapy for TNBC Regardless of PD-L1 Status

Data to be Presented at an Upcoming Medical Congress and Discussed with Regulatory Authorities

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the Phase 3 KEYNOTE-522 trial investigating KEYTRUDA, Merck's anti-PD-1 therapy, in combination with chemotherapy met one of the dual-primary endpoints of pathological complete response (pCR) following the neoadjuvant part of the neoadjuvant/adjuvant study regimen in patients with triple-negative breast cancer (TNBC). Based on an interim analysis conducted by the Independent Data Monitoring Committee (IDMC), KEYTRUDA in combination with chemotherapy demonstrated a statistically significant improvement in pCR rates compared with chemotherapy alone, regardless of PD-L1 status. A pathological complete response or pCR is defined as a lack of all signs of cancer in tissue samples analyzed following completion of neoadjuvant therapy and definitive surgery. Based on the recommendation of the DMC, the trial will continue without changes to evaluate the other dual-primary endpoint of event-free survival (EFS), per the trial design. The safety profile of KEYTRUDA in this trial was consistent with previously reported studies; no new safety signals were identified.

"These findings from this innovatively designed trial with KEYTRUDA mark the first time an anti-PD-1 therapy plus chemotherapy has demonstrated a statistically significant improvement in pathological complete response rate as a neoadjuvant, or pre-surgical, segment of treatment for triple-negative breast cancer," said Dr. Roger M. Perlmutter, president, Merck Research Laboratories. "TNBC is an aggressive malignancy with a high rate of recurrence within the first five years of diagnosis. We are encouraged by these results and plan to discuss these data with health authorities and to present these findings at an upcoming medical congress."

The KEYTRUDA breast cancer clinical development program encompasses several internal and external collaborative studies, including three ongoing registration-enabling studies for TNBC (KEYNOTE-355, KEYNOTE-242, and KEYNOTE-522).

Ongoing neoadjuvant phase III trials for MIBC

Trial ID	Sponsor	Primary endpoint (s)	Control arm	Experimental arm
CISPLATIN-ELIGIBLE				
NCT03661320	BMS	pCR, EFS	GC / Split Dose-GC	Control + Nivolumab + Placebo Control + Nivolumab + Linrodostat
NCT03732677	Astrazeneca	pCR, EFS	GC / Split Dose-GC	Control + Durvalumab
NCT03924856	Merck	pCR (all, PD-L1+) EFS (all, PD-L1+)	GC + Placebo	Control + Pembrolizumab
CISPLATIN-INELIGIBLE				
2018-002676-40	BMS	pCR, EFS	-	Nivolumab Nivolumab + NKTR-214
NCT03924895	Merck	pCR (all, PD-L1+) EFS (all, PD-L1+)	-	Pembrolizumab

Ongoing selected neoadjuvant phase II trials for MIBC

Therapy	Sponsor
IO ALONE	
Avelumab	Belgium
Atezolizumab	UCSF
Nivolumab + /- Urelumab (CD137 agonist)	Johns Hopkins
Nivolumab + /- Lirilumab (KIR agonist)	PrECOG
Durvalumab + Tremelimumab	MDACC
Nivolumab, Nivolumab + Ipilimumab	MSKCC
Durvalumab, Durvalumab + Oleclumab (CD73i)	DFCI, MGH
Pembrolizumab + Epacadostat (IDO1i)	Milan
IO + CHEMO	
GC + Pembrolizumab Gemcitabine + Pembrolizumab	HCRN
GC + Pembrolizumab	UNC
GC + Nivolumab	Minnesota, DFCI, Utah
Nivolumab + TAR200 (gem release intravesically)	Taris

Planned Phase III Trial by NRG, SWOG
ChemoRT +/- Concurrent → Adjuvant Atezolizumab

ATEZOLIZUMAB x 1 year

RT +
Chemotherapy
(5-FU-MMC,
Cisplatin +/- 5-FU)

Survival
PFS

OBSERVE

Pembrolizumab for BCG-refractory Non-Muscle Invasive Bladder Cancer (NMIBC)

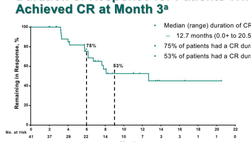
Pembrolizumab for BCG-refractory Carcinoma In Situ (CIS)

Overall Response Rate at Month 3[a]

Response	Total Population (N = 102)		
	n	%	95% CI
CR	**41**	**40.2**	**30.6-50.4**
Non-CR	57	55.9	45.7-65.7
Persistent[b]	41	40.2	30.6-50.4
Recurrent[c]	6	5.9	2.2-12.4
NMIBC stage progression[d]	9	8.8	4.1-16.1
Non-bladder malignancy[e]	1	1.0	0.0-5.3
Progression to T2	0	0	NA-NA
Nonevaluable[f]	4	3.9	1.1-9.7

[a]Summary of overall responses of HR NMIBC per central assessment at month 3 in all patients who received ≥1 dose of trial treatment, had baseline evaluations, and also had ≥1 postbaseline disease assessment. [b]Defined as patients with CIS at baseline who at month 3 also had CIS ± papillary tumor. [c]Defined as pathologically confirmed appearance of papillary tumor (high-grade Ta or T1) without CIS at month 3. [d]Increase in stage from CIS and/or high-grade Ta at baseline to T1 disease. [e]Defined as presence of lesions suspicious for locally advanced or metastatic bladder cancer on imaging. Patient developed new liver lesions, as seen on imaging, and was later found to have a second primary malignancy of pancreatic cancer. Subsequent review of the baseline scan showed subtle findings that, in retrospect, could be attributed to pancreatic cancer. [f]Patients whose protocol-specified efficacy assessments were missing or who discontinued from the trial for reasons other than progressive disease were considered not evaluable for efficacy.
Database cutoff: September 14, 2018.

Duration of Response for Patients Who Achieved CR at Month 3[a]



- Median (range) duration of CR
  - 12.7 months (0.0+ to 20.5+ months)
- 75% of patients had a CR duration ≥6 months
- 53% of patients had a CR duration ≥9 months

[a]1 month = 30.4367 days.
Database cutoff: September 14, 2018.

No progression to muscle invasive or metastatic disease

Balar et al, ASCO 2019, abstract 350

Ongoing selected phase III trials of PD1/L1 inhibitors for NMIBC

Trial ID	Setting	Sponsor	Primary endpoint (s)	Control arm	Experimental arm
NCT03528694	BCG-naive	Astrazeneca	DFS	BCG	Durvalumab + BCG ind Durvalumab + BCG ind + Maint
NCT03711032	Post-BCG induction	Merck	CR	BCG	Pembrolizumab + BCG
NCT03799835	BCG-naïve	Genentech	RFS	BCG	Atezolizumab + BCG

Oral FGFR inhibitors and other new intravesical agents also undergoing investigation

Are biomarkers ready for prime time to select patients for PD1/PD-L1 inhibitors?

- PD-L1 IHC assay
- Tumor mutation burden (TMB)
- DNA damage repair gene alterations
- Gene expression for intrinsic subtype
- IFN-Y gene expression signature

Variable Assays for PD-L1 Expression have been used by different companies

Immunotherapy (IO)	Atezolizumab[1,2]	Nivolumab[3]	Pembrolizumab	Durvalumab[5]	Avelumab[6]
Detection antibody	SP142	28-8	22C3	SP263	73-10
IHC platform	Ventana	Dako	Dako	Ventana	Dako
Cell types scored for urothelial cancer	IC	TC	TC + IC	IC + TC	IC + TC
Cutoff definitions for urothelial cancer	PD-L1+ (IHC 2/3) as ≥5% of ICs PD-L1+	PD-L1+ ≥1% TC expression	PD-L1+ ≥10% TC and IC staining	PD-L1+ as ≥25% of ICs and TCs with membrane PD-L1 staining	PD-L1+ as ≥5% TC or ≥10% ICstaining
Estimated PD-L1 prevalence in urothelial cancer trials					

1. Rosenberg JE et al. *Lancet* 2016;387:1909-1920. 2. Hoffman-Censits JH et al. *J Clin Oncol* 2016;34(Suppl 2S):Abstract 355.
3. Sharma P et al. *J Clin Oncol* 2016;34(Suppl):Abstract 4501. 4. Bellmunt J et al. *N Engl J Med* 2017;376:1015-1026.
5. Powles C et al. *J Clin Oncol* 2016;34:3119-3125. 6. Apolo AB et al. *J Clin Oncol* 2016;34(Suppl):Abstract 4514.

Use PD-L1 expression to select therapy for the first-line therapy of cisplatin-ineligible patients

5/18/2018

FDA Alert

- In two ongoing clinical trials (KEYNOTE-361 and IMVIGOR-130), the Data Monitoring Committees' (DMC) found patients in the **monotherapy arms of both trials with PD-L1 low status had decreased survival compared to patients who received cisplatin- or carboplatin-based chemotherapy.**

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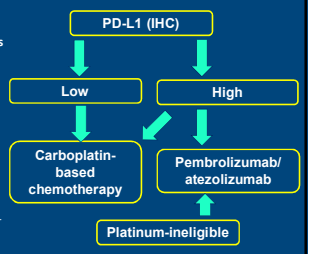
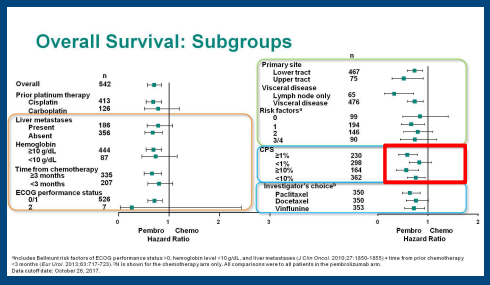
- **Platinum-ineligible patients remain ill-defined** (?both ECOG-PS=2 + Cr Cl <60, ECOG-PS=3, Cr Cl <30, comorbidities)



Phase III KEYNOTE-045 ASCO GU 2018 UPDATE: Pembrolizumab vs Taxane/Vinflunine as Post-Platinum Salvage → Survival Benefit Seen Regardless of PD-L1 Expression!



Bellmunt J, et al. 2018 ASCO GU. Abstract 410.

Phase III Atezolizumab vs Chemotherapy in Platinum-Refractory, PD-L1–Positive Disease: IMvigor211

Key Eligibility Criteria

- Urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
- Transitional cell predominant
- PD after 1-2 lines of platinum-based chemo or recurrence within 12 months of perioperative platinum-based therapy
- ECOG PS 0-1
- Provision of tumor sample for biomarker assessment

N = 234

R 1:1

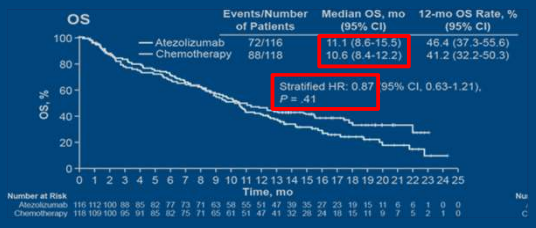
Atezolizumab 1200 mg IV 1x/3 wk

Paclitaxel 175 mg/m² 1x/3 wk
or
Docetaxel 75 mg/m² 1x/3 wk
or
Vinflunine 320 mg/m² 1x/3 wk

- **Key endpoints:** OS in PD-L1+ population (primary); OS in ITT population (hierarchical analysis)

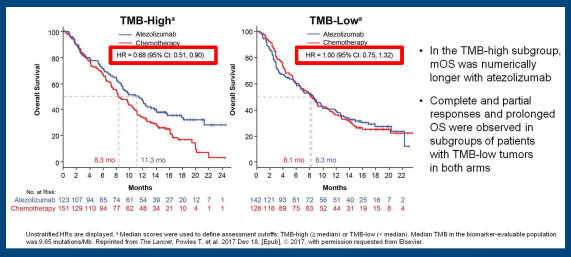
Powles T et al. 2018 Genitourinary Cancers Symposium (ASCO GU 2018). Abstract 409; Powles T, et al. Lancet. 2018;391(10122):748-757.

Phase III IMvigor211: Atezolizumab vs Chemotherapy in Biomarker-Positive, Platinum-Refractory UC



Powles T, et al. Lancet. 2018;391(10122):748-757.

OS Based on Tumor Mutational Burden (TMB): Phase III IMvigor211 Analysis

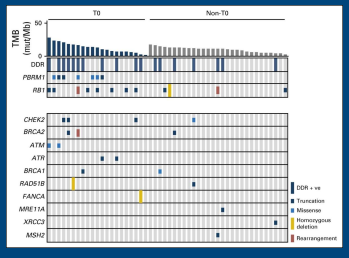


- In the TMB-high subgroup, mOS was numerically longer with atezolizumab
- Complete and partial responses and prolonged OS were observed in subgroups of patients with TMB-low tumors in both arms

Unstratified HRs are displayed. [a]Median scores were used to define assessment cutoffs: TMB-high (≥ median) or TMB-low (< median). Median TMB in the biomarker-evaluable population was 9.65 mutations/Mb. Reprinted from The Lancet, Powles T, et al. 2017 Dec 18. [Epub]. © 2017, with permission requested from Elsevier.

Powles T, et al. 2018 ASCO GU. Abstract 405.

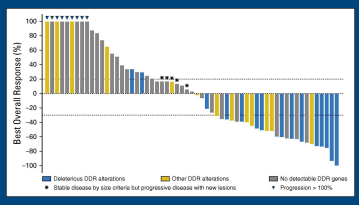
PD-L1 or TMB to select patients for IO alone for MIBC?



- pT0 was achieved in
  - 19 patients (54.3%) with PD-L1 CPS ≥ 10%
  - 2 patients (13.3%) with CPS < 10% (*P* = 0.011)
- A significant (*P* = 0.022) association between TMB and pT0 response with a cutoff of TMB ≥ 15 mut/Mb

Necchi A, GU-ASCO 2018, JCO 2018; Oct 20.

DDR alterations associated with response to PD-1/PD-L1 blockade in metastatic urothelial carcinoma.

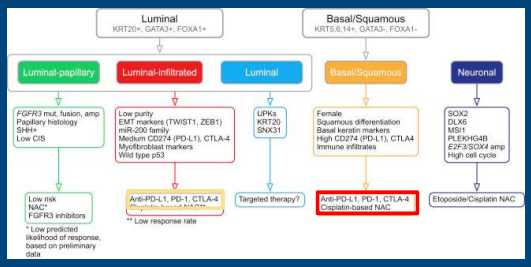


Any DDR alteration was associated with a higher response rate (67.9% v 18.8%; P < .001).

Higher response rate in those with likely deleterious DDR alterations (80%) compared with DDR alterations of unknown significance (54%) and in those with wild-type DDR genes (19%; P < .001).

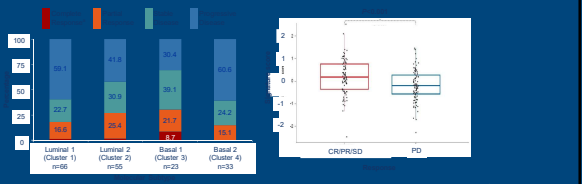
Min Yuen Teo,..Jonathan E. Rosenberg; *Journal of Clinical Oncology* 2018 361685-1694.

IS PRECISION MEDICINE POSSIBLE BASED ON TCGA GENE EXPRESSION SUBTYPES? Lerner,...Kwiatkowski; TCGA (N=412), ASCO 2017, CELL 2017



Association between UC molecular subtype, 25-gene interferon-γ signature, and response to nivolumab

- Basal 1 and luminal 2 have higher response rates vs the other 2 subtypes
- Interferon-γ genes are enriched in responders vs those with progressive disease (*P*<0.01)



*Basal 2 CR, 0%; luminal 1 CR,1.5%; luminal 2 CR, 1.8%

Signature score, 25-gene interferon-γ signature expression

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THE LANCET Oncology

VEGF inhibitors

CALGB 90601 Study Design
n=500

Enrollment: 2009-2014

- Metastatic or locally advanced unresectable urothelial carcinoma
- No prior chemotherapy for metastatic disease
- ECOG PS 0-1
- GFR ≥ 50 ml/min

RANDOMIZE 1:1

Gemcitabine 1000 mg/m2 IV days 1 and 8
Cisplatin 70 mg/m2 IV day 1*
Bevacizumab 15 mg/kg

Bevacizumab 15 mg/kg q3 week

Gemcitabine 1000 mg/m2 IV days 1 and 8
Cisplatin 70 mg/m2 IV day 1*
Placebo

Placebo

Treatment until cancer progression, unacceptable toxicity, or death

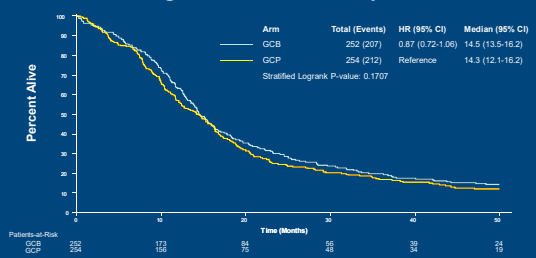
Primary Endpoint: Overall survival (OS)

454 deaths required to detect a HR of 0.74 with power of 0.87% and two sided α=0.05

DSMB approved the final OS analysis at 420 events

ASCO 2019 Abstract 4503 Rosenberg et al. 59

Bevacizumab does not improve overall survival in combination with gemcitabine and cisplatin



Abstract 4503 Rosenberg et al.

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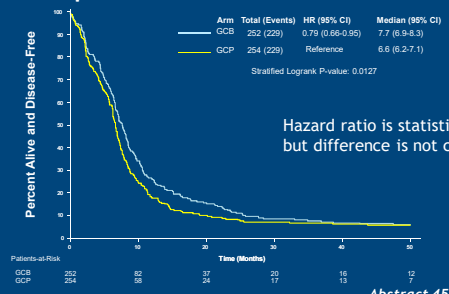
PFS is improved with bevacizumab



Arm	Total (Events)	HR (95% CI)	Median (95% CI)
GCB	252 (229)	0.79 (0.66-0.95)	7.7 (6.9-8.3)
GCP	254 (229)	Reference	6.6 (6.2-7.1)

Stratified Logrank P-value: 0.0127

Hazard ratio is statistically significant, but difference is not clinically significant

Abstract 4503 Rosenberg et al.

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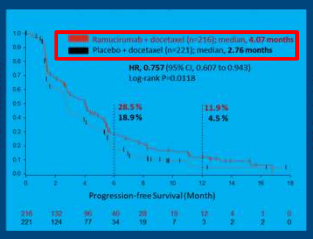
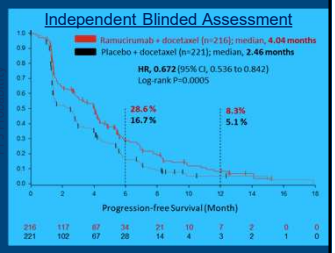
RANGE Phase III trial: Modest PFS (but not OS) Improvement by Adding Ramucirumab (VEGFR2 mAb) to Docetaxel for Post-Platinum Patients



Independent Blinded Assessment

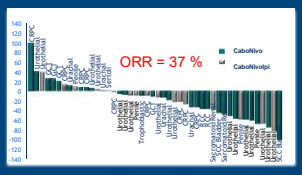


Median follow-up duration in the full ITT population was 5.0 months (interquartile range [IQR], 2.3–8.9)

Petrylak DP, et al; RANGE study investigators. Lancet. 2017;390(10109):2266-2277; Petrylak DP. 2018 ESMO.

