Bristol-Myers Squibb

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


Carl P Decicco

SVP, Head of Discovery

Bristol Myers-Squibb


March 31, 2016





Bristol-Myers Squibb

# 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.

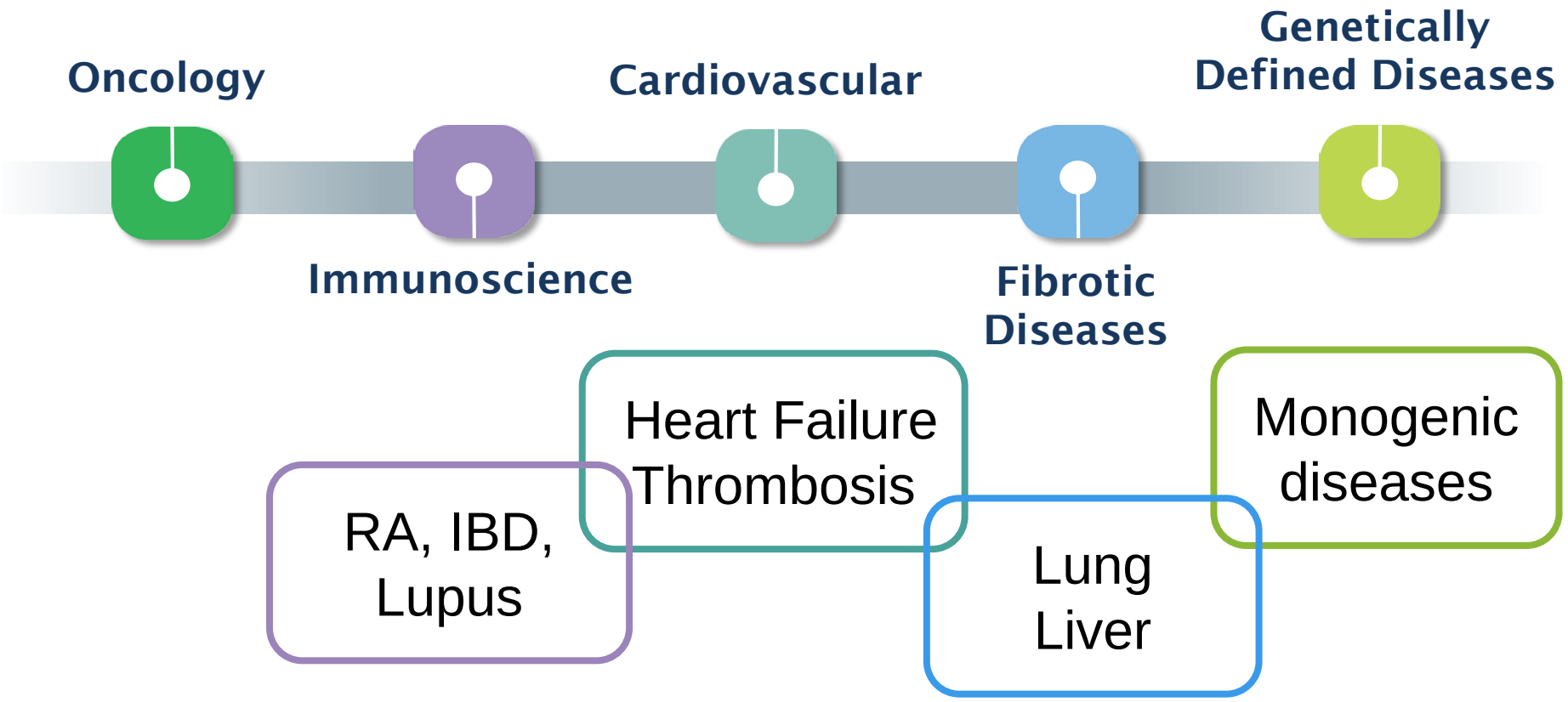
In addition, any forward-looking statements represent our estimates only as of the date hereof and should not be relied upon as representing our estimates as of any subsequent date. While we may elect to update forward-looking statements at some point in the future, we specifically disclaim any obligation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

