SITC Chicago Meeting





Immunotherapy for Lung Cancer, Head and Neck Cancer, Mesothelioma

Tanguy Seiwert, MD

Assistant Professor of Medicine Associate Director Head and Neck Cancer Program Fellow Institute for Genomics and Systems Biology The University of Chicago



Institute for Genomics & Systems Biology

THE UNIVERSITY OF CHICAGO MEDICINE

Disclosures

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

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



1899: Coley's Toxin



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

New York Times - July 29, 1908

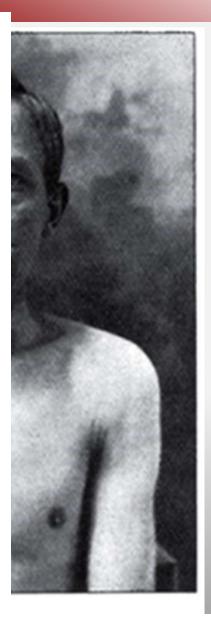
ERYSIPELAS GERMS ASCURE FOR CANCER

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. Lou's that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Colev of New York, it came out yester-



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

THE UNIVERSITY OF CHICAGO MEDICINE Head & Neck Cancer Program



Unpublished Data, University of Chicago

THE UNIVERSITY OF CHICAGO MEDICINE Head & Neck Cancer Program

Simple Conclusion...



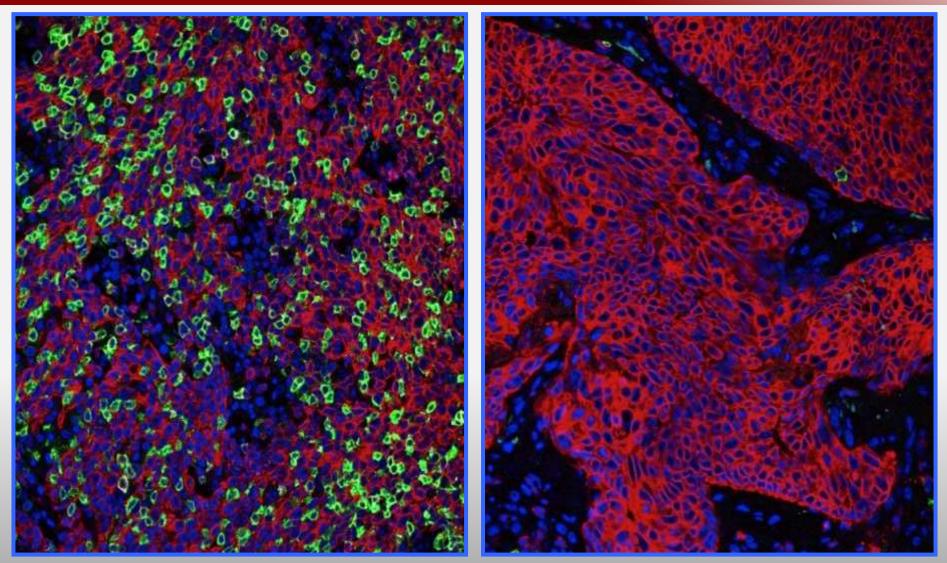
Overview



- I. Background
- II. Lung Cancer
- III. Head and Neck Cancer
- **IV.** Mesothelioma

I. Background

Tumor infiltrating Lymphocytes (TILs) in HNC

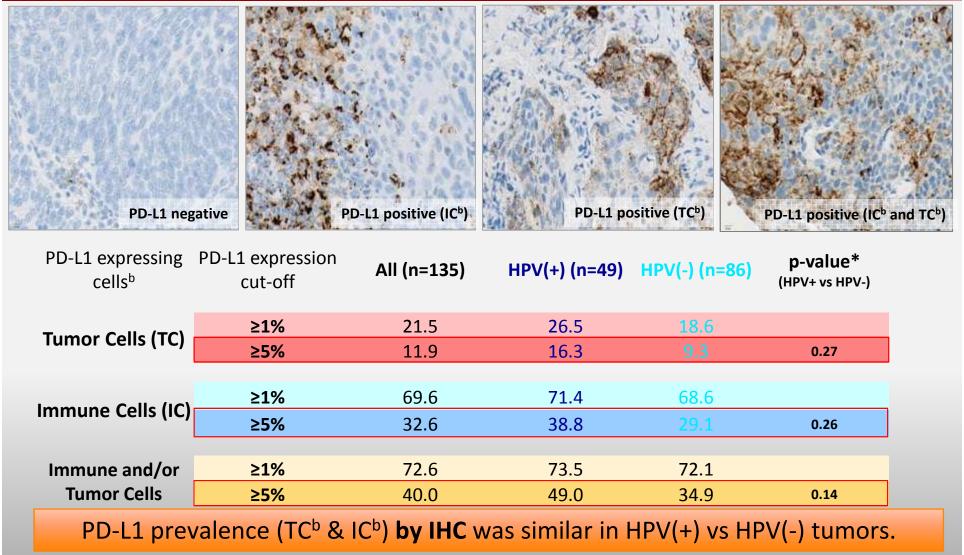


THE UNIVERSITY OF CHICAGO

MEDICINE

Head & Neck Cancer Program

PD-L1 <u>Prevalence</u> by IHC^a Tumor Cell (TC) & Immune Cell (IC) staining



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

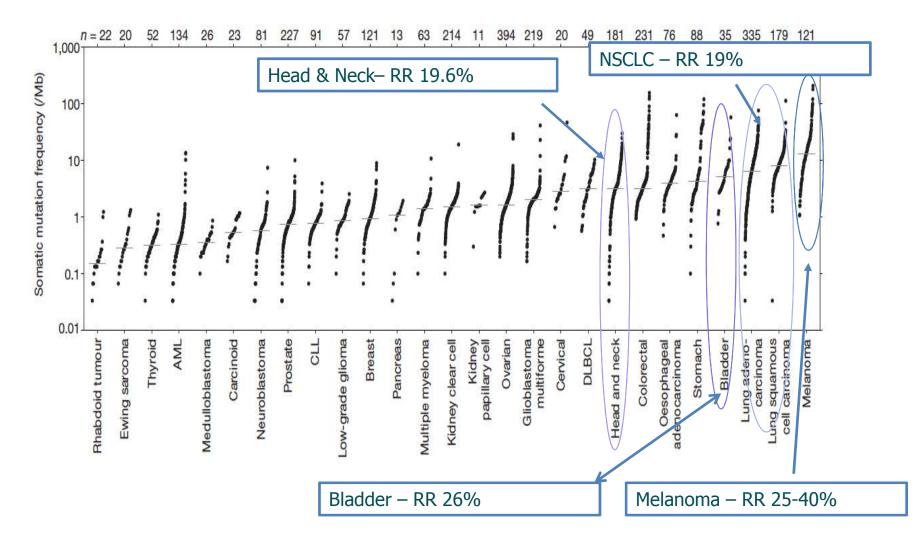
^b IC – tumor infiltrating immune cells; TC – tumor cells

* Fisher's exact test H. Koeppen, Y. Xiao, M. Kowanetz (Genentech)

THE UNIVERSITY OF

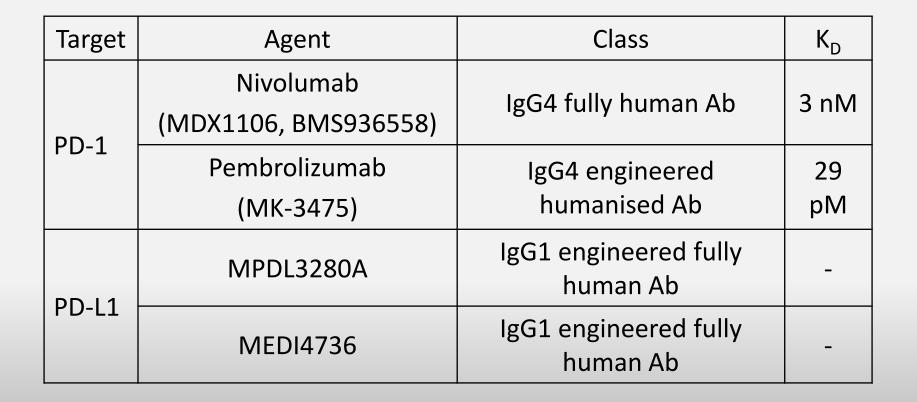
MEDICINE

Mutation landscape and response to PD-1 pathway blockade



Alexandrov et al, Nature 2013

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



CHICAGO

MEDICINE

II. Lung Cancer



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

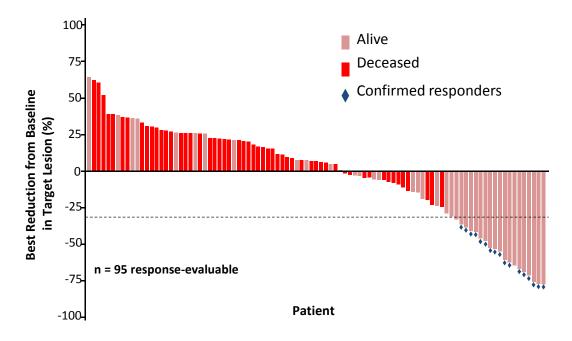
Efficacy of nivolumab monotherapy in patients with NSCLC