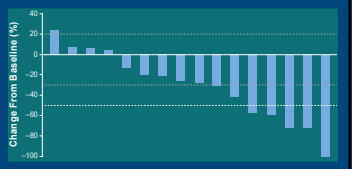
VEGF + PD1 +/- CTLA4 inhibition

Cabozantinib Plus Nivolumab +/- Ipilimumab for Metastatic Urothelial Carcinoma and Other GU Tumors



Apolo A, et al. ASCO 2017, GU-ASCO 2018

Lenvatinib + Pembrolizumab for Metastatic Urothelial Carcinoma



Vogelzang N, et al. ASCO -SITC, 2019

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Ongoing selected trials evaluating VEGF inhibitors

alone or in combination with PD1/L1 inhibitors

Population	Phase	Sample size (N)	Treatment	Endpoint	NCT #
Advanced (1st-line)	III	Pending	Pembrolizumab +/- Lenvatinib (Cisplatin-ineligible PD-L1+ or platinum ineligible)	OS	Pending
	II	39	Pembrolizumab + Cabozantinib (Platinum-ineligible)	ORR	NCT03534804
	II	40	Avelumab + Axitinib (cisplatin-ineligible)	ORR	NCT03472560
	Ib	30	Atezolizumab + Cabozantinib	ORR	NCT03170960
Advanced (post-platinum)	II	35	Regorafenib	PFS	NCT02459119
	Ib	152	Cabozantinib + Nivolumab + / - Ipilimumab	ORR	NCT02496208
	Ib	30	Atezolizumab + Cabozantinib	ORR	NCT03170960

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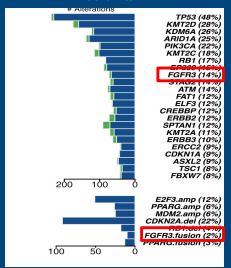
FGFR inhibitors

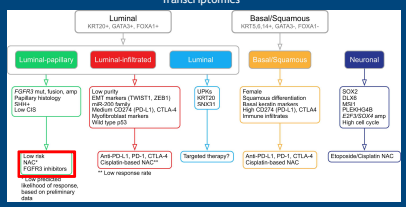
BIOLOGY OF UROTHELIAL CARCINOMA

Molecular heterogeneity but target-rich environment

Genomics



Transcriptomics



Robertson AG, et al. **Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer.** Cell. 2017 Oct 19;171(3):540-556.

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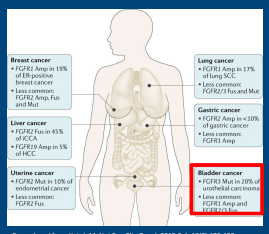
FGFR3 as a rational therapeutic target in bladder cancer



Reproduced from Katoh M. Nat Rev Clin Oncol. 2019 Feb;16(2):105-122.

FDA grants accelerated approval to erdafitinib for metastatic urothelial carcinoma

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

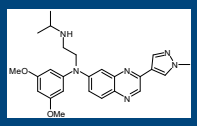
On April 12, 2019, the Food and Drug Administration granted accelerated approval to erdafitinib (BALVERSA, Janssen Pharmaceutical Companies) for patients with locally advanced or metastatic urothelial carcinoma with susceptible FGFR3 or FGFR2 genetic alterations, that has progressed during or following platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

Patients should be selected for this therapy based on an FDA-approved companion diagnostic for erdafitinib. Today, the FDA also approved the therascreen® FGFR RGQ RT-PCR Kit, developed by QIAGEN, for use as a companion diagnostic for this therapeutic indication.

1) Cappellen D, et al. *Nat Genet* 1999;23:18–20; 2) Nassar A., Sonpavde. JCO Precis Oncol May 2018; 3) Gust KM, et al. *Mol Cancer Ther* 2013;12:1245–54; 4) Grünewald S, et al. Int J Cancer. 2019 Feb 26; 5) Sfakianos JP Eur Urol. 2015 Dec;68(6):970-7.

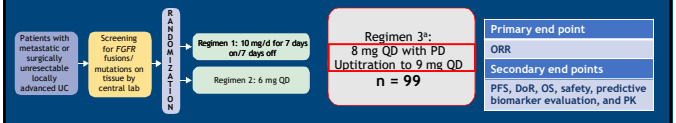
ERDAFITINIB

- Erdafitinib* is an oral pan-FGFR (1-4) inhibitor with IC_{50}s in the single-digit nanomolar range[1]
- Erdafitinib is taken up by lysosomes, resulting in sustained intracellular release, which may contribute to its long-lasting activity[1]
- Erdafitinib has demonstrated promising activity in patients with metastatic or unresectable UC and other histologies (eg, cholangiocarcinoma) with *FGFR* alterations[2-5]



1. Perera, TPS, et al. *Mol Cancer Ther*. 2017;16:1010-1020.
2. Tabernero J, et al. *J Clin Oncol*. 2016;33:3401-3408.
3. Soria J-C, et al. ESMO 2016. Abstract 783PD.
4. Loriot Y, et al. ASCO GU 2018. Abstract 411.
5. Siefker-Radtke A, et al. ASCO GU 2018. Abstract 450.

Phase 2 BLC2001 Study Design



Primary end point
- ORR

Secondary end points
- PFS, DoR, OS, safety, predictive biomarker evaluation, and PK

Patients
- Progression on ≥ 1 line prior systemic chemo or within 12 months of (neo)adjuvant chemo OR
- Chemo-naïve: cisplatin ineligible per protocol criteria[b]
- Prior immunotherapy was allowed

Primary hypothesis:
- ORR in Regimen 3 is > 25%
- One-sided α = 0.025
- 85% power

[a]Dose uptitration if ≥ 5.5 mg/dL target serum phosphate not reached by Day 14 and if no TRAEs.
[b]Ineligibility for cisplatin: impaired renal function or peripheral neuropathy.

Abbreviations: DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; QD, daily; TRAEs, treatment-related adverse events.

Arlene O. Siefker-Radtke, ASCO 2018

Erdafitinib Phase 2 BLC2001 Study: Baseline Characteristics

Patients, n (%)		8 mg continuous dose (n = 99)
Age, median years (range)		68 (36-87)
ECOG performance status	0 1 2	50 (51) 42 (42) 7 (7)
Pre-treatment	Progressed or relapsed after chemo Chemo-naïve Prior immunotherapy	87 (88) 12 (12) 22 (22)
Number of lines of prior treatment	0 1 2 ≥ 3	11 (11) 45 (46) 29 (29) 14 (14)
Visceral metastases	Present Absent	78 (79) 21 (21)
Hemoglobin Level	≥10 <10	84 (85) 15 (15)
Tumor location	Upper tract Lower tract	23 (23) 76 (77)
Creatinine clearance rate	< 60 mL/min ≥ 60 mL/min	52 (53) 47 (47)
FGFR alterations	*FGFR2* or *FGFR3* fusion *FGFR3* mutation	25 (25) 74 (75)

FGFR gene fusions
FGFR3-TACC3, FGFR3-BAIAP2L1
FGFR2-BICC1, FGFR2-CASP7 (n=6)

FGFR3 gene mutations
R248C, S249C, G370C, Y373C

Arlene O. Siefker-Radtke, ASCO 2018

Erdafitinib: Antitumor Activity

Study met the primary objective

		[95% CI]
Patients, n	99	
Response per investigator assessment*, n (%)		
ORR	40 (40.4)	[30.7-50.1]
CR	3 (3.0)	
PR	37 (37.4)	
SD	39 (39.4)	
PD	18 (18.2)	
Unknown	2 (2.0)	
Median time to response	1.4 months	
Median duration of response	5.6 months	[4.2-7.2]
ORR among patient subgroups, n (%)		
Chemo-naïve	5/12 (41.7)	
Progressed or relapsed after chemo	35/87 (40.2)	
With visceral metastases	30/78 (38.5)	
Without visceral metastases	10/21 (47.6)	

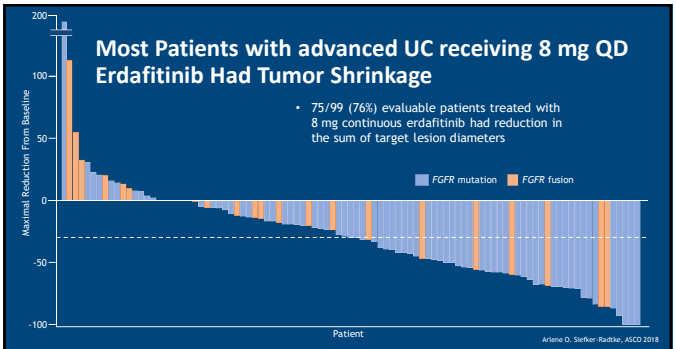
*Confirmed with second scan at least 6 weeks following the initial observation of response.

There were no confirmed responses in the FGFR2 fusion population (n=6)

Arlene O. Siefker-Radtke, ASCO 2018

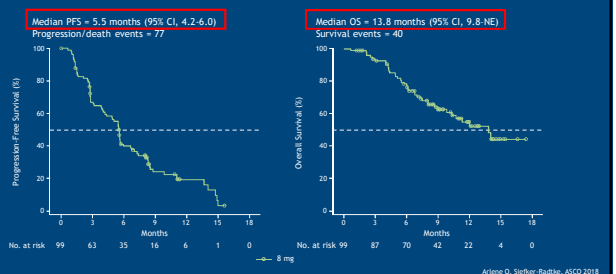
Most Patients with advanced UC receiving 8 mg QD Erdafitinib Had Tumor Shrinkage

- 75/99 (76%) evaluable patients treated with 8 mg continuous erdafitinib had reduction in the sum of target lesion diameters



Arlene O. Siefker-Radtke, ASCO 2018

Erdafitinib: PFS and OS



Arlene O. Siefker-Radtke, ASCO 2018

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Erdafitinib Exploratory Analysis

FGFR Alterations May Select for Patients With UC Unlikely to Respond to PD-(L1) Inhibitors

	8 mg continuous dose (n = 99)
Patients treated with prior immuno-oncology agent (IO), n	22
Patients with response (per investigator) to prior IO, n (%)	1/22 (5)[a]

[a]Patient had been previously treated with atezolizumab (PD) and atezolizumab and anti CSF1 (CR)

For 22 patients with prior IO, the ORR to erdafitinib was 59%, consistent with the general trial population

Arlene O. Siefker-Radtke, ASCO 2018

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Erdafitinib Treatment-Related AEs

All events

Reported in >20% of patients	8 mg continuous dose (n = 99)	
Patients with AEs, n (%)	Any grade	Grade 3
Hyperphosphatemia	72 (73)	2 (2)
Stomatitis	54 (55)	9 (9)
Dry mouth	43 (43)	0
Diarrhea	37 (37)	4 (4)
Dysgeusia	35 (35)	1 (1)
Dry skin	32 (32)	0
Alopecia	27 (27)	0
Decreased appetite	25 (25)	0
Hand-foot syndrome	22 (22)	5 (5)
Fatigue	21 (21)	2 (2)

Events of special interest

	8 mg continuous dose (n = 99)	
Patients with AEs, n (%)	Any grade	Grade ≥ 3
Hyperphosphatemia	72 (73)	2 (2)
Skin Events	48 (49)	6 (6)
Dry skin	32 (32)	0 (0)
Hand-foot syndrome	22 (22)	5 (5)
Nail Events	51 (52)	14 (14)
Onycholysis	16 (16)	2 (2)
Paronychia	14 (14)	3 (3)
Nail Dystrophy	16 (16)	6 (6)
Central serous retinopathy (CSR)	21 (21)	3 (3)
Non-CSR ocular events[a]	51 (52)	5 (5)

[a]Most common non-CSR ocular events included dry eye (19%), blurry vision (16%), increased lacrimation (11%), and conjunctivitis (9%).

Arlene O. Siefker-Radtke, ASCO 2018

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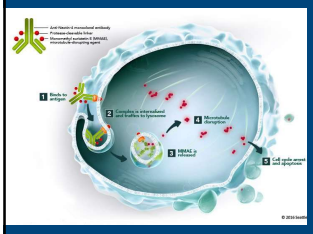
Ongoing selected key trials evaluating FGFR inhibitors

Population	Phase	Sample size (N)	Treatment	Endpoint	NCT #
Adjuvant	II	56	INCB054828 for FGFR mutations or fusions	Relapse-free survival	EudraCT 2017-004426-15
Advanced (post-platinum)	III	631	Erdafitinib vs Vinflunine or taxane or Pembrolizumab based on FGFR genomic alterations	OS	NCT03390504 (THOR)
	III	400	Rogaratinib vs chemotherapy based on FGFR gene over-expression	OS	NCT03410693 (FORT-1)
	II	300	Docetaxel + Placebo vs Docetaxel + Vofatamab vs Vofatamab post checkpoint inhibitor based on FGFR genomic alterations	PFS	NCT02401542
	II	125	Debio-1347	ORR	NCT03834220

Antibody Drug Conjugates (ADC)

Updated Results From the Enfortumab Vedotin Phase 1 (EV-101) Study in Patients With Metastatic Urothelial Cancer

J. Rosenberg,[1] S.S. Sridhar,[2] J. Zhang,[3] D. Smith,[4] J. Ruether,[5] T.W. Flaig,[6] J. Baranda,[7] J. Lang,[8] E.R. Plimack,[9] R. Sangha,[10] E. Heath,[11] J. Merchan,[12] D. Quinn,[13] S. Srinivas,[14] M. Milowsky,[15] C. Wu,[16] E. Gartner,[17] A. Methem-Bertrandt,[18] D. Petrylak[18]



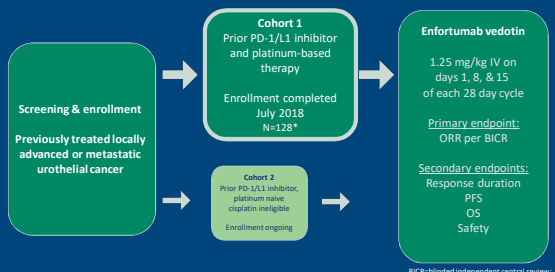
Monoclonal antibody targeting Nectin-4, conjugated by a protease-cleavable linker to the microtubule-disrupting agent monomethyl auristatin E

Nectin-4 is a transmembrane adhesion molecule, highly expressed in cancer, particularly UCC (93% in mUCC)

ORR 41% in chemo-treated mUCC (n=112)

Rosenberg et al ASCO 2018

EV-201: Single-arm, pivotal phase 2 trial



*3 patients did not receive enfortumab vedotin treatment: one each due to clinical deterioration, patient decision, and low hemoglobin after enrollment

BICR=blinded independent central review; ORR=objective response rate; OS=overall survival; PFS=progression free survival;

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Petrylak DP, et al. ASCO 2019

EV201: ORR assessed by BICR	Patients (N=125) n (%)
Confirmed objective response rate	**55 (44)**
95% confidence interval[a]	(35.1, 53.2)
Best overall response per RECIST v. 1.1, n (%)	
Complete response	15 (12)
Partial response	40 (32)
Stable disease	35 (28)
Progressive disease	23 (18)
Not evaluable[b]	12 (10)

Few treatment discontinuations because of TRAE (12%)

- Peripheral neuropathy was the most common TRAE leading to discontinuation (6%)
- Other common AE's: fatigue, rash, diarrhea, alopecia, anemia/neutropenia

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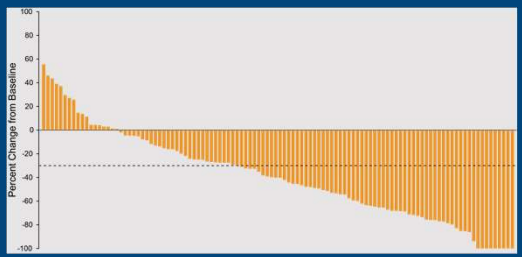
Petrylak DP, et al. ASCO 2019

EV-201: Cohort 1 Change in Tumor Measurements per BICR



- 10 patients had no post-baseline assessment
- 4 patients had no target lesions identified at baseline
- 1 patient had an uninterpretable post-baseline assessment

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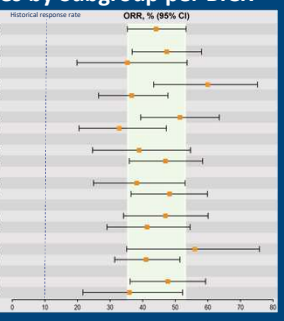
Petrylak DP, et al. ASCO 2019

EV-201: Cohort 1 Responses by Subgroup per BICR

Subgroup	n/N	% (95% CI)
Overall	55/125	44 (35.1, 53.2)
Age		
<75	43/91	47 (36.7, 58.0)
≥75	12/34	35 (19.7, 53.5)
ECOG performance status, n (%)		
Grade 0	24/40	60 (43.3, 75.1)
Grade 1	31/85	36 (26.3, 47.6)
Bellmunt risk score[1]		
0–1	37/72	51 (39.3, 63.3)
≥2	17/52	33 (20.3, 47.1)
Primary tumor sites		
Upper tract	17/44	39 (24.4, 54.5)
Bladder/Other	38/81	47 (35.7, 58.3)
Liver metastasis		
Yes	19/50	38 (24.7, 52.8)
No	36/75	48 (36.3, 59.8)
Number of prior therapies in metastatic UC setting		
1–2	29/62	47 (34.0, 59.9)
≥3	26/63	41 (29.0, 54.4)
Best response to prior PD-1/L1[2]		
Responder	14/25	56 (34.9, 75.6)
Non-responder	41/100	41 (31.3, 51.3)
PD-L1 expression[3]		
CPS <10	37/78	47 (36.0, 59.1)
CPS ≥10	15/42	36 (21.6, 52.0)

[1] Bellmunt risk score was not available for 1 patient; [2] Anti-PD-L1 or anti-PD-1 therapy; [3] Five patients were not evaluable for PD-L1 expression levels.