# Product Sampling – Late 1900's

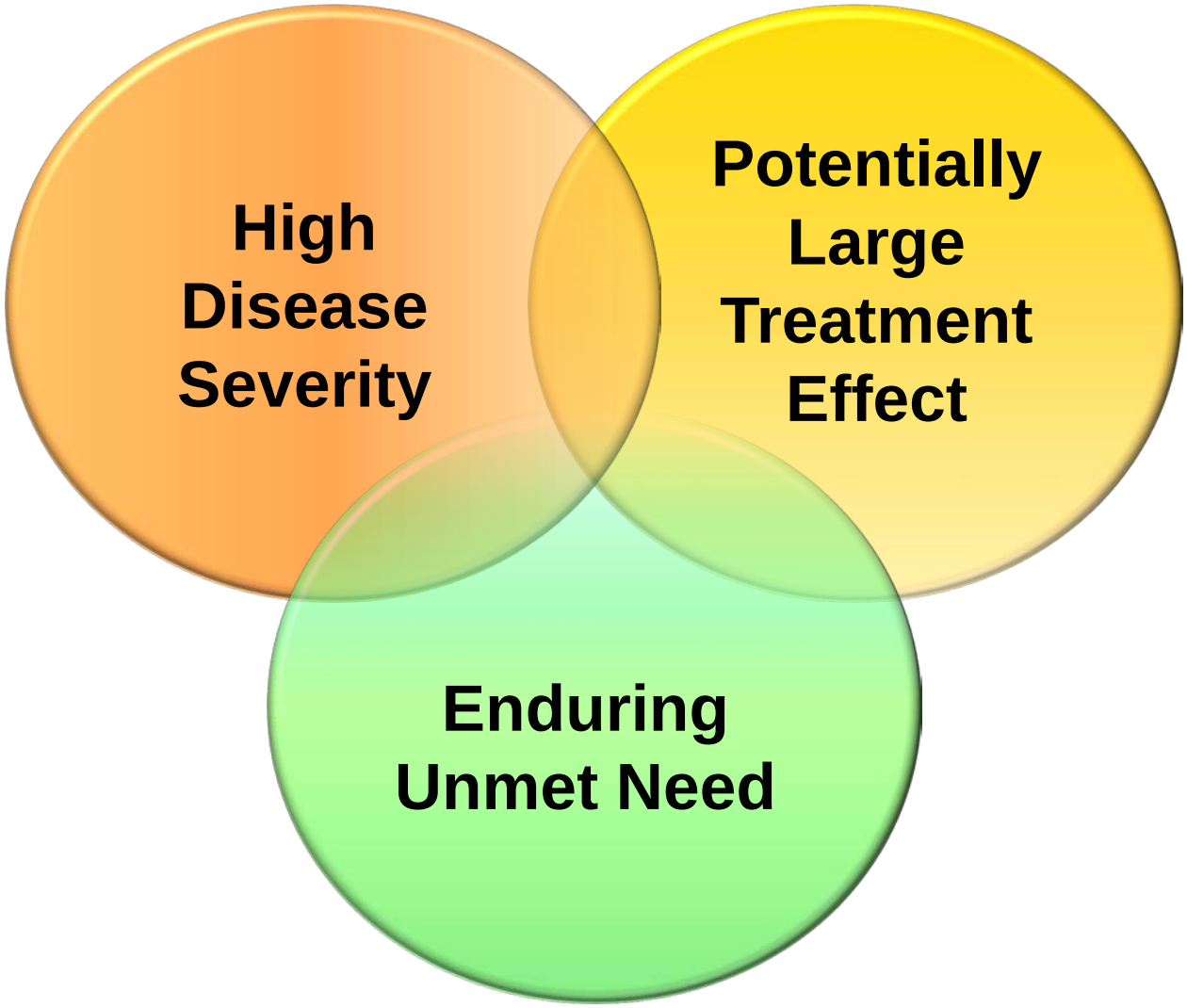
# BioPharma Transformation

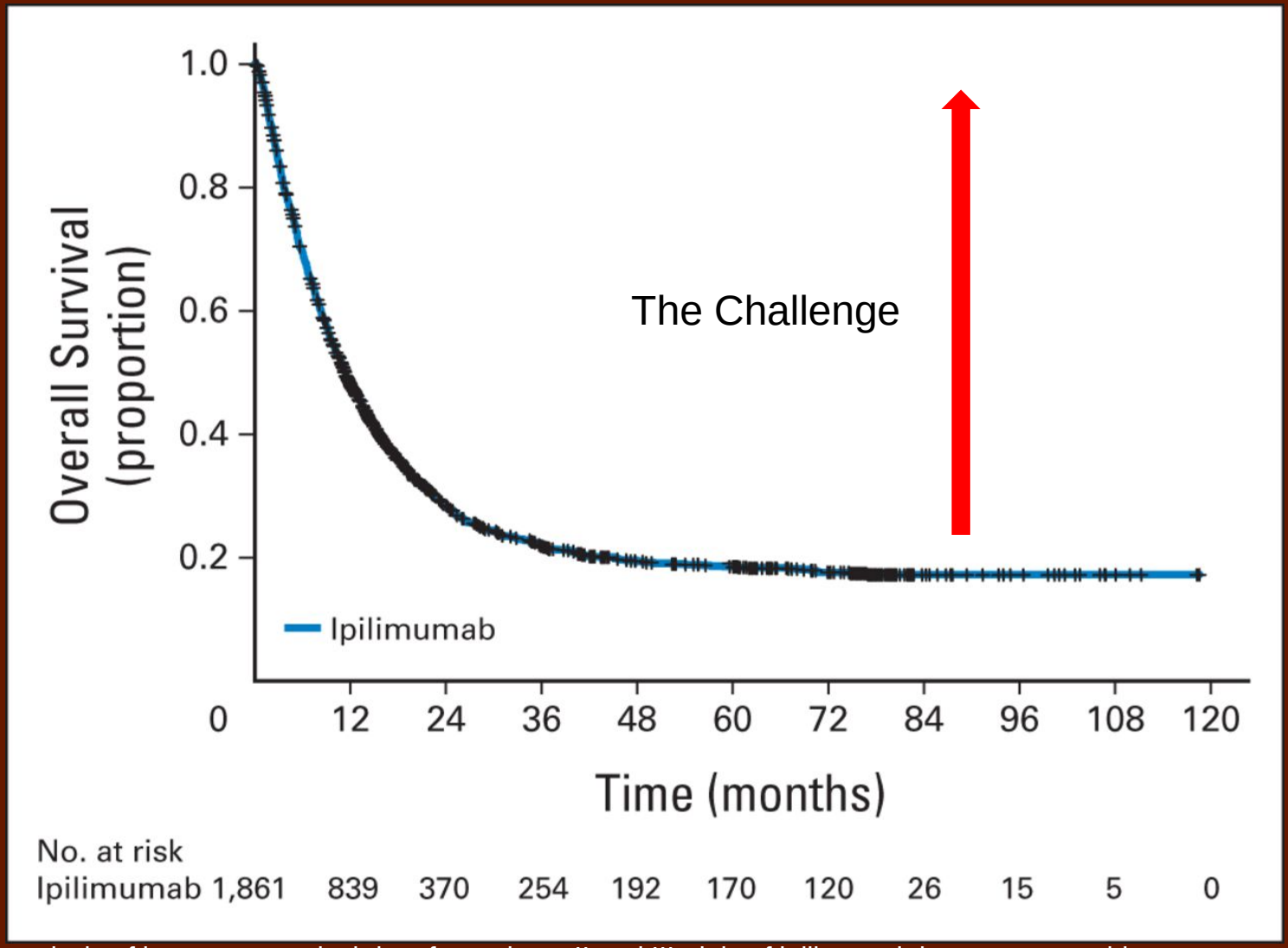
# Our R&D Strategic Focus

## DISEASE AREA FOCUS



# BMS Development Strategy






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

# FACTORS WHICH INFLUENCE LONGEVITY IN CANCER*

A STUDY OF 293 CASES

By William C. MacCarty, M.D.

of Rochester, Minn.

SECTION ON SURGICAL PATHOLOGY, MAYO CLINIC

* Presented before the Minnesota Pathological Society, November 15, 1921.

***Tumor lymphocytic infiltrate correlated with 20% increase in survival***

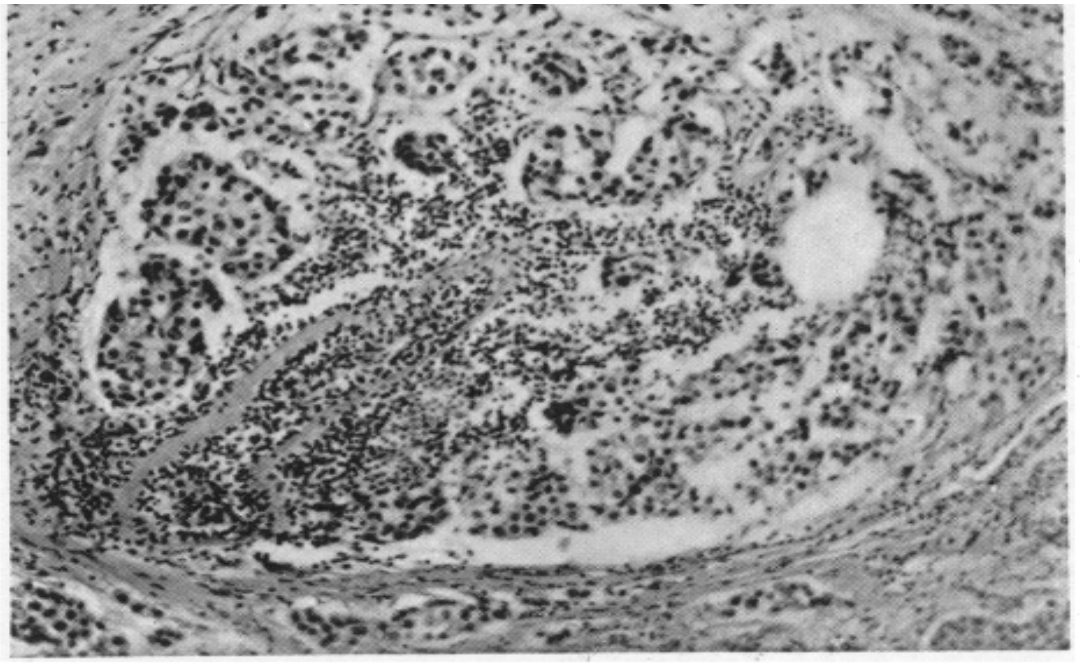
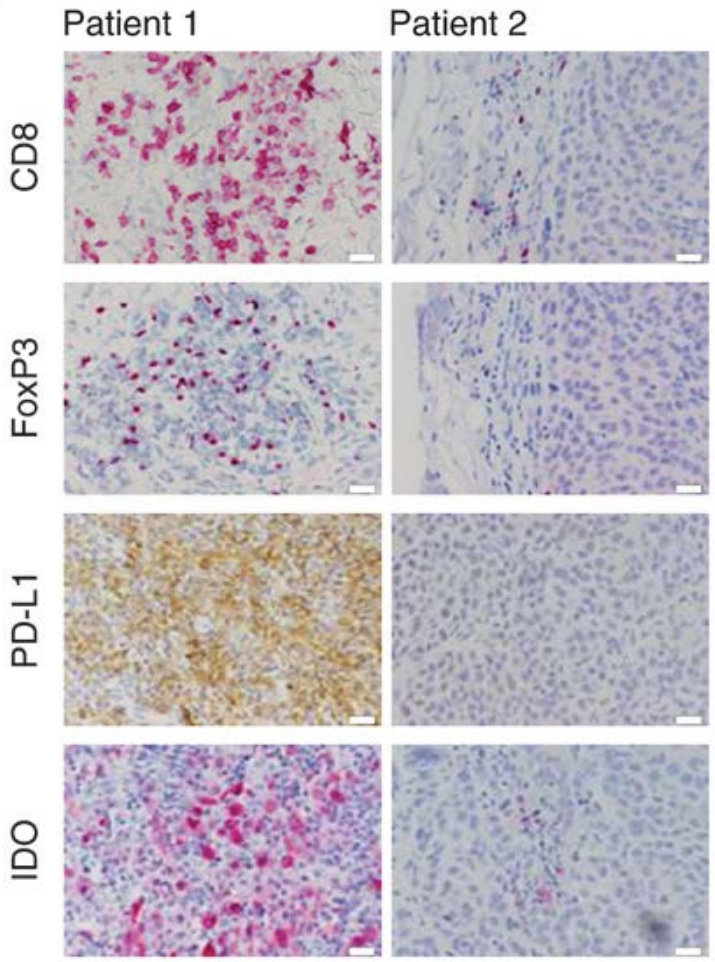


FIG. 1.—Lymphocytic infiltration intimately associated with cancer cells.

Annals of Surgery, 1922

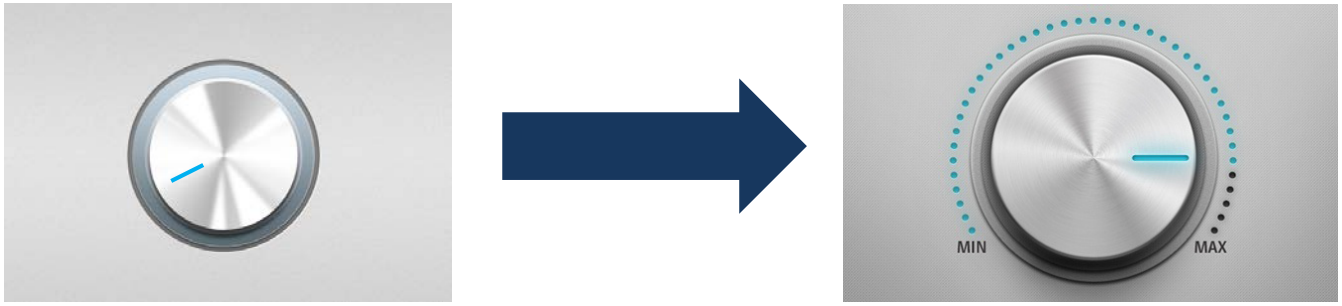
# A pro-inflammatory microenvironment dictates response to checkpoint blockade



