SITC Chicago Meeting

THE UNIVERSITY OF CHICAGO MEDICINE

Immunotherapy for Lung Cancer, Head and Neck Cancer, Mesothelioma

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Disclosures

Consultancy: Merck/MSD, Amgen, BMS, Jounce Therapeutics

Research Collaborations: Merck/MSD, Genentech/Roche, Oncosec, Jounce Therapeutics

1899: Coley's Toxin

New York Times - July 29, 1908

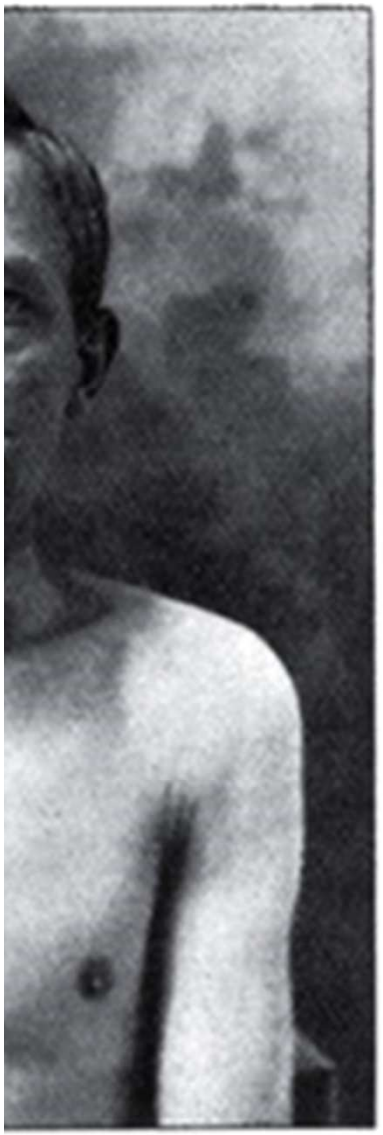
ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yester-



Nature Rev Cancer. 2009;9:361-371.

126 years later…
2015: anti-PD-1… + Coley's Toxin (?)

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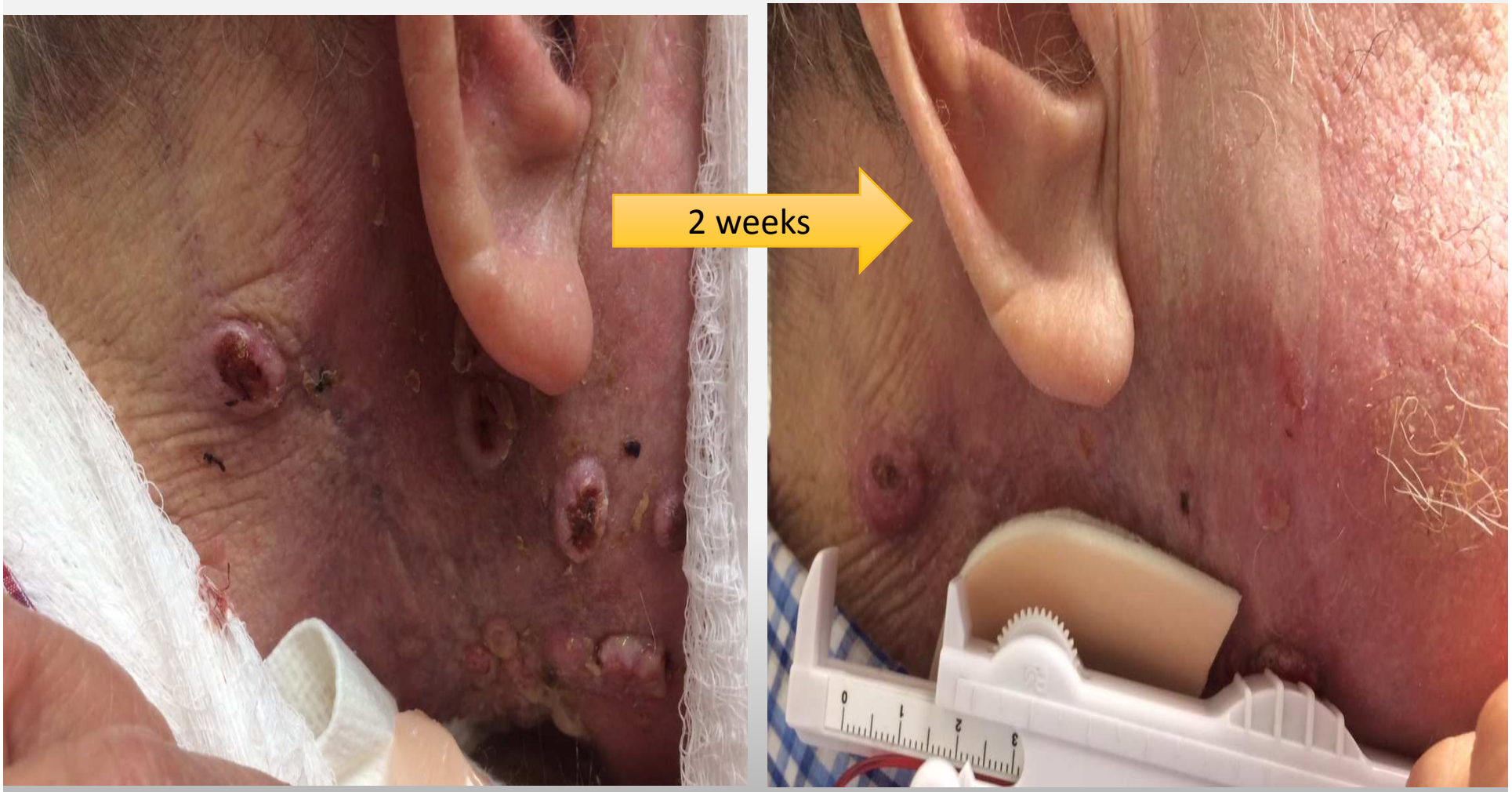

Unpublished Data, University of Chicago

Simple Conclusion…

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Overview

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I. **Background**

II. **Lung Cancer**

III. **Head and Neck Cancer**

IV. **Mesothelioma**

I. Background

Tumor infiltrating Lymphocytes (TILs) in HNC

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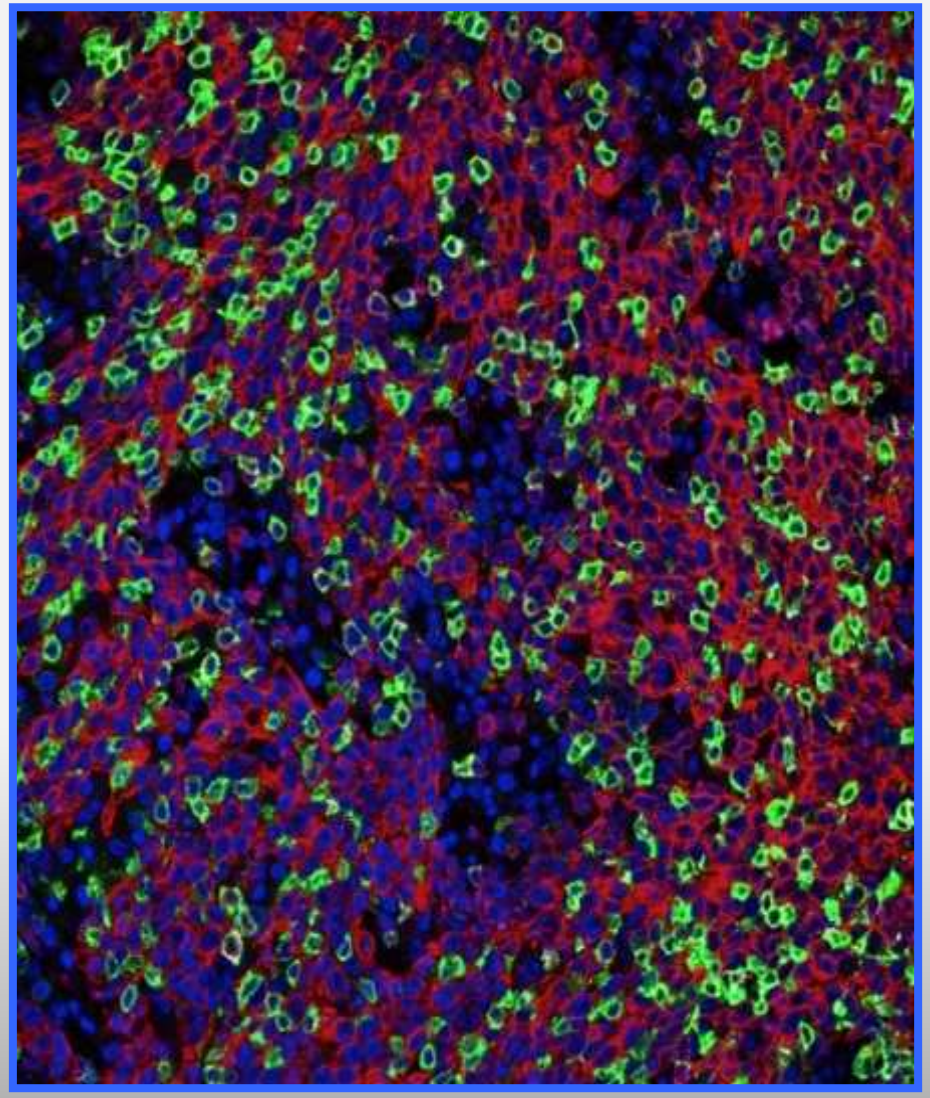

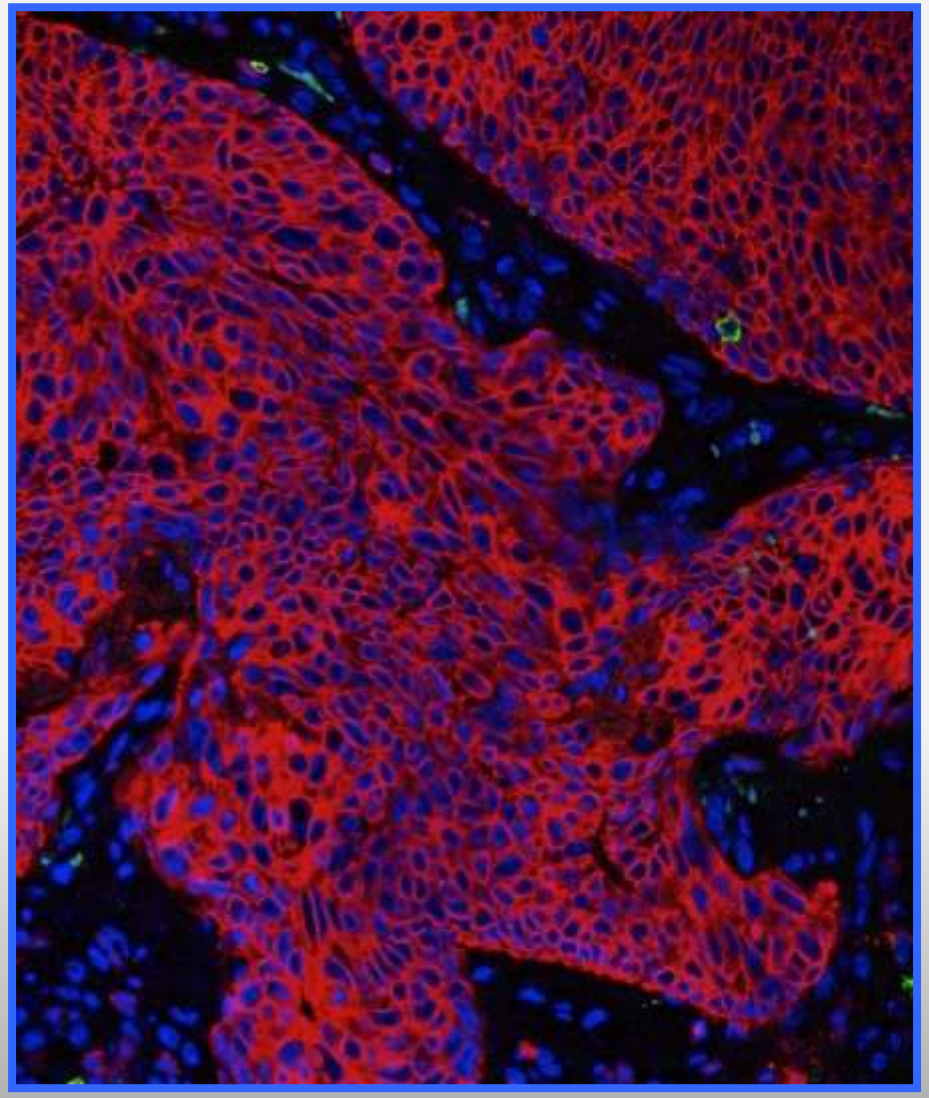

Keck/Seiwert, CCR 2015

PD-L1 Prevalence by IHC[a] Tumor Cell (TC) & Immune Cell (IC) staining

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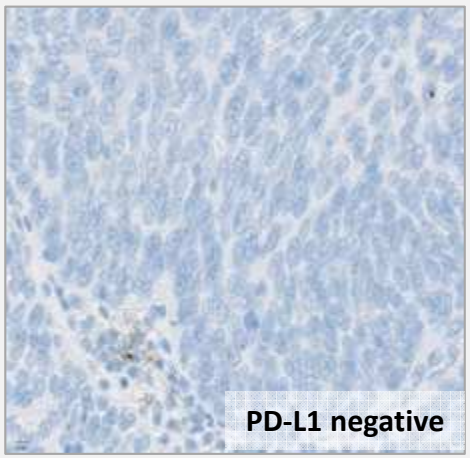
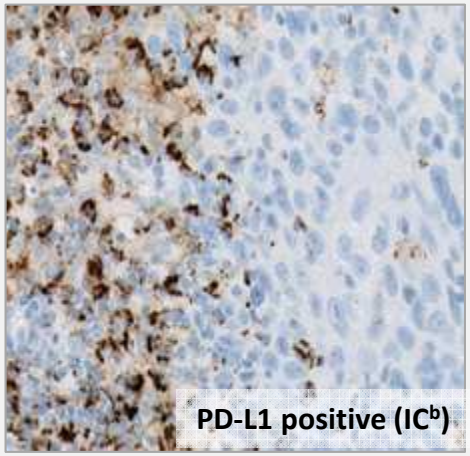
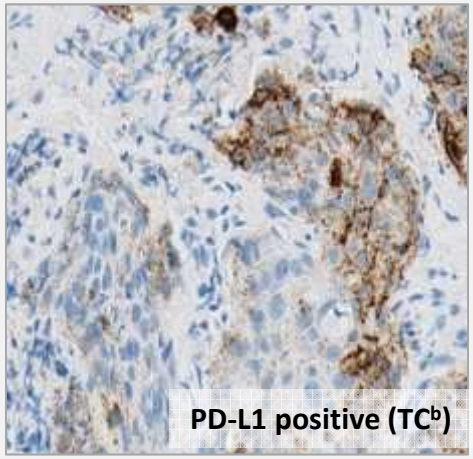
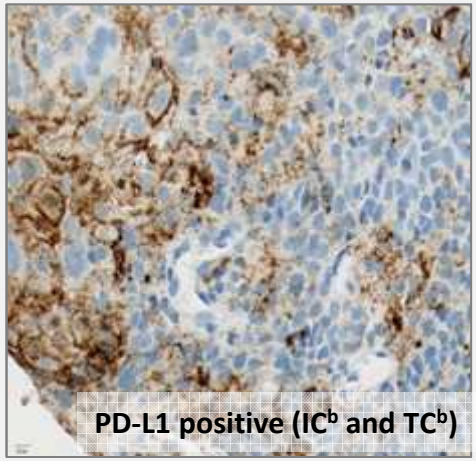








PD-L1 expressing cells[b]	PD-L1 expression cut-off	All (n=135)	HPV(+) (n=49)	HPV(-) (n=86)	p-value* (HPV+ vs HPV-)
Tumor Cells (TC)	**≥1%**	21.5	26.5	18.6	
	≥5%	11.9	16.3	9.3	**0.27**
Immune Cells (IC)	**≥1%**	69.6	71.4	68.6	
	≥5%	32.6	38.8	29.1	**0.26**
Immune and/or Tumor Cells	**≥1%**	72.6	73.5	72.1	
	≥5%	40.0	49.0	34.9	**0.14**

PD-L1 prevalence (TC[b] & IC[b]) **by IHC** was similar in HPV(+) vs HPV(-) tumors.

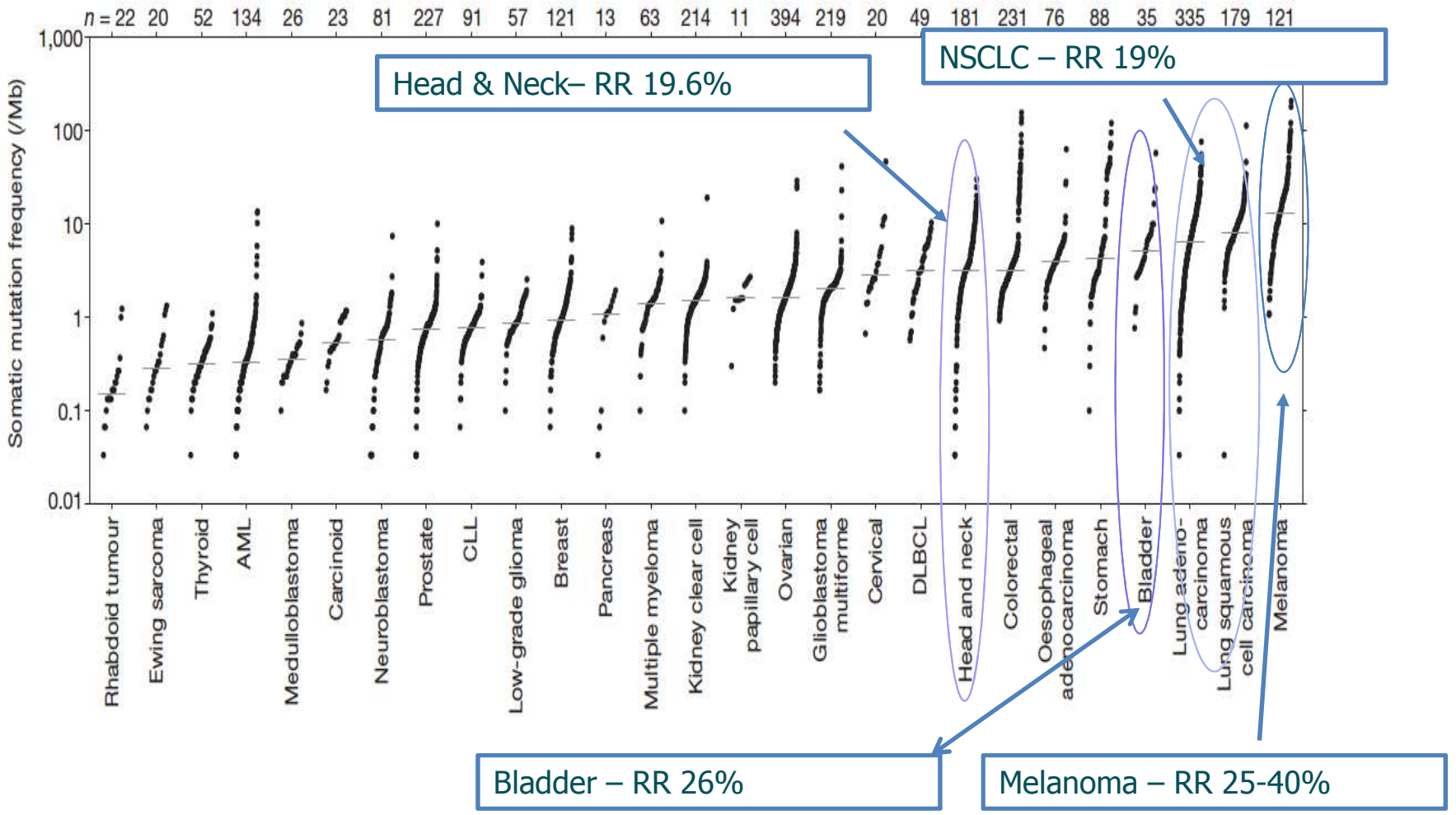
[a] PD-L1 assessed by proprietary Genentech/Roche IHC assay

