Inmunoterapia en cancer de pulmón.

Luis E. Raez MD FACP FCCP
President-elect Florida Society of Clinical Oncology (FLASCO)
Chief of Hematology/Oncology &
Medical Director
Memorial Cancer Institute/Memorial Health Care System
Clinical Professor of Medicine
Herbert Wertheim College of Medicine
Florida International University

Research Support: *BMS*

Genentech/Roche

Pfizer

Biodesix

MSD

Merck Serono

Lilly Oncology

Boheringer Ingelheim

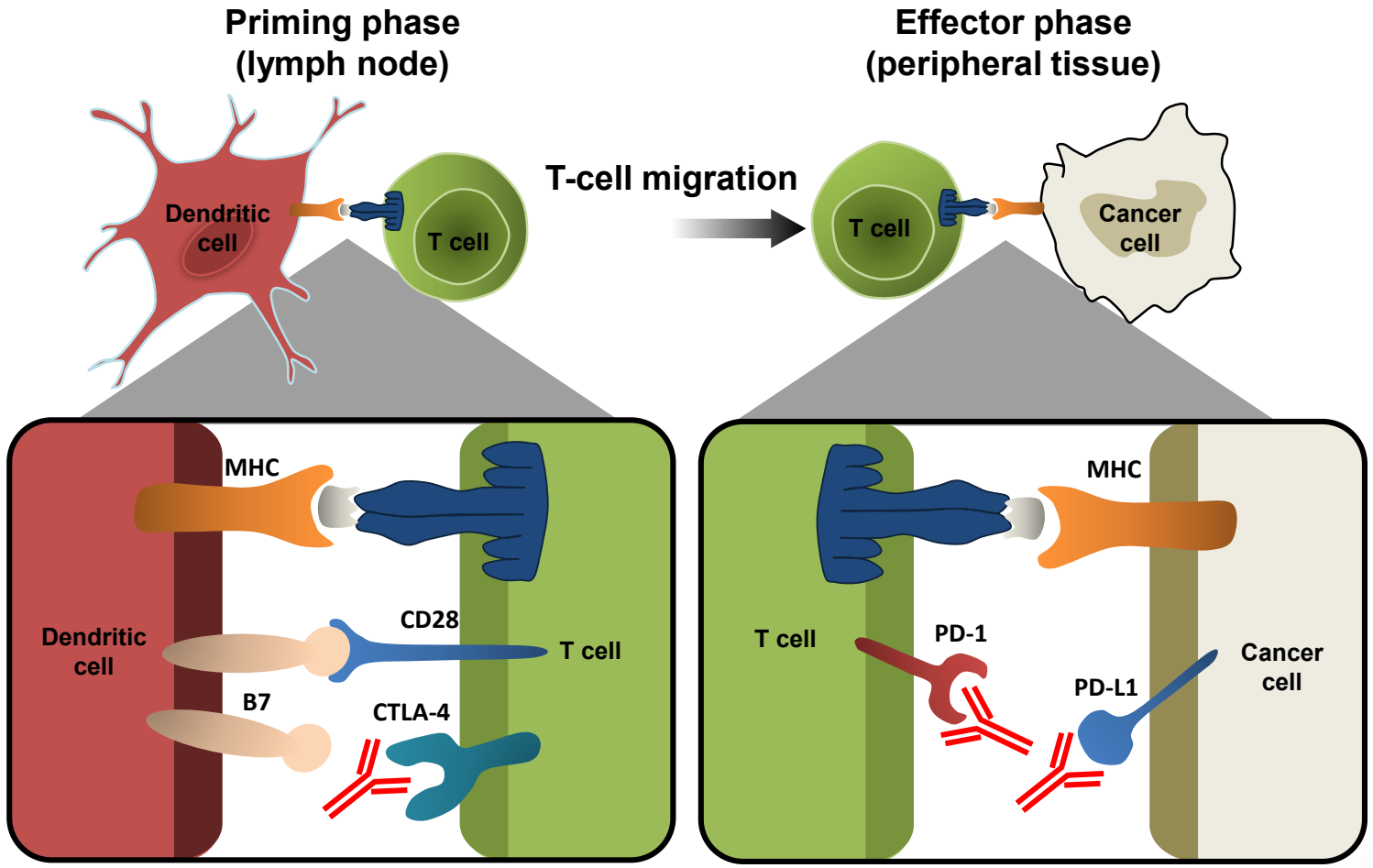
Novartis

Astra-Zeneca

Liquid Genomics

Speakers Bureau/Stocks: *None*

Immunotherapy: Checkpoint blockade



Ribas A. N Engl J Med. 2012;366:2517-2519.

Checkpoint Blockade

Anti-CTLA-4	Anti-PD-L1	Anti-PD-1
Ipilimumab (Fully human IgG1) FDA approved 2011	**MDX-1105** (Fully human IgG4) Phase I	**MDX-1106, Nivolumab** (Fully human IgG4) FDA approved for melanoma, NSCLC, urothelial carcinoma, RCC, HL, SCCHN
Tremelimumab (Fully human IgG2) Phase III	**MPDL3280A, RG7446, Atezolizumab** Phase II-III FDA approved 2016 NSCLC	**CT-011 Pidilizumab** (Humanized IgG1) Phase II
	MEDI4736, Durvalumab; Phase III	**MK3475 Pembrolizumab** (formerly Lambrolizumab) (Humanized IgG4) FDA approved for melanoma, NSCLC, SCCHN
	MSB0010718C, Avelumab Phase I-II	**AMP-224** (B7-DC/IgG1fusion protein) Phase I-II
		MEDI0680, AMP514 Phase I

Memorial Healthcare System

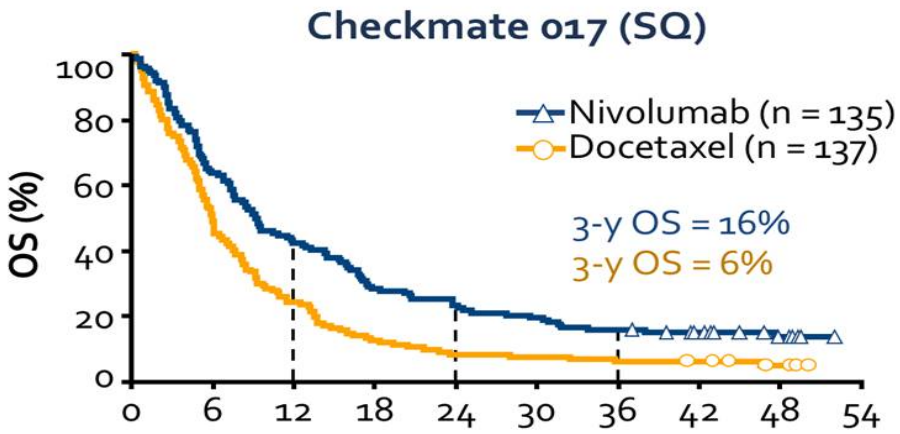
NSCLC Second line Immunotherapy

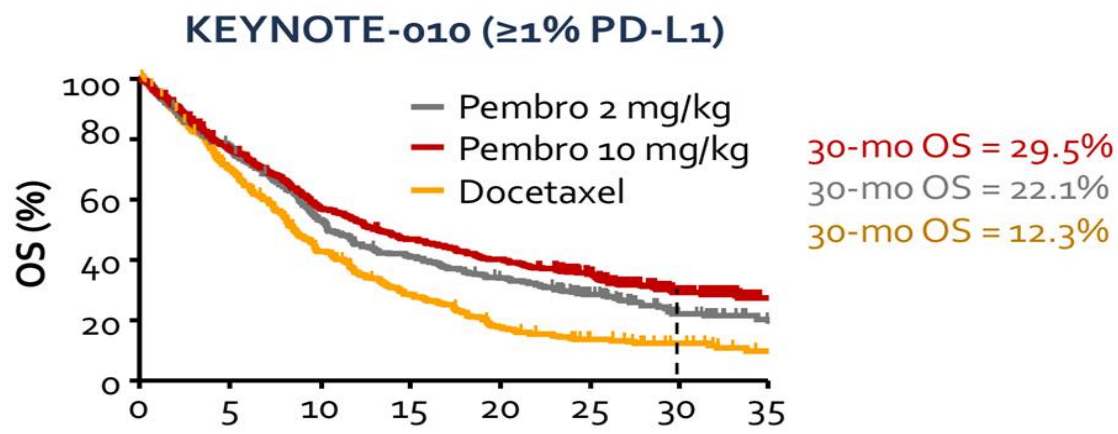
Nivolumab [Checkmate 057 and 017]

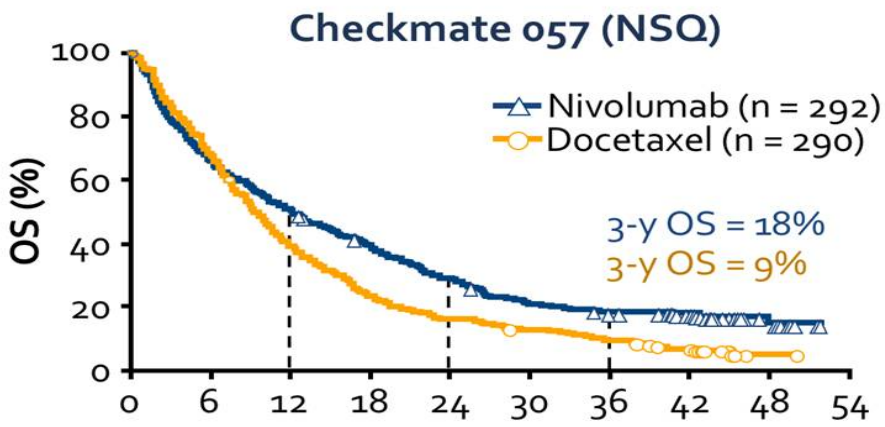
Pembrolizumab [Keynote 010]

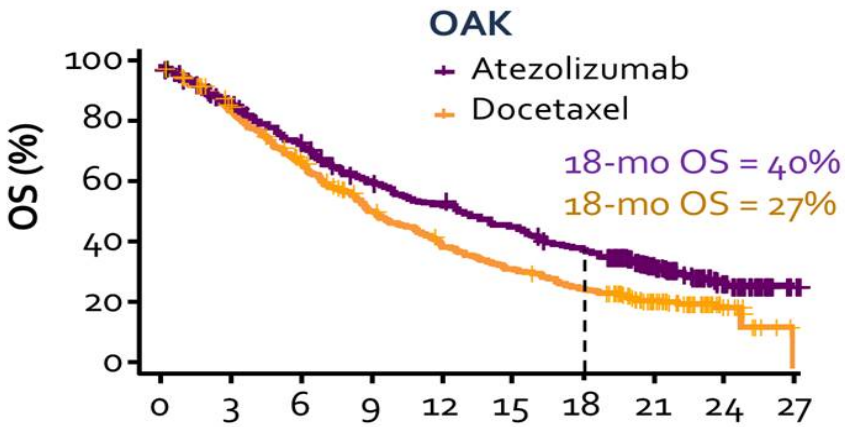
Atezolizumab [Oak]