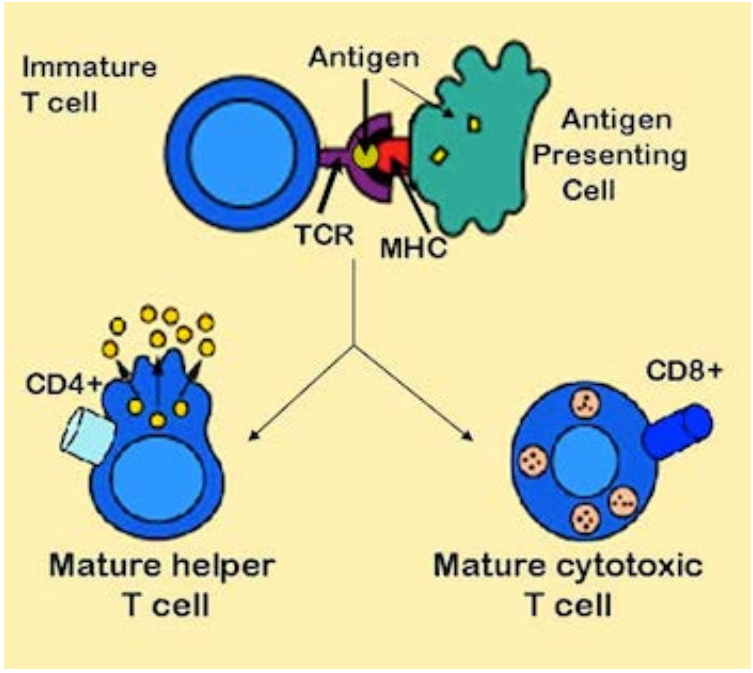

- Pre-existing, clonally expanded CD8 cytotoxic lymphocytes
- Type I/IFN-gamma driven "adaptive resistance"
- Tumor specific T-cells "primed and ready to eradicate" once the PD1-PDL1 "brake" is released

Spranger S. *et al. Sci Transl. Med 2013*

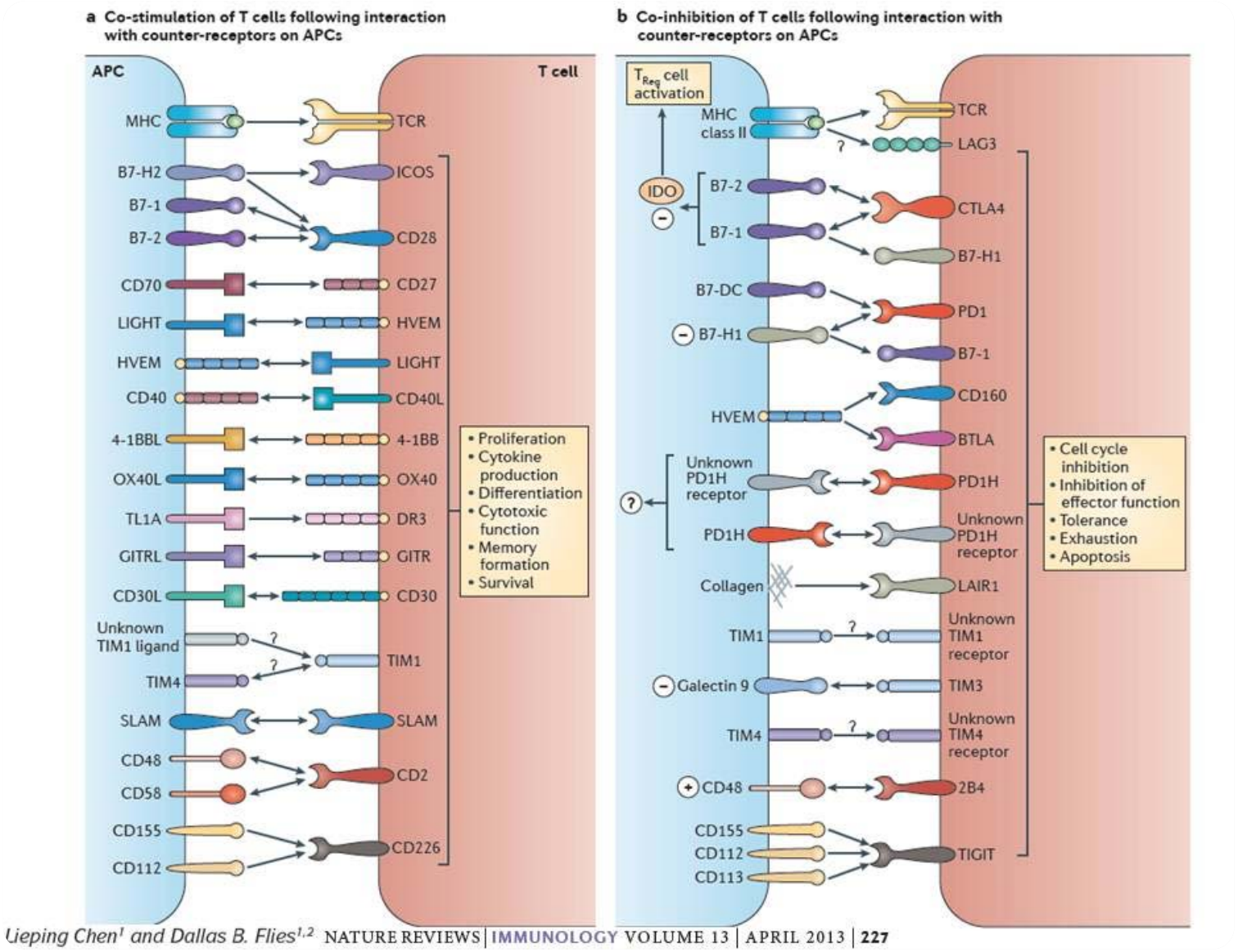
# Immunity and Cancer




**IL-2, γ-INF**



# Immuno-Oncology: Research & Preclinical Focus




Lieping Chen[1] and Dallas B. Flies[1,2] NATURE REVIEWS | IMMUNOLOGY VOLUME 13 | APRIL 2013 | 227

# Key Breakthroughs

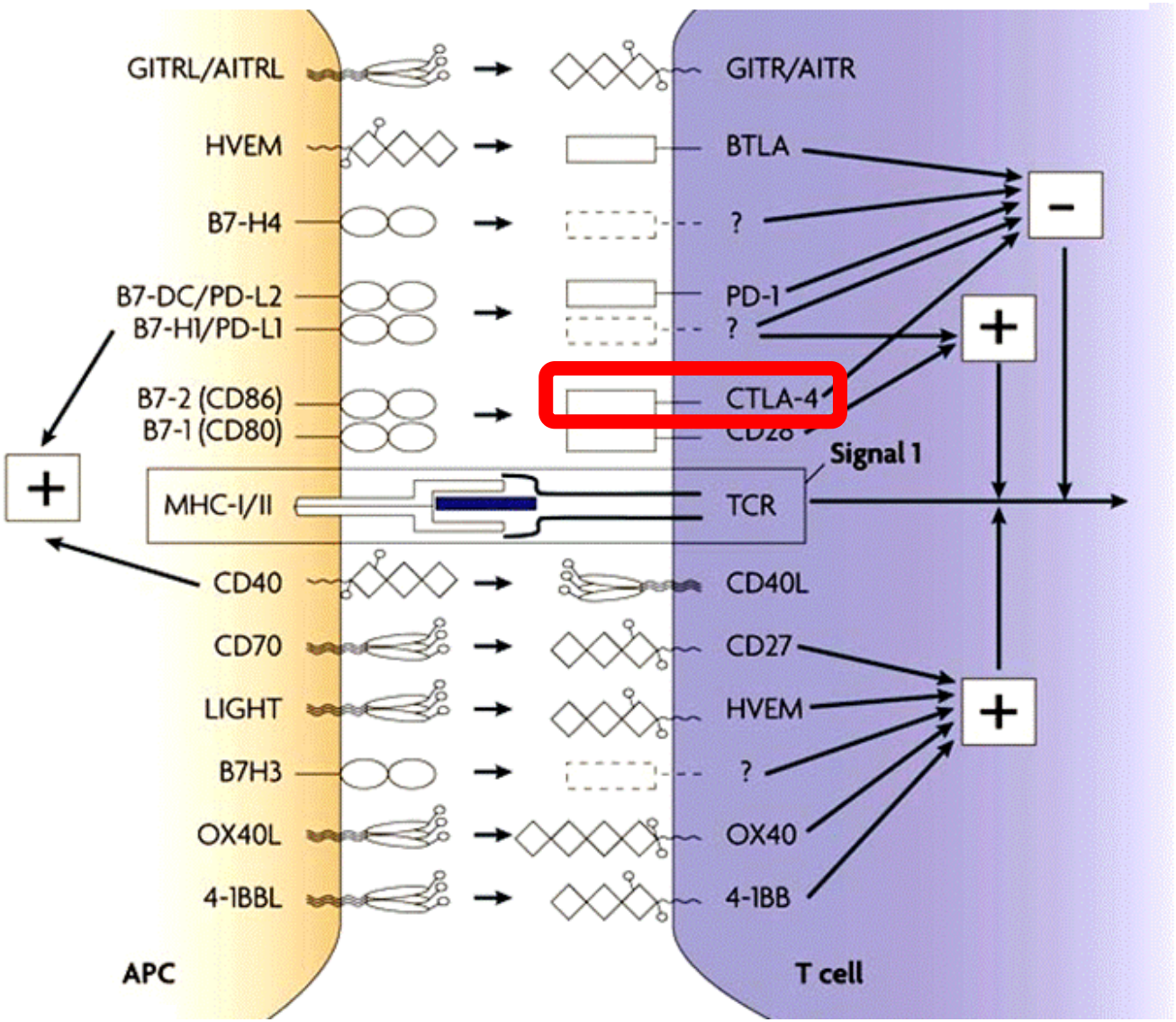
## 1991

- Peter Linsley at BMS discovered ligands for CTLA4 (JEM, 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



