Immunotherapy for Metastatic Non-Small Cell Lung Cancer

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

Memorial Cancer Institute

CANCER CENTER of EXCELLENCE
Florida HEALTH

First Line Lung Cancer Therapy with no actionable genes

NSQCC:

- Carboplatin/Pemetrexed/Pembrolizumab [Keynote 189]
- Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab [IMPOWER 150]

SQCC:

- Carboplatin/Paclitaxel or nab-paclitaxel/Pembrolizumab [Keynote 407]

NSQCC and SQCC:

- Cemiplimab/Chemotherapy [Empower Lung-3]

IO single Agent (NSQCC OR SQCC)

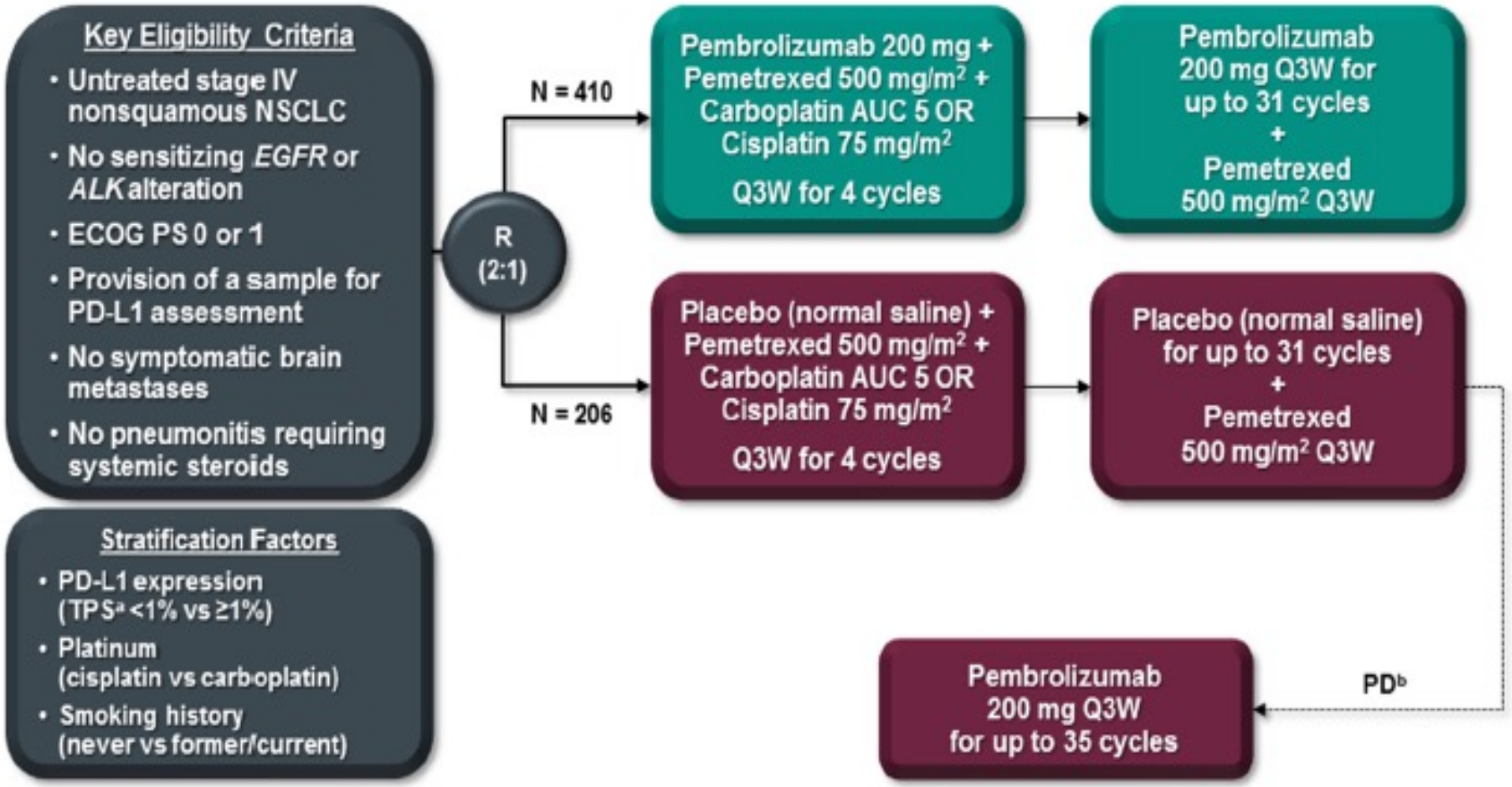
- Pembrolizumab [Keynote 024 and 042]
- Atezolizumab [IMPOWER 110]
- Cemiplimab [Empower Lung-1]

Immunotherapy combinations:

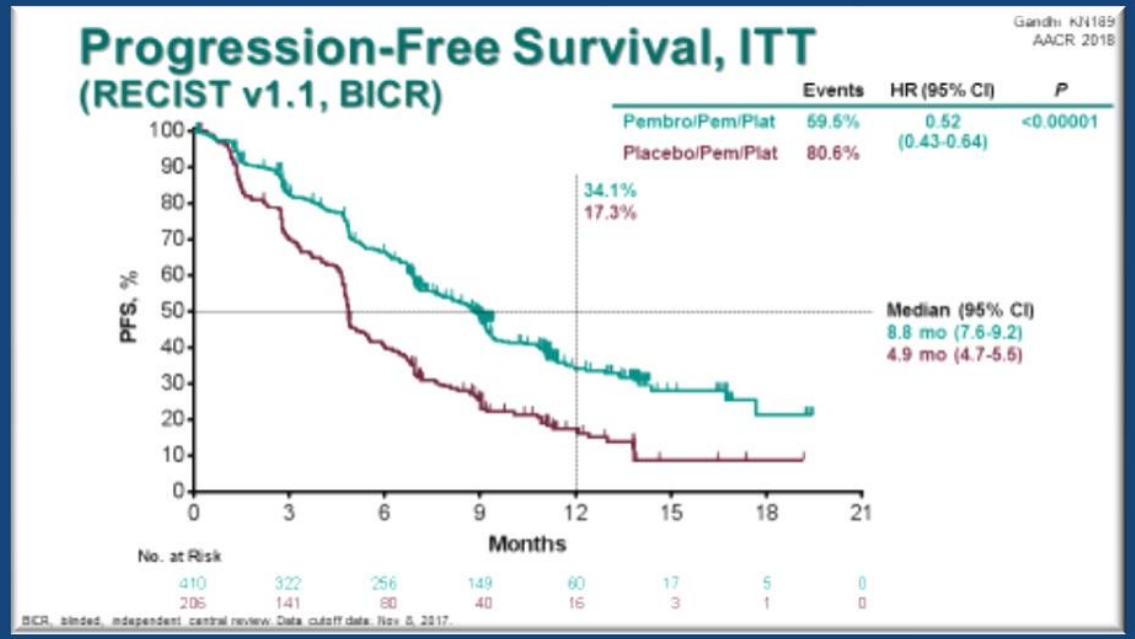
- Ipilimumab and Nivolumab [Checkmate 227]
- Ipilimumab and Nivolumab plus 2 cycles of chemotherapy [Checkmate 9LA]

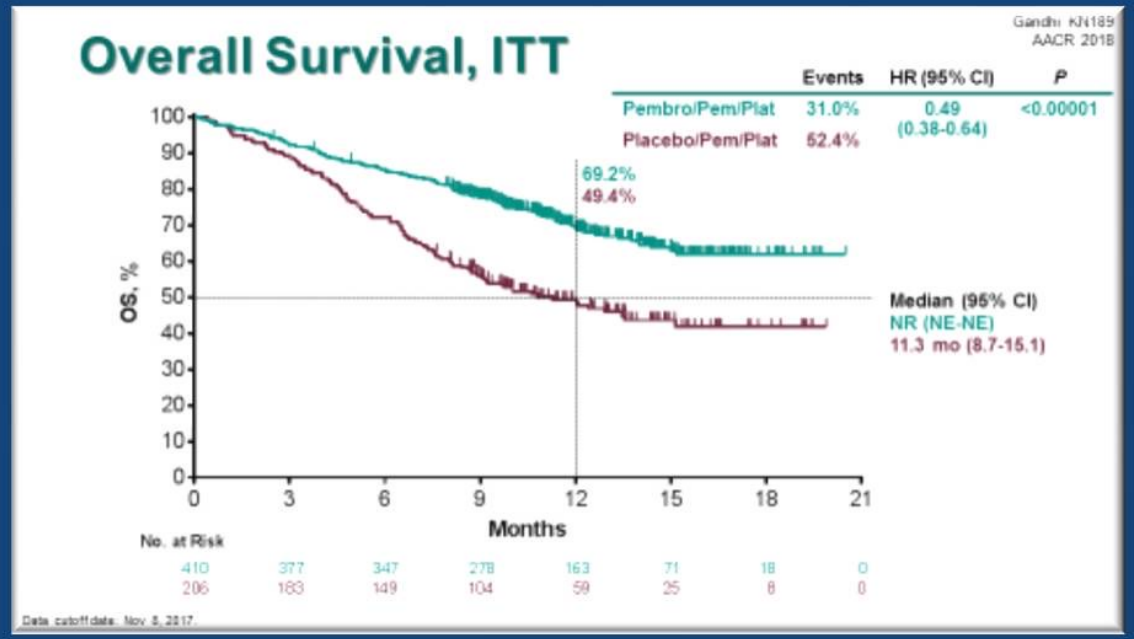
KEYNOTE 189

RANDOMIZED, DOUBLE-BLIND, PHASE III STUDY OF PLATINUM+PEMETREXED CHEMOTHERAPY WITH OR WITHOUT PEMBROLIZUMAB IN FIRST LINE METASTATIC NON-SQUAMOUS NON-SMALL CELL LUNG CANCER SUBJECTS



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*	

Slides are the property of the author, permission required for reuse.