[b] IC – tumor infiltrating immune cells; TC – tumor cells

* Fisher's exact test

H. Koeppen, Y. Xiao, M. Kowanetz (Genentech)

Mutation landscape and response to PD-1 pathway blockade



Alexandrov et al, *Nature* 2013

PD-1/PD-L1 inhibitors in late stage development

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Target	Agent	Class	K_D
PD-1	Nivolumab (MDX1106, BMS936558)	IgG4 fully human Ab	3 nM
	Pembrolizumab (MK-3475)	IgG4 engineered humanised Ab	29 pM
PD-L1	MPDL3280A	IgG1 engineered fully human Ab	-
	MEDI4736	IgG1 engineered fully human Ab	-

II. Lung Cancer

Bristol-Myers Squibb

CheckMate -017, A Phase 3 Study of Opdivo (Nivolumab) Compared to Docetaxel in Patients with Second-Line Squamous Cell Non-small Cell Lung Cancer, Stopped Early

Opdivo demonstrates superior overall survival in this Phase 3 trial

FDA News Release

FDA expands approved use of Opdivo to treat lung cancer

For Immediate Release

March 4, 2015

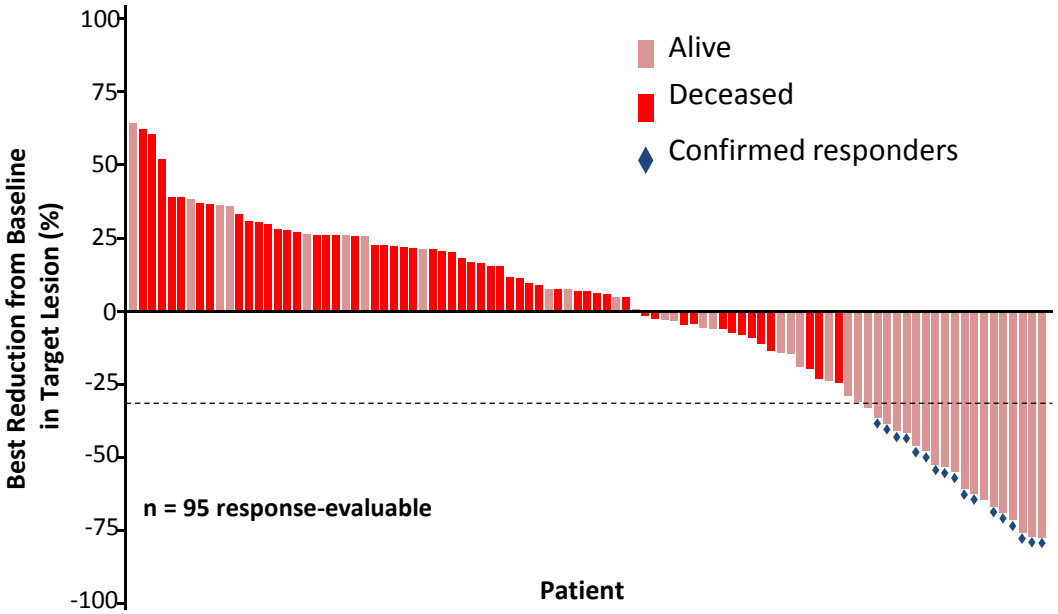
Efficacy of nivolumab monotherapy in patients with NSCLC

Dose, mg/kg	ORR, % (n/N)	Median DOR,* Wks (Range)	SD Rate ≥ 24 Wks, % (n/N)	Median PFS,† Mos (95% CI)	Median OS,† Mos (95% CI)
All doses	17.1 (22/129)	74.0 (6.1+, 133.9+)	10.1 (13/129)	2.3 (1.9-3.7)	9.6 (7.8-12.4)
1	3.0 (1/33)	63.9 (63.9, 63.9)	15.2 (5/33)	1.9 (1.8-3.6)	9.2 (5.6-11.1)
3	24.3 (9/37)	74.0 (16.1+, 133.9+)	8.1 (3/37)	1.9 (1.7-7.3)	14.9 (9.5-NE)
10	20.3 (12/59)	83.1 (6.1+, 117.1+)	8.5 (5/59)	3.6 (1.9-3.8)	9.2 (5.2-12.4)

- Durable responses; responses are ongoing in 45% of patients (10/22)
- Rapid responses; 50% of responding pts had response at first assessment (8 weeks)
- 7/16 responders who discontinued for reasons other than disease progression responded for ≥16 wks; 6/7 remain in response
- 6 pts with unconventional immune-related

Brahmer JR, *et al*. ASCO 2013. Abstract 8030.

Response and survival status by best reduction in target lesion (IRC assessed)[a]



	IRC-assessment (per RECIST 1.1)[a]
ORR, % (n) [95% CI]	**15 (17) [9, 22]**
Disease control rate, % (n)	**40 (47)**
Median DOR, months (range)	**NR (2+, 12+)**
Ongoing responders, % (n)	**59 (10)**
Median time to response, months (range)	**3 (2, 9)**

NR = not reached; ORR = objective response rate

Median OS, months (95% CI)	8.2 (6, 11)
1-year OS rate, % (95% CI)	41 (32, 50)
Number of events	72/117

Rizvi et al, *Lancet Oncology* (2015)

Lung Cancer - NSCLC (ASCO 2015)

Lung SCC – Nivo vs Docetax

Checkmate 17, PIII study

HR=0.59

PD-L1 biomarker did NOT work

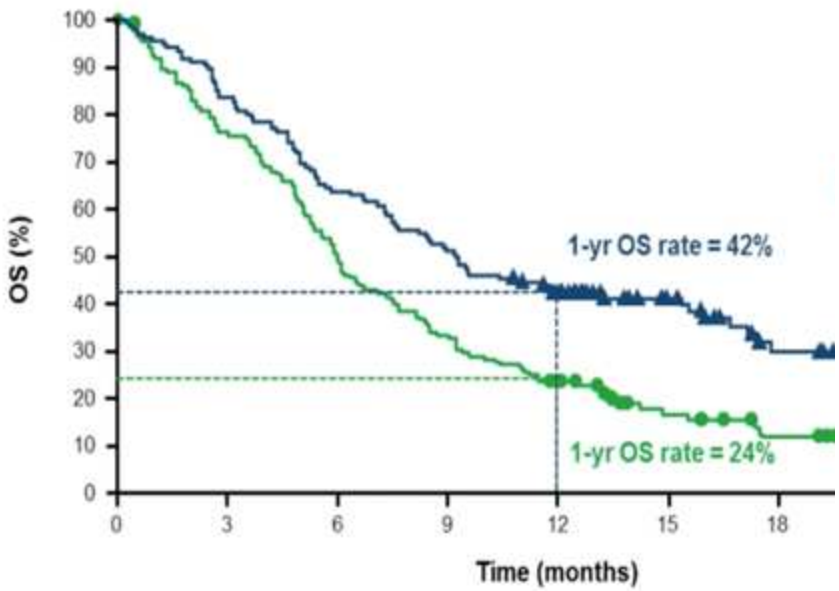
Lung Adeno – Nivo vs Docetax

Checkmate 57, PIII study

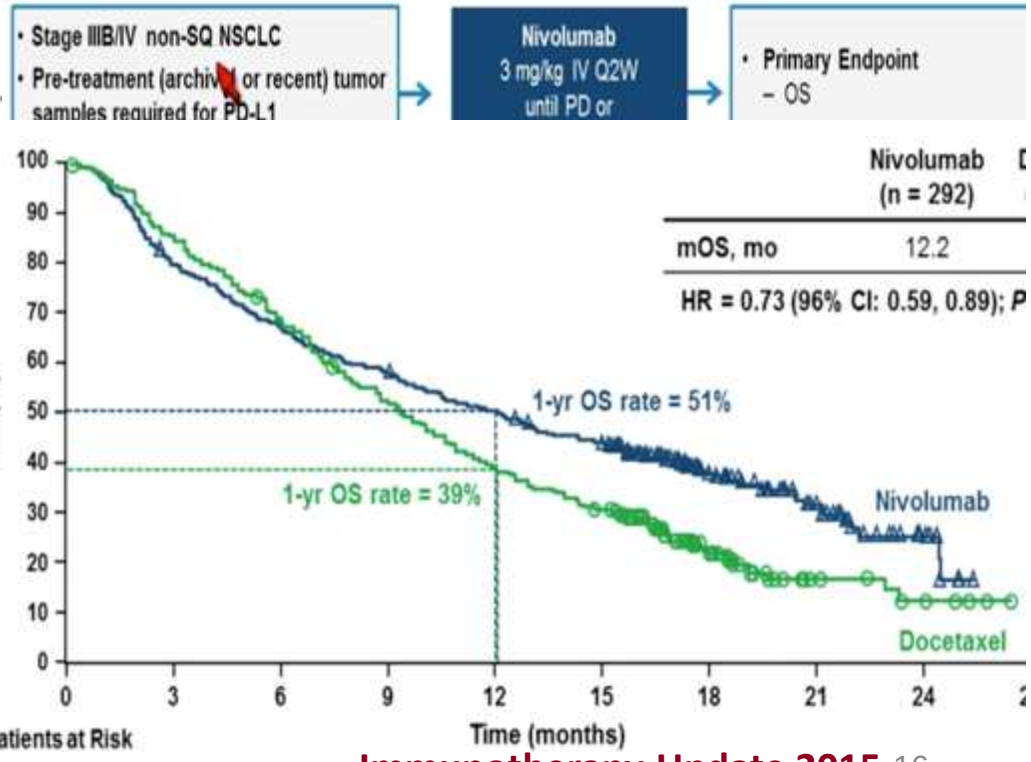
HR=0.73

PD-L1 biomarker worked

CheckMate 017 (NCT01642004) - Study Desig



CheckMate 057 (NCT01673867) Study Design



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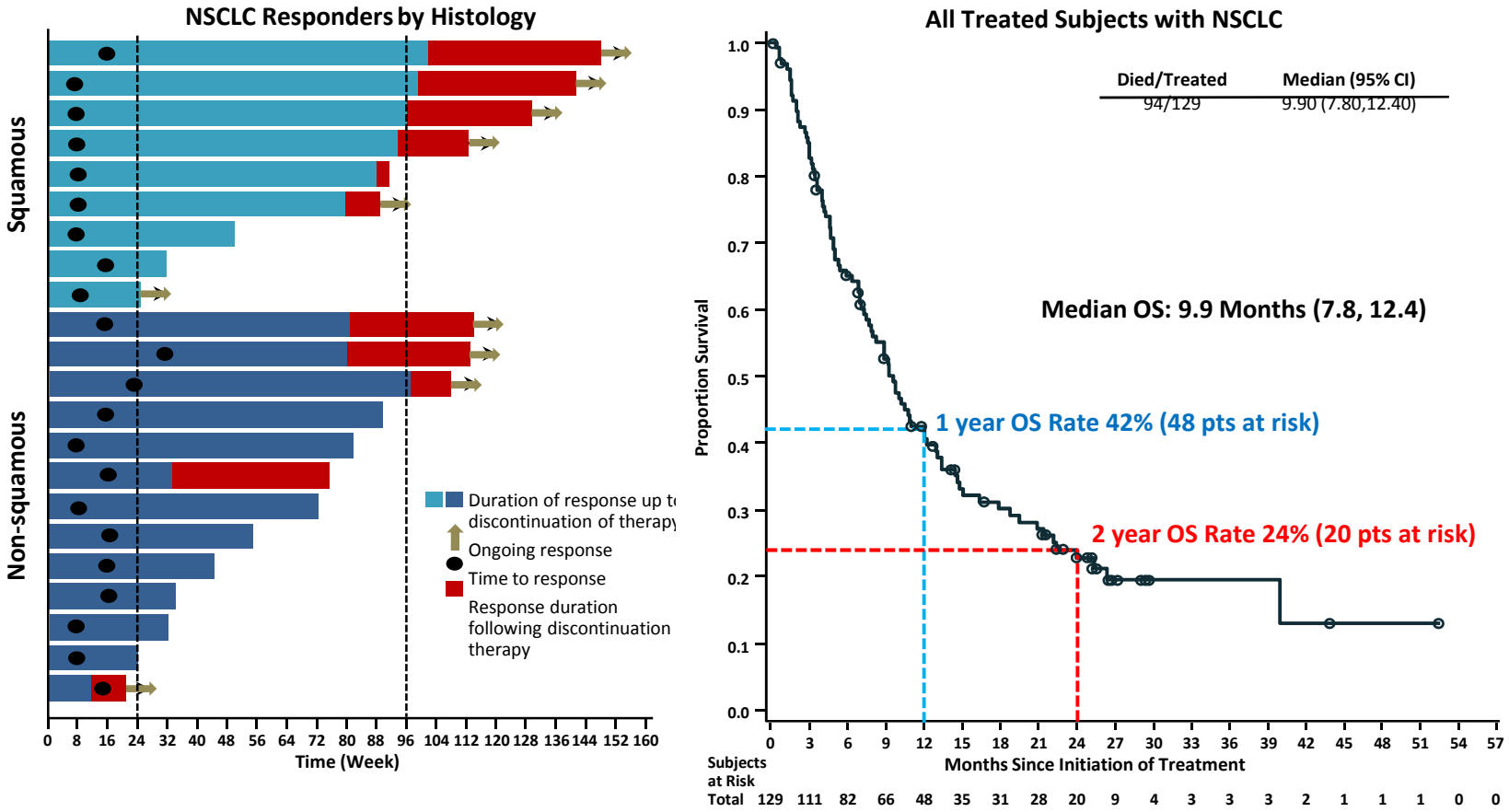
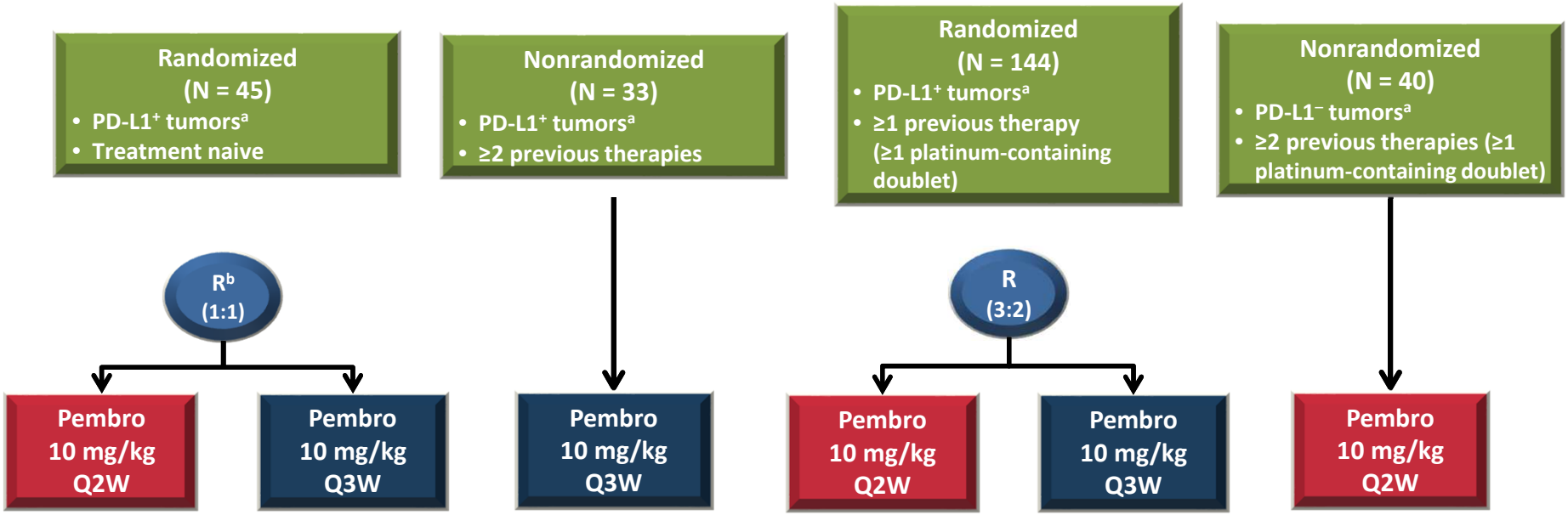
UC Cancer Research Foundation

Nivolumab: Duration of response and overall survival



Brahmer JR, et al. WCLC 2013. Abstract MO18.03.

Phase 1b KEYNOTE-001 Study: NSCLC Expansion Cohorts (N = 262)



- Response assessment
  - Primary measure: ORR by RECIST v1.1[1] per independent central review
  - Secondary measure: immune-related response criteria (irRC)[2] per investigator assessment
- Pembro was given until disease progression, unacceptable toxicity, or death
- Analysis cut-off date: March 3, 2014

Garon et al, ESMO 2014

Antitumor Activity
(RECIST v1.1, Central Review)

	N	ORR[a] % (95% CI)
Total	**236**	**21 (16-27)**
Previous treatment	236	
Treatment naive	42	26 (14-42)
Previously treated	194	20 (15-26)
Histology	230	
Nonsquamous	191	23 (17-29)
Squamous	39	18 (8-34)
Dose/schedule	236	
2 Q3W	6	33 (4-78)
10 Q3W	126	21 (14-29)
10 Q2W	104	21 (14-30)
PD-L1 expression[b]	236	
Positive	201	23 (18-30)
Negative	35	9 (2-23)

	N	ORR[a] % (95% CI)
Smoking history	230	
Current/Former	165	27 (20-34)
Never	65	9 (4-19)
Unknown	6	0 (0-46)
EGFR mutation	224	
Yes	36	14 (5-30)
No	188	22 (16-28)
KRAS mutation	140	
Yes	39	28 (15-45)
No	101	19 (12-28)
ALK rearrangement	210	
Yes	6	17 (0-64)
No	204	20 (15-26)

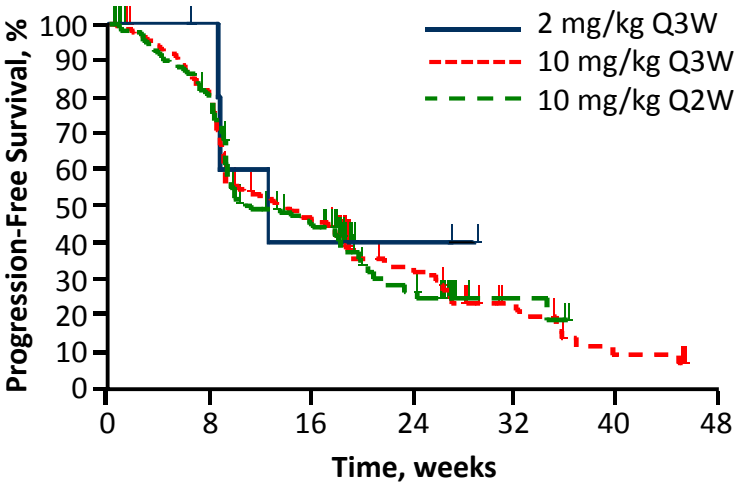
- In 45 additional patients treated at 2 mg/kg Q3W, ORR[a] is 20% (95% CI, 10%-35%) per irRC by investigator review

[a]Includes confirmed and unconfirmed responses.
[b]As assessed using a prototype assay. Positive was defined as staining in ≥1% of tumor cells.
Analysis cutoff date: March 3, 2014.

