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Melanoma Neoadjuvant Therapy with Kinase Inhibitors

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US Food & Drug Administriation (FDA)
And Melanoma Research Alliance (MRA)
Approaches to Neoadjuvant Treatment in Melanoma:
A Public Workshop Organized by the FDA and MRA

Session 2: Current Melanoma Neoadjuvant Experience

November 6, 2019

Disclosure information

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Session 2: Current Melanoma Neoadjuvant Experience
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Melanoma Neoadjuvant Therapy with Kinase Inhibitors

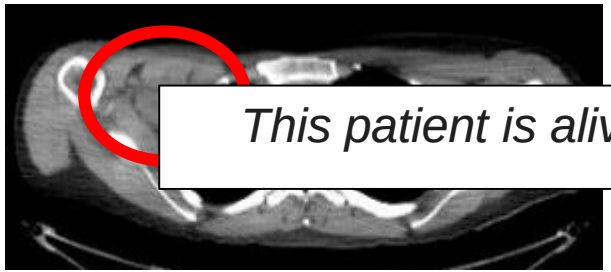
Jennifer A. Wargo MD MMSc

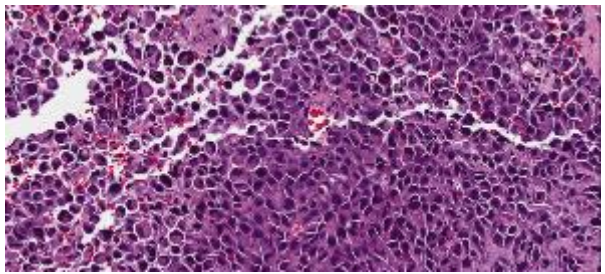
- I have the following financial relationships to disclose:

- Speaker's bureau: Imedex, Dava, Omniprex, Illumina, BMS
- Advisory board member: Roche - Genentech, GSK, Novartis, Astra-Zeneca
- Clinical trial support: Roche - Genentech, GSK, BMS, Novartis

Case example

- 45 yo female with prior hx of R arm melanoma presented in October 2013 with bulky adenopathy in R axilla (unresectable). She was referred to MDACC where a biopsy showed a $BRAF^{V600E}$ mutation

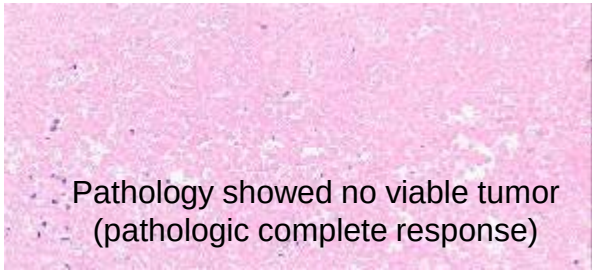




October 2013

neoadjuvant BRAF/MEK inhibitors and restaging showed a complete response

She was taken to surgery for an axillary lymph node dissection

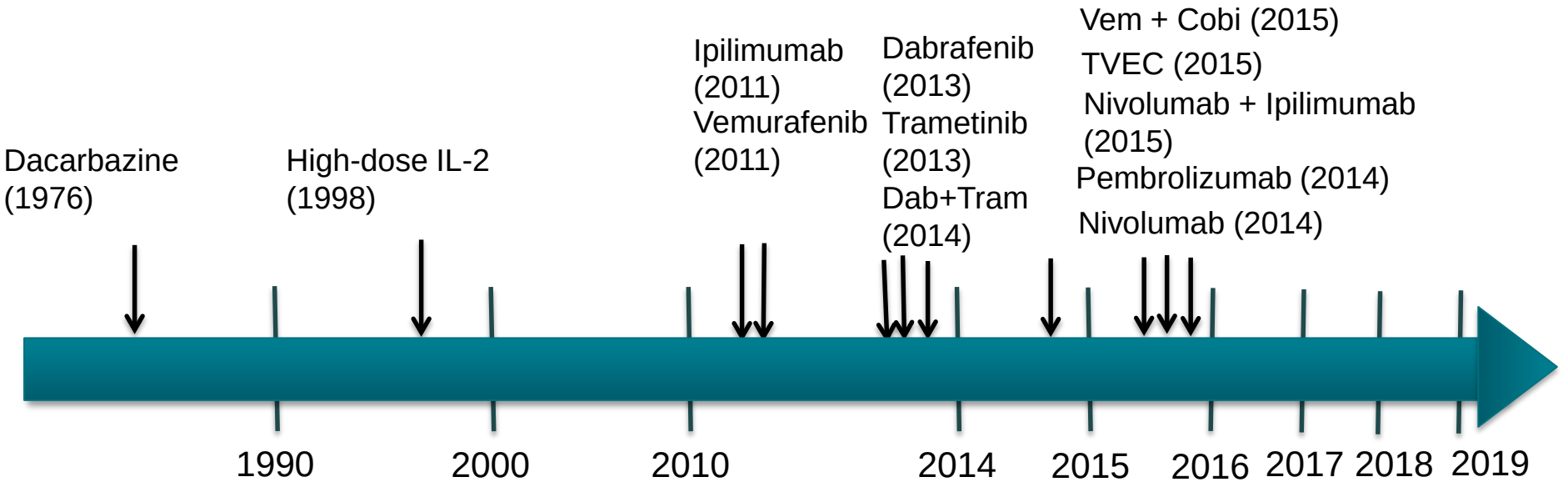


December 2013

This patient is alive, well, and free of disease 6 years later…

We have made major advances in the treatment of melanoma and other cancers through the use of targeted therapy and immunotherapy