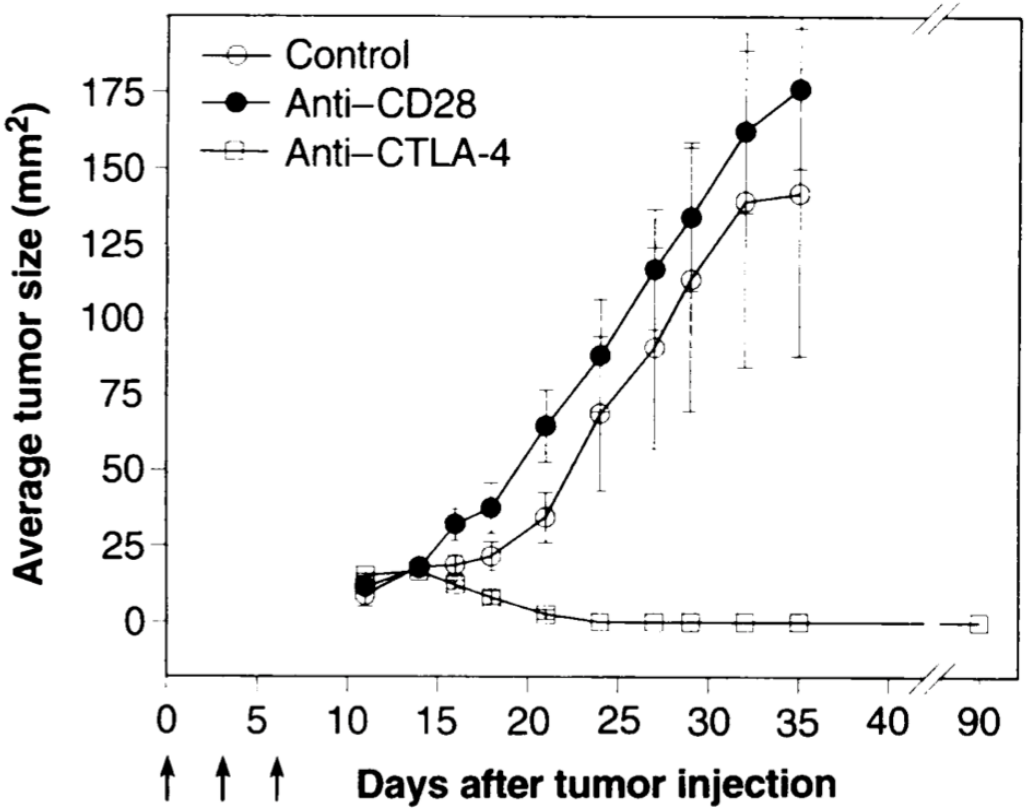

*Melero et al. (2007) Nature Rev. Cancer 7: 95*

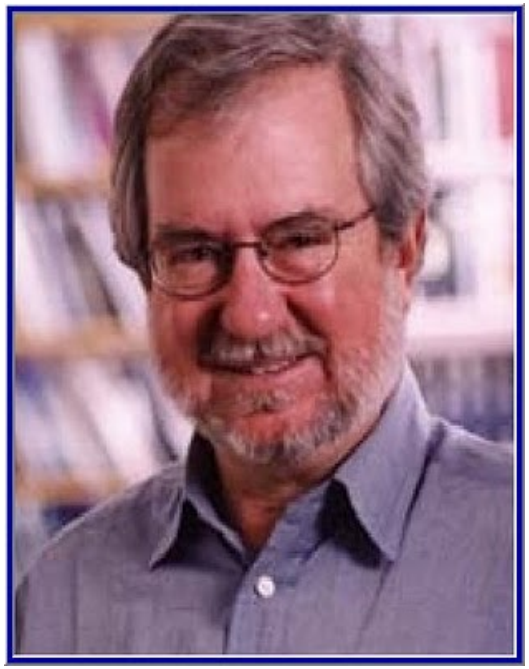
# 1996 Allison Proposes CTLA-4 Blockade for Cancer Therapy

SCIENCE • VOL. 271 • 22 MARCH 1996

## Enhancement of Antitumor Immunity by CTLA-4 Blockade

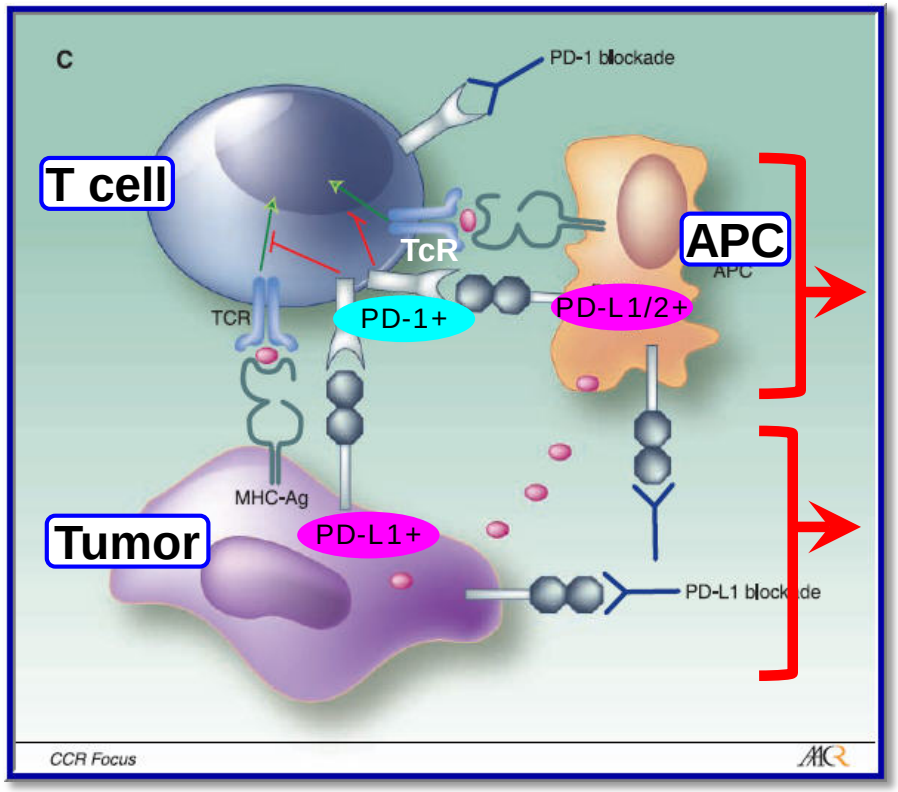
Dana R. Leach, Matthew F. Krummel, James P. Allison*



# 2015 Lasker-DeBakey Clinical Medical Research Award

# 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

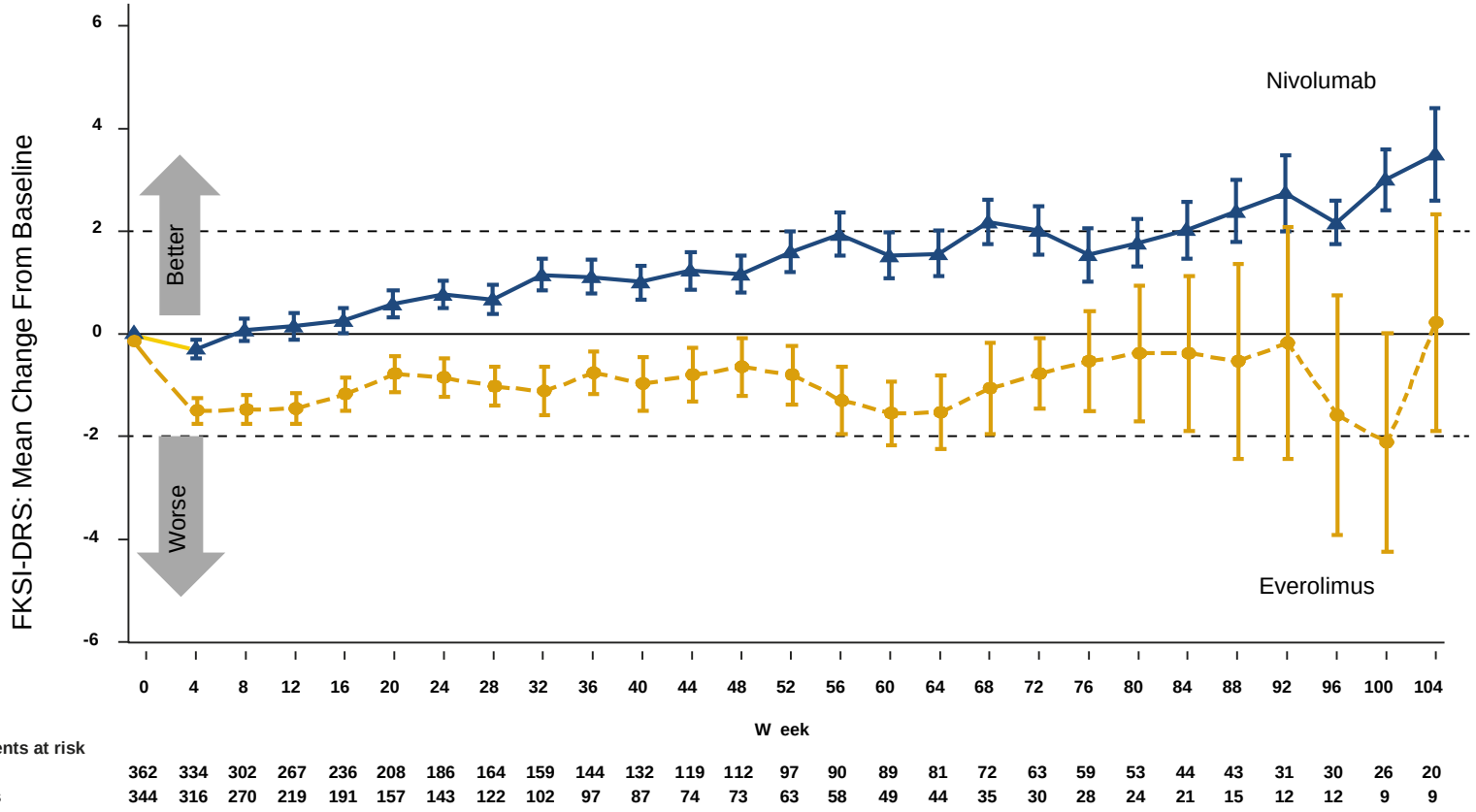
5 Phase III trials stopped early due to survival benefit