A consistent but limited OS benefit in 2nd line









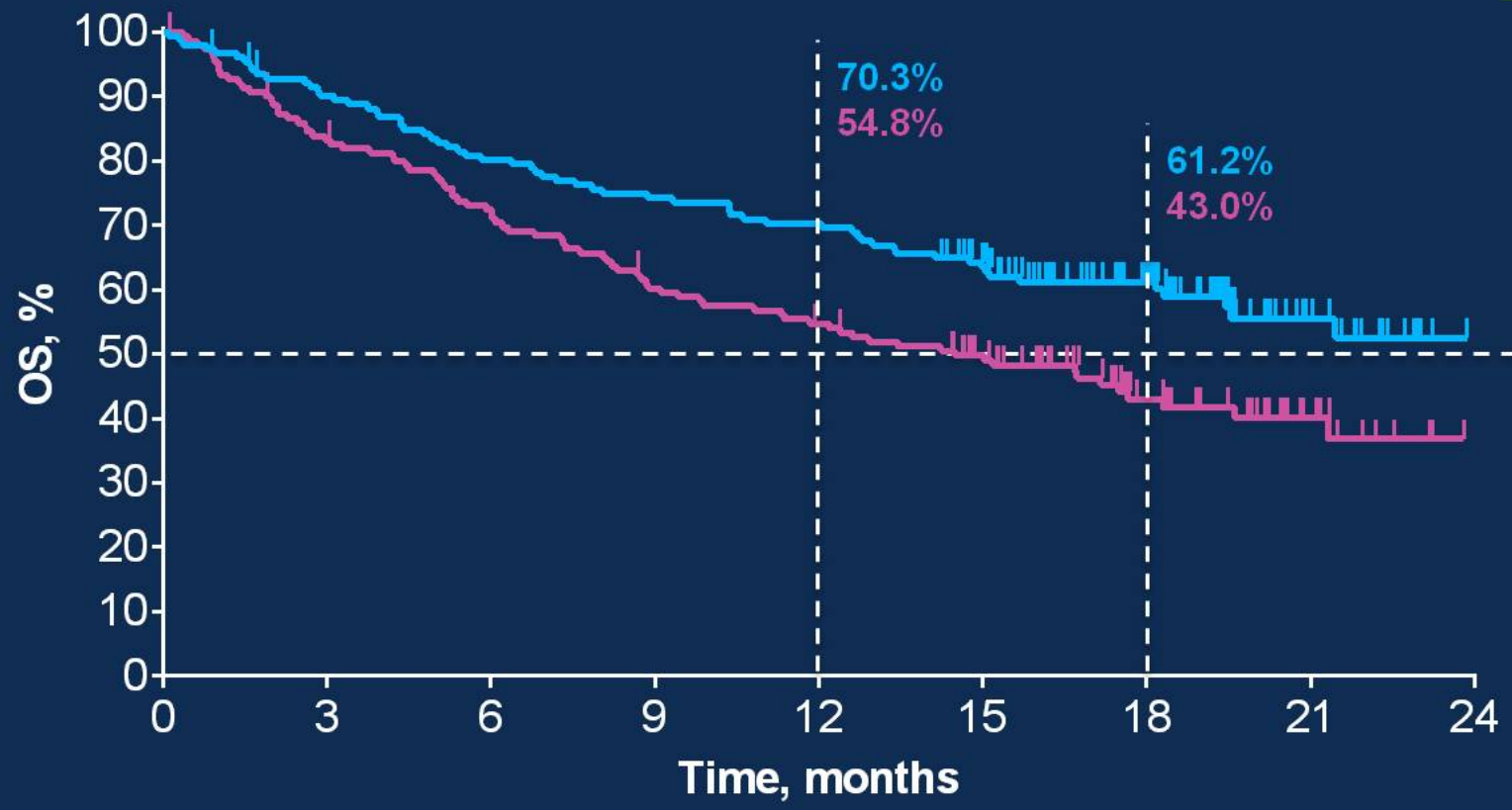
Felip, ESMO 2017; Herbst, ASCO 2017; Rittmeyer, Lancet 2017

Memorial Healthcare System

NSCLC First line Immunotherapy

Pembrolizumab [Keynote 024]

Kaplan-Meier Estimate of OS: Updated Analysis



	Events, n	HR (95% CI)
Pembrolizumab	63	0.63 (0.46-0.88) $P = 0.003$[a]
Chemotherapy	84	

Median (95% CI)
NR (19.4 mo-NE)
14.5 mo (9.8-19.6)

No. at risk

154	136	121	112	106	88	57	20	4
151	123	107	88	79	64	35	15	4

[a]Nominal *P* value.
Data cutoff: Jan 5, 2017.

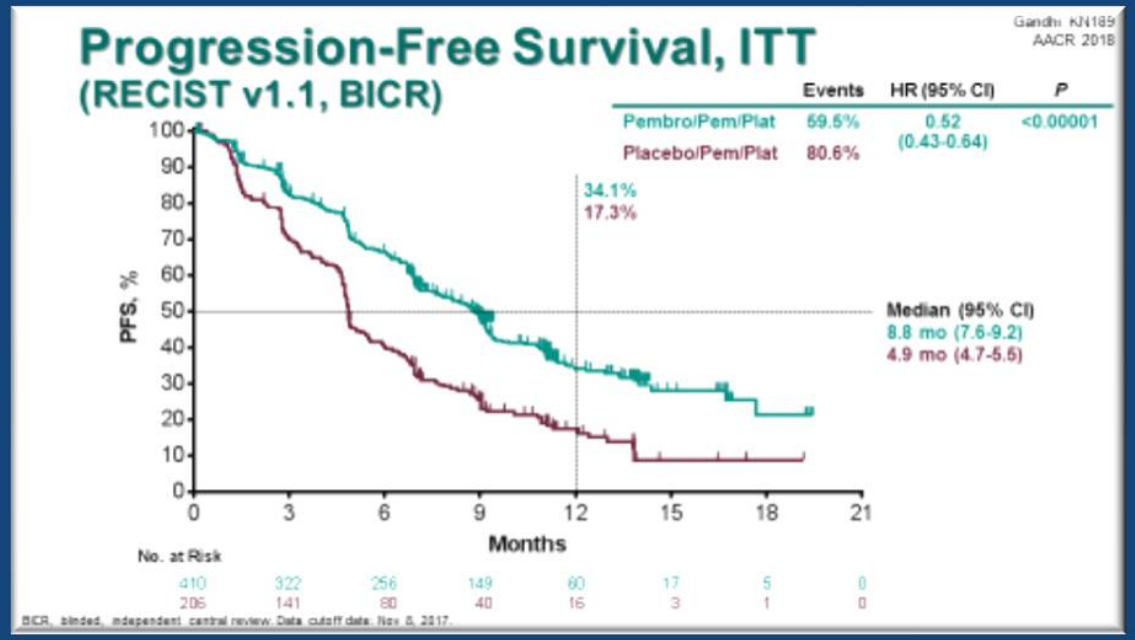
Memorial Healthcare System

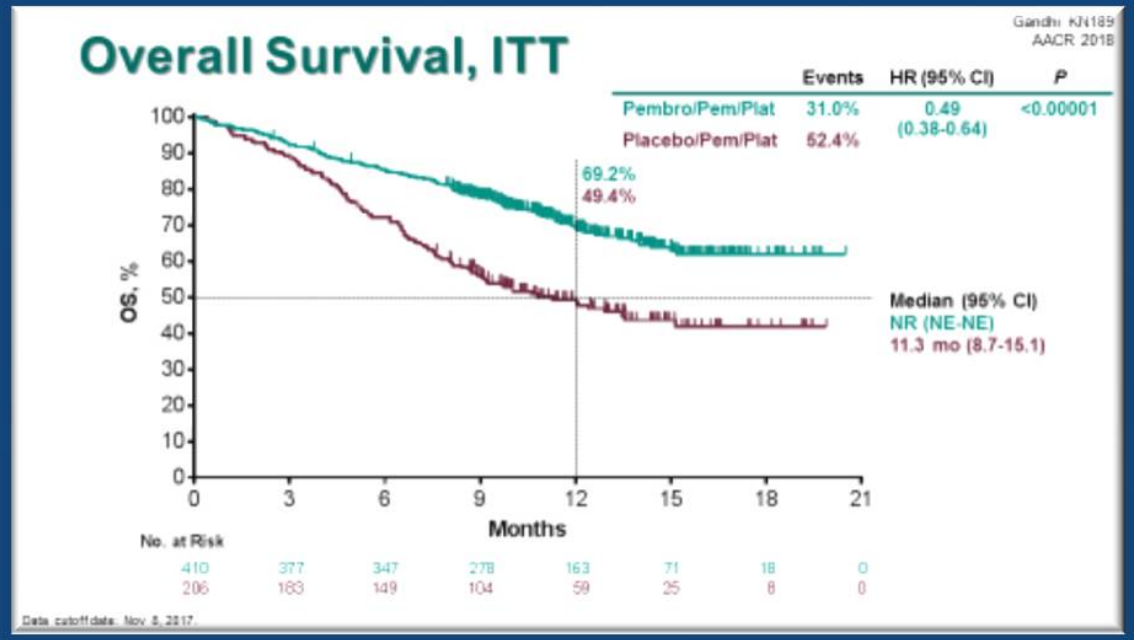
Combining Immunotherapy

1) Chemotherapy: (NSQCC)
   Carboplatin/Pemetrexed/Pembrolizumab
   [Keynote 021 (9/2017) and Keynote 189 (1/2018)]

2) Immunotherapy (NSQCC and SQCC)
   Ipilimumab and nivolumab
   [Checkmate 227 (2/2018)]

KEYNOTE 189 Co-primary endpoints: mPFS and mOS

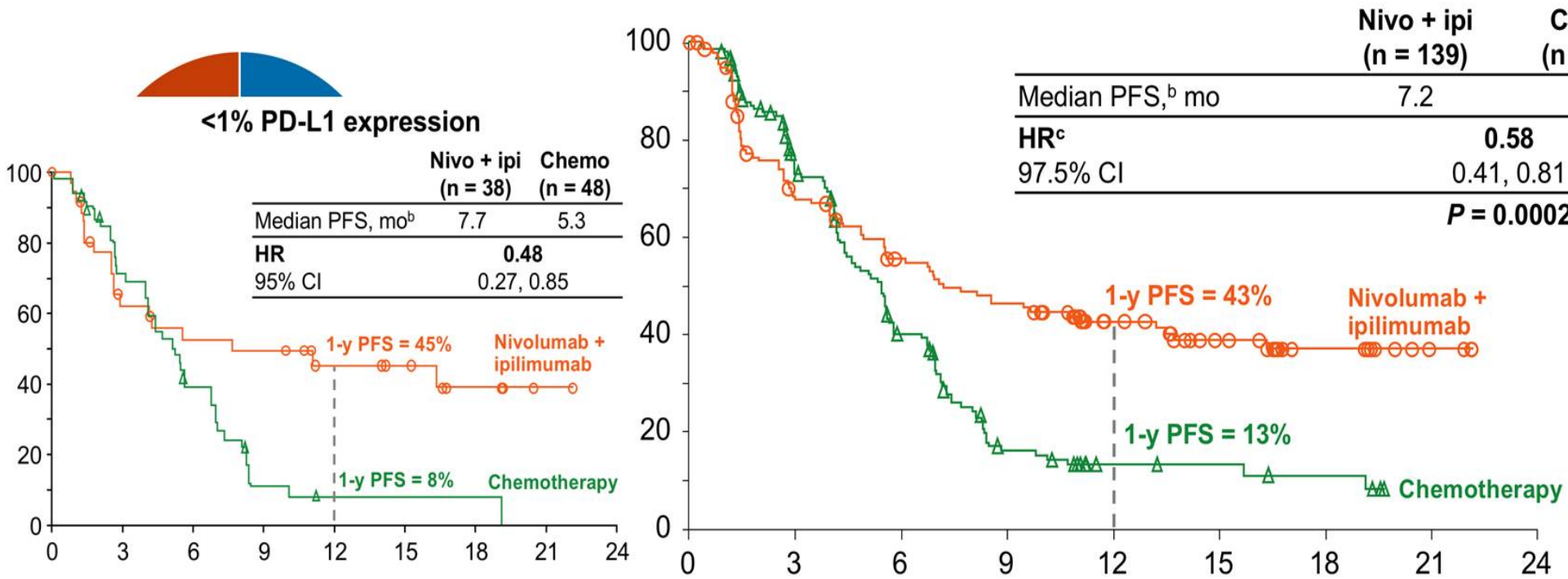




	CPP	Control
mPFS (mo)	8.8 (7.6-9.2)	4.9 (4.7-5.5)
HR, 95% CI, *p* value	0.52 (0.43-0.64) *P = <0.00001*	

	CPP	Control
mOS (mo)	NR	11.3 (8.7-15.1)
HR, 95% CI, *p* value	0.49 (0.38-0.64) *P = <0.00001*	

Ipilimumab/nivolumab is better than platinum chemotherapy in TMB ≥ 10Mb irrespective of PD-L1 CheckMate 227



Primary endpoint PFS in high TMB (≥10Mut/Mb)
HR 1.07 in <10Mut/Mb

Hellmann, NEJM 2018

ASCO 2018

- Keynote 042: First Line (NSQCC)

  Carbo/Pem vs Pembro [PD-L1 >1%]

- IMPOWER 150: First Line (NSQCC)

  Carbo/Paclit/Bev/Atezo vs SOC

- IMPOWER 131: First Line (SQCC)

  Carbo/Nab-Pac/Atezo vs SOC

- KEYNOTE 407: First Line (SQCC)

  Carbo/Paclit or Nab/Pembro vs SOC

KEYNOTE-042 Study Design

Key Eligibility Criteria

- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS ≥1%
- No sensitizing *EGFR* or *ALK* alterations
- ECOG PS 0 or 1
- No untreated or unstable CNS metastases
- No history of pneumonitis that required systemic corticosteroids

Stratification Factors

- Region (east Asia vs rest of the world)
- ECOG PS (0 vs 1)
- Histology (squamous vs nonsquamous)
- PD-L1 TPS (≥50% vs 1-49%)