FDA-approved agents for stage IV melanoma



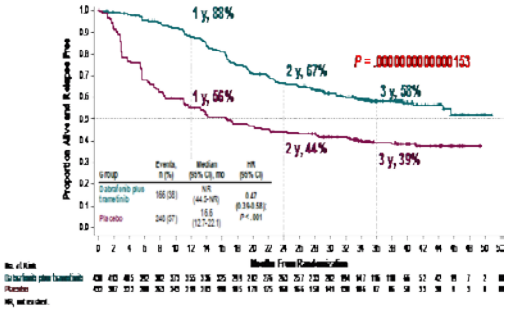
These agents are now being used successfully across the spectrum of disease (alone or in combination with other therapies) and in other cancer types

Dab, dabrafenib; FDA, Food and Drug Administration; IL-2, interleukin 2; Tram, trametinib – www.FDA.gov

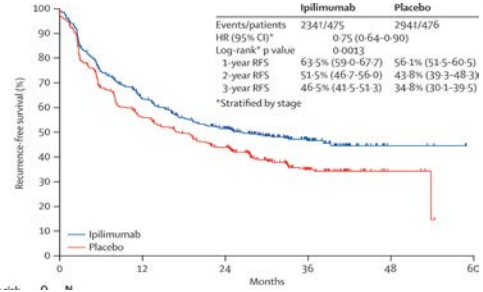
This includes the use of targeted therapy and immunotherapy in the adjuvant setting (i.e. after surgical resection for earlier stage disease)

And there is a strong rationale to use these in the "neoadjuvant" setting

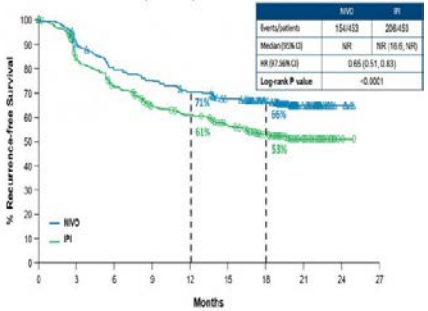
COMBI-AD



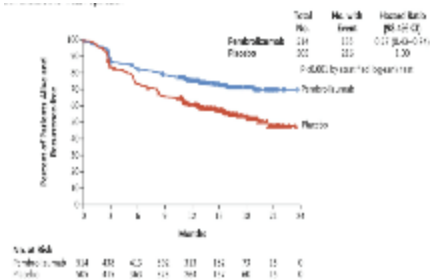
EORTC 1871

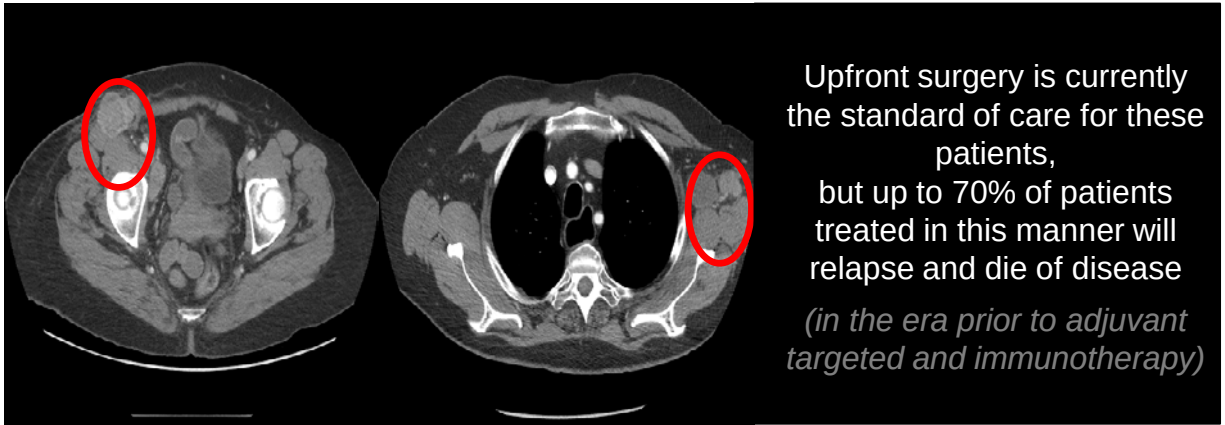


Checkmate 238



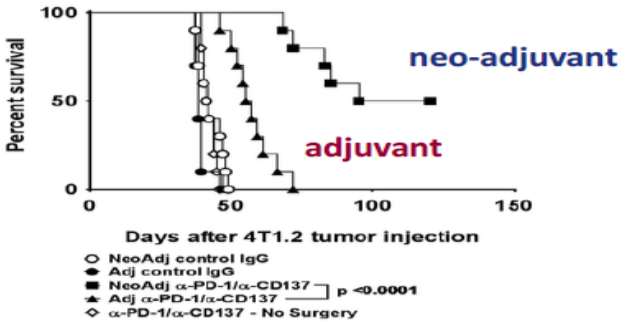
Keynote 054





Upfront surgery is currently the standard of care for these patients,
but up to 70% of patients treated in this manner will relapse and die of disease