Petrylak DP, et al. ASCO 2019

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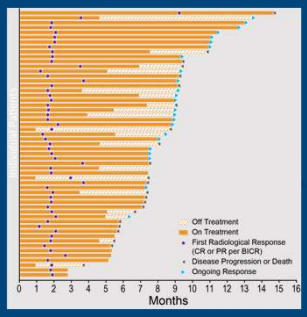
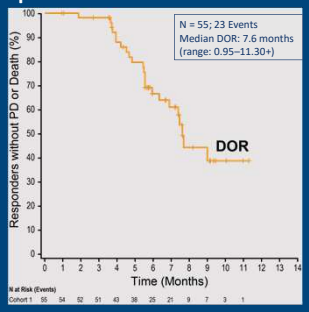
EV-201: Cohort 1 Duration of Response with Enfortumab Vedotin





Petrylak DP, et al. ASCO 2019

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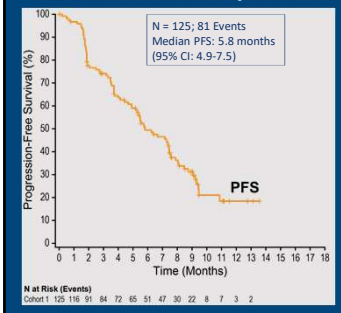
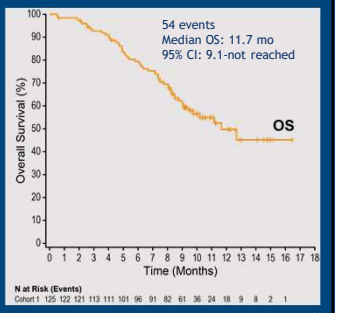
EV-201: Cohort 1 Kaplan-Meier Estimates of Survival





Petrylak DP, et al. ASCO 2019

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EV-201: Cohort 1 Treatment-Related Adverse Events

Treatment-related AEs by preferred term in ≥20% of patients (any Grade) or ≥5% (≥Grade 3)	Patients (N=125) n (%)	
	Any Grade	≥Grade 3
Fatigue	62 (50)	7 (6)
Alopecia	61 (49)	–
Decreased appetite	55 (44)	1 (1)
Dysgeusia	50 (40)	–
Peripheral sensory neuropathy	50 (40)	2 (2)
Nausea	49 (39)	3 (2)
Diarrhea	40 (32)	3 (2)
Dry skin	28 (22)	0
Weight decreased	28 (22)	1 (1)
Rash maculo-papular	27 (22)	5 (4)
Anemia	22 (18)	9 (7)
Neutropenia	13 (10)	10 (8)
Hyperglycemia	11%	6%

- Treatment-related AEs led to few discontinuations (12%)
  - Peripheral sensory neuropathy was the most common (6%)
- 1 treatment-related death reported by the investigator
  - Interstitial lung disease
  - Confounded by high-dose corticosteroid use and suspected *pneumocystis jirovecí* pneumonia

Petrylak DP, et al. ASCO 2019

EV-201: Cohort 1 Summary and Conclusions

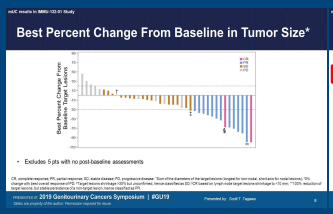
- Enfortumab vedotin: First novel ADC therapeutic to demonstrate substantial clinical activity in patients who progressed after platinum chemotherapy and a PD-1/L1 inhibitor
  - 44% response rate (CR 12%) and 7.6 months median duration of response
  - Responses observed across all subgroups and irrespective of response to prior PD-1/L1 inhibitor or presence of liver metastases
  - Tolerable with a manageable safety profile
  - pursuing FDA for accelerated approval
- If approved, enfortumab vedotin may have the potential to become a new standard of care in patients who have progressed after platinum and PD-1/L1 inhibitors

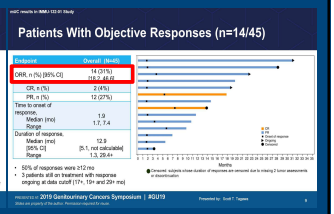
Ongoing enfortumab vedotin trials: **EV-201**: Cohort 2 enrolling cisplatin-ineligible patients without prior platinum (NCT03219333); **EV-301**: Randomized phase 3 trial of EV vs. SOC post-platinum and a PD-1/L1 inhibitor (NCT03474107); **EV-103**: EV in combination with pembrolizumab and/or chemotherapy (NCT03288545)

Petrylak DP, et al. ASCO 2019

Sacituzumab Govitecan: Phase I/II Best Response

ADC targeting TROP-2





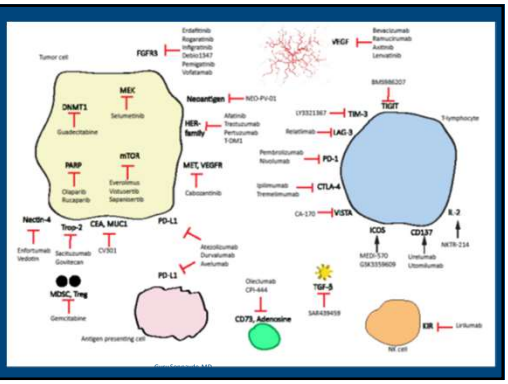
Phase II TROPHY-U-01
Ongoing single-arm, open-label, global study of SG in advanced UC - *NCT03547973*

Tagawa S, et al. GU-ASCO 2019.

A wealth of therapeutic targets→

1) role for multiple <u>targeted agents</u> in selected patients

2) challenge of multiple small molecular groups



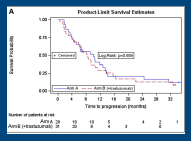
Grivas,..Sonpavde. ASCO Education Book 2019.

HER Kinase inhibitors

Her2 targeting deserves a second chance using newer potent drugs and combinations?

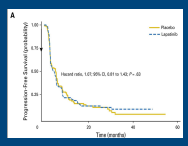
GC+/-Trastuzumab

Oudard S, et al. Eur J Cancer 2015 Jan;51(1):45-54.



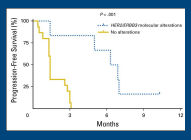
Lapatinib

Powles, et al. J Clin Oncol 2017; 35(1):48-55.



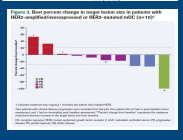
Afatinib (pan-HER TKI)

Choudhury NJ, et al. J Clin Oncol. 2016;34(18):2165-2171



Trastuzumab + Pertuzumab

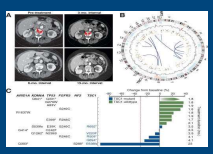
Bryce AH, GU-ASCO 2017



mTOR Kinase inhibitors

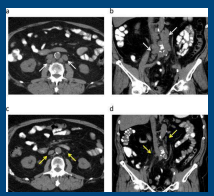
Signal of activity with activation of mTOR pathway (*TSC1, mTORC1* mutations)

Everolimus



Iyer G, et al. Science. 2012;338(6104):221.

Everolimus + Pazopanib



Wagle N, et al. Cancer Discov 2014;4(5):546-53

Selected trials evaluating kinase inhibitors

Population	Phase	Sample size (N)	Treatment	Endpoint	NCT #
Advanced (post-platinum)	II	30	Everolimus based on TSC1, TSC2, mTOR alterations	ORR	NCT02201212
	II	209	Sapanisertib based on TSC1, TSC2 mutations	ORR	NCT03047213
	I	65	Rogaratinib + Copanlisib (PI3Ki) based on FGFR gene over-expression	Toxicity	NCT03517956
	II	95	Afatinib (for HER-family alterations)	PFS	NCT02122172
	I/II	99	Trastuzumab Deruxtecan (Her2 ADC) With Nivolumab for Her2 expression	Feasibility, activity	NCT03523572
	I	78	PRS-343 (bispecific fusion protein targeting CD137 and HER2)	Toxicity	NCT03330561
	Ib	196	Durvalumab +/- • AZD4547 (FGFRi) • Olaparib (PARPi) • AZD1775 (Wee-1i) • Vistusertib (mTOR1-2i) • AZD9150 (Stat3 ASO) • Selumetinib (MEKi)	Toxicity	NCT02546661 (BISCAY)

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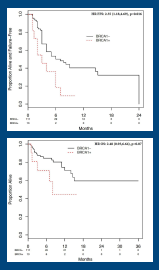
Rationale for PARP inhibitors +/- checkpoint inhibitors



- PARP inhibitors are approved in multiple settings of other malignancies with vulnerabilities defined by germline DNA damage repair gene alteration or platinum-sensitivity (olaparib, niraparib, rucaparib, talazoparib).
- DNA damage repair alterations are present in ctDNA (somatic) in a proportion of patients with metastatic urothelial carcinoma and appear associated with worse outcomes as shown in figures on left (Grivas,..Sonpavde. EU Oncol 2018)
- Tumor tissue DNA damage repair alterations may sensitize tumors to immune checkpoint inhibitors (Teo, ...Rosenberg, JCO 2018).
- Preclinical data exist showing activity of PARP inhibitors in selected urothelial carcinoma patients (Jian,..Sonpavde. Anti Cancer Drugs 2014).

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PARP inhibition trials

Population	Phase (I-III)	Sample size (N)	Treatment	Endpoint	NCT #
Advanced (1st-line)	II	150	Durvalumab +/- Olaparib (platinum-ineligible)	PFS	NCT03459846 (BAYOU)
Advanced (post-platinum)	II	200	Rucaparib	ORR	NCT03397394 (ATLAS)
	II	139	Rucaparib + Nivolumab (allows first-line cisplatin-ineligible)	ORR	NCT03824704 (ARIES)
	II	60	Olaparib based on DDR alterations	ORR	NCT03375307
	Ib	196	Durvalumab +/- • AZD4547 (FGFRi) • Olaparib (PARPi) • AZD1775 (Wee-1i) • Vistusertib (mTOR1-2i) • AZD9150 (Stat3 ASO) • Selumetinib (MEKi)	Toxicity	NCT02546661 (BISCAY)

Suspended (Efficacy did not meet the continuation criteria)

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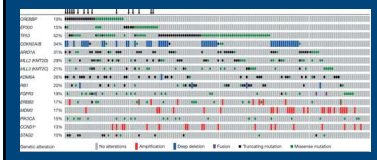
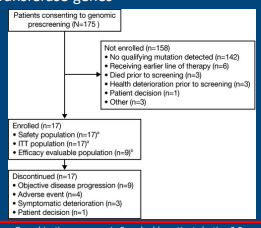
Epigenetic modulation

Mocetinostat (HDAC inhibitor) for previously treated metastatic urothelial carcinoma and inactivating alterations of acetyltransferase genes



- OncoPrint of genetic alterations in 150 patients.
- Thirty-three patients (21%) had ≥1 of the 40 qualifying tumor mutations in *CREBBP* or *EP300*

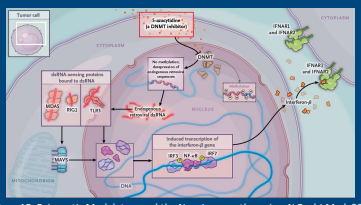


- One objective response in 9 evaluable patients lasting 3.9 months in patient with disease restricted to the lymph nodes.
- Toxicities impacted drug exposure.

Grivas P, et al. Cancer, 2018 ; 125 (4): 533-540.

Epigenetic modulation + immune checkpoint inhibition

- Hypomethylation may elicit viral mimicry (activate endogenous retroviral sequences) and render tumors more immunogenic.
- Epigenetic reprogramming of exhausted T cells may yield synergism with immune checkpoint inhibitors



Dear AE. Epigenetic Modulators and the New Immunotherapies. N Engl J Med. 2016

Alezolizumab + Guadecitabine in Patients With Checkpoint Inhibitor Refractory or Resistant Urothelial Carcinoma

ClinicalTrials.gov Identifier: NCT03179943

Adding guadecitabine (hypomethylating agent) to atezolizumab (PDL1 Inhibitor) in patients with resistance to checkpoint blockade will yield responses by eliciting viral mimicry and epigenetic programming of exhausted T cells.

Sponsor:
Fox Chase Cancer Center

Collaborators:
Stand Up To Cancer
Van Andel Research Institute

Information provided by (Responsible Party):
Fox Chase Cancer Center

Courtesy Elizabeth Plimack, MD

Urothelial carcinoma : Take home points

- Platinum-based chemotherapy remains conventional first-line therapy for most patients.
- 5 PD1/L1 inhibitors established as secondline therapy post-platinum
- Pembro/atezo are approved as firstline therapy for cisplatin-ineligible patients with PD-L1 high tumors or platinum-ineligible patients
- Erdafitinib is the first targeted agent approved for metastatic urothelial carcinoma (post-platinum with FGFR3/2 mutations/fusions)
- Enfortumab Vedotin shows encouraging activity in 3d line setting with a manageable toxicity profile.
- Anti-VEGF/VEGFR2 therapy in combination with chemotherapy has not shown a convincing OS signal.
- The role of pembrolizumab in combination with first-line chemotherapy and Avelumab in the switch maintenance setting following platinum-based chemotherapy may be established in the near future.
- The role of PD1/L1 inhibitors as perioperative therapy is undergoing phase III investigation (promising in phase II trials)
- Trials should preferred in all settings!

Anemia in Hematology and Oncology Practice

Ryan Woods, MD
Assistant Professor of Medicine, Section on Hematology and Oncology
Wake Forest school of Medicine

Charles L. Spurr Piedmont Oncology Symposium
Fall Symposium

Saturday, September 21, 2019

7:15 am Continental Breakfast and Exhibits

General Session

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

8:00 am **Thyroid Cancer**
Marcia S. Brose, MD, PhD
Associate Professor
Director, Thyroid Cancer Therapeutics
Director, Center for Rare Cancers and Personalized Therapy
University of Pennsylvania, Abramson Cancer Center

9:00 am **Cancer Pain Control During an Opioid Epidemic**
Judith A. Paice, PhD, RN
Director, Cancer Pain Program
Division of Hematology and Oncology
Northwestern University, Feinberg School of Medicine

10:00 am Break and Exhibits

10:30 am **GIST & Other Sarcomas: Making Sense of a Rare Family of Cancers**
Robert Maki, MD, PhD, FACP
Professor, Northwell-Hofstra Medical School
Professor, Cold Springs Harbor Laboratory

11:30 am **Geriatric Assessment for Older Adults with Cancer**
Heidi Klepin, MD, MS
Professor of Medicine, Section on Hematology and Oncology
Wake Forest School of Medicine

12:30 pm Adjourn

Thyroid Cancer
Marcia S. Brose, MD, PhD
Associate Professor
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University of Pennsylvania, Abramson Cancer Center

Thyroid Cancer

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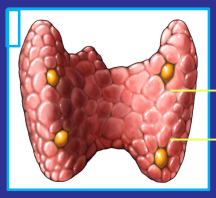
Associate Professor
Department of Otorhinolaryngology: Head and Neck Cancer
Department of Medicine, Division of Hematology/Oncology
Abramson Cancer Center
The University of Pennsylvania
Philadelphia, PA

Disclosures

- Companies: AstraZeneca, Bayer/Onyx, Eisai, Exelixis, Novartis, Roche/Genentech, Bristol-Myers Squibb, Sanofi/Genzyme, Loxo, Progenics
- Relationships: Advisory board consultant, honoraria, research grants, and primary investigator on phase II and phase III clinical trials
- I **WILL** include brief discussion of investigational or off-label use of a product in my presentation.

Thyroid cancer: clinical pathology



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

Parafollicular cells → Medullary (2%)

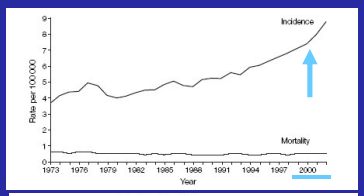
NOTE: Primary Thyroid Lymphoma is most often MALT but can be aggressive and is most often associated with Hashimotos Thyroiditis

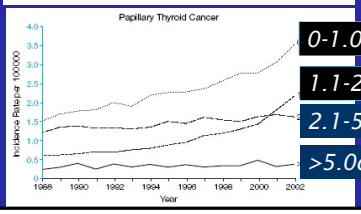
Treatment of Differentiated Thyroid Cancer includes:
- **Surgery – thyroidectomy**
- **Radioactive iodine**
- **Thyroid stimulating hormone (TSH) suppression**

Carling T and Udelsman 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 8th edition

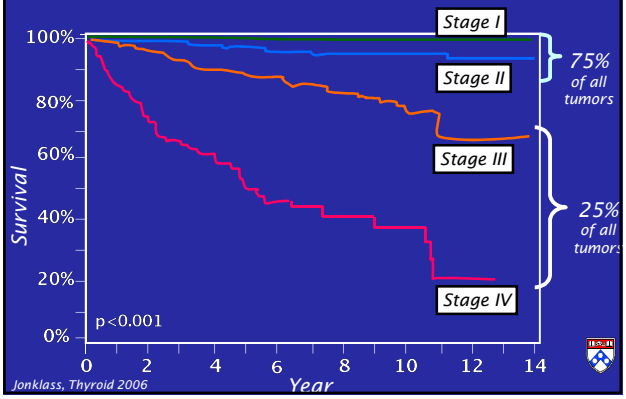
- Tumor (primary only)
  - T1 ≤ 2cm
  - T2 2-4cm
  - T3 > 4cm or gross extrathyroidal extension invading only strap muscles
  - T4 All other gross extrathyroidal extension
- Nodal metastases
  - N0
  - N1a Level VI
  - N1b Levels II-V or VII
  - Nx Regional lymph nodes can not be assessed
- Distant mets
  - M0 none
  - M1 present

MSB 05/09/08

AJCC/TNM 8th Addition 2018

Stage	<55 y.o.	≥ 55 y.o.
I	Any T, any N, M0	T1/T2, N0/Nx, M0
II	Any T, any N, M1	T1/T2, N1, M0
		T3, any N, M0
III		T4a, any N, M0
IVa		T1-T3, N1a, M0 T1-T3, N1b, M0
IVb		T4b, any N, M0
IVc		Any T, any N, M1

Initial disease stage predicts OVERALL SURVIVAL



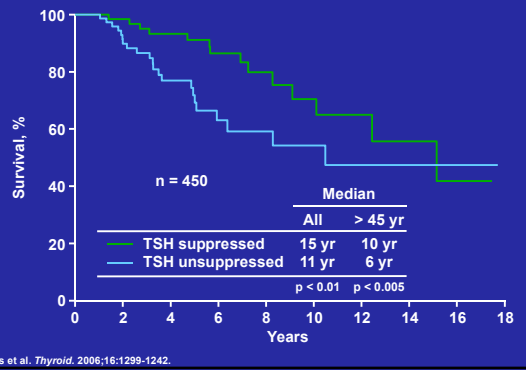
Thyroid Cancer: Staging Strategy

- Neck Ultrasound for surgical planning of lymph node involvement
- Ulstrasound guided FNA of nodule plus potential involved LNs
- CT scans (note to never use IV contrast as the iodine can block subsequent use of radioactive iodione). This can add information to the ulstrasound
- Chest XRAY – note over 90% of disease will be local so Chest CT is not required
- If Medullary thyroid cancer is suspected, then preop Calcitonin, CEA and urine metanepherines to rule out MEN2 should be obtained

Differentiated Thyroid Cancer: Treatment Strategy

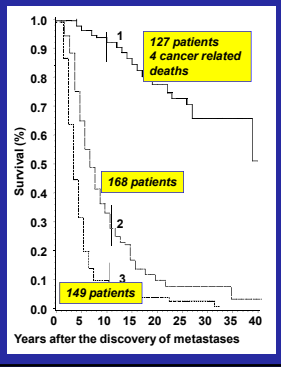
- Overview of Treatment for DTC
  - Total Thyroidectomy – in limited cases may be a hemithyroidectomy
  - RAI (^{131}I) Ablation – in certain cases may be omitted
  - TSH Suppression Therapy with Thyroid Hormone – risk based
  - Follow Serial Thyroglobulin Levels (Tg)
  - XRT for recurrent local disease/positive margins – no longer routinely recommended due to high morbidity
  - 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



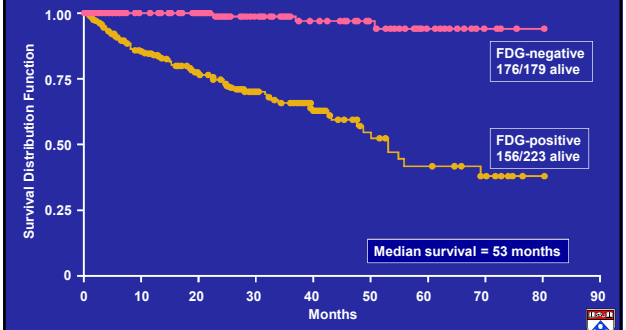
- Group 1: initial ^{131}I uptake and CR
  - Age < 40 years
  - Well-differentiated cancer
  - Small size of metastases
- Group 2: initial ^{131}I uptake and persistent disease
- Group 3: no initial ^{131}I uptake

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

RAI-Refractory Disease

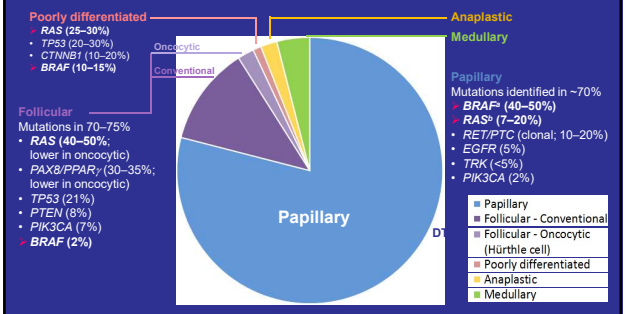
- 25-50% of Metastatic Thyroid Cancers loose ability to take up Iodine
- This is attributed to down regulation of the Na+/I- Symporter (NIS) and other genes of NaI metabolism
- This results directly in a loss of overall survival

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



[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

RAI-refractory disease: criteria

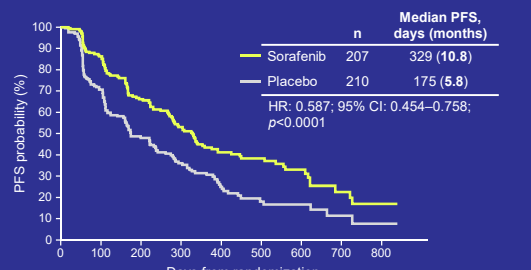
- We need to educate oncologists and endocrinologists when to refer patients to oncologists for treatment.
- RAI refractory means that there are **progressing lesions** that **do not take up RAI** (Note: there may still be some that do)
  - RAI uptake scan is negative and CT scan shows nodules
  - RAI 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;9:1167-214.
Hodak SP, Carty SE. Oncology. 2009;23:775-6.
Mehra R, Cohen RB. Hematol Oncol Clin North Am. 2008;22:1279-95,xi.