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	63.9	15.2	1.9	9.2
	(1/33)	(63.9, 63.9)	(5/33)	(1.8-3.6)	(5.6-11.1)
3	24.3	74.0	8.1	1.9	14.9
	(9/37)	(16.1+, 133.9+)	(3/37)	(1.7-7.3)	(9.5-NE)
10	20.3	83.1	8.5	3.6	9.2
	(12/59)	(6.1+, 117.1+)	(5/59)	(1.9-3.8)	(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

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



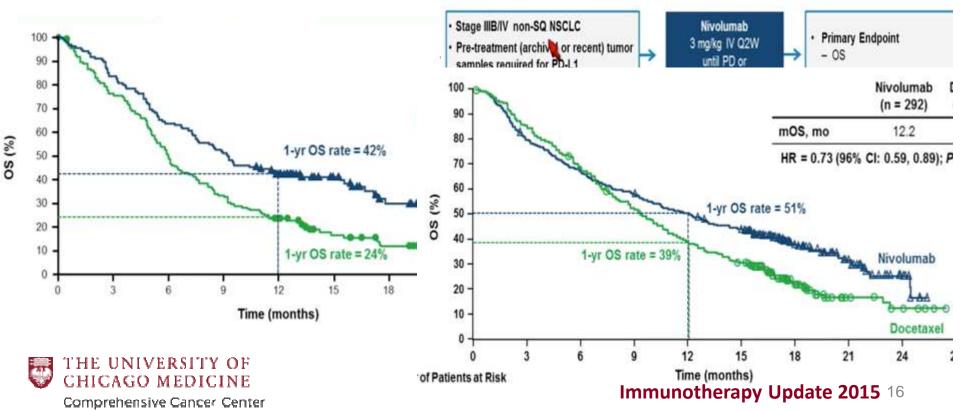
Median OS, months (95% CI)	8.2 (6, 11)
1-year OS rate, % (95% CI)	41 (32, 50)
Number of events	72/117

	IRC-assessment (per RECIST 1.1) ^a
ORR, % (n) [95% Cl]	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

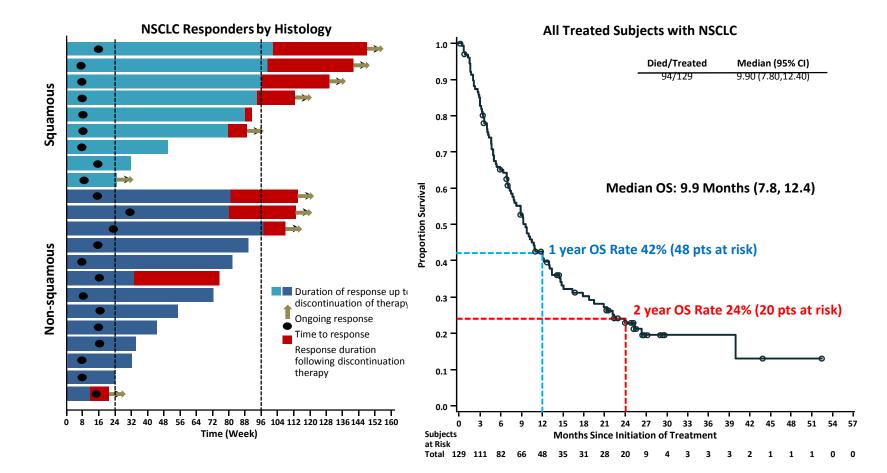
Lung Cancer - NSCLC (ASCO 2015)

Lung SCC – Nivo vs Docetax Checkmate 17, PIII study HR=0.59 PD-L1 biomarker did NOT work CheckMate 017 (NCT01642004) - Study Design Lung Adeno – Nivo vs Docetax Checkmate 57, PIII study HR=0.73 PD-L1 biomarker worked CheckMate 057 (NCT01673867) Study Design

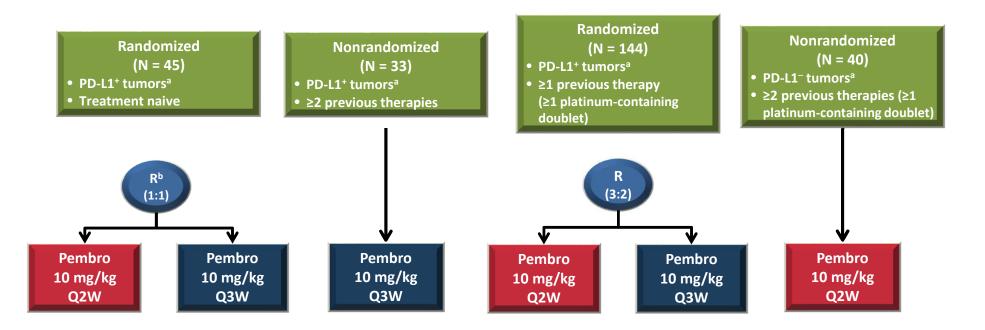


UC Cancer Research Foundation

Nivolumab: Duration of response and overall survival



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



- Response assessment
 - Primary measure: ORR by RECIST v1.1¹ 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

Antitumor Activity (RECIST v1.1, Central Review)

	N	ORRª % (95% CI)	
Total	236	21 (16-27)	Smoking history
Previous treatment	236		Current/Former
Treatment naive	42	26 (14-42)	Never
Previously treated	194	20 (15-26)	Unknown
Histology	230		EGFR mutation
Nonsquamous	191	23 (17-29)	Yes
Squamous	39	18 (8-34)	No
Dose/schedule	236		KRAS mutation
2 Q3W	6	33 (4-78)	Yes
10 Q3W	126	21 (14-29)	No
10 Q2W	104	21 (14-30)	ALK rearrangement
PD-L1 expression ^b	236	, , ,	Yes
Positive	201	23 (18-30)	No
Negative	35	9 (2-23)	 In 45 additional patie 20% (95% Cl, 10%-35)

% (95% CI) 230 27 (20-34) 165 9 (4-19) 65 0 (0-46) 6 224 14 (5-30) 36 22 (16-28) 188 140 39 28 (15-45) 101 19 (12-28) 210 17 (0-64) 6 204 20 (15-26)

Ν

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

^aIncludes confirmed and unconfirmed responses.

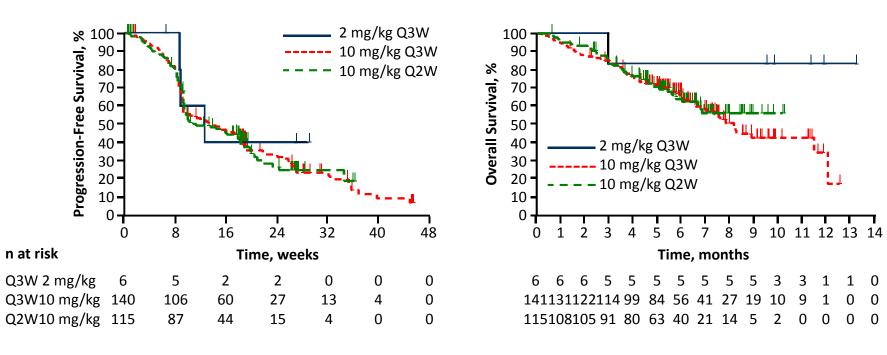
^bAs assessed using a prototype assay. Positive was defined as staining in ≥1% of tumor cells. Analysis cutoff date: March 3, 2014.