20+ tumor types

with over 50 trials in I-O

# Change from Baseline in Quality of Life Scores on FKSI-DRS

**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)**




| No. of patients at risk | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 362 | 334 | 302 | 267 | 236 | 208 | 186 | 164 | 159 | 144 | 132 | 119 | 112 | 97 | 90 | 89 | 81 | 72 | 63 | 59 | 53 | 44 | 43 | 31 | 30 | 26 | 20 |
| Everolimus | 344 | 316 | 270 | 219 | 191 | 157 | 143 | 122 | 102 | 97 | 87 | 74 | 73 | 63 | 58 | 49 | 44 | 35 | 30 | 28 | 24 | 21 | 15 | 12 | 12 | 9 | 9 |

*Open-label study

# Transformational Science & Medicine

## The New England Journal of Medicine

## 8 Publications in 10 months

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

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma
S.M. Ansell, M.D., et al. December 6, 2014

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma
J. Larkin, et al. May 31, 2015

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation
C. Robert, M.D., Ph.D., et al. November 16, 2014

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma
M.A. Postow, M.D., et al. April 20, 2015

Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma
Sagar Lonial, M.D., et al. June 2, 2015

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer
J. Brahmer, M.D., et al. May 31, 2015

Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1
D.L. Wyles, M.D., et al. August 20, 2015

YERVOY™ (ipilimumab) Injection for intravenous infusion

OPDIVO™ (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL

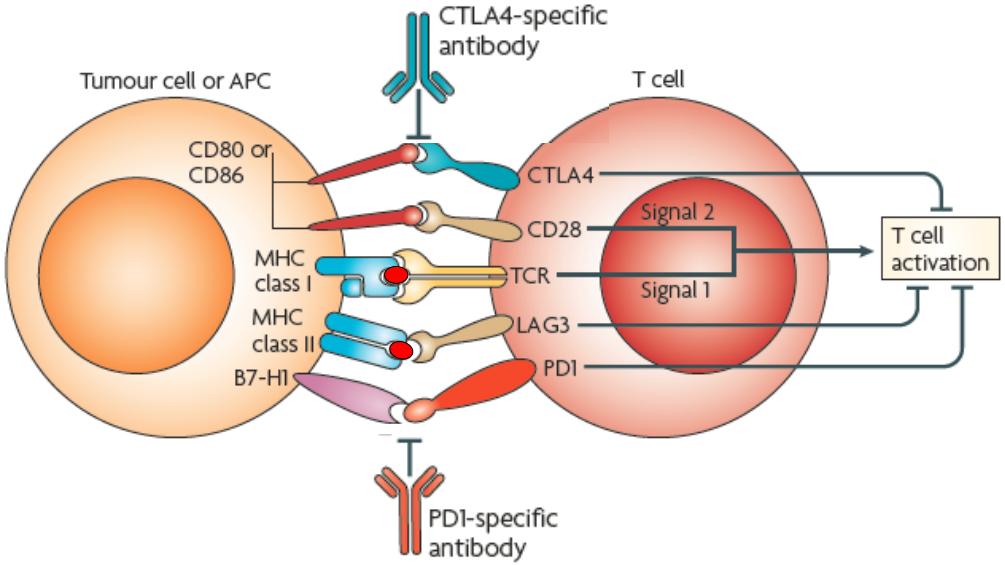
Empliciti™ (elotuzumab)

Daklinza™ (daclatasvir) 60 mg tablets

# 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



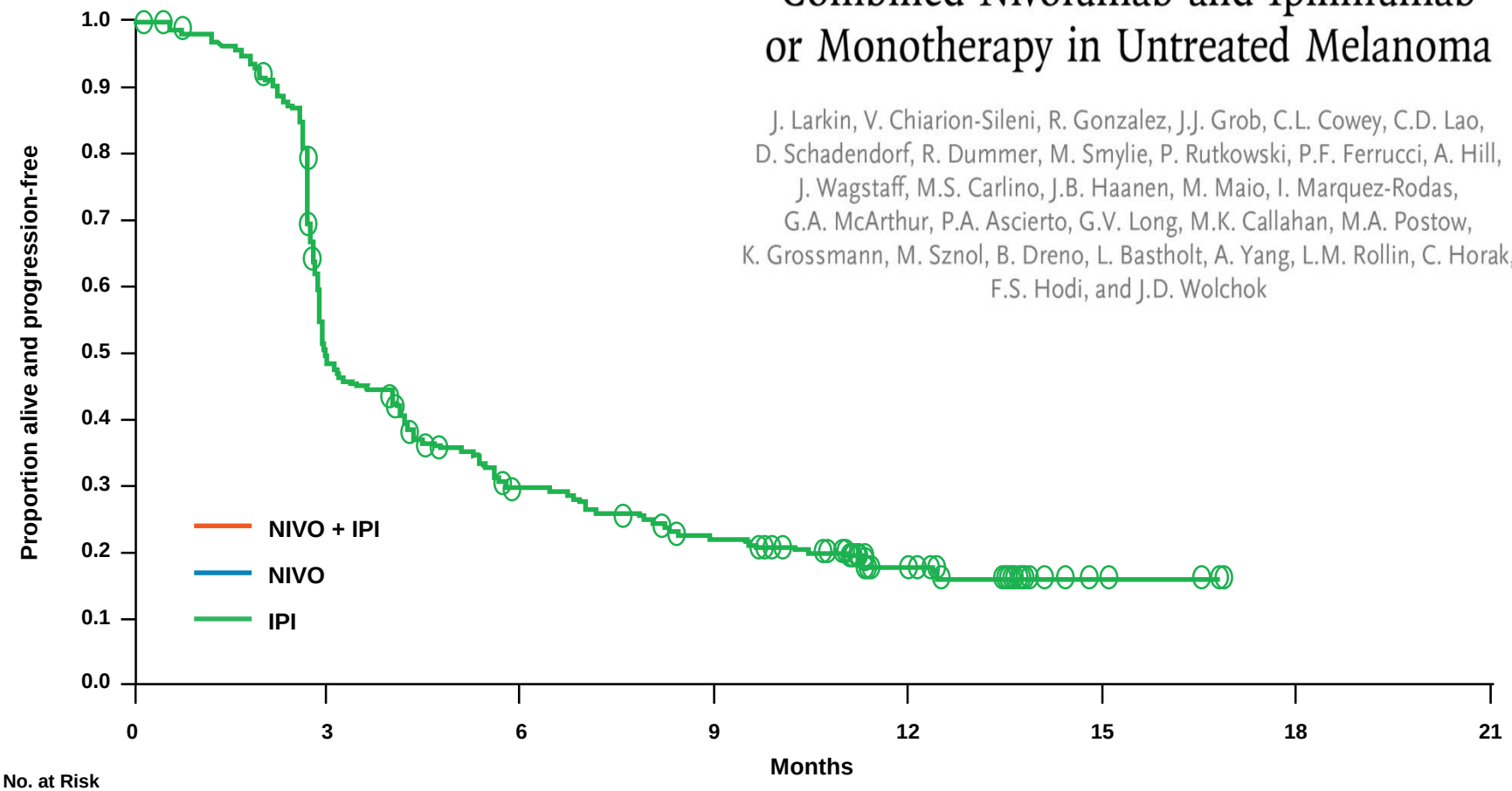

**OPDIVO® is associated with the following Warnings and Precautions including immune-mediated: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, rash, encephalitis, other adverse reactions; infusion reactions; and embryo-fetal toxicity.**
**Yervoy is associated with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

Drake, C. Nat Rev Immunol. 2010 Aug.

ORIGINAL ARTICLE

# Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok




No. at Risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| NIVO + IPI | 314 | 219 | 173 | 151 | 65 | 11 | 1 | 0 |
| NIVO | 316 | 177 | 147 | 124 | 50 | 9 | 1 | 0 |
| IPI | 315 | 137 | 77 | 54 | 24 | 4 | 0 | 0 |

