Melanoma Neoadjuvant Therapy with Kinase Inhibitors

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US Food & Drug Administration (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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Melanoma Neoadjuvant Therapy with Kinase Inhibitors

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• 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.

Pathology showed no viable tumor (pathologic complete response).

She was treated with neoadjuvant BRAF/MEK inhibitors and restaging showed a complete response.

She was taken to surgery for an axillary lymph node dissection.

Pathology showed no viable tumor (pathologic complete response).

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**

- Dacarbazine (1976)
- High-dose IL-2 (1998)
- Ipilimumab (2011)
- Vemurafenib (2011)
- Dabrafenib (2013)
- Trametinib (2013)
- Dabrafenib + Trametinib (2014)
- Pembrolizumab (2014)
- Nivolumab (2014)
- Nivolumab + Ipilimumab (2015)
- Vem + Cobi (2015)
- TVEC (2015)
- Vem + Cobi (2015)
- Nivolumab + Ipilimumab (2015)
- Pembrolizumab (2014)
- Nivolumab (2014)

*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

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

**Arm A**
SOC - Upfront surgery

**Arm B**
Neoadjuvant BRAFi/MEKi x 8 weeks

**Clinical and radiographic follow-up**
CT scans with RECIST, Surgical resection

**Adjuvant BRAF/MEK x 44 weeks**

**Pathologic assessment (pCR rate)**
Assess relapse-free survival, overall survival, toxicity

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

Blood draws q 3 months with restaging

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

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.
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%)

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

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)

Stratify by Stage and PDL1 Status

Primary Endpoint: Path response
Secondary endpoints:
- RECIST
- RFS
- DMFS
- OS
- Toxicity
- correlatives

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

Trial was stopped early given some signals on efficacy and toxicity

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

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

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

Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma
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.
What about the role of gender / sex hormones on cancer & therapy response?

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

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 immunotherapy.

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