Differentiated Thyroid Cancer: Andvanced Stage Treatment Strategy

- FDA approved agents
  - Sorafefenib 2013 (Brose et al., *Lancet*, 2012)
  - Lenvatinib 2015 (Schlumberger et al., *NEJM*, 2015)
- Phase II Data
  - Vemurafenib for BRAF V600E pos (Brose et al., Lancet Oncology, 2016)
  - Dabrafenib for BRAF V600E pos (Shah et al., *JCO* 2017)

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

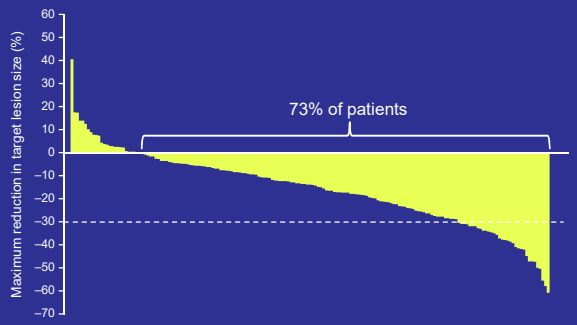
Full analysis set.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

ORR and Median TTP 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.

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



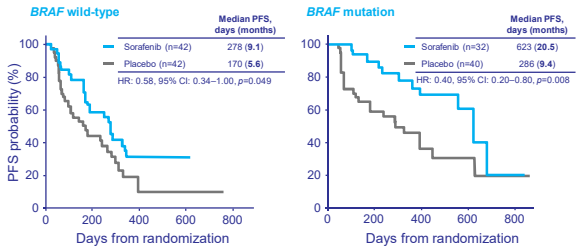
Maximum reduction is defined as the difference in the sum of the longest diameter of target lesions from baseline. Negative values refer to maximal reduction and positive values to the minimal increase.

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

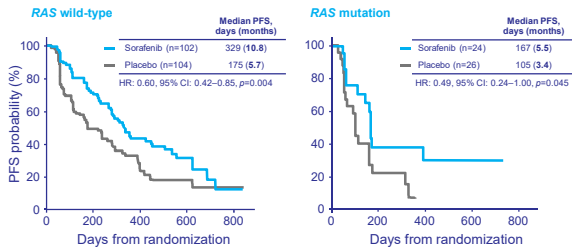
*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0

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)



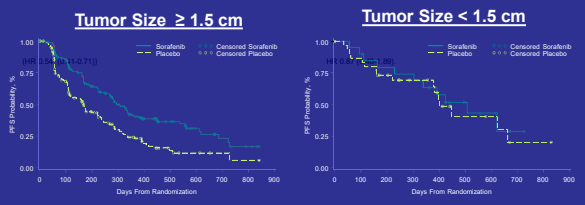
RAS mutation was not an independent prognostic factor for PFS

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)

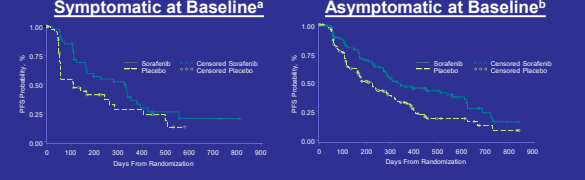
DECISION: A Post Hoc Subgroup Analysis by Maximum Tumor Size



- 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.

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



- 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/patlib/projects/439006/14295/stat/prod_query11/pgms/i-ema-25.sas.eqb 21JAN2014 17:07:1

[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/patlib/projects/439006/14295/stat/prod_query11/pgms/i-ema-25b.sas eqb 01APR2014 11:41:1

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

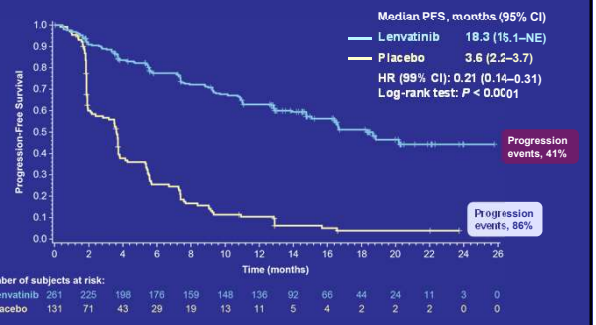
Lenvatinib (Optional, open-label)

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

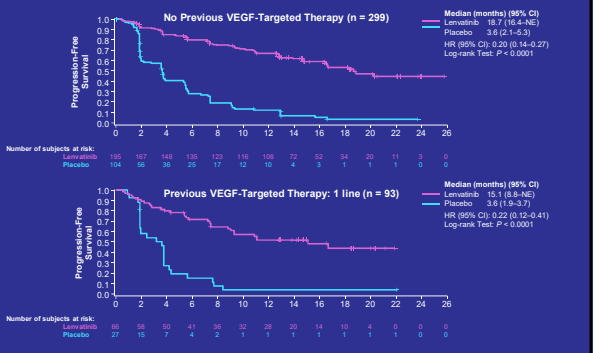
25

SELECT: Primary Endpoint: Kaplan-Meier Estimate of PFS



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.

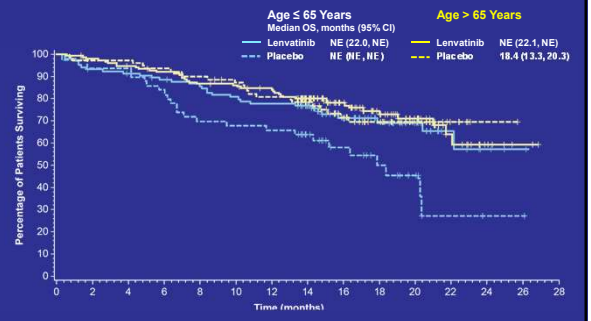
Presented by: Martin Schlumberger, MD

SELECT: 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

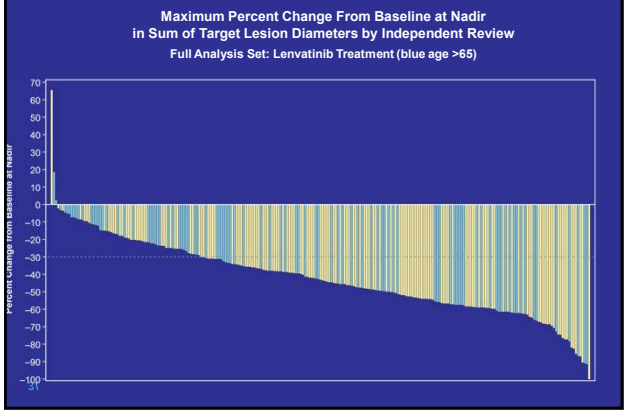
Presented by: Martin Schlumberger, MD

SELECT: Overall Survival, by Age



Brose et al JCO 2017

SELECT: Lenvatinib Responses



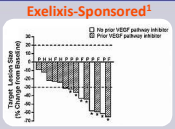
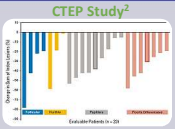
Summary: RAI refractory DTC 2018

- 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.

Differentiated Thyroid Cancer: Andvanced Stage Treatment New Data

- Cabozantinib (first and second line)
- Pembrolizumab (PD-L1 positive tumors)
- Larotrectinib (TRK Translocations)
- Second Generation RET inhibitors (RET translocations)
  - Loxo-292
  - Blu-667
- NOTE: Phase III Data Adjuvant Setting
  - Solumetanib for High Risk patients prior to RAI recently closed early (negative study – ATA 2018)

Clinical Activity in DTC Supports Further Development of Cabozantinib

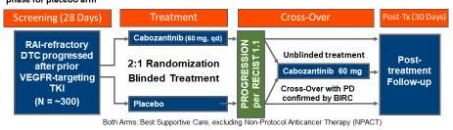
Exelixis-Sponsored[1]	CTEP Study[2]	Investigator-Initiated[3]
		
Phase I DDI • RAI-refractory • 80% ≥ 1 prior systemic agent, N=15 • **53% ORR** • **40% SD** • **mDOR: NR (2.0 – 14.5m)** • **mPFS: NR (10.3 - 17.0)**	**Phase 2** • RAI-refractory • 1-2 prior VEGFR-targeted therapy, N=25 • **40% ORR** • **52% SD** • **mDOR: 11.3 (10.3 - NR)** • **mPFS: 12.7m (10.9 - 34.7)**	**Phase 2** • RAI-refractory • 1L DTC, N=35 • **63% ORR** • **34% SD** • **mDOT: 40 weeks** • **mPFS: NR**

DDI: drug-drug interaction; DOR: duration of response; DOT: duration of therapy; NR: not reached; RAI: radioactive iodine.

COSMIC-311

COSMIC-311 Study Schema

Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of cabozantinib in subjects with RAI-refractory DTC (who have progressed after prior VEGFR-targeted therapy), with treatment cross-over phase for placebo arm

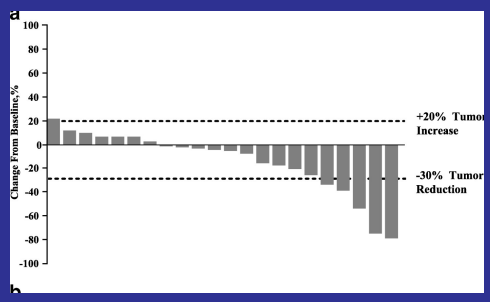


Both Arms: Best Supportive Care, excluding Non-Protocol Anticancer Therapy (NPACT)

- **Treatment Phase - Randomization to oral cabozantinib or placebo stratified by:**
  - Receipt of prior Lenvatinib (yes vs. no)
  - Age at informed consent (< 65 years vs. ≥ 65 years)
- **Cross-Over Phase:**
  - Placebo Arm: Upon Blinded Independent Radiology Committee (BIRC)-confirmed disease progression, subjects randomized to placebo will have the opportunity to crossover to receive cabozantinib
  - Cabozantinib Arm: Unblinded subjects randomized to cabozantinib may continue on study treatment if the Investigator believes the subject is deriving clinical benefit

EXELIXIS COSMIC

Safety and antitumor activity of the anti–PD-1 antibody pembrolizumab in patients with advanced, PD-L1–positive papillary or follicular thyroid cancer



Mehnert et al. *BMC Cancer*, Published online February, 2019

Safety and antitumor activity of the anti–PD-1 antibody pembrolizumab in patients with advanced, PD-L1–positive papillary or follicular thyroid cancer

Response evaluation ($N = 22$)	n	% (95% CI) or median (range)
ORR[a,b], % (95% CI)	2	9 (1–29)
CR	0	0 (0–15)
PR	2	9 (1–29)
SD	13	59 (36–79)
PD	7	32 (14–55)
CBR[b], % (95% CI)	11	50 (28–72)
SD ≥6 months, % (95% CI)	9	69 (39–91)
TTR (months), median (range)	2	5 (4–5)
DOR (months), median (range)	2	14 (8–20)
Follow-up duration (months), median (range)	22	31 (7–34)

Abbreviations: *CBR* clinical benefit rate, *CR* complete response, *DOR* duration of response; *NR* not reached, *ORR* objective response rate, *PD* progressive disease, *PR* partial response, *SD* stable disease, *TTR* time to response

Mehnert et al. *BMC Cancer*, Published online February, 2019

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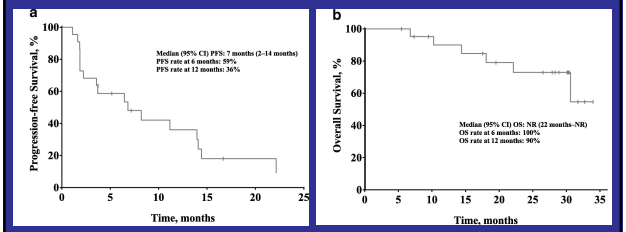
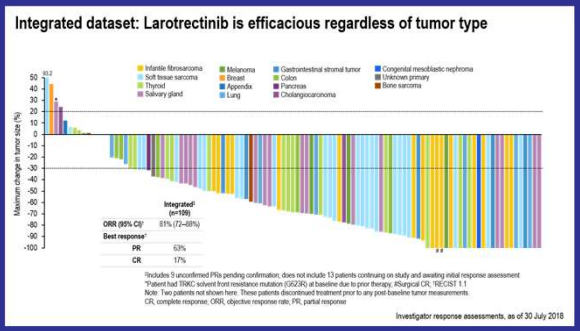


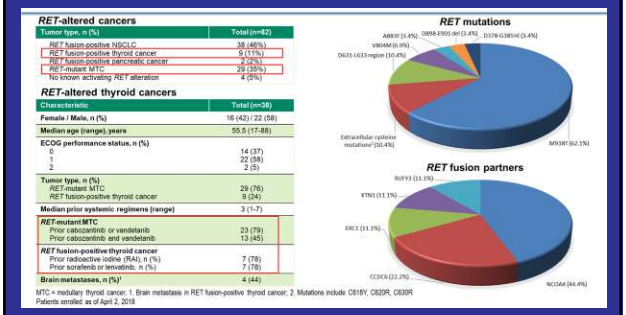
Mehnert et al. *BMC Cancer*, Published online February, 2019

Larotrectinib in TRK Fusion Cancers



Esmo 2018

RET altered Thyroid Cancer



***RET*-altered cancers**

Tumor type, n (%)	Total (n=62)
RET fusion-positive NSCLC	38 (46%)
RET fusion-positive thyroid cancer	9 (11%)
RET fusion-positive pancreatic cancer	2 (2%)
RET-mutant MTC	29 (35%)
No known activating *RET* alteration	4 (5%)

***RET*-altered thyroid cancers**

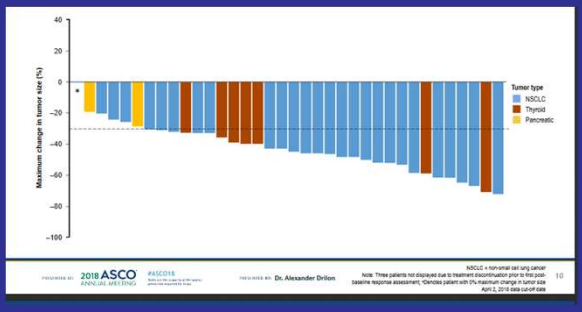
Characteristic	Total (n=38)
Female / Male, n (%)	16 (42) / 22 (58)
Median age (range), years	55.5 (17-88)
ECOG performance status, n (%)	
0	14 (37)
1	22 (58)
2	2 (5)
Tumor type, n (%)	
RET-mutant MTC	29 (76)
RET fusion-positive thyroid cancer	9 (24)
Median prior systemic regimens (range)	3 (1-7)
RET-mutant MTC	
Prior cabozantinib or vandetanib	23 (79)
Prior cabozantinib and vandetanib	13 (45)
RET fusion-positive thyroid cancer	
Prior radioactive iodine (RAI), n (%)	7 (78)
Prior sorafenib or lenvatinib, n (%)	7 (78)
Brain metastases, n (%)[1]	4 (44)

MTC = medullary thyroid cancer; 1. Brain metastasis in RET fusion-positive thyroid cancer; 2. Mutations include C618Y, C620R, C630R
Patients enrolled as of April 2, 2018

***RET* mutations**

***RET* fusion partners**

Efficacy of Loxo-292 (RET) in RET fusion cancers



Summary: RAI refractory DTC 2019

- 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 2019

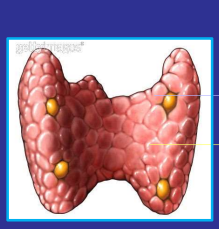
- As all patients will ultimately progress, both agents will be needed and will be used sequentially, as well as additional strategies
- ASTRA: Phase III of a MEK inhibitor to increase cures when used prior to RAI was NEGATIVE.
- A Phase III study of cabozantinib in the second or thirdline setting is underway based on strong activity in three phase I and II studies.
- A phase II of the addition of everolimus to sorafenib at the time of progression results in a PFS of 13.9 additional months.
- Patients with TRK translocations (adolescents) should be treated with larotractinib (FDA approved 2018).
- RET translocations also will be able to have options coming soon

Brose et al ASCO Annual Meeting 2014, Brose et al, ASCO/ASTRO Head and Neck February 2018

Summary: RAI refractory DTC 2019

- BRAF inhibitors vemurafenib and dabrafenib have been shown to have activity in Phase II studies and may be considered for patients who harbor the BRAF V600E mutation.
- No Role for immunotherapy at this time – Single agent Phase Ib data were disappointing
- Trials of RET and TRK inhibitors are showing promise in Phase I/II studies for patients with RET and TRK Translocations which can occur in DTC, so testing for these fusions is warranted.

Thyroid Cancer: Clinical Pathology



Follicular cells → Differentiated → Papillary, Follicular, Hurtle Cell
Follicular cells → Anaplastic
Parafollicular cells → Medullary → Sporadic, Familial

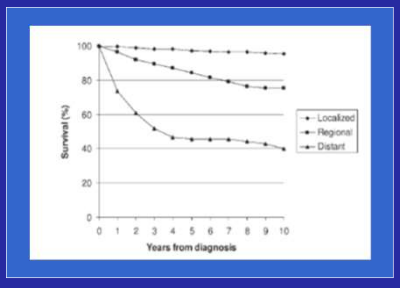
Medullary Thyroid Cancer: Advanced Stage Treatment Strategy

- FDA approved agents
  - Vandetanib 2011 (Wells et al., *JCO*, 2013)
  - Cabozantinib 2012 (Elisei et al., *JCO*, 2013)
- Phase II Data (accruing)
  - Loxo-292 for RET mut and translocation pos
  - Blu-667 for RET mut and translocation pos

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

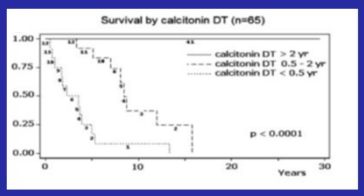


- 10-year overall survival: 40%
- Median overall survival: 3.2 years

Roman et al. 2005.

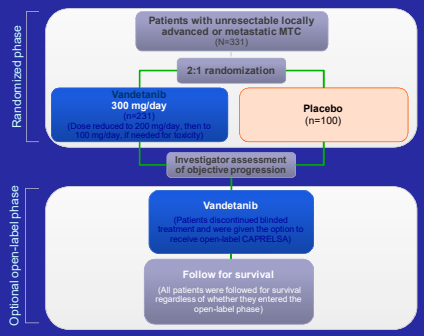
Risk Stratification Using Serum Calcitonin Doubling Time (DT)

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



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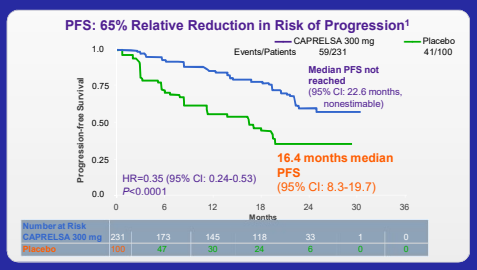
ZETA Study: Vandetanib Significantly Prolonged PFS[a] vs Placebo



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]

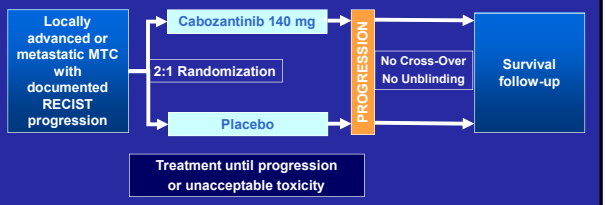
1. CAPRELSA® (vandetanib) Tablets [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. **2.** Wells SA Jr et al. *J Clin Oncol*. 2012;30(2):134-141.