PFS: Intent to treat

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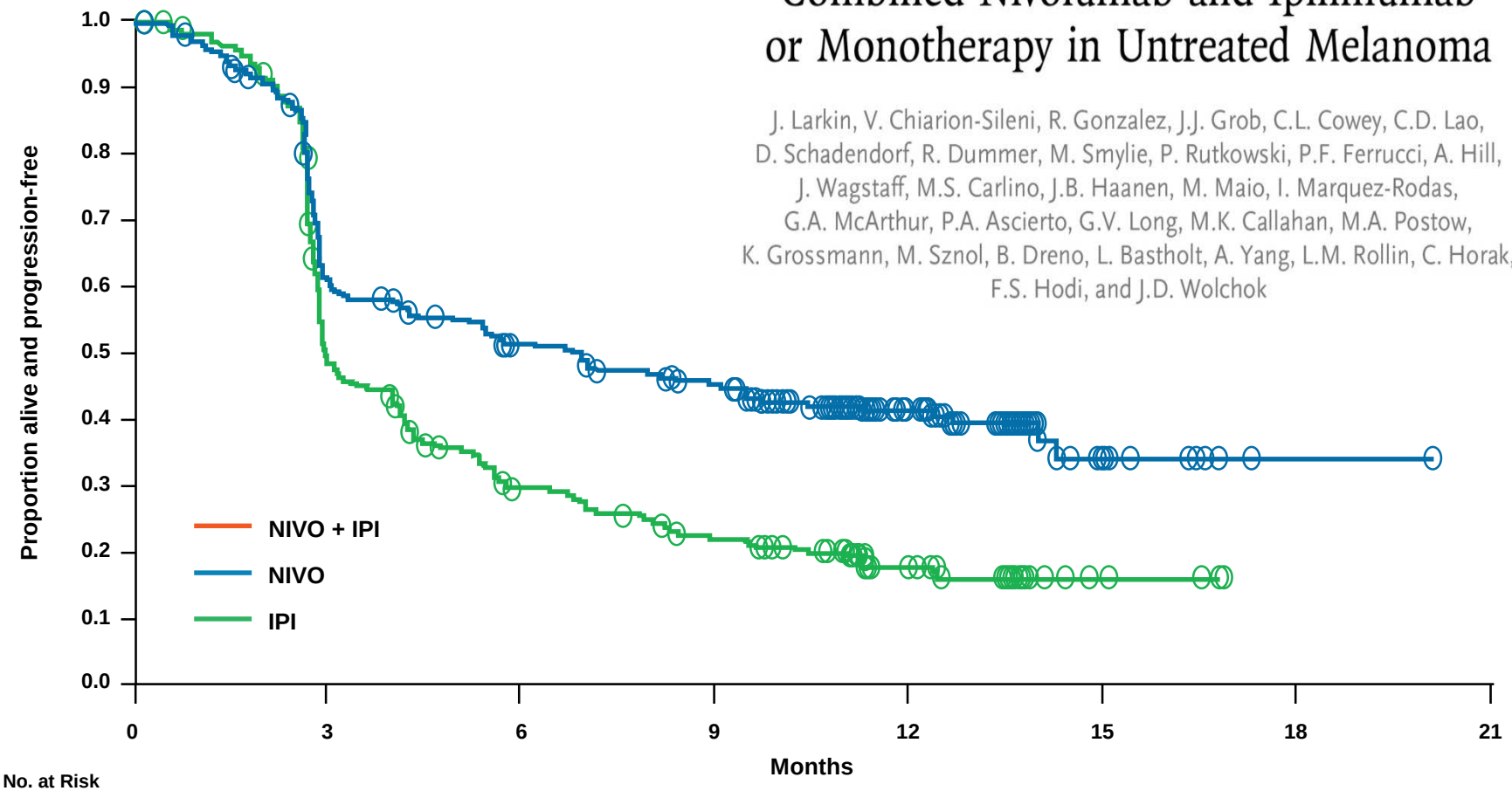


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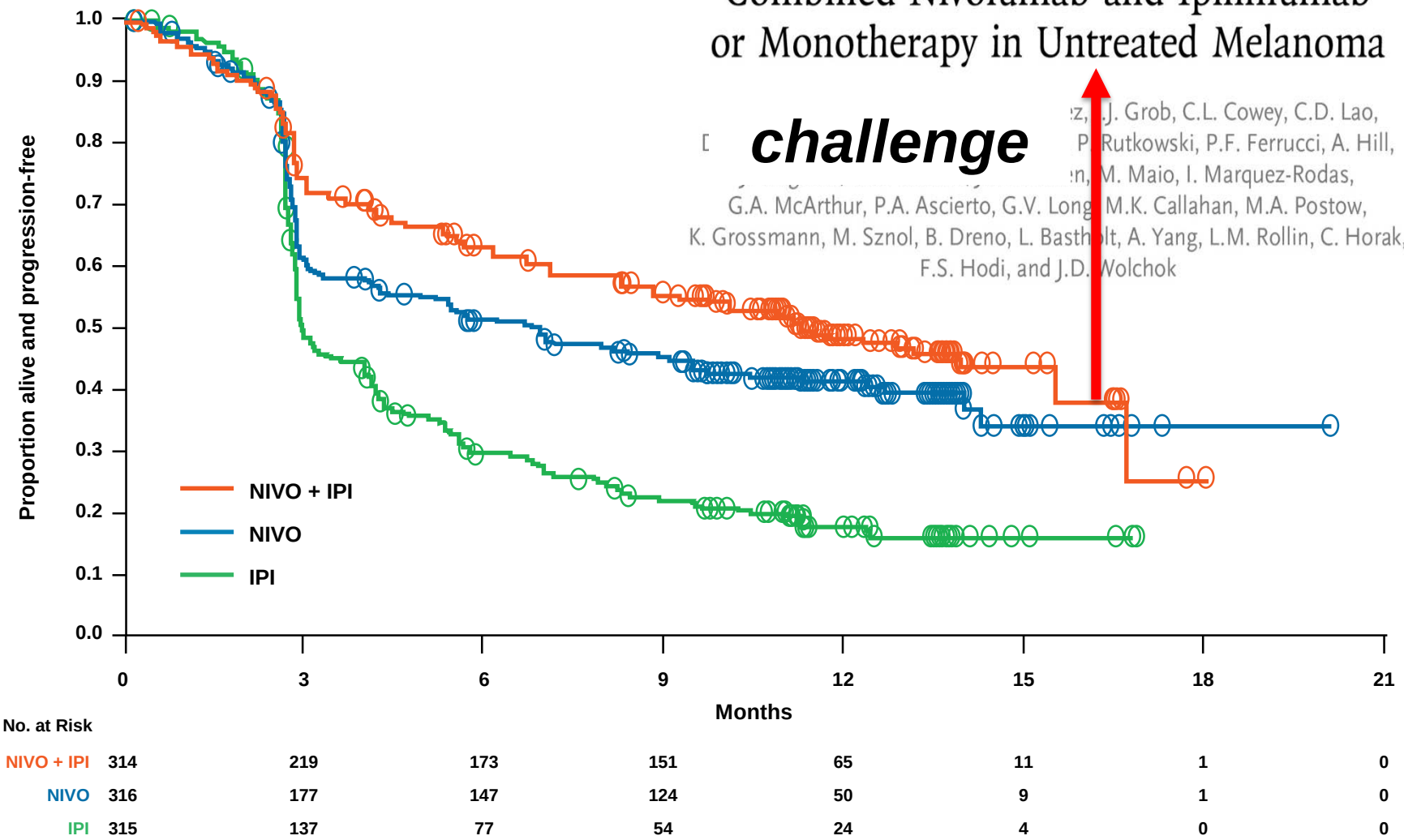
***challenge***




