CONSENSUS OR CONTROVERSY?

Clinical Investigators Provide Perspectives on the Treatment of Metastatic Non-Small Cell Lung Cancer in Patients Without Targetable Tumor Mutations

March 17, 2017
7:30 PM – 9:00 PM

Faculty

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Corey J Langer, MD
Naiyer Rizvi, MD
Heather Wakelee, MD

Moderator

Neil Love, MD

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Disclosures for Dr Brahmer

Advisory Committee	Bristol-Myers Squibb Company, Merck
Consulting Agreements	Bristol-Myers Squibb Company, Celgene Corporation, Lilly, Merck
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Merck

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Disclosures for Dr Rizvi

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Ownership Interest	Gritstone Oncology

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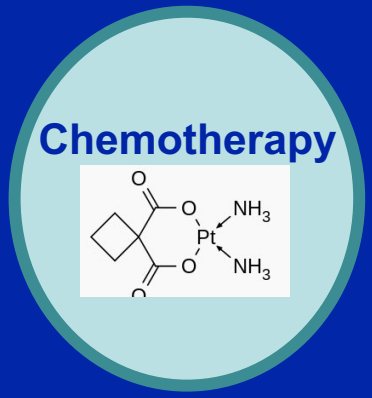
Grants	Clovis Oncology, Exelixis Inc, Gilead Sciences Inc, Pharmacyclics LLC, an AbbVie Company, Xcovery

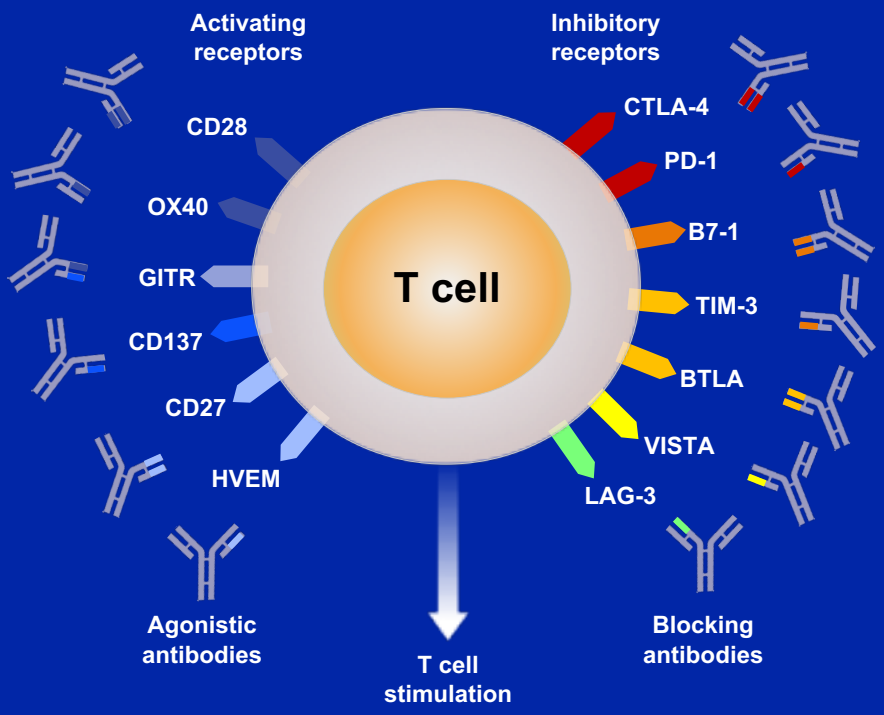
Disclosures for Moderator Neil Love, MD

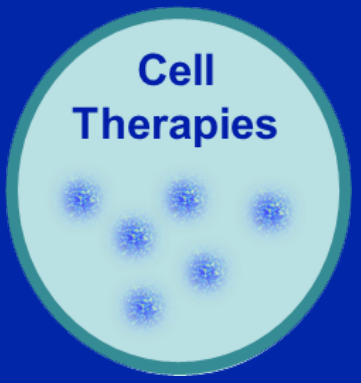
Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma, Agendia Inc, Amgen Inc, Ariad Pharmaceuticals Inc, Array BioPharma Inc, Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Baxalta Inc, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, CTI BioPharma Corp, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Foundation Medicine, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Halozyme Inc, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Lexicon Pharmaceuticals Inc, Lilly, Medivation Inc, a Pfizer Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, NanoString Technologies, Natera Inc, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals, an Amgen subsidiary, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seattle Genetics, Sigma-Tau Pharmaceuticals Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro Inc, Teva Oncology, Tokai Pharmaceuticals Inc and VisionGate Inc.

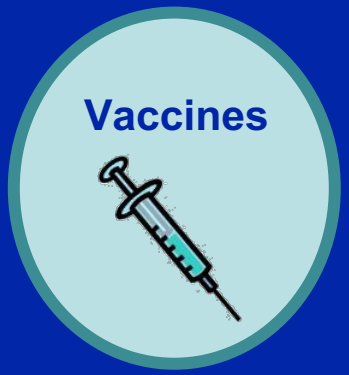
Module 4: Ongoing Investigation, Future Directions with Immune Checkpoint Inhibitors

T-Cell Immune Checkpoints as Targets for Immunotherapy









Adapted from Mellman I et al. *Nature* 2011;480:481-9.