Garon et al, ESMO 2014

Kaplan-Meier Estimates of Survival

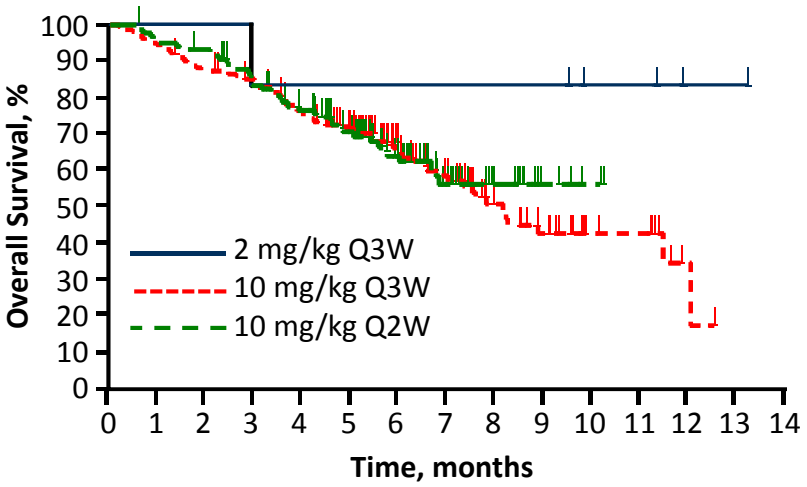
PFS (RECIST v1.1, Central Review)



n at risk							
Q3W 2 mg/kg	6	5	2	2	0	0	0
Q3W10 mg/kg	140	106	60	27	13	4	0
Q2W10 mg/kg	115	87	44	15	4	0	0

- Pooled population
  - Median PFS: 13.0 weeks (95% CI, 9.4-17.9)
  - 24-week PFS: 30%

OS



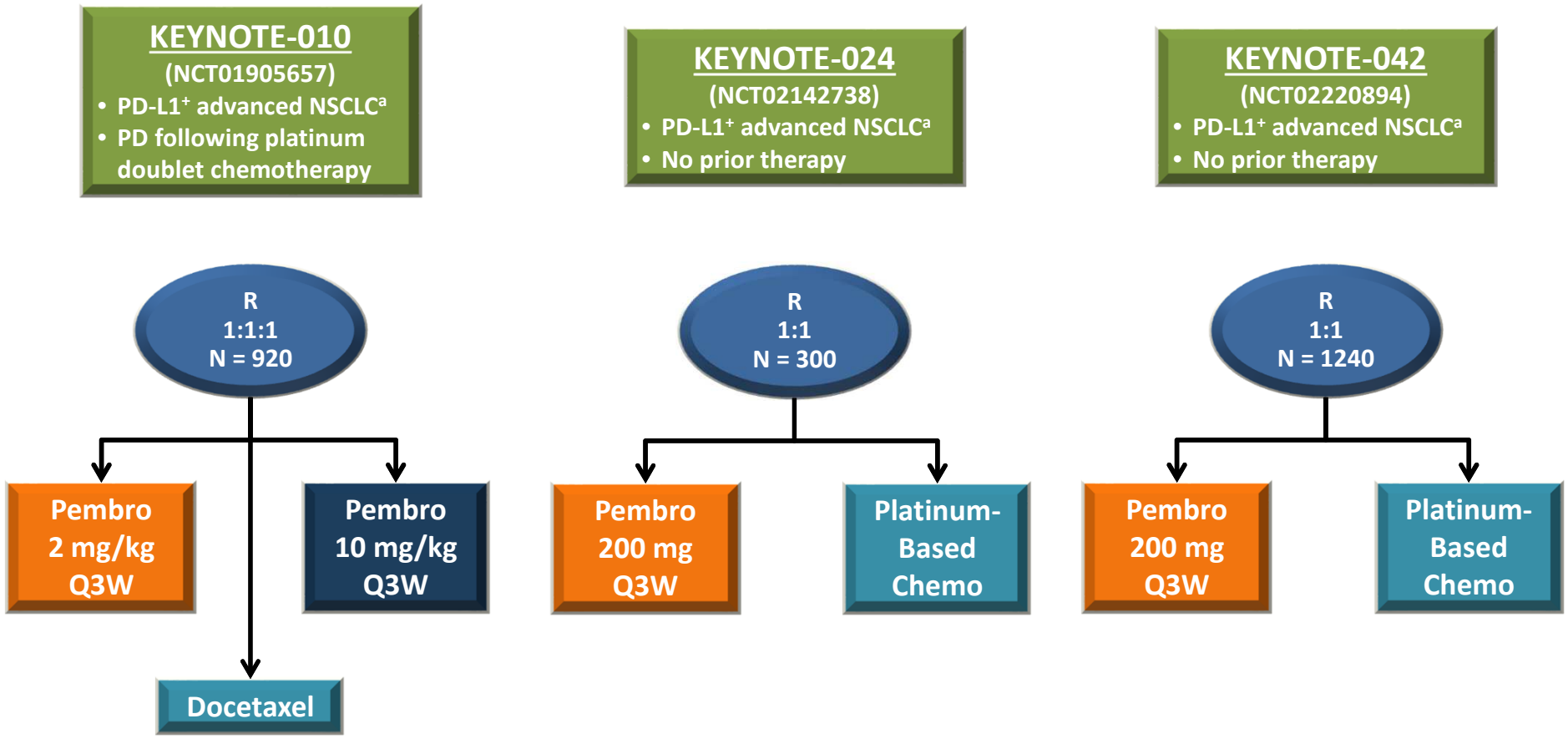
6	6	6	5	5	5	5	5	5	5	3	3	1	1	0
141	131	122	114	99	84	56	41	27	19	10	9	1	0	0
115	108	105	91	80	63	40	21	14	5	2	0	0	0	0

- Pooled population
  - Median OS: 8.2 months (95% CI, 7.3-NR
  - 6-month OS: 64%

Analysis cutoff date: March 3, 2014.

Garon et al, ESMO 2014

Ongoing Studies of Pembrolizumab in NSCLC



- **Primary end points: OS, PFS**
- **Primary end point: PFS**
- **Primary end point: OS**

[a]As assessed using the clinical trial assay and the 22C3 antibody.

Summary of Exposure and Treatment-Related AEs

	N = 262
Exposure	
Median (range) time on therapy, days	85.5 (1-400)
Median (range) doses, n	5.50 (1-23)
Treatment-related AE summary, n (%)	
Any grade	175 (67)
Grade 3-5	24 (9)
Serious	19 (7)
Death	1 (0.4)
Discontinued	8 (3)

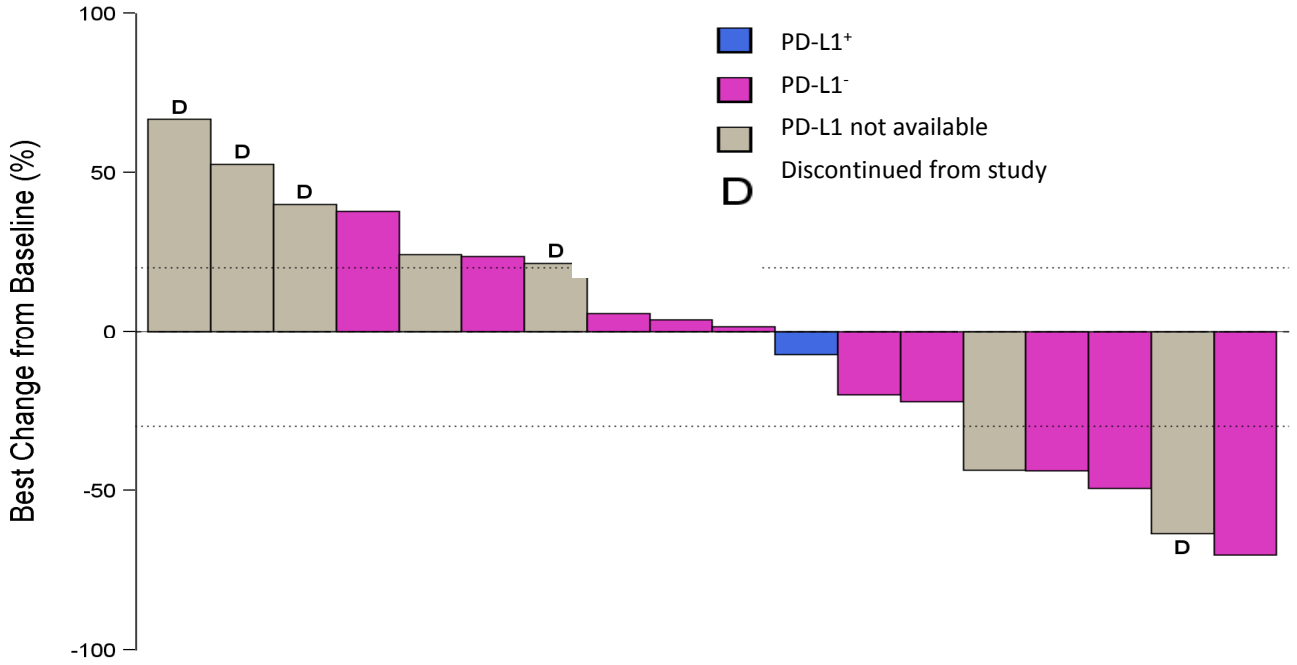
- Other potentially immune-mediated AEs that occurred in <1% of patients were colitis, hyponatremia, and hypersensitivity reaction

AE, n (%)	N = 262	
	Any Grade	Grade 3-5
Treatment-related with incidence ≥5%		
Fatigue	20	<1
Pruritus	9	0
Arthralgia	8	<1
Decreased appetite	8	0
Diarrhea	7	0
Hypothyroidism	6	0
Pyrexia	6	0
Rash	6	0
Nausea	5	<1
Other of clinical interest		
Pneumonitis	10 (4)	5 (2)
Hyperthyroidism	5 (2)	1 (0.4)

Garon et al, ESMO 2014

Clinical activity:
Durvalumab (MEDI4736) + tremelimumab

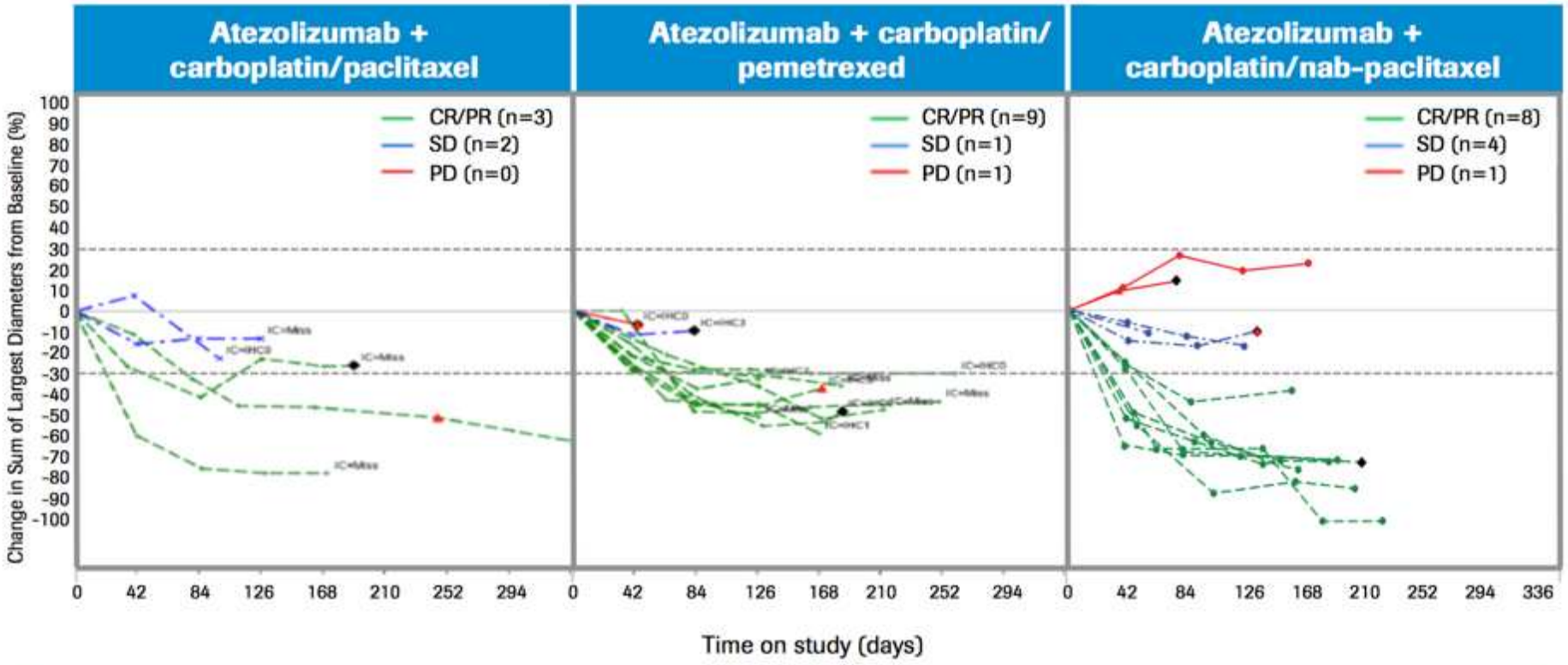
	MEDI4736 + tremelimumab combination		
	All patients[a]	PD-L1$^-$	PD-L1$^+$
RECIST response (ORR), % (n/N)	28 (5/18)	30 (3/10)	0 (0/1)
Stable disease, % (n/N)	28 (5/18)	40 (4/10)	100 (1/1)



Antonia S, *et al*. Poster presented at ESMO 2014 [1327P]

Combination with Chemo (ASCO 2015)

Combinations with chemotherapy appear to extend the benefit of atezolizumab in NSCLC patients



Chemotherapy can promote Th1-type inflammation in tumors

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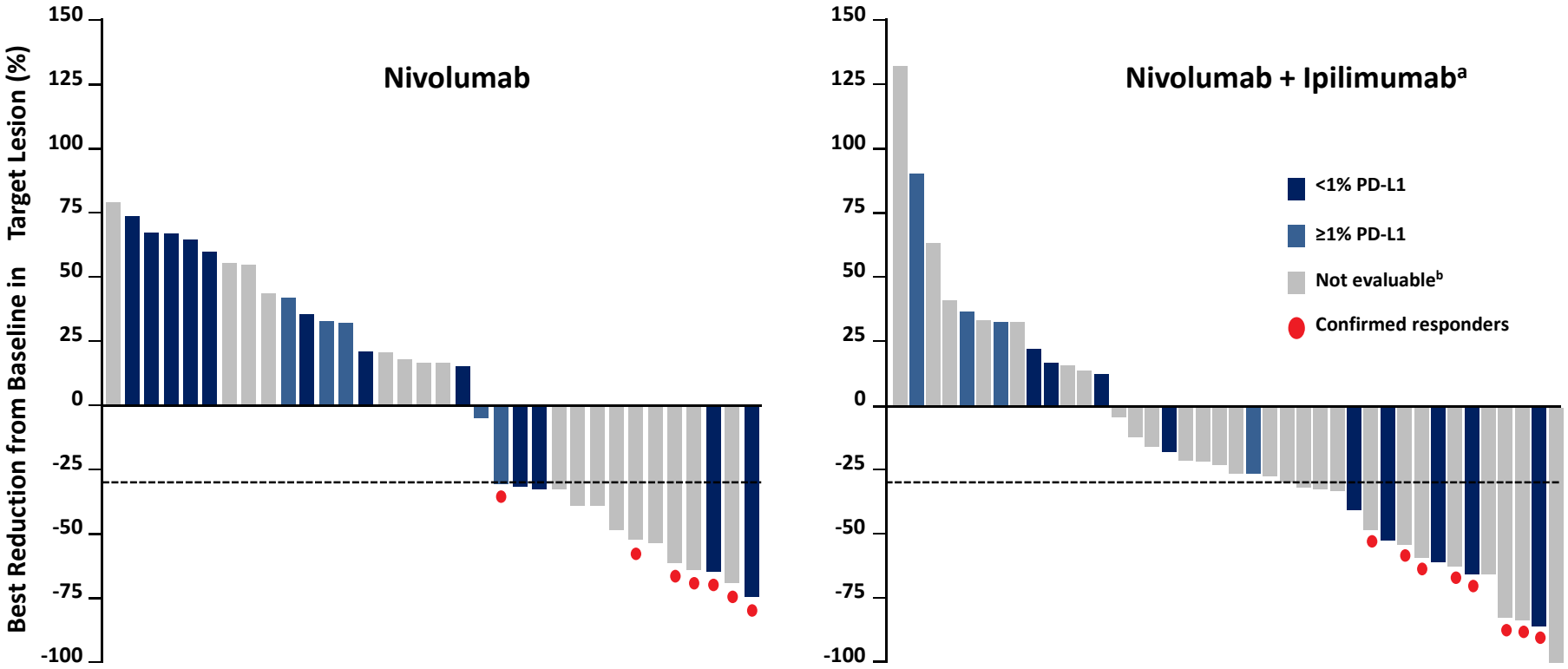
Comprehensive Cancer Center
UC Cancer Research Foundation

Liu *et al.* ASCO 2015

Lung Cancer - SCLC (Antonia et al, ASCO 2015)

Tumor Responses

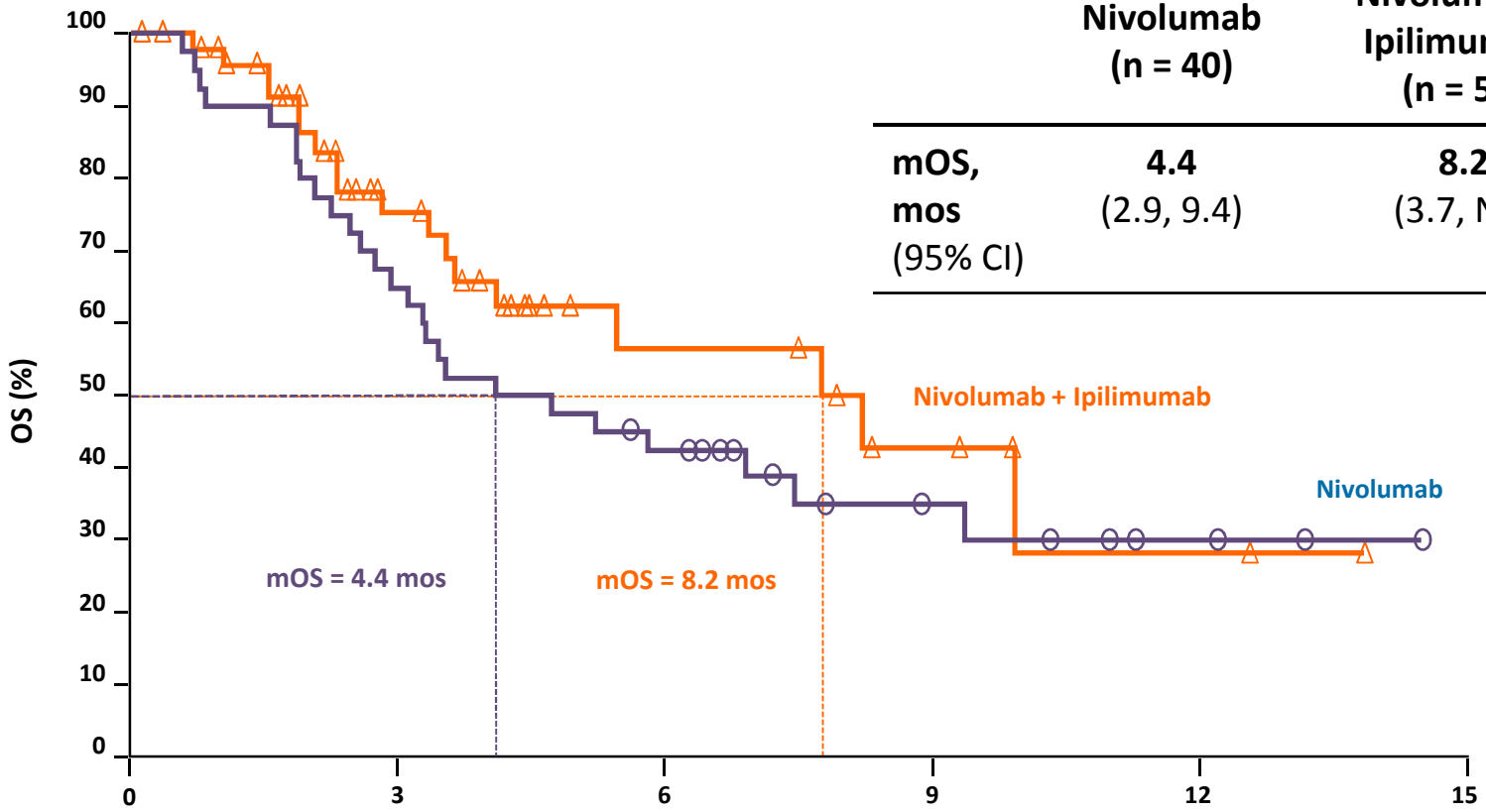


	Nivolumab (n = 40)	Nivolumab + Ipilimumab[a] (n = 46)
ORR, %	**18**	**17**
Complete response, %	0	2.2
Partial response, %	18	15

[a]Combined data for nivolumab 1 + ipilimumab 1 and nivolumab 1 + ipilimumab 3 cohorts. [b]Not evaluable due to specimens that are not quantifiable, indeterminate, or not yet obtained; 10 nonevaluable samples and 8 not yet obtained in the nivolumab arm, 6 nonevaluable samples and 26 not yet obtained in the nivolumab 1 + ipilimumab 3 arm. Only pts with target lesion at baseline and ≥1 on-treatment tumor assessment are included (nivolumab, n = 34, nivolumab + ipilimumab, n = 40).