ORR^a

Kaplan-Meier Estimates of Survival

PFS (RECIST v1.1, Central Review)



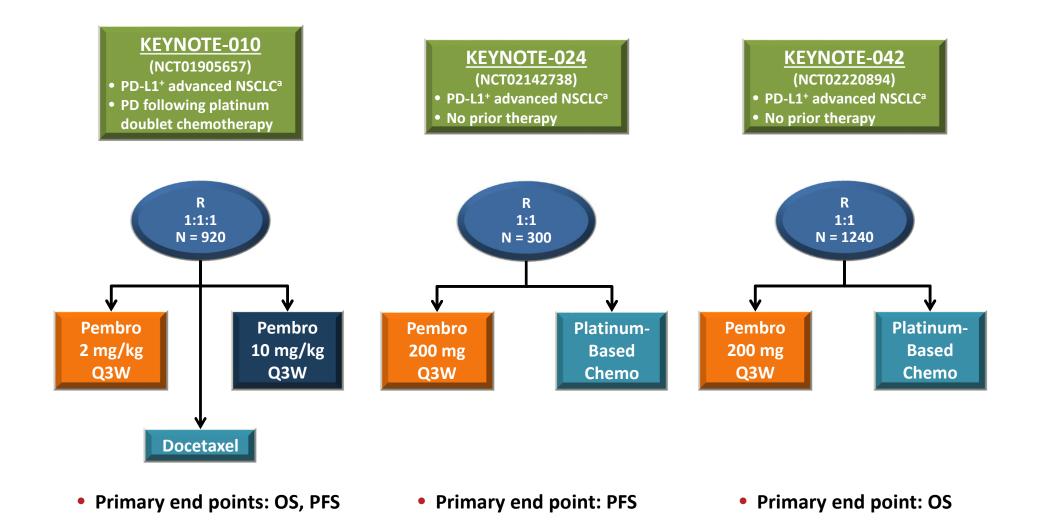


- Pooled population
 - Median PFS: 13.0 weeks (95% Cl, 9.4-17.9)
 - 24-week PFS: 30%

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

Garon et al, ESMO 2014

Ongoing Studies of Pembrolizumab in NSCLC



Summary of Exposure and Treatment-Related AEs

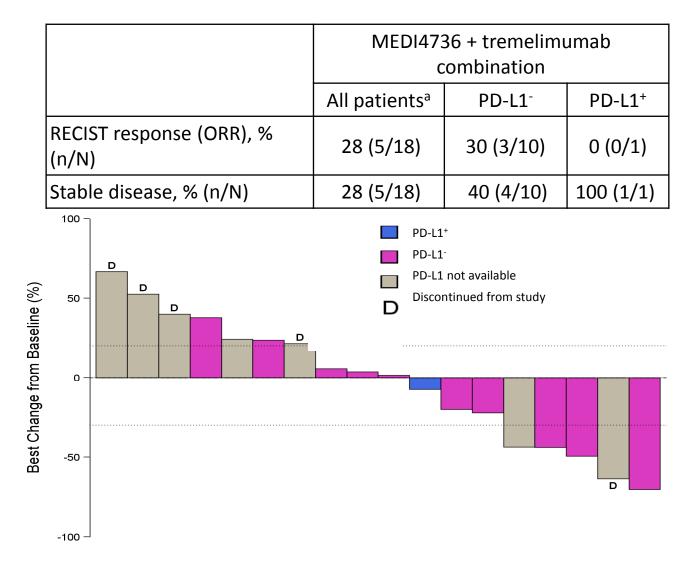
	N = 262			
Exposure				
Median (range) time on therapy, days	85.5 (1-400)			
Median (range) doses, n	5.50 (1-23)			
Treatment-related AE summary, n (%)				
Any grade	175 (67)			
Grade 3-5	24 (9)			
Serious	19 (7)			
Death	1 (0.4)			
Discontinued	8 (3)			

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

	N = 262				
AE, n (%)	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)			

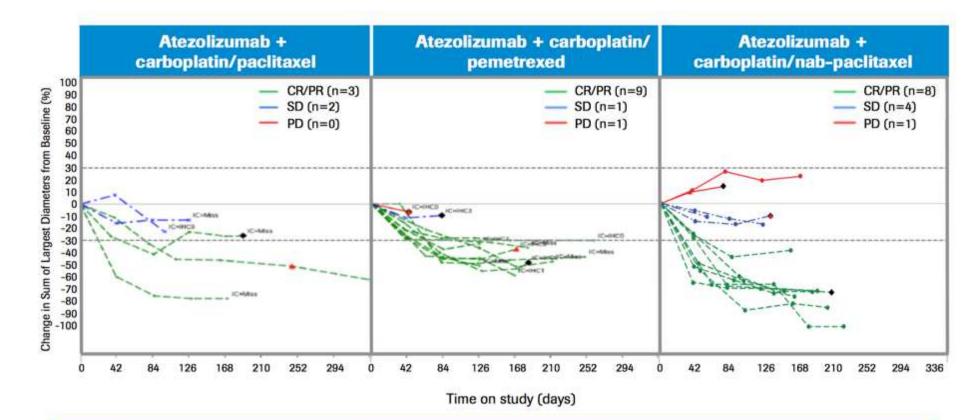
Garon et al, ESMO 2014

Clinical activity: Durvalumab (MEDI4736) + tremelimumab



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

THE UNIVERSITY OF CHICAGO MEDICINE

Comprehensive Cancer Center UC Cancer Research Foundation Liu et al. ASCO 2015

Immunotherapy Update 2015 24

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

150

125

100

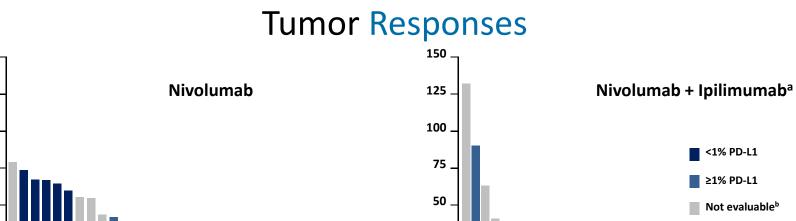
75

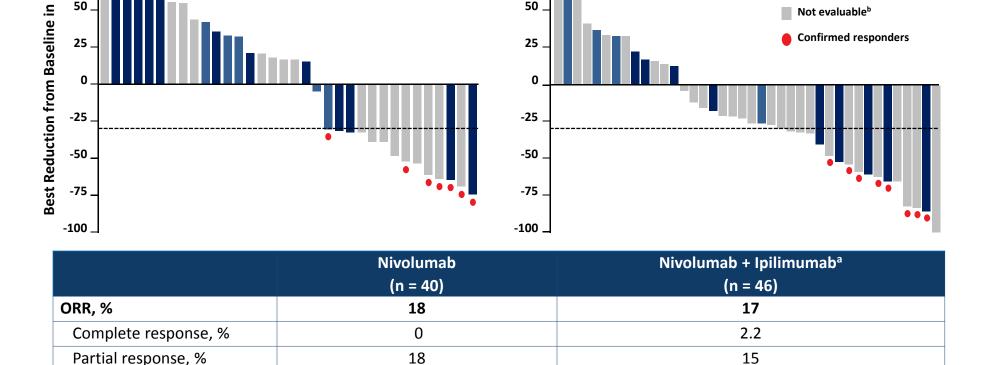
50

25

0

Target Lesion (%)





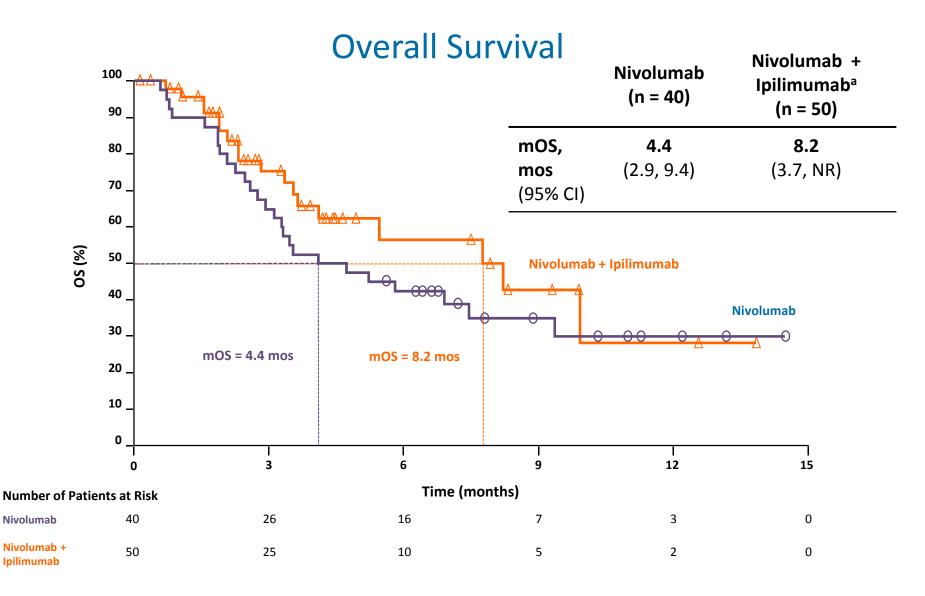
25

0

Confirmed responders

^aCombined data for nivolumab 1 + ipilimumab 1 + ipilimumab 3 cohorts. ^bNot 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 ontreatment tumor assessment are included (nivolumab, n = 34, nivolumab + ipilimumab, n = 40).