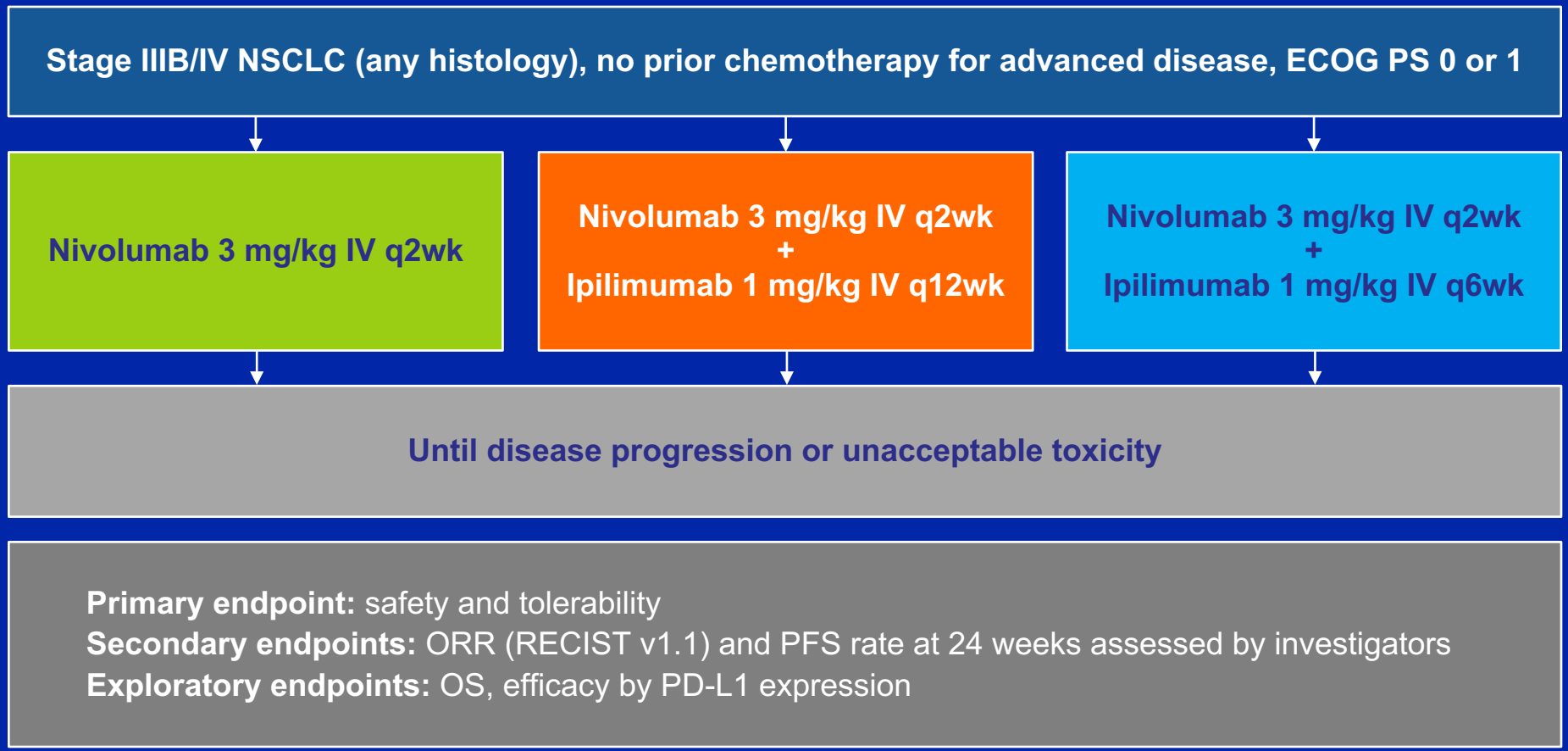
Anti-PD/PD-L1 as Backbone to Combination Tx?

Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
- Chemotherapy - Radiation/ablation - EGFR/ALK TKI - Anti-VEGF/VEGFR inhibitor - Vasc disrupt agent - Hypomethylating agent - HDAC inhibitor - SPK inhibitor - C-Met inhibitor - Glutaminase inhibitor - Dasatinib - Vaccine - Gene therapy - IL15 agonist - PEG IL10 - $TGF_{\beta}R1$ inhibitor - Anti-CD27 - Anti-CXCR4 - Anti-CSF-1R - IDO-1 inhibitor - Anti-CTLA4 - Anti-LAG - Anti-TIM-3 - Anti-KIR	- Chemotherapy - Radiation - EGFR/ALK TKI - Anti-VEGF/VEGFR inhibitor - Hypomethylating agent - HDAC inhibitor - CDK inhibitor - BTK inhibitor - PI3K inhibitor - KIT/CSF1R/FLT3 inh - FGFR inhibitor - JAK1 inhibitor - CRM1 inhibitor - FAK inhibitor - Anti-EGFR - Anti-CEACAM1 - PEG hyaluronidase - Vaccine - Oncolytic - PEG IL10 - Anti-CSF-1 - IDO1 inhibitor - Anti-CTLA4 - Anti-B7-H3	- Chemotherapy - Radiation - EGFR/ALK TKI - Anti-VEGF/Ang-2 - MEK inhibitor - Vaccine - Adoptive cell therapy - Anti-CEA/CD3 - Anti-CEA/IL-2 - Anti-OX40 - Anti-CD40 - Anti-CD27 - Anti-CSF-1 - Adenosine A2A inhibitor - IDO-1 inhibitor - Anti-CTLA4 - Anti-TIGIT	- Chemotherapy - Radiation - EGFR/ALK TKI - VEGFR inhibitor - BTK inhibitor - MEK inhibitor - HAD inhibitor - PARP inhibitor - WEE1 inhibitor - ATR inhibitor - Anti-OX40 - CXCR4 inhibitor - CSF - Anti-CD73 - Anti-CCR4 - Anti-CSF1R - Anti-NKG2A - Adenosine A2a inhibitor - IDO1 inhibitor - Anti-CTLA4 - Anti-PD-1
		Avelumab: ALK inhibitor (crizotinib and lorlatinib), anti-41BB, anti-OX40	

Are there any situations in which you would use the combination of an anti-PD-1/PD-L1 antibody and an anti-CTLA-4 antibody outside of a trial setting?

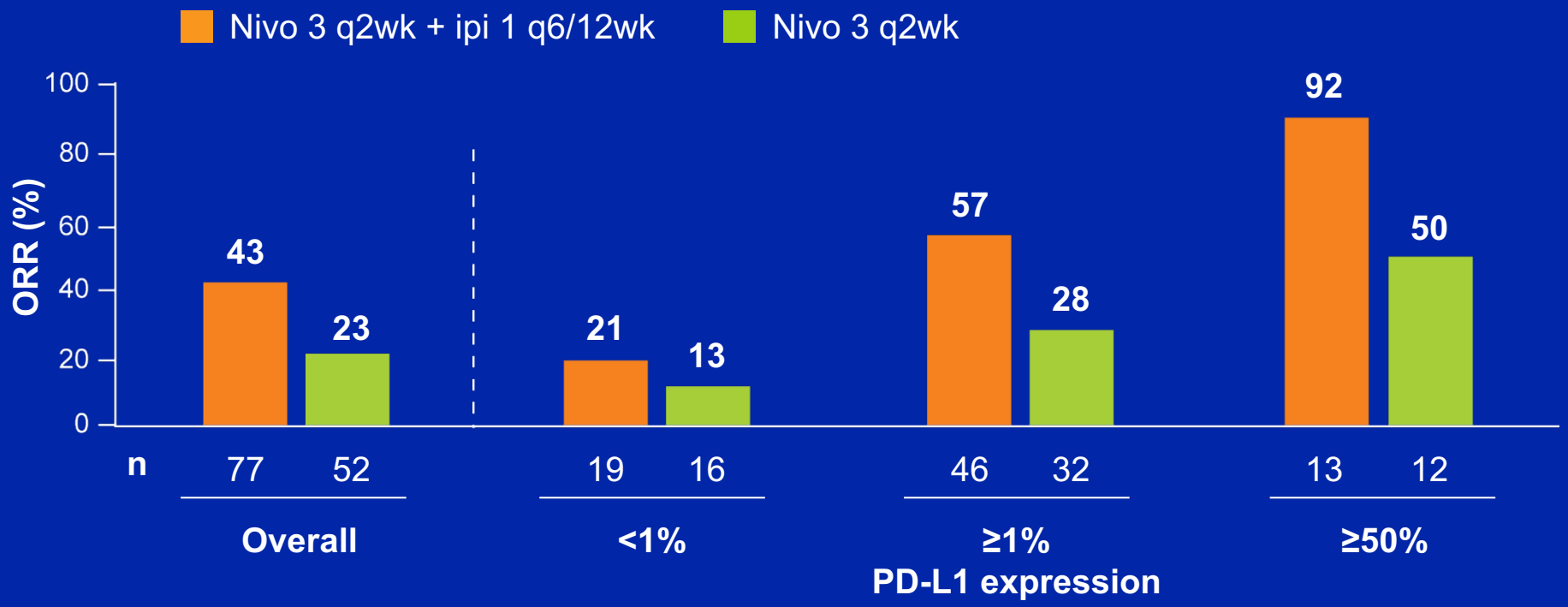
 JULIE R BRAHMER, MD	Yes, small cell lung cancer, second line
 COREY J LANGER, MD	Yes, small cell lung cancer
 HEATHER WAKELEE, MD	Yes, second- or third-line therapy
 RAMASWAMY GOVINDAN, MD	No
 JOEL W NEAL, MD, PHD	Yes, very functional patient with small cell lung cancer
 GREGORY J RIELY, MD, PHD	Yes, small cell lung cancer

