National Cancer Policy Forum

Chris Boshoff MD PhD
SVP Immuno-Oncology, Early Development and Translational Oncology
July, 2018
Agenda

Modeling to Predict Efficacy: VEGFR Inhibition

Randomization to Detect ESoE: CDK4/6 Inhibition

RWD to Determine Efficacy: PARP Inhibition
Rationale for Combining Anti-Angiogenic Treatment With Anti-PD-L1

VEGFR2 is selectively expressed by FOXP3^{high} CD4+ Treg

Simultaneous blockade of PD-1 and VEGFR2 induced synergistic anti-tumour effect *in vivo*, in various models
Clin & Exp Immunology, 2013, Yasuda et al.

Anti-angiogenesis therapies may partially depend on their effects on vessel normalization and the consequent reprogramming of the immune TME
Tian, L, Nature, 544, 250–254, 13 April 2017
Axitinib + Avelumab, 1L RCC, Change in Tumor Burden

Change in Baseline in sum of Diameters in Target Lesions by PD-L1 Expression on Tumor-associated Immune Cells
Potential Impact of avelumab + axitinib on Tumor Size Compared with Historical Data of sunitinib as Evaluated by a Modeling and Simulation Approach

Avelumab + axitinib appear to have a greater impact on tumor burden than sunitinib
Axitinib + Pembrolizumab in 1L RCC: Phase 1 Overall Survival

Atkins et al, Lancet Oncology, Vol 19, March 2018

1L RCC Ph 3 Studies

- Nivolumab + NKT214 (IL-2PEG)
- Axitinib + Avelumab
- Axitinib + Pembrolizumab
- Lenvatinib + Pembrolizumab
- Cabozantinib + Nivolumab
- Bevacizumab + Atezolizumab*

Nivolumab + Ipilimumab**

Number at risk (censored)

<table>
<thead>
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<th>Ph 1/2</th>
<th>Ph 3</th>
<th>Approved</th>
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| Nivolumab + Ipilimumab**

*IMmotion 151 Reported positive PFS, Feb 2018
**FDA approves nivolumab + ipilimumab combination for intermediate or poor-risk RCC, April, 2018
Targeting the Cell Cycle: CDK4/6 Inhibition and Immunity

CDK4 expression and activity are necessary to establish IL-2 responsiveness in T-lymphocytes
Modiano et al, J Immunol, Dec 2000, 165: 6693
Palbociclib Preferentially Inhibits Proliferation of Luminal ER+ Human Breast Cancer Cell Lines

CDK4/6 inhibitors activate tumor cell expression of endogenous retroviral elements, increasing intracellular levels of double-stranded RNA. This induces type III interferons and tumor antigen presentation.
CDK4/6 Inhibition + ICB

CDK4/6 inhibitors decrease T cell proliferation, but increase tumor T-cell infiltration and activation of effector T cells.
Randomized Experience to Test Preclinical Hypothesis

**Palbociclib After CDK and Endocrine Therapy (PACE)**
Phase 2 Study

- Fulvestrant
- Fulvestrant + Palbociclib
- Fulvestrant + Palbociclib + Avelumab

Endocrine Pre-treated ER+/HER2- MBC

NCT03147287
DNA Damage-Driven Inflammation and Immunity

- DNA damage accumulates with age, leading to the persistent activation of DNA damage sensors and the DDR.

- Chronic activation of DDR triggers inflammatory responses leading to age-related pathologies including cancer.

- DDR defects are present in 2-30% of all cancers and could indicate sensitivity to PARP inhibitors or other DNA repair targeted therapies.
Subclonal Genetic Variations Amongst Breast Cancer

Estimated number of Mutations

- Fully clonal
- Subclonal 50–95%
- Subclonal 25–50%
- 95% posterior intervals

Immunotherapy / PARP Inhibitor: Rational Combination?
Association Between DDR Status & Responses to Atezolizumab in UCC


<table>
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<tr>
<th>Variant</th>
<th>Mean TMB</th>
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<tbody>
<tr>
<td>EGFR</td>
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Spigel, et al. ASCO, 2017
Avelumab (anti-PD-L1) + talazoparib (PARPi)
Somatic BRCA1 Mutant Ovarian Cancer

25.9mm x 20.3mm
Oct 2017

7.8mm x 6.3mm
Apr 2018

58% RECIST PR (ongoing)

Courtesy of Timothy A. Yap, MDACC
Tissue Agnostic Approach: Avelumab (anti-PD-L1) + talazoparib (PARPi)

Javelin BRCA/ATM: Phase 2

BRCA or ATM Mutant Solid Tumors

Avelumab + Talazoparib

RWD of Outcomes for BRCA /ATM mut tumors

NCT03565991