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



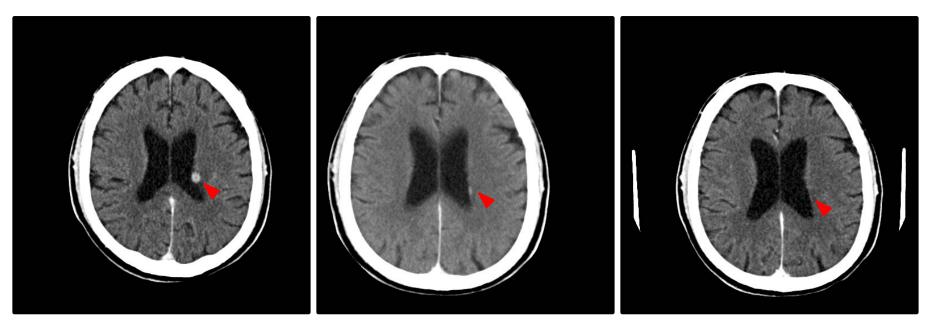
^aCombined data for nivolumab 1 + ipilimumab 1 and nivolumab 1 + ipilimumab 3 cohorts

Response to nivolumab in SQ NSCLC brain metastasis

Pre-treatment

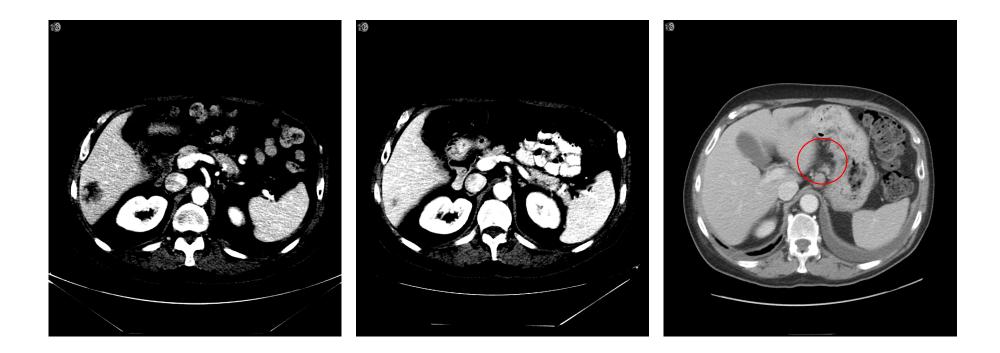
Week 14

Week 68

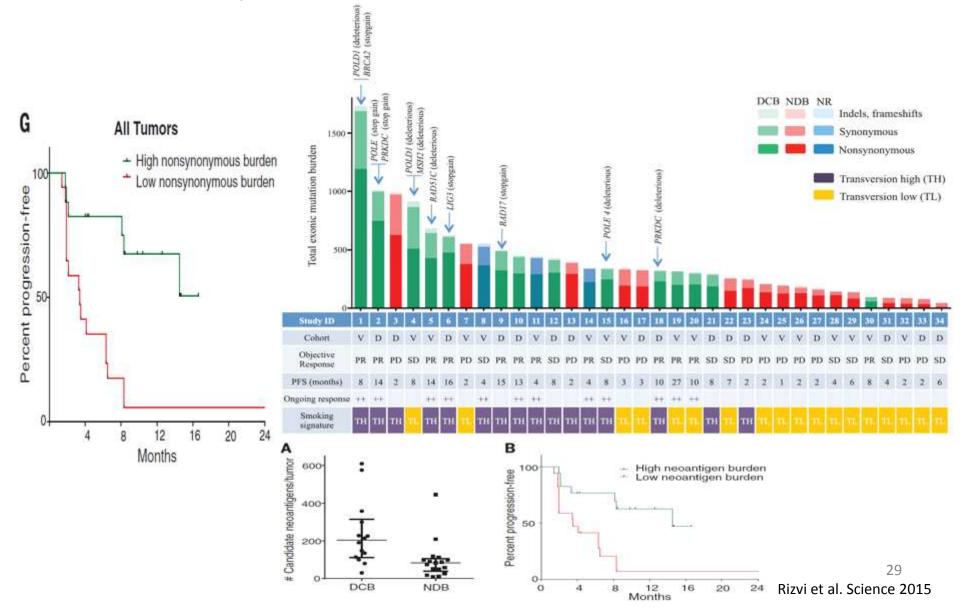


- 73 year-old male, stage IIIb, former smoker
- Prior radiotherapy (mediastinal), 3 prior systemic regimens (cisplatin/gemcitabine, docetaxel, vinorelbine)
- No prior CNS-directed therapy

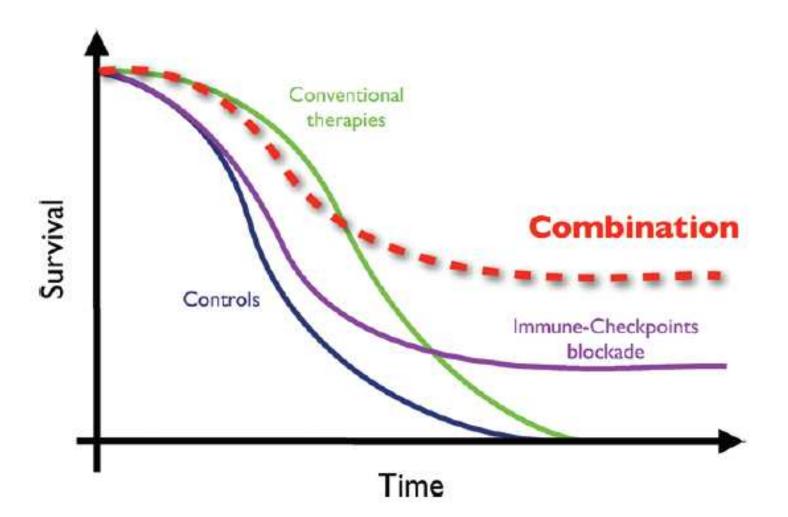
Acquired resistance to PD-1 progression



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



Combination Approaches



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

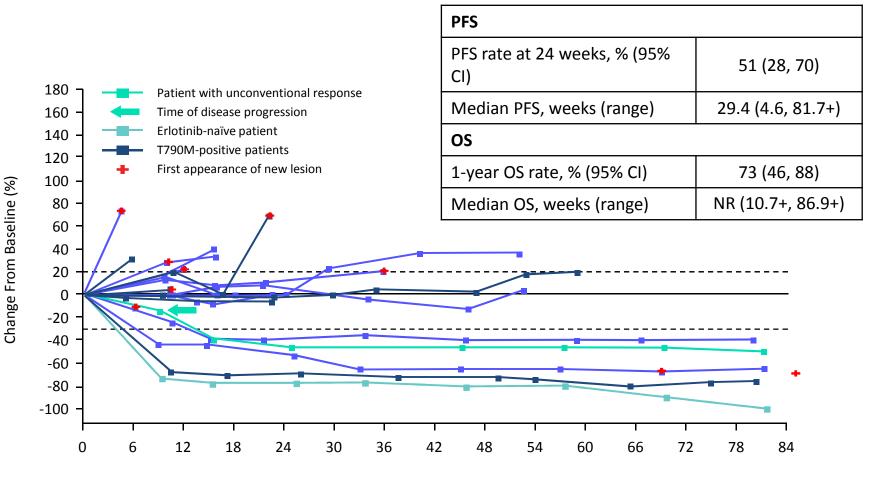
nivolumab + erlotinib

Chemotherapy-naïve patients with stage IIIB or IV NSCLC (non-squamous; EGFR MT) Nivolumab 3 mg/kg IV Q2W + erlotinib 150 mg/day PO until disease progression or unacceptable toxicity

Primary objective: safety and tolerability

Secondary objectives: ORR and PFS rate at 24 weeks

CA209-012 study design: nivolumab in combination with erlotinib



Time Since First Dose (Weeks)

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

Tanguy Seiwert,¹ Robert Haddad,² Shilpa Gupta,³ Ranee Mehra,⁴ Makoto Tahara,⁵ Raanan Berger,⁶ Se-Hoon Lee,⁷ Barbara Burtness,⁴ Dung Le,⁸ Karl Heath,⁹ Amy Blum,⁹ Marisa Dolled-Filhart,⁹ Kenneth Emancipator,⁹ Kumudu Pathiraja,⁹ Jonathan D. Cheng,⁹ Laura Q Chow¹⁰

Presented by:

Tanguy Seiwert, MD

Assistant Professor of Medicine Associate Director Head and Neck Cancer Program Fellow, Institute of Genomics and Systems Biology The University of Chicago

¹Department of Medicine, The University of Chicago, Chicago, IL, USA; ²Dana Farber Cancer Institute, Boston, MA, USA; ³H.Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; ⁴Fox Chase Cancer Center, Philadelphia, PA, USA; ⁵National Cancer Center Hospital East, Kashiwa, Japan; ⁶Sheba Medical Center, Tel Hashomer, Israel, ⁷Seoul National University Hospital, Seoul, Korea; ⁸Johns Hopkins University, Baltimore, MD, USA; ⁹Merck & Co., Inc. Kenilworth, NJ, USA, ¹⁰University of Washington, Seattle, WA, USA.