(in the era prior to adjuvant targeted and immunotherapy)



Liu, et al., Cancer Discovery 2016

Pre-clinical models suggest improved outcomes in neoadjuvant vs. adjuvant treatment

We first studied the use of neoadjuvant targeted therapy in patients with high-risk resectable melanoma with a BRAF mutation

Phase II trial to test the hypothesis that treatment with neoadjuvant (+ adjuvant) BRAF/MEK inhibitors would improve RFS over SOC upfront surgery

Patients with resectable stage IIIB/IIIC melanoma, + BRAF mutation

n=28

Arm A
SOC -Upfront surgery

Surgical resection

SOC adjuvant therapy

Clinical and radiographic follow up

Pathologic

Trial was stopped by the DSMB early due to major differences in outcomes

survival, toxicity

n=56

Arm B
Neoadjuvant BRAFi/MEKi x 8 weeks

CT scans with RECIST, Surgical resection

Adjuvant BRAF/MEK x 44 weeks

Clinical and radiographic follow up

Biopsy & blood draw

Biopsy & blood draw on-treatment (wk 3, 5)

Biopsy & blood draw at surgery

Blood draws q 3 months with restaging

Biopsy & blood draw on relapse

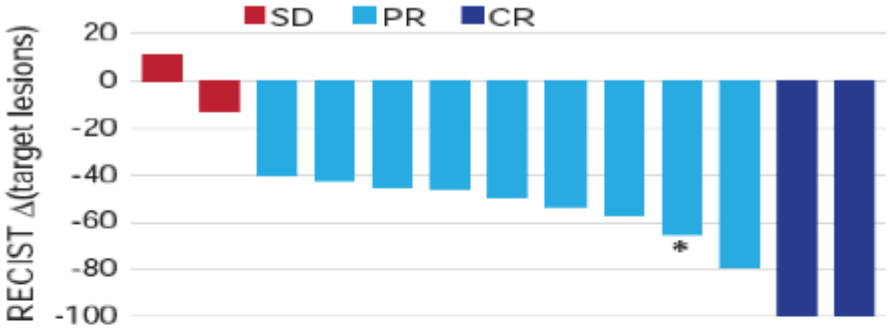
Molecular & immune profiling in longitudinal tissue and blood samples

Roda Amaria MD

Amaria, Prieto et al, Lancet Oncology 2018

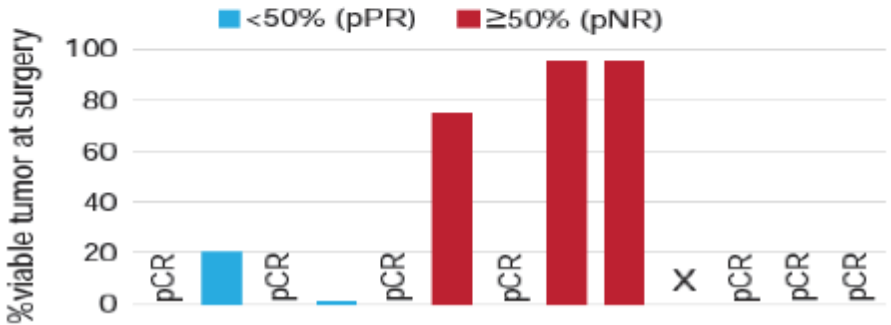
Peter Prieto MD MPH

Treatment with neoadjuvant BRAF/MEKi was associated with a high RECIST response rate and pCR rate, and improved RFS over SOC surgery

