Immuno-Oncology: Past, Present and Future...

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Forward-Looking Information

This presentation contains statements about the Company’s future plans and prospects that constitute forward-looking statements for purposes of the safe harbor provisions under the Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated as a result of various important factors, including those discussed in the company’s most recent annual report on Form 10-K and reports on Form 10-Q and Form 8-K. These documents are available from the SEC, the Bristol-Myers Squibb website or from Bristol-Myers Squibb Investor Relations.

In addition, any forward-looking statements represent our estimates only as of the date hereof and should not be relied upon as representing our estimates as of any subsequent date. While we may elect to update forward-looking statements at some point in the future, we specifically disclaim any obligation to do so, even if our estimates change.
Our R&D Strategic Focus

DISEASE AREA FOCUS

Oncology

Immunoscience

Cardiovascular

Heart Failure Thrombosis

RA, IBD, Lupus

Lung Liver

Fibrotic Diseases

Genetically Defined Diseases

Liver

Monogenic diseases
BMS Development Strategy

- High Disease Severity
- Potentially Large Treatment Effect
- Enduring Unmet Need
The Challenge

Pooled analysis of long term survival data from phase II and III trials of ipilimumab in unresectectable or metastatic melanoma

Dirk Schadendorf et al. JCO 2015;33:1889-1894
Hot Science: Cancer Immunotherapy

Breakthrough of the year
Immunity and Cancer

• Coley
  - Some cancers spontaneously regress after erysipelas infection

• HIV
  - Viral infection of T-cells, many patients died of cancer

• Boy in the Bubble
  - No immune system, Burkitt’s lymphoma
Tumor lymphocytic infiltrate correlated with 20% increase in survival

Annals of Surgery, 1922
A pro-inflammatory microenvironment dictates response to checkpoint blockade

- Pre-existing, clonally expanded CD8 cytotoxic lymphocytes
- Type I/IFN-gamma driven “adaptive resistance”
- Tumor specific T-cells “primed and ready to eradicate” once the PD1-PDL1 “brake” is released

Immunity and Cancer

IL-2, γ-INF

[Diagram showing the interaction between immune cells and cancer cells, including CD4+ and CD8+ T cells, TCR, MHC, and antigen-presenting cells.]

[Images of mechanical knobs indicating a transition from MIN to MAX settings.]
Immuno-Oncology: Research & Preclinical Focus

**Diagram:**

**Panel a:** Co-stimulation of T cells following interaction with counter-receptors on APCs
- APC: MHC, B7-H2, B7-1, B7-2, CD70, LIGHT, HVEM, CD40, CD40L, 4-1BB, OX40L, TL1A, GITRL, CD30L, Unknown TIM1 ligand, TIM1, SLAM, CD48, CD58, CD155, CD112, CD226
- T cell: TCR, ICOS, CD28, CD27, CD40L, 4-1BB, OX40, DR3, GITR, CD30, TIM1, SLAM, CD48, CD58, CD155, CD112
- Proliferation, Cytokine production, Differentiation, Cytotoxic function, Memory formation, Survival

**Panel b:** Co-inhibition of T cells following interaction with counter-receptors on APCs
- APC: MHC class II, Treg cell activation, IDO, B7-2, B7-1, B7-DC, B7-H1, HVEM, CD160, BTLA, LAIR1
- T cell: TCR, LAG3, CTLa4, PD1, B7-1, CD160, PD1H, Unknown PD1H receptor, Collagen, TIM1, TIM4, Unknown TIM1 receptor, Unknown TIM4 receptor
- Cell cycle inhibition, Inhibition of effector function, Tolerance, Exhaustion, Apoptosis

*Liaping Chen¹ and Dallas B. Fikes¹,²* NATURE REVIEWS | IMMUNOLOGY VOLUME 13 | APRIL 2013 | 227
Key Breakthroughs

1991

• Peter Linsley at BMS discovered ligands for CTLA4 (J EM, 1991) and discovered abatacept CTLA4Ig

1995

• Knockout mouse phenotype unambiguously shows that CTLA-4 is a negative signaling molecule
Checkpoint Pathways in T Cell Activation

1996 Allison Proposes CTLA-4 Blockade for Cancer Therapy

Enhancement of Antitumor Immunity by CTLA-4 Blockade

Dana R. Leach, Matthew F. Krummel, James P. Allison*

![Graph showing the enhancement of antitumor immunity by CTLA-4 blockade](image)

- Control
- Anti–CD28
- Anti–CTLA-4

Days after tumor injection

Average tumor size (mm²)
2015 Lasker-DeBakey Clinical Medical Research Award

James P. Allison, Awardee

Alan Korman, BMS I-O collaborator

Nils Lonberg
BMS I-O collaborator (photographer)
Nivolumab: PD-1 / PD-L1 Biology

↓ TcR signaling in PD-1+ T cells
- Chronic Ag stim ► High PD-1
- ‘T cell exhaustion’

