Year in Review

Proceedings from a Multitumor CME Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Immunotherapy for Melanoma — Adil Daud, MD

Select Publications

Daud A et al. **Long-term efficacy of pembrolizumab (pembro; MK-3475) in a pooled analysis of 655 patients (pts) with advanced melanoma (MEL) enrolled in KEYNOTE-001.** *Proc ASCO* 2015;**Abstract 9005**.

Larkin J et al. **Combined nivolumab and ipilimumab or monotherapy in untreated melanoma.** *N Engl J Med* 2015;373(1):23-34.

Postow MA et al. **Nivolumab and ipilimumab versus ipilimumab in untreated melanoma.** *N Engl J Med* 2015;372(21):2006-17.

Robert C et al. **Pembrolizumab versus ipilimumab in advanced melanoma.** *N Engl J Med* 2015;372(26):2521-32.

Wolchok JD et al. **Atypical patterns of response in patients (pts) with metastatic melanoma treated with pembrolizumab (MK-3475) in KEYNOTE-001.** *Proc ASCO* 2015;**Abstract 3000**.

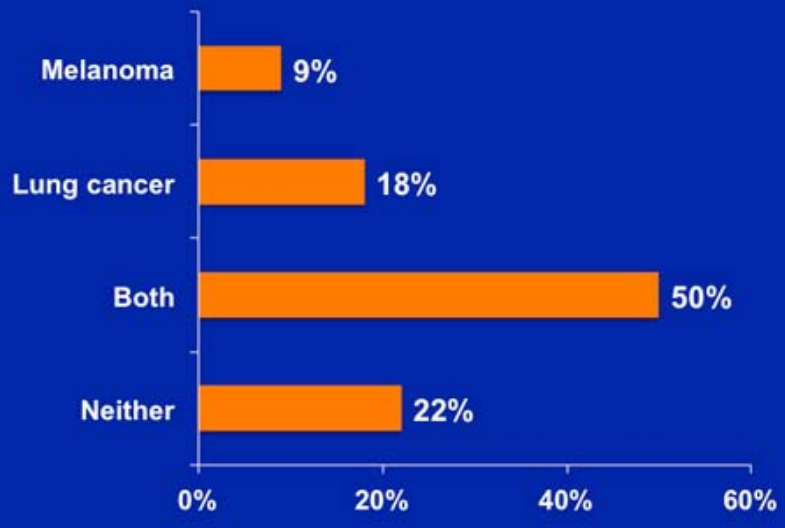
Wolchok JD et al. **Efficacy and safety results from a phase III trial of nivolumab (NIVO) alone or combined with ipilimumab (IPI) versus IPI alone in treatment-naive patients (pts) with advanced melanoma (MEL) (CheckMate 067).** *Proc ASCO* 2015;**Abstract LBA1**.

Disclosures

Advisory Committee	Amgen Inc, Genentech BioOncology, GlaxoSmithKline, OncoSec Medical
Consulting Agreements	Bristol-Myers Squibb Company, Merck, Novartis Pharmaceuticals Corporation, OncoSec Medical, Takeda Oncology
Contracted Research	Bristol-Myers Squibb Company, Genentech BioOncology, GlaxoSmithKline, Merck, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche Laboratories Inc, Takeda Oncology