CheckMate 012: A 3-Arm Phase I Trial of Nivolumab Alone or with Ipilimumab in NSCLC



Gettinger S et al. *Proc WCLC* 2016;Abstract OA03.01

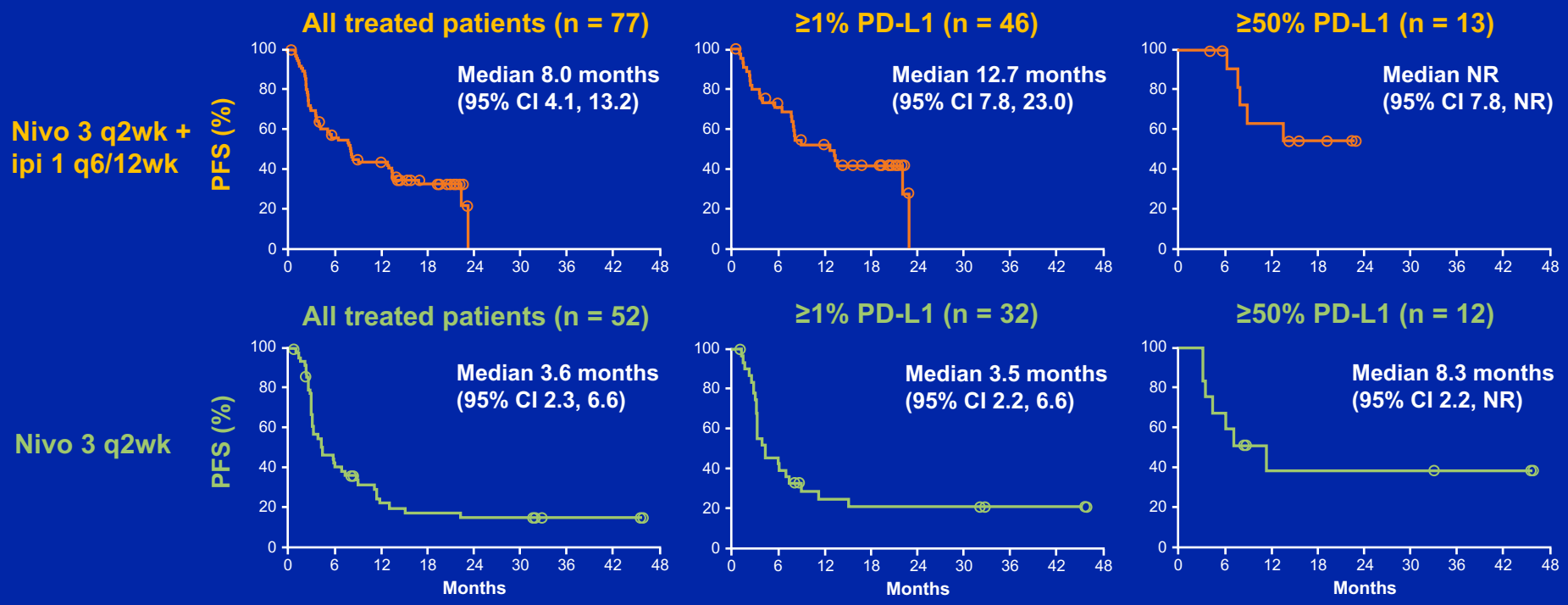
CheckMate 012: Response by PD-L1 expression



- 5 CRs (10% were achieved in the nivolumab monotherapy cohort (1 in a patient with tumor PD-L1 expression <1%)
- 6 CRs (8%) were achieved in the nivolumab + ipilimumab cohorts (3 in patients with tumor PD-L1 expression <1%)

Gettinger S et al. *Proc WCLC* 2016;Abstract OA03.01

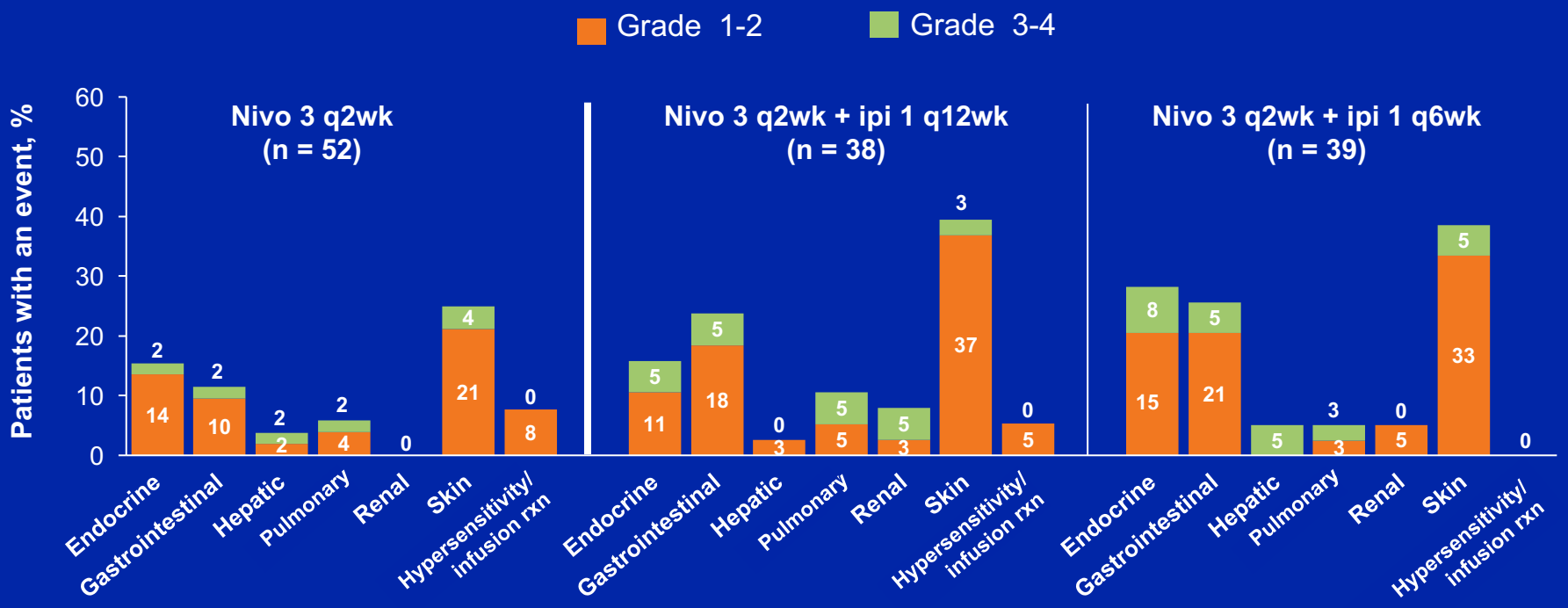
CheckMate 012: PFS by PD-L1 expression



- Data are based on median follow-up durations of 16 months (combination cohorts) and 22 months (monotherapy)

