Disclosures:

Inventor of intellectual property owned by the University of California, Berkeley, licensed to Bristol Meyers-Squibb

Recipient of royalties from Bristol Meyers-Squibb

Founder, Jounce Therapeutics

Scientific Advisory Board, Kite Pharmaceuticals
Immune Checkpoint Blockade in Cancer Therapy: New Insights and Opportunities

Jim Allison
Chair, Department of Immunology
Director, Immunotherapy Platform
Deputy Director, David H Koch Center for Genitourinary Oncology Research,
MD Anderson Cancer Center

Advances in Cancer Immunotherapy
MD Anderson Cancer Center
Dynamic Integration of TCR and Costimulatory Signals

No Proliferation Anergy?

TCR pMHC CD28

Activation, Initiation

CTLA-4 pMHC CD28 IL-2

Cdk4 Cdk6 Cyclin D3

Inhibition

Bcl-xL, g p27kip

IL-2

B7-1 B7-2

Restricted Proliferation

Cdk4 Cdk6 Cyclin D3
Localization of CD28 and CTLA-4 to the T Cell-APC Interface

CD28

CTLA-4

~ 5 minutes
CTLA-4 Blockade Enhances Tumor-Specific Immune Responses

Attenuated or Terminated Proliferation

Unrestrained Proliferation

Chemotherapy Irradiation Vaccines Peptide-pulsed DCs GM-CSF Hormone therapy Anti-angiogenesis, etc.

Tumor

CTLA-4

TCR CD28

B7-1 pMHC B7-2

IL-2
Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma

Anti-CD28
Anti-CTLA-4
No Rx

Average Tumor Size (mm$^2$)

Days After Tumor Injection

Rx
Leach
anti-CTLA-4/GVAX therapy activates the tumor vasculature and increases infiltration of tumors by CD4 and CD8 effector cells.
αCTLA-4/GVax Increases Teff/Treg Ratio In Tumor

CD4/Foxp3

CD8/Foxp3

Quezada
Blockade of CTLA-4 on both Teff and Treg compartments is necessary for optimal anti-tumor activity.
Effects of $\alpha$CTLA-4 on Treg

Peripheral Lymph Nodes
Expand due to blockade of cell intrinsic inhibition of proliferation by CTLA-4

Tumor
Killed by ADCC by Fc$\gamma$R-IV on macrophages due to higher expression of CTLA-4 on Treg than Teff and higher levels of macrophages in tumor
Ipilimumab Rx reduces Foxp3+ T cells in bladder cancer patients
α-CTLA-4 antibody functions by multiple mechanisms

- Release of CTLA-4 inhibition
- Depletion of T_{reg} by FcyRs
- Blockade of CD80/CD86 trans-endocytosis
Ipilimumab
(Medarex, Bristol-Myers Squibb)

Fully human antibody to CTLA-4

>17,000 patients treated to date:

- Objective responses in melanoma, prostate, ovarian, lung, & kidney cancer, glioblastoma
- Adverse events: colitis, rashes, hepatitis, hypophysitis. Manageable with systemic steroids
Baseline and 5 months post-MDX-010 treatment CT scans of patient with metastatic melanoma (1 month status post dendritic cell vaccine) who experienced regression of all known sites of disease. The patient continues without relapse at last reported follow-up visit.
The longest survivor on ipilimumab

May 2001, after progression on IL-2

10 years later...
Complete Responder: Melanoma

Experienced complete resolution of 2 subcutaneous nodules, 31 lung metastases and 0.5 cm brain metastasis.
Complete Responder: Melanoma

Experienced complete resolution of 2 subcutaneous nodules, 31 lung metastases and 0.5 cm brain metastasis.
Complete Responder: Prostate Cancer

Screening 14 months

Phase III trials ongoing

BMS
Baseline 11/28/06

Wolchok (MSKCC)
Evolution of Response: Patient Example

Screening

Week 12
Initial increase in total tumor burden (mWHO PD)

Week 16
Responding

Week 72
Durable & ongoing response without signs of IRAEs

20006

Harmankaya
Kaplan-Meier Analysis of Survival

<table>
<thead>
<tr>
<th>Survival Rate</th>
<th>Ipi + gp100 N=403</th>
<th>Ipi + pbo N=137</th>
<th>gp100 + pbo N=136</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>44%</td>
<td>46%</td>
<td>25%</td>
</tr>
<tr>
<td>2 year</td>
<td>22%</td>
<td>24%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Hodi et al. NEJM 2010
Ipilimumab
(Bristol-Myers Squibb)

• Metastatic Melanoma
  • Ipilimumab was approved by FDA in 2011 for second and front line therapy.
  • Trial of ipilimumab plus dacarbazine showed enhanced survival over dacarbazine alone.

• Castrate-resistant Prostate Cancer
  • Randomized Phase III registration trails ongoing of ipilimumab following palliative radiation
Critical Issues for Further Clinical Development of anti-CTLA-4

• What are the cellular and molecular mechanisms involved in the anti-tumor effect?

• What distinguishes between responders and non-responders?

• What are the best conventional therapies or vaccines to be used combinatorially?