ORR[a] and OS

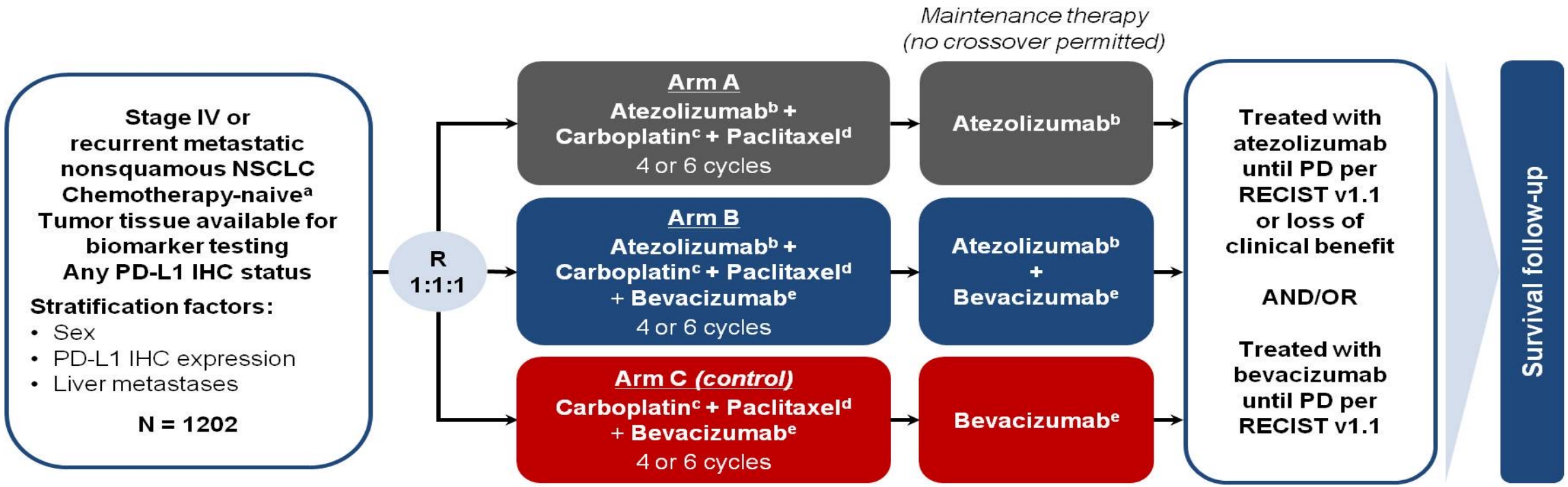
Patients Who Completed 35 Cycles (2 Years) of Pembrolizumab

Best response	N = 56
Objective response, n (%)	49 (87.5)
Best objective response, n (%)	
CR	6 (10.7)
PR	43 (76.8)
SD	7 (12.5)

- 2-year OS rate from completion of 35 cycles (2 years) was 79.6%
- At data cutoff, 45/56 patients (80.4%) were alive, 28 without PD
- 7 patients started second-course pembrolizumab
  - 2 had a second-course best response of SD by investigator assessment
  - 2 had best response of PD, and 3 were not assessed as of data cutoff

[a]Based on blinded independent central review per RECIST v1.1.
Data cutoff: August 28, 2020

IMpower150 Study Design

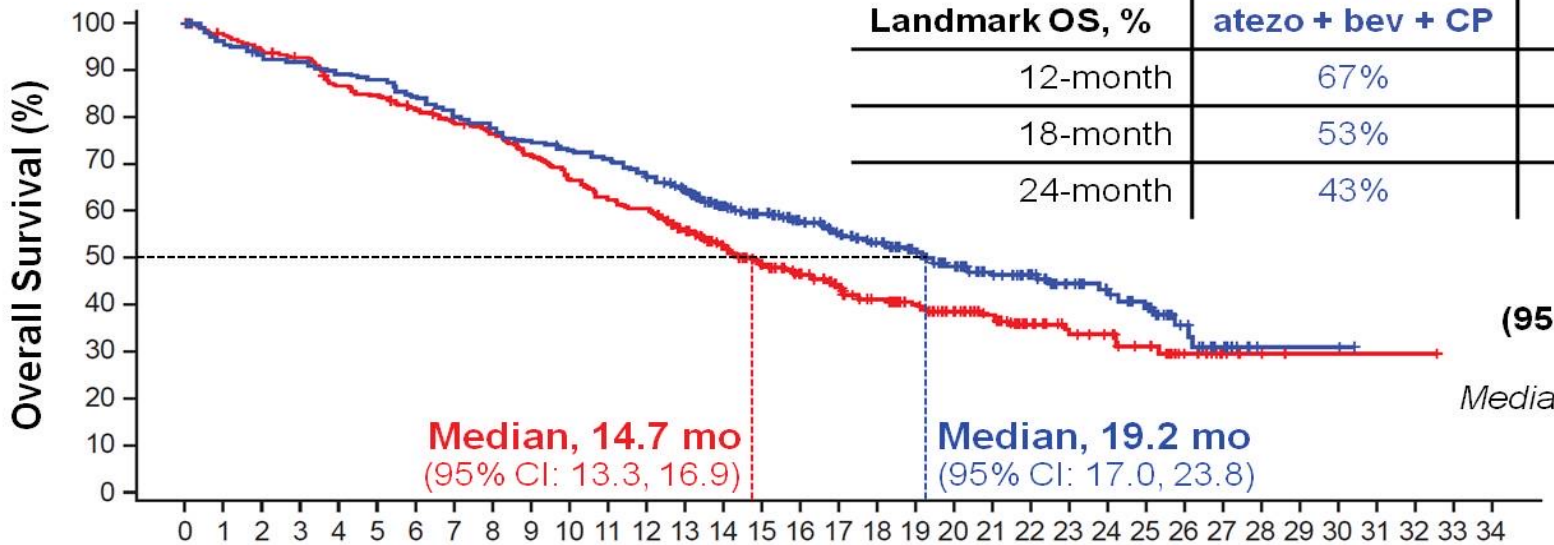


[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w. [d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg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

Slides are the property of the author, permission required for reuse.

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

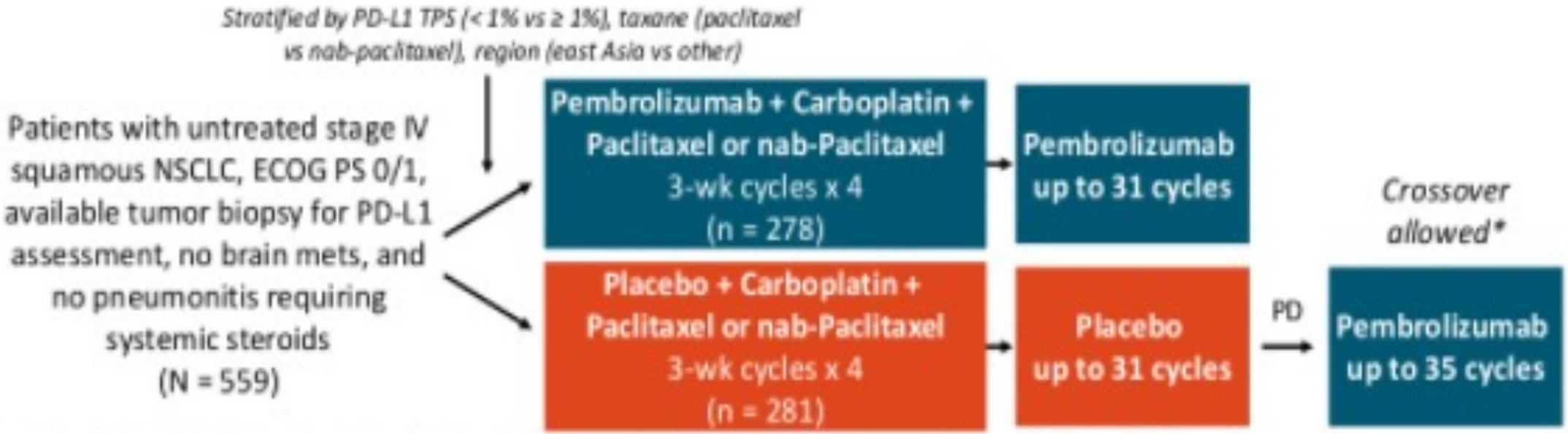
- Statistically significant and clinically meaningful OS benefit with atezolizumab + bevacizumab + chemotherapy vs bevacizumab + chemotherapy was observed

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

Slides are the property of the author, permission required for reuse.

KEYNOTE-407: Study Design

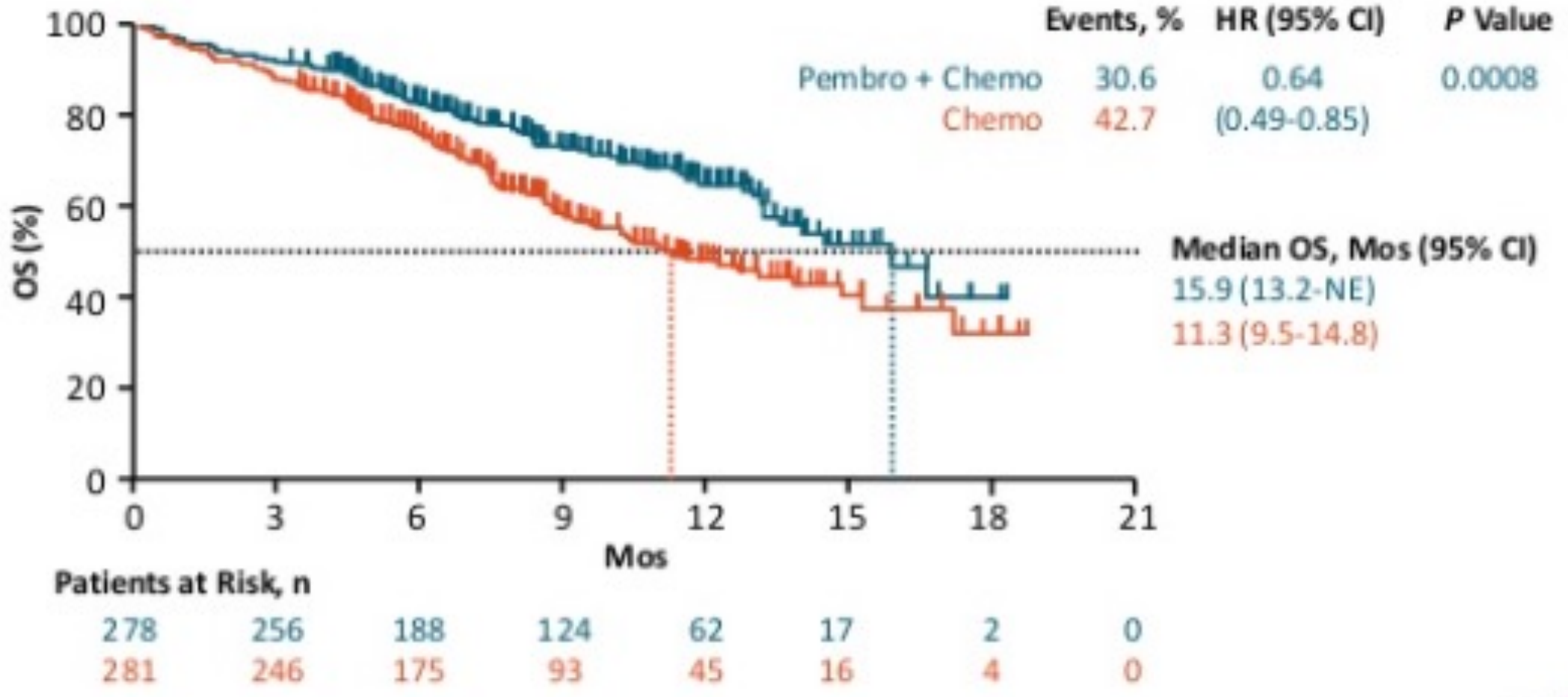
- Randomized, double-blind phase III trial



Carboplatin AUC 6 Q3W, nab-paclitaxel 100 mg/m^2 QW, paclitaxel 200 mg/m^2 Q3W, pembrolizumab 200 mg Q3W.
*Upon confirmation of PD and safety criteria by BICR, optional crossover could occur during combination or monotherapy.