2 key T cell interactions
1. **T cell: APC**
   - ↓ activation, effector functions

2. **T cell: PD-L1+ tumor cell**
   - ↓ tumor killing
   - Blockade of PD-1:PD-L1 can restore T cell function

Success of Opdivo highlights the importance of the PD-1:PD-L1 pathway
Leading the Way in Immuno-Oncology

- **LEADING IN I-O**
- **9** Positive registrational trials
- **5** Phase III trials stopped early due to survival benefit
- **20+** tumor types with over **50** trials in I-O
- **25** Ongoing and planned I-O registrational trials
Statistically significant improvement in QoL scores* for mRCC patients was observed between nivolumab and everolimus through 76 weeks of follow-up (questionnaire completion rate: ≥80% during the first year of follow-up)

*Open-label study
Transformational Science & Medicine

The New England Journal of Medicine

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma
A. Snyder, M.D., et al. November 19, 2014

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

8 Publications in 10 months

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin’s Lymphoma

Nivolumab in Previously Untreated Melanoma without BRAF Mutation

Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma

Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1
I-O Future Lies in Combination Therapies

**ipilimumab & nivolumab:**

- Target the immune system (rather than the tumor) to reactivate pre-existing, but quiescent, immune responses to cancer cells

OPDIVO® is associated with the following Warnings and Precautions including immune-mediated: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, rash, encephalitis, other adverse reactions; infusion reactions; and embryo-fetal toxicity. Yervoy is associated with immune-mediated adverse reactions. The most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis, neuropathy and endocrinopathy.”

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma


PFS: Intent to treat

No. at Risk

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Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma


PFS: Intent to treat
Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

**challenge**

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PFS: Intent to treat
I-O and BMS Intellectual Property

- BMS, with partner Ono, have led the way in discovering and developing PD-1 based therapies.

- We have many granted patents and pending patent applications covering immuno-oncology innovations.

- Given our leadership, we will defend our intellectual property when it is being infringed as evidenced by global patent litigations brought by BMS and Ono against Merck’s Keytruda.
BMS Immuno-Oncology Vision

- Displace standard of care (SOC) in multiple tumor types, lines of therapy and histologies
- Use I-O combinations to meaningfully increase likelihood of long-term survival
- Expand and accelerate broad portfolio of novel mechanisms
Immuno-Oncology Agent(s) Expected to be Foundational in the Treatment of Multiple Cancers: Example of Lung Cancer

**Strategic Goal:** 80% of patients with advanced lung cancer survive >2 years
Multiple diverse pathways of immune attenuation involve diverse cell types, signals, and targets:
Multiple diverse pathways of immune attenuation involve diverse cell types, signals, and targets:

Blocking a single immune-suppressive pathway may not be sufficient to fully restore anti-cancer immunity in all patients or histologies: **combination therapy may provide the solution**
Gut Bacteria Modify Immunotherapy Effectiveness

CANCER IMMUNOTHERAPY
Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota

CANCER IMMUNOTHERAPY
Commensal Bifidobacterium promotes antitumor immunity and facilitates anti–PD-L1 efficacy

IMMUNITY
Article
Binding of the Fap2 Protein of *Fusobacterium nucleatum* to Human Inhibitory Receptor TIGIT Protects Tumors from Immune Cell Attack

Published by AAAS
Alexandra Snyder et al. Science 2015;350:1031-1032
2016: Diversifying in Immuno-Oncology

Next wave of innovation: areas of focus

8 Additional I-O Assets in Clinical Development

- Priming & Activation
- Antigen Presentation
- Antigen Release
- Tumor Microenvironment

- NK cell
- T Cell

- T Cell Trafficking and Infiltration
- T Cell Activation
- NK Cell Activation

- BMS assets beginning clinical studies in 2016

- anti-CSF1R
- IDO
- anti-CD73

- Urelumab (anti-CD137)
- anti-LAG3

- anti-GITR
- anti-OX40

- Lirilumab (anti-KIR)
- Empliciti (elotuzumab)
The Future of I-O Drug Development

Underscores the challenge of identifying the most promising combination I-O therapies that may potentially prolonged survival in patients with cancer.
Medical Insights

**LUNG**

- Only PD-1 indicated for all 2nd line NSCLC patients in US, EU*, and JP
- No testing requirement
- Strong access and reimbursement

**MELANOMA**

- Broad range of treatment options
- First I-O combination regimen approved

**RENAL**

- First I-O agent in 2nd line in US and EU*
- Meaningful improvement over a standard of care

*CHMP Positive Opinion - not yet approved*
Acknowledgments

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Countless other BMS scientists, clinicians, leaders.

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James Yang, NCI
Giao Phan, NCI
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Julie Brahmer, Johns Hopkins
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Naiyer Rizvi, Columbia University
Working Together for Patients
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