How can we increase the response rate?
Combinations to Increase Efficacy of CTLA-4 Blockade

• Vaccines
  GVAX, DNA, Protein
(But *not* minimal Class I MHC restricted peptides)
Anti-CTLA-4 and GM-CSF Tumor Cell Vaccine Synergize to Eradicate Established B16 Melanoma

van Elsas, Hurwitz
Combinations to Increase Efficacy of CTLA-4 Blockade

- Vaccines
- Conventional Therapies
  - Chemotherapies, Local radiation, Cryoablation
Combining Cryoablation with Anti-CTLA-4

Day -21

1x10^6 TRAMP C2 Left Flank

Day 0

C57BL/6 Mouse

Cryoablate 1st Tumor

Day 1

-175° C
1-2 min.

0.5x10^6 TRAMP C2 Right Flank

Day 11-34

Measure Tumor Growth of 2nd Right Flank Tumor

Anti-CTLA-4 Day 1, 4, 7

Waitz, Solomon, Norton
TRAMP C2 Cryoablation +/- Anti-CTLA-4

All Mice

Complete Ablation Only

Tumor Free Survival All Mice: Survival proportions

Tumor Free Survival Complete Ablation: Survival proportions

Waitz, Solomon, Norton
Ipi +/- XRT in CRPC

All Cohorts

10mg/kg +/- XRT

(Greatest change in PSA by day 85 of study)

Slovin et al. Annals Oncol. 2013
Regression of metastatic disease after ipilimumab plus androgen deprivation

Aparicio and Sharma (MDACC)
Combinations to Increase Efficacy of CTLA-4 Blockade

- Vaccines
- Conventional Therapies
- Targeted Therapies
Targeted Therapies

• High response rates, rapid tumor regression in patients with target

• Responses are often of short durability, not necessarily associated with overall survival

• Recurrence is associated with drug resistance

• Success may require iterative identification of targets, development of additional drugs
Efficacy of Vemurafunib in V600E+ Melanoma

Overall Survival (%)

Hazard ratio, 0.37; 95% CI, 0.26 to 0.55; P<0.001
Targeting Neoantigens: Drugs as Vaccines

• Breast and colorectal tumors contain ~100 missense mutations/cell (Vogelstein)
• Many of these (~50%) may be neoantigens (Segal and Allison)

• Exome Sequencing shows varying numbers of missense mutations in different tumors:
  • Prostate: 30-70
  • Glioblastoma: 30-50
  • Melanoma: 400-500

• Killing tumor cells should release multiple neoantigens and prime multiple T cell responses

• Sustaining these responses by immune checkpoint blockade may result in durable responses
HSP90 Inhibitor Enhances Efficacy of CTLA-4 Blockade in Rx of TRAMP-C2 Prostate Tumors

C57/Bl6 mouse

Treat 17-AAG
Day 1,3

CTLA-4 Blockade
Day 5,8,11

17-AAG
• HSP 90 inhibitor
• Blocks antigen presentation

TUNEL STAIN

Ariayan, Rosen
Combinations to Increase Efficacy of CTLA-4 Blockade

- Vaccines
- Conventional Therapies
- Targeted Therapies
- Combinations of Checkpoint Inhibitors
  - PD-1, PD-L1, B7-H3, B7-H4,
  - Vista, Tim-3, Lag-3
Combination of Multiple Immune Checkpoint Blockers

- ICOS-L
- CD28
- CTLA-4
- PD-L1
- PD-L2
- B7x
- B7-H3
- ICOS
- PD-1
- B7-1
- B7-2
- Limits Responses
- Inhibit Effector Function
- Costimulates
- Promotes Survival?
- Inhibits Proliferation
Programmed Death 1

http://www.melanoma.org/community/mpip-melanoma-patients-information-page/video-how-anti-pd-1-therapy-works-immune-system
Anti – PD-1 (BMS-936558)

296 Patients with Metastatic Cancer
1, 3, 10 mg/kg, MTD not reached

Safety: Adverse events similar to Ipilimumab, but 4% pneumononitis (3 deaths)

Clinical Activity:
Melamona (n= 94): 28% CR/PR, 6% SD
NSCLC (n=76): 18% CR/PR, 7% SD
RCC (n= 33): 27% CR/PR, 27% SD
CRC (n=19), CRPC (n=13): No responses

ASCO, NEJM 2012
Combination blockade of the CTLA-4 and PD-1 pathways promotes rejection of B16 melanoma

Combination FVAX (B16-Flt3-ligand)+ Antibody

Curran
Clinical Activity in Melanoma Patients Receiving Nivolumad (αPD-1) and Ipilimumab (αCTLA-4)

40% Objective CR+PR
65% Clinical Activity

ASCO 2013
NEJM 6/2/2013
Combinations to Increase Efficacy of CTLA-4 Blockade

- Vaccines
- Conventional Therapies
- Targeted Therapies
- Combinations of Checkpoint Inhibitors
- Stimulation of Additional Costimulatory Pathways
  OX40, CD137, ICOS
Tissue Macrophage

Regulatory T cell

Effector T cell Proliferation and/or Function

Peripheral Tissues

Tumors
Improving Survival with Combination Therapy

- Control
- Standard or Other Therapy
- Immunotherapy (e.g., anti-CTLA4)
- Combination