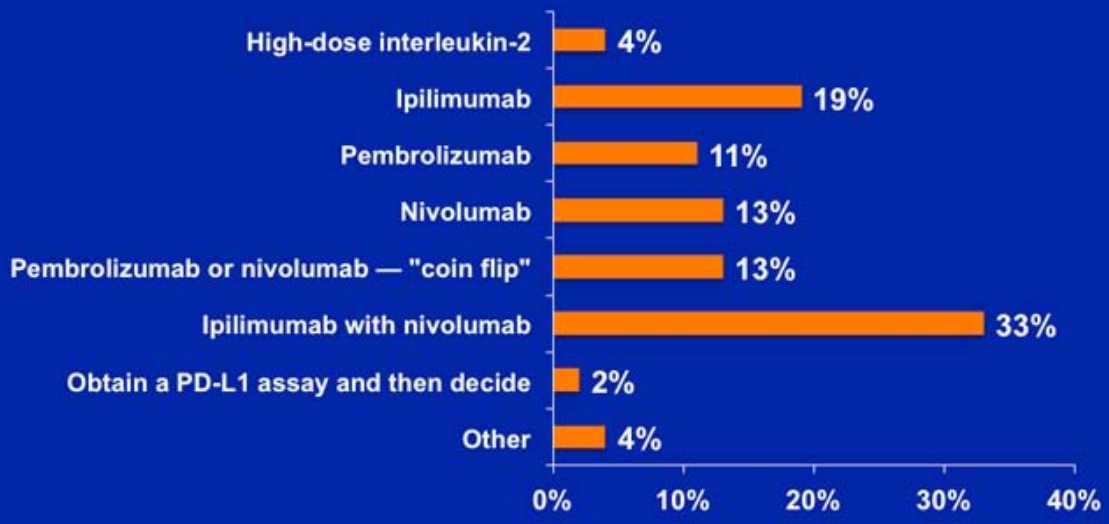
AUDIENCE POLL

Have you administered an anti-PD-1 antibody outside of a clinical trial setting to a patient with…



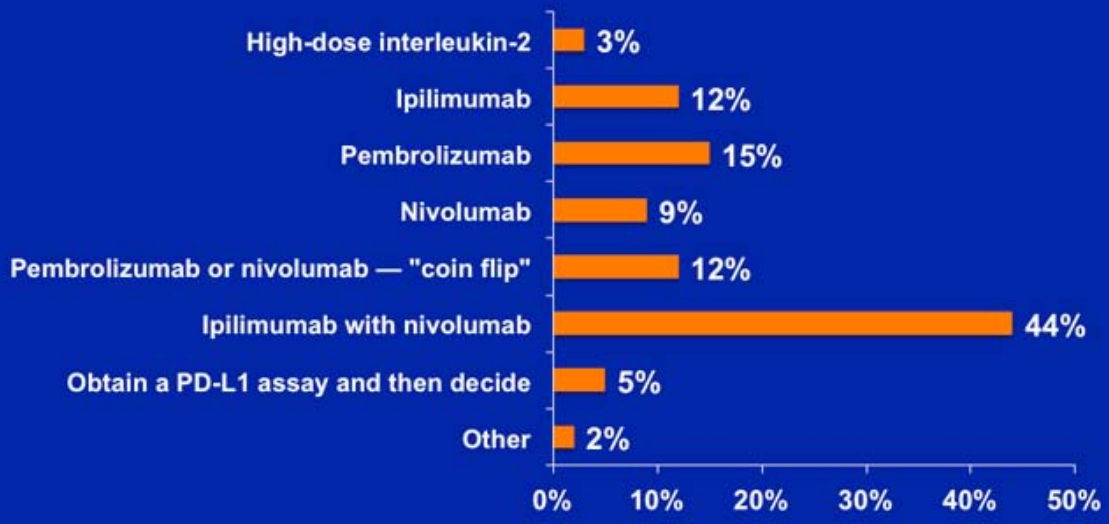
AUDIENCE POLL

A 54-year-old asymptomatic patient with a surgically excised primary melanoma is found 1 year later to have several small bilateral metastases in the lung on routine follow-up, confirmed to be BRAF wild type. PS = 0. In general, what would you recommend as first-line systemic treatment?



AUDIENCE POLL

A 54-year-old symptomatic patient with a surgically excised primary melanoma is found 1 year later to have metastatic disease in the lung and liver, confirmed to be BRAF wild-type melanoma. In general, what would you recommend as first-line systemic treatment?