- Primary endpoint: PFS by RECIST v1.1 (BICR), OS
- Secondary endpoints: ORR and DoR by RECIST v1.1 (BICR), safety

KEYNOTE-407: OS in ITT Population



EMPOWER

EMPOWER-Lung 3 (Part 2) Study Design (NCT03409614)

Background: Cemiplimab (a high-affinity, fully human anti–PD-1) is approved as first-line monotherapy for advanced NSCLC with PD-L1 ≥50% (EMPOWER-Lung 1 Study[1])

Key eligibility criteria
- Treatment-naive advanced NSCLC (non-squamous and squamous histology; Stage IIIb/c[†], IV)
- Any PD-L1 expression
- No *EGFR*, *ALK*, or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases[‡]

Stratification factors
- PD-L1 expression: <1% vs 1–49% vs ≥50%
- Histology: non-squamous vs squamous

R 2:1

Arm A
Cemiplimab 350 mg Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles[§] → PD or 108 weeks

Arm B
Placebo Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles[§] → PD or 108 weeks

Follow-up

Endpoints
- Primary: OS
- Key secondary: PFS and ORR
- Additional secondary: DOR, BOR, safety, and PRO

N=466

Two interim analyses were prespecified per protocol
Second interim analysis (14 June 2021) presented here

[†]Patient not a candidate for definitive chemoradiation. [‡]Patient must have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). [§]For patients with non-squamous NSCLC, pemetrexed is mandatory as maintenance therapy for those patients initially assigned to receive a pemetrexed-containing regimen. *ALK*, anaplastic lymphoma kinase gene; BOR, best overall response; chemo, chemotherapy; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor gene; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRO, patient-reported outcomes; Q3W, every 3 weeks; R, randomised; *ROS1*, c-ros oncogene 1.

1. Sezer A et al. Lancet 2021;397:592–604.

2021 ESMO congress

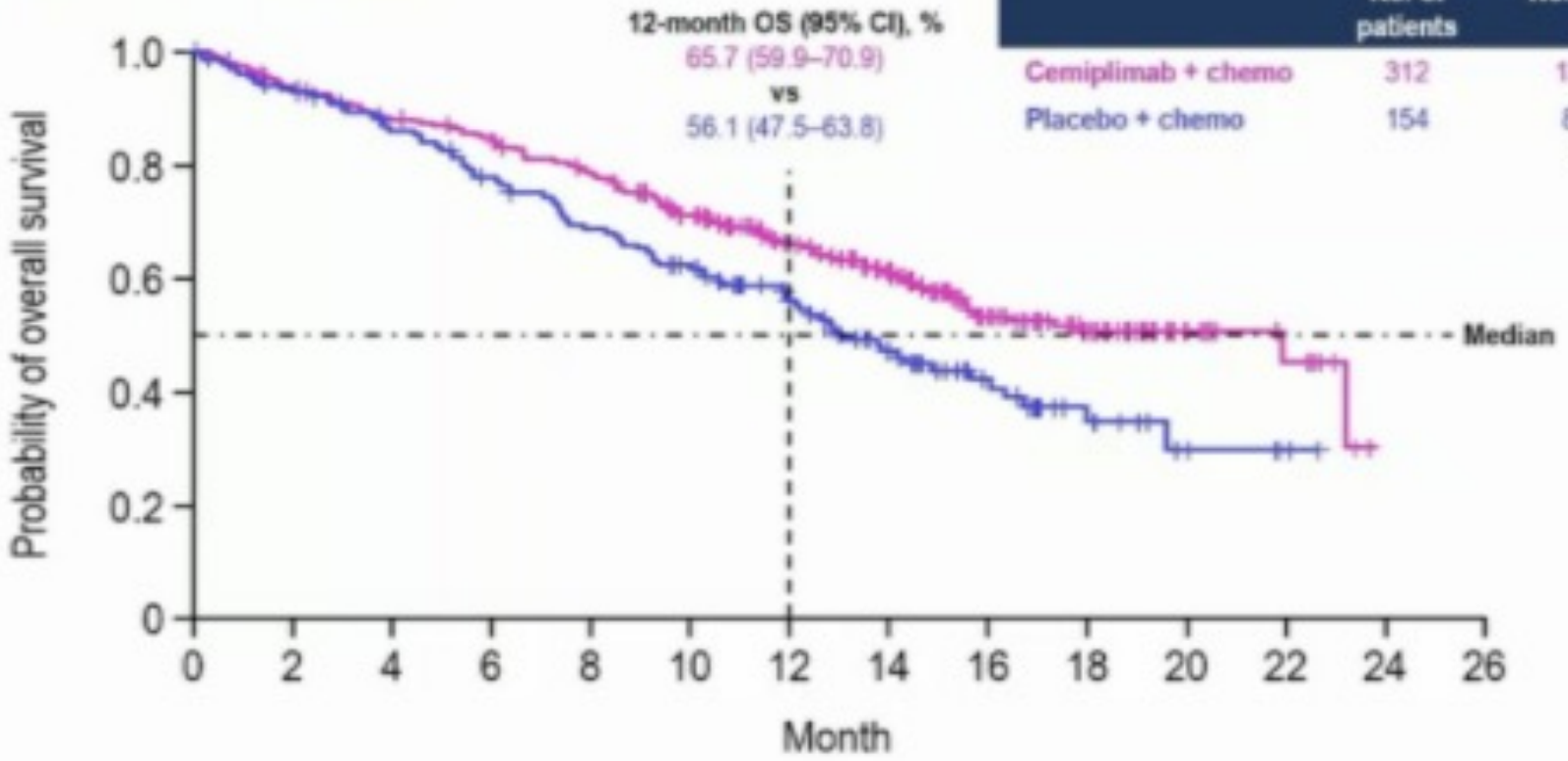
EMPOWER

Overall Survival

Median duration of follow-up (range): 16.4 (8.5–24.0) months

	No. of patients	No. of events, n (%)	OS, median (95% CI), months
Cemiplimab + chemo	312	132 (42.3)	21.9 (15.5–NE)
Placebo + chemo	154	82 (53.2)	13.0 (11.9–16.1)

HR (95% CI) = 0.71 (0.53–0.93); *P*=0.014



No. at risk:

Cemiplimab + chemo	312	289	269	256	233	199	162	131	86	52	18	8	0	0
Placebo + chemo	154	141	126	112	98	85	65	46	26	14	5	2	0	0

2021 ESMO congress

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival.

Data cut-off date:
14 June 2021

First Line Lung Cancer Therapy with no actionable genes

NSQCC:

- Carboplatin/Pemetrexed/Pembrolizumab [Keynote 189]
- Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab [IMPOWER 150]

SQCC:

- Carboplatin/Paclitaxel or nab-paclitaxel/Pembrolizumab [Keynote 407]

NSQCC OR SQCC

- Pembrolizumab [Keynote 024 and 042]
- Atezolizumab [IMPOWER 110]
- Cemiplimab **

Immunotherapy combinations:

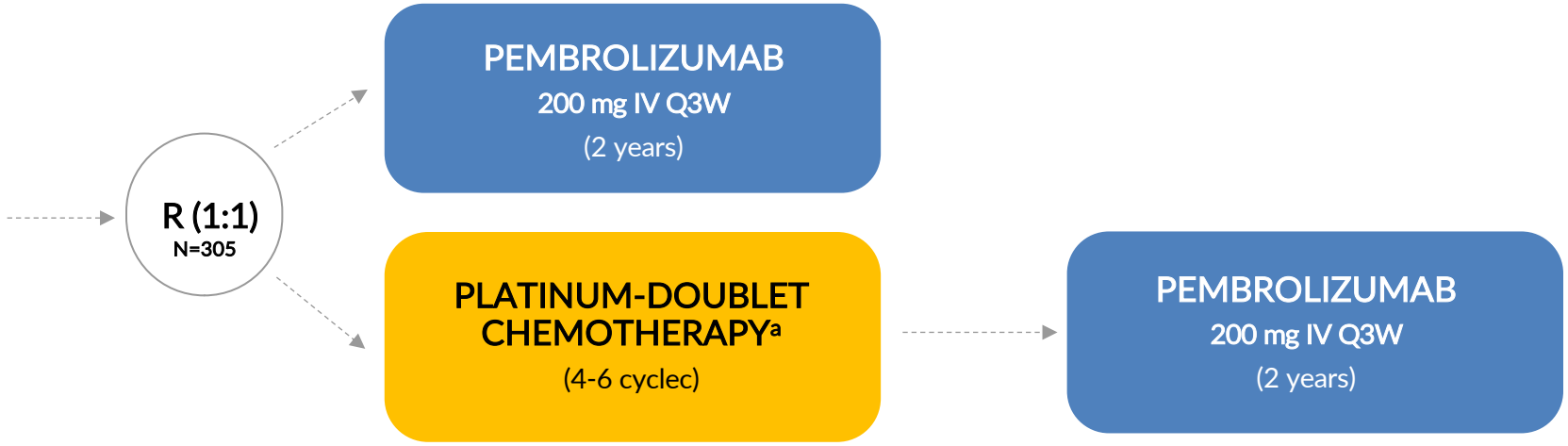
- Ipilimumab and Nivolumab [Checkmate 227]
- Ipilimumab and Nivolumab plus 2 cycles of chemotherapy [Checkmate 9LA]

KEYNOTE 024

PD-L1 >50%

KEY ELIGIBILITY CRITERIA

- Untreated stage IV NSCLC
- PD-L1 PS 0-1
- No activating EGFR mutation or ALK translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy



Primary endpoint

- PFS (RECIST v1.1, blinded independent central review)

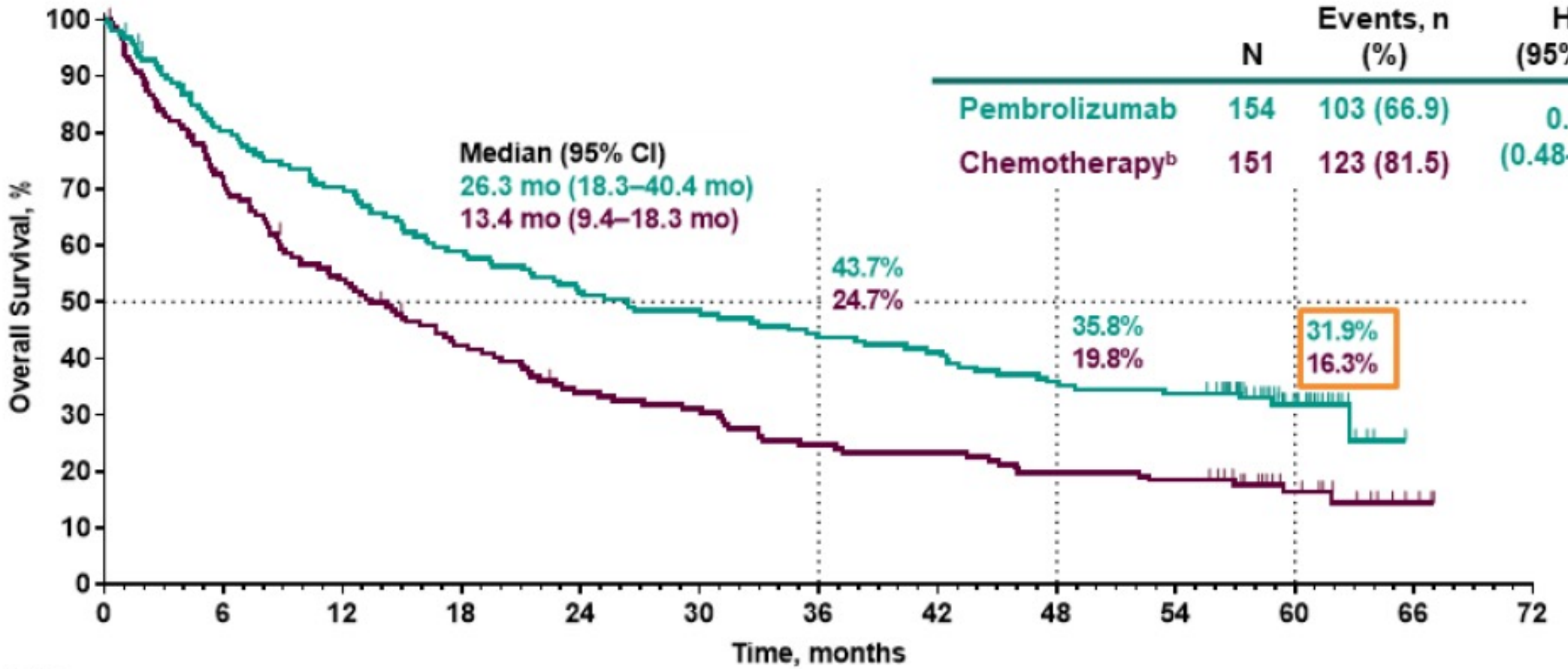
Secondary endpoint

- OS, ORR, Safety

Exploratory endpoint

- DOR, PFS2

Overall Survival[a]



[a]ITT population.