51

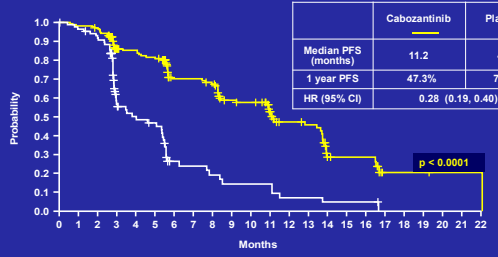
ZETA: Important Issues to note

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)
4. Was first effective systemic agent FDA approved for progressive or symptomatic MTC in 2011

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



EXAM: 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)	

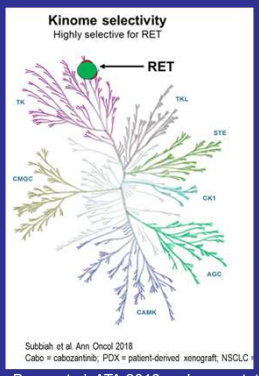
- **Significant difference in tumor response rate**
  - 28% in cabozantinib vs. 0% placebo; p<0.0001
- **Median duration of response: 14.6 months**

ASCO 2012 oral presentation

Medullary Thyroid Cancer: Advanced Stage Treatment New Data

- New Phase II Data
  - RET-292 (RET mutated cancers)
  - Blu-667 (RET mutated cancers)

Loxo-292 In Advanced MTC



LOXO292 and BLU667 Advantages:

No VEGFR Side Effects

Brain penetration (although Cabozantinib may have some)

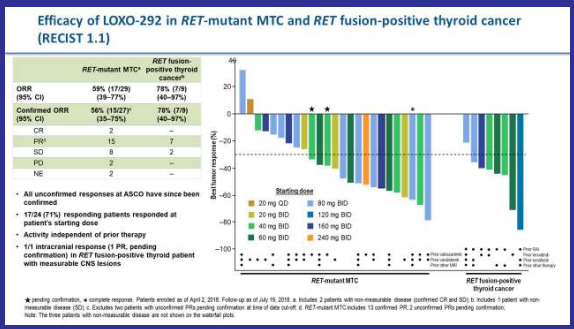
LOXO292 and BLU667 Disadvantages:

No Activity in nonRET mutated MTC

No Anti VEGFR anti-tumor activity

Brose et al. ATA 2018 oral presentation

Loxo-292 In Advanced MTC



Brose et al. ATA 2018 oral presentation

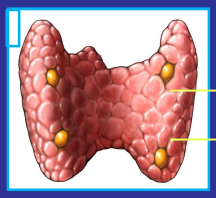
EXAM: Important Issues to note

1. Eligibility required progressive disease. Thus many patients enrolled were different from ZETA study.
2. No difference in overall survival was observed in spite of lack of crossover due to presence of other active agents (vandetanib).
3. Cabozantinib can be associated with fistula formation or perforations of the GI tract (often in associated with known diverticulits). Higher risk in the neck if external beam is used (XRT should be avoided).
4. Was second effective systemic agent FDA approved for progressive or symptomatic MTC in 2012.

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.

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 Udelsman 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.

Anaplastic Thyroid Cancer (1-2%)

Defining Characteristics:

- Most aggressive solid tumor with heterogenous histology
- May have associated poorly differentiated or papillary thyroid cancer (better prognosis)
- Metastasis are not uncommon but often represent a more differentiated component
- Prognosis is 3 to 12 months depending on ability to have surgery and local invasion (although patients living longer is observed not infrequently).

Anaplastic Thyroid Cancer (1-2%)

Treatment Approaches:

- Rarely is full resection possible but if it is it should be attempted
- Treatment is not uniform but include radiation with sensitizing chemotherapy (no regimen is considered standard)
- Due to the poor prognosis, palliation is the goal of care in most cases. More research is needed.
- New 2018 – FDA approves Dabrafenib plus Trametanib for BRAF V600E mutated anaplastic thyroid cancer (Subbiah, V et al JCO 2018)
  - Benefit is controversial because no control arm, and BRAF V600E mutated anaplastic thyroid cancers likely do better regardless of treatment modality

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 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

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

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

- Answer is A: At this point it is unclear how long the MTC has been there. The most appropriate is to check CEA and Calcitonin levels and restage in three months. If the disease is progressing on scans then systemic therapy may be indicated.

Thank You

Marcia.Brose@pennmedicine.upenn.edu

Cancer Pain Control During an Opioid Epidemic

Judith A. Paice, PhD, RN
Director, Cancer Pain Program
Division of Hematology and Oncology
Northwestern University, Feinberg School of Medicine

Disclosure Information

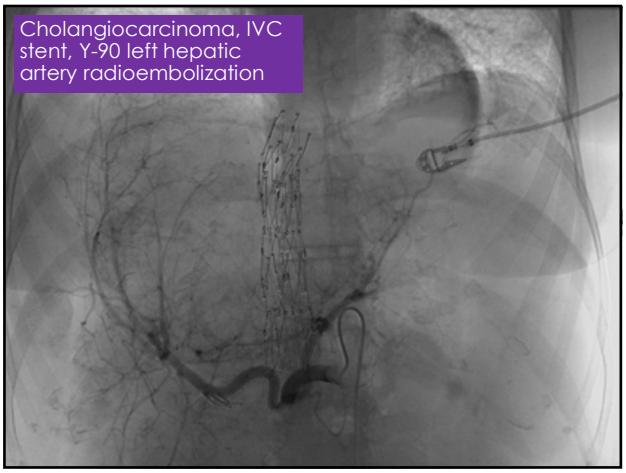
I have no financial relationships to disclose.

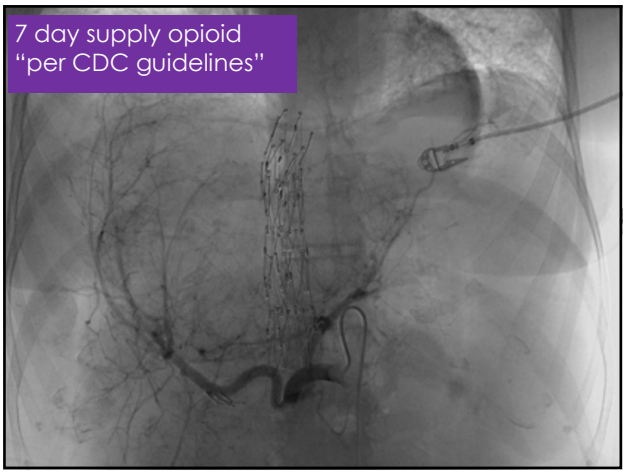
Objectives

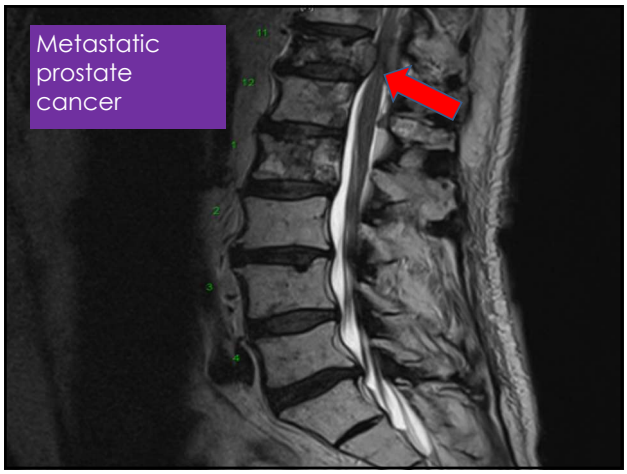
- Review the scope and impact of the United States opioid crisis and the necessity for careful prescription of opioid medications.
- Describe the necessity of opioid medications for pain management in patients with cancer and survivors, and discuss strategies to ensure that patients have access to medications necessary for managing pain.
- Define strategies to maintain patient safety and minimize the risks of opioid misuse and abuse during chronic opioid use.

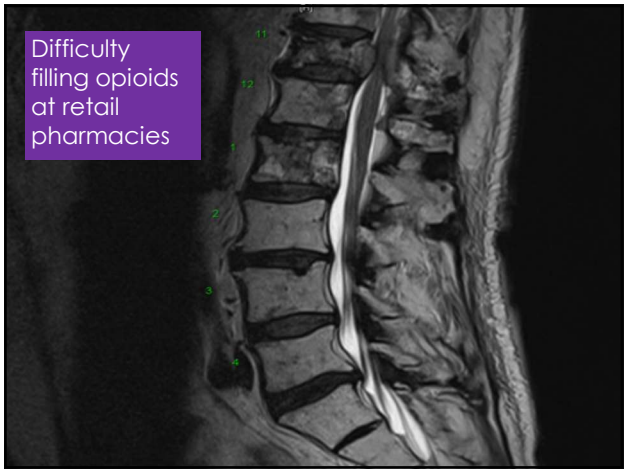
Unintended Consequences

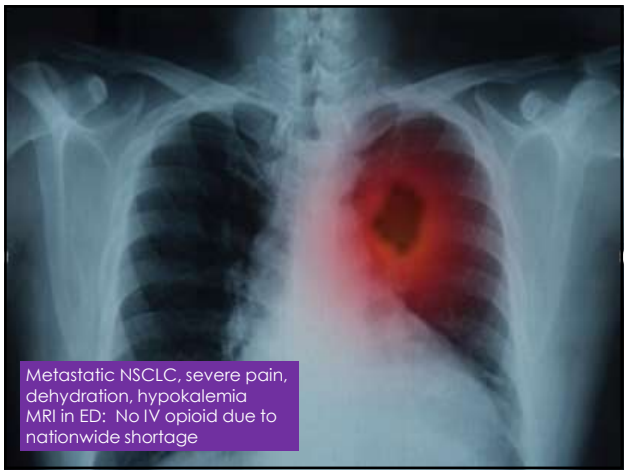
- Unrelieved pain is a public health crisis
- Opioid misuse and overdose deaths are emergencies
- Unintended consequences of efforts to reduce opioid overdoses include further stigma and unrelieved pain
- Simple solutions helped create the current crisis
- Comprehensive, complex solutions are needed to resolve these two public health crises

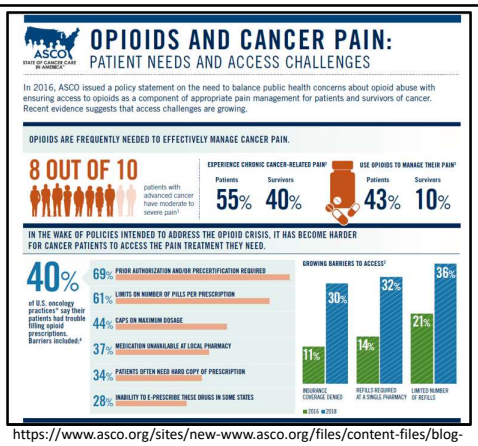




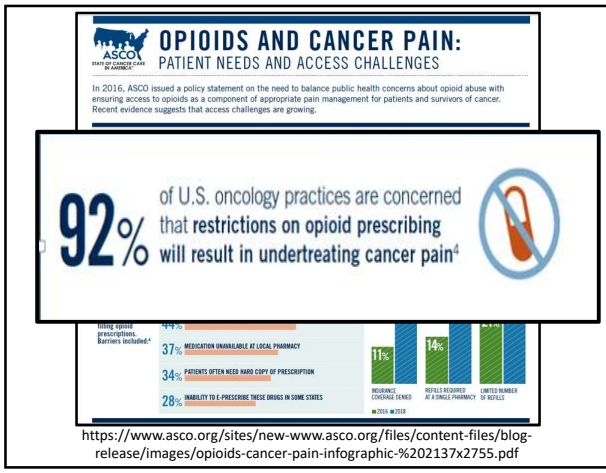

Metastatic prostate cancer


Difficulty filling opioids at retail pharmacies


Metastatic NSCLC, severe pain, dehydration, hypokalemia
MRI in ED: No IV opioid due to nationwide shortage



https://www.asco.org/sites/new-www.asco.org/files/content-files/blog-release/images/opioids-cancer-pain-infographic-%202137x2755.pdf



https://www.asco.org/sites/new-www.asco.org/files/content-files/blog-release/images/opioids-cancer-pain-infographic-%202137x2755.pdf

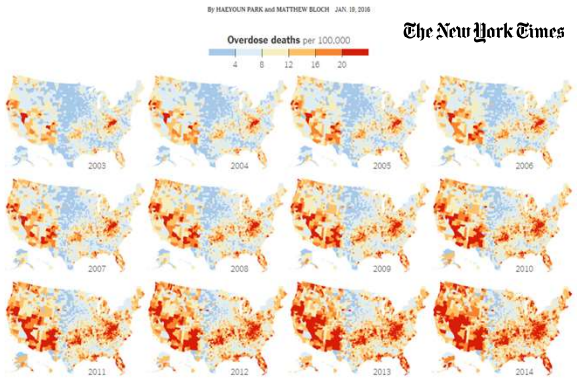
Cancer Prevalence

- In 2012, new cancer cases worldwide – 14.1 million, 8.2 million deaths, **32.6 million people living with cancer**
- By 2030, 21.7 million new cases, 13 million cancer deaths, **52.2 million survivors?**

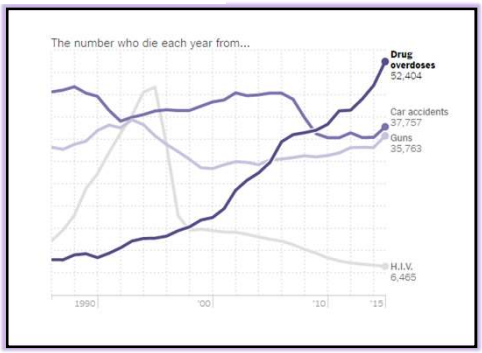
Global Cancer Facts & Figures, 3rd Edition, 2015, American Cancer Society (ACS) and International Agency for Research on Cancer (IARC)

Good News/Bad News

- Good news – more treatments are leading to better survival from a variety of serious illnesses
- Bad news – more persistent pain syndromes
- More bad news – opioid abuse epidemic

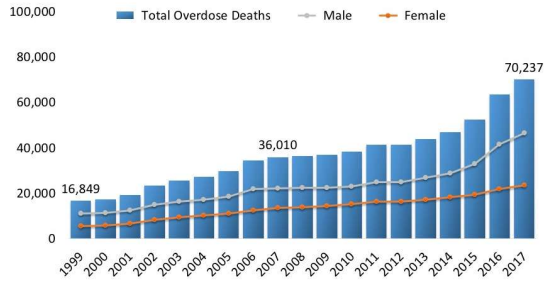


The New York Times



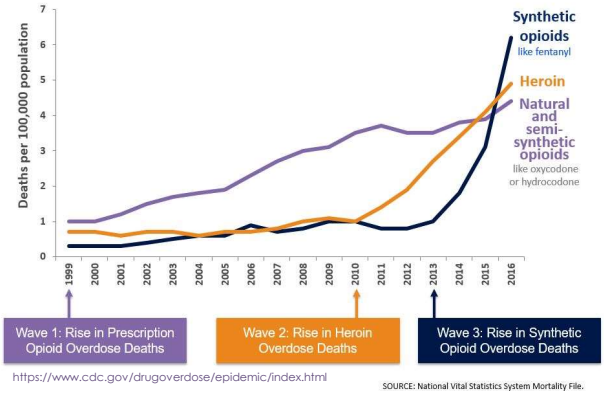
April 14, 2017

Figure 1. **National Drug Overdose Deaths**
Number Among All Ages, by Gender, 1999-2017



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018

3 Waves of the Rise in Opioid Overdose Deaths



https://www.cdc.gov/drugoverdose/epidemic/index.html

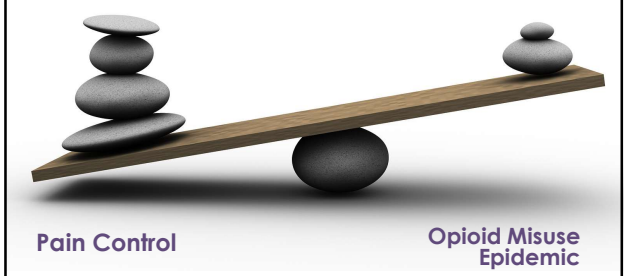
SOURCE: National Vital Statistics System Mortality File.

Released March 18, 2016

CDC Recommendations

5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to **50 morphine milligram equivalents** (MME) or more per day, and should avoid increasing dosage to 90 MME or more per day or carefully justify a decision to titrate dosage to 90 MME or more per day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. **Three days or less will often be sufficient; more than 7 days will rarely be needed.**

How Do We Achieve Balance?



Substance Use Disorder

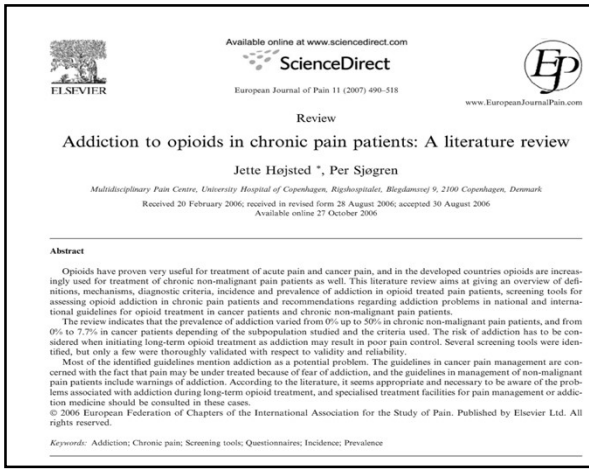
- Addiction: "chronic disease of brain reward, motivation, memory, and related circuitry," characterized by "an individual pathologically pursuing reward and/or relief by substance use and other behaviors"
- Addiction is not a choice or a moral failure
- Stigma
  - "Abuser"
  - "Frequent flyer"
- Leads to judgment, punitive beliefs rather than compassion

https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drug-abuse-addiction

Substance Use Disorders are Chronic Medical Illnesses

- Drug/alcohol continuous abstinence 1 year post discharge ~40-60%
- Optimal adherence to treatment
  - Diabetes < 60%
  - Hypertension < 40%
  - Adult onset asthma < 40%
- Proportion of patients requiring medical care to re-establish control
  - Adults with type 1 diabetes 30-50%
  - Adults with hypertension or asthma 50-70%

McLellan AT, et al. *JAMA*; 2000:284:1689-1695.



Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pain 11 (2007) 490–518
www.EuropeanJournalPain.com

Review

Addiction to opioids in chronic pain patients: A literature review

Jette Højsted *, Per Sjøgren

Multidisciplinary Pain Centre, University Hospital of Copenhagen, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark

Received 20 February 2006; received in revised form 28 August 2006; accepted 30 August 2006
Available online 27 October 2006

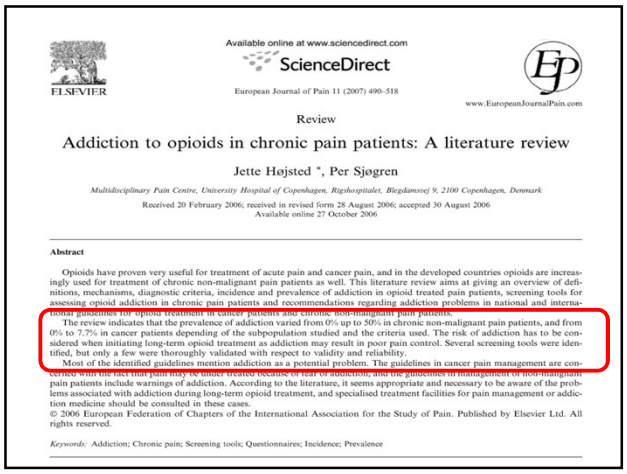
Abstract

Opioids have proven very useful for treatment of acute pain and cancer pain, and in the developed countries opioids are increasingly used for treatment of chronic non-malignant pain patients as well. This literature review aims at giving an overview of definitions, mechanisms, diagnostic criteria, incidence and prevalence of addiction in opioid treated pain patients, screening tools for assessing opioid addiction in chronic pain patients and recommendations regarding addiction problems in national and international guidelines for opioid treatment in cancer patients and chronic non-malignant pain patients.