Lung Cancer - SCLC (Antonia et al, ASCO 2015)

Overall Survival



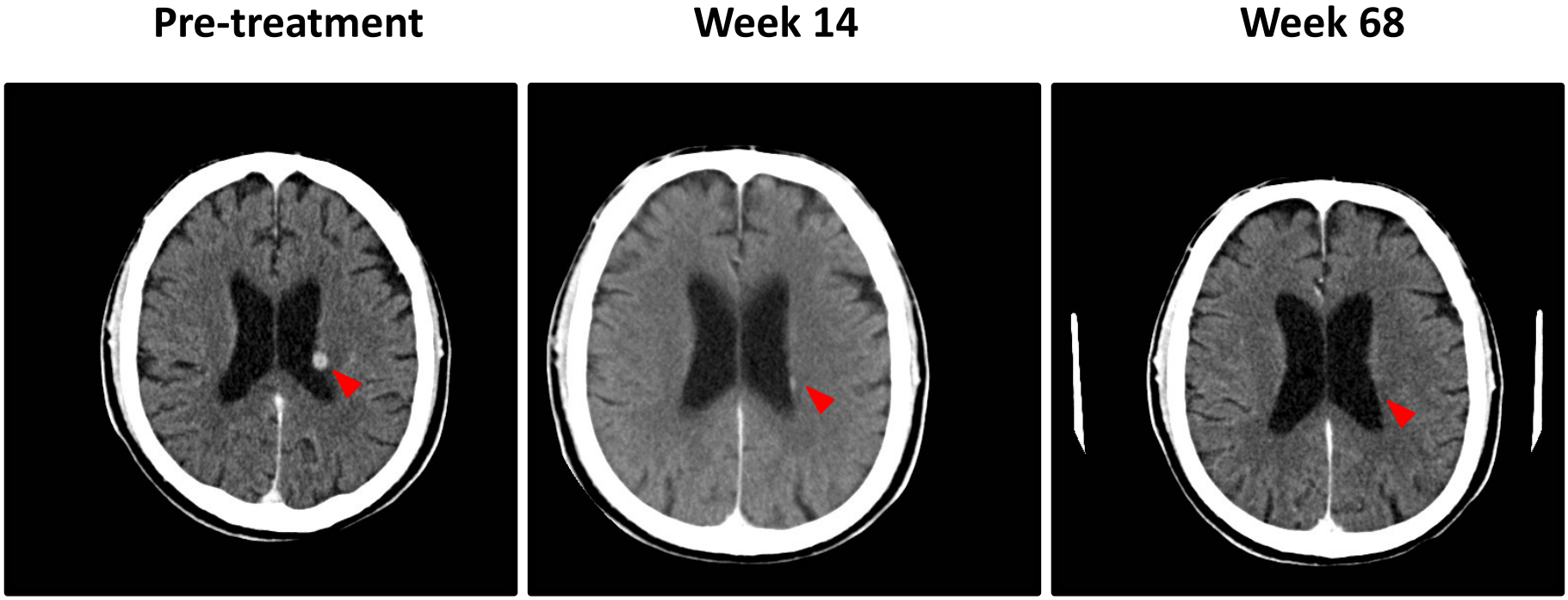
	Nivolumab (n = 40)	Nivolumab + Ipilimumab[a] (n = 50)
mOS, mos (95% CI)	**4.4** (2.9, 9.4)	**8.2** (3.7, NR)

Number of Patients at Risk

Nivolumab	40	26	16	7	3	0
Nivolumab + Ipilimumab	50	25	10	5	2	0

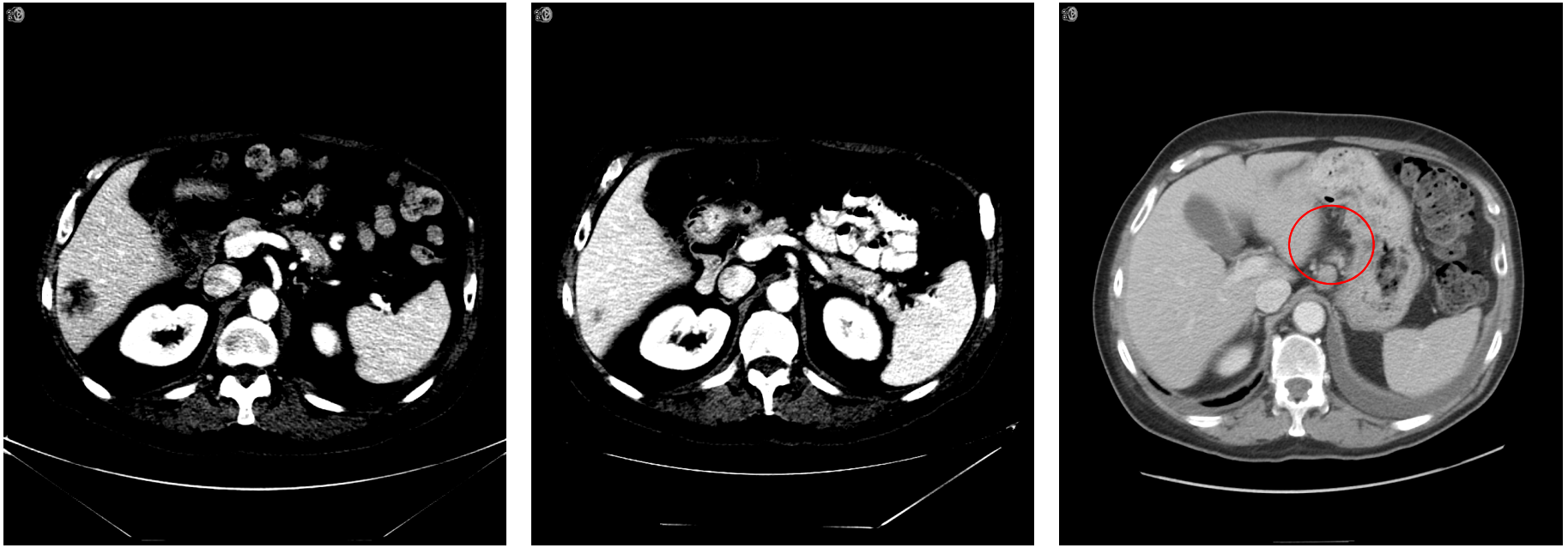
[a]Combined data for nivolumab 1 + ipilimumab 1 and nivolumab 1 + ipilimumab 3 cohorts

Response to nivolumab in SQ NSCLC brain metastasis

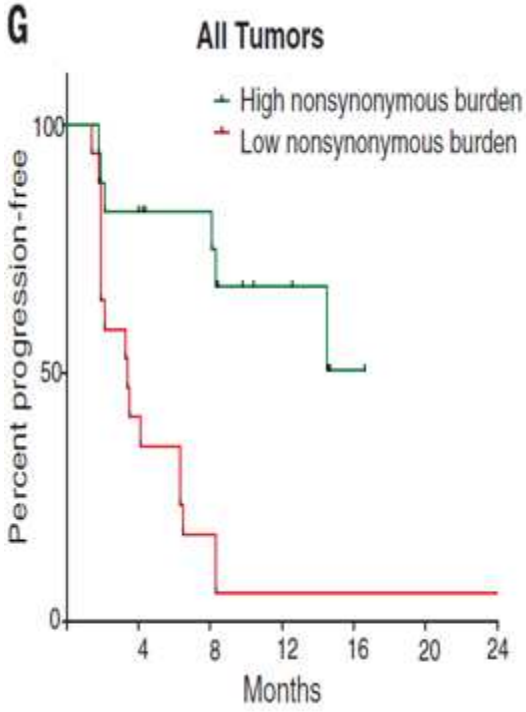


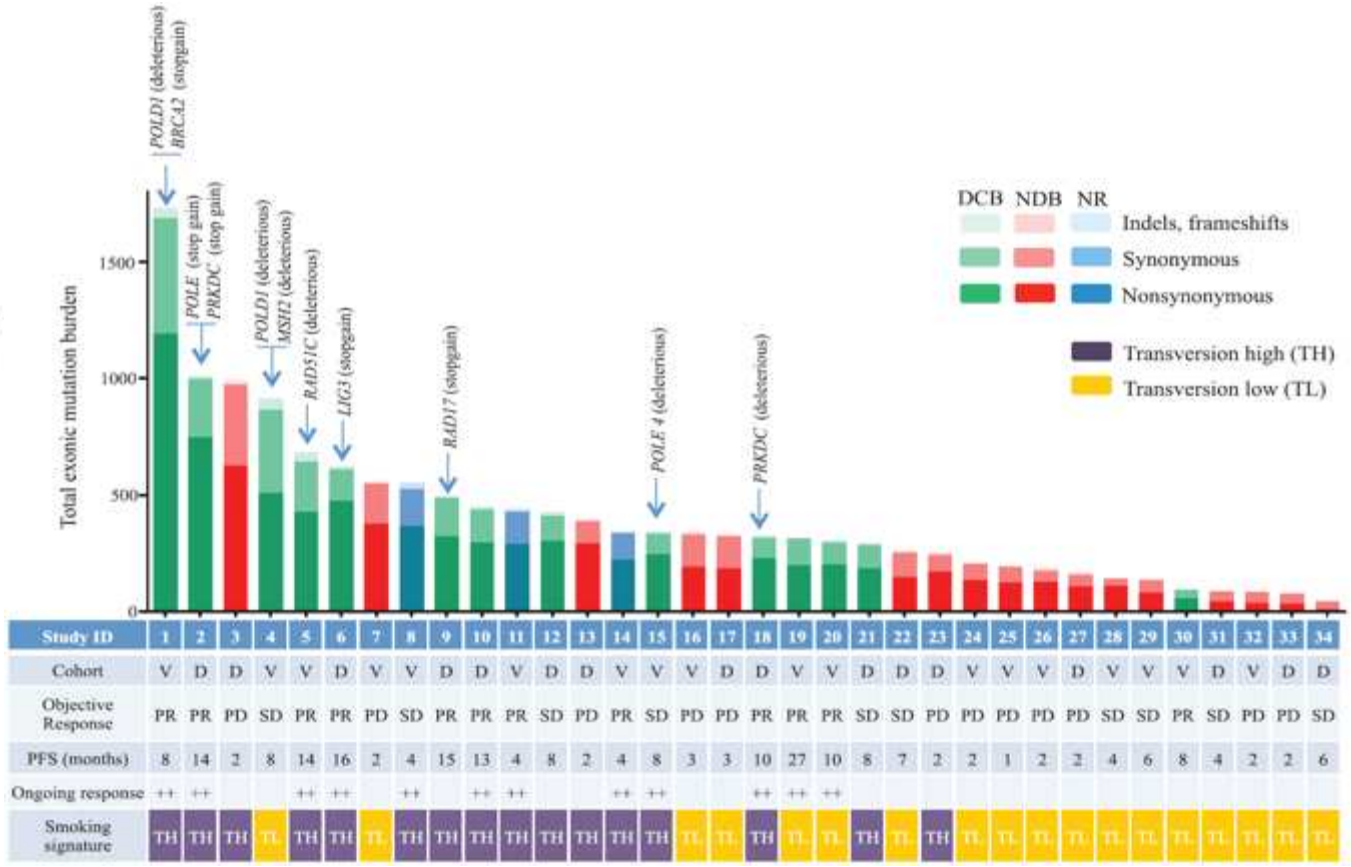
- 73 year-old male, stage IIIb, former smoker
- Prior radiotherapy (mediastinal), 3 prior systemic regimens (cisplatin/gemcitabine, docetaxel, vinorelbine)
- No prior CNS-directed therapy

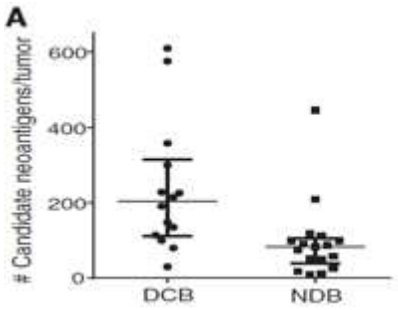
Acquired resistance to PD-1 progression

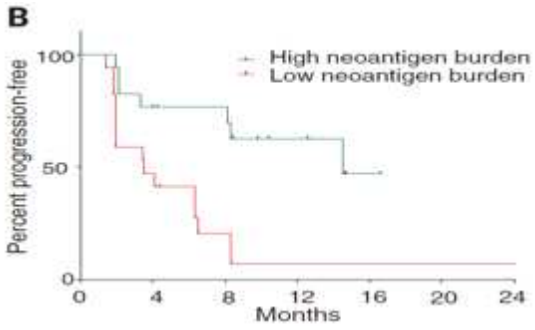


Mutational load and response to anti-PD1 (pembrolizumab) in NSCLC



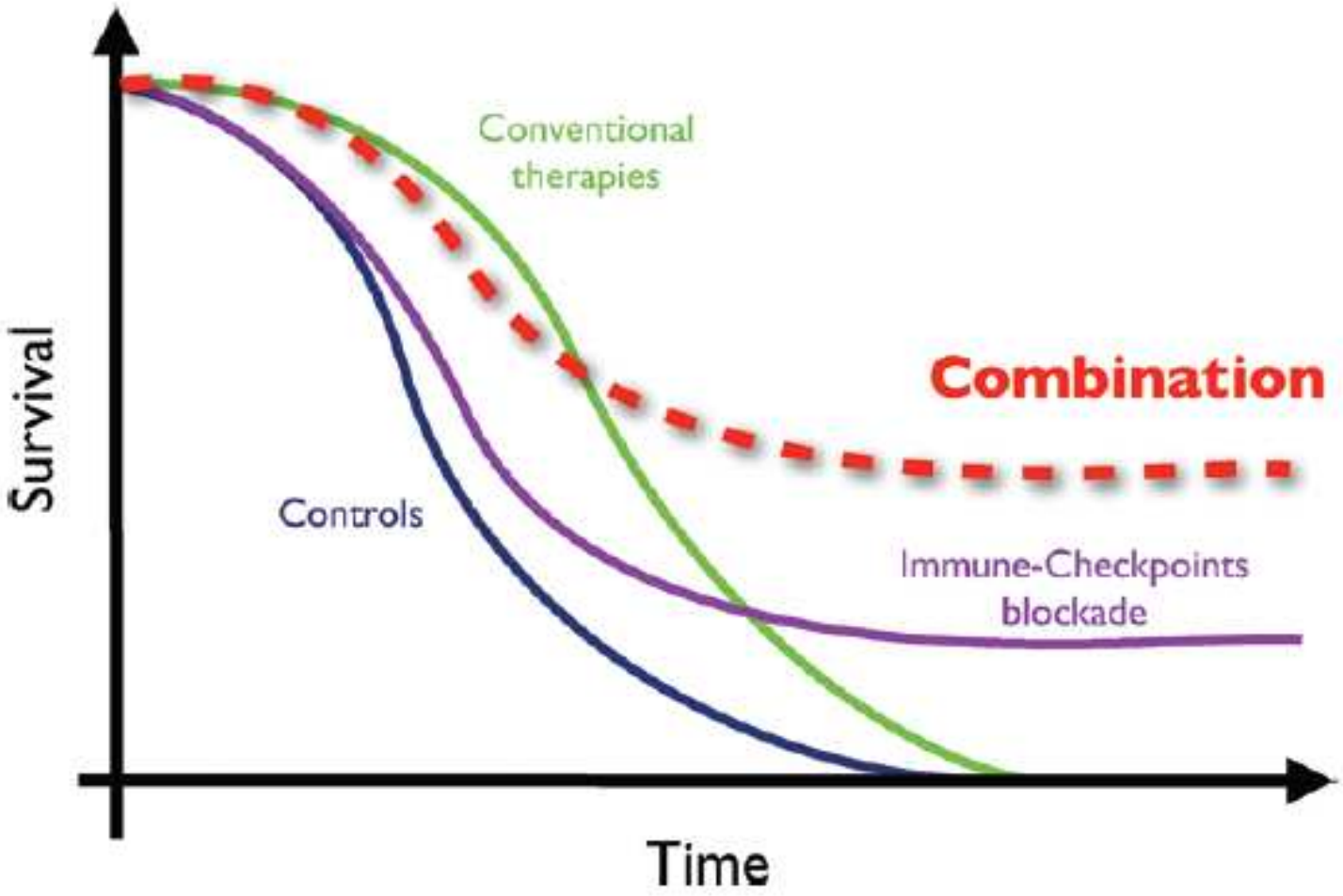






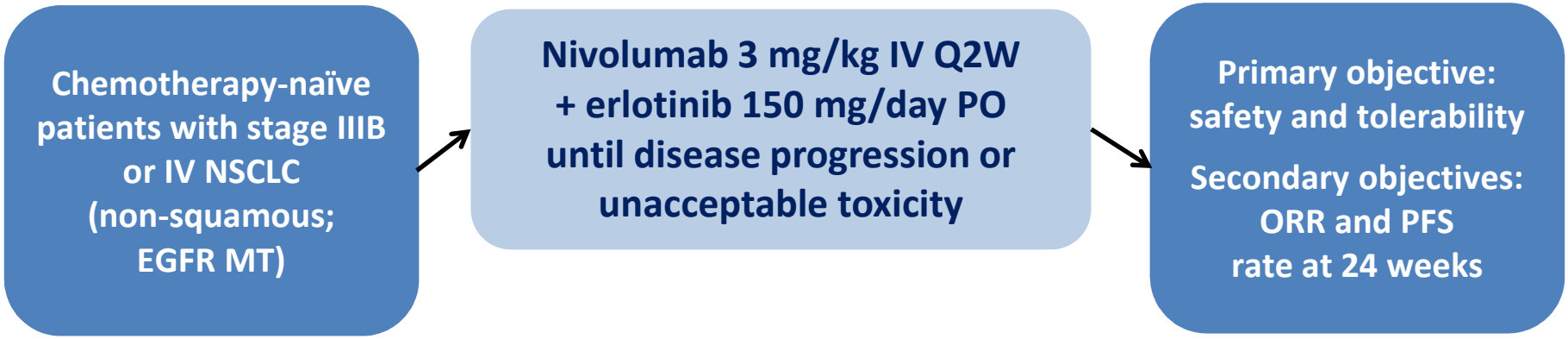
Rizvi et al. Science 2015

Combination Approaches



Adapted from: Ribas A, et al. Clin Cancer Res. 2012;18:336-341.