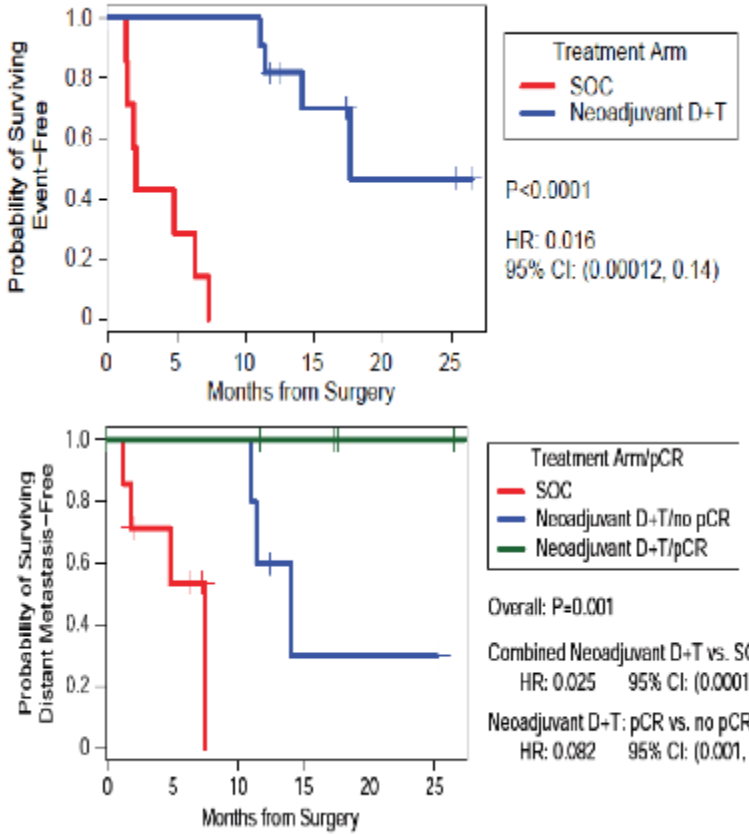


RECIST response rate 85%

No correlation between RECIST and path responses



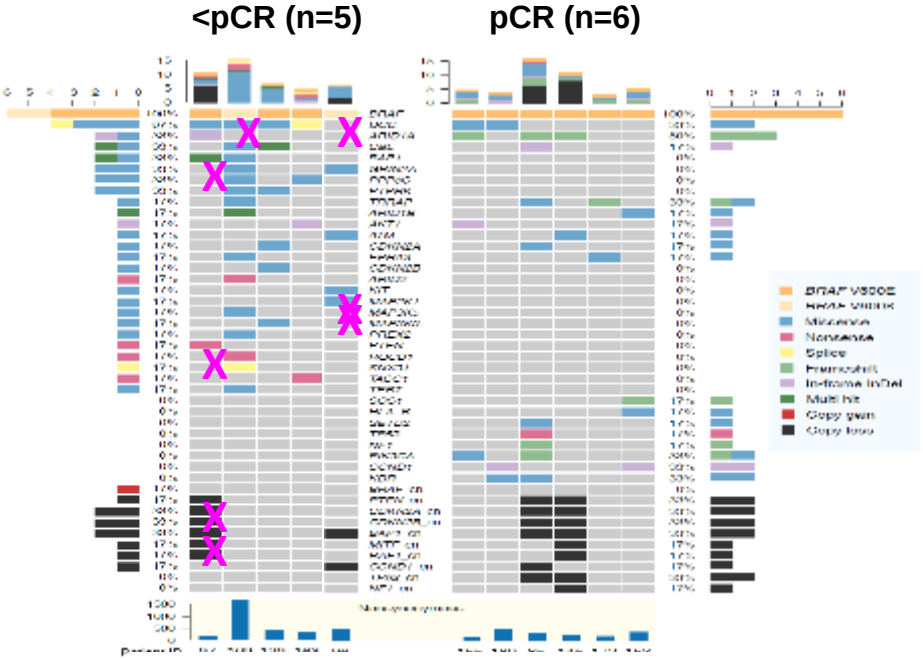
Path CR rate 58%



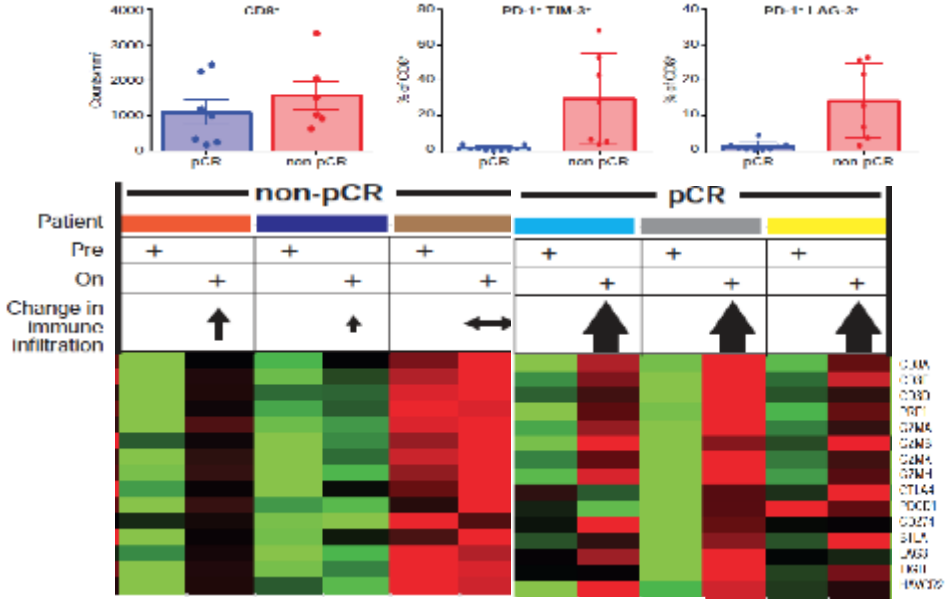
Amaria, Prieto et al, Lancet Oncology 2018

Correlative studies on longitudinal tumor samples revealed potential predictors / targets of therapeutic resistance

Patients with < pCR had a higher frequency of known resistance conferring mutations (activating MAPK)