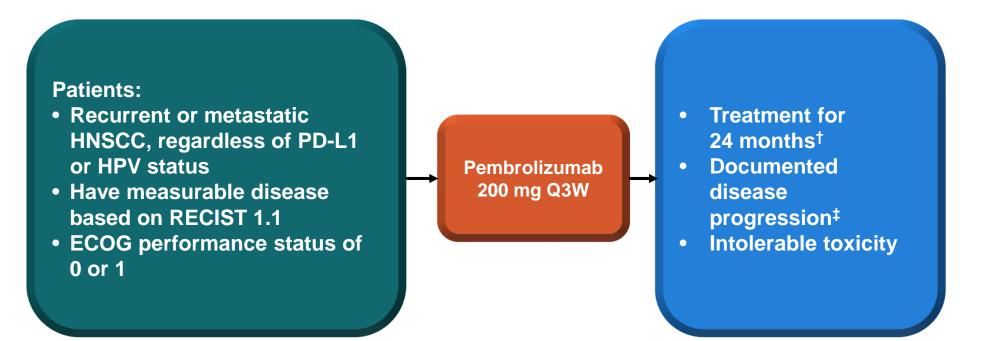
Head and Neck Squamous Cell Cancer

- 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 setting¹
 - Commonly used agents: platinum cetuximab taxanes 5-EU, methotrexate
- Median OS of 6-months in patients previously treated²
- 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.

35



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



PRESENTED AT:

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.

36

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE

Baseline Demographics

Characteristic	N = 132*		Characteristic	N = 132*		
	N (%)		Gharacteristic	N (%)		
Median age (range), years	60 (25–84)		Prior adjuvant/neoadj therapy	uvant systemic		
Male	110 (83.3)		Yes	53 (40.2)		
Race			Prior lines of therapy for			
White	White 96 (72.7)		recurrent/metastatic disease			
Asian	28 (21.2)		0	22 (16.7)		
Other	8 (6.1)		1	30 (22.7)		
ECOG PS			2	28 (21.2)		
[0] Normal Activity	38 (28.8)		3 or more	50 (37.9)		
[1] Symptoms, but ambulatory	94 (71.2)		Unknown	2 (1.5)		

Data cutoff date: March 23, 2015

*Includes patients who received ≥1 dose of pembrolizumab

37

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	Total N = 117 [†]		HP n =	V+ 34	HPV– n = 81	
response	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

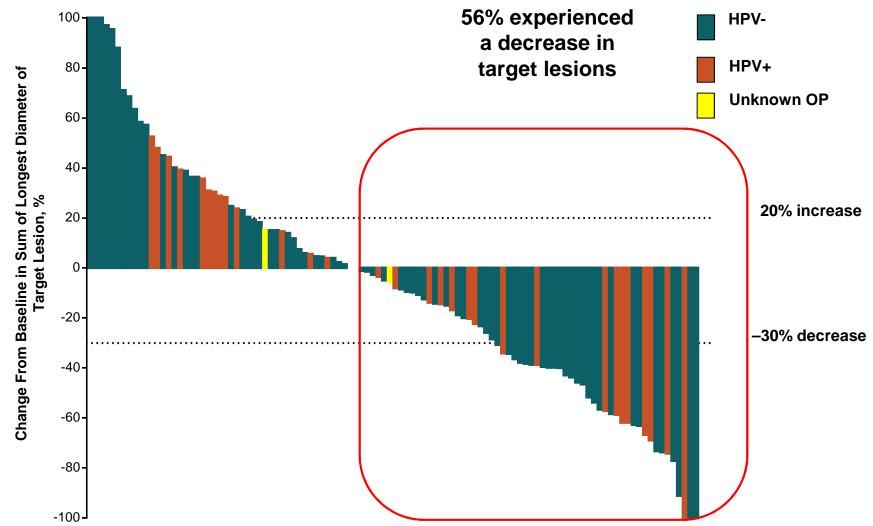
*Unconfirmed and confirmed RECIST v 1.1 responses

[†]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) ASCOP Annual 15 SLIDES 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

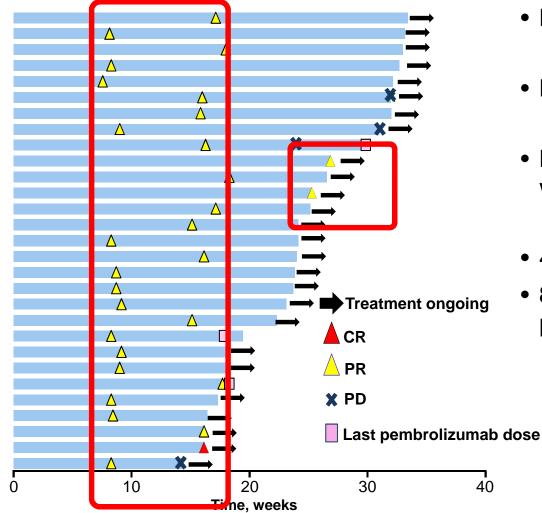
*2 oropharynx cancer patient are HPV unknown. Cancers outside the oropharynx are considered HPV negative by convention

40 Data cutoff date: March 23, 2015. OP = oropharyngeal primary

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.



Treatment Exposure and Response Duration of Patients Who Responded



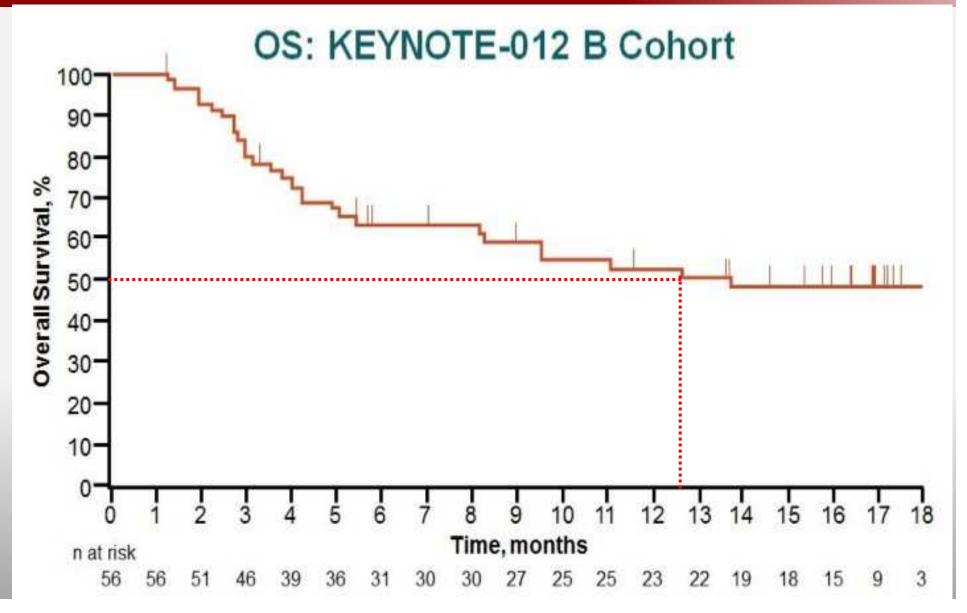
- Median follow-up duration:
 5.7 (0.2 8.7) months
- Median time to response:
 9.0 (7.6–18.0) weeks
- Median duration of response was not reached
 - Range: 7.3+ 25.1+ weeks
- 40 patients remain on therapy
- 86% (25/29) of responding patients remain in response

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



THE UNIVERSITY OF CHICAGO MEDICINE Head & Neck Cancer Program

Overall Survival Data





Durvalumab (MEDI4736) Efficacy in HNC:





26-30 September 2014, Madrid, Spain

esmo.org

Presented by: Matt Fury, ESMO 2014

Durvalumab/MEDI4736: Clinical Data – ASCO 2015

Safety and Efficacy of MEDI4736, an Anti-PD-L1 Antibody, in Patients from a Squamous Cell Carcinoma of the Head and Neck (SCCHN) Expansion Cohort

N H. Segail, S-H.I. Ou², A.S. Balmanoukian³, M.G. Fury¹, E. Massarell⁴, J.R. Brahmen³, J. Weiss¹⁰, P. Schoffski⁷, S.J. Antonia⁴, C. Massard⁹, D.P. Zandberg¹⁰, S.N. Khiel¹¹, X. Li¹², M.C. Rebelatto¹², K.E. Steele¹², P.B. Robbins¹², J.A. Blake-Haskins¹², M.O. Butter¹³ what Black Actions (Camer Alex Not California Invince Strend of Medicine Invince California Invince Strenge and Research Institute California Action on Canadi Institute Lauren, Naturen, Naturen, Naturen, Canadi Annue, Marcell, Farrier, Nonversto of Marcelland Canadi C