Randomize 1:1

N = 637 → Pembrolizumab 200 mg Q3W for up to 35 cycles

N = 637 → Carboplatin AUC 5 or 6 Q3W + Paclitaxel 200 mg/m^2 Q3W[a] OR Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m^2 Q3W[a] for up to 6 cycles

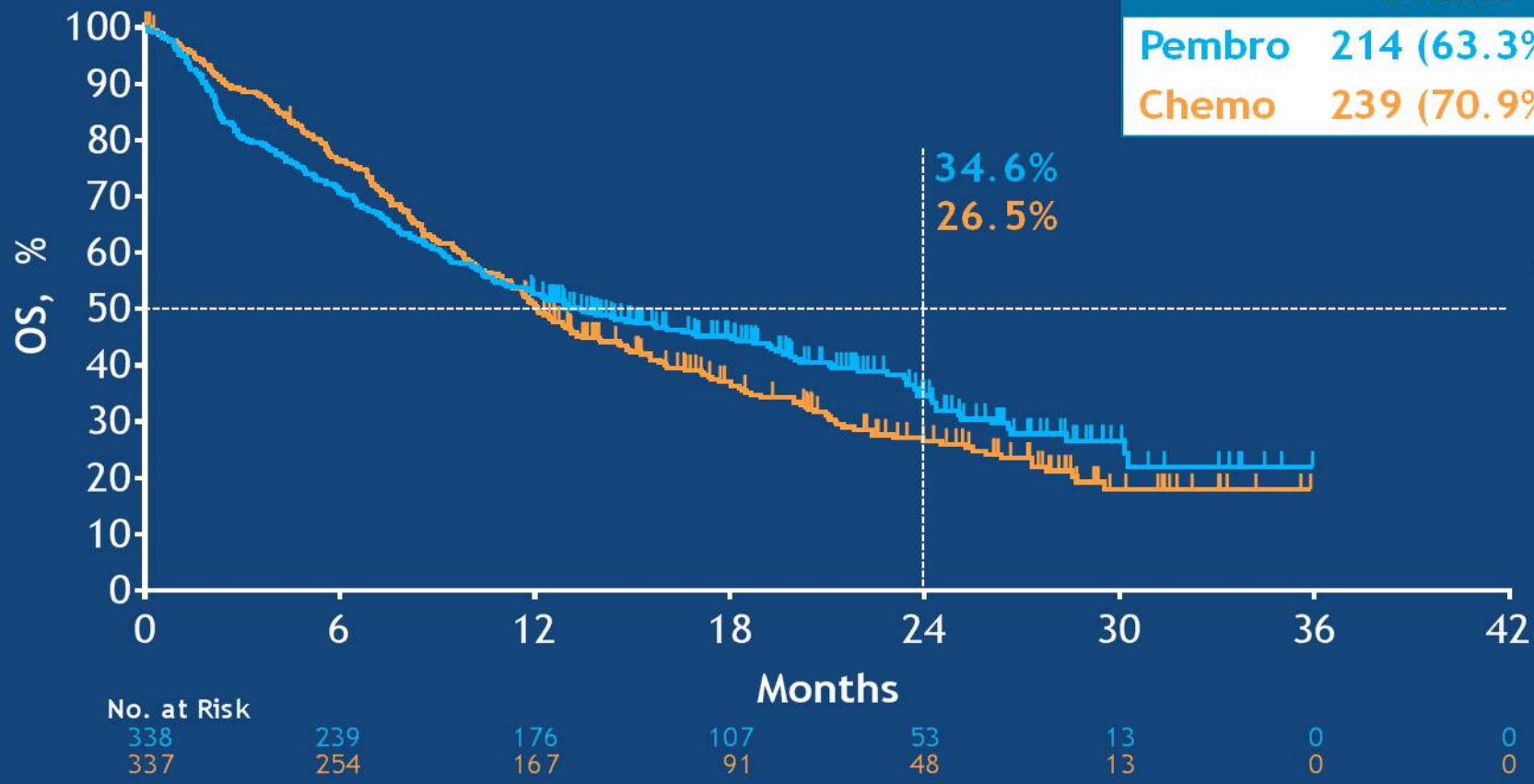
End points

- Primary: OS in PD-L1 TPS ≥50%, ≥20%, and ≥1%
- Secondary: PFS and ORR in TPS ≥50%, ≥20%, and ≥1%; safety in TPS ≥1%

[a]Pemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology.

Overall Survival: TPS ≥1-49% (Exploratory Analysis[a])

	Events	HR (95% CI)
Pembro	214 (63.3%)	0.92 (0.77-1.11)
Chemo	239 (70.9%)	



Median (95% CI)
13.4 mo (10.7-18.2)
12.1 mo (11.0-14.0)

[a]No alpha allocated to this comparison.

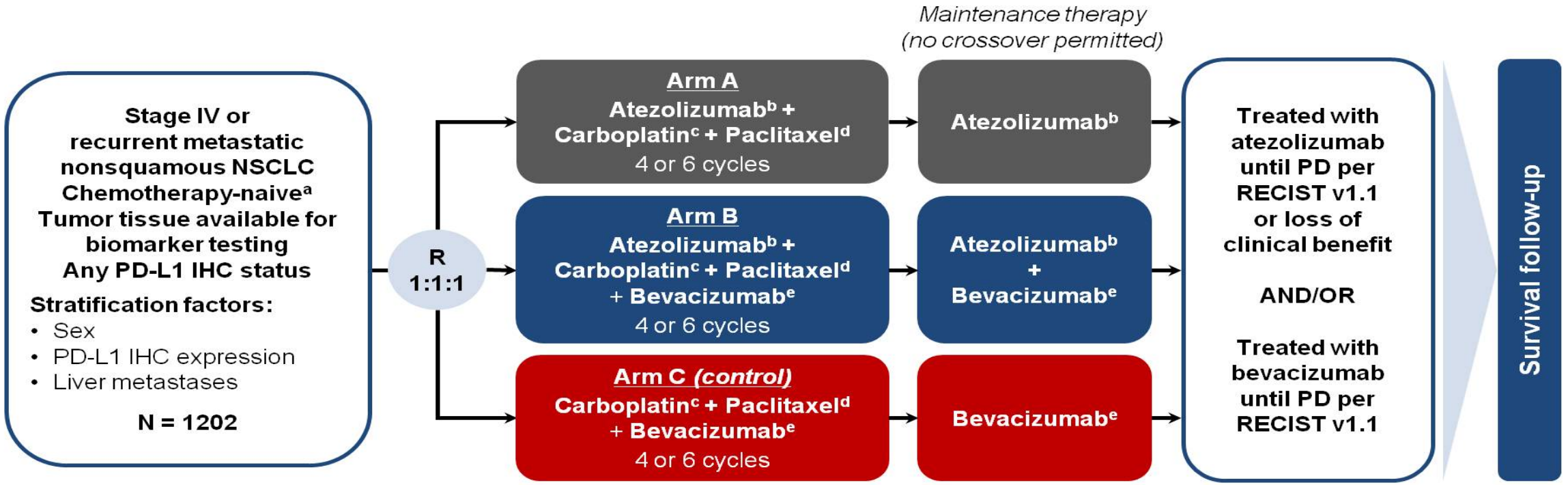
IMpower150: Overall Survival Analysis of a Randomized Phase III Study of Atezolizumab + Chemotherapy ± Bevacizumab vs Chemotherapy + Bevacizumab in 1L Nonsquamous NSCLC

Mark A. Socinski,[1] Robert Jotte,[2] Federico Cappuzzo,[3] Francisco Orlandi,[4] Daniil Stroyakovskiy,[5] Naoyuki Nogami,[6] Delvys Rodríguez-Abreu,[7] Denis Moro-Sibilot,[8] Christian A. Thomas,[9] Fabrice Barlesi,[10] Gene Finley,[11] Claudia Kelsch,[12] Anthony Lee,[12] Shelley Coleman,[12] Yijing Shen,[12] Marcin Kowanetz,[12] Ariel Lopez-Chavez,[12] Alan Sandler,[12] Martin Reck[13]

[1]Florida Hospital Cancer Institute, Orlando, FL; [2]Rocky Mountain Cancer Centers, Denver, CO and US Oncology, Houston, TX; [3]Azienda Unità Sanitaria Locale della Romagna, Ravenna, Italy; [4]Instituto Nacional del Torax, Santiago, Chile; [5]Moscow City Oncology Hospital, Moscow, Russia; [6]National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; [7]Complejo Hospitalario Univesitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain; [8]Centre Hospitalier Universitaire de Grenoble Alpes, Grenoble, France; [9]New England Cancer Specialists, Scarborough, ME; [10]Aix Marseille University, Assistance Publique Hôpitaux de Marseille, Marseille, France; [11]Allegheny Health Network Cancer Institute, Pittsburgh, PA; [12]Genentech, Inc., South San Francisco, CA; [13]Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany

Presented By Mark Socinski at 2018 ASCO Annual Meeting

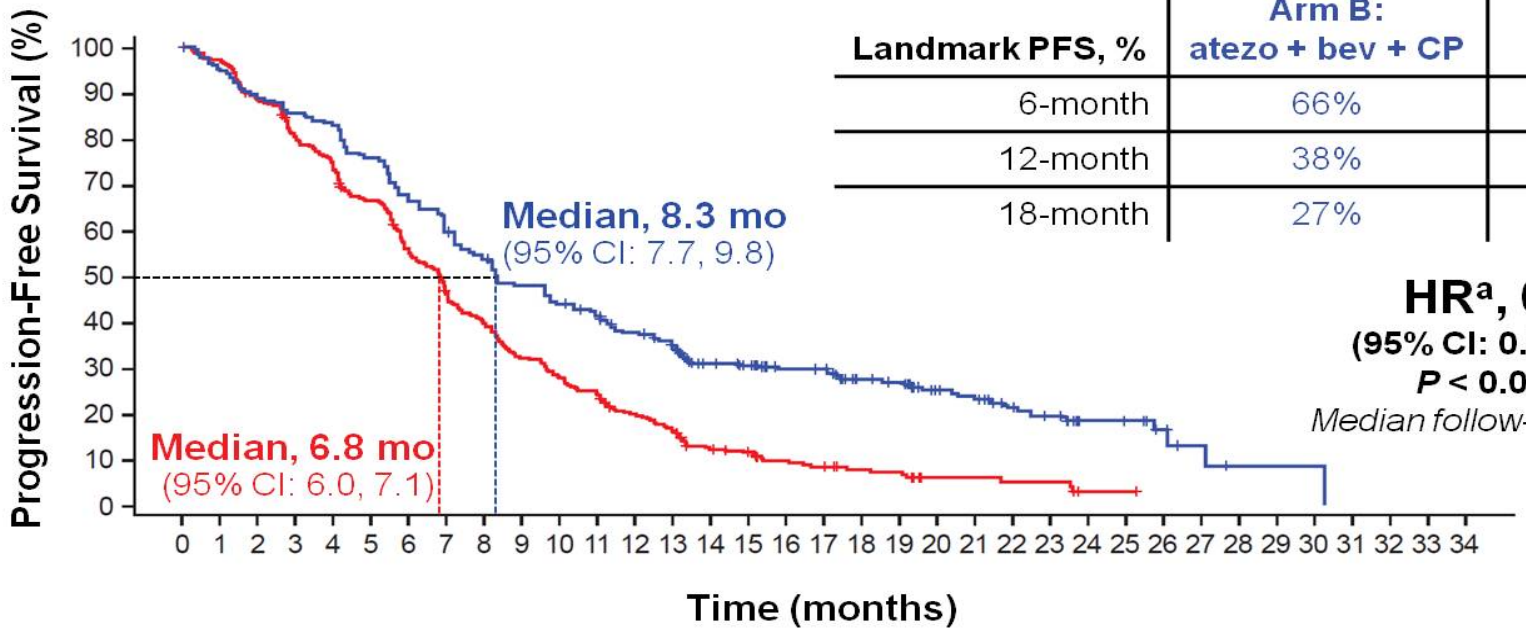
IMpower150 Study Design



[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w. [d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

Presented By Mark Socinski at 2018 ASCO Annual Meeting

Updated PFS Analysis in the ITT-WT (Arm B vs Arm C)



Landmark PFS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
6-month	66%	56%
12-month	38%	20%
18-month	27%	8%