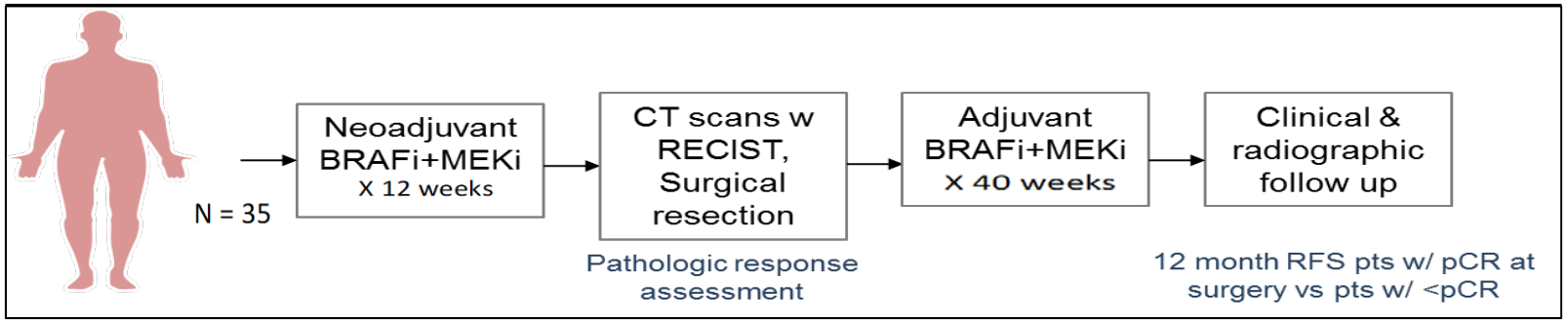


Immune mechanisms of therapeutic resistance were also identified, with high expression of PD-1, Tim-3, Lag-3 in TILs of pts with < pCR and failure to induce an immune infiltrate in early on-treatment biopsies

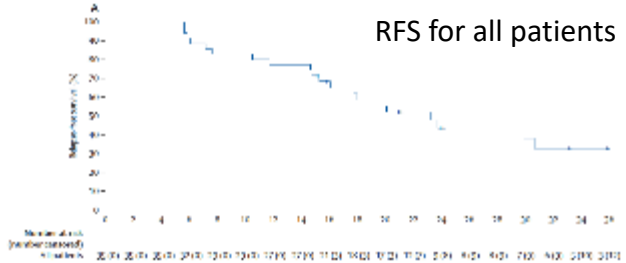


Amaria, Prieto et al, Lancet Oncology 2018

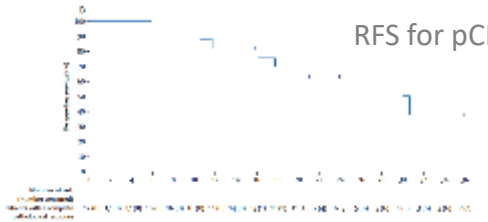
Importantly, other groups have run neoadjuvant targeted therapy trials with similar results (RECIST response 86%, pCR rate 49%)



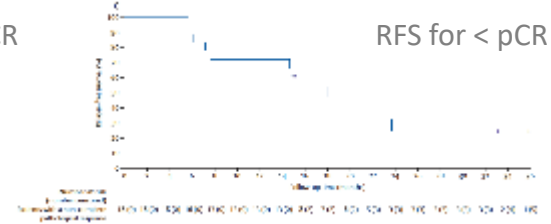
RFS for all patients



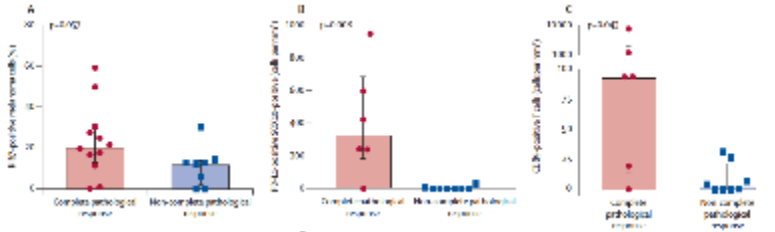
RFS for pCR



RFS for < pCR



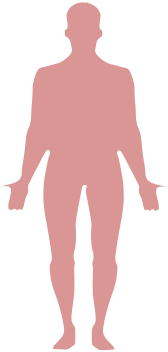
Patients who had a pCR had a higher proliferative index in melanoma cells within the tumor, higher PD-L1 expression, and higher baseline CD8+ T cell



Long, et al Lancet Oncology 2019

We also studied the use of neoadjuvant immune checkpoint blockade in patients with high-risk resectable melanoma

Phase II trial to test the hypothesis that treatment with neoadjuvant (+ adjuvant) checkpoint blockade would enhance responses in this subset of patients



Patients with resectable stage IIIB/IIIC melanoma, no brain mets or prior ICB

Stratify by Stage and

Ipi 3mg/kg + Nivo 1 mg/kg q 3 wks x 3 doses (n=20)

Nivo 3mg/kg q 2 wks x 4 doses (n=20)

RECIST restaging and

Nivo 3 mg/kg

months

Trial was stopped early given some signals on efficacy and toxicity

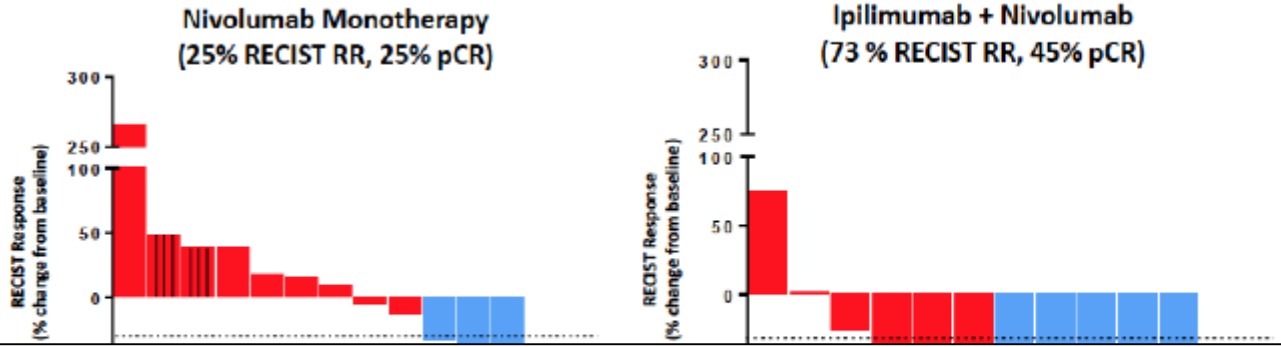
Primary Endpoint:
Path response
Secondary endpdoints:
-IST
-FS
-DMFS
-OS
-Toxicity
- correlatives