The review indicates that the prevalence of addiction varied from 0% up to 50% in chronic non-malignant pain patients, and from 0% to 7.7% in cancer patients depending of the subpopulation studied and the criteria used. The risk of addiction has to be considered when initiating long-term opioid treatment as addiction may result in poor pain control. Several screening tools were identified, but only a few were thoroughly validated with respect to validity and reliability.

Most of the identified guidelines mention addiction as a potential problem. The guidelines in cancer pain management are concerned with the fact that pain may be under treated because of fear of addiction, and the guidelines in management of non-malignant pain patients include warnings of addiction. According to the literature, it seems appropriate and necessary to be aware of the problems associated with addiction during long-term opioid treatment, and specialised treatment facilities for pain management or addiction medicine should be consulted in these cases.

Keywords: Addiction; Chronic pain; Screening tools; Questionnaires; Incidence; Prevalence



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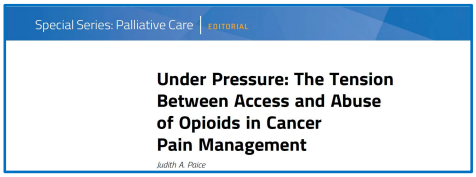


Special Series: Palliative Care | EDITORIAL

Under Pressure: The Tension Between Access and Abuse of Opioids in Cancer Pain Management

Judith A. Paice

- Similar histories of cancer and SUD (stigma, fear, blame)
- DEA reduced opioid manufacturing 25% in 2017; 20% in 2018; 10% in 2019 (of 6 frequently abused opioids)
- 444 bills proposed 2018
  - Enhanced education, develop guidelines
  - Limit opioids to certain groups, time limits (3-7 day supply, maximum dosage (100 mg OME/day)
  - Some exempt hospice/palliative care, few exempt cancer

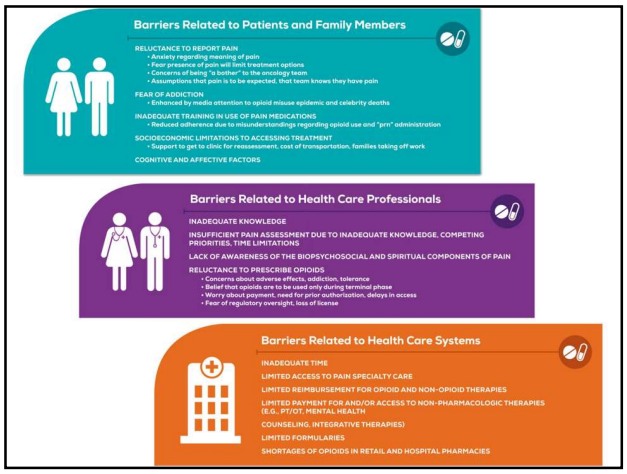
Paice JA: J Oncol Pract 2017;13(9):595-596

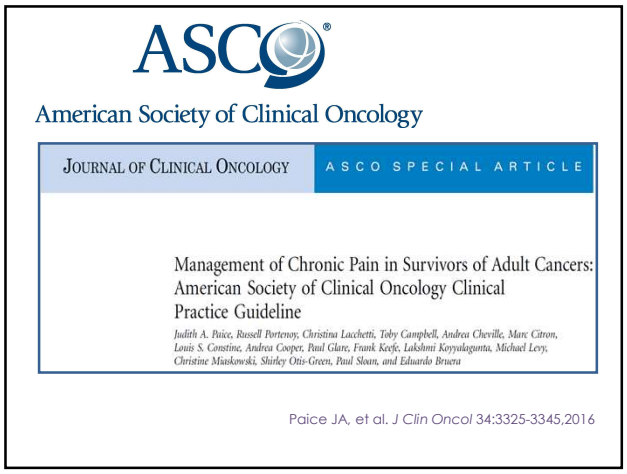
Review Article

Cancer Pain Management and the Opioid Crisis in America: How to Preserve Hard-Earned Gains in Improving the Quality of Cancer Pain Management

Judith A. Paice, PhD, RN [1,2]

Cancer 2018;124:2491-2497.





Paice JA, et al. *J Clin Oncol* 34:3325-3345,2016

What is a Cancer Survivor?

National Coalition for Cancer Survivorship
- Survivor - from the moment of diagnosis through the rest of their life

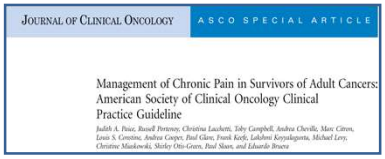
National Cancer Institute's Office of Cancer Survivorship
- Survivor is a person with a history of cancer who is beyond the acute diagnosis and treatment phase

- 14 million in the United States
- 2/3 living 5 years or longer
- Prevalence of pain 40% or higher

https://www.canceradvocacy.org/
https://cancercontrol.cancer.gov/ocs/
Van den Beuken-van Everdingen MH, et al. *J Pain Symptom Manage* 51: 1070-1090, 2016

Key Recommendations

- Screening and Comprehensive Assessment (cancer treatment syndromes)
- Treatment and Care Options
- Risk Assessment, Mitigation and Universal Precautions


JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Judith A. Paice, Russell Portenoy, Christina Lacchetti, Toby Campbell, Andrea Cheville, Marc Citron, Lewis S. Constine, Andrea Cooper, Paul Glare, Frank Keefe, Lalitomi Koyyalagunta, Michael Levy, Christine Miaskowski, Shirley Otis-Green, Paul Sloan, and Eduardo Bruera

Chemotherapy-related pain syndromes
Bony complications of long-term corticosteroids
Avascular necrosis
Vertebral compression fractures
Carpal tunnel syndrome
Chemotherapy-induced peripheral neuropathy
Raynaud's syndrome
Hormonal therapy–related pain syndromes
Arthralgias
Dyspareunia
Gynecomastia
Myalgias
Osteoporotic compression fractures
Radiation-related pain syndromes
Chest wall syndrome
Cystitis
Enteritis and proctitis
Fistula formation
Lymphedema
Myelopathy
Osteoporosis
Osteoradionecrosis and fractures
Painful secondary malignancies
Peripheral mononeuropathies
Plexopathies: brachial, sacral

Chronic Pain Syndromes Associated with Cancer Treatment

Evaluate for recurrent disease*

Paice JA, et al. *J Clin Oncol* 34:3325-3345,2016

Chronic Pain Syndromes Associated with Cancer Treatment

Stem-cell transplantation–mediated graft-versus-host disease
Arthralgias/myalgias
Dyspareunia, vaginal pain
Dysuria
Eye pain
Oral pain and reduced jaw motion
Paresthesias
Scleroderma-like skin changes
Surgical pain syndromes
Lymphedema
Postamputation phantom pain
Postmastectomy pain
Postradical neck dissection pain
Postsurgery pelvic floor pain
Post-thoractomy pain/frozen shoulder
Postsurgery extremity pain (eg, sarcoma)

Paice JA, et al. *J Clin Oncol* 34:3325-3345,2016

Nonpharmacologic Interventions

Table 4. Disciplines and Interventions for Chronic Pain

Disciplines	Examples of Possible Interventions	Strength of Evidence and Recommendation
Physical medicine and rehabilitation	Physical therapy, occupational therapy, recreational therapy, individualized exercise program, orthotics, ultrasound, heat/cold	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
Integrative therapies	Massage, acupuncture, music	Evidence-based; benefits outweigh harms; evidence quality: low; strength of recommendation: weak
Interventional therapies	Nerve blocks, neuraxial infusion (epidural/intrathecal), vertebroplasty/kyphoplasty	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
Psychological approaches	Cognitive behavioral therapy, distraction, mindfulness, relaxation, guided imagery	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
Neurostimulatory therapies	TENS, spinal cord stimulation, peripheral nerve stimulation, transcranial stimulation	Evidence-based; benefits outweigh harms; evidence quality: low; strength of recommendation: weak

Abbreviation: TENS, transcutaneous electrical nerve stimulation.

Paice JA, et al. *J Clin Oncol* 34:3325-3345,2016

Adverse Effects Associated with Long-Term Opioid Use

Persistent common adverse effects
Constipation
Mental clouding
Upper GI symptoms (pyrosis, nausea, bloating)
Endocrinopathy (hypogonadism/hyperprolactinemia)
Fatigue
Infertility
Osteoporosis/osteopenia
Reduced libido
Reduced frequency/duration or absence of menses
Neurotoxicity
Myoclonus
Other changes in mental status (including mood effects, memory problems, increased risk of falls in the elderly)
Risk of opioid-induced hyperalgesia (incidence and phenomenology uncertain, but escalating pain in tandem with dose escalation raises concern)
Sleep-disordered breathing
Increased risk of concurrent benzodiazepine in patients predisposed to sleep apnea
New-onset sleep apnea
Worsening of sleep apnea syndromes

Paice JA, et al. *J Clin Oncol* 34:3325-3345,2016

Risk Assessment

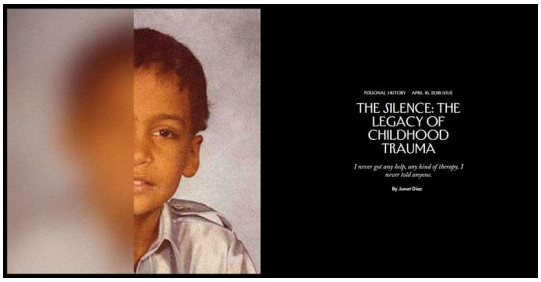
- Pain
- Function
- Misuse/abuse of drugs
  - Current/past misuse of prescription or illicit drugs
  - Alcohol, smoking, gambling
- Environmental/genetic exposure
  - Family, friends with substance misuse disorder
- Sexual abuse, PTSD

Blackhall LJ, et ak. Screening for substance abuse and diversion in Virginia hospices. *J Palliat Med* 2013;16(3):237-242.
Dev R, et al. Undocumented alcoholism and its correlation with tobacco and illegal drug use in advanced cancer patients. *Cancer* 2011;117(19):4551-4556

Table 3. Risk Factors for Substance Use Disorders

Smoking history
Past or current alcohol use disorder; risky alcohol intake (eg, binge drinking)
Past or current use of recreational substances
First use of substances at an early age (eg, 15 years of age or younger)
Family history of alcohol abuse or substance use disorder
Trauma (eg, sexual abuse, posttraumatic stress disorder)
Legal problems, history of incarceration, other issues

Paice JA. Managing cancer pain during an opioid epidemic. *Oncology* 2018; 32(8)

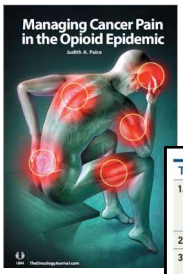


https://www.newyorker.com/magazine/2018/04/16/the-silence-the-legacy-of-childhood-trauma

Universal Precautions

- Prescription Drug Monitoring Programs
- Urine toxicology
- Agreements/contracts

Starrels JL, et al. Systematic review: treatment agreements and urine drug testing to reduce opioid misuse in patients with chronic pain. *Ann Intern Med* 2010;152(11):712-720.



Oncology 2018; 32(8)

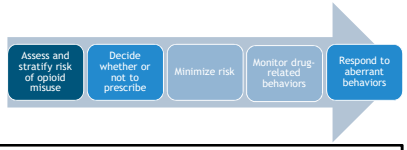


Table 4. Universal Precautions for Opioid Use in Chronic Cancer Pain Management

1. Assess pain and risk of opioid misuse.	• Assess pain and risk for substance use disorder. • Conduct examination and review medical record. • Review prescription drug monitoring program. • Conduct urine drug screening.
2. Decide whether or not to prescribe.	• Stratify risk of diversion and abuse.
3. Minimize risk.	• Optimize adjuvant analgesics. • Use multimodal pain therapy. • Obtain treatment for psychiatric illness, including anxiety, depression, and sleep disorders.
4. Monitor drug-related behaviors.	• Evaluate effectiveness (decreased intensity and improved function). • Review and treat adverse effects. • Monitor adherence.
5. Respond to aberrant behaviors.	• Assess for behaviors that may indicate uncontrolled pain, compulsive use, use to treat other conditions (anxiety, depression, sleep), or diversion. • Intervene by prescribing small amounts at shorter intervals, using pill counts, and using drug screening more frequently. • Consult psychiatric and/or addiction specialists.

Data from: Paice et al. J Clin Oncol. 2016;[6].

Structure Based Upon Risk

Minimal Structure

- Annual urine toxicology
- Review of PDMP every 3 months
- Clinic appointments every 3 months
- Prescriptions provided for 30 day supply – may provide 3 prescriptions (e.g. "may fill on or after June 1, 2019")

Higher Structure

- Frequent urine toxicology
- Review of PDMP with each refill
- Reassess pain, function, aberrant behaviors frequently; reconsider need
- Prescriptions provided for 1-2 week supply
- Engage family
- Taper when indicated
- Refer to addiction specialist

Issuance of multiple prescriptions for Schedule II controlled substances. Diversion Control Division, Drug Enforcement Agency. https://www.deadiversion.usdoj.gov/faq/mult_rx_faq.htm

Paice JA. Risk assessment and monitoring of patients with cancer receiving opioid therapy. *The Oncologist* 2019; 24: 1-5

When Opioids are No Longer Beneficial: Weaning

- Slow downward titration – 10% reduction/week
- Offer psychosocial support
- Optimize nonopioids and adjuvant analgesics
- Use antidepressants rather than benzodiazepines to treat irritability and sleep disturbances
- Provide a clear verbal and written plan

The Management of Opioid Therapy for Chronic Pain Working Group. *VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain* Washington, DC; 2010.
Chou R, et al: Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain* 10:113-30, 2009

Safe Storage & Disposal

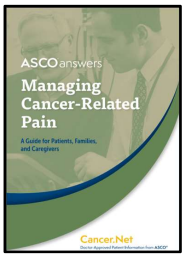
- Educate patients/families regarding safe medication practices
  - Don't leave medications out, medicine cabinet
  - Lock boxes
- Safe disposal
  - Take back programs – pharmacies, police depts
  - Mix drug in wet coffee grounds or kitty litter until dissolved, then dispose in garbage – do not flush down toilet (FDA recommends flushing opioids)

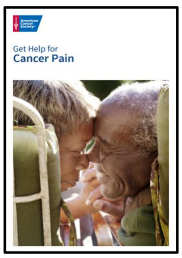
National Take Back Day
October 26, 2019

DEA NATIONAL Rx TAKE BACK

www.deadiversion.usdoj.gov

Educational Tools



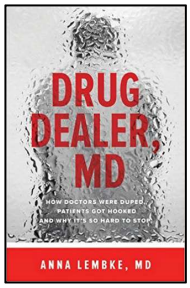


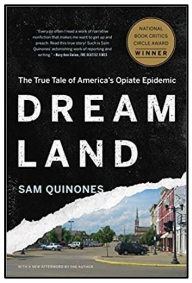
https://www.cancer.net/sites/cancer.net/files/managing_pain_booklet.pdf
https://www.cancer.net/sites/cancer.net/files/asco_answers_safe_storage_and_disposal.pdf
https://www.cancer.org/content/dam/cancer-org/cancer-control/en/booklets-flyers/get-help-for-cancer-pain.pdf

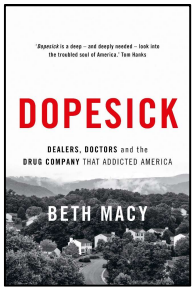
Solutions

- Research
- Education
- Evidence based guidelines for managing pain in those with current/past history of SUD
- Access to care – pain, addiction, mental health counseling, PT/OT

- Partnerships
- Be aware of implicit bias
- Advocate!







The New York Times

Opinion

LETTERS

Ways to Address the Opioid Crisis

To the Editor:

Your editorial about the opioid crisis brought to mind the words of the great American journalist H. L. Mencken: "For every complex problem there is an answer that is clear, simple and wrong." Ignoring the social determinants that drive drug use and minimizing the critical medical roles of pain assessment and opioids, as your editorial does, are a disservice to those struggling with opioid dependence and those suffering from pain.

A few scientific facts: Heroin is now the most frequent opioid of first illicit use, not legally prescribed opioids. Heroin and synthetic fentanyl account for most opioid-related deaths, and their use is rising. Concurrently, 100 million Americans experience pain that impairs their ability to work, delays surgical recovery, causes depression and reduces life expectancy.

We do not minimize the contributions of drug advertising and inappropriate prescribing on the opioid epidemic. We do not disagree that we need better education in pain management, prescription monitoring systems and nonopioid treatments.

But unless we meaningfully address the complex problems of poverty and lack of gainful employment, mental illness and social isolation, we are creating a solution that is not only wrong but will also lead to unnecessary suffering for millions.

R. SEAN MORRISON
JAMES CLEARY, NEW YORK

"Never doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it is the only thing that ever has".

Margaret Mead

GIST & Other Sarcomas: Making Sense of a Rare Family of Cancers
Robert Maki, MD, PhD, FACP
Professor, Northwell-Hofstra Medical School
Professor, Cold Springs Harbor Laboratory

GIST & other sarcomas :
making sense of a rare family of cancers

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Northwell-Hofstra Medical School and
Cold Spring Harbor Laboratory
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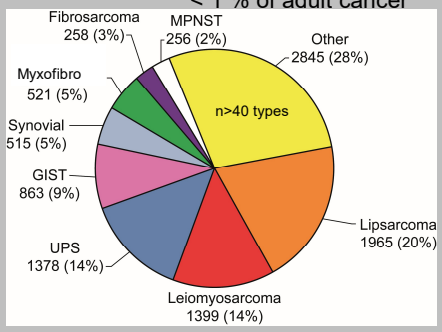
Today's outline

- Identify the most common forms of sarcoma and other connective tissue neoplasms
- Review newer GIST and sarcoma trials to highlight the data that impact daily practice

Soft tissue sarcoma (STS) – 12 750 cases per year (USA)

50+ subtypes

< 1 % of adult cancer

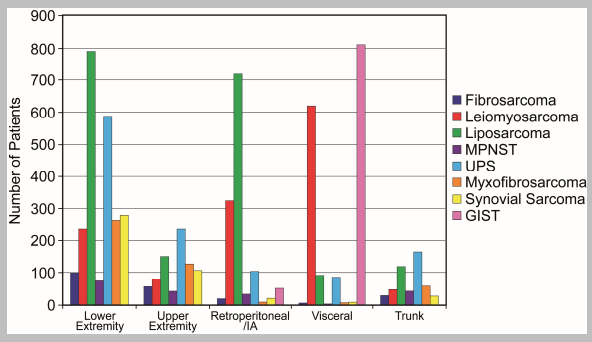


n = 10 000

1982-2015

Brennan MF et al. Management of soft tissue sarcomas, Springer, 2017.

STS histology as function of anatomy



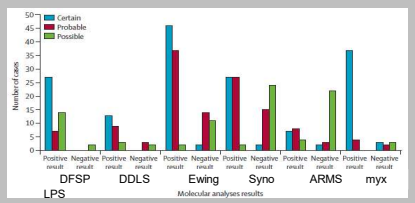
Brennan MF et al. Management of soft tissue sarcomas, Springer, 2017.