Background

mit 174 of patients with assertions call increasing of the basis and basis (22) are diagramed with teachy advanted damage with a figure service late of aggregative 2017, in the material of service, the service with teach or patients with present with response Wantshi themasa First for pellation beamond for patients, and heavy secondari at also menulate 20.00

SCON incluins pictourn insent systems connectments? Area are re standed as eners in Red Scilles.

approx. And ACOM approximate interaction and increases, using a programment of home population into other approximate interaction in the control of the ACOM approximate approximate interaction in the control of the ACOM approximate in approximate interaction in the ACOM and approximate interaction. For all memory approximate interaction in the ACOM approximate interaction of the ACOM approximate approximate interaction in the ACOM approximate in the ACOM approximate in the ACOM approximate interaction approximate in the ACOM approximate in the ACOM approximate interaction approximate in the ACOM approximate in the ACOM ACOM approximate interaction approximate in the ACOM approximate in the ACOM ACOM approximate in the ACOM approximate in the ACOM approximate in the ACOM ACOM approximate in the ACOM approximate in the ACOM approximate in the ACOM ACOM approximate interaction approximate in the ACOM approximate in the ACOM ACOM approximate in the ACOM approximate i

PDL1 block bas inputter/ regulation receptors on T cells: programmad cell death-1 (PDL1) and COBORT 1. Biologics (PDL1 accurs an intelline signal, walking cyberry productors and T cell profession. Broding to COBORT 1 stocks actuation of T cells. Pringh GCOX timetry"

MED14738

17 teaching to PD+1 (IC., 011 WILlaws CORC-0C., 1 O4 WILL (Figure 1)

Other way attributes of MEDI-472E millions

He briding to PD1.2.1 attain pays a role to participing influenceation or re-(with expression of large machigrages and APC) ⁽¹⁾ final may help to avoid PC-L2 method at remains weather tomorrow from these latent observed in granted mathem ⁽¹⁾

At anglesevel triple mutation in the Fg durasit to remain antibody dependent call metamot photoscily and complement dependent usin/pxcity¹⁰ on minimum (2%) of anti-drug antipulae later 63(32,327), tautred et 45(3)

MCDHTNE two demonstrated at acceptable safety profile and promoting clinical activity advect nullaid Lorent Topped

Figure 1. Mechanism of Action of MEDIA738

Name 1.0 photosi, incollizanter, operavisidari study ti in evaluate th while and efficient of MCO4078 in settimer will point turned. Chronic Train on the time ND: Results have the 3000HI school face lower previously presented". have on erup pendit

Shafe Desired this of a standard 3×3 does excitation prace follower by an experiment ph Taky constants of a second 2-1 data and the present followed by a second property of the present of the presen

Figure 1 Study Depler 10, programme desiner 2012 programmed and most space 1, spin were

annie (the state) They inclusion and exclusion others for the ophical of patients with SCOHI are highlighted in Takin 1

1111

Table 1. Key Englishity Orthogo

Aug Bechalterentherin	Segural and a local
Comparison and Add and	Adda antenna hanna
8000 Pt 8-1	The second property and
Reserve age backer	The second is a second process.
Prior and CTLA & Branges permitted	
FOLT and POLY address	the second second second
the state of the s	the second se

The second **Study Endpoints**

Ponary emports milute

Saldy and transition

- Advance events (26), and service Ada ones graded according in the National Dation methods: Community Colored to Associate Electric Venuel 400 (HD CTEAE) 4420
- indary industrie instals - Antisandr activity, assessed by Response Evaluation Onlines in Solid Parente (RECOT) 41.1 Assessed by composed temporarily of magnetic resonance triaging at baseline and at 5, 12, and 18 seems, and source 8 seems hereafter

Eighentery startfree indute: Analysis of linear and blood samples collected larbos, storing and other invativent a large performed to sequence the mailtainings between monute capacity, specificity, activated and and cloud' occome to help codemand and predict improves to monumberapy Applied and Tald; Same base samples seen taken at baseline for prossenant of PO-U

above on the PO-L1 (SPOR) immunoritationhermonic assets. Samples were incorporated moted and were considered PD-LY where the memory of LDNL Lance calls started to PD-LY at any elements (see ADCO 2013 Press) (2023)

Table 2. Beseline Demographics and Disease Characteristics MEDATIS 15 make cits (Invite NAME OF TAXABLE 部 22

solida far 1954 5 collected and some Car S. Theory, or the even all in Labor Innov Laboration control of Laboratory ing the others and with the active on PUL

Sety free palents restrict a restar of 8 does (resp. 1-27) of 8020-078 adversion as 10 Highly LDW Safety and Tolerability

- The splits posts is patients with ICO-II was compared with that pressure mental in the
- The same process is process and solutions proceeding and the same though process T-AAS is not explained in 10% of palamete 10 S-Q-C and C-ABS is alway grade 10 S-D and T-ABS in the same process 10 S-D and T-ABS is same the 10 S-D and S-ABS is same to the same same 10 S-D and S-ABS is same to the same same 10 S-D and S-B and S-B and S-B and S-B and S-B 10 S-D and S-B and S-B and S-B and S-B and S-B 10 S-D and S-B and S-B and S-B and S-B and S-B and S-B 10 S-D and S-B and S-B and S-B and S-B and S-B and S-B 10 S-D and S-B and

Treatment Parameters

- - · A safety survey is provided in Table 2, safet improvated ADs of recent we prove in Table 4

Table 3. Safety Summary

		Manager of the state of the state of the
1	Anna All	1.12
the anti-const. (+ 1)	An All Dools 2.4 All Dools 2.4 All Dools 2.4 All All Dools 2.4 All All Dools 2.4 All	N 20 170 70 80 85

Table 4 Select Ones whether All a of its

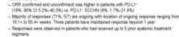
		ARTISTS 10 1	ging also proces
	trans.	All growther a right	Branne b.d
Entrema	Paperty-milet	3.0	202104007
Advantation	Martine	1010 MINUTE	LUCKWOO
Pauloides) describel:	Happen Southern download	1.00.	119180
	Bart for the second second because	12	12
Readings 1.0	Permitte	100	110.00
	Forberto Forber Rett - cylineratur Anti- cylineratur	100 miles	Rolling

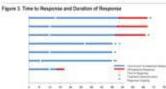
Cannot any party for configure Alls of wards, and ranks from specify a previously of the configuration prove. They limit is not prove they are single previous provided to the set of the

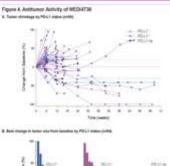
1.100

Cilvinial Activity

12 patients were evaluable for requiring with 124 panels of following Consumpting without a solivity want observed with responses some standark (Fisperies 7 avril 4). Tables 6 avril 41









the local of the PDu

Takin S. Turnur Hexanoxia Overalt and by PO-L1 Status

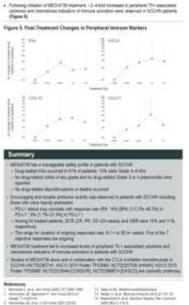
	and the second second	WENTH TRAINE			
	an patients and the	NUMBER OF	140		
MCCC asperty SMA (ALC) MCCC	1963/10. K1 20#	42 (B) 52-61	12216		
IN House of the	AMONG AMONG	11-41	11.04		
Received and any list in contract.	11041-004	40.04141	101-004		
Ing any summer starts	CLI MAYNE	STOCKED STOCKED	1100		

Hagerine (CR) is partice requirement (CR) is space towards. (CR) where a set (CR) is provided by the CR and the comparison of the CR and the

lable 6. Lonor Hergenius to Bubly-maps'

	HESHI'H YI HUYU				
	-	-		-	
MACONT SERVICE STATUS MIN-23	115.00	425,100	108.00 8-8-17.5	101 CT	
NUM DE COMPANY	10.00	104.00	TAXA	1000	

and (C) the works of man in Willing A.A. "State errors nazimenti arlangite 12 peterla atti presse offi allas. 3. setteme escal 2021 desse poto del 271 turar sesteme enal 278 seprine teamer de



Peripheral Sizmarkers of Iromane Artivation

Annual Contractory and Contractory Contractory and Contractory and Contractory Contractory (Contractory Contractory Contractor 2011/ Parts & a a second line at the line line is a a fee fee that the second line we'r are fee fee fee fee to the second we'r are fee fee fee fee fee to the second WAR AR AND IN TRACTOR -k legt to A.a. An Doc 27120 Said & Human People 18 Annuals and the free Statistical Automative

(2) (2) Y. Sin H. Chen, J. Re Annual 2014 (4) (41) (7) (an HL and allow the resource 2014 (6) (7) (76) Factors (6) and (conserved 2014 (7) (7))). Another (6) and (conserved 2014 (7)) (7) (2) (2) and (conserved 2014 (7)) (7).