Molecular & immune profiling in longitudinal tissue and blood samples

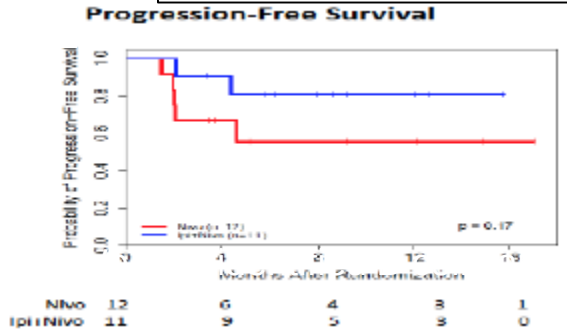
Roda Amaria MD

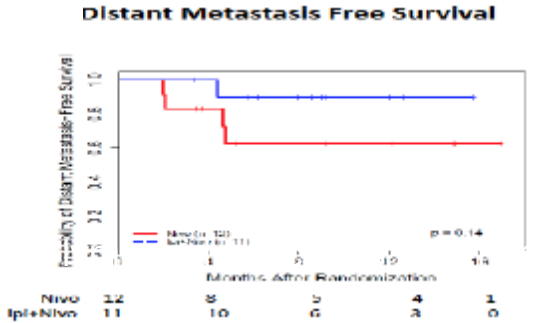
Sangeetha Reddy MD MS

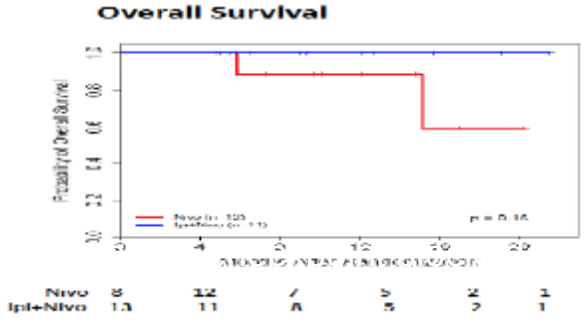
Treatment with neoadjuvant Ipi Nivo was associated with a higher RECIST response rate and pCR rate, and improved RFS over Nivo monotherapy



But with a much higher rate of ≥ grade 3 adverse events
(which is improved with altered dose regimens as published by others)







Amaria Reddy et al, Nature Medicine 2018

Importantly, investigators worldwide have come together to establish an International Neoadjuvant Melanoma Consortium (www.melanoma-inc.org)

INTERNATIONAL NEOADJUVANT MELANOMA CONSORTIUM
INMC

Who We Are

- >240 International Members
- Pharma engagement
- Multidisciplinary
- Pooled analyses
- White papers & guidelines

Our Goals

1. Consistent trial design across international sites
2. Align translational plans and efforts to understand biology of response and resistance
3. Develop a platform for rapid drug development
4. Determine if neoadjuvant therapy is superior to adjuvant therapy

ESMO

Annals of Oncology 0: 1–8, 2018
doi:10.1093/annonc/mdy226
Published online 25 June 2018

ORIGINAL ARTICLE

Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma

M. T. Tetzlaff[1,2*], J. L. Messina[3], J. E. Stein[4], X. Xu[5], R. N. Amaria[6], C. U. Blank[7], B. A. van de Wiel[7], P. M. Ferguson[8], R. V. Rawson[8], M. I. Ross[9], A. J. Spillane[10], J. E. Gershenwald[9,11], R. P. M. Saw[8], A. C. J. van Akkooi[7], W. J. van Houdt[7], T. C. Mitchell[12], A. M. Menzies[10], G. V. Long[13], J. A. Wargo[9,14], M. A. Davies[2,6,15], V. G. Prieto[1,16], J. M. Taube[4†] & R. A. Scolyer[8†]

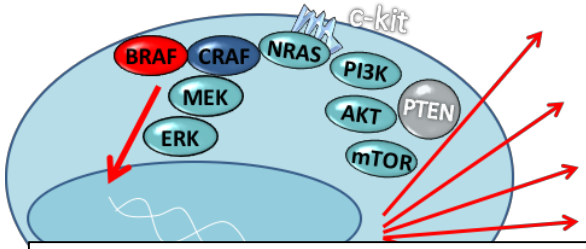
Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium

Rodabe N Amaria, Alexander M Menzies*, Elizabeth M Burton*, Richard A Scolyer*, Michael T Tetzlaff*, Robert Antdbacka, Charlotte Ariyan, Roland Bassett, Brett Carter, Adil Daud, Mark Faries, Leslie A Fecher, Keith Flaherty, Jeffrey E Gershenwald, Omid Hamid, Angela Hong, John Kirkwood, Serigne Lo, Kim Margolin, Jane Messina, Michael Postow, Helen Rizos, Merrick I Ross, Elisa A Rozeman, Robyn P M Saw, Vernon Sondak, Ryan J Sullivan, Janis M Taube, John F Thompson, Bart A van de Wiel, Alexander M Eggermont, Michael A Davies, The International Neoadjuvant Melanoma Consortium members†, Paolo A Ascierto†, Andrew J Spillane†, Alexander C J van Akkooi†, Jennifer A Wargo†, Christian U Blank†, Hussein A Tawbi†, Georgina V Long†*

How can we further improve responses to neoadjuvant therapy in melanoma?