Two general classes of sarcomas

- Single specific genomic abnormality
  - Somatic translocations generating fusion oncogenes
    - Lots of these…especially in patients under age 40
  - Activating point mutations
    - *KIT* or *PDGFRA* in GIST (or other alterations)
    - *CTNNB1* in some desmoid tumors
  - Tumor suppressor gene inactivation
    - *SMARCB1 - INI1/SNF5* in rhabdoid tumors, epithelioid sarcomas
    - *NF1* in MPNST (but also aneuploidy)
    - *APC* in some desmoid tumors
  - Larger scale gene amplifications
    - *MDM2* and *CDK4* in WD/DD liposarcomas, surface osteosarcomas, etc
- Multiple, complex genomic aberrancies: chromothripsis?
  - Like most other cancers
    - Leiomyosarcoma
    - Undifferentiated pleomorphic sarcoma (UPS)
    - Osteogenic sarcoma

The pathologist is the most important clinician in sarcoma management

- 20% of diagnoses were changed when reviewed at an expert center
- In sarcoma, even the experts have to be humble



- **32 French centers**
- **Prospective study**
- **n = 384 sarcomas**

Pathologist commits to dx, molecular diagnostic then run

Diagnosis changed in 53 / 384 cases, management/prognosis in 46

Italiano A et al. Lancet Oncol 2016; 17: 532

What is one to do about all these different diagnoses?

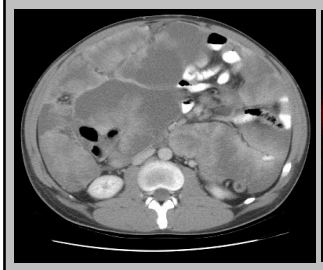
Understand a few types and you understand many sarcomas

- GIST
  - Imatinib, sunitinib, regorafenib for metastatic disease
  - 3 years adjuvant imatinib for intermediate to high risk primary disease
- Liposarcoma (3 genetic flavors)
- Leiomyosarcoma
- Undifferentiated pleomorphic sarcoma (ex-MFH)
- Synovial sarcoma

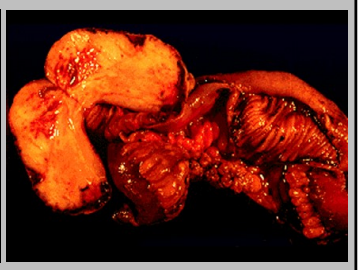
GIST

- ? Most common sarcoma
- Most driven by *KIT* mutation
- Well defined strategy for management
  - 3 years adjuvant imatinib for higher risk tumors
  - Metastatic disease mantra: imatinib, sunitinib, regorafenib
  - New positive phase III trial in 4th line: ripretinib (DCC2618)
  - Pending data on another agent (avapritinib, BLU-285)

Gastrointestinal stromal tumor (GIST)



Large necrotic masses on CT scan



GIST in wall of ileum

Gastrointestinal stromal tumor (GIST)

- Former “GI leiomyosarcoma”, GANT, other terms
- KIT (CD117)+ , CD34+, DOG1+ (ANO1)
- Origin: interstitial cells of Cajal (or precursors)
  - Pacemaker cells of gut
- Impervious to cytotoxic chemotherapy
- Most common gastrointestinal sarcoma
  - 10-12 / million incidence
  - ~3 500 in US in 2019 of ~16 000 sarcomas, 1.76 M cancers
  - Some epidemiology studies indicate 4 000-6 000 per year

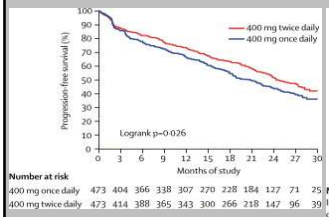
First line metastatic GIST

Imatinib & GIST: unique among sarcomas

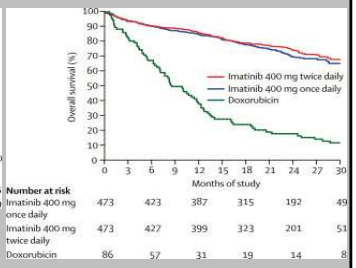
- Lab data showed imatinib is active
- Single patient and Phase I activity
- Phase II study: >50% response rate
- Phase III studies:
  - Europe/Australia: n>900
  - U.S.: n>700
- FDA, EMA, other regulators approved Rx
- Adjuvant studies
  - 0 vs 1 year (ACOSOG Z9001)
  - 1 year vs 3 years (SSG XVIII)

1st line metastatic GIST: 400 vs 800 mg qd

Progression-free Survival



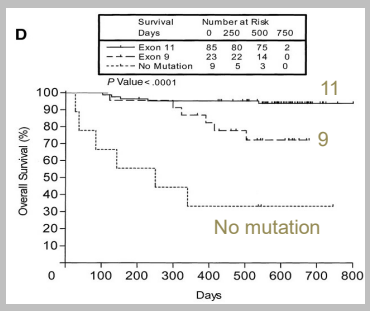
Overall Survival



946 allocated patients

Verweij J et al. Lancet 2004; 364:1127

KIT genotype predicts survival for patients with metastatic GIST on imatinib



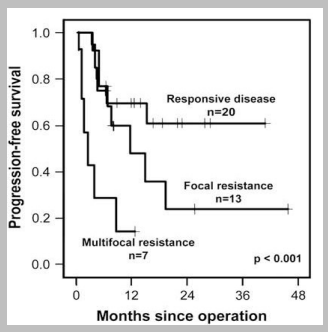
Heinrich MC et al. J Clin Oncol. 2003; 21: 4342

Second line metastatic GIST

Imatinib resistance: what then?

- 1st line standard of care: 400 mg oral daily for most patients
- Increase dose to (up to) 400 mg PO BID upon progression
- Surgery if “limited progression”
- Sunitinib remains 2nd line standard of care

(Active) tumor bulk and TTP

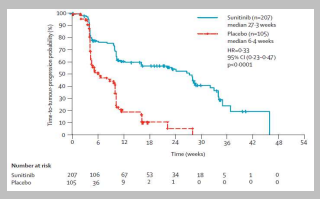


DeMatteo RP et al. Ann Surg 2007;245:347

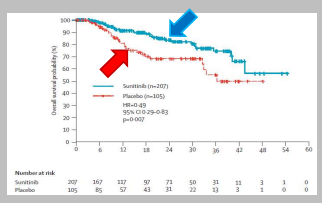
Sunitinib in GIST

- Positive phase III placebo vs. sunitinib study
- FDA approved dose/schedule:
  - 50 mg daily x 28 q 42 days
  - Investigational: 37.5 mg oral daily
- *Never tested* in the imatinib-naïve state

Sunitinib vs placebo phase III



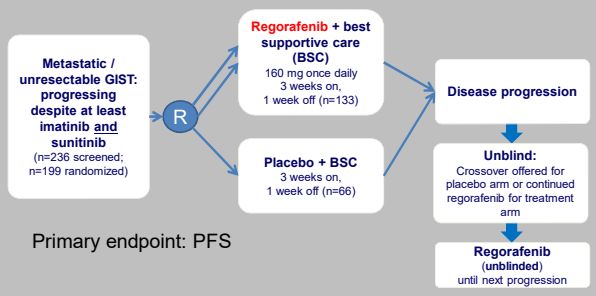
PFS



OS

Demetri GD et al. Lancet 2006; 368:1329

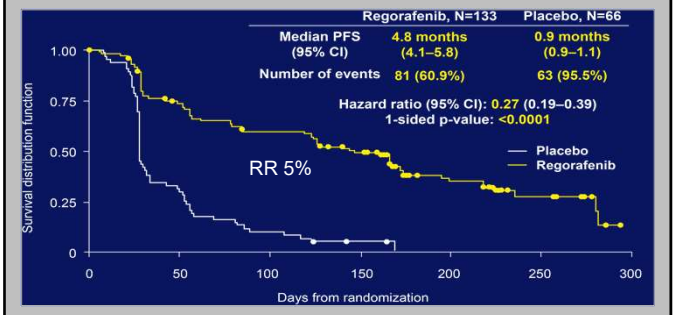
Regorafenib phase III in metastatic GIST



Primary endpoint: PFS

Demetri GD et al. Lancet. 2013; 381:295

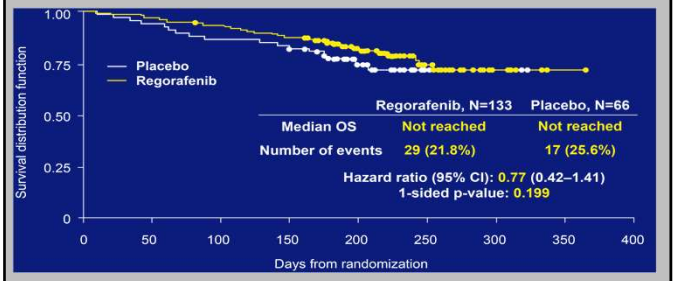
GRID phase III results



Demetri GD et al. Lancet. 2013; 381:295

GRID study: overall survival

(following 85% cross-over of patients on placebo arm)



Because of the crossover design,
lack of statistical significance between regorafenib and placebo was **expected**

Demetri GD et al. Lancet. 2013; 381: 295

Newer kinase inhibitors

- (+) Phase III trial in 4th line, n=129
  - **Ripretinib** (DCC2618) vs. placebo, crossover allowed
  - Press release 08/13/2019
- mPFS 6.3 mo vs. 1 mo, HR = 0.15, p<0.0001
  - RR 9% vs 0%, p=0.0504
  - mOS 15.1 mo vs. 6.6 mo, nominal p=0.004, but was dependent upon RR endpoint
    - Should placebo have been allowed ?
- Principal AEs
  - Alopecia (52% vs 5%), Nausea (39% vs 12%), Fatigue (42% vs 23%), Myalgia (32% vs 12%), Diarrhea (28% vs 14%), PPE (21% vs. 0%), Headache (19% vs 5%), Incr bili (16% v s. 0%)

Another new GIST targeted agent : avapritinib = BLU-285

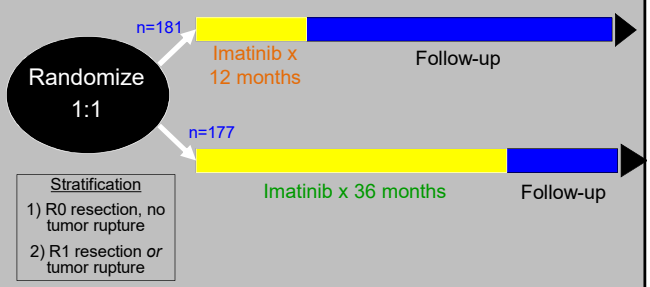
- Phase I study shows activity in several GIST molecular subtypes, esp *KIT* exon 17, *PDGFRA* D842V
- N=40 phase I, 30→600 mg oral qd
  - 7 PR, 10 SD in PDGFRA D842V patients, ORR 41%
  - 2 PR, 5 SD in KIT mutant pts Rx at at least 135 mg qd
- AEs: Nausea (48%), fatigue (45%), peripheral edema, periorbital edema, vomiting (30% each), diarrhea (25%), anemia, dizziness, and lacrimation (23% each)

Heinrich MC et al. Proc ASCO 2017; Abstr 11011

GIST: Adjuvant therapy

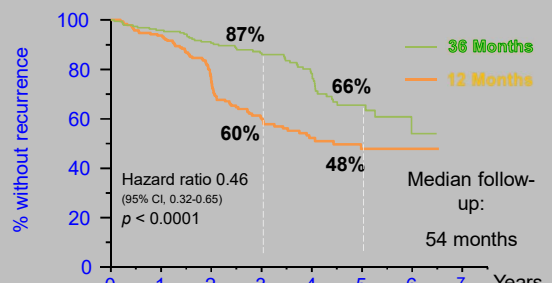
SSG XVIII: study design

Open-label phase III study



Joensuu H et al. JAMA 2012; 307:1265

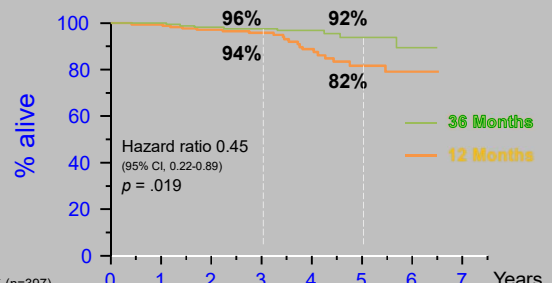
SSG XVIII: recurrence-free survival (ITT)



No. at risk (n=397)								
36 Months of imatinib	198	184	173	133	82	39	8	0
12 Months of imatinib	199	177	137	88	49	27	10	0

Joensuu H et al. JAMA 2012; 307:1265

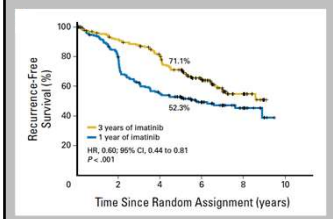
SSG XVIII: overall survival (ITT)

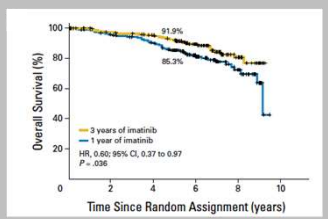


No. at risk (n=397)								
36 Months of imatinib	198	192	184	152	100	56	13	0
12 Months of imatinib	199	188	176	140	87	46	20	0

Joensuu H et al. JAMA 2012; 307:1265

Updated data: continued decay of benefit of treated group over time





Joensuu H et al. JCO 2015; 34: 244

If you choose to give adjuvant imatinib, choose higher risk patients?

Size	Mitoses (per 50 hpf)	Recurrence risk (%) Gastric	Jejunal, ileal	Duodenal	Rectal
≤ 2 cm	≤ 5	0	0	0	0
2-5 cm	≤ 5	2	4	8	9
5-10 cm	≤ 5	4	24	--	--
>10 cm	≤ 5	12	52	34	57*
≤ 2 cm	> 5	0*	50*	No cases	54
2-5 cm	> 5	16	73	50	52
5-10 cm	> 5	55	85	--	--
>10 cm	> 5	86	90	86	71

* Small number of cases in this subset

Adapted from Miettinen and Lasota, Semin Diagn Pathol 2006; 23: 70

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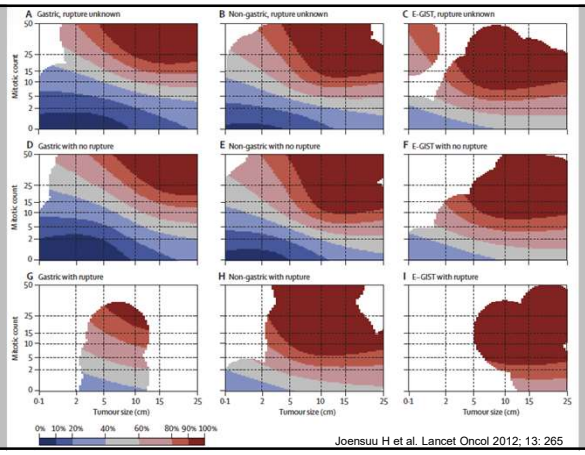
Adapted from Miettinen and Lasota, Semin Diagn Pathol 2006; 23: 70

Not the entire story?
Risk stratification heat map

- Patient data on 2 560 patients from 10 studies collated, in era before adjuvant imatinib
- Size, mitotic rate, anatomic primary site, tumor rupture status included as independent prognostic factors
- No data on molecular testing included

Joensuu H et al. Lancet Oncol 2012; 13: 265



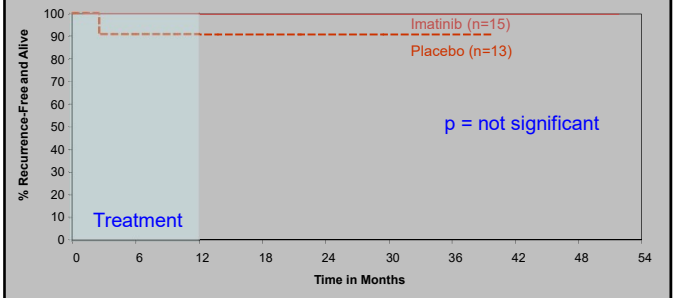
Joensuu H et al. Lancet Oncol 2012; 13: 265

Mutation status: another layer of complexity

- Most GIST have exon 11 *KIT* mutations
- What about GIST with other mutations?
- Imatinib is probably helpful only *PDGFRA* mutations **not** involving D842V
- Data from Z9001 (0 vs 1 year adj imatinib Rx)
  - Data so far unavailable from SSG XVIII
- Further useful data from 1500 patient retrospective analysis from era before imatinib

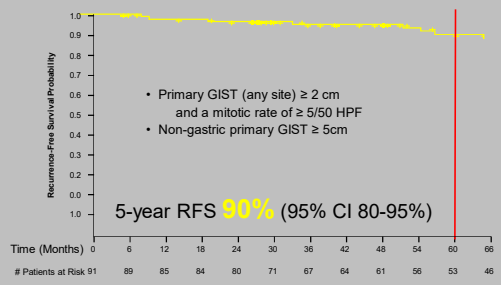
Joensuu H et al. J Clin Oncol. 2015; 33:634

RFS for *PDGFRA* D842V patients by arm: 1 year imatinib vs placebo Z9001 trial



Corless CL et al. J Clin Oncol. 2014; 32:1563

Newer trial: higher risk GIST, phase II imatinib 5 year Rx



Corless CL et al. J Clin Oncol. 2014; 32:1563

GIST adjuvant therapy 2019

- High risk GIST, completely resected: 3 years adjuvant imatinib
- New SSG study examining 3 vs 5 years imatinib for highest risk GIST

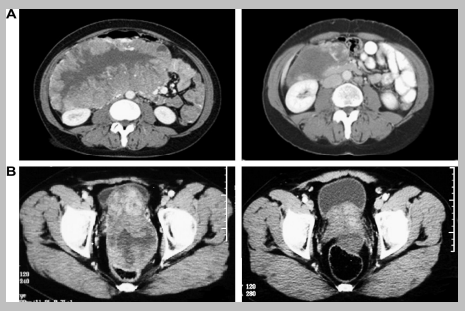
Subtypes that appear to benefit
- *KIT* exon 11 mutation
- *PDGFRA* mutation (non-D842V)

Subtypes that appear to NOT benefit (incomplete data)
- *KIT* exon 9
- *PDGFRA* D842V
- Wild type

Joensuu H et al. J Clin Oncol. 2015; 33:634
Corless CL et al. J Clin Oncol. 2014; 32:1563

"Unresectable" GIST: neoadjuvant therapy

Options for very large GIST



0 +7-15 mo

Rutkowski P et al. J Surg Oncol 2006; 93:304
Fiore M et al. Eur J Surg Oncol 2009; 35: 739

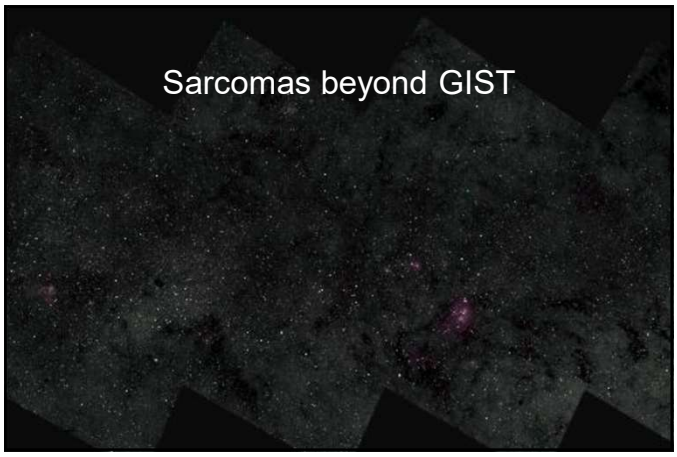
Neoadjuvant imatinib

- Try to restrict to exon 11 *KIT* mutant GIST
- Neoadjuvant imatinib 400 mg daily
- Resect at time of best response
  - Usually 3-9 months
- *Nearly all patients recur off imatinib*
- Continue treatment post-op for a total of at least 3 years (adjuvant data)…or even longer?