HR[a], 0.59
(95% CI: 0.50, 0.70)
***P* < 0.0001[b]**
Median follow-up: ~20 mo

No. at Risk

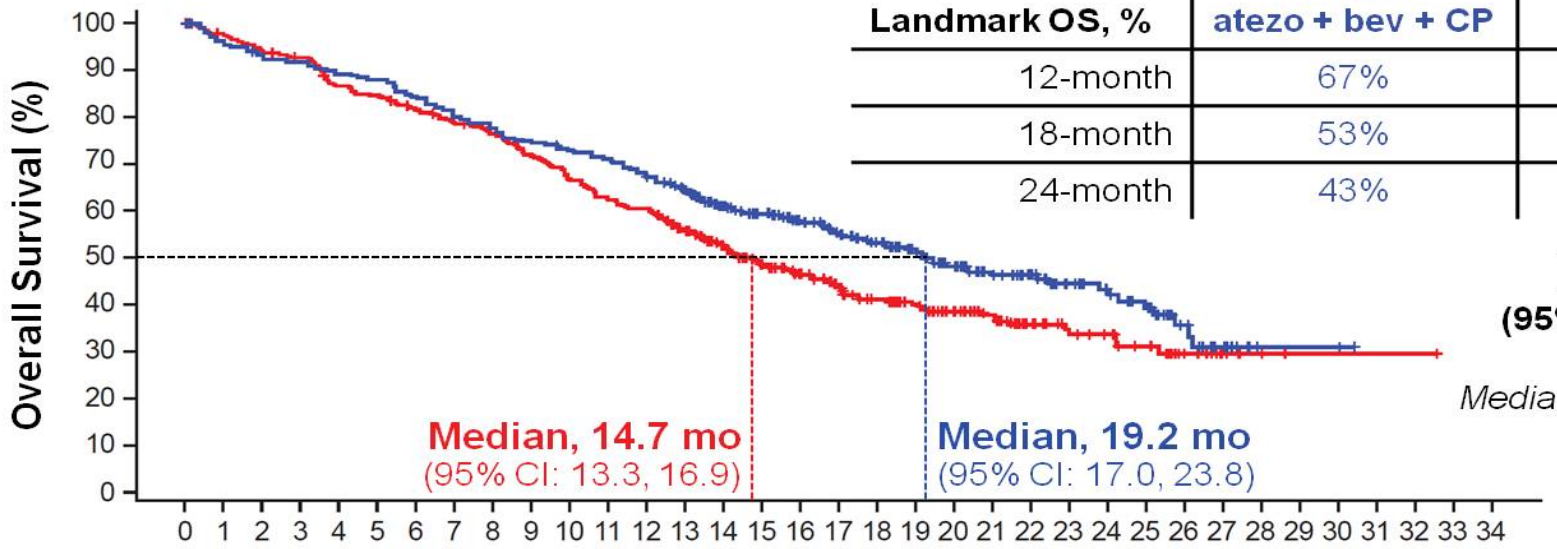
Atezo+Bev+CP	359	336	315	301	293	267	234	213	190	168	154	146	125	112	85	80	69	68	53	50	37	33	24	20	12	11	6	3	1	1	1
Bev+CP	337	323	294	263	244	215	180	148	127	103	89	78	61	50	35	29	21	18	14	13	6	6	5	5	1	1					

- Statistically significant and clinically meaningful PFS benefit with atezolizumab + bevacizumab + chemotherapy vs bevacizumab + chemotherapy was previously observed[1] and continued to improve with additional follow-up

[a] Stratified HR. [b] For descriptive purposes only. Data cutoff: January 22, 2018
1. Reck M, et al. ESMO IO 2017 [abstract LBA1_PR].

OS in the ITT-WT (Arm B vs Arm C)

Landmark OS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
12-month	67%	61%
18-month	53%	41%
24-month	43%	34%



HR[a], 0.78
(95% CI: 0.64, 0.96)
***P* = 0.0164**
Median follow-up: ~20 mo

No. at Risk

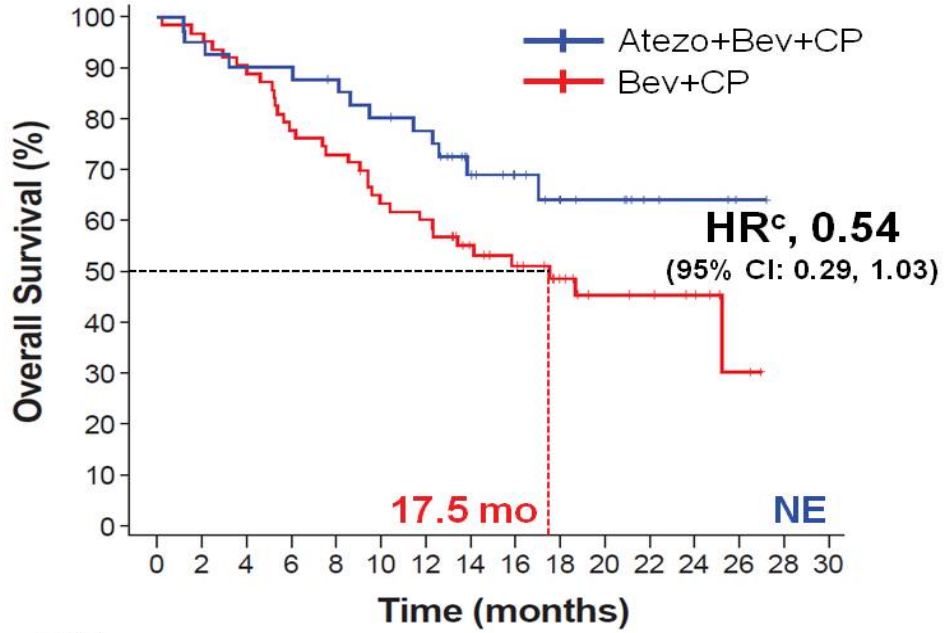
Atezo+Bev+CP	359	339	328	323	314	310	296	284	273	264	256	250	235	218	188	167	147	133	119	103	84	66	57	41	34	28	16	9	2	2	2
Bev+CP	337	326	315	308	287	280	268	255	247	233	216	203	196	174	152	129	115	101	87	77	66	56	40	32	29	22	13	6	3	1	1	1	1

- Statistically significant and clinically meaningful OS benefit with atezolizumab + bevacizumab + chemotherapy vs bevacizumab + chemotherapy was observed

[a] Stratified HR.
Data cutoff: January 22, 2018

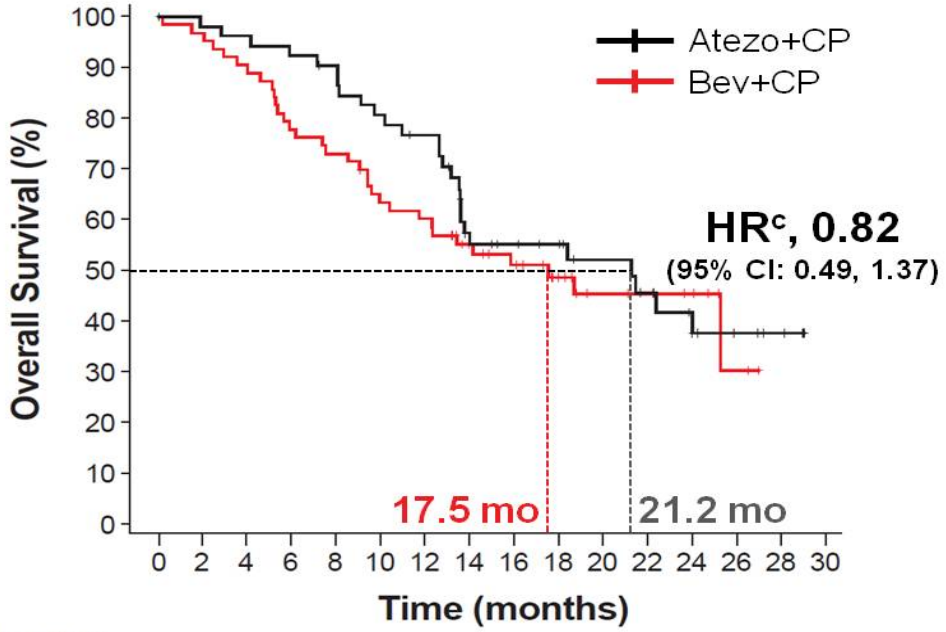
Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of *EGFR/ALK*+ Patients[a]

Arm B[b] vs Arm C



No. at Risk														
Atezo+Bev+CP	41	39	37	37	35	32	30	20	15	11	9	5	4	2
Bev+CP	63	61	57	49	46	39	37	28	24	17	12	11	7	2

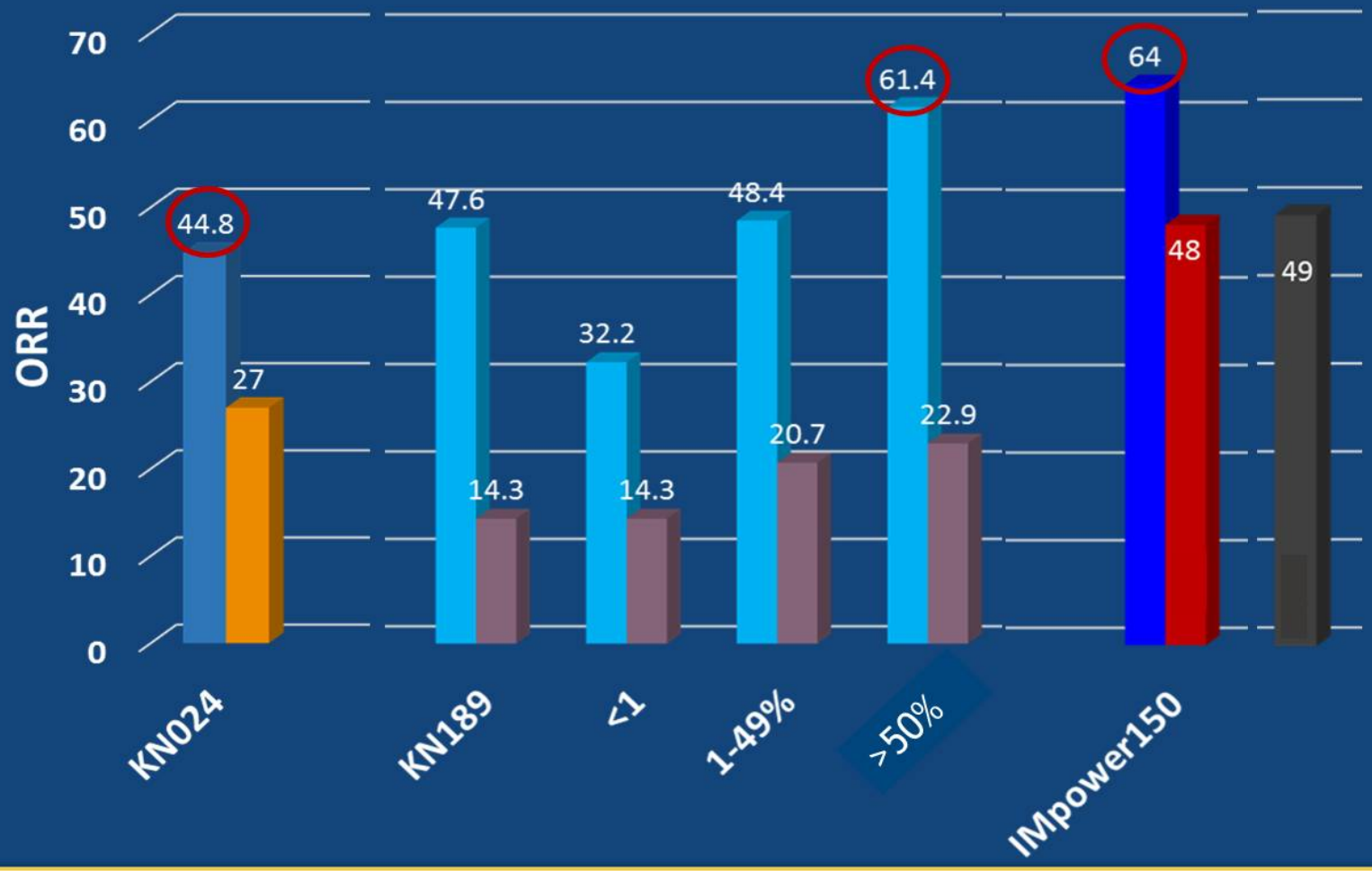
Arm A vs Arm C



No. at Risk														
Atezo+CP	53	51	50	48	46	41	37	24	22	20	16	13	8	6	4
Bev+CP	63	61	57	49	46	39	37	28	24	17	12	11	7	2

[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[b] One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab. [c] Unstratified HR.
Data cutoff: January 22, 2018