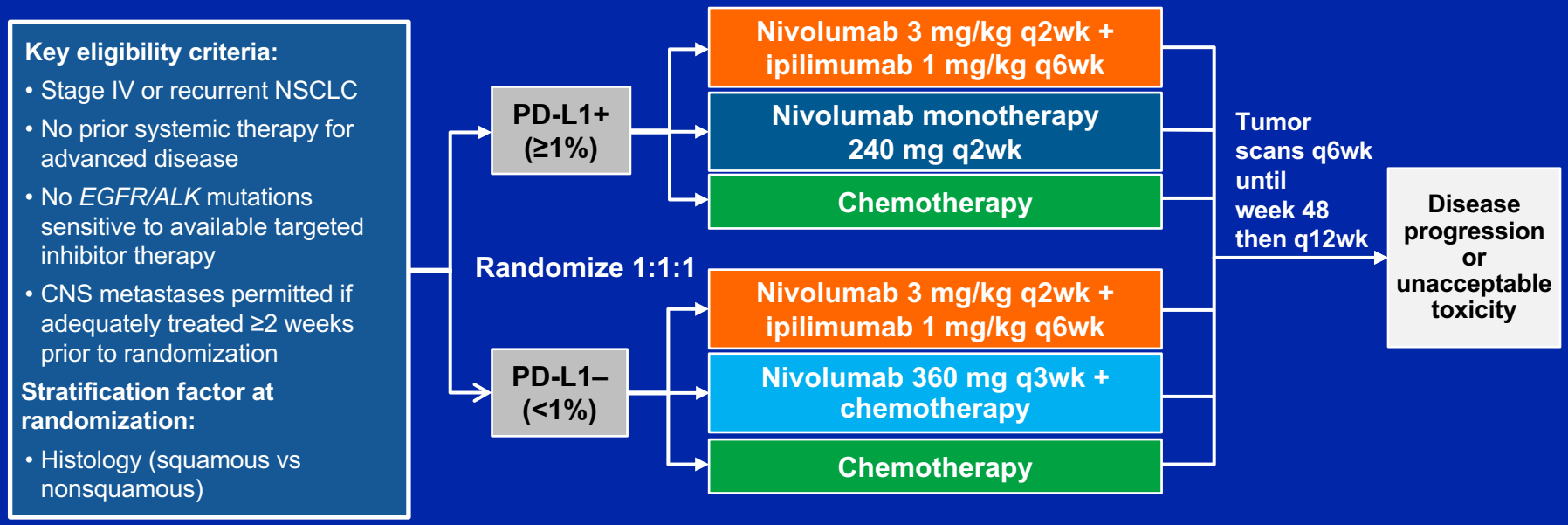
Gettinger S et al. *Proc WCLC* 2016;Abstract OA03.01

CheckMate 012: Treatment-Related AEs



Gettinger S et al. *Proc WCLC* 2016;Abstract OA03.01

CheckMate 227: A Phase III Trial of Nivolumab Alone or in Combination with Ipilimumab or Chemotherapy



January 19, 2017: Company stated that it would NOT ask for accelerated approval of this combination based on (unknown to us) data available at the time.

http://investor.bms.com/investors/news-and-events/press-releases/press-release-details/2017; www.clinicaltrials.gov. Accessed March 2017

KEYNOTE 021 – Cohorts D and H

- N = 44 patients
- Pembrolizumab 2 mg/kg q3wk + ipilimumab 1 mg/kg q3wk
- ORR only 25%, not related to PD-L1 expression
- Significant toxicity

Gubens MA et al. *Proc ASCO* 2016;Abstract 9027.

Safety and antitumour activity of durvalumab plus tremelimumab in non-small-cell lung cancer: a multicentre, phase 1b study

Scott Antonia, Sarah B Goldberg*, Ani Balmanoukian, Jamie E Chaft, Rachel E Sanborn, Ashok Gupta, Rajesh Narwal, Keith Steele, Yu Gu, Joyson J Karakunnel, Naiyer A Rizvi*

Summary

Background PD-L1 and CTLA-4 immune checkpoints inhibit antitumour T-cell activity. Combination treatment with the anti-PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab might provide greater antitumour activity than either drug alone. We aimed to assess durvalumab plus tremelimumab in patients with advanced squamous or non-squamous non-small-cell lung cancer (NSCLC).

Lancet Oncol 2016; 17: 299–308

Published Online
February 5, 2016
http://dx.doi.org/10.1016/S1470-2045(15)00544-6

Lancet Oncol 2016;17(3):299-308.