[b]Effective crossover rate from chemotherapy to anti–PD-(L)1 therapy, 66.0% (99 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti–PD-[L]1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-[L]1 therapy). Data cutoff: June 1, 2020.

KEYNOTE 042

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%)

R
(1:1)

N=637

PEMBROLIZUMAB
200 mg IV Q3W
For up to 35 cycles

N=637

CARBOPLATIN
AUC 5 or 6 Q3W +

PACLITAXEL
200mg/m² Q3W[a]

OR

CARBOPLATIN
AUC 5 or 6 Q3W +

PEMETREXED
500mg/m² Q3W[a]
for up to 6 cycles

Primary endpoint

- OS in PD-L1 TPS ≥50%, ≥20%, and ≥1%

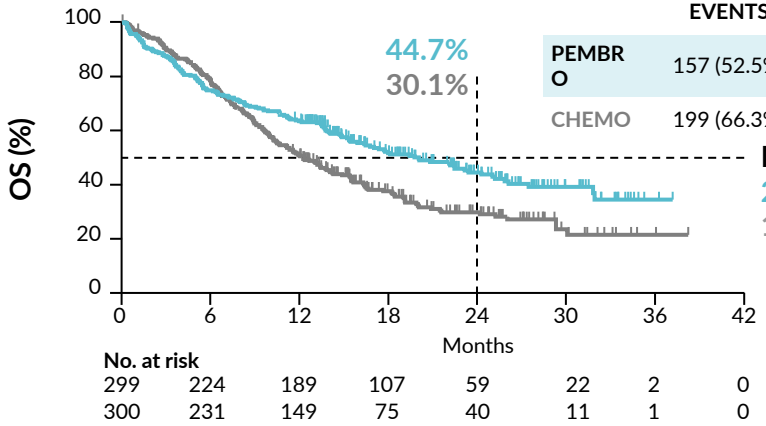
Secondary endpoint

- PFS and ORR in TPS ≥50%, ≥20%, and ≥1%; safety in TPS ≥1%

Lopes G, et al. ASCO 2018. Abstract LBA4.

KEYNOTE 042

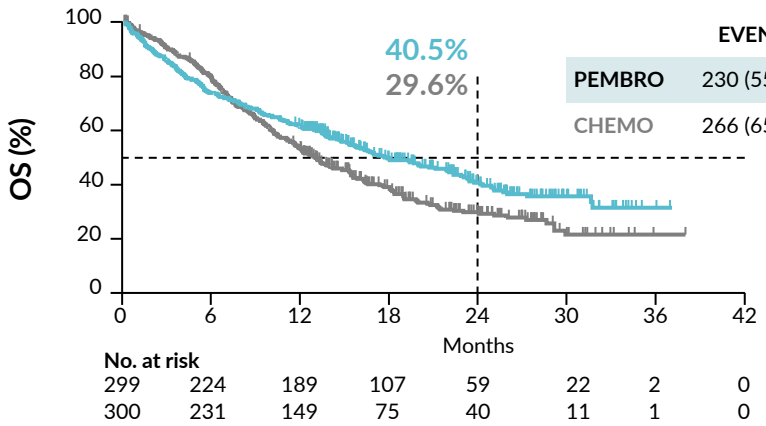
OVERALL SURVIVAL: TPS ≥50%



	EVENTS	HR (95% CI)	P
PEMBRO	157 (52.5%)	0.69 (0.56-0.85)	0.0003
CHEMO	199 (66.3%)		

MEDIAN (95% CI)
20.0 MO (15.4-24.9)
12.2 MO (10.4-14.2)

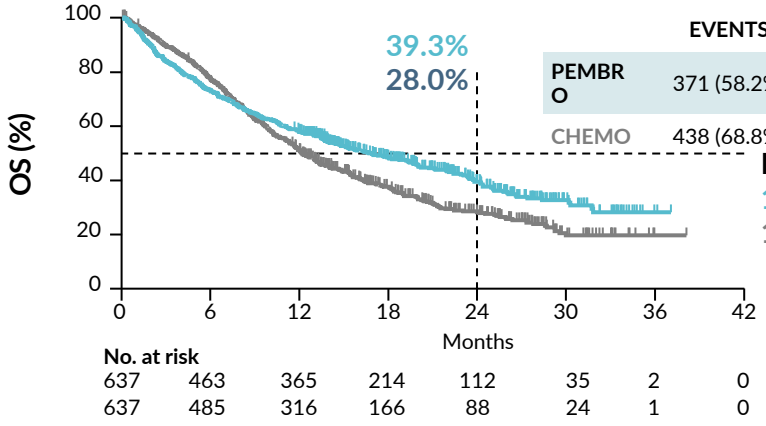
OVERALL SURVIVAL: TPS ≥20%



	EVENTS	HR (95% CI)	P
PEMBRO	230 (55.7%)	0.77 (0.64-0.92)	0.0020
CHEMO	266 (65.7%)		

MEDIAN (95% CI)
17.7 MO (15.3-22.1)
13.0 MO (11.6-15.3)

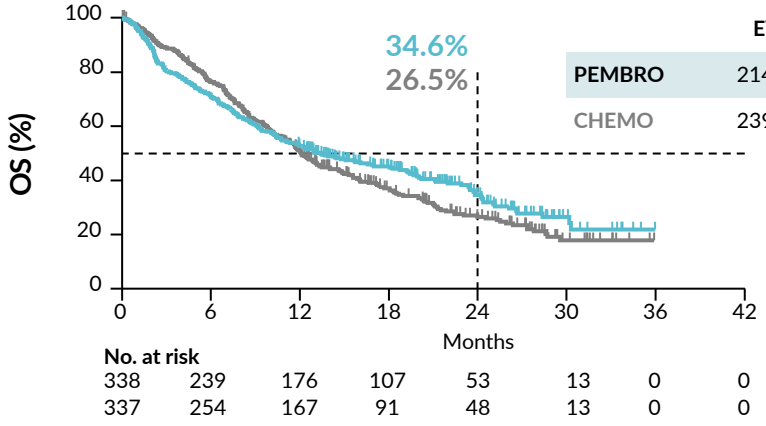
OVERALL SURVIVAL: TPS ≥1%



	EVENTS	HR (95% CI)	P
PEMBRO	371 (58.2%)	0.81 (0.71-0.93)	0.0018
CHEMO	438 (68.8%)		

MEDIAN (95% CI)
16.7 MO (13.9-19.7)
12.1 MO (11.3-13.3)

OVERALL SURVIVAL: TPS ≥1-49% (EXPLORATORY ANALYSIS[A])

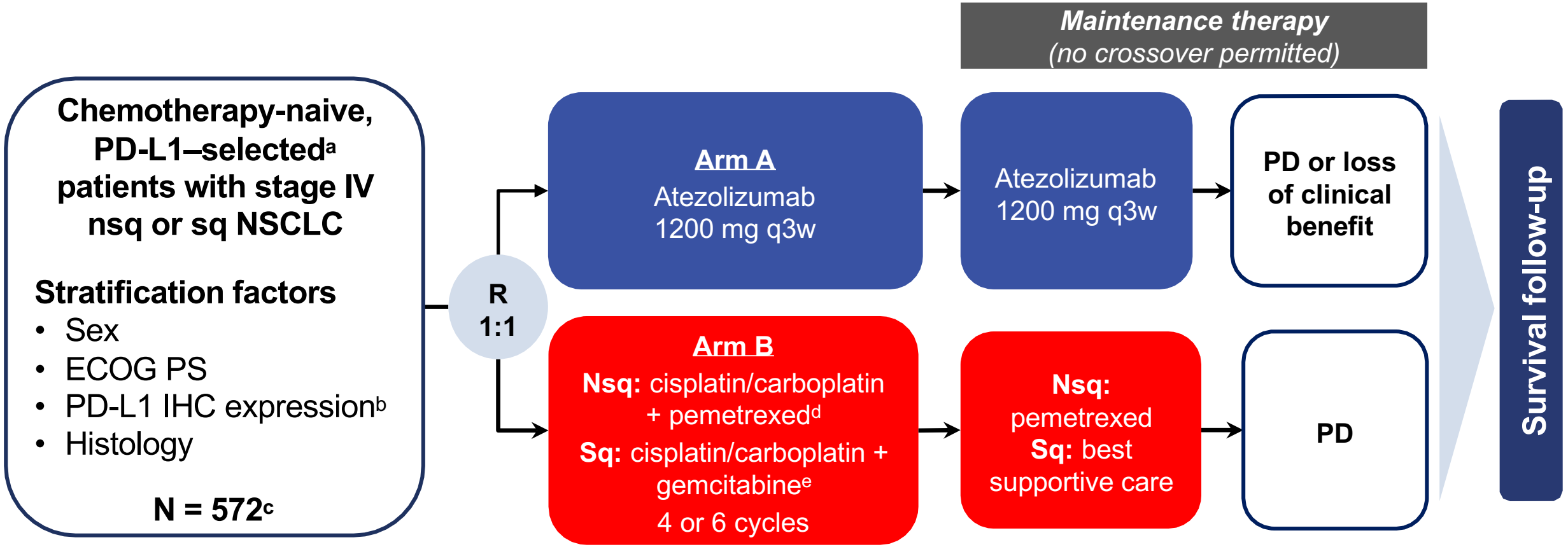


	EVENTS	HR (95% CI)
PEMBRO	214 (63.3%)	0.92 (0.77-1.11)
CHEMO	239 (70.9%)	

MEDIAN (95% CI)
13.4 MO (10.7-18.2)
12.1 MO (11.0-14.0)

Lopes G, et al. ASCO 2018. Abstract LBA4.