Chemotherapy does improve ORR



Pembrolizumab
Chemotherapy

Pembrolizumab + Platinum/Pemetrexed
Chemotherapy

Atezolizumab + Carboplatin + Paclitaxel + Bevacizumab
Bevacizumab + CP

Atezolizumab + CP

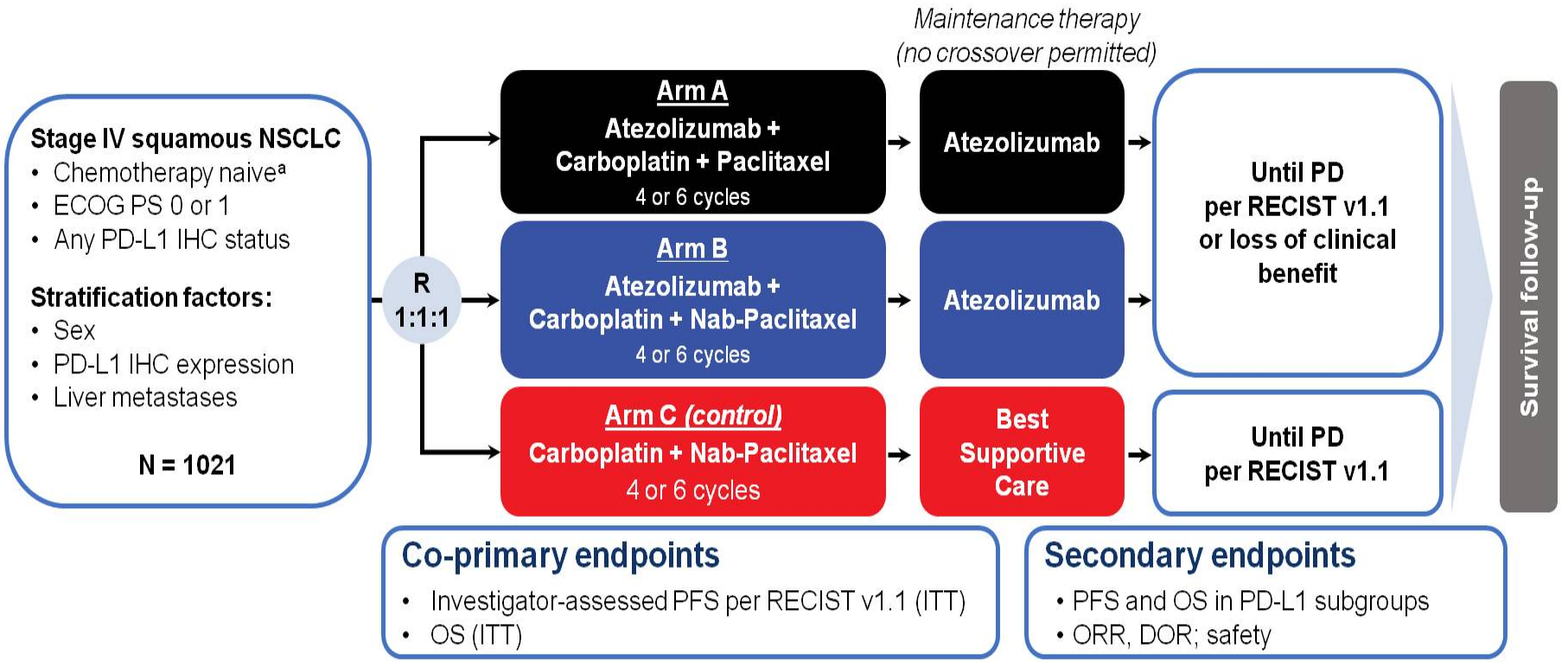
IMpower131: Primary PFS and Safety Analysis of a Randomized Phase III Study of Atezolizumab + Carboplatin + Paclitaxel or Nab-Paclitaxel vs Carboplatin + Nab-Paclitaxel as 1L Therapy in Advanced Squamous NSCLC

Robert Jotte,[1,2] Federico Cappuzzo,[3] Ihor Vynnychenko, [4] Daniil Stroyakovskiy,[5] Delvys Rodriguez Abreu,[6] Maen Hussein,[7] Ross Soo,[8] Henry J. Conter,[9] Toshiyuki Kozuki,[10] Carlos da Silva,[11] Vilma Graupner,[12] Shawn W. Sun,[13] Ray Lin,[13] Helen Jessop,[12] Marcin Kowanetz,[13] Tien Hoang,[13] Alan Sandler,[13] Mark A. Socinski[14]

[1]Rocky Mountain Cancer Centers, Denver, CO; [2]US Oncology, Houston, TX; [3]Azienda Unità Sanitaria Locale della Romagna, Ravenna, Italy; [4]Sumy State University, Sumy, Ukraine; [5]Moscow City Oncology Hospital, Moscow Healthcare Department, Moscow Oblast, Russia; [6]Complejo Hospitalario Universitario Insular-Materno Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Spain; [7]Sarah Cannon Research Institute/Florida Cancer Specialists, Lady Lake, FL; [8]Department of Haematology-Oncology, National University Hospital, Singapore; [9]William Osler Health System, Brampton, ON, Canada; [10]Department of Thoracic Oncology and Medicine, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; [11]Fundação Pio XII Institution – Cancer Hospital of Barretos, Barretos, São Paulo, Brazil; [12]F. Hoffmann-La Roche, Ltd, Basel, Switzerland; [13]Genentech, Inc., South San Francisco, CA; [14]Florida Hospital Cancer Institute, Orlando, FL

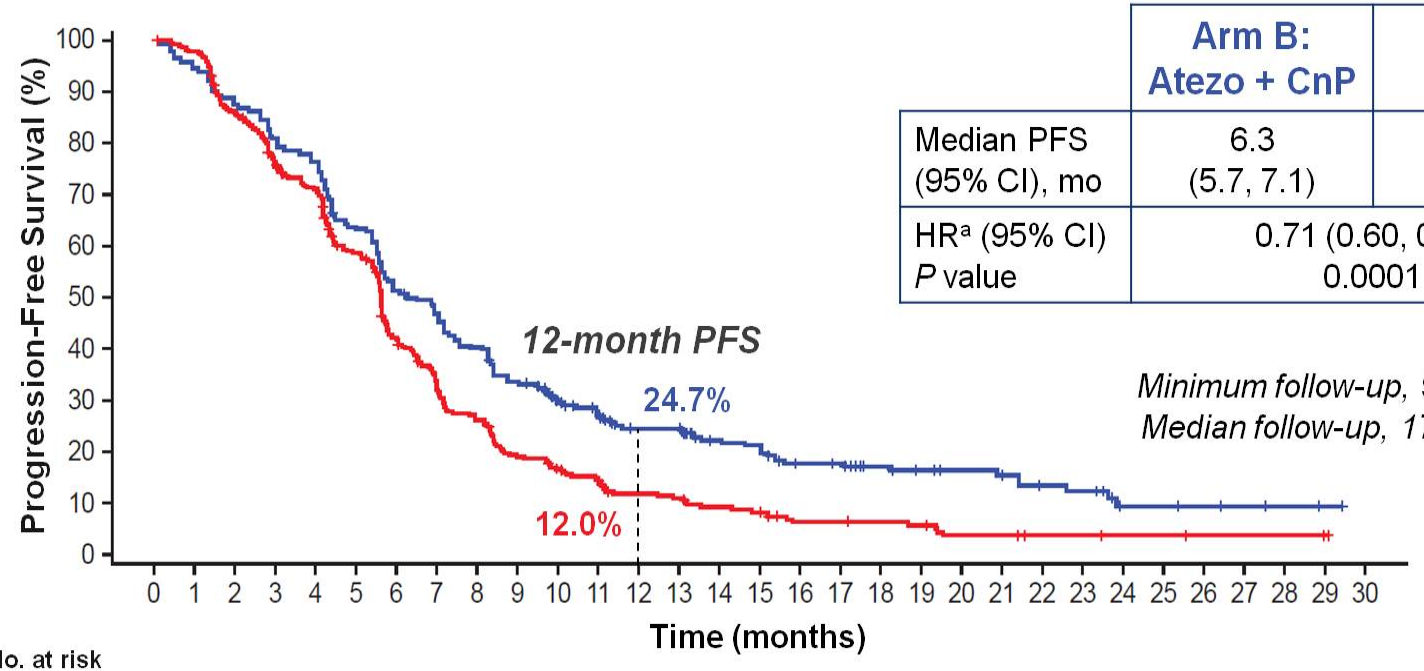
PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

IMpower131: Study Design



Atezolizumab 1200 mg IV q3w; carboplatin AUC 6 IV q3w; nab-paclitaxel 100 mg/m^2 IV qw; paclitaxel 200 mg/m^2 IV q3w.
[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance to treatment with ≥ 1 approved targeted therapies. Testing for *EGFR* mutation or *ALK* translocation was not mandatory.
[b] PD-L1 expression was evaluated using the VENTANA SP142 IHC assay.

INV-Assessed PFS in the ITT Population (Arm B vs Arm C)



	Arm B: Atezo + CnP	Arm C: CnP
Median PFS (95% CI), mo	6.3 (5.7, 7.1)	5.6 (5.5, 5.7)
HR[a] (95% CI)	0.71 (0.60, 0.85)	
P value	0.0001	

Minimum follow-up, 9.8 mo
Median follow-up, 17.1 mo

No. at risk

Atezo + CnP	343	318	294	268	257	212	172	151	134	111	88	76	61	61	44	42	33	32	24	21	18	16	12	11	5	5	4	3	2	1
CnP	340	322	279	244	227	183	128	95	79	57	48	40	28	26	21	19	12	12	11	10	6	6	4	4	3	3	2	2	2	1

Data cutoff: January 22, 2018.
INV, investigator. [a] Stratified HR.

Presented By Robert Jotte at 2018 ASCO Annual Meeting

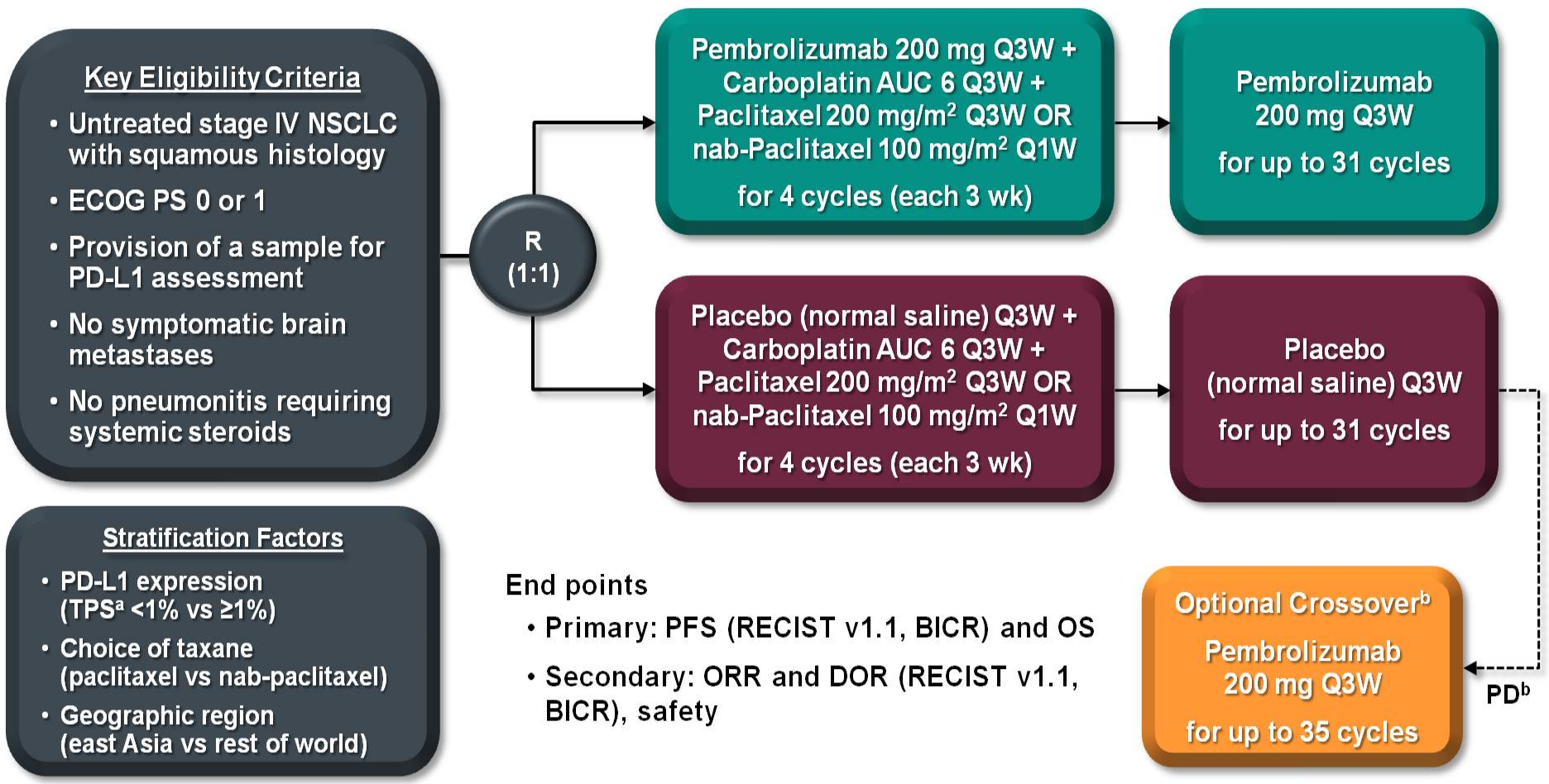
KEYNOTE-407: Phase 3 Study of Carboplatin-Paclitaxel/Nab-Paclitaxel With or Without Pembrolizumab for Metastatic Squamous NSCLC