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

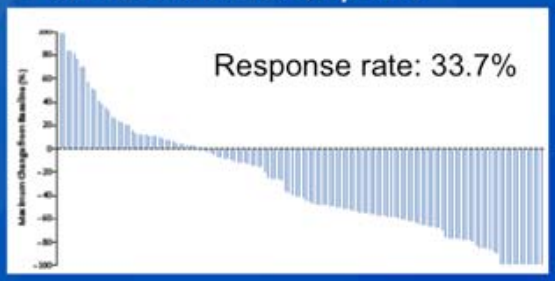
Pembrolizumab versus Ipilimumab in Advanced Melanoma

Caroline Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D., Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omid Hamid, M.D., Christine Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nageatte Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*

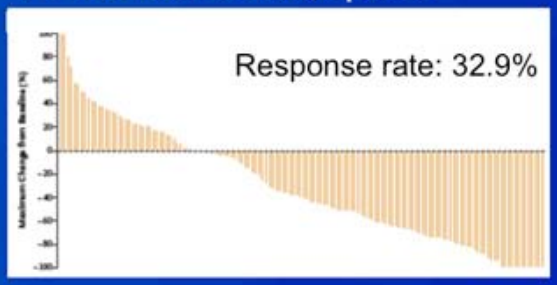
Robert C et al. *N Engl J Med* 2015;372(26):2521-32.

KEYNOTE-006: Change in Tumor Burden

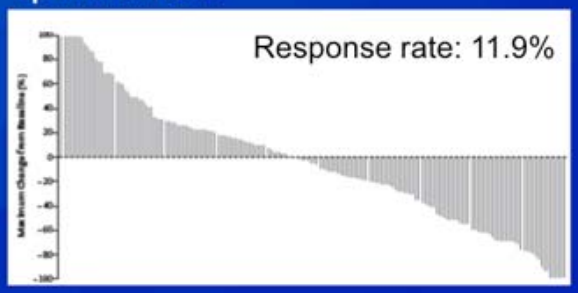
Pembrolizumab, q2wk



Pembrolizumab, q3wk



Ipilimumab



Robert C et al. *N Engl J Med* 2015;372(26):2521-32.

Conclusions

Critical finding(s): Pembrolizumab beats ipilimumab in a head-to-head comparison in up-front melanoma, with superior PFS OS and better Grade 3/4 toxicity.

Clinical implication(s): When a patient walks into your office, the first treatment should be PD-1 antibody.

Research relevance: Cements the place of pembrolizumab in first-line treatment. Does not show a difference between these 2 high-dose regimens with either q2wk or q3wk dosing.

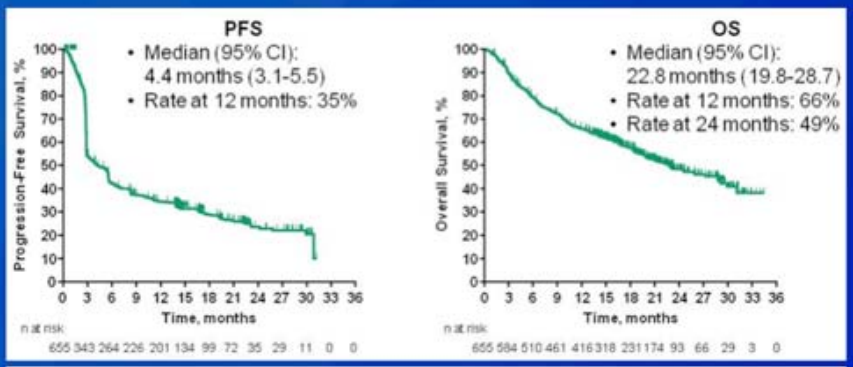
Long-Term Efficacy of Pembrolizumab in a Pooled Analysis of 655 Patients with Advanced Melanoma Enrolled in KEYNOTE-001

Daud A et al.

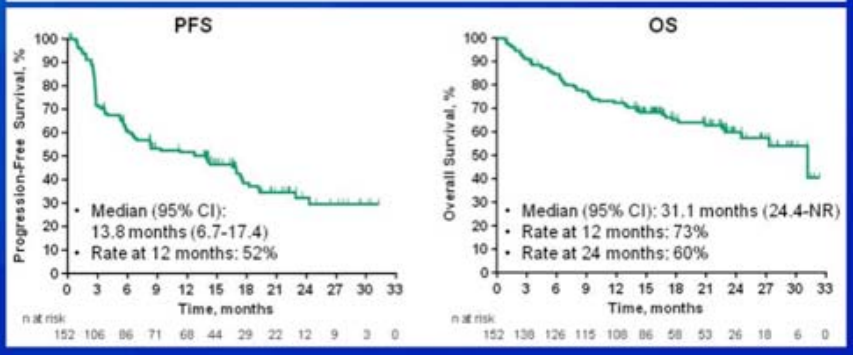
Proc ASCO 2015;Abstract 9005.