IMpower110 Study Design



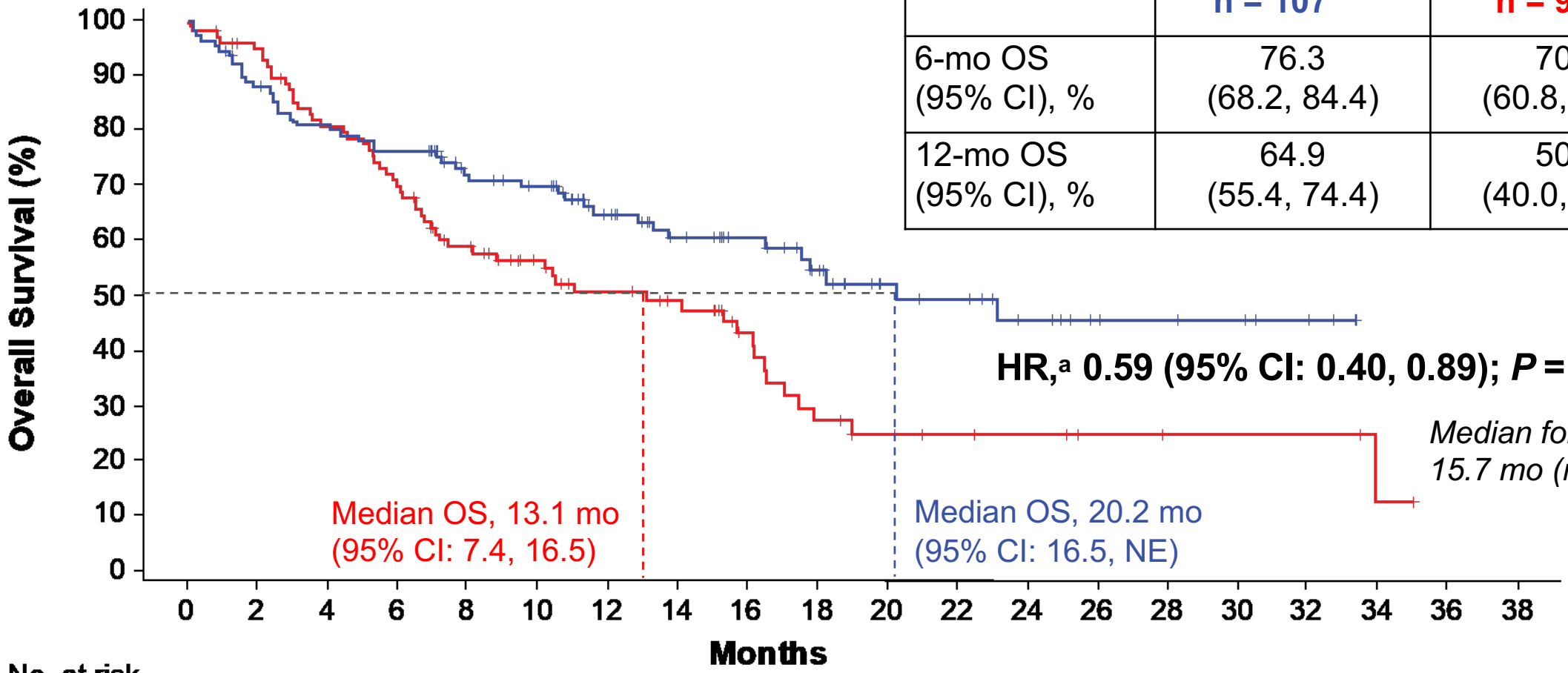
- Primary endpoint: OS in WT population[f]
- Key secondary endpoints: investigator-assessed PFS, ORR and DOR (per RECIST version 1.1)

IC, tumour-infiltrating immune cells; IHC, immunohistochemistry; nsq, non-squamous; PD, progressive disease; q3w, every 3 weeks; R, randomised; sq, squamous; TC, tumour cells; WT, wild-type. [a] PD-L1 expression (VENTANA SP142 IHC assay) ≥ 1% on TC or IC. [b] TC1/2/3 and any IC vs TC0 and IC1/2/3. [c] 554 patients in the WT population. [d] Cisplatin 75 mg/m^2 or carboplatin area under the curve (AUC) 6 + pemetrexed 500 mg/m^2 IV q3w. [e] Cisplatin 75 mg/m^2 + gemcitabine 1250 mg/m^2 or carboplatin AUC 5 + gemcitabine 1000 mg/m^2 IV q3w. [f] WT population excludes patients with *EGFR*+ and/or *ALK*+ NSCLC.

Spigel et al. IMpower110 Interim OS Analysis https://bit.ly/2lxRNHQ

OS: TC3 or IC3 WT

Landmark	Arm A (atezo) n = 107	Arm B (chemo) n = 98
6-mo OS (95% CI), %	76.3 (68.2, 84.4)	70.1 (60.8, 79.4)
12-mo OS (95% CI), %	64.9 (55.4, 74.4)	50.6 (40.0, 61.3)



No. at risk

Atezolizumab	107	94	85	80	66	61	48	40	34	25	18	16	11	7	6	5	2	
Chemotherapy	98	89	75	65	50	40	33	28	19	12	9	7	6	4	3	3	3	1

NE, not estimable. [a] Stratified. [b] Stratified log-rank.
Data cutoff: 10 September 2018.

Spigel et al. IMpower110 Interim OS Analysis
https://bit.ly/2lxRNHQ

VIRTUAL 2020 ESMO congress

Key Eligibility Criteria
- Treatment-naïve advanced NSCLC
- PD-L1 ≥50%
- No *EGFR*, *ALK* or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases and controlled hepatitis B or C or HIV were allowed

Stratification Factors:
- Histology (squamous vs non-squamous)
- Region (Europe, Asia or ROW)

R 1:1

Arm A
Cemiplimab monotherapy IV
350 mg Q3W
Treat until PD or 108 weeks

PD → **Optional continuation of cemiplimab + 4 cycles of chemotherapy**

Arm B
4–6 cycles of investigator's choice chemotherapy

PD → **Optional crossover to cemiplimab monotherapy**

Follow-up

Endpoints:
- Primary: OS and PFS
- Secondary: ORR (key), DOR, HRQoL and safety

N=710

Five interim analyses were prespecified per protocol

Second interim analysis (1 March 2020) presented here

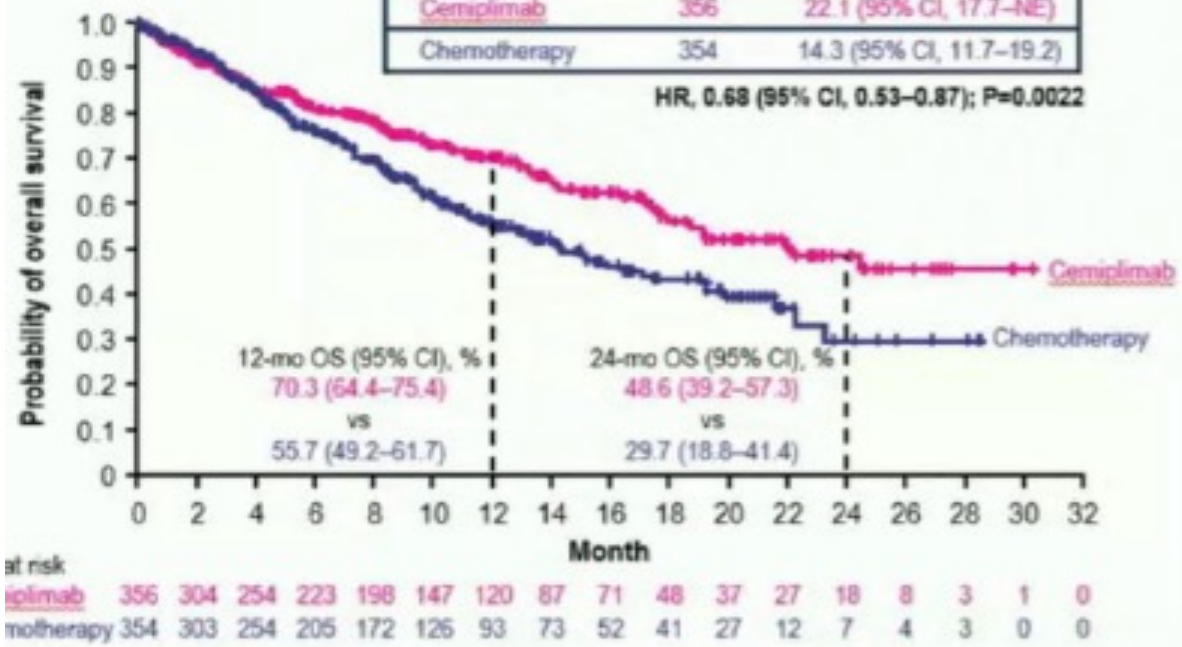
VIRTUAL 2020 ESMO congress

Top Line Survival Results

ITT

	No. of Patients	Median OS (95% CI) *mo*
Cemiplimab	356	22.1 (95% CI, 17.7–NE)
Chemotherapy	354	14.3 (95% CI, 11.7–19.2)

HR, 0.68 (95% CI, 0.53–0.87); P=0.0022



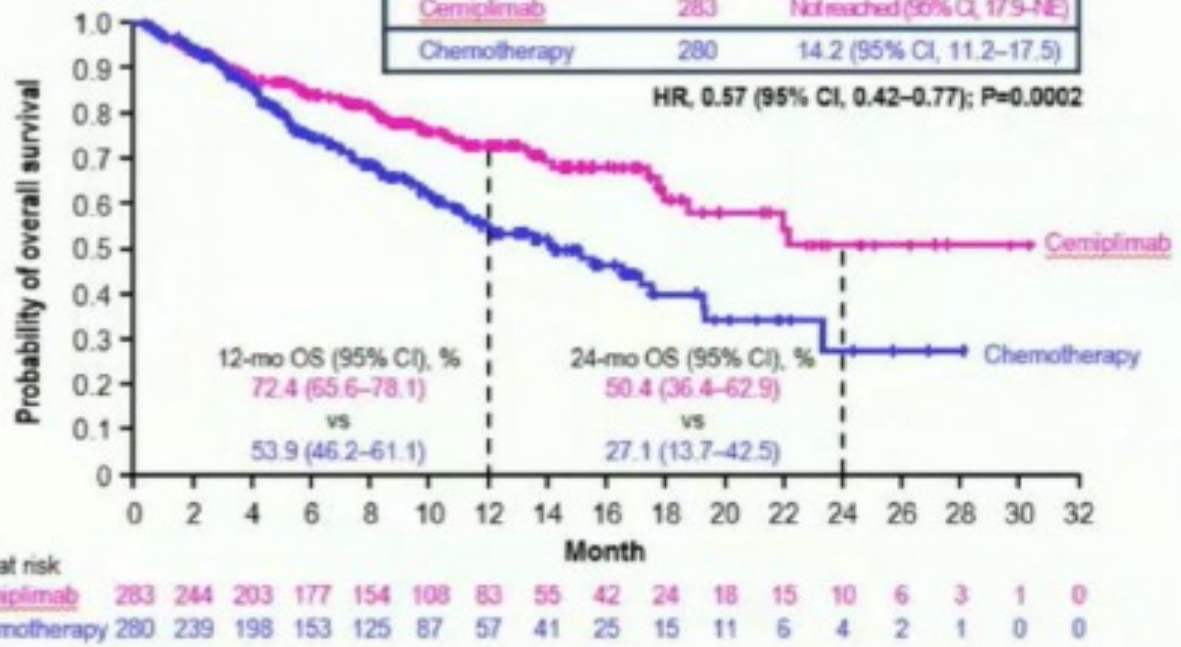
at risk

iplimab	356	304	254	223	198	147	120	87	71	48	37	27	18	8	3	1	0	
motherapy	354	303	254	205	172	126	93	73	52	41	27	12	7	4	3	0	0	

PD-L1 ≥50% ITT

	No. of Patients	Median OS (95% CI) *mo*
Cemiplimab	283	Not reached (95% CI, 17.9–NE)
Chemotherapy	280	14.2 (95% CI, 11.2–17.5)

HR, 0.57 (95% CI, 0.42–0.77); P=0.0002



No. at risk

Cemiplimab	283	244	203	177	154	108	83	55	42	24	18	15	10	6	3	1	0	
Chemotherapy	280	239	198	153	125	87	57	41	25	15	11	6	4	2	1	0	0	