Luis Paz-Ares,[1] Alexander Luft,[2] Ali Tafreshi,[3] Mahmut Gümüş,[4] Julien Mazières,[5] Barbara Hermes,[6] Filiz Çay Senler,[7] Andrea Fülöp,[8] Jeronimo Rodriguez Cid,[9] Shunichi Sugawara,[10] Ying Cheng,[11] Silvia Novello,[12] Balazs Halmos,[13] Yue Shentu,[14] Xiaodong Li,[14] Gregory M Lubiniecki,[14] Bilal Piperdi,[14] Dariusz Kowalski[15]

[1]Hospital Universitario 12 de Octubre, Madrid, Spain; [2]Leningrad Regional Clinical Hospital, St. Petersburg, Russia; [3]Wollongong Hospital, Wollongong, NSW, Australia; [4]Kartal Research and Training Hospital, Istanbul, Turkey; [5]Centre Hospitalier Universitaire de Toulouse, Toulouse, France; [6]Universitätskinikum Tübingen, Tuebingen, Germany; [7]Ankara University, Ankara, Turkey; [8]Országos Korányi TBC és Pulmonológiai Intézet, Budapest, Hungary; [9]Oncology Center, Medica Sur Hospital, Mexico City, Mexico; [10]Sendai Kousei Hospital, Sendai, Japan; [11]Cancer Hospital of Jilin Province, Changchun, China; [12]University of Turin, Orbassano, Italy; [13]Albert Einstein College of Medicine, Bronx, NY, USA; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Maria Skłodowska-Curie Institute of Oncology, Warsaw, Poland

Presented By Luis Paz-Ares at 2018 ASCO Annual Meeting

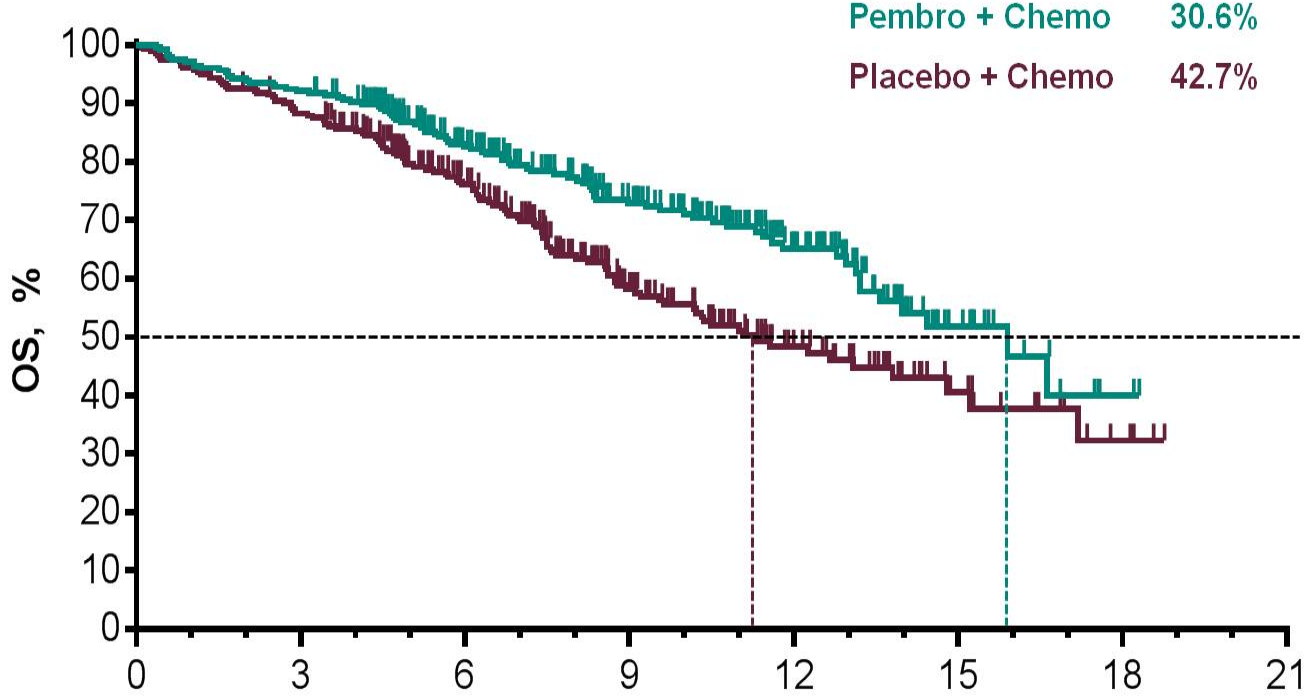
KEYNOTE-407 Study Design (NCT02775435)



BICR, blinded independent central radiologic review. [a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay.
[b]Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.

Overall Survival at IA2, ITT

	Events	HR (95% CI)	*P*
Pembro + Chemo	30.6%	0.64 (0.49-0.85)	0.0008
Placebo + Chemo	42.7%		



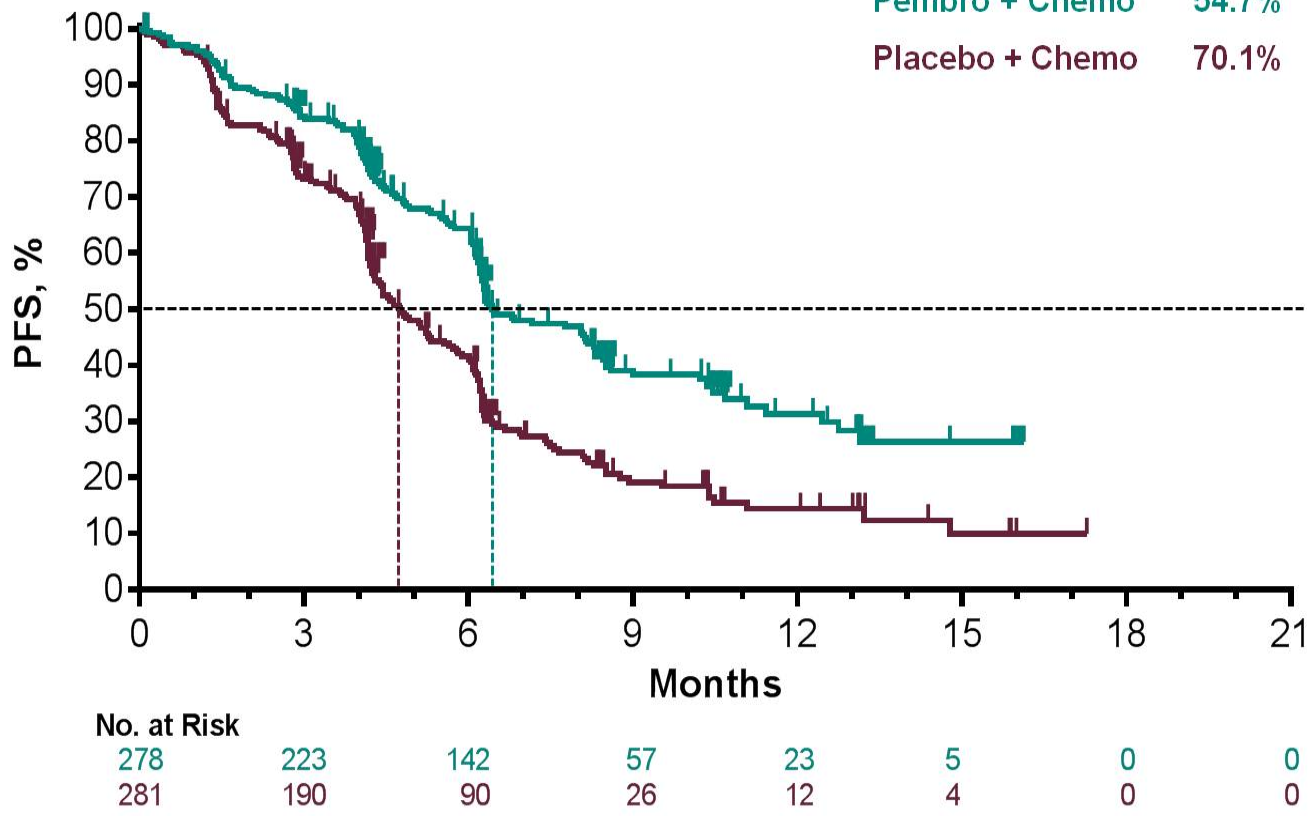
Median (95% CI)
15.9 mo (13.2-NE)
11.3 mo (9.5-14.8)

No. at Risk							
278	256	188	124	62	17	2	0
281	246	175	93	45	16	4	0

Data cutoff date: Apr 3, 2018.

Progression-Free Survival at IA2, ITT
(RECIST v1.1, BICR)

	Events	HR (95% CI)	*P*
Pembro + Chemo	54.7%	0.56 (0.45-0.70)	<0.0001
Placebo + Chemo	70.1%		



BICR, blinded, independent central review. Data cutoff date: Apr 3, 2018.

Conclusions ASCO 2018

KEYNOTE 042: Carbo/Pem vs Pembro [PD-L1 >1%].

Better OS except group PDL-1: 1-49%

IMPOWER 150: Carbo/Paclit/Bev/Atezo vs SOC.