Rutkowski P et al. J Surg Oncol 2006; 93:304
Fiore M et al. Eur J Surg Oncol 2009; 35: 739

Progression on imatinib, sunitinib, regorafenib: what to do

- Soon: Ripretinib (DCC2618)
- Continue last TKI if tolerated
- Another TKI – nothing else yet approved
  - Ponatinib
  - Dasatinib
- Add an mTOR inhibitor
- Imatinib rechallenge



1. Adjuvant / neoadjuvant therapy of STS

Pediatric sarcoma: standard of care: a reminder

- Ewing sarcoma (U.S. Rx)
  - Vincristine – doxorubicin – cyclophosphamide alternating with ifosfamide – etoposide (VAC-IE)
  - Cycle every 2-3 weeks (2 weeks in children where possible, no proved benefit in adults) – supports the Norton-Simon hypothesis
- Osteogenic sarcoma
  - Cisplatin – Doxorubicin backbone
  - Methotrexate: used in younger patients despite lack of randomized data
  - MTP-PE where available (not in the US, but that's another story)
  - Ifosfamide: not helpful in the adjuvant setting
- Rhabdomyosarcoma
  - Usually VAC-IE or Vincristine-Dactinomycin-Cyclophosphamide for pediatric subtypes

Largest adjuvant study in adults: no survival advantage for doxorubicin + ifosfamide (AIM)

- Largest randomized study of adjuvant AIM in STS
  - 351 pts recruited, 1995-2003
  - 5 cycles of doxorubicin 75 mg/m2 + ifosfamide 5 gm/m2 q21 days
- Interim analysis for futility led to early study closure

	Estimated 5 yr RFS	Estimated 5 yr OS
Treatment	52%	64%
Observation	52%	69%

- The hypothesis that adjuvant chemotherapy improves recurrence free survival and overall survival was *rejected*.

Woll PJ et al, Lancet Oncol 2012; 13: 1045

However…2008 meta-analysis showed improved survival for ifosfamide-based therapy

- Largest adjuvant study compiled to date
- Update to a 1997 meta-analysis
  - Greater use of ifosfamide
  - 18 trials
  - 1953 pts
- New data are still needed…

HAZARD RATIOS	Overall survival
Any chemo	0.77 (p=0.01)
Dox only	0.84 (p=0.09)
Dox + Ifos	0.56 (p=0.01)

Pervaiz N et al. Cancer 2008; 113: 573

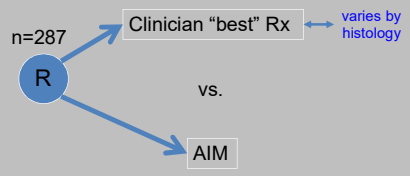
STS adjuvant therapy: general suggestions

- Greatest benefit : males over age 40
  - RFS, not OS benefit seen from two pooled studies (n>800)
  - Benefit to men or age over 40
  - Patients had inferior RFS if female or under age 40
  - Not beneficial in older patients over 60 (hard to give ifosfamide)
- Some histologies do NOT benefit – avoid in ASPS, clear cell sarcoma, SFT, EHE…
- Rule out situations where it is less likely to help, then 1:1 conversation

Le Cesne A et al. Ann Oncol. 2014; 25:2425

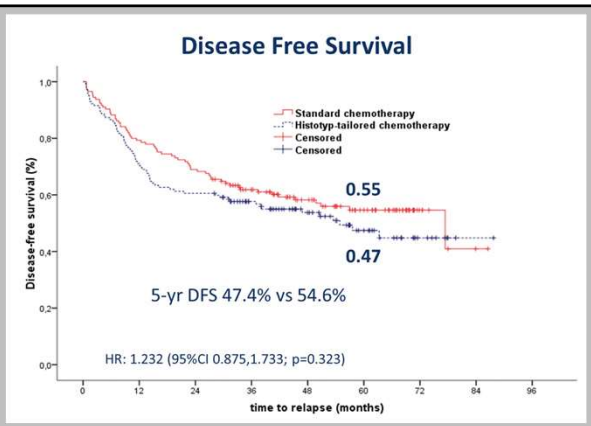
Neoadjuvant data: a different story? tailored vs standard Rx

- STS Dx:

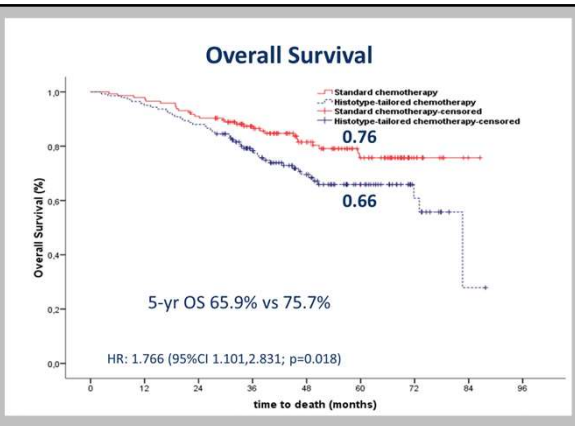


- Outcomes
  - RFS
  - Overall survival

Gronchi A et al. Lancet Oncol. 2017; 18:812



Gronchi A et al. Lancet Oncol. 2017; 18:812



Gronchi A et al. Lancet Oncol. 2017; 18:812

Totally opposite result than expected

- AIM better than tailored therapy
  - This was comparison to active therapy, not placebo
  - Nominal p-value superior for standard therapy
  - …but this was NOT the primary endpoint of the study
  - Histology tailored therapy “not superior” and probably worse
  - Is this an issue of neoadjuvant therapy vs adjuvant therapy
  - Is this an issue of epirubicin over doxorubicin?

2. First-line treatment of metastatic STS

1st line chemotherapy for metastatic STS

EORTC 62012

Eligibility
- High grade STS (2-3)
- Age 18-60
- No previous chemo for advanced/metastatic disease
- WHO PS < 2

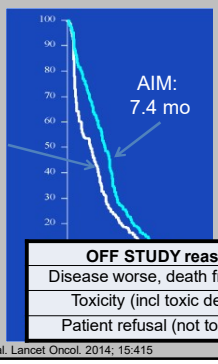
Stratification:
- Age (<50 vs ≥50)
- PS (0 vs 1)
- Liver metastases (0 vs +)
- Histological grade (2 vs 3)

R

- Single-agent Doxorubicin (75 mg/m^2 bolus or as a 72 hour continous i.v. infusion)
- Doxorubicin 25 mg/m^2 d 1-3 + Ifosfamide 2.5 g/m^2 d 1-4 + PEG-Filgrastim 6 mg s.c. d5

Judson I et al. Lancet Oncol. 2014; 15:415

EORTC 62012: progression free survival, response rate, and overall survival



PFS HR = 0.74 (95%CI 0.6– 0.9)
Stratified log-rank p=0.003

RR:
27% AIM
14% doxorubicin

OS HR = 0.83 (95%CI 0.67–1.03)
Stratified log-rank p=0.08

OFF STUDY reason	DOX	DOX+IFOS
Disease worse, death from PD	42%	21%
Toxicity (incl toxic death)	3%	**18%**
Patient refusal (not toxicity)	2%	4%

Judson I et al. Lancet Oncol. 2014; 15:415

2015 1st line study

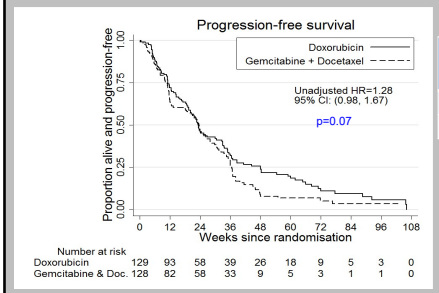
- GEDDiS : Gemcitabine – Docetaxel vs Doxorubicin as 1st line therapy for sarcoma
  - U.K. randomized phase II trial
  - Predominance of leiomyosarcomas on study
  - Bottom line: No PFS difference, no OS difference
  - Gemcitabine-docetaxel more expensive

Seddon B et al. Clin Sarcoma Res 2015; 5:13

GeDDiS Trial

Gemcitabine + Docetaxel vs Doxorubicin

Similar Progression-Free Survival



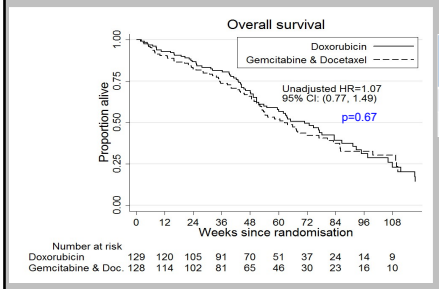
	Median PFS (months)	24 week PFS
Dox	5.4	46%
G / D	5.5	46%

Seddon B et al. Clin Sarcoma Res 2015; 5:13

GeDDiS Trial

Gemcitabine + Docetaxel vs Doxorubicin

Similar Overall Survival



	Median OS (months)	24 week OS
Dox	16.4	87%
G / D	14.5	82%

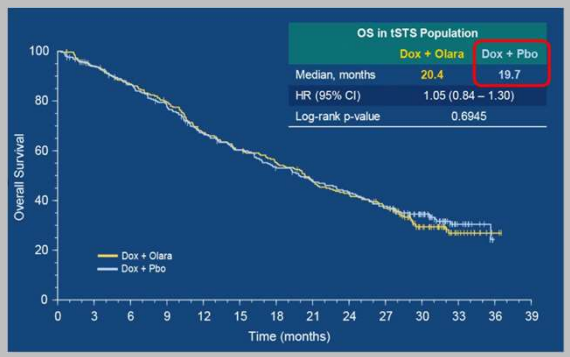
Seddon B et al. Clin Sarcoma Res 2015; 5:13

Best 1st line treatment for metastatic STS?

- Are there symptoms from advanced disease?
  - If **yes**, combination regimens might have better chance of symptom-alleviating responses.
  - If **no** symptoms, single agents are reasonable
  - Doxorubicin and gemcitabine-docetaxel yielded similar results
- Also consider Rx based on histology

	MORE active	LESS active
Synovial sarcoma	Ifosfamide	Gemcitabine-docetaxel
Myxoid-round cell liposarcoma	Trabectedin, ifosfamide	Gemcitabine-docetaxel
Angiosarcoma	Taxanes, anthracyclines	Ifosfamide
Leiomyosarcoma, SFT	Anthracycline, DTIC	Ifosfamide
ASPS, SFT	VEGFR inhibitors	Doxorubicin, Gemcitabine-docetaxel
Endometrial stromal sarcoma	Anti-estrogens, ifosfamide	Gemcitabine-docetaxel

Olaratumab: here yesterday, gone today



Tap W et al. Proc ASCO 2019, Late breaking abstract

Final thoughts on newer agents

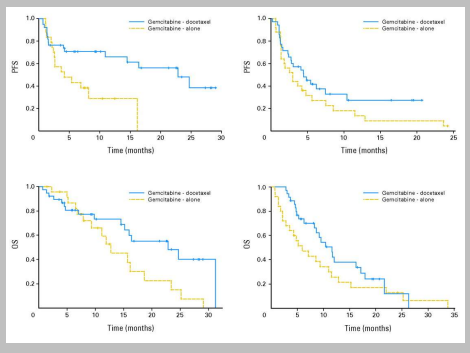
- We are back to doxorubicin or doxorubicin / ifosfamide
- Doxorubicin / ifosfamide OK if a response is needed quickly
- Doxorubicin alone is otherwise still a good standard of care
- GeDDiS: OK to use gem-docetaxel in 1st line as well

2nd+ line therapy for metastatic STS

2nd+ line: Gemcitabine & docetaxel > gemcitabine

PFS

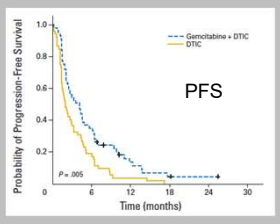
OS



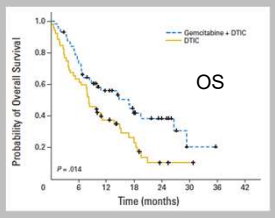
ECOG = 0 ECOG > 0

Maki RG et al. JCO 2007; 25:2755

2nd+ line: Gemcitabine/DTIC > DTIC



PFS



OS

Median PFS DTIC: 2 mo
Gem+DTIC : 4.2 mo

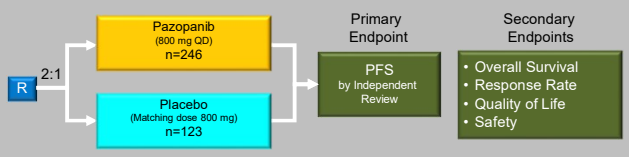
Median OS DTIC : 8.2 mo
Gem+DTIC : 16.8 mo

RR DTIC: 4%
Gem+DTIC : 12%

Garcia del Muro X et al. JCO 2011; 29: 2528

Newer choices for 2nd+ line metastatic STS therapy

Phase III study in chemo-refractory STS
Pazopanib vs placebo, no crossover



n = 369

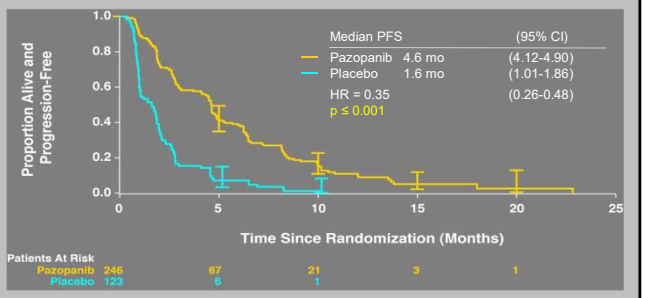
Stratification Factors:

- Performance status
- Prior lines of systemic therapy for advanced disease

Van der Graaf WTA et al. Lancet Oncol 2012; 379: 1879

Pazopanib significantly improved PFS in metastatic STS progressing after standard chemotherapy

Overall survival not improved on pazopanib



Van der Graaf WTA et al. Lancet Oncol 2012; 379: 1879

One slide on other agents

- **Trabectedin**: Approved for beyond 1st line therapy for leiomyosarcoma and liposarcoma based on phase II, III trials
  - Myxoid / round cell liposarcoma best target for this drug
- **Eribulin** approved beyond 1st line for metastatic liposarcoma only
  - Pleomorphic liposarcoma probably best target of this agent

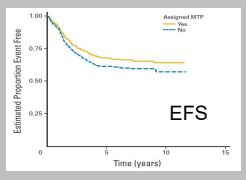
Bottom line: 2nd+ line therapy for STS

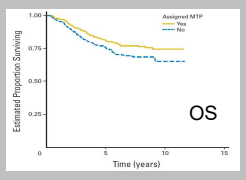
- Trabectedin approved in US for liposarcoma and leiomyosarcoma
  - Translocation sarcomas appear a good target also
- Eribulin only approved in US for liposarcoma
  - Still encompasses three histologies
- Pazopanib approved in STS other than liposarcoma
  - Also not approved for GIST

But who care about anything except immunotherapy?

Non-specific immunotherapy

- Mifamurtide: Muramyl tripeptide or MTP - nonspecific immunotherapy for osteogenic sarcoma





- Akin to BCG story in bladder cancer?
- Limiting factor: approved in Europe, elsewhere, not in US
- Could this work in other sarcomas?

Meyers PA et al. JCO 2008; 26: 633

Key initial US immunotherapy trials

- SARC 28: anti-PD1 mAb
- Alliance: anti-PD1 mAb ± anti-CTLA4
  - Cooperative group-wide, 300+ centers, 80 pts
- Academic and industrial trials
  - PD1 and PDL1 mAb combination phase I studies
- T cell based therapy
  - NCI, MSKCC, CHOP (NY ESO 1)
  - Univ Washington (NY ESO 1)
  - NCI (mesothelin, VEGF, others)

SARC28

- Phase II: n=40 soft tissue tumors + n=40 bone tumors
- Pembrolizumab single agent 200 mg IV q3wk
- Median follow up ~ 18 mo
- Only 3/70 tumors PDL1(+):
  - -- 3 were UPS
  - -- all 3 had CD8+ T cell infiltration
- 7 / 40 patients with PR; 11% with immune related SAE

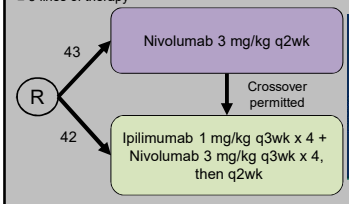
UPS:	1/10 CR, 3/10 PR
DD LPS:	2/10 PR
Leiomyosarcoma:	n=10, no responses
Synovial:	1/10 PR
Osteosarcoma:	1/22 PR
Chondrosarcoma:	1/5 PR (dediff chondro)
Ewing sarcoma:	0/13 PR

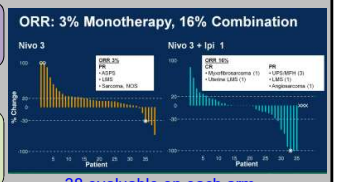
Tawbi HA et al. Lancet Oncol 2017; 18: 1493

ALLIANCE nivo ± ipi

Randomized phase II

58% had received ≥ 3 lines of therapy





38 evaluable on each arm

Primary endpoint:
RECIST response rate
(5/38 = promising)
Pick the winner / non comparative

PR
ASPS
LMS
Sarcoma NOS

CR
Myxofibro
ULMS

PR
UPS (3)
LMS
Angio

D'Angelo SP et al. Lancet Oncol. 2018; 19:416

ALLIANCE nivo ± ipi

Randomized phase II

Combination vs nivolumab alone:

mPFS: 4.5 vs 2.6 mo

6 mo PFS: 36 vs 16%

mOS: 14.3 vs 10.7 mo

D'Angelo SP et al. Lancet Oncol. 2018; 19:416

GSF-GETO phase II

Pembrolizumab + cyclophosphamide

- Cyclophosphamide used to ?decrease Treg
- Cy 50 mg oral BID x 7 days ➜ off 7 days, 14 d cycle
- Pembrolizumab 200 mg IV q3wk
- n=57, 50 evaluable
- 1 PR in UPS patient, 3 total with any tumor shrinking
- 6 mo non progression rate 0, 0, 11%, 14% in LMS, UPS, GIST, other sarcomas
- Only responder was PDL1+ (>10%)
- High IDO expression and Kyn/W ratio noted

Toulmonde M JAMA Oncol. 2018; 4:93

Talimogene laherparepvec (T-VEC) & pembrolizumab in (locally adv +) metastatic STS

- n=20 patients presented
- Pembro 200 mg IV every 3 weeks, T-VEC ≤ 4 cc
- Primary endpoint = PR or better at 24 weeks
- Histologies of treated patients: **n=**
  - Leiomyosarcoma 5
  - Cutaneous angiosarcoma 3
  - Sarcoma NOS 3
  - UPS 2
  - Other specific sarcoma 7
- 4 PR, 9 SD among 19 evaluable patients
- No G4-5 toxicity

Kelly CM et al. Proc ASCO 2018; Abstr 11516

STS ImmunoRx: other smaller studies

- Nivolumab with no activity in ULMS (0/12)
- Engineered T cells against NY-ESO-1 active vs synovial sarcoma
- Axitinib and pembrolizumab active vs alveolar soft part sarcoma (ASPS), but responding patients have low TMB
- Thus: aneuploidy / mutation burden in and of itself does not seem the sole reason for responses

Wilky BA et al. Lancet Oncol 2019; 20: 837

Summary

- Get the diagnosis right
  - Good pathology review
  - Argument can be made for molecular testing for all, given French data
- Standard cytotoxic and kinase-directed therapy are better defined for many sarcoma subtypes as of 2019
- Antigen-specific and -independent cancer immunotherapy is in its infancy
  - **Synovial sarcoma** and **myxoid-round cell liposarcoma** are prime targets
  - Since translocation sarcomas have so few mutations, highly aneuploid tumors may be the best targets for immune checkpoint inhibitors
- Epigenetic and other new classes of agents are also exciting routes to pursue
  - Combination with immunotherapeutics?

Thank you for your attention

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Geriatric Assessment for Older Adults with Cancer

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Wake Forest School of Medicine