Two Populations: In 235 patients the first PD-L1 assay had some issues and needed to be repeated. Of these, 88 were eventually included upon retest

A. Sezer EMPOWER-Lung 1 *ESMO 2020: LBA 52*

First Line Lung Cancer Therapy with no actionable genes

NSQCC:

- Carboplatin/Pemetrexed/Pembrolizumab [Keynote 189]
- Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab [IMPOWER 150]

SQCC:

- Carboplatin/Paclitaxel or nab-paclitaxel/Pembrolizumab [Keynote 407]

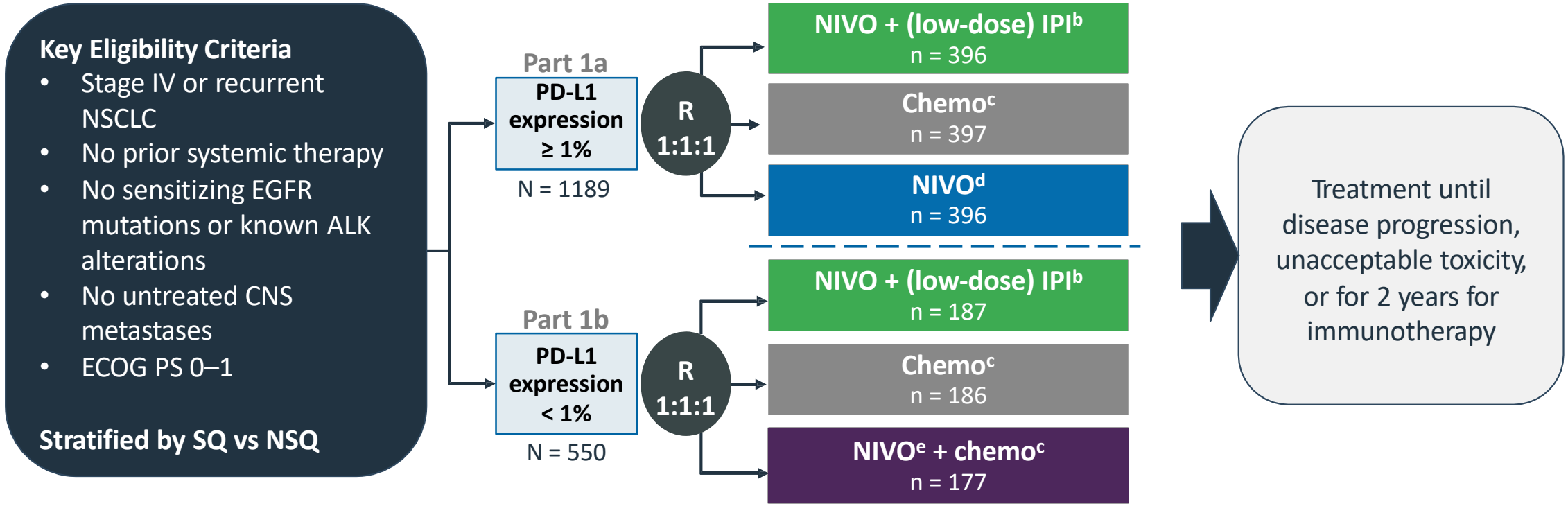
NSQCC OR SQCC

- Pembrolizumab [Keynote 024 and 042]
- Atezolizumab [IMPOWER 110]
- Cemiplimab **

Immunotherapy combinations:

- Ipilimumab and Nivolumab [Checkmate 227]
- Ipilimumab and Nivolumab plus 2 cycles of chemotherapy [Checkmate 9LA]

CheckMate 227: Part 1 final analysis of nivolumab + low-dose ipilimumab vs platinum-doublet chemotherapy in 1L advanced NSCLC



Independent co-primary endpoints: NIVO + IPI vs chemo

- PFS in high TMB (≥10 mut/Mb) population[f]
- **OS in PD-L1 ≥ 1% population[g]**

Secondary endpoints (PD-L1 hierarchy):

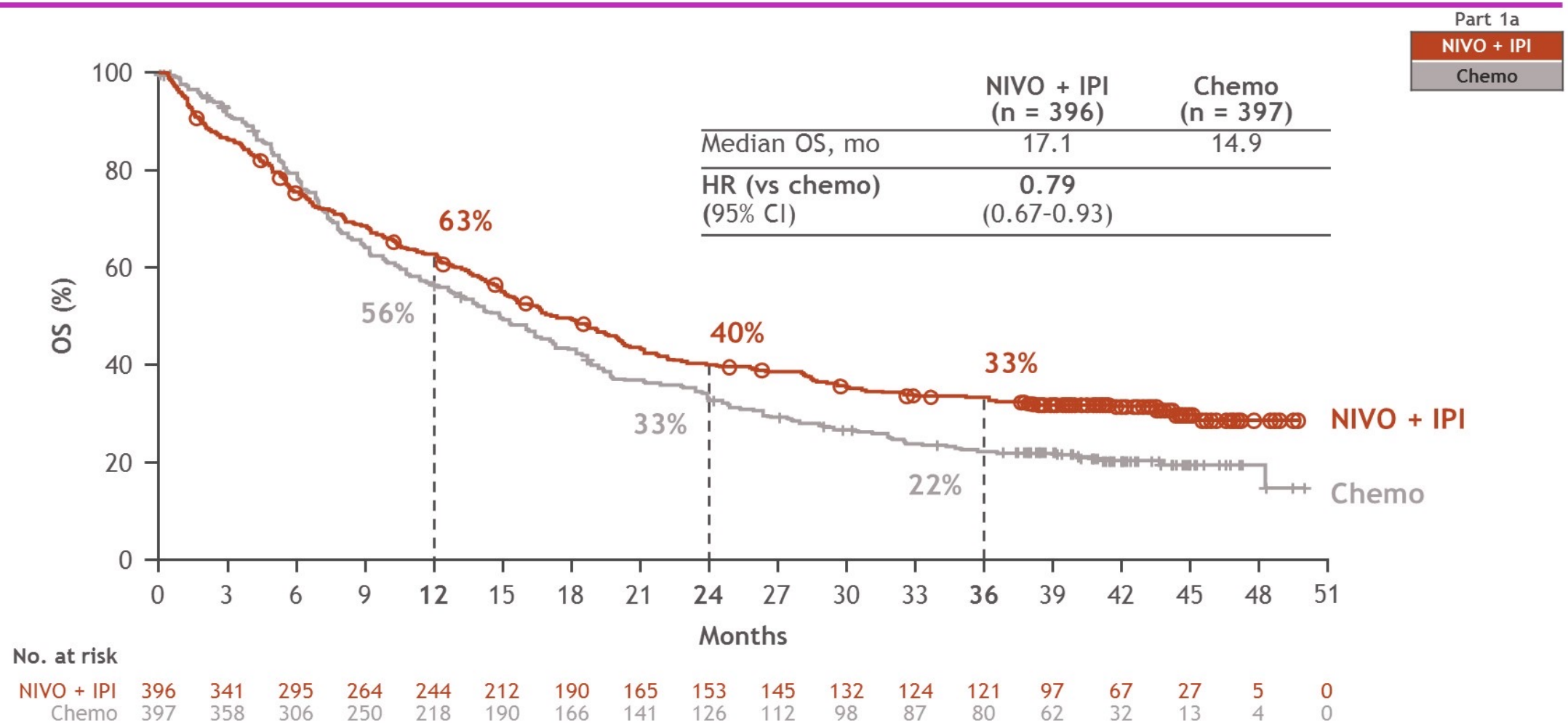
- PFS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO vs chemo** in PD-L1 ≥ 50%

Database lock: July 2, 2019; **minimum follow-up for primary endpoint: 29.3 months**

[a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]TMB primary endpoint analysis conducted at January 24, 2018 database lock in subset of patients randomized to NIVO + IPI or chemo; alpha allocated was 0.025; [g]Alpha allocated was 0.025 overall (0.023 for final analysis)

Peters S, et al. ESMO 2019. Abstract LBA4_PR

3-year update: OS with NIVO + IPI vs chemo (PD-L1 ≥ 1%)



Database lock: February 28, 2020; minimum follow-up for OS: 37.7 months.

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W). Among patients who were alive at 3 years, subsequent systemic therapy was received by 35% in the NIVO + IPI arm and 76% in the chemo arm; subsequent immunotherapies were received by 13% and 71%, respectively, and subsequent chemotherapy was received by 28% and 30%, respectively.

First Line Lung Cancer Therapy with no actionable genes

NSQCC:

- Carboplatin/Pemetrexed/Pembrolizumab [Keynote 189]
- Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab [IMPOWER 150]

SQCC:

- Carboplatin/Paclitaxel or nab-paclitaxel/Pembrolizumab [Keynote 407]

NSQCC OR SQCC

- Pembrolizumab [Keynote 024 and 042]
- Atezolizumab [IMPOWER 110]
- Cemiplimab

Immunotherapy combinations:

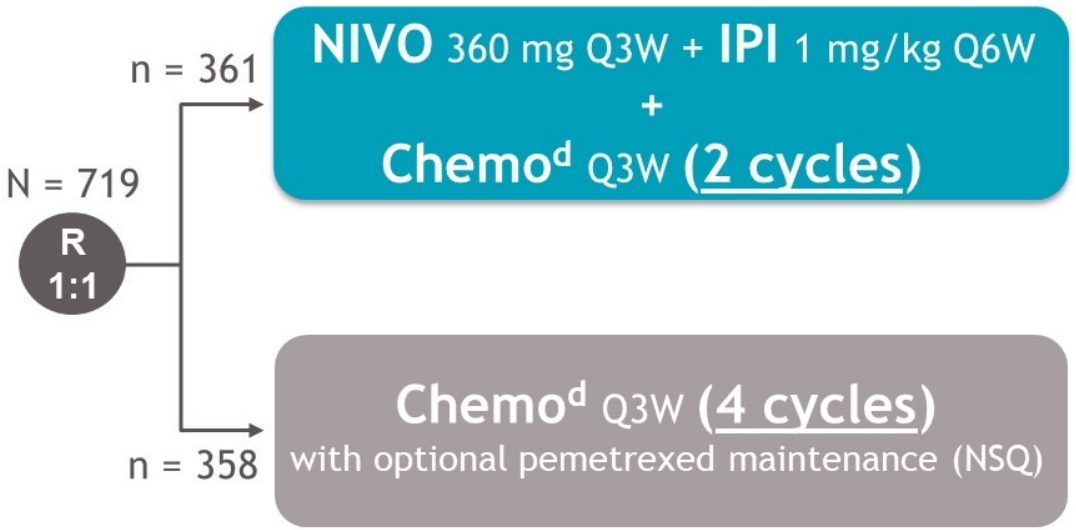
- Ipilimumab and Nivolumab [Checkmate 227]
- Ipilimumab and Nivolumab plus 2 cycles of chemotherapy [Checkmate 9LA]

CheckMate 9LA study design[a]

Key eligibility criteria

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0-1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)



Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

Primary endpoint
- OS

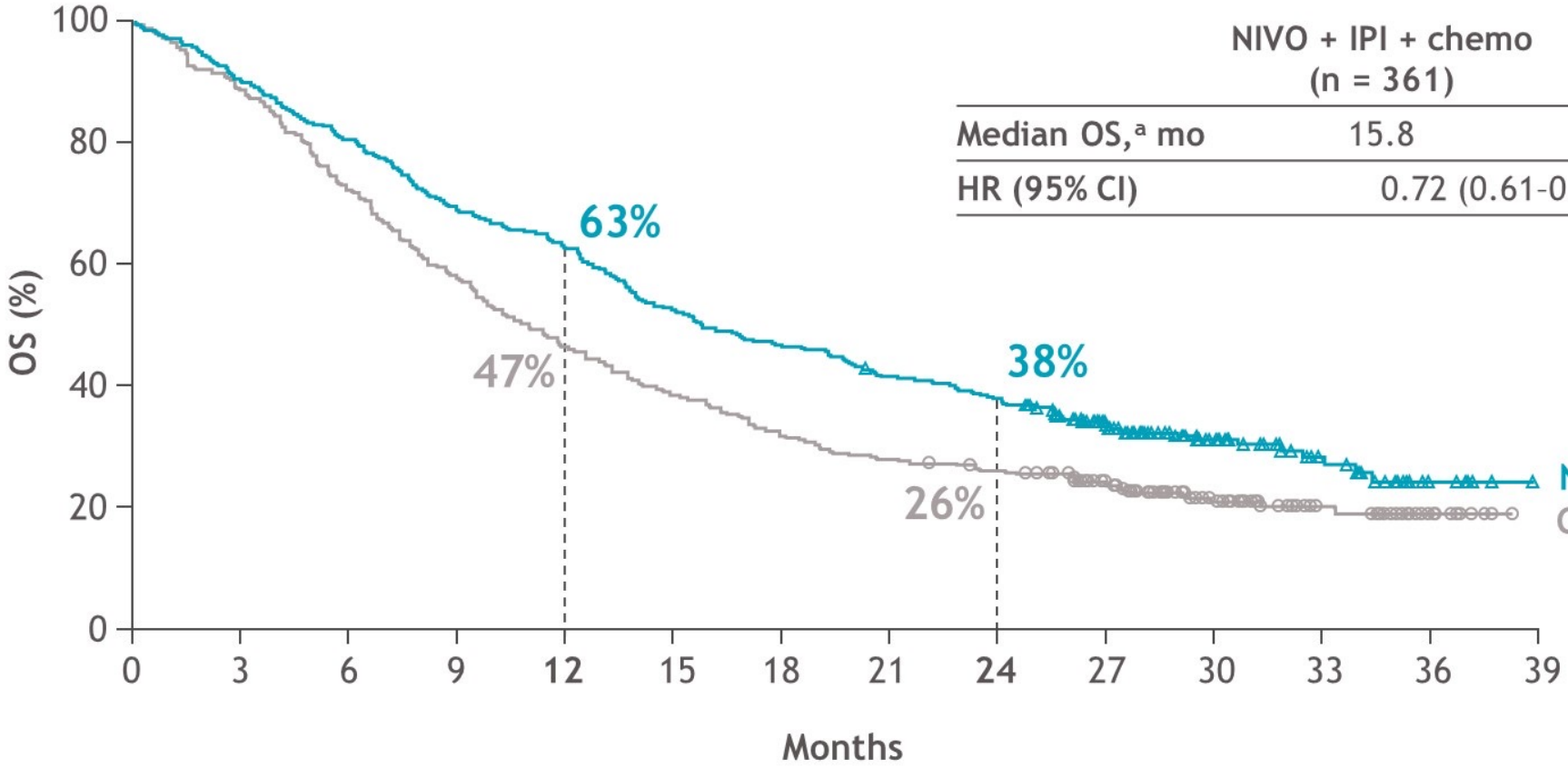
Secondary endpoints
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

Exploratory endpoints
- Safety

DBL: February 18, 2021; minimum / median follow-up for OS: 24.4 months / 30.7 months.

[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

2-Year update: OS in all randomized patients



	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS,[a] mo	15.8	11.0
HR (95% CI)	0.72 (0.61-0.86)	

No. at risk														
NIVO + IPI + chemo	361	326	292	250	227	191	170	150	137	95	50	23	7	0
Chemo	358	319	260	208	168	139	115	102	93	69	40	18	8	0

Minimum follow-up: 24.4 months.
[a]95% CI = 13.9-19.7 (NIVO + IPI + chemo) and 9.5-12.7 (chemo).

ORR slightly in favor of combination

	KN 24 (TPS > 50%)	KN 42 (TPS > 50%)	IMPW 10 TC3/IC3 (>50% and >10%)	KN 407 (TPS > 50%)	KN 189 (TPS > 50%)
ORR	45%	39.5%	30.7%	60.3%	61.4%
DOR	Nr (1.8-20.6 m)	20.2 m	Nr (1.8-29.3m)	7.7 m (all patients)	11.2 m (all patients)

Reck M, NEJM 2016, Mok T et al, Lancet 2019, Paz Ares, NEJM 2018, Ghandi, NEJM 2018

Adverse Events

	KN-42		KN-24		KN-189		KN-407	
	Pembro	CT	Pembro	CT	Pembro + CT	CT	Pembro + CT	CT
All TRAE (%)	62.7%	89.9%	76.6%	90.0%	99.8%	99.0%	98.2%	97.9%
Grade 3-5 TRAE (%)	17.8%	41%	31.2%	53.3%	67.2%	65.0%	69.8%	68.2%
Discontinuation rate (any) (%)	9%	9.4%	13.6%	10.7%	27.7%	14.9%	23.4%	11.8%
Led to death	0.2%	0%	1.3%	2.0%	6.7%	5.9%	8.3%	6.4%

2022 ASCO® ANNUAL MEETING

FDA

Outcomes of anti-PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC) with PD-L1 score ≥50%: FDA Pooled Analysis

Oladimeji Akinboro[1], Jonathon Vallejo[1], Erica Nakajima[1], Yi Ren[1], Pallavi Mishra-Kalyani[1], Erin Larkins[1], Paz Vellanki[1], Nicole Drezner[1], Mathieu Luckson[1], Shenghui Tang[1], Martha Donoghue[1,2], Richard Pazdur[1,2], Julia A. Beaver[1,2], Harpreet Singh[1,2]

[1]Center for Drug Evaluation and Research, U.S. Food and Drug Administration

[2]Oncology Center of Excellence, U.S. Food and Drug Administration

Oladimeji Akinboro, MD, MPH

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

ASCO® AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Clinical trials of first-line Chemo-IO and IO regimens included in FDA pooled analysis

Chemo-IO Trials		IO-only Trials	
Trial	Investigational Regimen	Trial	Investigational Regimen
KEYNOTE-021*	**Pembrolizumab** + Chemo**	CheckMate 026	**Nivolumab****
KEYNOTE-189	**Pembrolizumab** + Chemo**	KEYNOTE-024	**Pembrolizumab****
KEYNOTE-407	**Pembrolizumab** + Chemo**	KEYNOTE-042	**Pembrolizumab****
IMpower150	**Atezolizumab** + Bevacizumab + Chemo***	IMpower110	**Atezolizumab****
IMpower130	**Atezolizumab** + Chemo**	CheckMate 227	**Nivolumab** + **Ipilimumab****
CheckMate-9LA	**Nivolumab** + **Ipilimumab** + Chemo**	EMPOWER-Lung 1	**Cemiplimab****

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy immunotherapy; IO=immunotherapy.
* Cohort G
** Control arms: Platinum-based doublet chemotherapy
*** Control arm in IMpower150: Bevacizumab plus platinum-based doublet chemotherapy

PRESENTED BY:
Oladimeji Akinboro, MD, MPH
Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Exploratory OS, PFS, and ORR: NSCLC PD-L1 ≥50%

FDA

	Chemo-IO (*N*=455)		IO-alone (*N*=1,298)
OS			
Median, months (95% CI)	25.0 (19.0, NE)		20.9 (18.5, 23.1)
HR (95% CI)		0.82 (0.62, 1.08)	
PFS			
Median, months (95% CI)	9.6 (8.4, 11.1)		7.1 (6.3, 8.3)
HR (95% CI)		0.69 (0.55, 0.87)	
ORR			
% (95% CI)	61 (56, 66)		43 (41, 46)
Odds ratio		1.2 (1.1, 1.3)	

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; HR-hazards ratio; IO=immunotherapy; *N*=number; NSCLC=non-small-cell lung cancer; NE=not estimable; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival.

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

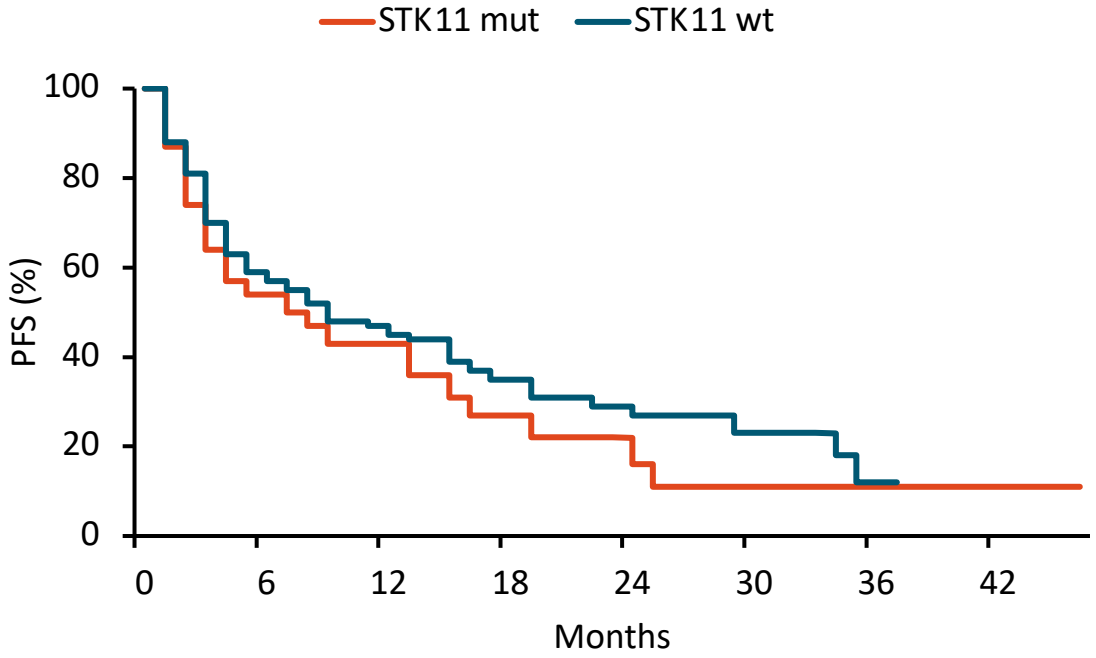

Cancer
Immune-desert tumour
Immune-excluded tumour
Inflamed tumour
Tolerance
Immunologic ignorance
No priming
No co-stimulation
No T-cell help
No danger signals
No APC to LN
No B7.1 B7.2
No other co-stimulatory ligands
Regulatory T cells
Suppressive cytokines
No danger signals
Non-inflammatory conditions
↓ 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
Vascular
Fas ligand
VEGF
Extracellular matrix
Collagen
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
Cytokines
Amino-acid catabolism
Glutaminase
TDO
Arginase 1
IDO
Tumour cells
PD-L1
Adenosine A2A receptor
Amino-acid catabolism
IDO
TDO
Poliovirus receptor
Cytokines