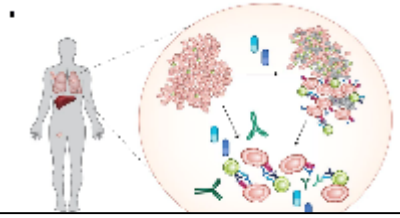
Targeted therapy can be combined with immunotherapy to improve responses

We know that oncogenic mutations may lead to immune evasion and blocking them can make tumors more immunogenic

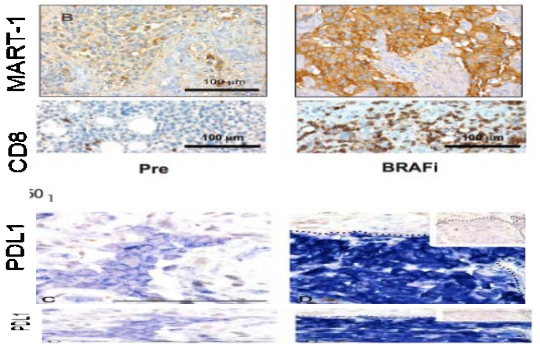


3 papers were co-published in Nature Medicine this year demonstrating efficacy of this approach in patients with advanced melanoma

Rozemann & Blank, Nature Medicine 2019



Neoadjuvant melanoma trials are now being designed and are underway assessing the use of combined targeted therapy and immunotherapy



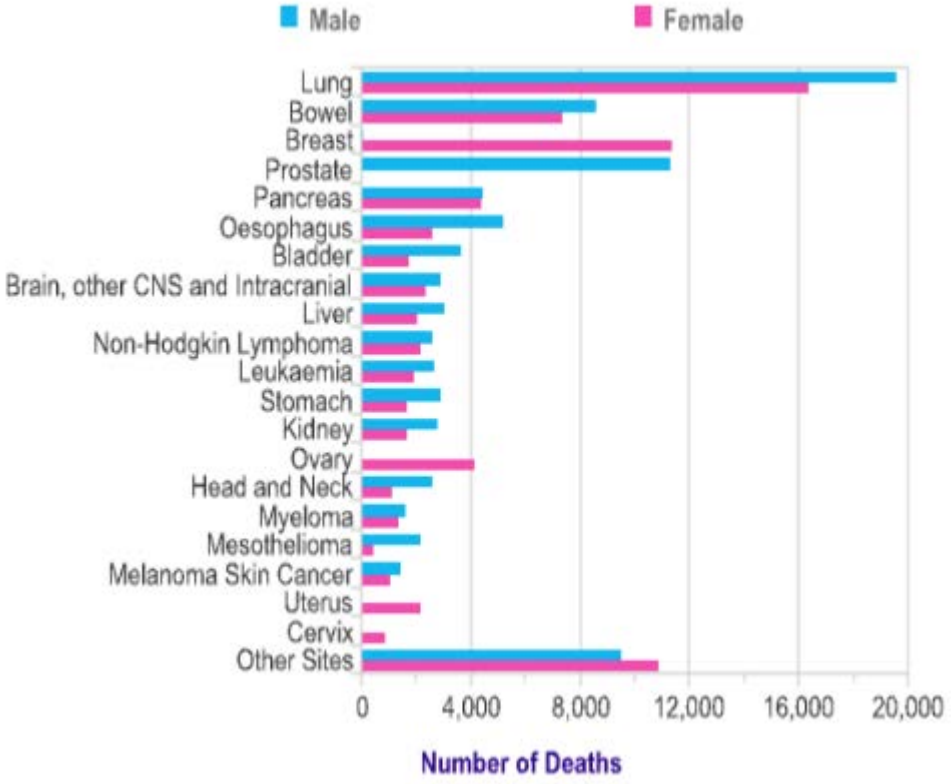
Providing the rationale for combining targeted therapy with immune checkpoint blockade

Combined BRAF and MEK inhibition with PD-1 blockade immunotherapy in *BRAF*-mutant melanoma

Dabrafenib, trametinib and pembrolizumab or placebo in *BRAF*-mutant melanoma

Atezolizumab plus cobimetinib and vemurafenib in *BRAF*-mutated melanoma patients

What about the role of gender / sex hormones on cancer & therapy response?