Aritrophylophysics. No desponse automatical de Malances, Marcia esta de la constante autore provide la districa en 1952 de constantes autores de la consegue (dans la constante, con dans de la constante de la co

Designment Topics of the association of through Land Temporan CET and and the present and only The tax of the association of the distance that the CET with the address of the present Same Section Concernation of the section of the



3011

Postor prevented at the American Society of Clinical Oncology (ASCO) Meeting: Chicago, K.; USA: May 29-June 2, 2018



Comprehensive Cancer Center **UC Cancer Research Foundation**

Segal et al. ASCO 2015

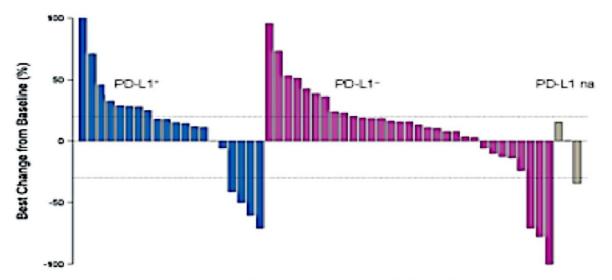
ASCO 2015: Advances in Head 44 and Neck Cancer

Durvalumab/MEDI4736: Clinical Data – ASCO 2015

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

	MEDI4736 10 mg/kg					
	All patients	PD-L1*	PD-L1-			
	(n=62)	(n=22)	(n=37)			
RECIST response (ORR), n/N (%)	7/62 (11)	4/22 (18)	3/37 (8)			
95% Cl	4.7-21.9	5.2-40.3	1.7–21.9			
DCR 24 weeks*, n/N (%)	9/62 (15)	4/22 (18)	4/37 (11)			
95% Cl	6.9–25.8	5.2-40.3	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
 - o Active in heavily pretreated population
 - Responses were durable \rightarrow 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

16 -

14 -

12 -

10 -

8 -

6 -

104 Patients screened:

PD-L1 positive: 78% (81)

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

PD-L

[†]Cer

of H

Distribution of PD-L1 <u>Positive</u> Results in Enrolled Patients:

*3 Pts with tumor (-) but stroma (+) IHC

HPV (-)

HPV (+)

• PD-L1 expression correlates with Response

umber of Patients (n)

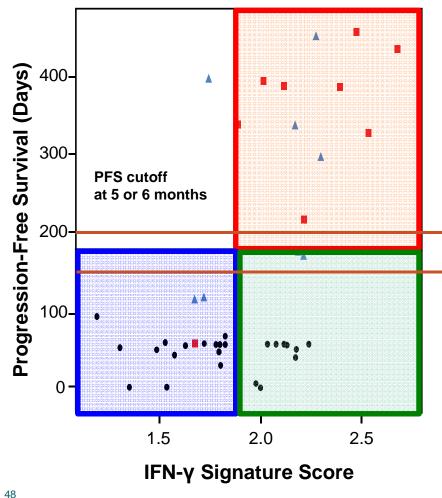
- Using a Youden-Index derived, preliminary PD-L1 cut point:
 - Above cutpoint: 45.5% (5/11) RR
 - Below cutpoint: 11.4% (5/44) RR

	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

Presented by: Tanguy Seiwert, ASCO Annual Meeting 2014

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

Other
 Partial Response
 Stable Disease



1. <u>IR-group: Inflamed – Responders</u>

- Gamma-IFN Inflamed
- Benefitting from anti-PD1 therapy

2. <u>INR-group: Inflamed –</u> 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. <u>NI-group: Non-Inflamed</u>

- 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

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

Presented by: Tanguy Seiwert PRESENTED AT:



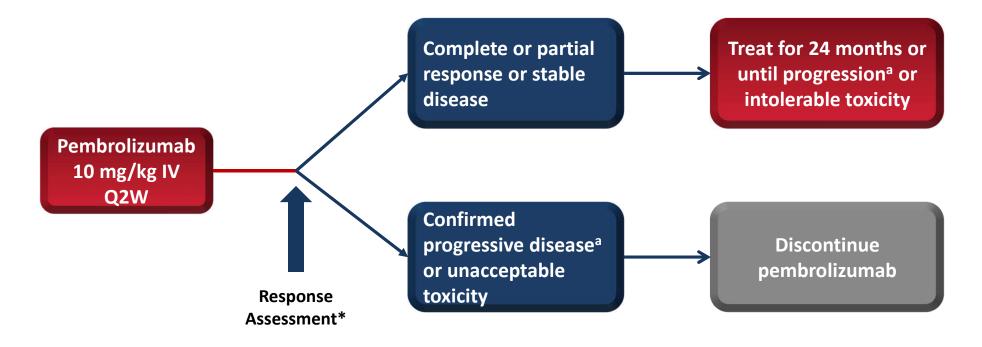
IV. Mesothelioma

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. Schellens⁵

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

^aIf 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.

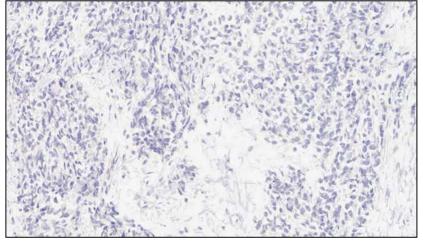
Key Eligibility Criteria

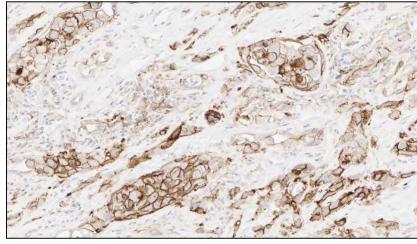
- Age ≥18 years
- Locally advanced or metastatic malignant pleural mesothelioma
- Failure of or inability to receive standard therapy
- Measurable disease per RECIST v1.1
- ECOG performance status of 0 or 1
- PD-L1–positive tumor
- Adequate organ function
- No autoimmune disease or interstitial lung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

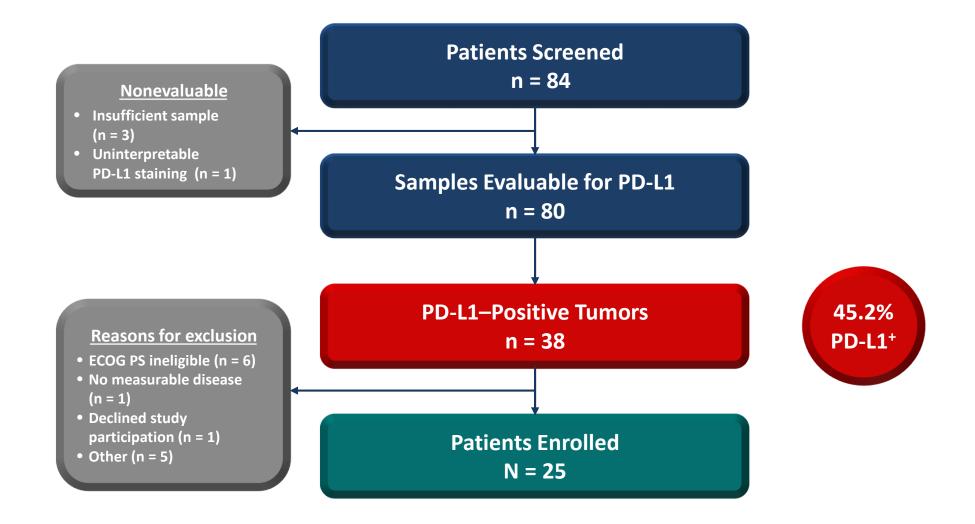




PD-L1 Negative

PD-L1 Positive

PD-L1 Screening: MPM Cohort

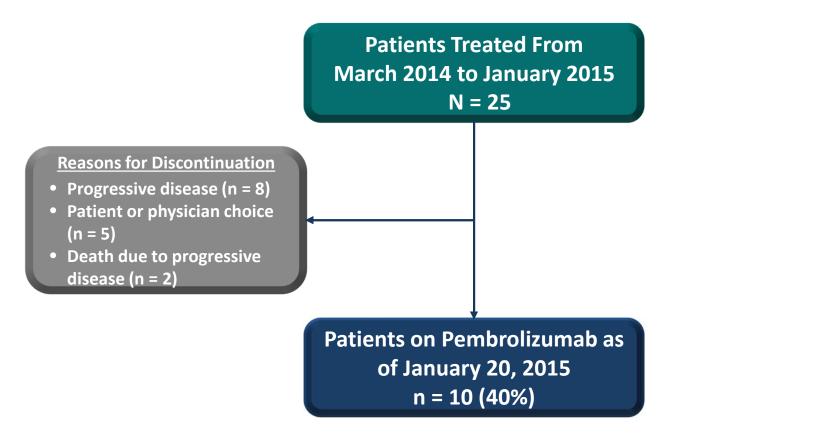


Baseline Characteristics

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

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

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+)