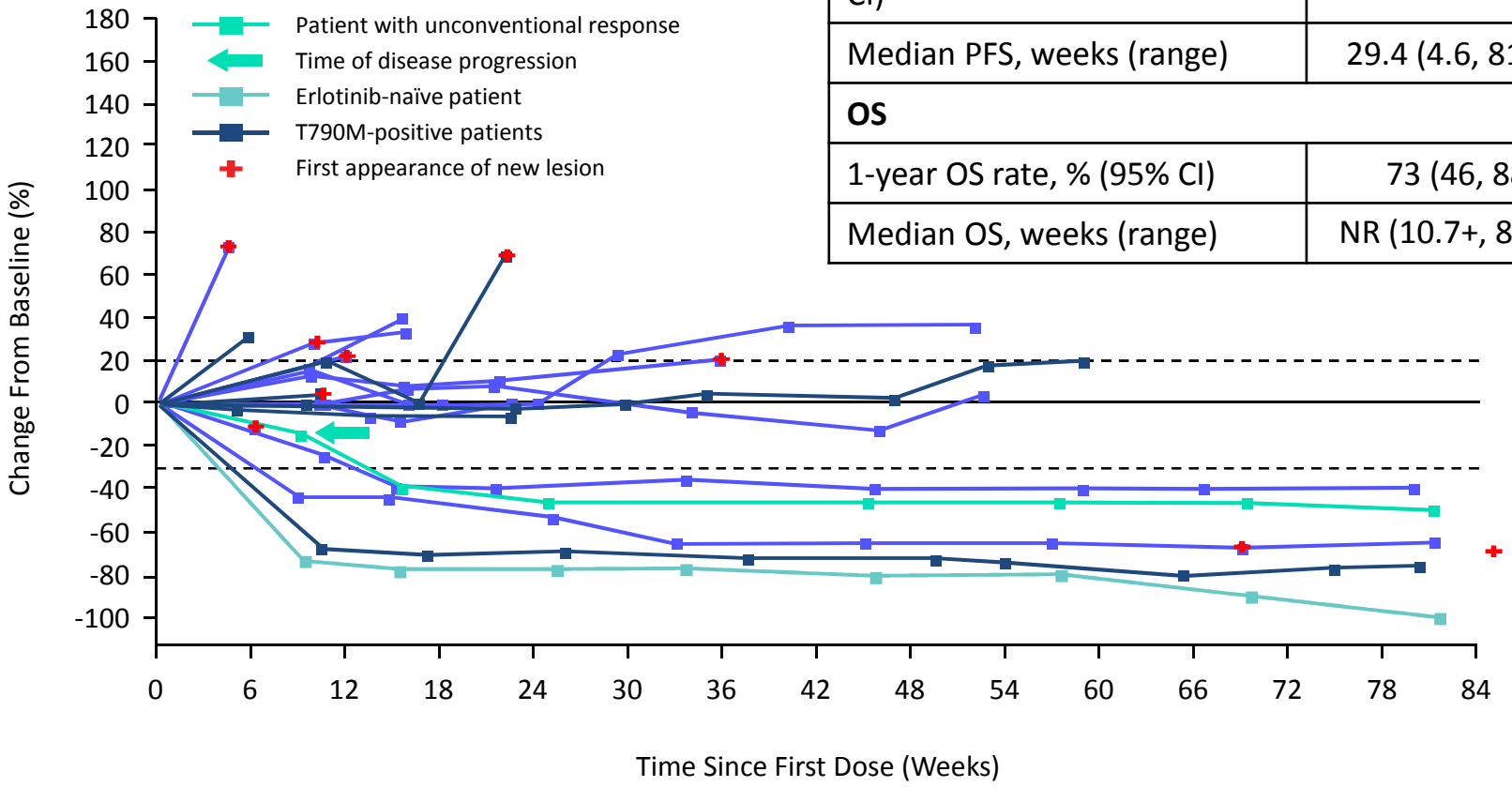
nivolumab + erlotinib



Rizvi et al ASCO 2014

CA209-012 study design: nivolumab in combination with erlotinib

PFS	
PFS rate at 24 weeks, % (95% CI)	51 (28, 70)
Median PFS, weeks (range)	29.4 (4.6, 81.7+)
OS	
1-year OS rate, % (95% CI)	73 (46, 88)
Median OS, weeks (range)	NR (10.7+, 86.9+)



IIII. Head and Neck Cancer

Antitumor Activity of the anti-PD-1 Antibody Pembrolizumab in biomarker-unselected Patients with R/M Head and Neck Cancer:

Preliminary Results from the KEYNOTE-012 Expansion Cohort

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PRESENTED AT: ASCO Annual '15 Meeting

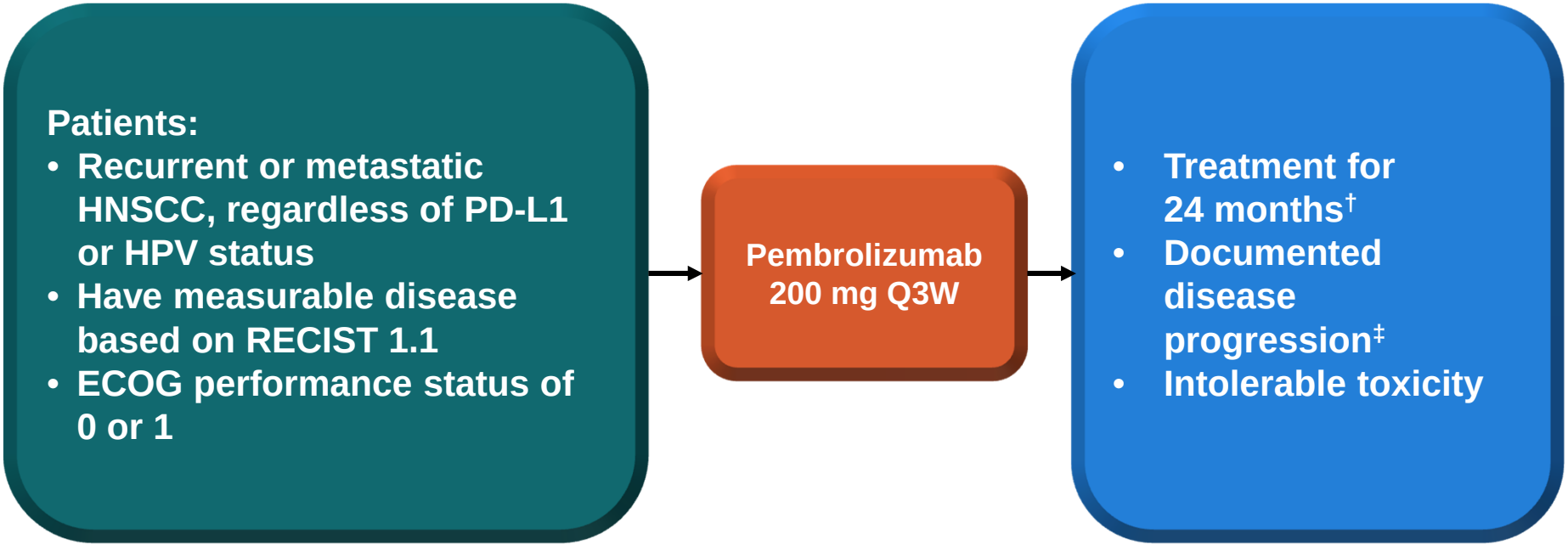
Head and Neck Squamous Cell Cancer

- Head and Neck Squamous Cell Cancer (HNSCC): 5th most common cancer worldwide
- Recurrent/metastatic HNSCC remains poorly treatable with a median OS of 10 months
  in the first-line setting[1]
  - Commonly used agents: platinum, cetuximab, taxanes, 5-FU, methotrexate
- Median OS of 6-months in patients previously treated[2]
- **Prominent immune escape** observed in HNSCC[3,4]
  - T-cell inflamed phenotype (TILs + PD-L1 expression)
  - Present in both HPV(-) and HPV(+) tumors
  - HPV related "foreign" antigens present in HPV(+) tumors

➔ **Blocking PD-1 interaction with PD-L1 or PD-L2 may reactivate immune surveillance and elicit anti-tumor activity**

1. Vermorken J et al. *N Engl J Med*. 2008;359(11):1116-27.
2. Stewart JSW, et al *J Clin Oncol.* 27:1864-1871.
3. Saloura V et al. *J Clin Oncol* 2014;32 (Suppl 5): Abstract 6009
4. Lyford-Pike S et al. *Cancer Res* 2013;73(6):1733-1741.

HNSCC expansion cohort of the KEYNOTE-012 Nonrandomized, Phase 1b Multi-cohort trial*



Response assessment: Every 8 weeks

Primary end points: ORR per modified RECIST v1.1 by investigator review; safety

Secondary end points: PFS, OS, duration of response

*Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
†Treatment beyond progression was allowed.
‡Re-treatment was permitted.

Baseline Demographics

Characteristic	N = 132* N (%)
Median age (range), years	60 (25–84)
Male	110 (83.3)
Race	
White	96 (72.7)
Asian	28 (21.2)
Other	8 (6.1)
ECOG PS	
[0] Normal Activity	38 (28.8)
[1] Symptoms, but ambulatory	94 (71.2)

Characteristic	N = 132* N (%)
Prior adjuvant/neoadjuvant systemic therapy	
Yes	53 (40.2)
Prior lines of therapy for recurrent/metastatic disease	
0	22 (16.7)
1	30 (22.7)
2	28 (21.2)
3 or more	50 (37.9)
Unknown	2 (1.5)

Data cutoff date: March 23, 2015

*Includes patients who received ≥1 dose of pembrolizumab

Treatment-Related Adverse Events

AE in ≥5 % of Patients	N = 132* N (%)
Any	79 (59.8)
Fatigue	20 (15.2)
Hypothyroidism	12 (9.1)
Decreased appetite	10 (7.6)
Rash	10 (7.6)
Dry skin	9 (6.8)
Pyrexia	9 (6.8)
Arthralgia	7 (5.3)
Nausea	7 (5.3)
Weight decreased	7 (5.3)

Grades 3-5 (≥2 patients)	N = 132* N (%)
Any	13 (9.8)
Swelling face	2 (1.5)
Pneumonitis	2 (1.5)

- No treatment-related deaths occurred

*Includes patients who received ≥1 dose of pembrolizumab
Data cut off date: March 23, 2015.

Overall Response Rate [Site Radiology Review]*

Best overall response	Total N = 117†		HPV+ n = 34		HPV– n = 81	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
ORR	**29 (24.8)**	17.3-33.6	7 (20.6)	8.7-37.9	22 (27.2)	17.9-38.2
Complete Response	1 (0.9)	0.0-4.7	1 (2.9)	0.1-15.3	0 (0)	0-4.5
Partial Response	28 (23.9)	16.5-32.7	6 (17.6)	6.8-34.5	22 (27.2)	17.9-38.2
Stable Disease	29 (24.8)	17.3-33.6	9 (26.5)	12.9-44.4	19 (23.5)	14.8-34.2
Progressive Disease	48 (41.0)	32.0-50.5	13 (38.2)	22.2-56.4	34 (42.0)	31.1-53.5
No Assessment#	9 (7.7)	3.6-14.1	4 (11.8)	3.3-27.5	5 (6.2)	2.0-13.8
Non-evaluable±	2 (1.7)	0.2-6.0	1 (2.9)	0.1-15.3	1 (1.2)	0.0-6.7

*Unconfirmed and confirmed RECIST v 1.1 responses

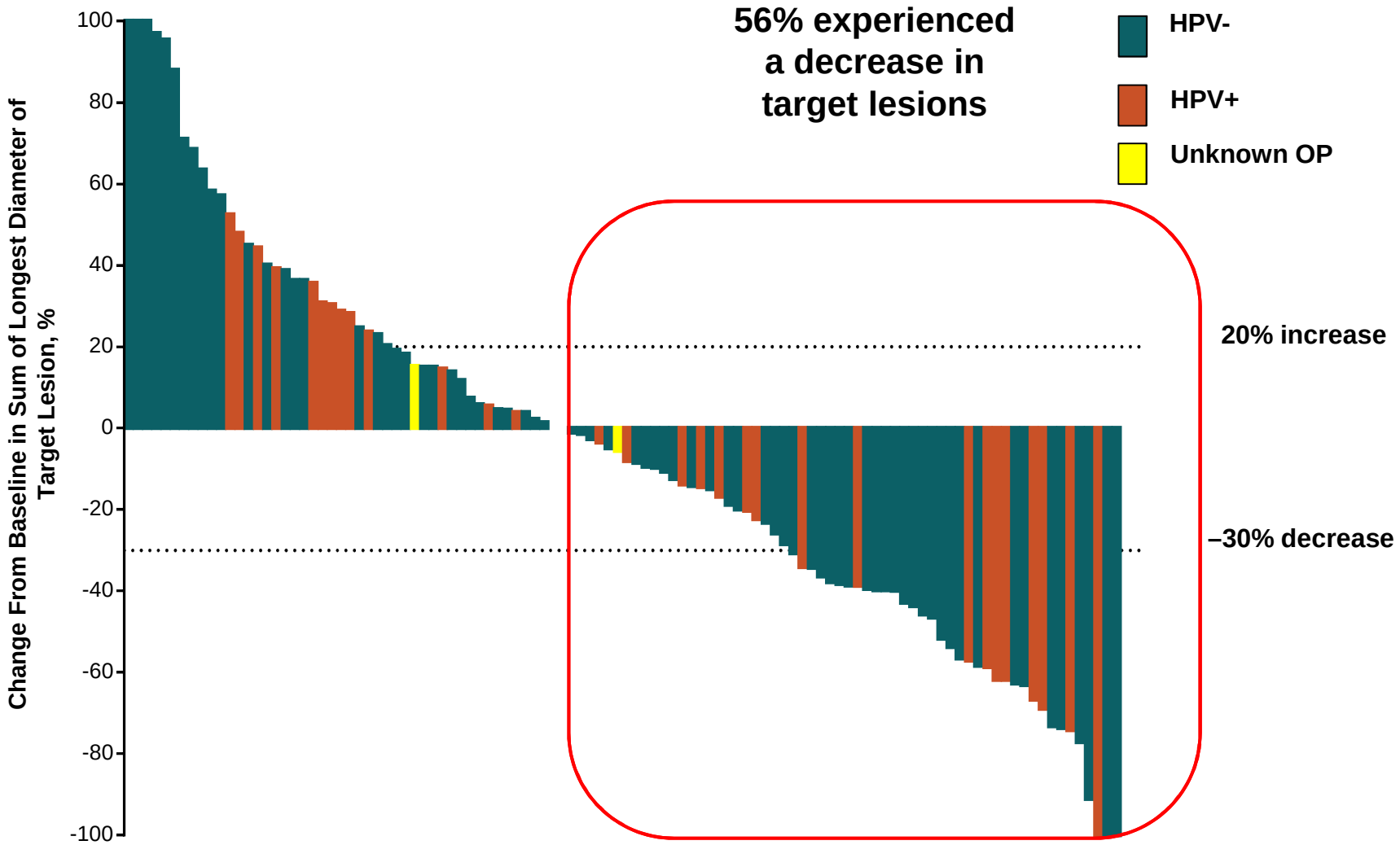
†Includes patients who received ≥1 dose of pembrolizumab, had measurable disease at baseline and ≥1 postbaseline scan or discontinued due to PD or DRAE. 15 patients not included in this analysis: 2 did not have baseline scans within screening window, 13 did not have post-baseline assessment and discontinued due to non-drug related AE (7), subject withdrawal of consent (4), other (2).

#No assessment: Discontinued without post-baseline radiographic assessment due to drug related AE (2 patients), clinical PD (6 patients), death due to PD (1 patient)

±Non-evaluable: Images were not of sufficient quality to be evaluable

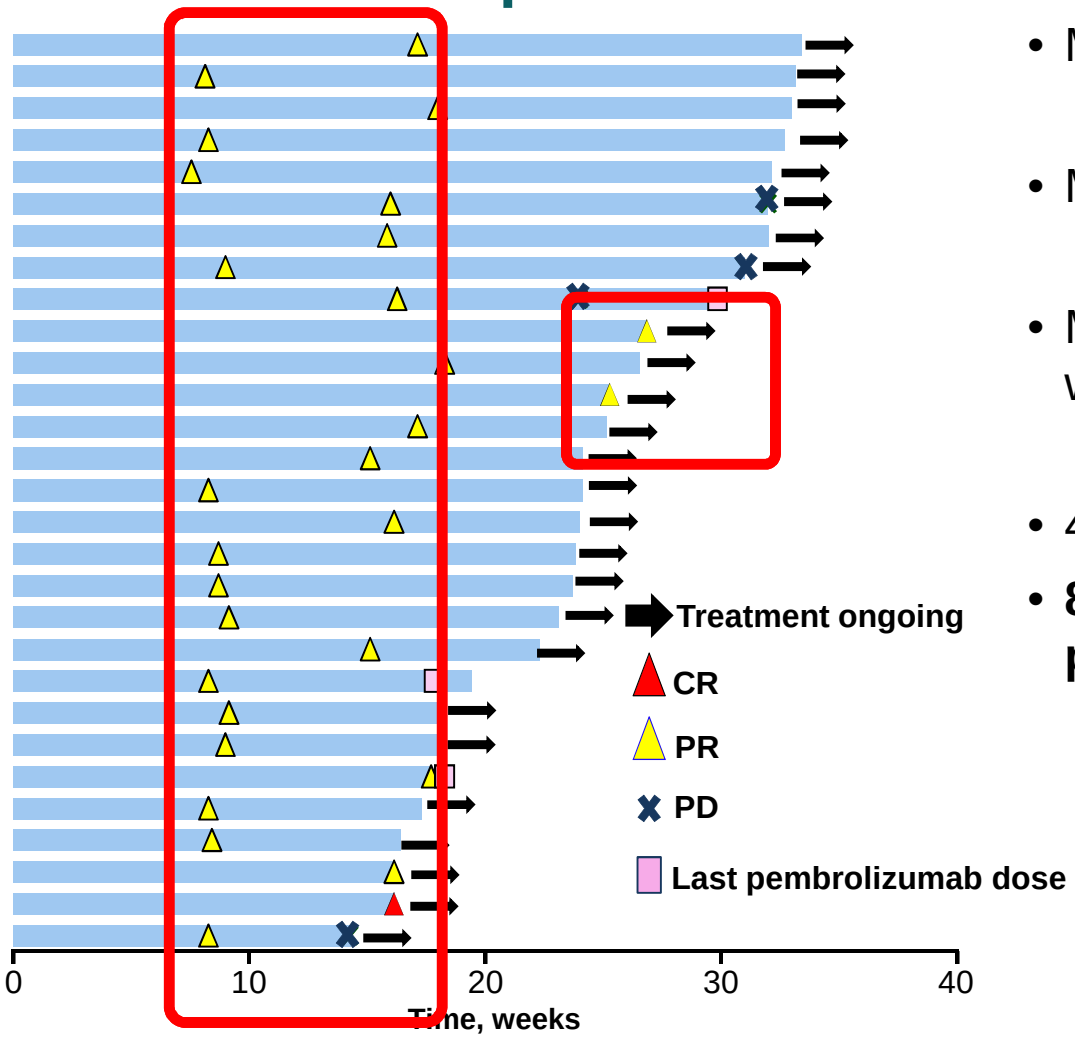
HPV status missing for 2 patients with oropharynx cancer. Cancers outside the oropharynx are considered HPV negative by convention.

Tumor Shrinkage



Analysis includes patients with measurable disease at baseline who received ≥1 pembrolizumab dose and had ≥1 post-baseline tumor assessment (n = 106)
Unconfirmed and confirmed RECIST v 1.1 responses by site radiology review
*2 oropharynx cancer patient are HPV unknown. Cancers outside the oropharynx are considered HPV negative by convention
Data cutoff date: March 23, 2015. OP = oropharyngeal primary

Treatment Exposure and Response Duration of Patients Who Responded



- Median follow-up duration:
  - 5.7 (0.2 – 8.7) months
- Median time to response:
  - 9.0 (7.6−18.0) weeks
- Median duration of response was not reached
  - Range: 7.3+ − 25.1+ weeks
- 40 patients remain on therapy
- **86% (25/29) of responding patients remain in response**

Unconfirmed and confirmed RECIST v 1.1 responses
Data cutoff date: March 23, 2015.