Survival Analyses: Overall Population (N = 655) and Treatment-Naïve (N = 152)

Overall
PFS: 4.4 mo
OS: 22.8 mo



Treatment-Naïve
PFS: 13.8 mo
OS: 31.1 mo



Daud A et al. *Proc ASCO* 2015;Abstract 9005.

Conclusions

Critical finding(s): Updates show that up-front treatment with pembrolizumab is associated with excellent outcomes in melanoma, including BRAF-mutant melanoma.

Clinical implication(s): PD-1 antibodies may be an excellent choice for BRAF-mutant patients up front prior to BRAF-MEK inhibitor treatment in some cases.

Research relevance: Answers the question whether BRAF mutation confers an adverse risk on immunotherapy with PD-1.

The NEW ENGLAND JOURNAL of MEDICINE

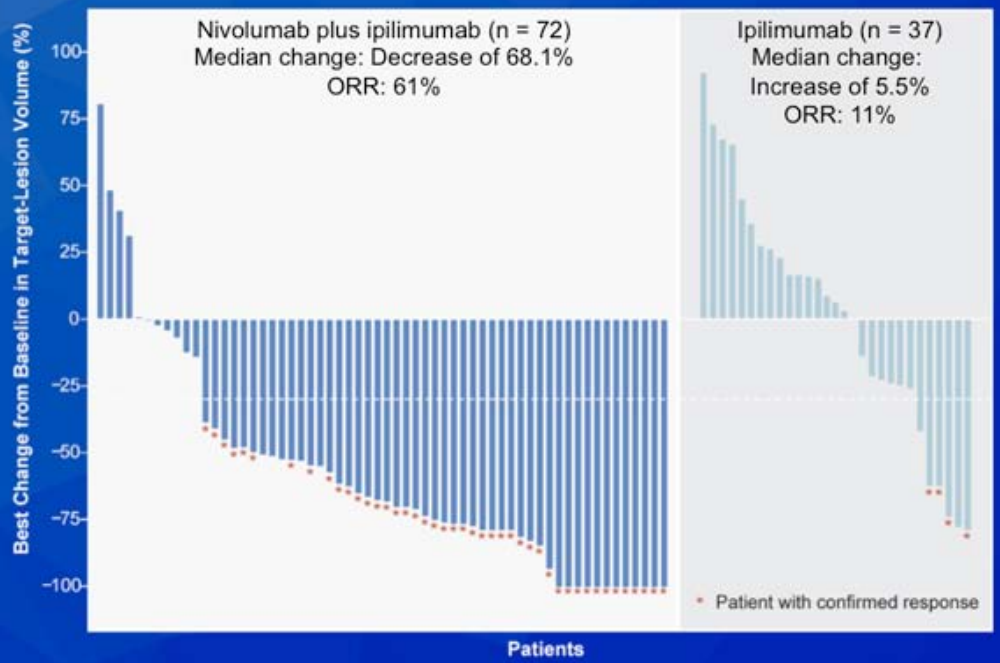
ORIGINAL ARTICLE

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

Michael A. Postow, M.D., Jason Chesney, M.D., Ph.D., Anna C. Pavlick, D.O., Caroline Robert, M.D., Ph.D., Kenneth Grossmann, M.D., Ph.D., David McDermott, M.D., Gerald P. Linette, M.D., Ph.D., Nicolas Meyer, M.D., Jeffrey K. Giguere, M.D., Sanjiv S. Agarwala, M.D., Montaser Shaheen, M.D., Marc S. Ernstoff, M.D., David Minor, M.D., April K. Salama, M.D., Matthew Taylor, M.D., Patrick A. Ott, M.D., Ph.D., Linda M. Rollin, Ph.D., Christine Horak, Ph.D., Paul Gagnier, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and F. Stephen Hodi, M.D.

Postow MA et al. *N Engl J Med* 2015;372(21):2006-17.