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

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

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	

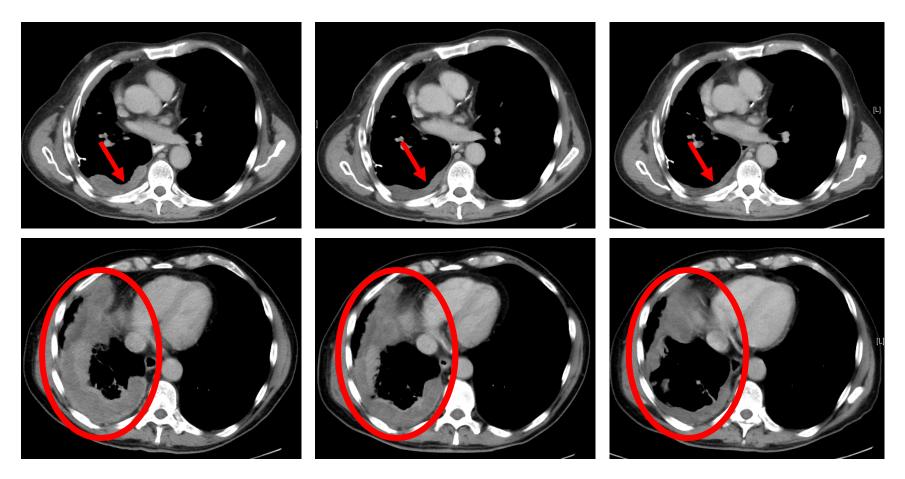
Objective response rate: 28% (95% CI, 12-49)

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

^aIncludes confirmed and unconfirmed responses.

^bPatients 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

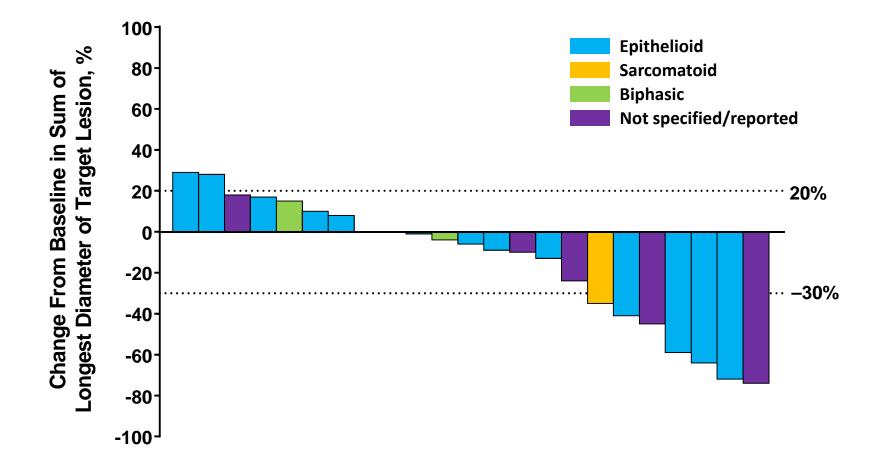


Pretreatment

Week 8

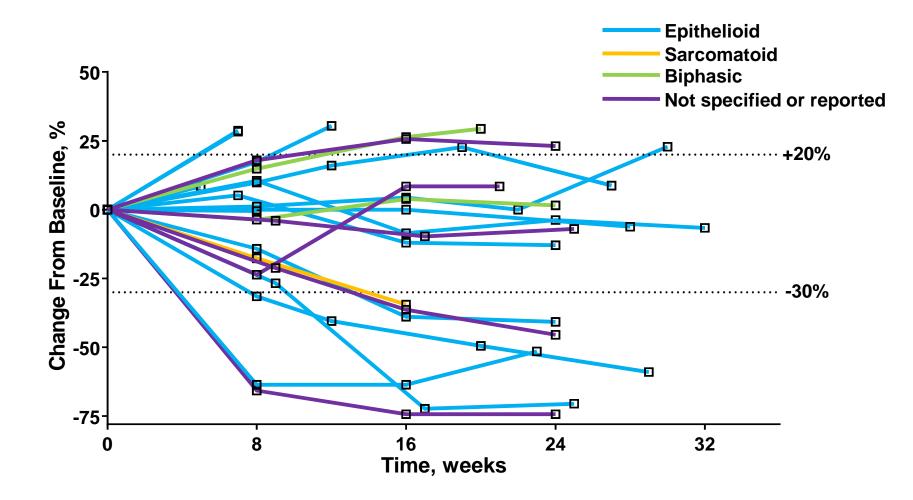
Week 16

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



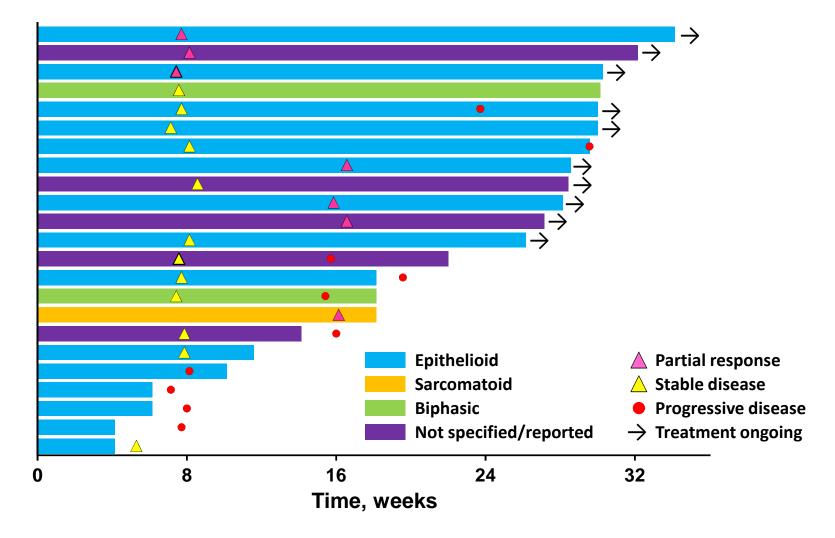
^aIncludes patients with ≥1 postbaseline tumor assessment (n = 23). Analysis cut-off date: January 20, 2015.

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



^aIncludes patients with \geq 1 postbaseline tumor assessment (n = 23). Analysis cut-off date: January 20, 2015.

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



^aIncludes 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

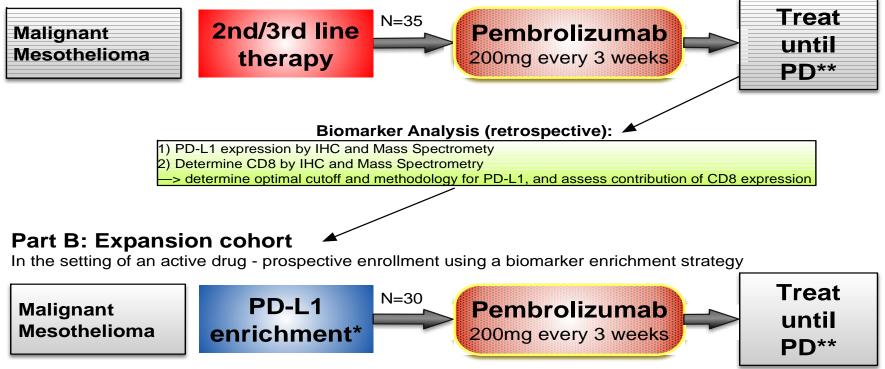
Mesothelioma F/u Study at UofC

• 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



* assessed on fresh tissue if medically feasible

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

Conclusions



- 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!

/					
	<u>Seiwert Lab:</u>	<u>UChicago HNC Group:</u>	Lung Cancer:	<u>Columbia:</u>	
	Zhixiang Zuo	Everett Vokes	Ravi Salgia	Naiyer Rizvi	
	Valia Saloura	Mark Lingen	Everett Vokes		
	Arun Khattri	Ralph Weichselbaum	Victoria Villaflor		
	Michaela Keck	Daniel Haraf	Michael Maitland		
	UChicago Immunology:	Elizabeth Blair	Phil Hoffman		
	Thomas Gajewski	Lou Portugal			
	Pete Savage	Jonas DeSouza	<u>Mesothelioma:</u>		
	Jason Luke	Victoria Villaflor	Hedy Kindler		
	Justin Kline				
	Yusuke Nakamura				
				Attack	100 G
	Macrophage Help	Der 🕡 🏹 DC	11-00	Attack him!	Buzzle
O BI	Izzle.com T C	ell CTL	Macrophage		0

Slide Modified from Jason Luke, MD

http://goldenprague.us/strategies-for-cancer-vaccine-development/