Overall Survival Data

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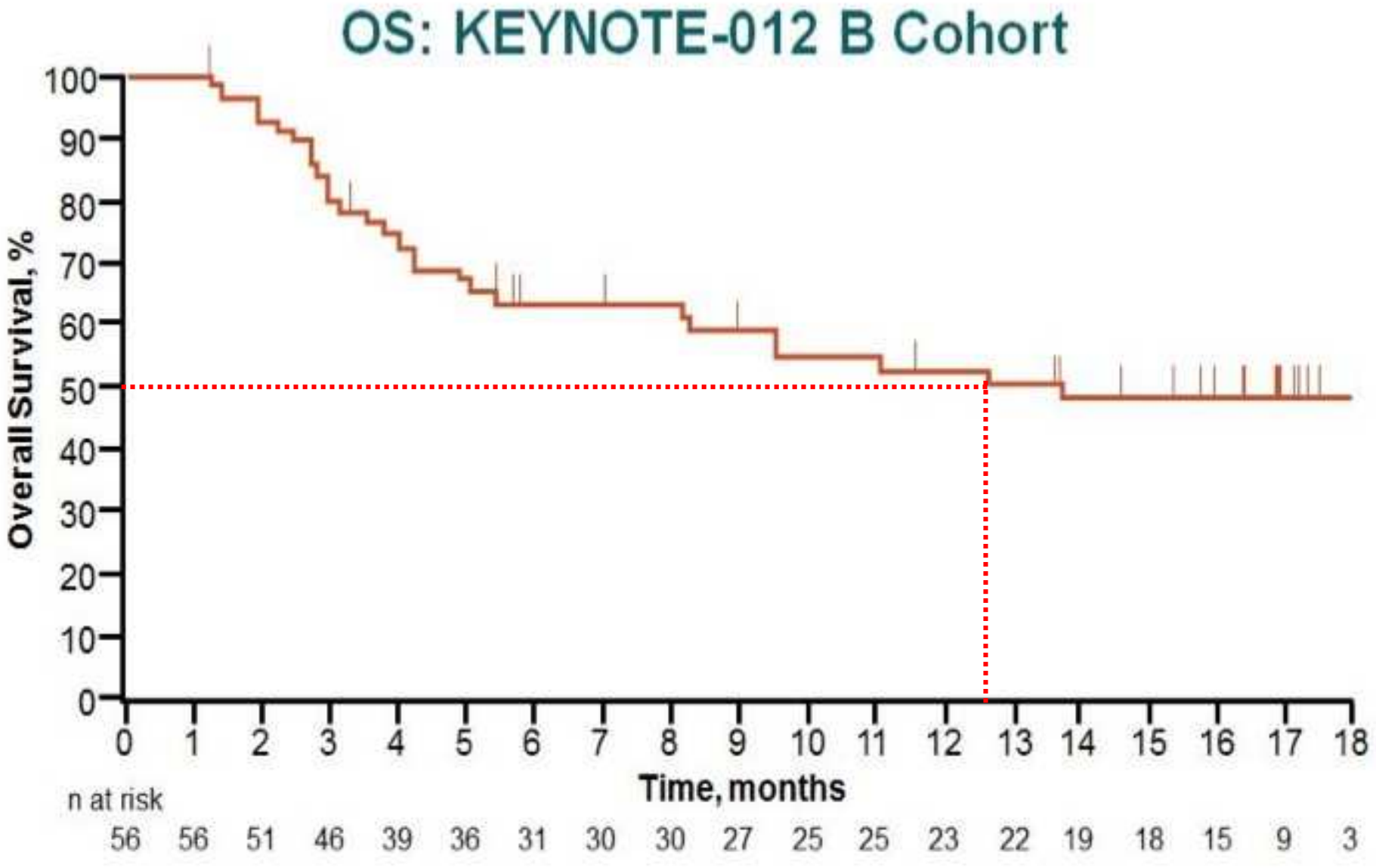
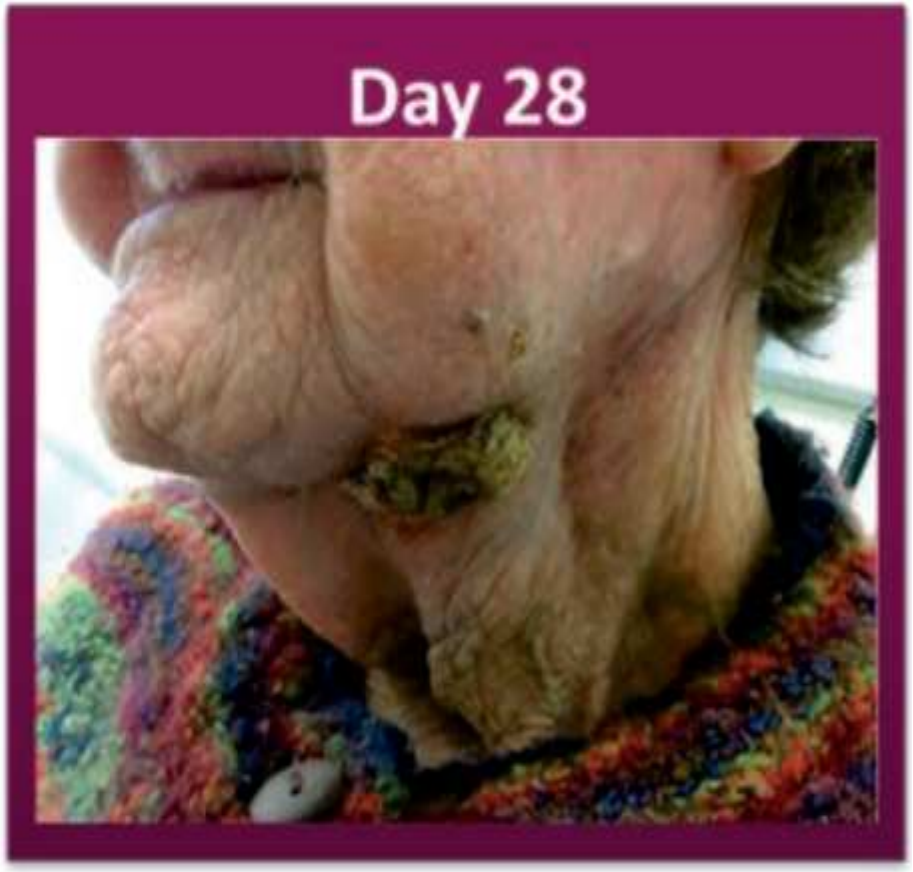


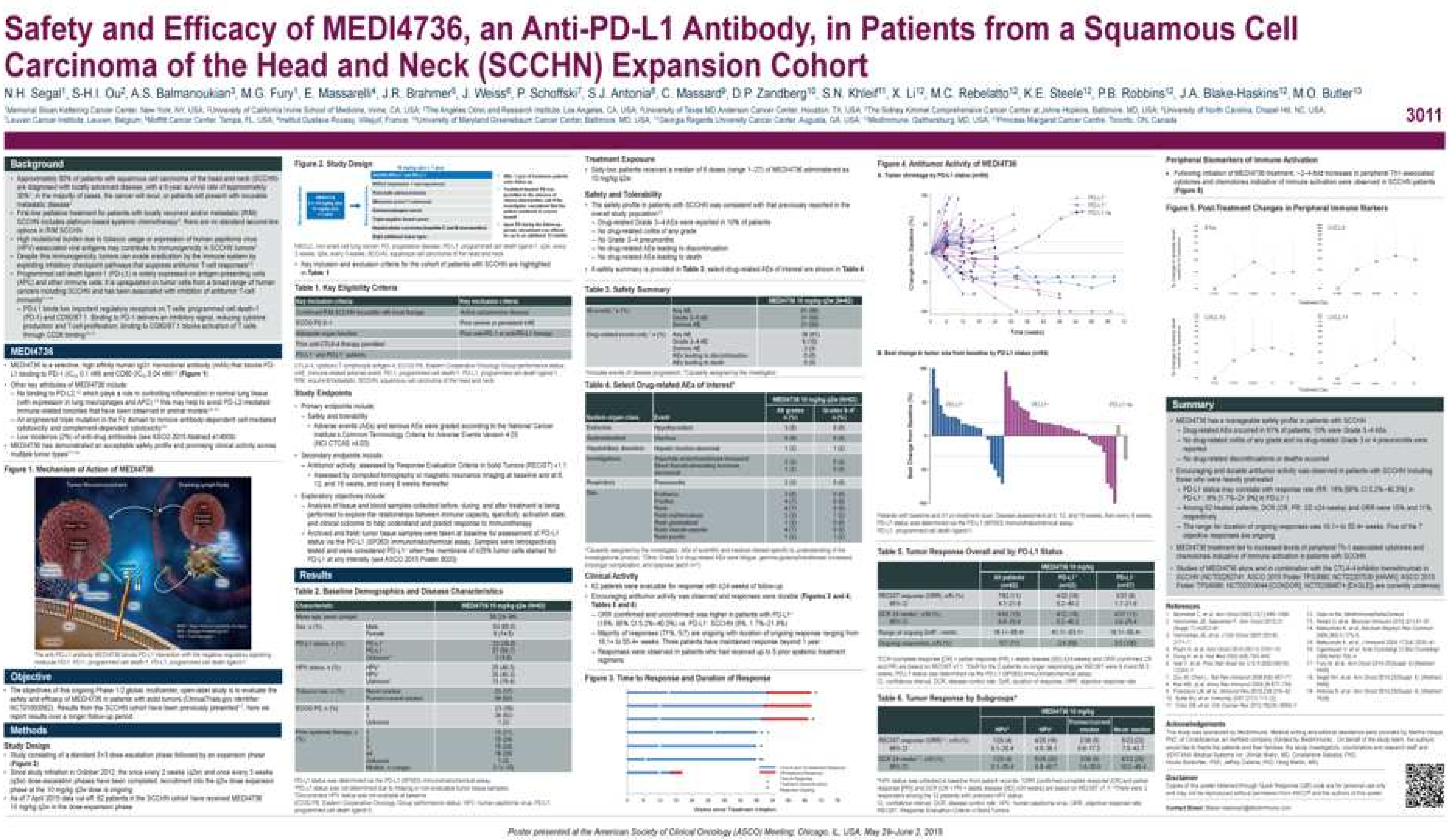
MADRID 2014 ESMO congress

Durvalumab (MEDI4736) Efficacy in HNC:



Presented by: Matt Fury, ESMO 2014

Durvalumab/MEDI4736: Clinical Data – ASCO 2015



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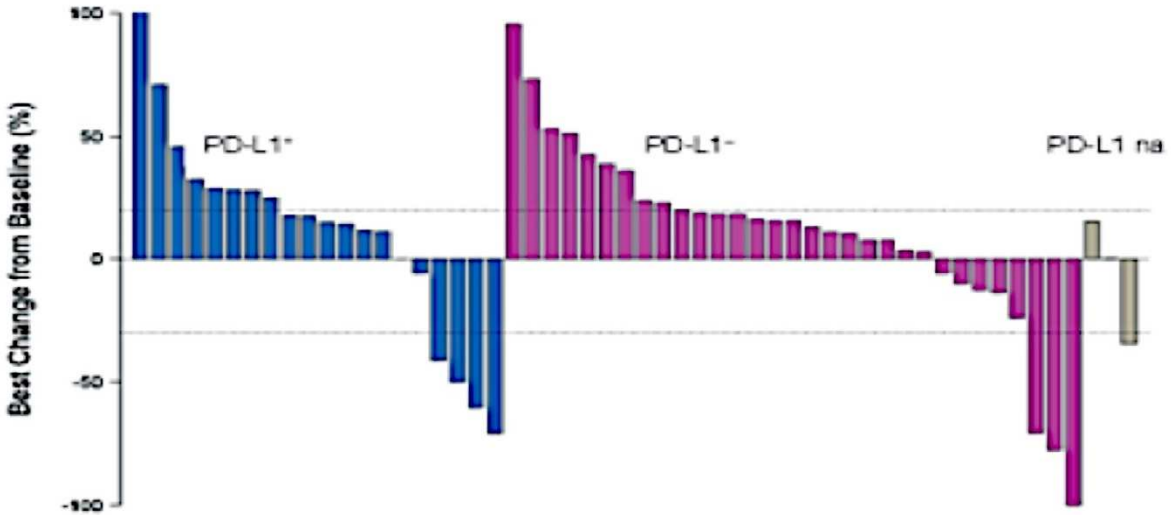
Segal et al. ASCO 2015

Durvalumab/MEDI4736: Clinical Data – ASCO 2015

Table 5. Tumor Response Overall and by PD-L1 Status

	MEDI4736 10 mg/kg		
	All patients (n=62)	PD-L1+ (n=22)	PD-L1- (n=37)
RECIST response (ORR), n/N (%) 95% CI	7/62 (11) 4.7–21.9	4/22 (18) 5.2–40.3	3/37 (8) 1.7–21.9
DCR 24 weeks*, n/N (%) 95% CI	9/62 (15) 6.9–25.8	4/22 (18) 5.2–40.3	4/37 (11) 3.0–25.4
Range of ongoing DoR†, weeks	16.1+–55.4+	41.1+–53.1+	16.1+–55.4+
Ongoing responders, n/N (%)	5/7 (71)	2/4 (50)	3/3 (100)

B. Best change in tumor size from baseline by PD-L1 status (n=54)



Segal et al. ASCO 2015

Patients with baseline and ≥1 on-treatment scan. Disease assessment at 6, 12, and 16 weeks, then every 8 weeks.
PD-L1 status was determined via the PD-L1 (SP263) immunohistochemical assay.
PD-L1, programmed cell death ligand-1.

Conclusions

- Largest experience of immunotherapy in head and neck cancer (N =132 patients)

- 56% of patients experienced any decrease in target lesions
  - Response rate of 25%
  - Broadly active in both HPV(+) and HPV(-) patients
  - Active in heavily pretreated population
  - Responses were durable ➔ 86% of responding patients remain in response

- Pembrolizumab administered at a fixed dose of 200 mg every 3 weeks was well tolerated

- Pembrolizumab is currently being evaluated in two phase III trials to investigate the clinical benefit of pembrolizumab vs standard of care chemotherapy (using the 200mg every 3 week dose schedule)

PD-L1 Screening Results

104 Patients screened:

PD-L1 positive: 78% (81)

- Study Eligible n = 61*
  - *HPV (-) n = 36†*
  - *HPV (+) n = 23†*
  - *HPV (na) n = 2*

PD-L

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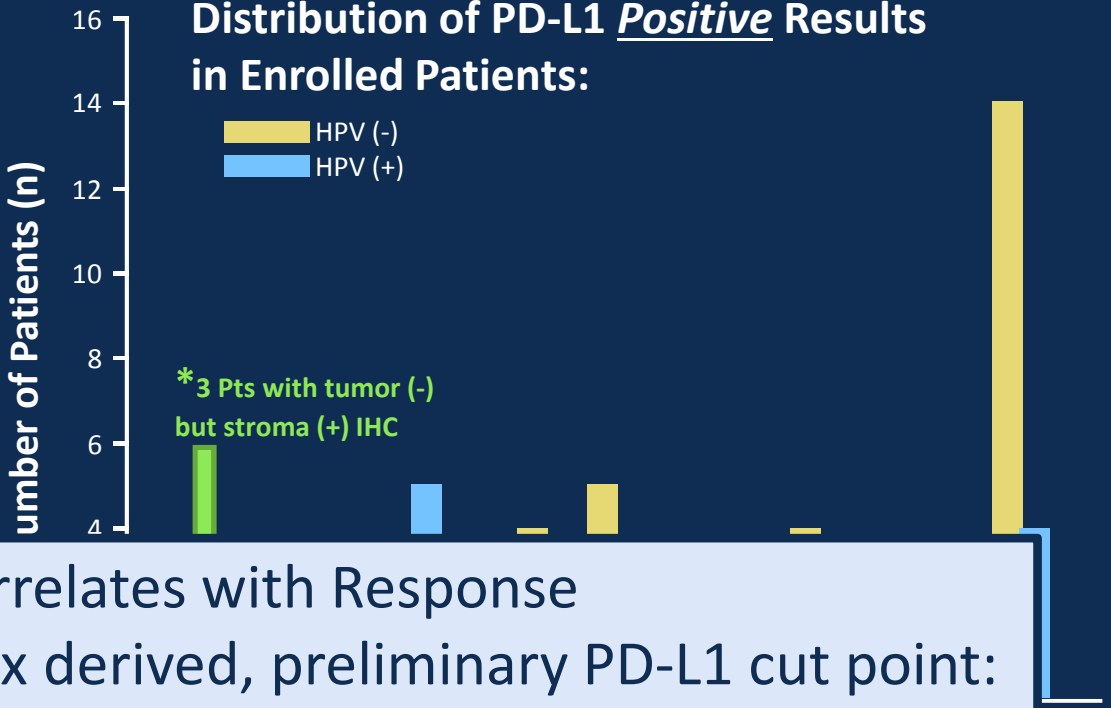
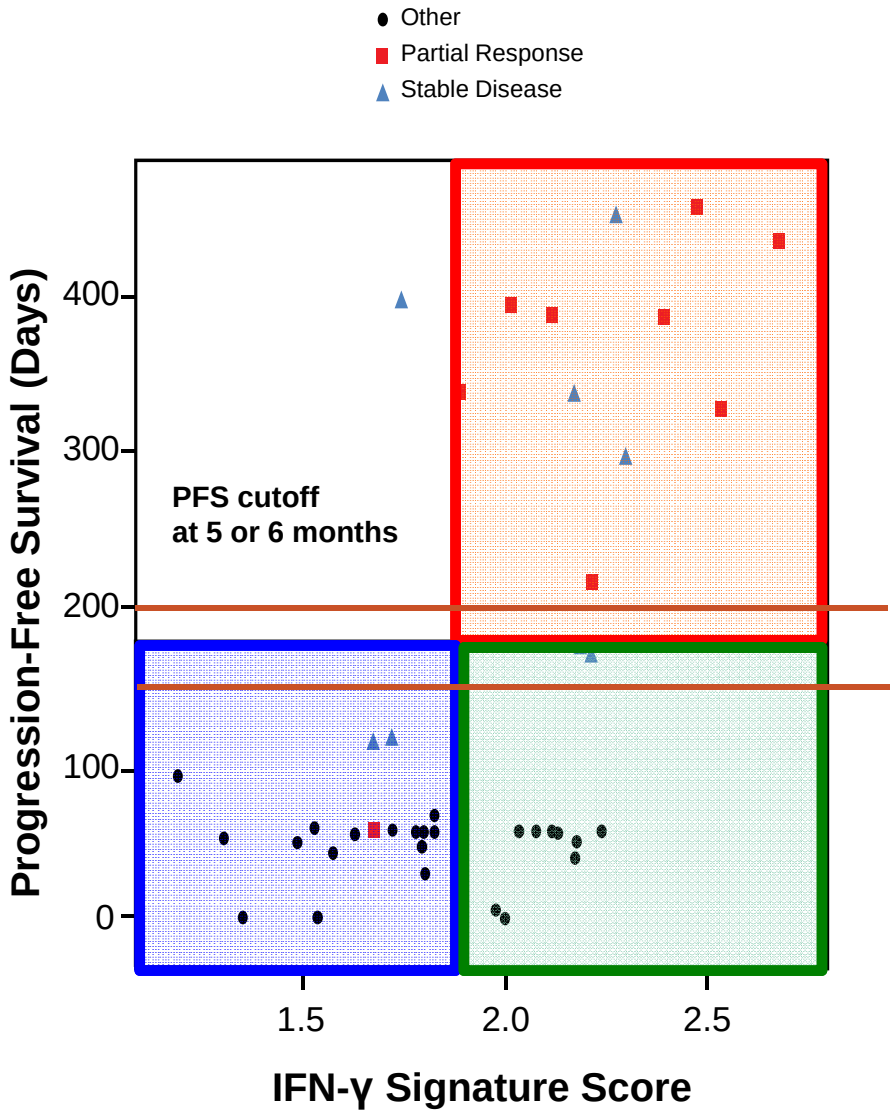