No. at Risk

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PFS: Intent to treat

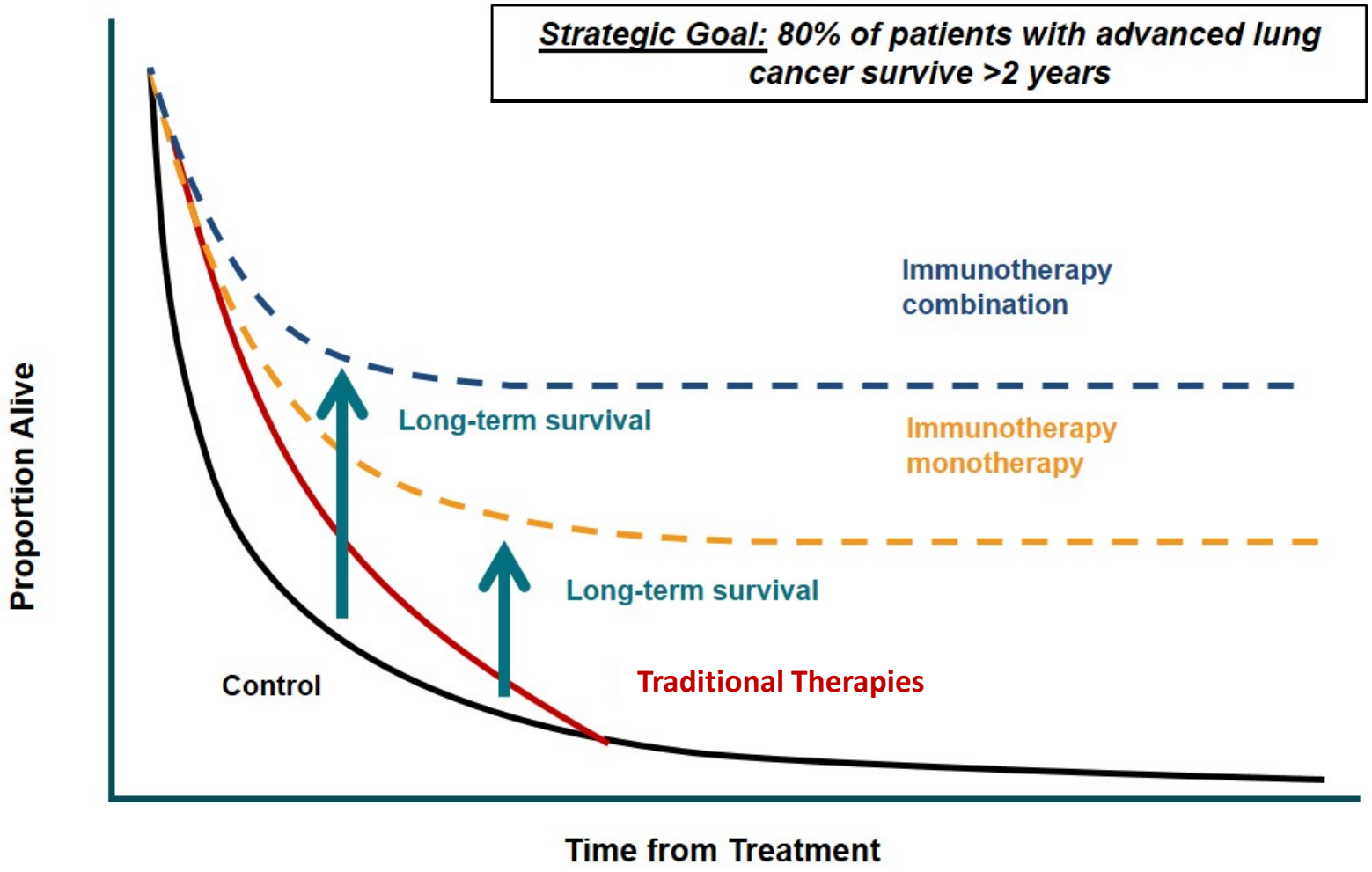
# I-O and BMS Intellectual Property

- 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

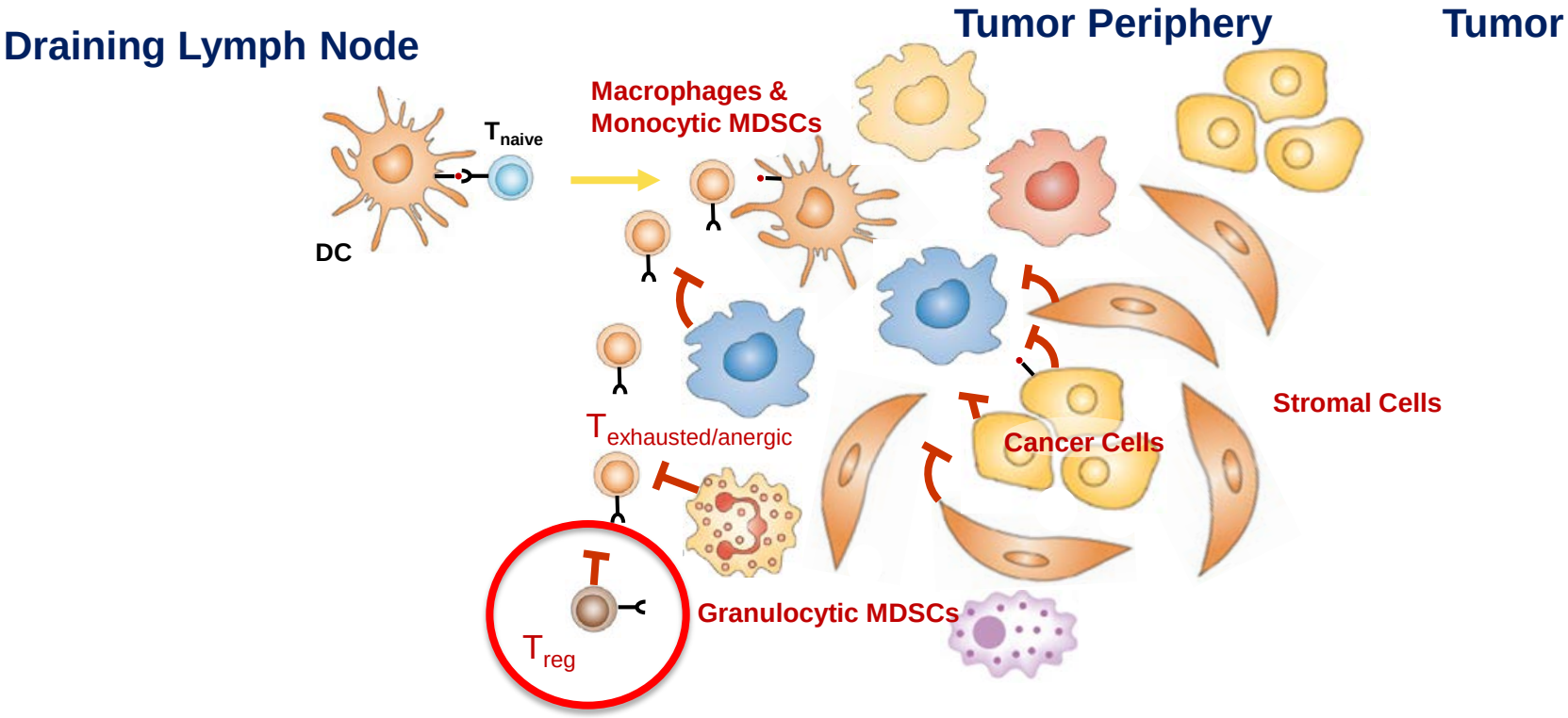
- Displace standard of care (SOC) in multiple tumor types, lines of therapy and histologies
- Use I-O combinations to meaningfully increase likelihood of long-term survival
- Expand and accelerate broad portfolio of novel mechanisms

# Immuno-Oncology Agent(s) Expected to be Foundational in the Treatment of Multiple Cancers: Example of Lung Cancer



# Immuno-Oncology: Research & Preclinical Focus

## Multiple diverse pathways of immune attenuation involve diverse cell types, signals, and targets:



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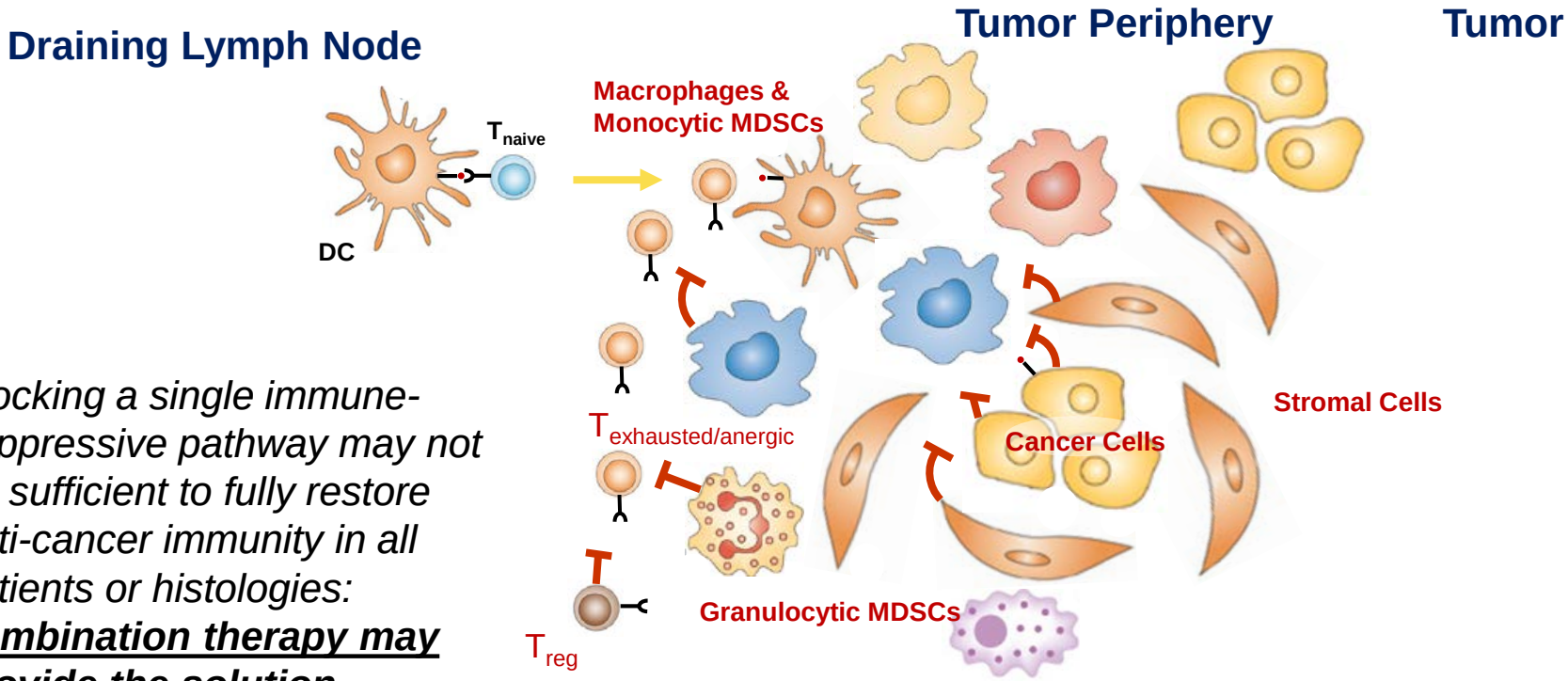



*Blocking a single immune-suppressive pathway may not be sufficient to fully restore anti-cancer immunity in all patients or histologies:* ***combination therapy may provide the solution***