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JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

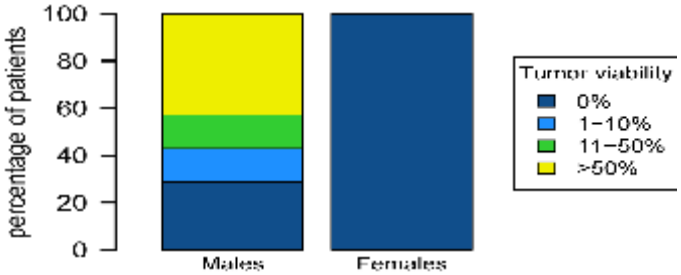
Sex Differences in Efficacy and Toxicity of Systemic Treatments: An Undervalued Issue in the Era of Precision Oncology

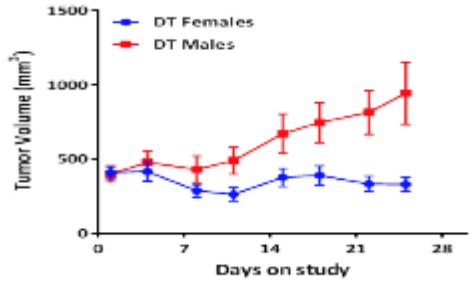
Berna C. Özdemir, *Lausanne University Hospital; and International Cancer Prevention Institute, Lausanne, Switzerland*
Chantal Csajka, *Lausanne University Hospital; and University of Lausanne, Lausanne, Switzerland*
Gian-Paolo Dotto, *International Cancer Prevention Institute; University of Lausanne, Lausanne, Switzerland; and Massachusetts General Hospital, Charlestown, MA*
Anna Dorothea Wagner, *Lausanne University Hospital, Lausanne, Switzerland*

Ozdemir et al, JCO 2018

In one of our neoadjuvant studies, we noted a strong sexual dimorphism in response to therapy (which was confirmed in additional cohorts)

Patients who achieved pCR to neoadjuvant targeted therapy had long-term benefit *(and a majority of these patients were female)*





We validated these findings in a murine model

(and gained insights into potential mechanisms – appear to be hormonal)

Sex-specific differences are also noted in immunity and may impact response to immunotehrapy

Variation of immune cell responses in humans reveals sex-specific coordinated signaling across cell types

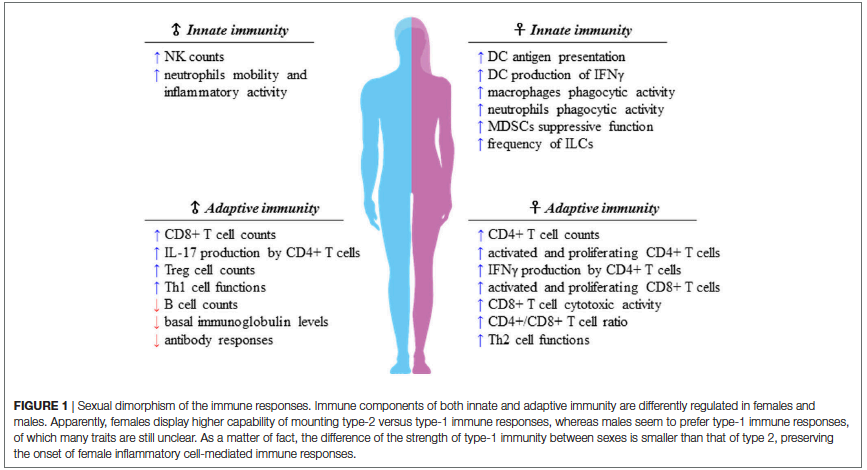


FIGURE 1 | Sexual dimorphism of the immune responses. Immune components of both innate and adaptive immunity are differently regulated in females and males. Apparently, females display higher capability of mounting type-2 versus type-1 immune responses, whereas males seem to prefer type-1 immune responses, of which many traits are still unclear. As a matter of fact, the difference of the strength of type-1 immunity between sexes is smaller than that of type 2, preserving the onset of female inflammatory cell-mediated immune responses.

Miles Andrews MD PhD

Swathi Arur PhD

Tim Heffernan PhD

Fragiadakis…Nolan et al, bioRxiv 2018; Capone et al, Frontiers Immunology 2018

Conclusions and potential implications of these findings:

- Treatment with neoadjuvant targeted therapy in melanoma is associated with high response rates (via RECIST) and high pathologic complete response rates
- Achieving a pCR is a good surrogate for long-term benefit in melanoma patients treated with neoadjuvant targeted therapy, however patients who achieve a pCR may still relapse (particularly within the CNS)
- As we move forward, we need to embrace a concerted and organized effort with novel clinical trial designs and a “Team Science” approach – with interrogation of novel biomarkers and strategies to improve therapeutic responses
- There is still a great deal to learn, and the strongest gains are made through collaboration (*and we owe this to our patients*)

Thank you

- All the staff, patients and families across the trials
- INMC membership group

Georgina Long
Christian Blank
Roda Amaria
Liz Burton
Hussein Tawbi
Richard Scolyer
Mike Tetzlaff
Andrew Spillane
Alexander van Akkooi
Paolo Ascierto
Michael Davies

Jeff Gershenwald
Omid Hamid
Angela Hong
John Kirkwood
Robert Andtbacka
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Adil Daud
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Leslie Fecher
Keith Flaherty

Lisette Rozeman
Serigne Lo
Robyn Saw
Helen Rizos
Bart van de Wiel
Kim Margolin
Jane Messina
Michael Postow
Merrick Ross
Vernon Sondak
Janis Taube
John Thompson
Ryan Sullivan
Alexander Eggermont

Cogdill, Andrews, Wargo *British Journal of Cancer (submitted)*