Better OS across all levels of PD-L1

IMPOWER 131: (SQCC) Carbo/Nab-Pac/Atezo vs SOC

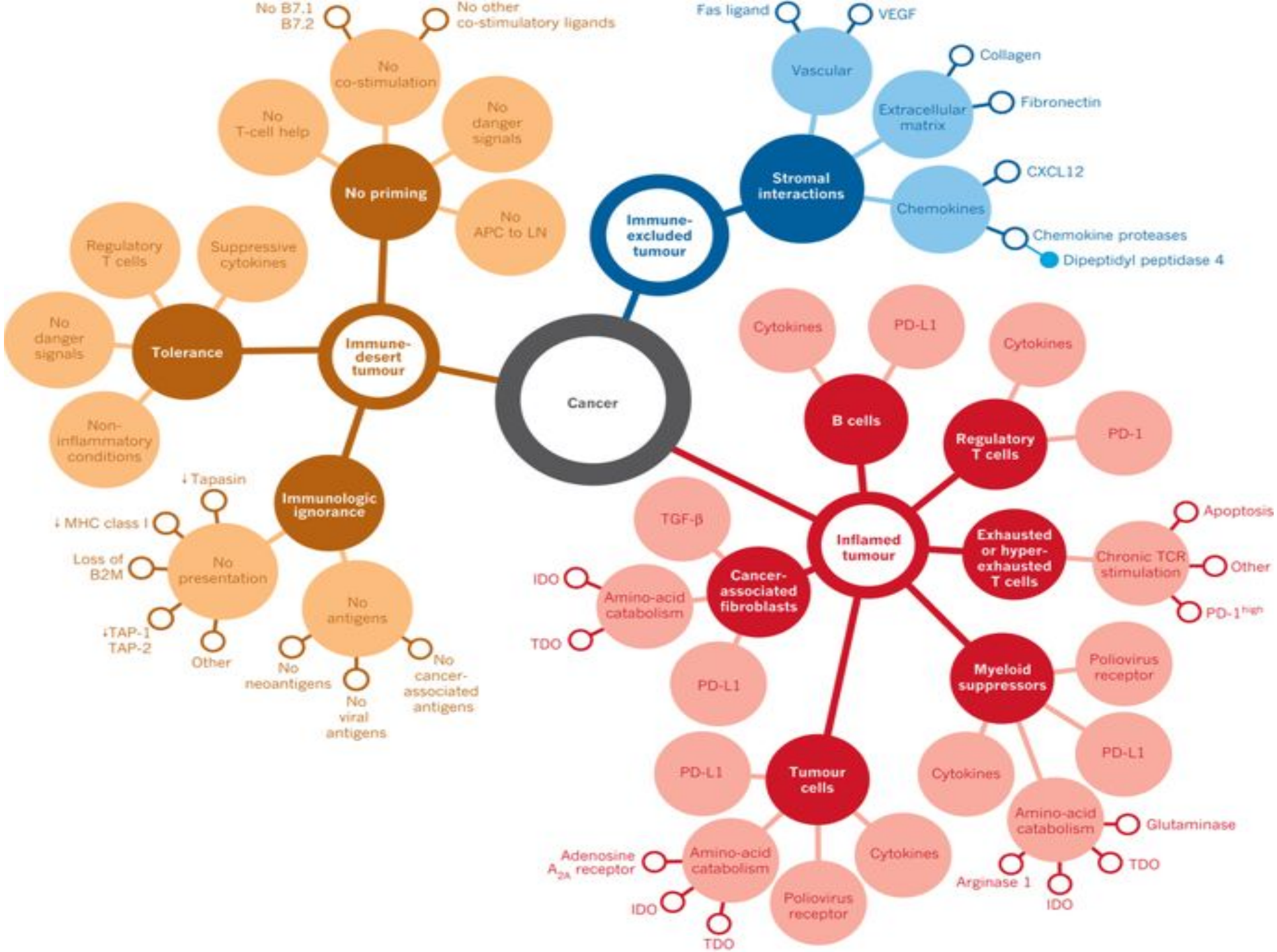
Better PFS, potential new SOC

KEYNOTE 407: (SQCC) Carbo/Paclit or Nab/Pembro vs SOC

Better OS all PD-L1 groups (NEW SOC)

Adds to KEYNOTE 189: Carbo/Pem/Pem for NSQCC and

Checkmate 227: Ipi+Nivo better PFS for all in pts high TMB


Cancer
Immune-desert tumour
Immune-excluded tumour
Inflamed tumour
Tolerance
Immunologic ignorance
No priming
No co-stimulation
No T-cell help
No danger signals
No APC to LN
No B7.1 B7.2
No other co-stimulatory ligands
Regulatory T cells
Suppressive cytokines
No danger signals
Non-inflammatory conditions
↓Tapasin
↓MHC class I
Loss of B2M
No presentation
↓TAP-1 TAP-2
Other
No antigens
No neoantigens
No viral antigens
No cancer-associated antigens
Stromal interactions
Fas ligand
VEGF
Vascular
Collagen
Extracellular matrix
Fibronectin
Chemokines
CXCL12
Chemokine proteases
Dipeptidyl peptidase 4
B cells
Cytokines
PD-L1
Regulatory T cells
Cytokines
PD-1
Exhausted or hyper-exhausted T cells
Chronic TCR stimulation
Apoptosis
Other
PD-1high
Cancer-associated fibroblasts
TGF-β
IDO
Amino-acid catabolism
TDO
PD-L1
Myeloid suppressors
Poliovirus receptor
PD-L1
Tumour cells
PD-L1
Adenosine A2A receptor
Amino-acid catabolism
IDO
TDO
Cytokines
Poliovirus receptor
Cytokines
Amino-acid catabolism
Glutaminase
Arginase 1
IDO
TDO

What is new for Immunotherapy in NSCLC

- Deacetylase Inhibitors
- Vaccines (Heat shock Protein gp96)
- STK11/LKB1 and KEAP
- Cytokines
- Adenosine pathway
- Combination checkpoints
- Adoptive T cell therapies (TILs, TILs + anti PD(L)-1, TCRs)
- B-catenin pathway

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG
#WCLC2018

Efficacy/safety of entinostat and pembrolizumab in NSCLC patients previously treated with anti-PD-(L)1 therapy

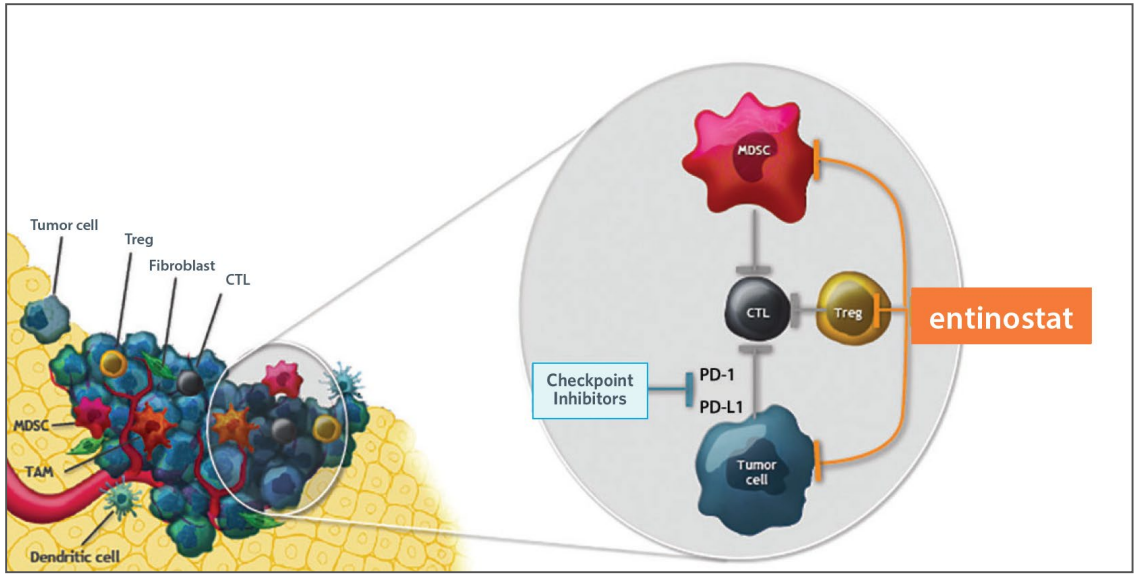
Matthew D. Hellmann[1], Pasi A. Jänne[2], Mateusz Opyrchal[3], Navid Hafez[4], Luis E. Raez[5], Dmitry Gabrilovich[6], Fang Wang[6], Peter Ordentlich[7], Susan Brouwer[7], Serap Sankoh[7], Emmett Schmidt[8], Michael L. Meyers[7], Suresh S. Ramalingam[9]

[1]Memorial Sloan Kettering Cancer Center, New York, USA, [2]Dana-Farber Cancer Institute, Boston, MA, USA, [3]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA, [4]Yale Cancer Center, New Haven, CT, USA, [5]Memorial Cancer Institute, Pembroke Pines, FL, USA, [6]The Wistar Institute, Philadelphia, PA, USA, [7]Syndax Pharmaceuticals, Inc., Waltham, MA, USA, [8]Merck & Co., Inc., Kenilworth, NJ, USA, [9]The Winship Cancer Institute of Emory University, Atlanta, GA, USA

WCLC 2018

Treatment options are limited for patients with NSCLC whose disease has progressed on anti-PD-(L)1 therapy[1]

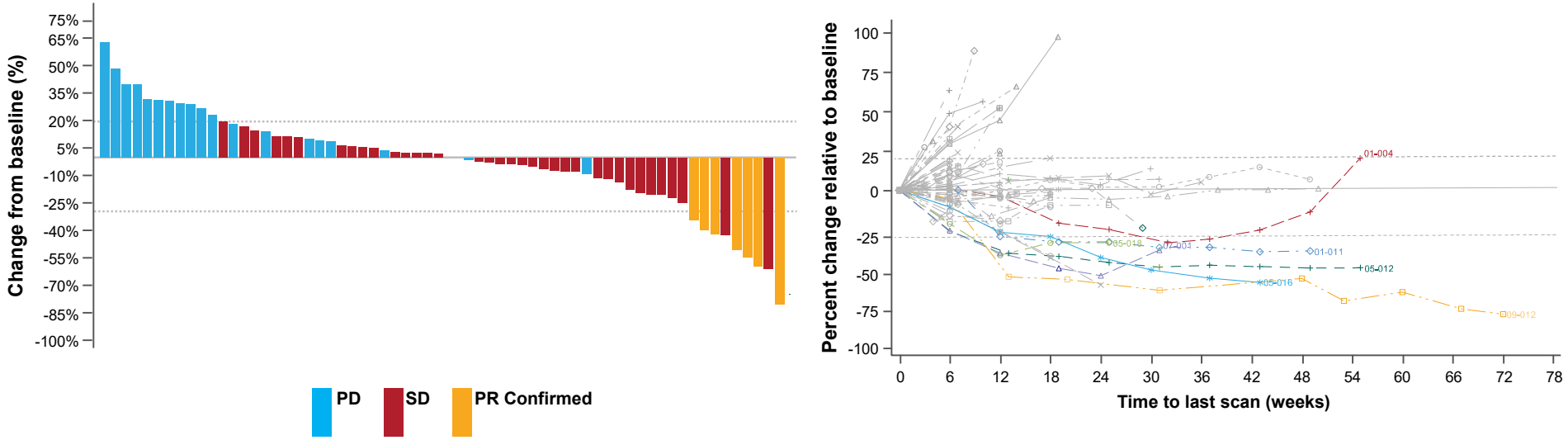
- Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor[2]
- ENT leads to downregulation of immunosuppressive cell types in the tumor microenvironment[2]
- Synergy with anti-PD1 inhibition in preclinical models[2]
- Promising activity shown in combination with pembrolizumab in patients with melanoma and lung cancer[3,4]



NSCLC, non-small cell lung cancer.

1. Zimmer L, et al. *Eur J Cancer*. 2017;75:47-55. **2.** Orillion A, et al. *Clin Cancer Res*. 2017;23:5187-5201. **3.** Agarwala SS, et al. Presented at ASCO 2018. Abstract 9530. **4.** Gandhi L, et al. Presented at ASCO 2018. Abstract 9036.

Durable responses were observed in patients who experienced progression on prior anti-PD(L)1 therapy



- Objective response rate with ENT + PEMBRO was 10% (7 of 72, 95% CI: 4-19%)
  - Median duration of response was 5.3 months
  - An additional 50% of patients achieved disease stabilization
- Median progression-free survival = 2.8 months (95% CI: 2.1-4.1)

CI, confidence interval; ENT, entinostat; PEMBRO, pembrolizumab; PD, progressive disease; PR, partial response; SD, stable disease.