CheckMate 069: Change in Tumor Burden in Patients with BRAF Wild-Type Tumors



Median PFS: Not reached (combination therapy) vs 4.4 mo (ipi monotherapy)

Postow MA et al. *N Engl J Med* 2015;372(21):2006-17.

CheckMate 069: Select Treatment-Related Adverse Events

Adverse event (%)	Nivolumab + ipilimumab (n = 94)		Ipilimumab (n = 46)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any treatment-related adverse event	91	**54**	93	**24**
Diarrhea	45	11	37	11
Rash	41	5	26	0
Fatigue	39	5	43	0
Colitis	23	17	13	7
Increased ALT	22	11	4	0
Increased AST	21	7	4	0

Postow MA et al. *N Engl J Med* 2015;372(21):2006-17.

Conclusions

Critical finding(s): Ipi/nivo outperforms ipi but also adds a fair amount of side effects.

Clinical implication(s): Not a lot

Research relevance: Not a lot

The NEW ENGLAND JOURNAL of MEDICINE

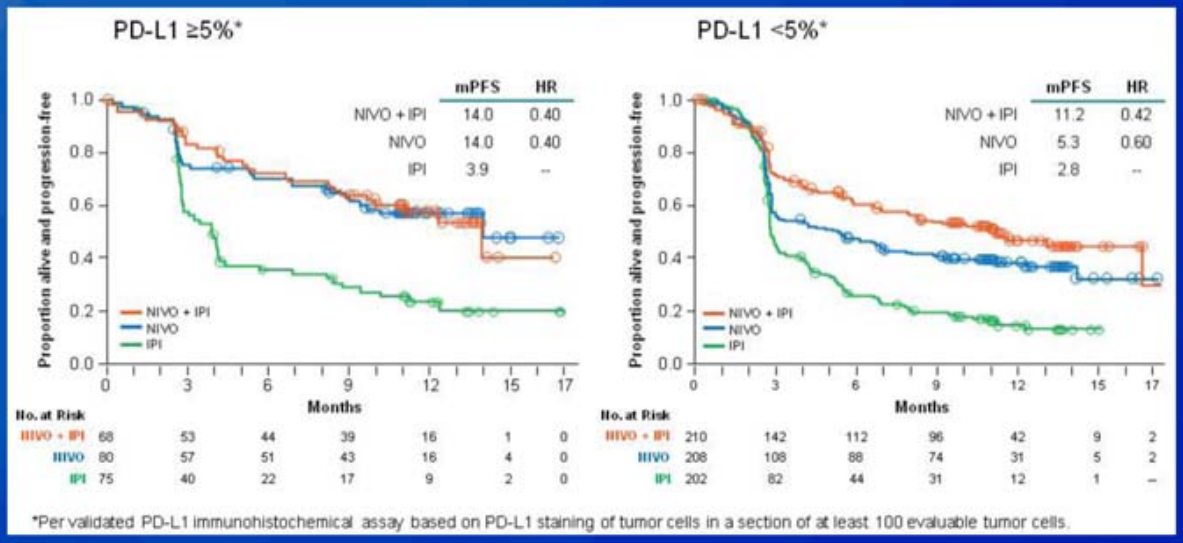
ORIGINAL ARTICLE

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

Larkin J et al. *N Engl J Med* 2015;373(1):23-34.
Wolchok JD et al. *Proc ASCO* 2015;Abstract LBA1.