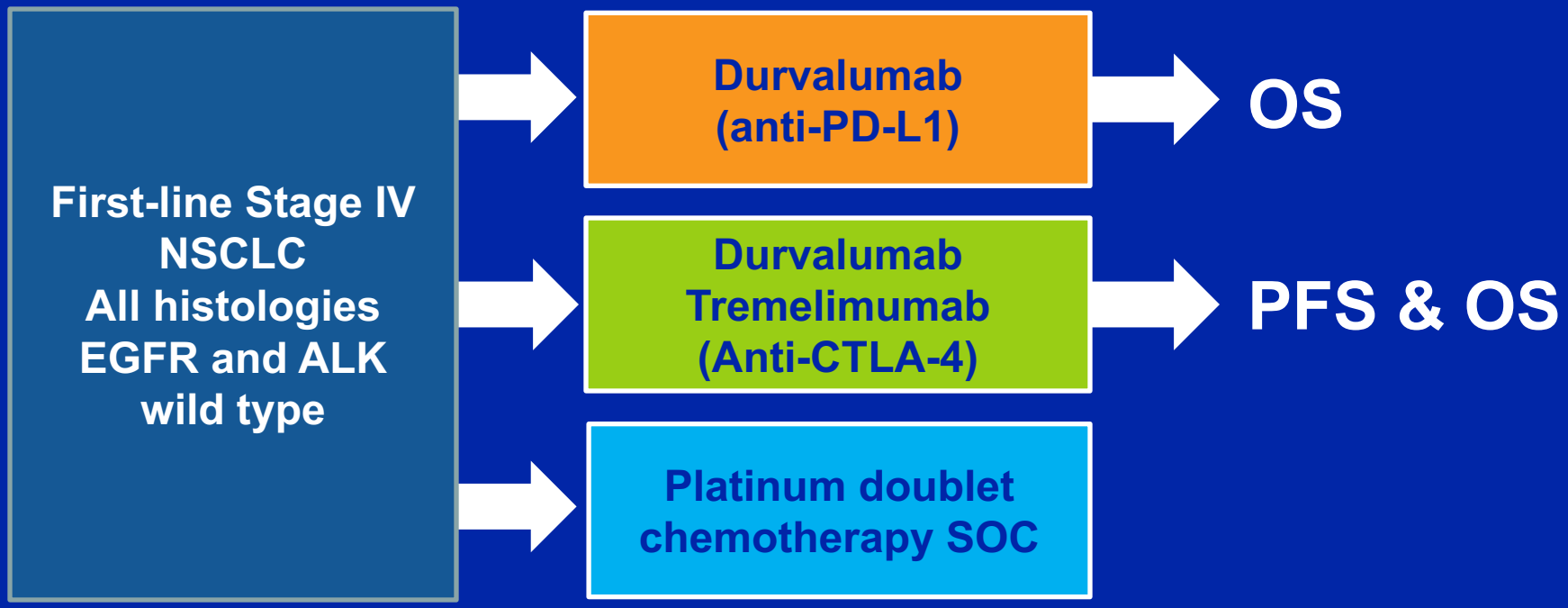
Objective Response Rate with Durvalumab Combined with Tremelimumab

	Durvalumab 10-20 mg/kg q2 or 4wk + tremelimumab 1 mg/kg	Durvalumab 10-20 mg/kg q2 or 4wk + tremelimumab 3 mg/kg	Durvalumab 15 mg/kg q4wk + tremelimumab 10 mg/kg
All evaluable	6/26 (23%)	5/25 (20%)	0/9 (0%)
PD-L1 ≥ 25%	2/9 (22%)	2/5 (40%)	0/4 (0%)
PD-L1 < 25%	4/14 (29%)	2/17 (12%)	0/4 (0%)
PD-L1 negative	4/10 (40%)	1/10 (10%)	0/3 (0%)

Antonia S et al. *Lancet Oncol* 2016;17(3):299-308.

MYSTIC: A Phase III Trial of Durvalumab with or without Tremelimumab versus Standard of Care in NSCLC

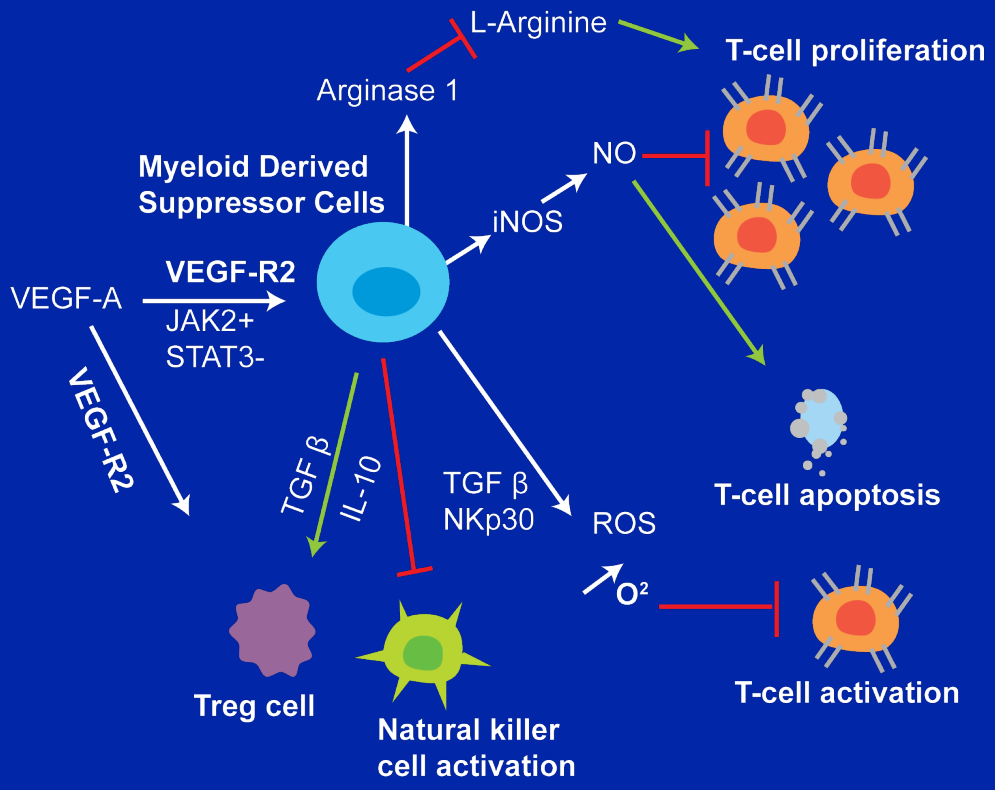
NCT02453282 (Closed)



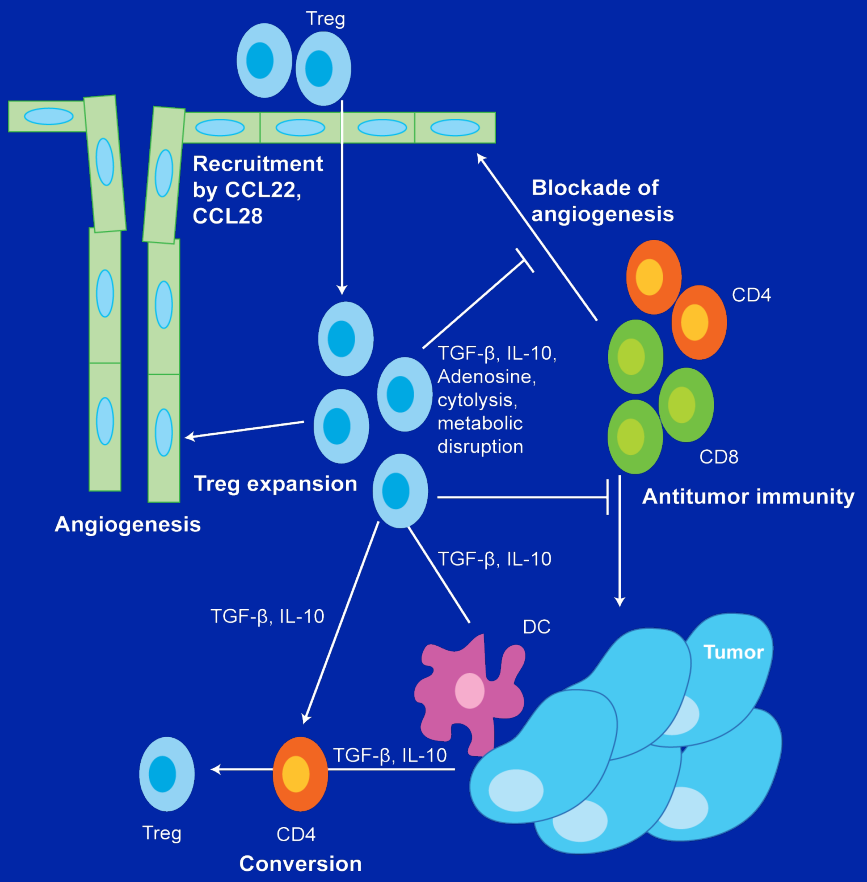
www.clinicaltrials.gov. Accessed March 2017

