Systemic Therapy for Advanced Melanoma

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Statewide Virtual Melanoma Tumor Board & Educational Updates Program
Timeline of FDA approved treatments (unresectable/metastatic)

1980: Dacarbazine
1990: High-dose IL-2
2000: Vemurafenib, Ipilimumab
2010: Dabrafenib, Trametinib, Pembrolizumab, Nivolumab, Encorafenib/Binimetinib
2015: Ipi/Nivo, T-Vec, cobimetinib
2020: Ipi/Nivo, T-Vec, cobimetinib, Vemurafenib, Ipilimumab
2 Year Overall Survival

2 year OS (%)

Dacarbazine* 10
IL-2** 25
Iplimumab 25
Dabrafenib/Trametinib 51
Vemurafenib/Cobimetinib 48
Pembrolizumab 50
Nivolumab 48
Nivolumab/Iplimumab 64

*Avril MF, JCO 2004
**Atkins MB, JCO 1999
Clinical trials for metastatic melanoma

BMS: NKTR-214 + Nivolumab

- Phase III, open-label, randomized trial for treatment naïve metastatic melanoma
  - Note – prior adjuvant therapy allowed depending on timing

- Nivolumab vs NKTR-214 + Nivolumab

- NKTR-214: PEG-IL2, preferential binding to IL-2 receptor on effector CD8+ T cells rather than the IL-2 receptor on Tregs.
Stage IV IO-Naïve 1L Melanoma Cohort at RP2D: Achieved Pre-Specified Efficacy Criteria

Stage 1: ORR 11/13 (85%)
Stage 2: Best Overall Response ORR=14/28 (50%); DCR=20/28 (71%)

Median Time on Study 4.6 Months (N=28)
As of May 29, 2018

ORR PD-L1 (-) 5/12 (42%)
ORR PD-L1 (+) 8/13 (62%)
ORR PD-L1 Unknown 1/3 (33%)

Data cut: May 29, 2018

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria. -100% is PR for complete clearance of target lesions. CR is a complete response. "u": Unconfirmed. "s": Best overall response is PD; SD for target lesions but PD due to a new lesion. "o": Off study treatment with confirmed CR due to patient decision.

One PD-L1(-) patient had PD due to non-target lesions and target lesions were not assessed, therefore 27/28 patients included in waterfall plot.
Clinical trials for metastatic melanoma

- *Merck: Lenvatinib + Pembrolizumab*

- VEGF has an immunosuppressive effect on the tumor microenvironment.
  - Increased MDSCs & Tregs in tumor microenvironment and impaired dendritic cell maturation

- **Pembrolizumab (anti-PD1) + lenvatinib** (multikinase inhibitor: VEGFR, FGFR)

- **Lenvatinib**: shown to decrease tumor associated macrophages and increase infiltrating CD8+ T cells in mouse models

- **Toxicity:**
  - Expected side effects of lenvatinib and pembrolizumab. No synergistic toxicity observed
Clinical trials for metastatic melanoma

- Merck: Lenvatinib + Pembrolizumab
- Phase III trials – Merck, including both PD-1/PD-L1 inhibitor naïve and refractory metastatic melanoma patients
- Phase Ib/II trial: 48% ORR in melanoma
Clinical trials for metastatic melanoma

Syndax: SNDX-6352-0502

- Phase I dose escalation clinical trial – combo:
  - SNDX-6352: IgG4 antibody against CSF1R
  - Durvalumab: IgG1 antibody against PD-L1
- Open to patients with advanced melanoma and other solid tumors
CD47 blockade: checkpoint linking innate with adaptive immunity

**Figure 1** The CD47 immune checkpoint. CD47 blocking antibodies (1) and pro-phagocytic molecules such as calreticulin (2) cooperate to enhance tumor engulfment by APCs (3), enabling the processing and presentation of tumor antigens as peptides in the groove of MHC class I molecules (4) and the priming of CD8$^+$ T cells specific for tumor antigens (5). MHC, major histocompatibility complex; TCR, T cell receptor.

Vonderheide, RH. Nature Medicine 2015; No 10, vol 21, 1122-1123
Clinical trials for metastatic melanoma

Trillium: TTI-621

- Fusion protein: SIRP alpha + Fc
- Phase I trial: intra-lesional injection in combination with Pembrolizumab
- Open to various solid tumors (including melanoma) with cutaneous and superficial lymph node metastases (injectable lesions)