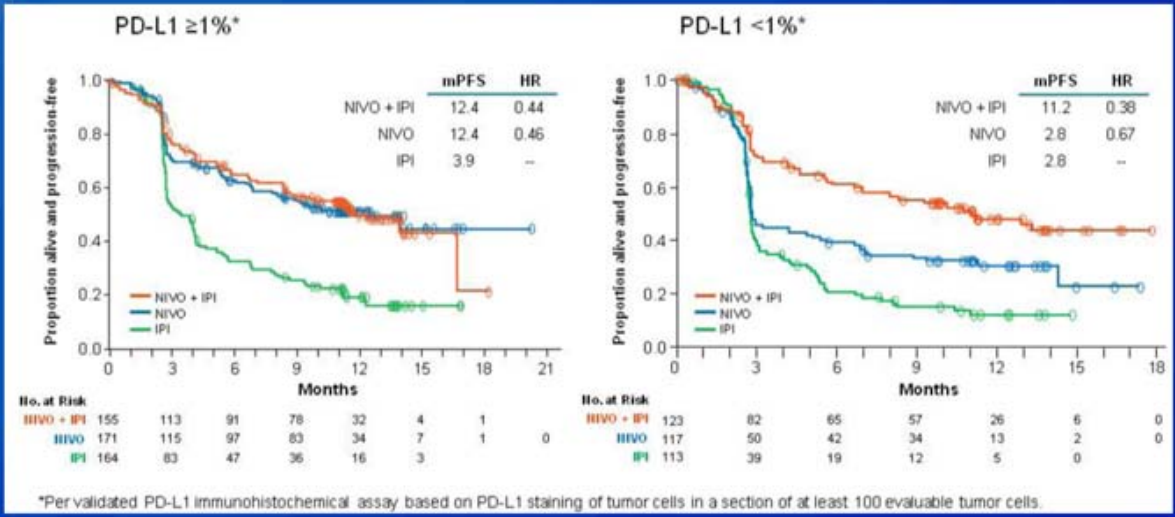
CheckMate 067: PFS According to PD-L1 Expression Levels (5%)



*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

Larkin J et al. *N Engl J Med* 2015;373(1):23-34.
Wolchok JD et al. *Proc ASCO* 2015;Abstract LBA1.

CheckMate 067: PFS According to PD-L1 Expression Levels (1%)



Larkin J et al. *N Engl J Med* 2015;373(1):23-34.
Wolchok JD et al. *Proc ASCO* 2015;Abstract LBA1.

CheckMate 067: Select Adverse Events

Adverse event (%)	Nivolumab (n = 313)		Nivolumab + ipilimumab (n = 313)		Ipilimumab (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related adverse event	82.1	**16.3**	95.5	**55.0**	86.2	**27.3**
Diarrhea	19.2	2.2	44.1	9.3	33.1	6.1
Fatigue	34.2	1.3	35.1	4.2	28.0	1.0
Rash	25.9	0.6	40.3	4.8	32.8	1.9
Increased ALT	3.8	1.3	17.6	8.3	3.9	1.6
Increased AST	3.8	1.0	15.3	6.1	3.5	0.6
Colitis	1.3	0.6	11.8	7.7	11.6	8.7

Larkin J et al. *N Engl J Med* 2015;373(1):23-34.
Wolchok JD et al. *Proc ASCO* 2015;Abstract LBA1.

Conclusions

Critical finding(s): Blockbuster study that changes everything. The combination of ipi and nivo outperforms nivo in both PD-L1 negatives and positives, especially in the PD-L1 negatives, where it has a better PFS by a wide margin.

Clinical implication(s): The combination of anti-CTLA-4 antibody and anti-PD-1 antibody should be the standard therapy for many patients with melanoma.

Research relevance: Understanding better who could get equal benefits from PD-1 and who needs the combination is now a top priority.

