Combining Immunotherapy and Targeted Therapy in Melanoma

8:45 am - 9:15 am

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Disclosure Information
Antoni Ribas

I have the following financial relationships to disclose:
• Consultant for: Kite Pharma
• Speaker’s Bureau for: None
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-and-

• I will discuss the following off label use and/or investigational use in my presentation: vemurafenib
Limitations of Tumor Immunotherapy

1. Suboptimal antigen presentation
2. Low frequency of tumor antigen-specific T cells
3. Limited CD8+ CTL activation and expansion (CTLA4, PD1)
4. Lack of antigen recognition (Low TAP, MHC)
5. Immune suppressive tumor milieu (Treg, MDSC, IDO, VEGF, IL-10, PgE2, TGF-β)
6. Insensitivity to pro-apoptotic signals from immune cells

Cancer Immunotherapy

Immunosensitization
Immunosensitization with Targeted Therapies

- Desired features for an immune sensitizing agent:
  - On tumor cells:
    - Target a key oncogenic pathway
    - Inhibit anti-apoptotic molecules
    - Increase pro-apoptotic molecules
    - Increase ligands for immune cells (tumor antigen, MHC, NK activating receptors)
  - On immune system cells:
    - Not kill immune cells
    - No interference on key signaling events in immune system cells (TCR, NK receptor)

Perspective

Targeted Therapies to Improve Tumor Immunotherapy
Jonathan Begley\textsuperscript{1,2} and Antoni Ribas\textsuperscript{2,3,4}
Testing of the Concept of Immunosensitization in Animal Models

- Bortezomib (proteasome inhibitor) to sensitize to NK cells
  - Schumacher et al. JI 2005

- ABT-737 (Bcl-2 inhibitor) to sensitize to T cells
  - Begley et al. CII 2008

- LAQ824 (HDAC inhibitor) to sensitize to T cells
  - Vo et al. CR 2009
CD8+ T Cell

Melanoma Cell

Death Receptor

Caspase-8

Procaspase-8

GmB

GrnB

Perforin

Apoptosis

Effector Caspases

Bcl-2 Inh

Bcl-2

Bcl-w

HDAC Inh

FLIP

Caspase-8

Apaf-1

Cytochrome C

IAP'S

Caspase-9

Proteasome Inh

Proteasome Break

Signal Transduction Pathway

Receptor

Tyrosine Kinase

TKi?
Testing of the Concept of Immunosensitization in Animal Models

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  - Begley et al. CII 2008

- LAQ824 (HDAC inhibitor) to sensitize to T cells
  - Vo et al. CR 2009

- PLX4032 (BRAF inhibitor) to sensitize to T cells
  - Comin-Anduix et al. CCR 2010
  - Koya et al. CR 2012
Pre-clinical evidence supporting the feasibility of combinations of BRAFi + immunotherapy

Oncogenic BRAF-induced production of immune suppressive factors (IL-6, IL-10, VEGF) is inhibited with a MEK inhibitor

Vemurafenib increases melanosomal antigen expression and T cell recognition

Human T cells exposed to vemurafenib are fully functional
Pre-clinical evidence against the feasibility of combinations of BRAFi + immunotherapy

Selective BRAF inhibition decreases tumor-resident lymphocyte frequencies in a mouse model of human melanoma

PLX4720 treatment leads to a decreased frequency of immune cells in BRAFV600E/PTEN-/- melanomas and this cannot be restored by CTLA-4 blockade

Addition of anti-CTLA-4 mAb treatment to PLX4720 treatment does not further improve tumor growth control
Clinical evidence supporting the feasibility of combinations of BRAFi + immunotherapy

CD8+ T cell infiltration in regressing melanoma lesions after BRAFi therapy

T cells from patients treated with dabrafenib are fully functional
How can BRAF targeted therapy increase the activity of tumor immunotherapy?

- Increased antigen presentation
- Increased antigen cross-presentation
- Activation of T cells and increased homing
- Decreased immune suppressive factor release

BRAF, BRAFi
SM1: A BRAF<sup>V600E</sup>-driven Melanoma Syngeneic to Immunocompetent Mice


Richard Koya, MD, PhD
Stephen Mok

Koya <i>et al.</i> Cancer Res 2012
Gene copy number variations (CNV) in SM1 is similar to human melanomas.
pmel-1 ACT immunotherapy + BRAF targeted therapy against SM1 (murine melanoma driven by $BRAF^{V600E}$)

3 replicate experiments, $p < 0.0001$ by log rank test
How can BRAF targeted therapy increase the activity of tumor immunotherapy?

Koya et al. CR 2012:
- No change in gp100 or MHC expression by SM1 exposed to vemurafenib
- No change in adoptively transferred T cell distribution by BLI
- No increase in intratumoral infiltrates by adoptively transferred T cells
Differential effects of BRAF inhibition in $BRAF^{V600}$ mutant melanoma and activated T cells

$BRAF^{V600}$ mutant melanoma

Activated T cells

Paradoxical MAPK activation with RAF inhibitors

Paradoxical activation of pERK with exposure of lymphocytes to vemurafenib

Koya et al. Cancer Res 2012
Conclusions

• Novel targeted therapies may synergize with immunotherapy:
  – Improve antigen presentation
  – Sensitize cancer cells to apoptotic death
  – Inhibit suppressive factors in the tumor
  – Improve lymphocyte function

• In a mouse model, increased benefit of a BRAF inhibitor with ACT immunotherapy is mediated by:
  – Increased immune cell functionality (paradoxical MAPK activation)
  – Modulation of the tumor microenvironment?
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