Ramucirumab: Immunological Pathways (MDSC and Treg)

VEGF-A through binding to VEGF-R2 induces immunosuppression



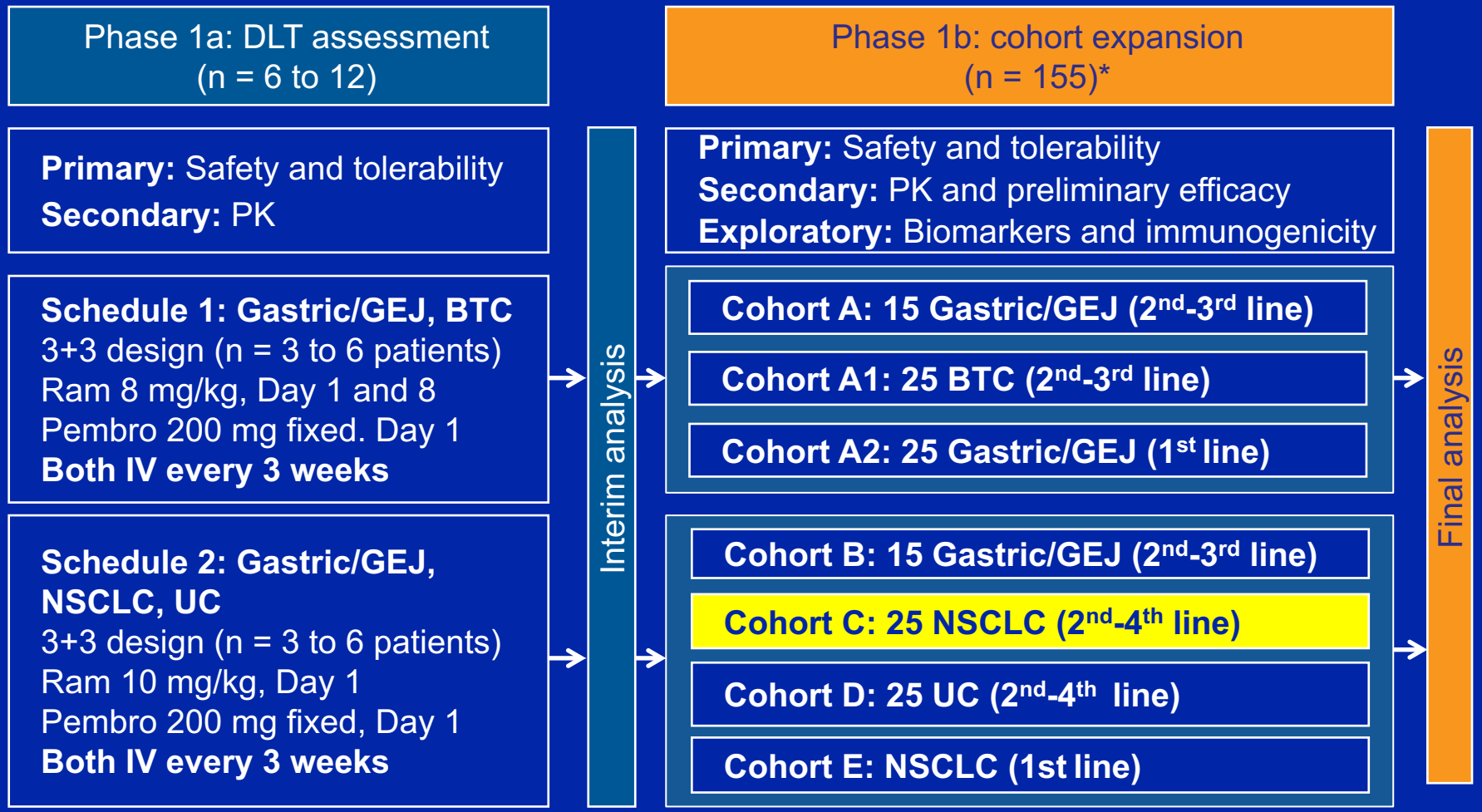
Treg: limit antitumor immunity and promote angiogenesis



T. Voron, et al., Frontiers in Oncology, April 2014 Volume 4 Article 70
Andrea Facciabene et al. Cancer Res 2012;72:2162-71.