# Gut Bacteria Modify Immunotherapy Effectiveness

CANCER IMMUNOTHERAPY

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

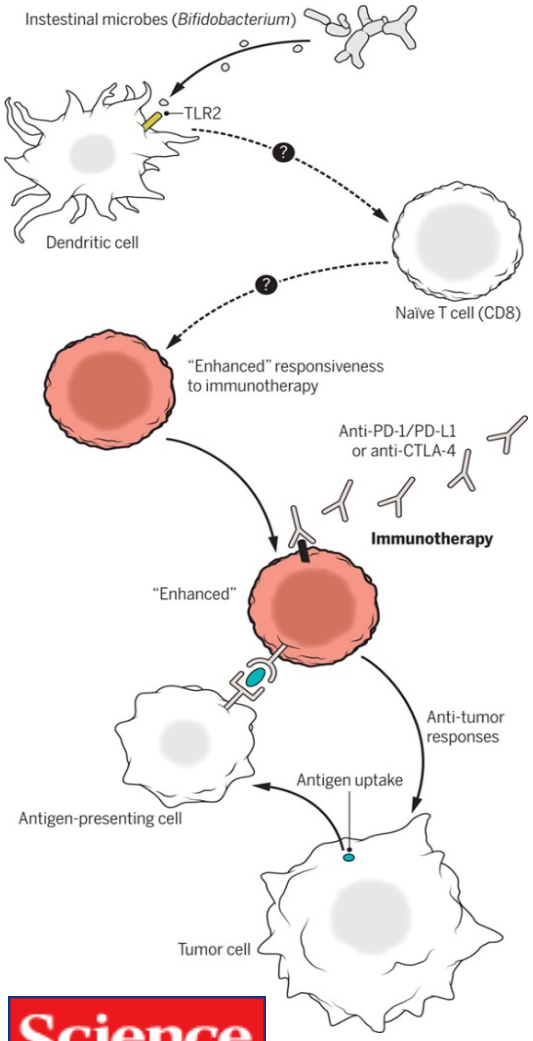
CANCER IMMUNOTHERAPY

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

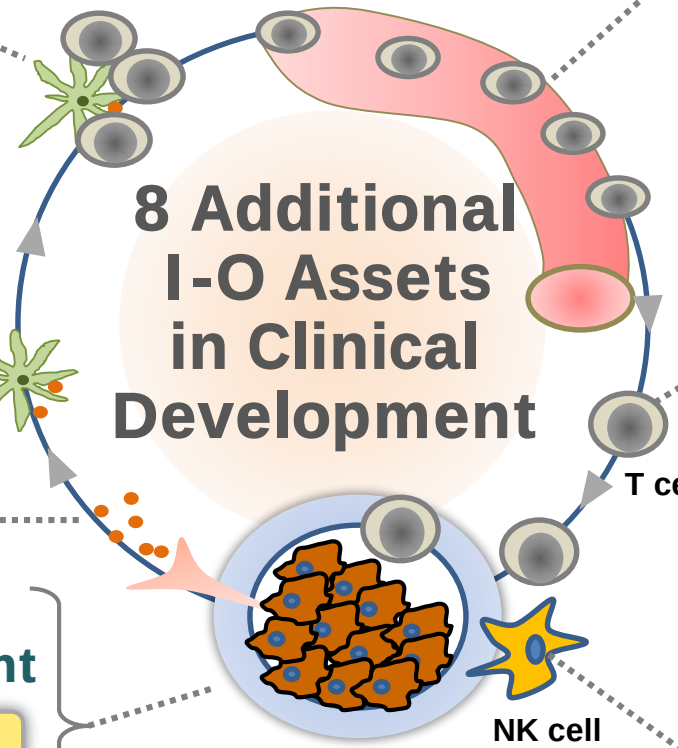



Published by AAAS

Alexandra Snyder et al. Science 2015;350:1031-1032

# 2016: Diversifying in Immuno-Oncology

*Next wave of innovation: areas of focus*




**Priming & Activation**

YERVOY (ipilimumab)
Injection for intravenous infusion

**Antigen Presentation**

**Antigen Release**

**Tumor Microenvironment**

- anti-CSF1R
- IDO
- anti-CD73

**T Cell Trafficking and Infiltration**

**T Cell Activation**

OPDIVO (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

- anti-LAG3
- Urelumab (anti-CD137)
- anti-GITR
- anti-OX40

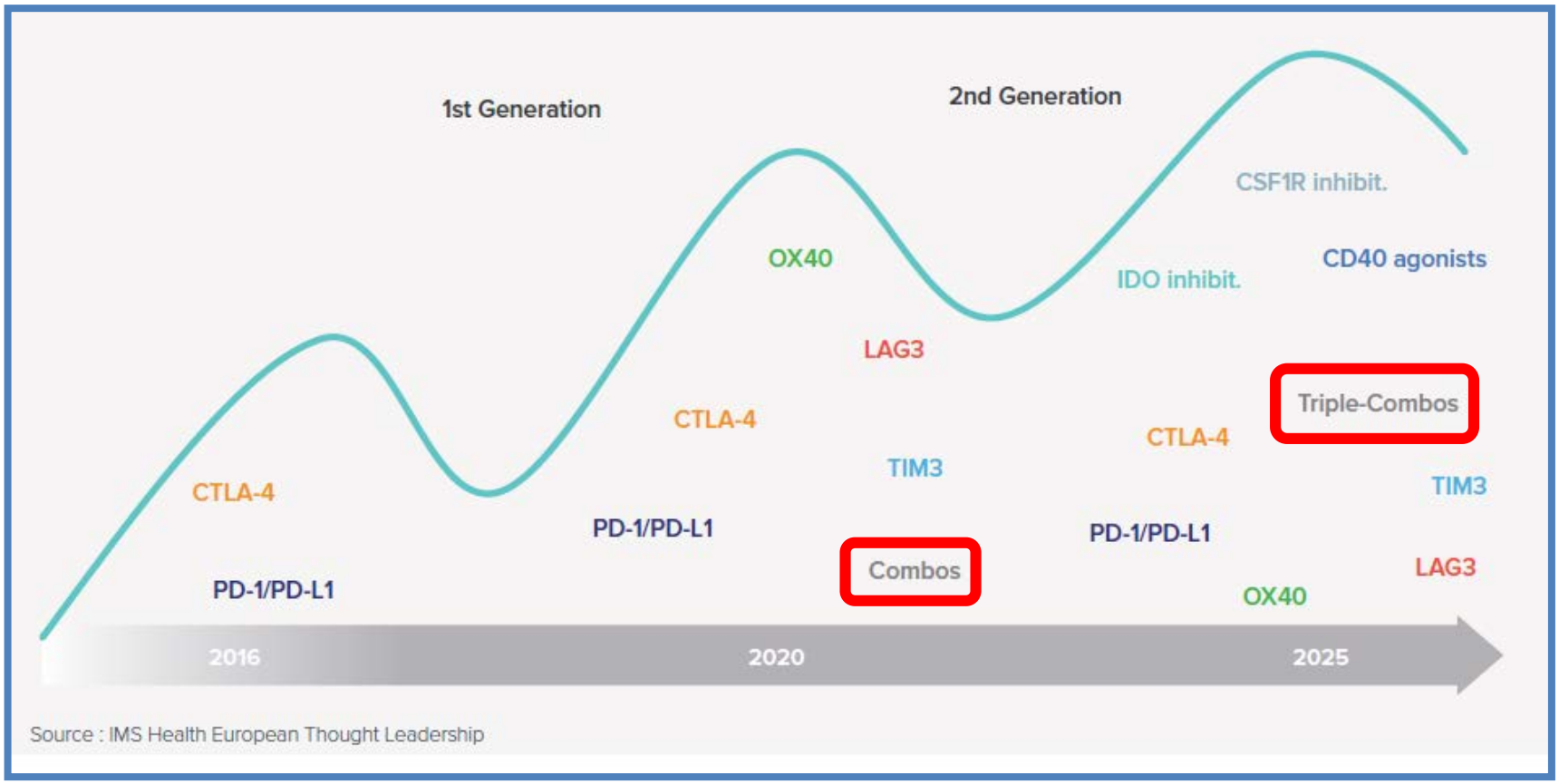
**NK Cell Activation**

Empliciti (elotuzumab)

- Lirilumab (anti-KIR)

**BMS assets beginning clinical studies in 2016**

# The Future of I-O Drug Development



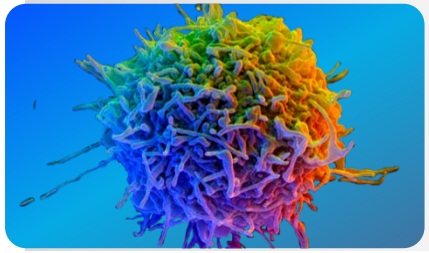

Underscores the challenge of identifying the most promising combination I-O therapies that may potentially prolonged survival in patients with cancer

# Medical Insights

YERVOY™ (ipilimumab) Injection for intravenous infusion

OPDIVO™ (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL

## LUNG

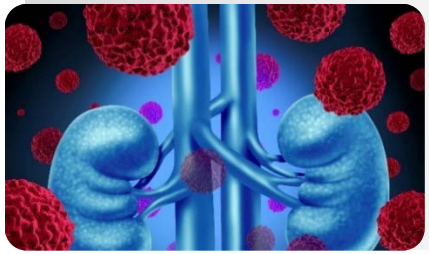


- **Only PD-1 indicated for all 2nd line NSCLC patients in US, EU*, and JP**
- **No testing requirement**
- **Strong access and reimbursement**

## 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

**NILS LONBERG**
**ALAN KORMAN**

**Countless other BMS scientists, clinicians, leaders.**

**JAMES ALLISON**

**Clinical Collaborators**

Jedd Wolchok, MSKCC
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Robert Motzer, MSKCC
Mario Sznol, Yale CC
Steve Hodi, Dana Farber CC
Jeffrey Weber, H.L. Moffitt CC
Walter Urba, Providence CC
Steven O'Day, Los Angeles SCI
Eric Small, UCSF
Simon Tchekmedyian, Pacific Shores MG
Steven Rosenberg, NCI
James Yang, NCI
Giao Phan, NCI
Suzanne Topalian, Johns Hopkins
Julie Brahmer, Johns Hopkins
Caroline Robert, Gustave Roussy
Naiyer Rizvi, Columbia University

# Working Together for Patients

Bristol-Myers Squibb

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


Carl P Decicco

SVP, Head of Discovery

Bristol Myers-Squibb


March 31, 2016