Vol.2, No.1, 9-18 (2013)
doi:10.4236/alc.2013.21002

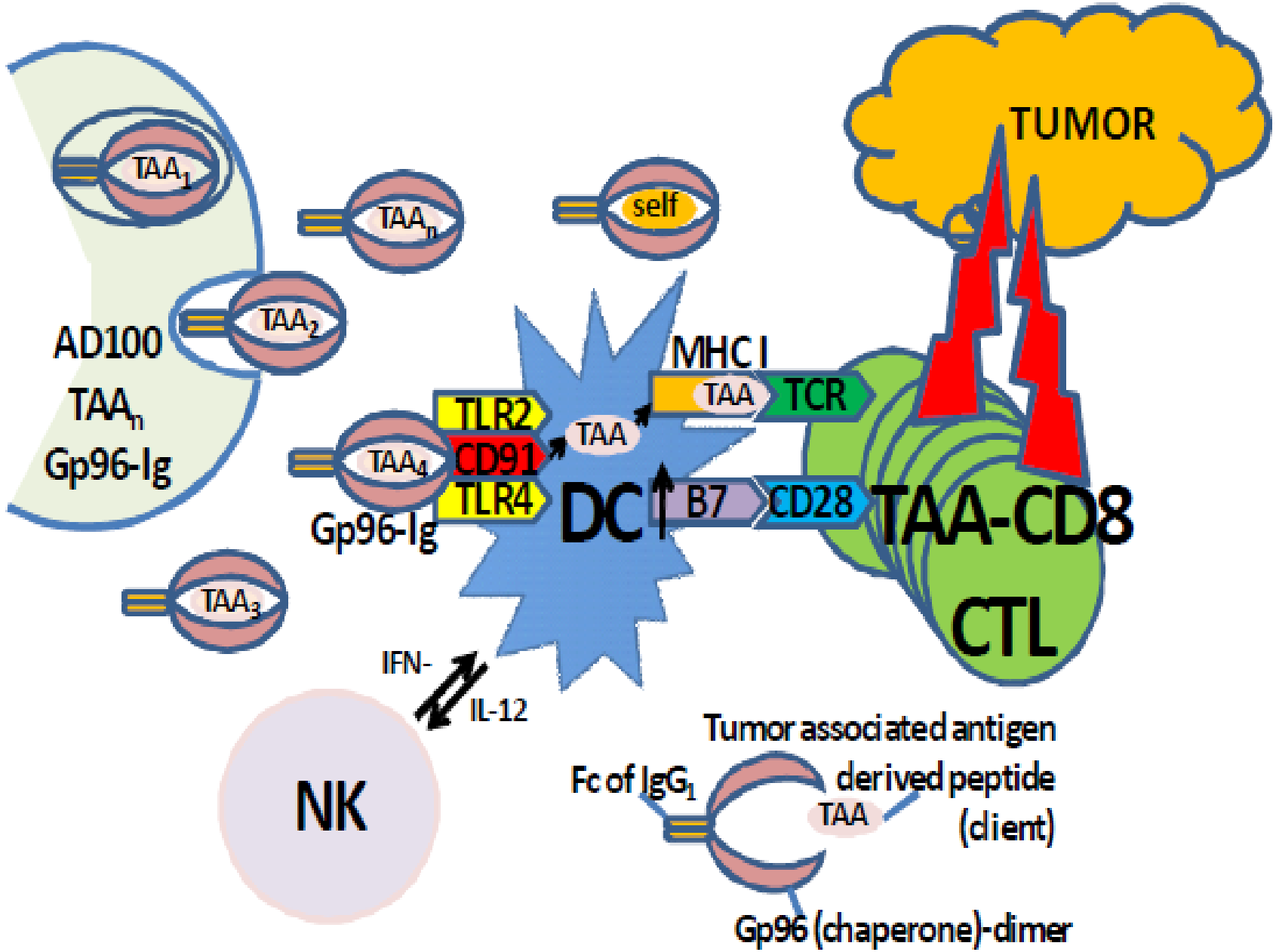
Advances in Lung Cancer

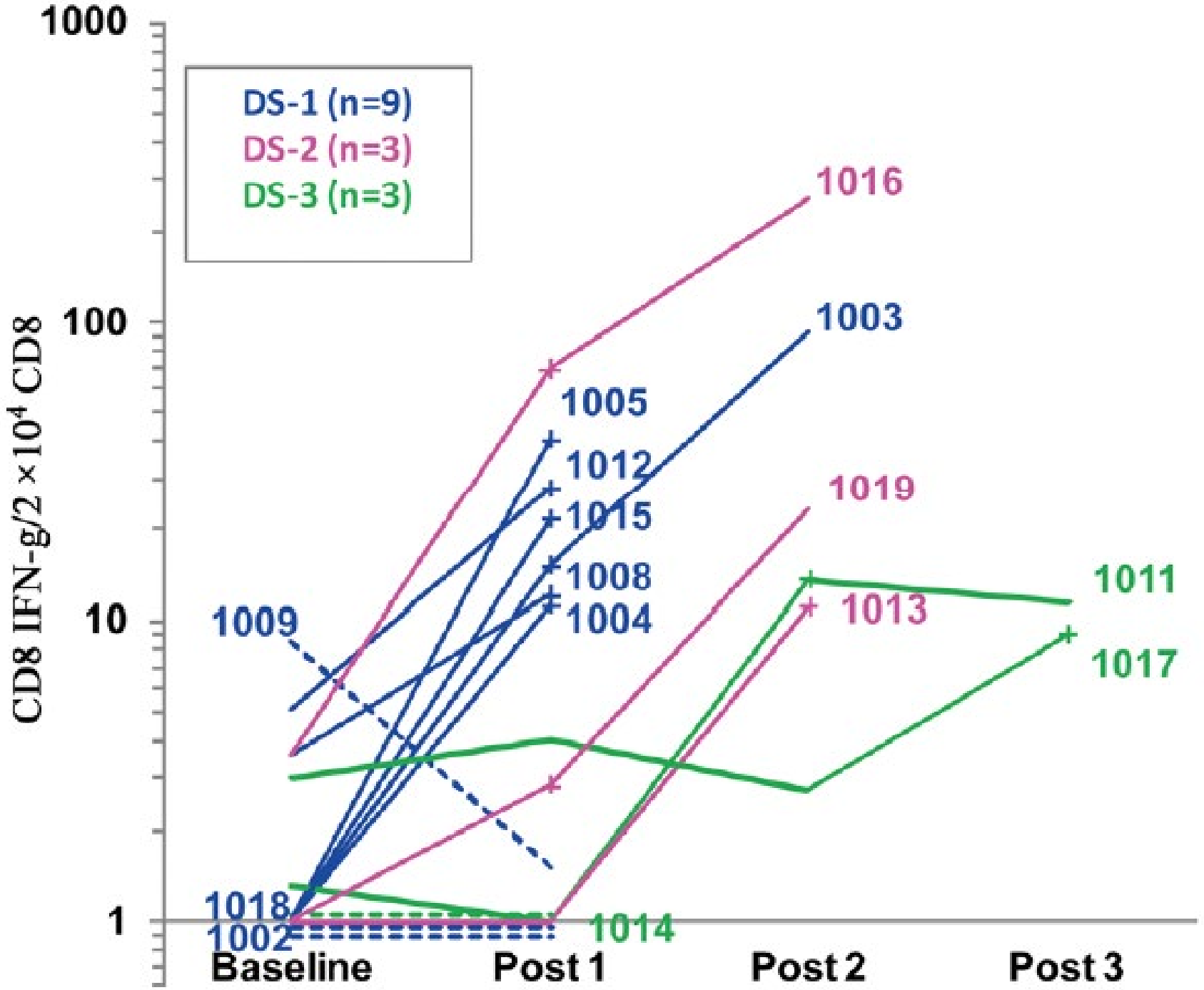
CD8 T cell response in a phase I study of therapeutic vaccination of advanced NSCLC with allogeneic tumor cells secreting endoplasmic reticulum-chaperone gp96-Ig-peptide complexes*

Luis E. Raez[1], Gail R. Walker[2], Paulette Baldie[1], Eva Fisher[3], Jorge E. Gomez[1], Khaled Tolba[1], Edgardo S. Santos[1], Eckhard R. Podack[3#]

[1]Department of Medicine, Division of Hematology/Oncology, University of Miami, Miller School of Medicine, Miami, USA
[2]Sylvester Comprehensive Cancer Center, Biostatistics Core Facility, University of Miami, Miller School of Medicine, Miami, USA
[3]Department of Microbiology and Immunology, University of Miami, Miller School of Medicine, Miami, USA;
[#]Corresponding Author: epodack@miami.edu

Received 21 December 2012; revised 22 January 2013; accepted 8 February 2013


TUMOR
TAA1
TAAn
self
AD100
TAAn
Gp96-Ig
TAA2
MHC I
TAA
TCR
TLR2
CD91
TLR4
TAA
TAA4
Gp96-Ig
DC
B7
CD28
TAA-CD8
CTL
TAA3
IFN-
IL-12
NK
Tumor associated antigen
derived peptide
(client)
Fc of IgG1
TAA
Gp96 (chaperone)-dimer


1000
100
10
1
CD8 IFN-g/2 ×10⁴ CD8
DS-1 (n=9)
DS-2 (n=3)
DS-3 (n=3)
1016
1003
1005
1012
1015
1008
1004
1009
1019
1013
1011
1017
1018
1002
1014
Baseline
Post 1
Post 2
Post 3

STK11/LKB1 mutation

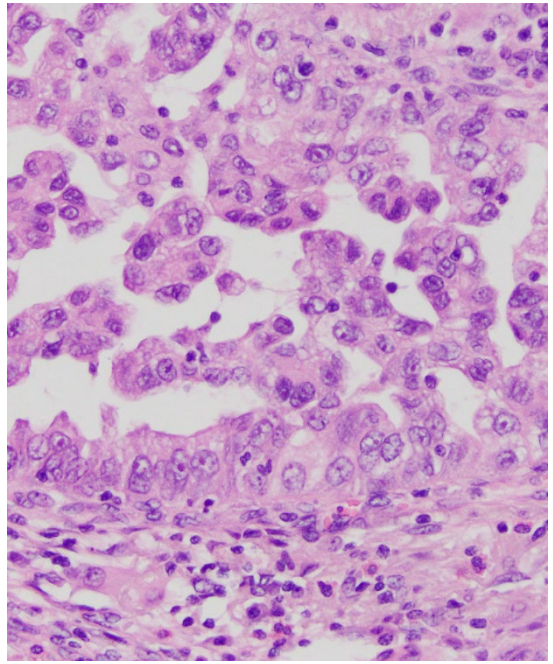
Enriched in KRAS-mutated adenocarcinomas

Generally exclusive of TP53 mutations

Associated with loss of LKB1 protein expression

A negative prognostic indicator

Promotes neutrophil recruitment and suppresses T cell activity

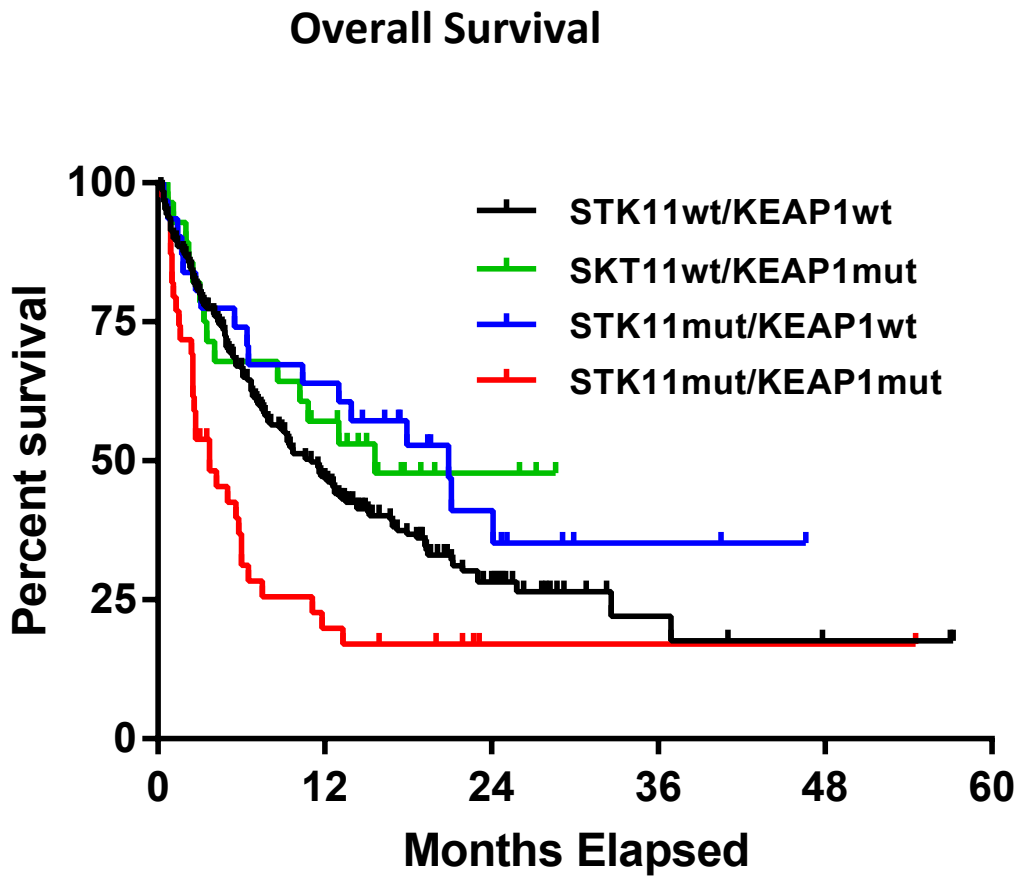


Calles et al. Clin Cancer Res. 2015 Jun 15;21(12):2851-60. Koyama et al. Cancer Res. 2016 Mar 1;76(5):999-1008.

Retrospective single center analysis.

In 308 patients who have received PD-1/PD-L1 therapy (majority at ≥2nd line), those with STK11/KEAP1 mut (n=39):

- Were almost universally smokers
- Showed significantly worse OS and PFS than WT tumors
  -despite significantly higher TMB than WT tumors (9.4 vs 6.1 mut/mb)
- In a separate cohort of tumors, STK11/KEAP1 mut and STK11mut/KEAP1WT patients have low PD-L1 expression



Memorial Regional Hospital | Memorial Regional Hospital South | Joe DiMaggio Children's Hospital
Memorial Hospital West | Memorial Hospital Miramar |Memorial Hospital Pembroke