Multicohort Phase I Study of Ramucirumab with Pembrolizumab

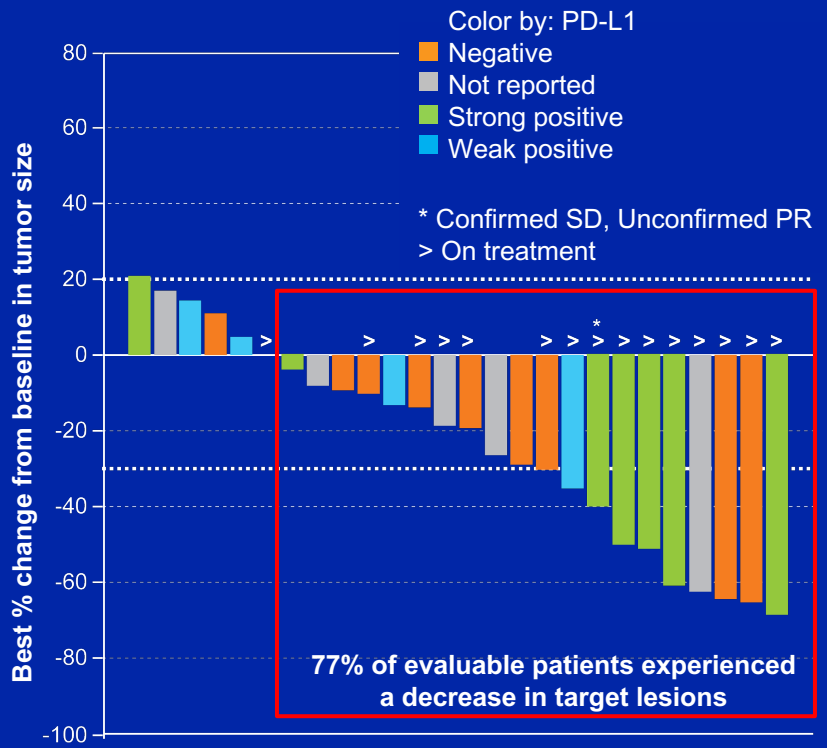
NCT02443324

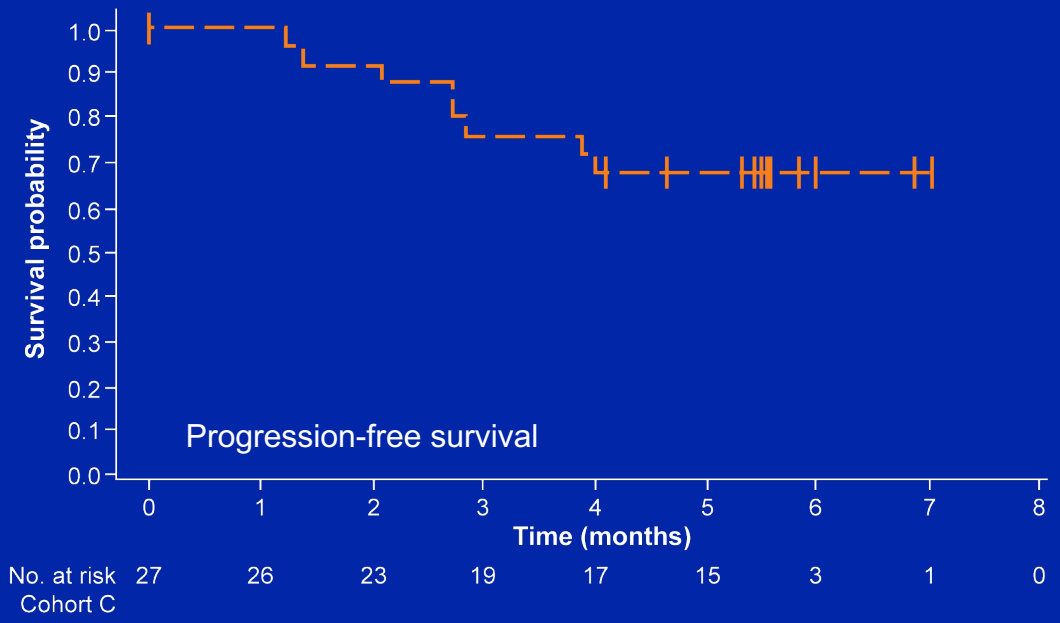


* Patients may continue treatment for up to 35 cycles, until confirmed progressive disease or discontinuation for any other reason.

Herbst RS et al. *Proc ESMO* 2016;Abstract LBA38.

Cohort C: Interim Analysis





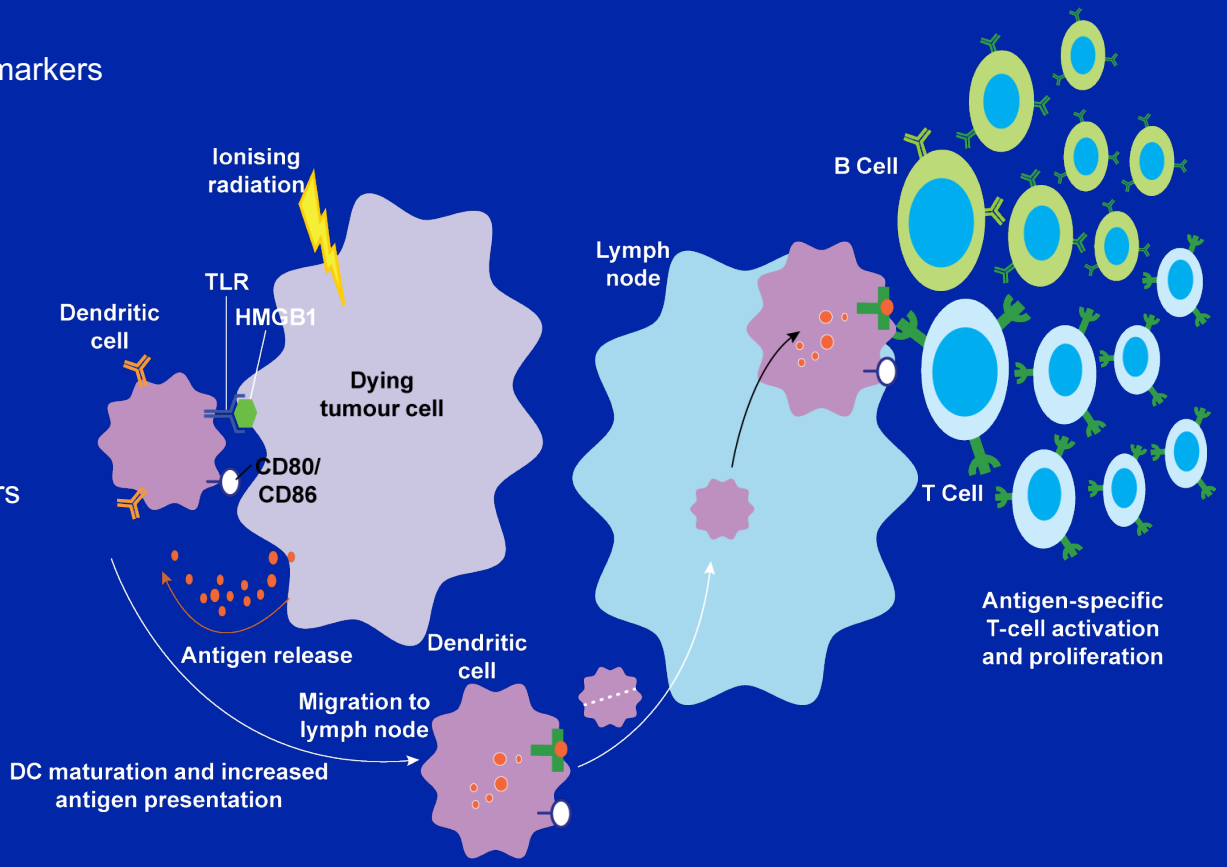
ITT population	Cohort C NSCLC (n = 27)
Objective response rate, n (%)	8 (30%)
Disease control rate, n (%)	23 (85%)

PD-L1 Status	Patients	Events	Median PFS, Mo (95% CI)
All patients	27	8	NR (3.98, —)
Negative	10	2	NR
Weak positive	4	2	3.98 (2.76, —)
Strong positive	7	2	NR
Not reported	6	2	NR

Herbst RS et al. *Proc ESMO* 2016;Abstract LBA38.