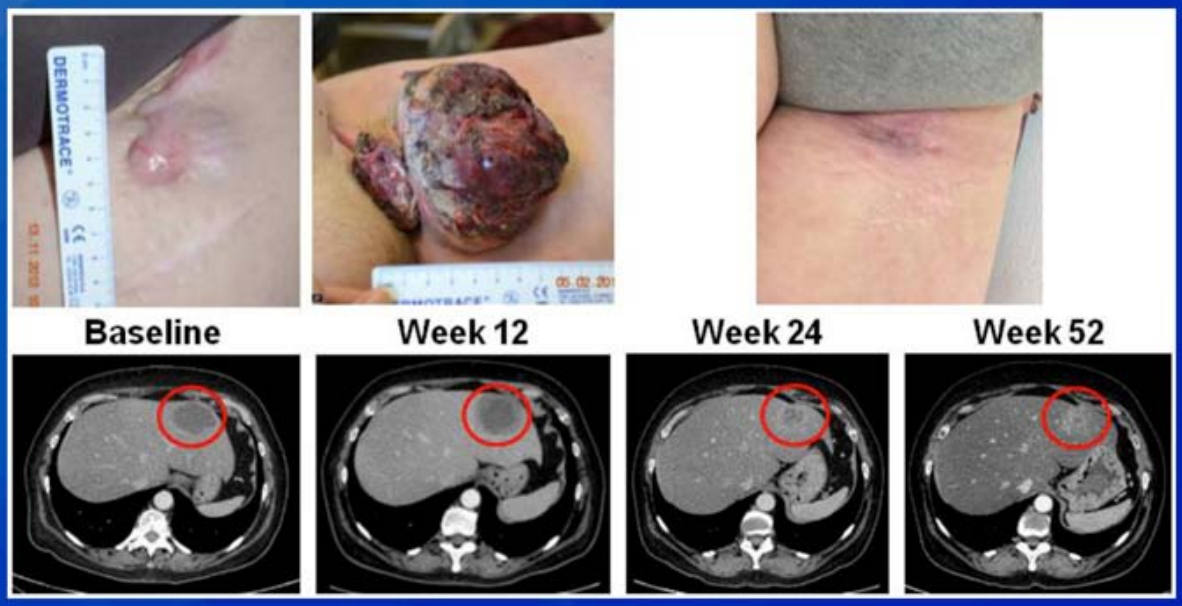
Atypical Patterns of Response in Patients with Metastatic Melanoma Treated with Pembrolizumab in KEYNOTE-001

Wolchok JD et al.

Proc ASCO 2015;Abstract 3000.

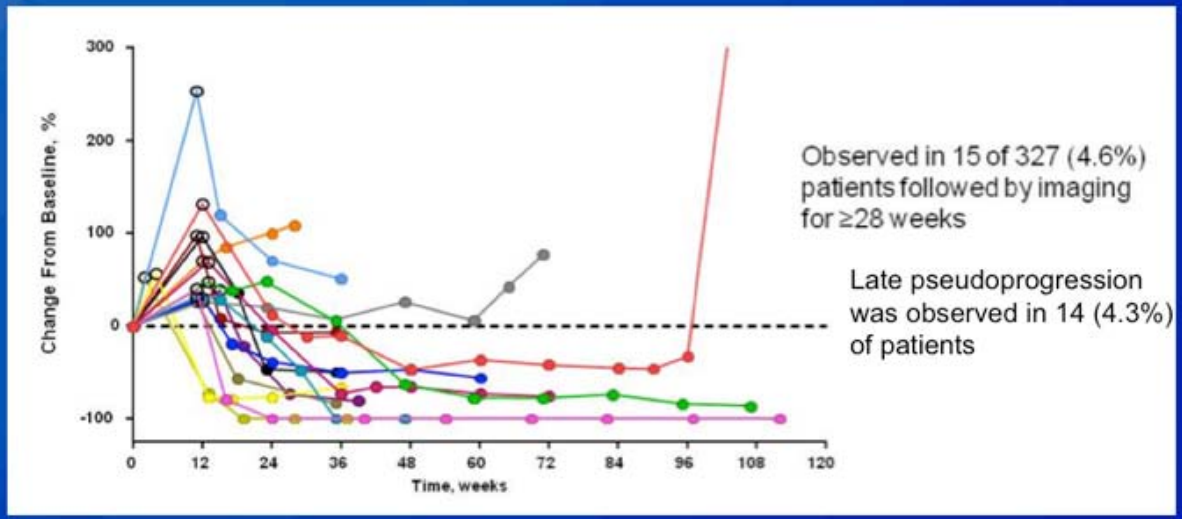
Patient with Melanoma Treated in KEYNOTE-001

Overt Radiographic and Clinical Progression by Week 12 with Major Response by Weeks 24 and 52