- PD-L1 expression correlates with Response
- Using a Youden-Index derived, preliminary PD-L1 cut point:
  - ➢ Above cutpoint: **45.5% (5/11) RR**
  - ➢ Below cutpoint: **11.4% (5/44) RR**

	PD-L1 Staining in Tumors of Screened Patients (N = 104)										
Staining (%)	0	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100
n	**26***	**24**	**8**	**9**	3	2	2	4	3	2	**21**

Association of IFNγ Signature and Progression-Free Survival in Patients with Head and Neck Cancer



1. ***IR-group*: Inflamed – Responders**
   - Gamma-IFN Inflamed
   - Benefitting from anti-PD1 therapy
2. ***INR-group*: Inflamed – NonResponders**
   - Gamma-IFN Inflamed
   - Not Benefitting from anti-PD1 therapy
   - Given biologic signal - Can these patients be converted into responders e.g. via combinations, vaccine etc.
3. ***NI-group*: Non-Inflamed**
   - Very high negative predictive value
   - Not benefitting from anti-PD1 therapy
   - Clinically potentially useful: Identify patients who shout NOT receive PD-1 therapy
   - Unclear whether non-inflamed phenotype can be converted into inflamed phenotype

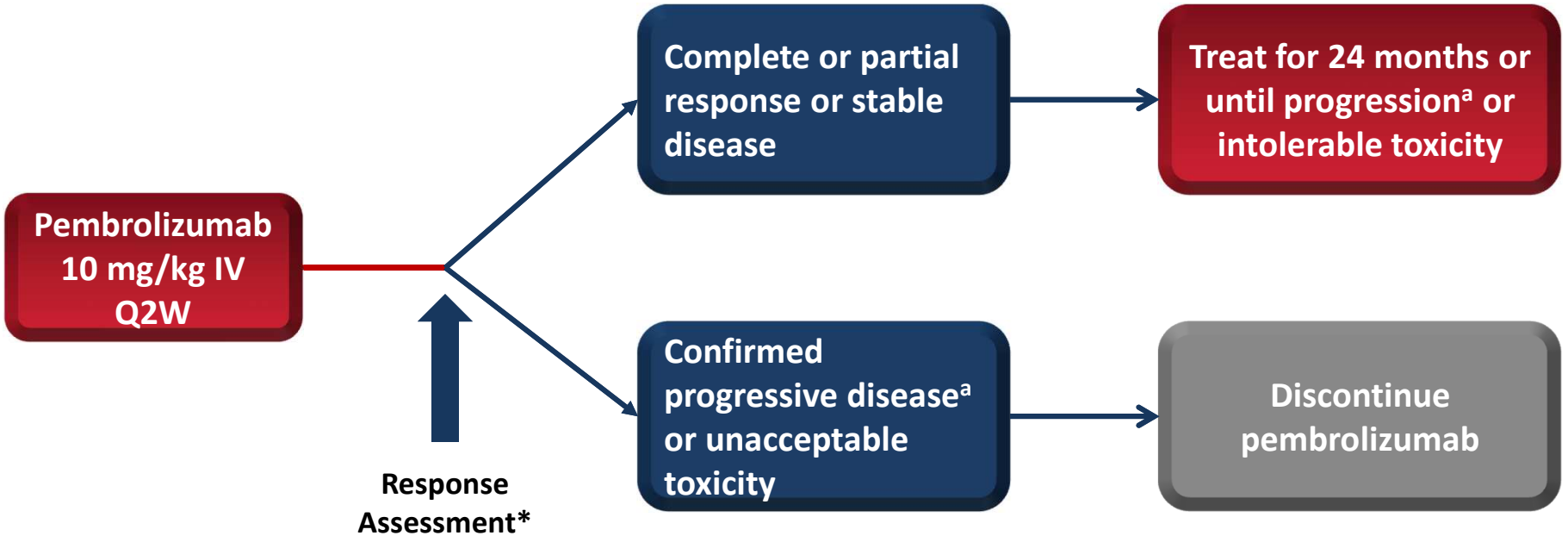
IV. Mesothelioma

Clinical Safety and Efficacy of Pembrolizumab (MK-3475) in Patients with Malignant Pleural Mesothelioma (MPM): Preliminary Results from KEYNOTE-028

Evan Alley,[1] L. Rhoda Molife,[2] Armando Santoro,[3] Kim Beckey,[4] Shuai Sammy Yuan,[4] Jonathan Cheng,[4] Bilal Piperdi,[4] Jan H.M. Schellens[5]

[1]University of Pennsylvania, Philadelphia, PA; [2]Royal Marsden Hospital, London, UK; [3]Istituto Clinico Humanitas, Milan, Italy; [4]Merck & Co, Inc., Kenilworth, NJ, USA; [5]Netherlands Cancer Institute, Plesmanlaan, Netherlands

KEYNOTE-028 (NCT02054806): Phase 1b Multi-Cohort Study of Pembrolizumab for PD-L1+ Advanced Solid Tumors



***Response assessment**: Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end points: ORR per RECIST v1.1 and safety

Secondary end points: PFS, OS, duration of response

Power: With ~22 subjects enrolled, this study provides 80% power to demonstrate that the ORR exceeds 10%

[a]If clinically stable, patients are to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. Patients who experience progression may be eligible for up to 1 year of additional pembrolizumab if no other anticancer therapy is received.

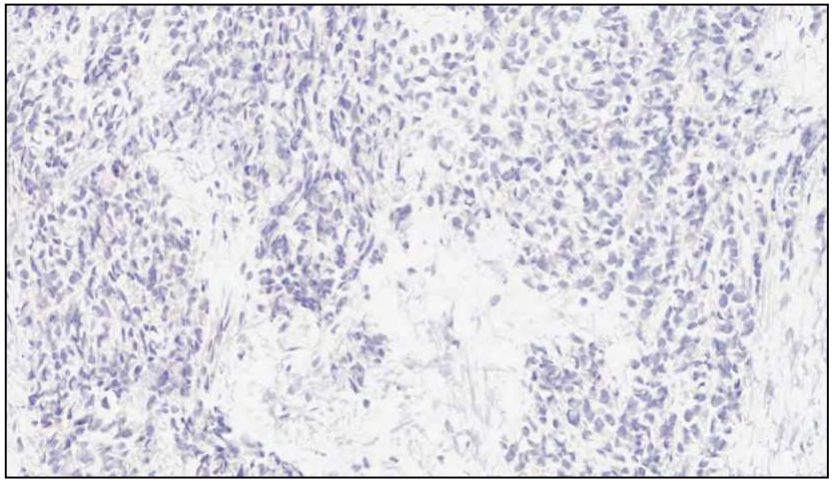
Key Eligibility Criteria

- Age ≥18 years
- Locally advanced or metastatic malignant pleural mesothelioma
- Failure of or inability to receive standard therapy
- Measurable disease per RECIST v1.1
- ECOG performance status of 0 or 1
- PD-L1–positive tumor
- Adequate organ function
- No autoimmune disease or interstitial lung disease
- No active brain metastases

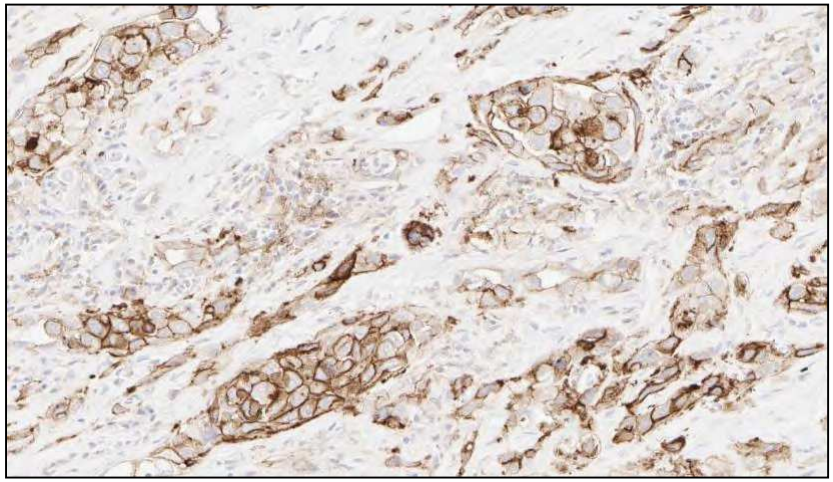
Analysis of PD-L1 Expression

- Tumor samples: archival or newly obtained core or excisional biopsy of a nonirradiated lesion
- Analyzed at a central laboratory using a prototype immunohistochemistry assay and the 22C3 antibody clone (Merck)
- Positivity: membranous expression in ≥1% of cells in tumor nests or PD-L1–positive bands in stroma

Examples of PD-L1 Staining in MPM Specimens from KEYNOTE-028

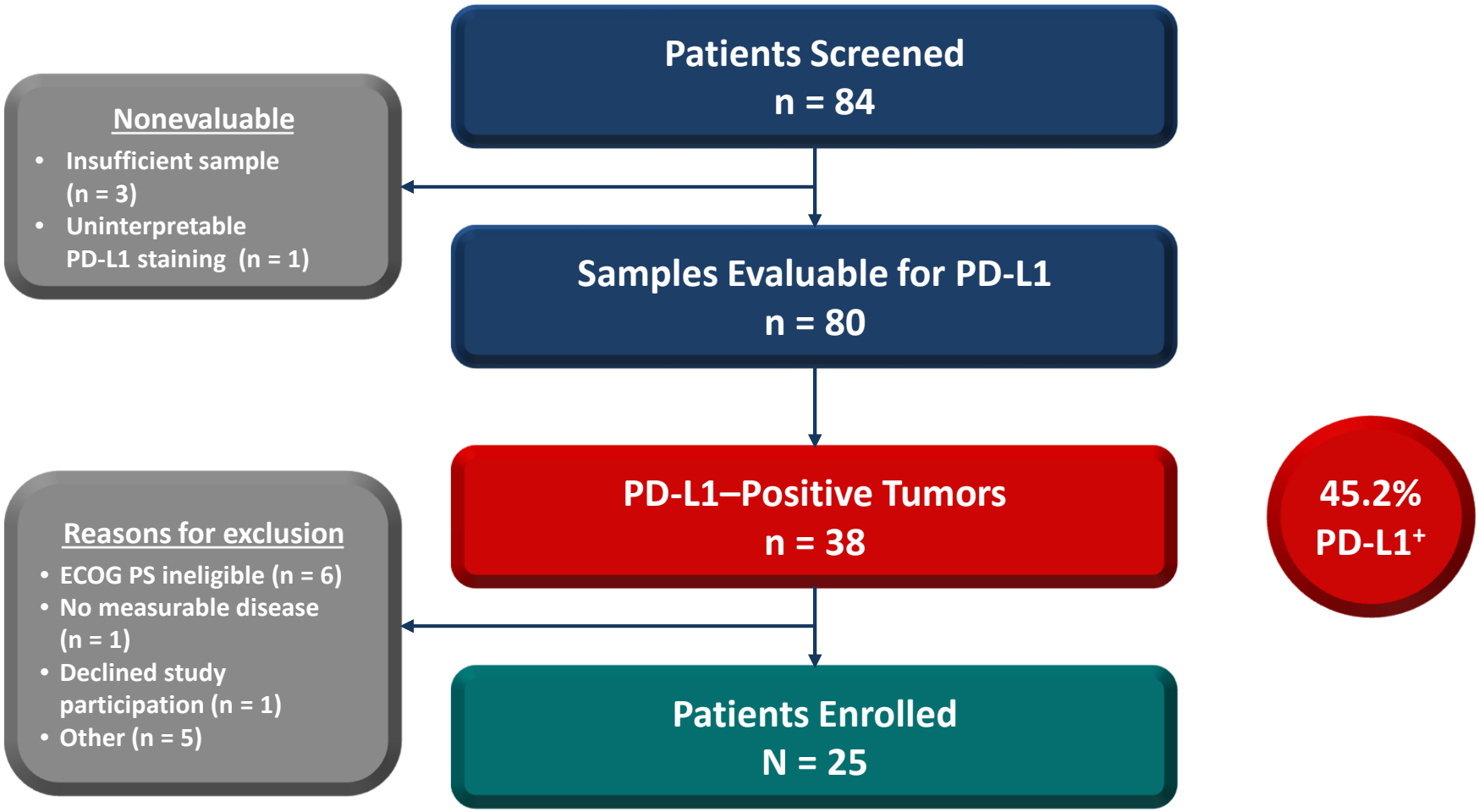


PD-L1 Negative



PD-L1 Positive

PD-L1 Screening: MPM Cohort



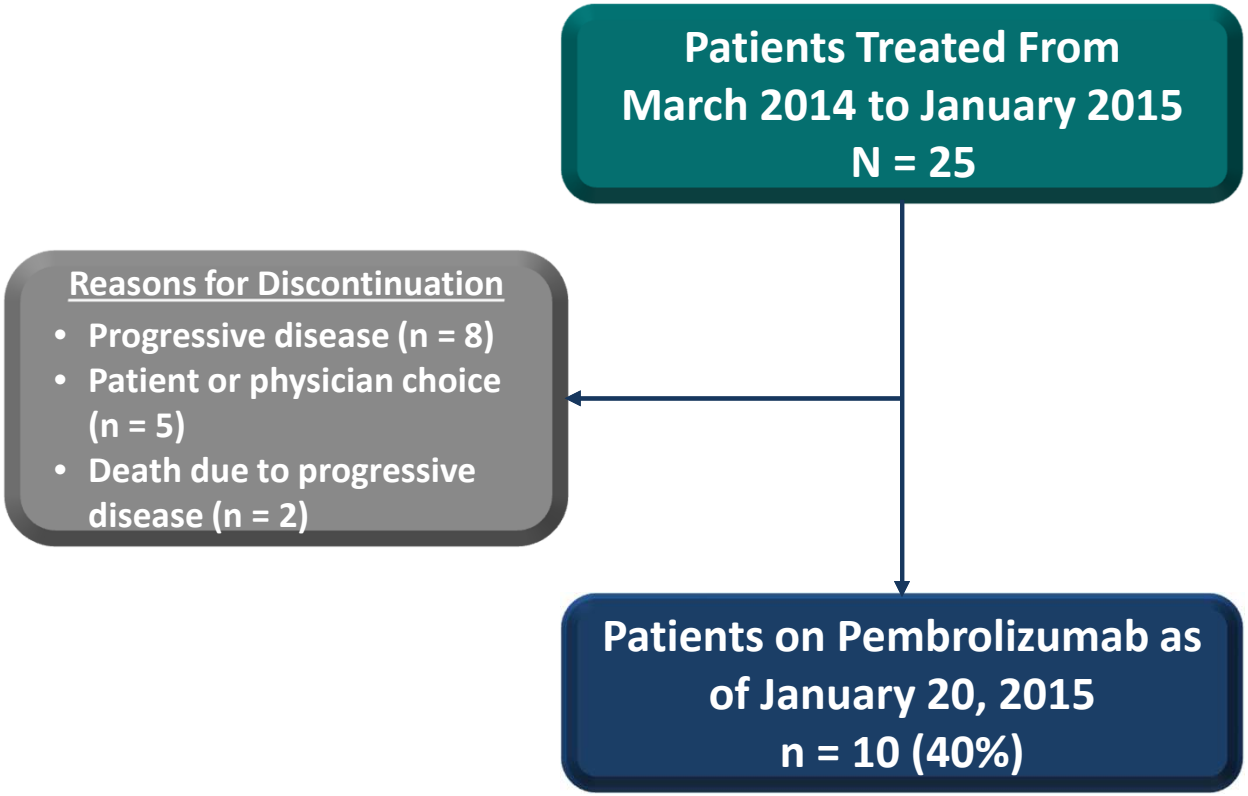
Baseline Characteristics

Characteristic, n (%)	N = 25
Median age, year (range)	65 (32 – 86)
Sex	
Male	17 (68)
Female	8 (32)
Prior Lines of Therapy	
0	3 (12)
1	15 (60)
≥2	7 (28)
Histology	
Epithelioid	16 (64)
Sarcomatoid	2 (8)
Biphasic	2 (8)
Not specified or reported	5 (20)

Characteristic, n (%)	N = 25
ECOG performance status	
0	9 (36)
1	16 (64)
Race	
White	21 (84)
Asian	2 (8)
Unknown	2 (8)
Prior chemotherapy[a]	
Cisplatin/carboplatin	21 (84)
Pemetrexed	20 (80)
Gemcitabine	4 (16)
Vinorelbine	1 (4)

[a]Patients could have received ≥1 prior chemotherapy agent.
Analysis cut-off date: January 20, 2015.

Patient Disposition



	Total (N = 25)	On Therapy (n = 10)
Time on therapy, weeks, mean (range)	22.0 (0.1 to 34.1+)	29.2 (26.1+ to 34.1+)
Number of doses, median (range)	10 (1 to 22+)	18 (16+ to 22+)

Analysis cut-off date: January 20, 2015.

Treatment-Related Adverse Events

Any Grade Observed in ≥2 Patients

Adverse Event, n (%)	N = 25
Any	15 (60)
Fatigue	6 (24)
Nausea	6 (24)
Arthralgia	4 (16)
Pruritus	3 (12)
Dry mouth	3 (12)
Headache	2 (8)
Maculopapular rash	2 (8)

Grade 3-4 Observed in ≥1 Patient

Adverse Event, n (%)	N = 25
ALT increased (grade 3)	1 (4)
Thrombocytopenia (grade 3)	1 (4)

- No treatment-related deaths
- No discontinuations due to treatment-related AE

Analysis cut-off date: January 20, 2015.

Adverse Events of Special Interest

Adverse Event, n (%)	Total N = 25	Resulted in Interruption	Resulted in Discontinuation
Rash[a] (all grade 1)	4 (16)	No	No
ALT/AST increased (grade 3)	1 (4)	Yes	No
Hypersensitivity (grade 2)	1 (4)	No	No
Iridocyclitis (uveitis) (grade 2)	1 (4)	Yes	No

[a]Includes maculopapular rash.
Analysis cut-off date: January 20, 2015.