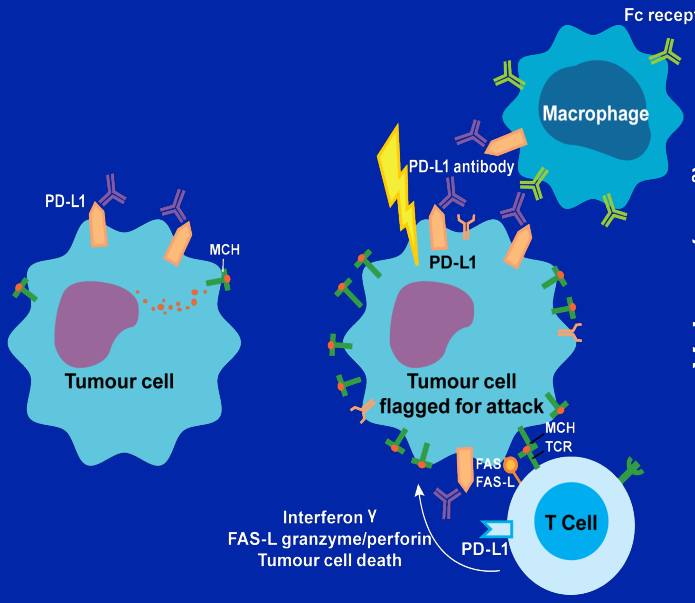
Immunomodulatory Effects of Radiotherapy

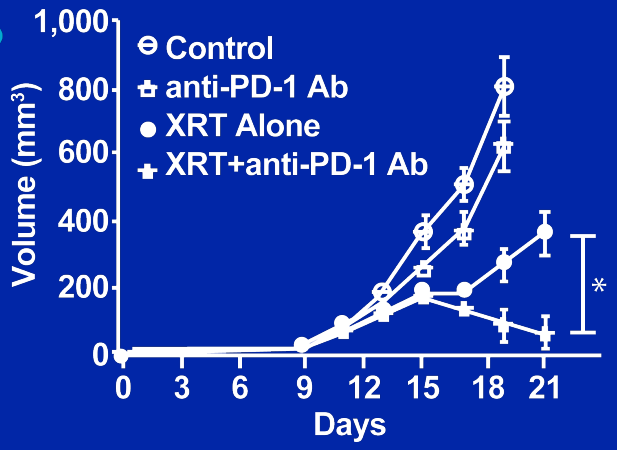
- Tumor debulking and releasing tumor antigens
- Not systemically immunosuppressive
- Upregulation of PD-L1
- Upregulation of immunogenic cell surface markers
  - ICAM-1
  - MHC-1
  - Fas
- Secretion of danger signals & cytokines
  - IFN–g
  - TNFa
  - IL-1b
- Induction of immunogenic cell death
  - Calreticulin
  - HMGB-1
- Increased homing of immune cells to tumors
  - Normalization of tumor vasculature
  - Secretion of chemo-attractants (cxcl16)
  - Endothelial expression of VCAM-1
  - Improved T-cell homing to tumors
- Improved antigen presentation by APCs
  - Irradiated tumors prime dendritic cells
  - Improved antigen presentation via TLR-4
- Depletion of immunosuppressive cells
- Shifting TAM polarization to M1



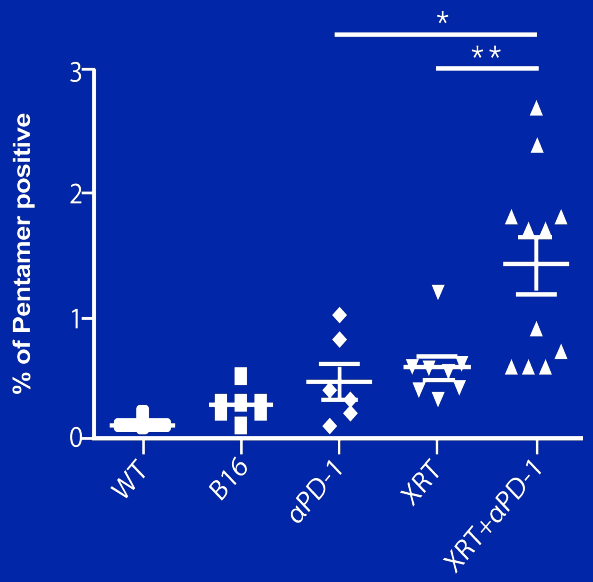
Dovedi et al. Cancer Res. 2014;74:5458; Chakraborty et al. J Immunol. 2003;170:6338; Formenti et al. Lancet Oncol. 2009;10:718; Chakraborty et al. J Immunol. 2003;170:6338; Lugade et al. J Immunol. 2008;180:3132; Formenti et al. Lancet Oncol. 2009;10:718; Formenti et al. Lancet Oncol. 2009;10:718; Obeid et al. Cell Death Differ. 2007;14:1848; Apetoh et al. Nature Med. 2007;13(9):1050; Ganss et al. Cancer Res. 2002;62:1462; Matsumura et al. J Immunol. 2008;181:3099; Lugade et al. J Immunol. 2008;180:3132; Klug et al. Cancer Cell. 2013;24:589-602; Strome et al. Cancer Res. 2002;62:1884; Apetoh et al. Nature Med. 2007;13(9):1050; Wu et al. Clin Cancer Res. 2014;20:644-57; Klug et al. Cancer Cell. 2013;24:589-602; Lock M. Cureus 2015.

Preclinical Evidence for Synergy Between Radiation and PD-1 Pathway Inhibitors





OVA-B16 melanoma model
Anti PD-1 Ab given 1 day prior to XRT (day 12) q 3 days x 3
*$p < 0.05$



Tumor antigen specific T cells
*$p < 0.05$; **$p < 0.01$

Sharabi AB et al. *Lancet Oncol* 2015;16(13):e498-509; Sharabi AB et al. *Cancer Immunol Res* 2015;3(4):345-55.

Clinical Trials: Radiation Therapy Combined with Immune Checkpoint Inhibitors

	Trial Name
1	Atezolizumab and Stereotactic Body Radiation Therapy in Treating Patients With NSCLC
2	MPDL3280A and Stereotactic Ablative Radiotherapy in Patients With Non-small Cell Lung Cancer
3	A Pilot Study of MPDL3280A and HIGRT in Metastatic NSCLC
4	Hypofractionated Radiation Therapy to Improve Immunotherapy Response in Non-Small Cell Lung Cancer
5	MK-3475 and Hypofractionated Stereotactic Radiation Therapy in Patients with NSCLC
6	Pembrolizumab and Stereotactic Radiosurgery for Melanoma or NSCLC Metastases
7	Hypofractionated Radiation Therapy to Improve Immunotherapy Response in Non-Small Cell Lung Cancer
8	Neoadjuvant Chemoradiation Plus Pembrolizumab Followed By Consolidation Pembrolizumab in NSCLC
9	A Randomized Two Arm Phase II Trial of Pembrolizumab Alone or Sequentially Following Single Fraction Non-ablative Radiation to One of the Target Lesions, in Previously Treated Patients With Stage IV NSCLC
10	Hypofractionated Radiation Therapy to Improve Immunotherapy Response in Non-Small Cell Lung Cancer
11	Trial of Nivolumab With Radiation or Nivolumab and Ipilimumab With Radiation for the Treatment of Intracranial Metastases From Non-Small Cell Lung Cancer
12	Combining Radiosurgery and Nivolumab in the Treatment of Brain Metastases

www.clinicaltrials.gov. Accessed March 2017.