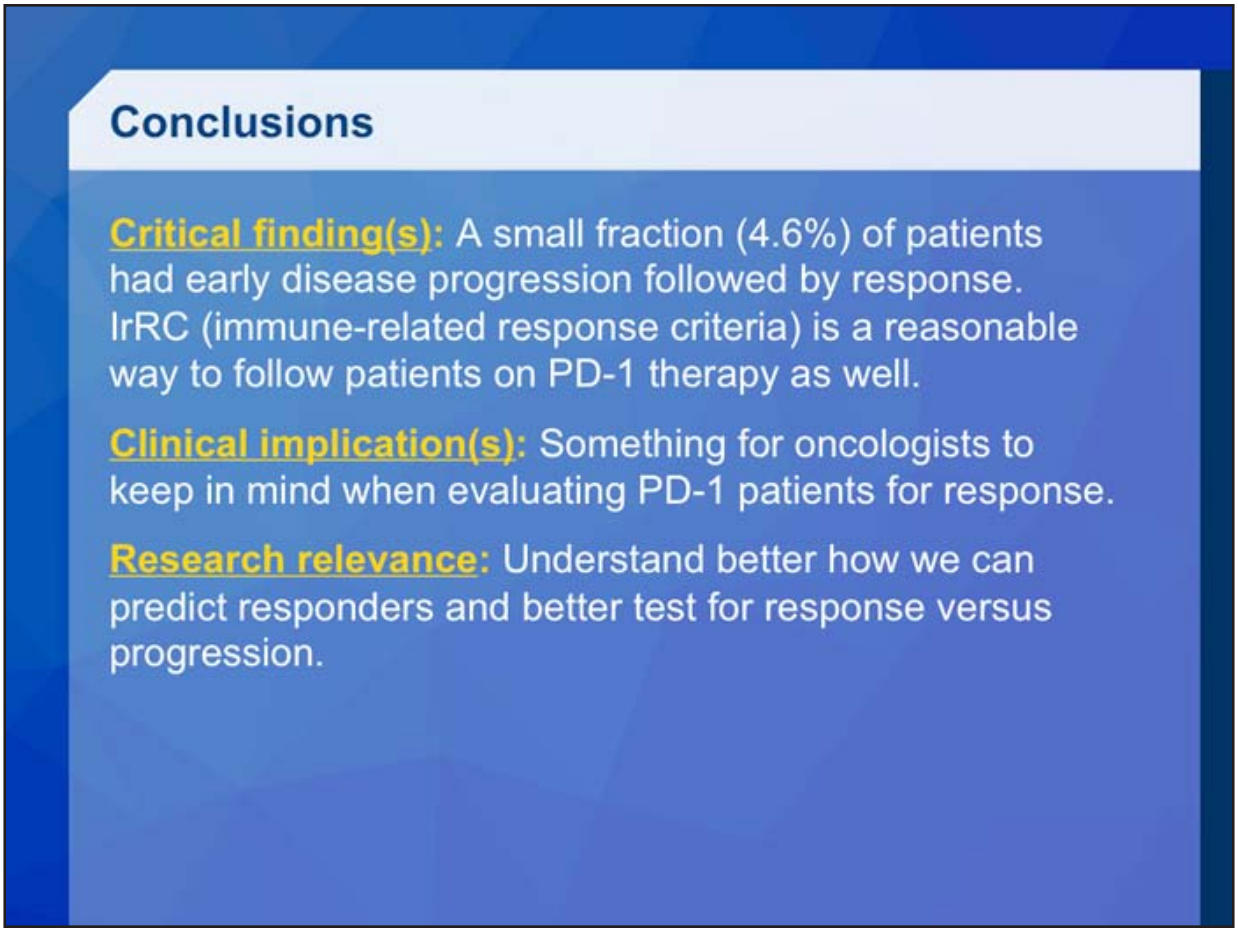


Wolchok JD et al. *Proc ASCO* 2015;Abstract 3000.

KEYNOTE-001: Early Pseudoprogression (irRC, Central Review)



Wolchok JD et al. *Proc ASCO* 2015;Abstract 3000.


Conclusions
Critical finding(s): A small fraction (4.6%) of patients had early disease progression followed by response. IrRC (immune-related response criteria) is a reasonable way to follow patients on PD-1 therapy as well.
Clinical implication(s): Something for oncologists to keep in mind when evaluating PD-1 patients for response.
Research relevance: Understand better how we can predict responders and better test for response versus progression.