Antitumor Activity (RECIST v1.1, Investigator Review)

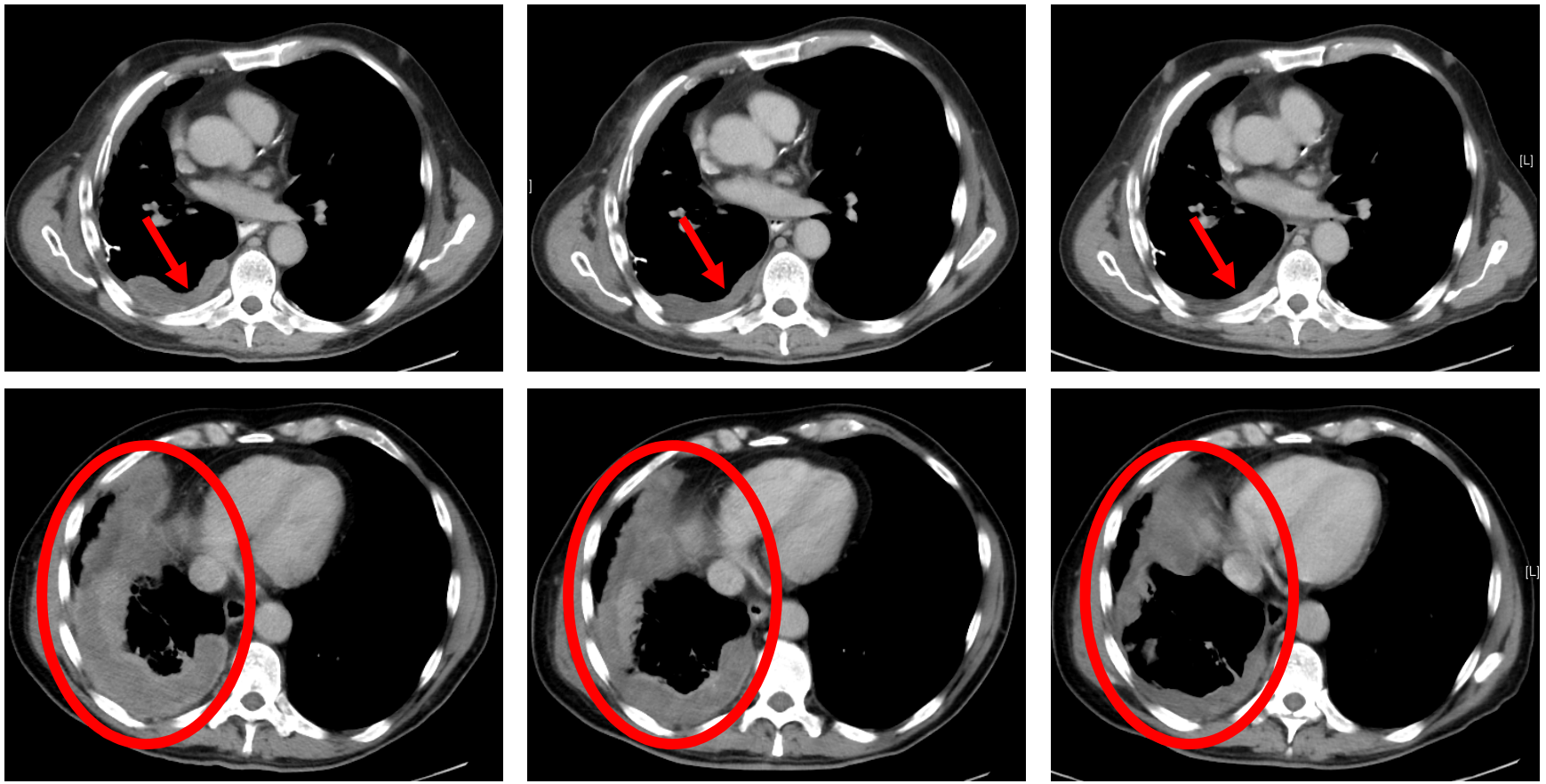
	N = 25	
Best Overall Response	**n**	**%**
Complete response	0	0
Partial response[a]	7	28
Stable disease	12	48
Progressive disease	4	16
No assessment[b]	2	8

Objective response rate: 28% (95% CI, 12-49)

Disease control rate: 76% (95% CI, 55-91)

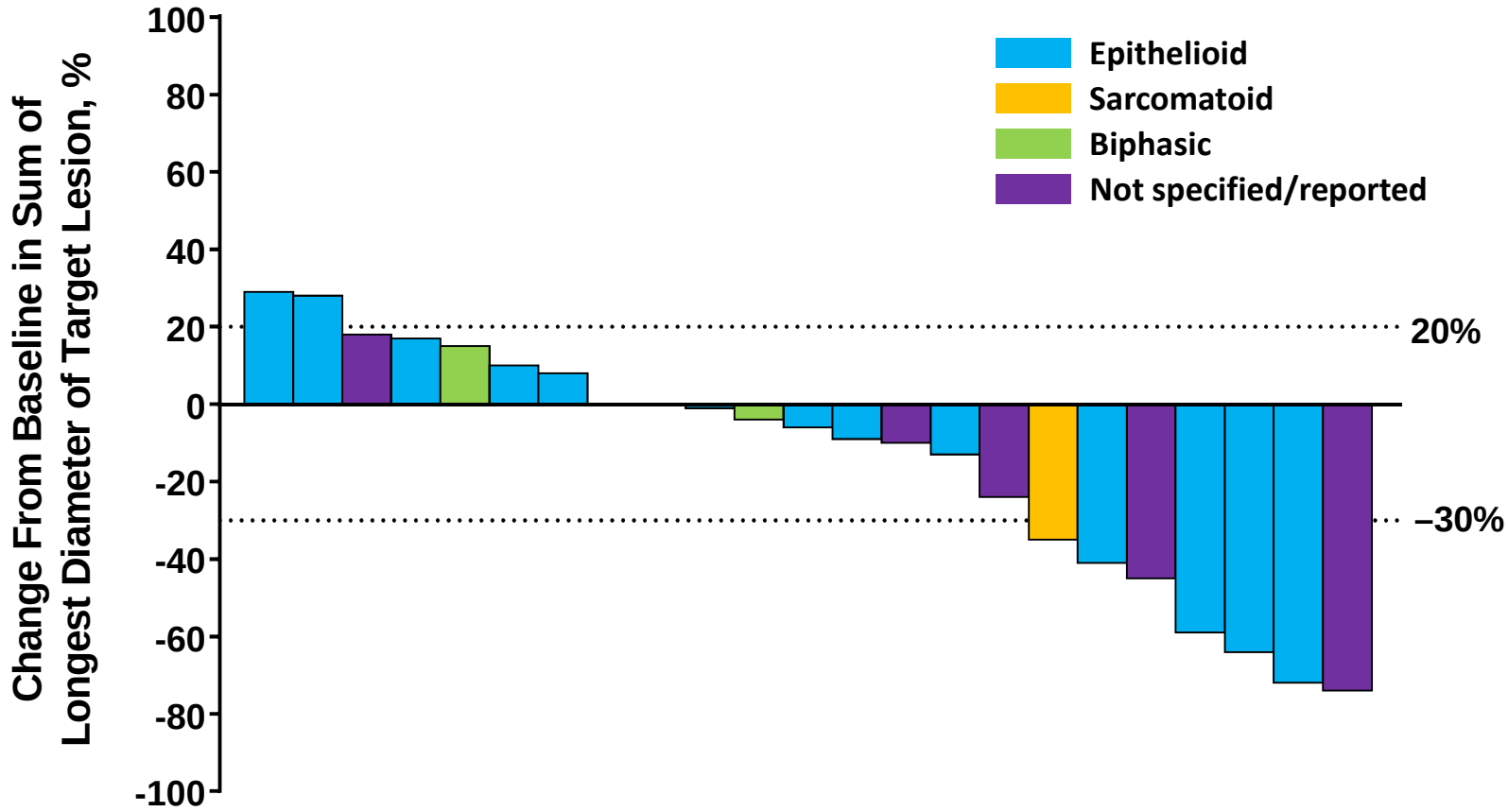
[a]Includes confirmed and unconfirmed responses.
[b]Patients who discontinued therapy before the first post-treatment scan due to progressive disease.
Analysis cut-off date: January 20, 2015.

Example of Pembrolizumab Antitumor Activity in a Patient With MPM



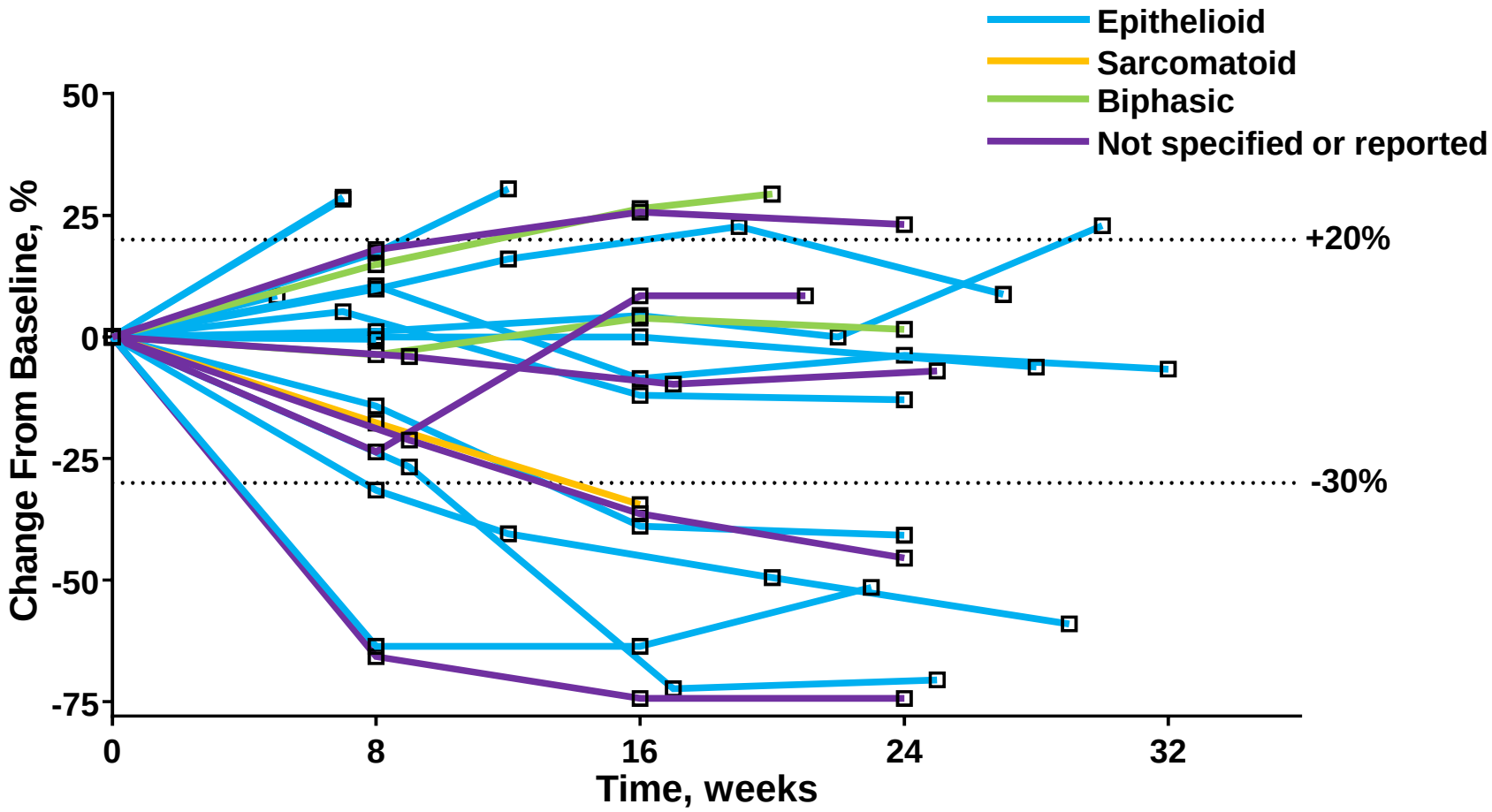
Pretreatment | Week 8 | Week 16

Maximum Percentage Change From Baseline in Target Lesions[a] (RECIST v1.1, Investigator Review)



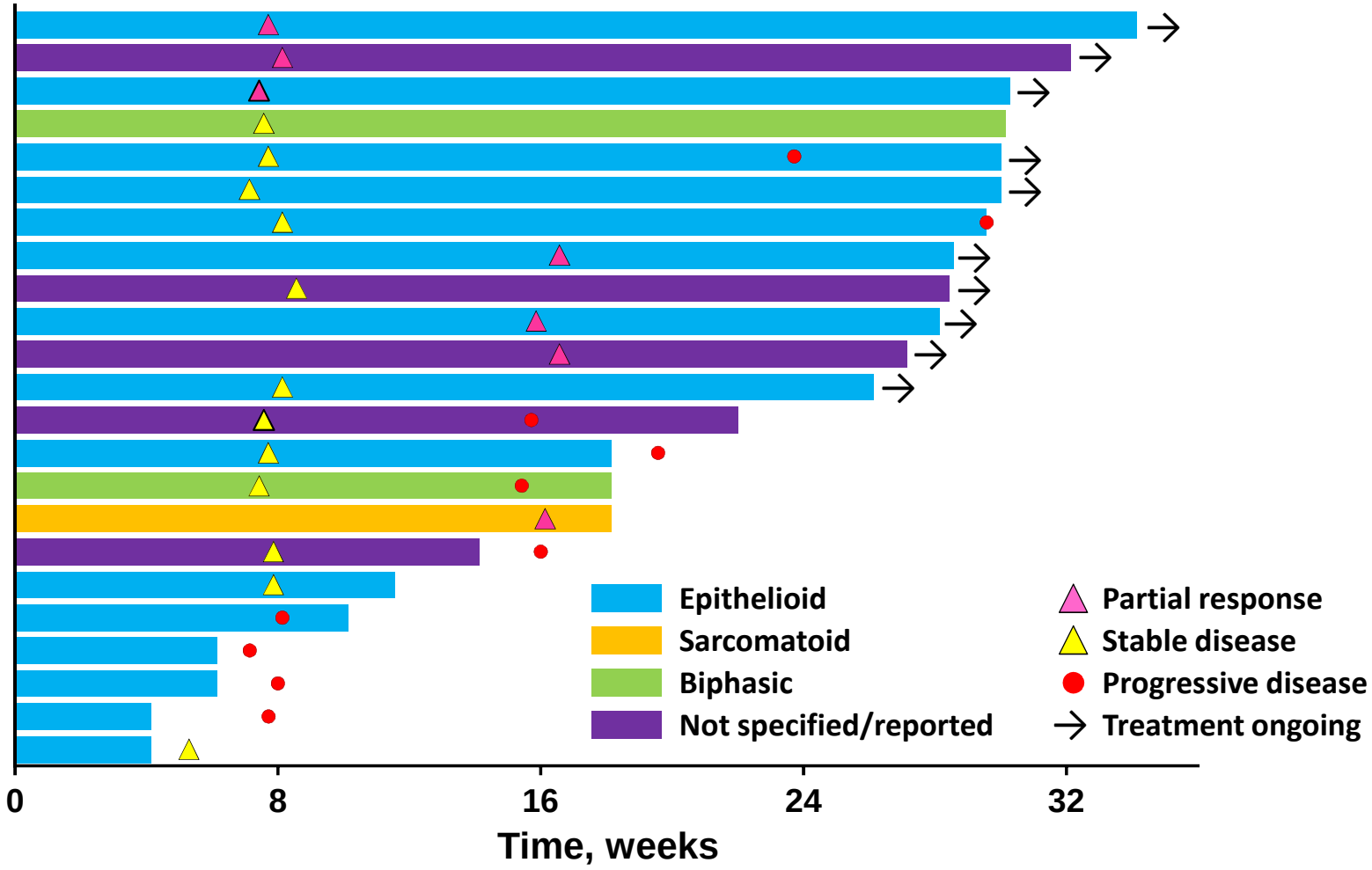
[a]Includes patients with ≥1 postbaseline tumor assessment (n = 23).
Analysis cut-off date: January 20, 2015.

Longitudinal Change From Baseline in Tumor Size (RECIST v1.1, Investigator Review)



[a]Includes patients with ≥1 postbaseline tumor assessment (n = 23).
Analysis cut-off date: January 20, 2015.

Treatment Exposure and Response Duration[a] (RECIST v1.1, Investigator Review)



[a]Includes patients with ≥1 postbaseline tumor assessment (n = 23). The length of each bar corresponds to the duration of treatment.
Analysis cut-off date: January 20, 2015.

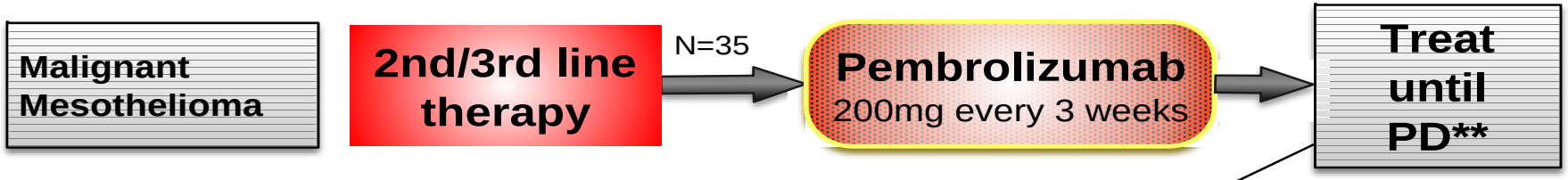
Conclusions

- Manageable safety and toxicity profile
  - No treatment-related mortality
  - No discontinuations due to treatment-related AEs
- 28% ORR and 76% DCR better than historical response rate for second-line chemotherapy
  - Some responses observed at first imaging assessment
  - All responses ongoing at time of data cutoff
- Further evaluation of pembrolizumab in mesothelioma is warranted
  - Ongoing phase 2 trial (NCT02399371) evaluating pembrolizumab 200 mg Q3W as second-line therapy for advanced MPM

Mesothelioma F/u Study at UofC

- Currently enrolling - only open study nationwide
  - Co-PIs: Kindler / Seiwert *(PIII in planning)*

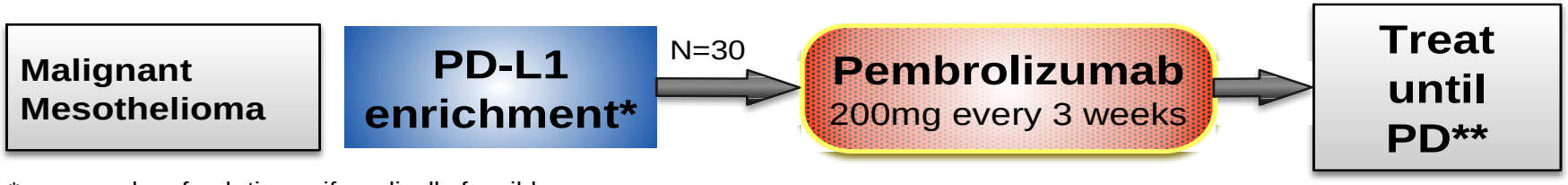
Part A:
Determine anti-tumor activity in an unselected group of Mesothelioma patients, and assess optimal PD-L1 cutoff



Biomarker Analysis (retrospective):

1) PD-L1 expression by IHC and Mass Spectromety
2) Determine CD8 by IHC and Mass Spectrometry
—> determine optimal cutoff and methodology for PD-L1, and assess contribution of CD8 expression

Part B: Expansion cohort
In the setting of an active drug - prospective enrollment using a biomarker enrichment strategy



* assessed on fresh tissue if medically feasible

** Treatment beyond PD is allowable under specific circumstance (see respective paragraph in protocol)

Conclusions

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1. Immunotherapy is active in Lung Cancer
   - Including both Squamous and Adenocarcinoma histologies
   - However EGFR/ALK driven tumors should continue to be treated with targeted therapies in first/second line
   - Multiple clinical trials available at UChicago and other centers

1. Immunotherapy is active in Head and Neck Cancer
   - Twice the response rate of Cetuximab
   - Active in both HPV(+) and HPV(-) tumors
   - Multiple trials available at UChicago and other centers

3. Immunotherapy is active in Malignant Mesothelioma
   - Active in both epitheliod and sarcomatoid histologies
   - Nationwide only trial available at UChicago

Thanks!

Seiwert Lab:
Zhixiang Zuo
Valia Saloura
Arun Khattri
Michaela Keck

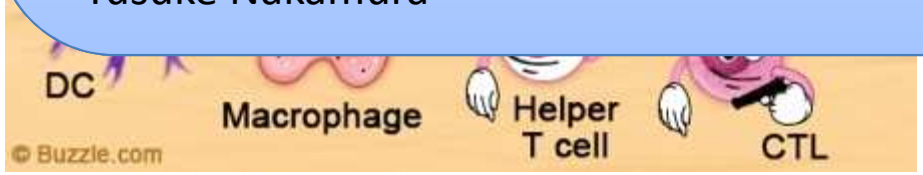
UChicago Immunology:
Thomas Gajewski
Pete Savage
Jason Luke
Justin Kline
Yusuke Nakamura

UChicago HNC Group:
Everett Vokes
Mark Lingen
Ralph Weichselbaum
Daniel Haraf
Elizabeth Blair
Lou Portugal
Jonas DeSouza
Victoria Villaflor

Lung Cancer:
Ravi Salgia
Everett Vokes
Victoria Villaflor
Michael Maitland
Phil Hoffman

Mesothelioma:
Hedy Kindler

Columbia:
Naiyer Rizvi



Slide Modified from Jason Luke, MD
http://goldenprague.us/strategies-for-cancer-vaccine-development/