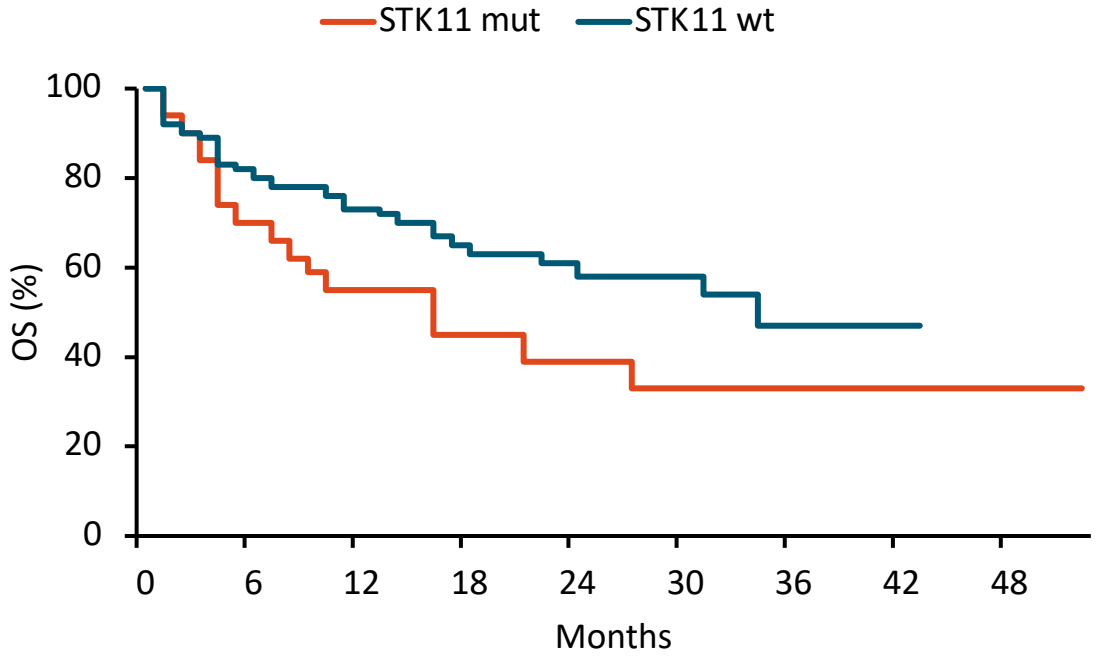
STK11/LKB1, KRAS mutations and immune-related adverse events as predictors of response to immunotherapy in lung cancer

Luis E. Raez, MD[1]; Richie Uba, PharmD[2,3]; Aaron North, PharmD[2,3]; Katerine Dumais, PharmD, MPH[1]; Hermán W. Powery II, PharmD, BCOP[1]; Gelenis Domingo, MD[1]; Brian Hunis, MD[1]; Paola Izquierdo, ARNP[1]; Frank Gentile, PharmD, BCOP[1]

[1]Memorial Cancer Institute, Pembroke Pines, FL; [2]Florida A&M University, Davie, FL; [3]Memorial Regional Hospital, Hollywood, FL

Results: PFS and OS by STK11 Status

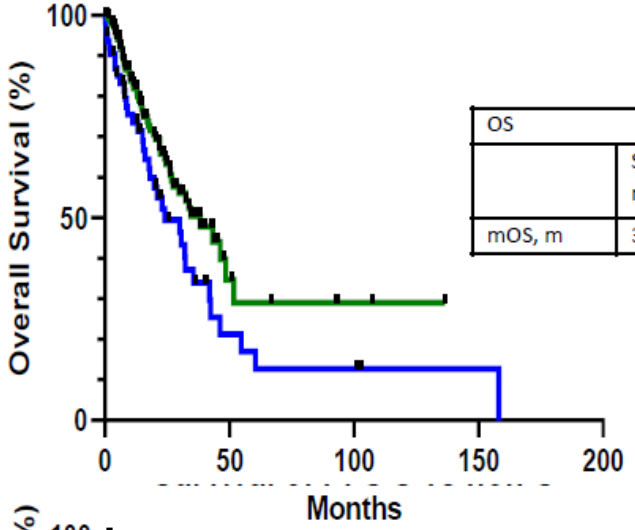




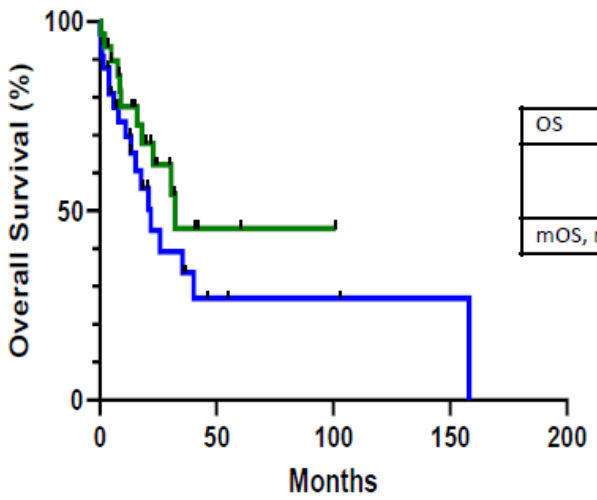
	STK11 wt n = 96	STK11 mut n = 31	HR (95% CI)	p
mPFS	6.3m	5.6m	1.35 (0.76-2.1)	0.35
12-m PFS	45%	43%	-	0.85

	STK11 wt n = 96	STK11 mut n = 31	HR (95% CI)	p
mOS	12.1m	8.6m	1.7 (1.0-3.6)	0.03
12-m OS	73%	55%	-	0.03

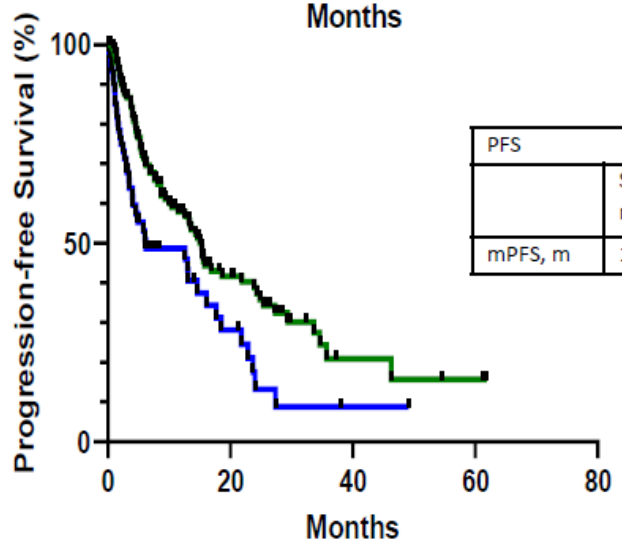
Favorable survival with co-mutation of STK11 and KRAS



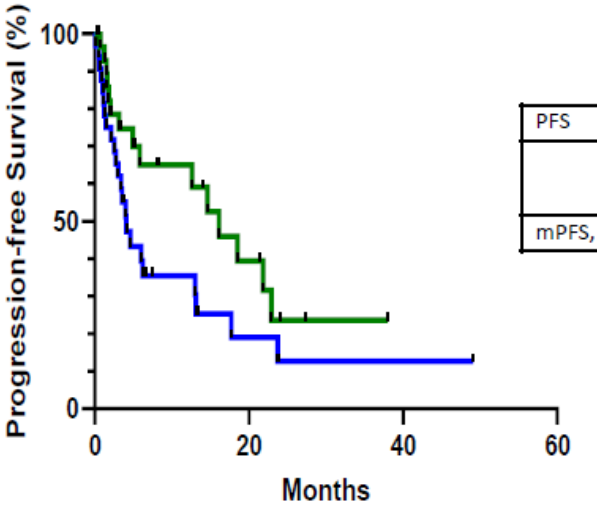
OS				
	STK11 wt n = 144	STK11 mut n = 63	HR (95% CI)	p
mOS, m	38.3	24	0.61 (0.38-0.97)	0.035



OS				
	S/Kmut n = 30	S/Kwt n = 33	HR (95% CI)	p
mOS, m	32.3	21.8	0.61 (0.29-1.28)	0.21



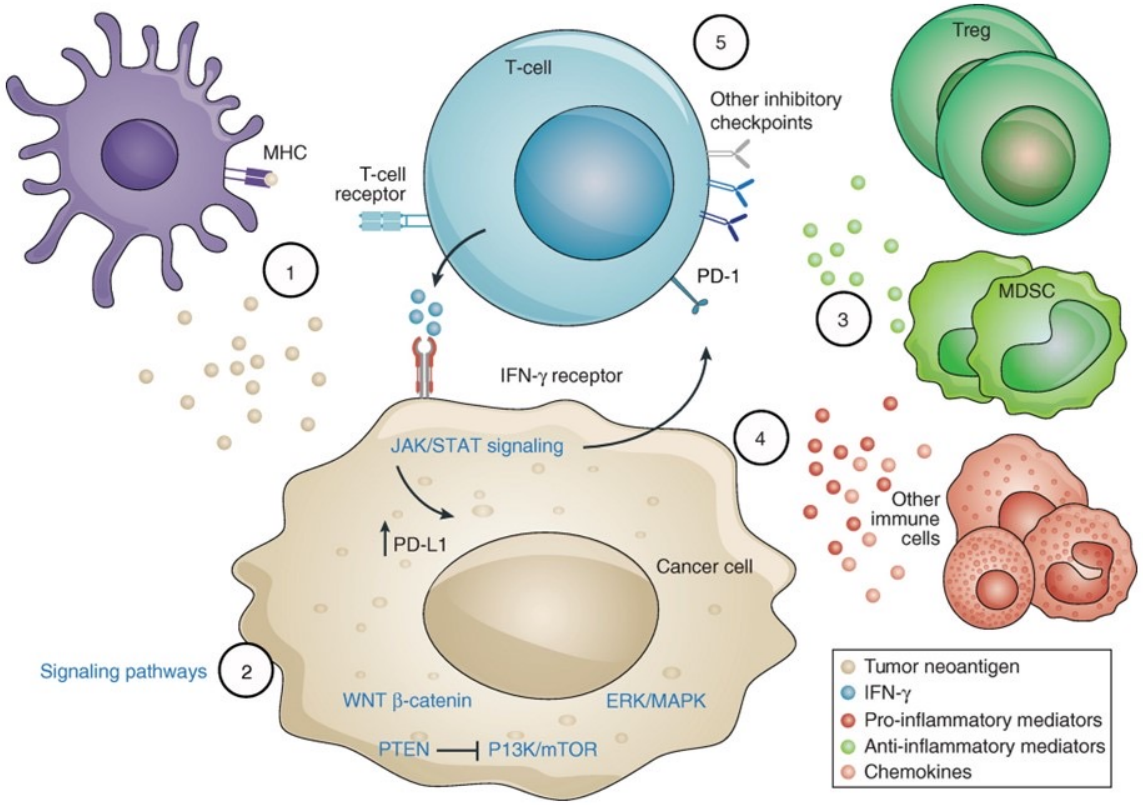
PFS				
	STK11 wt n = 144	STK11 mut n = 63	HR (95% CI)	p
mPFS, m	15.3	6.2	0.52 (0.34-0.80)	0.003



PFS				
	S/Kmut n = 30	S/Kwt n = 33	HR (95% CI)	p
mPFS, m	16.1	4.1	0.55 (0.29-0.95)	0.041

Basher F, Raez et al. WCLC 2021

Mechanisms of resistance to checkpoint inhibitors



1) Changes in tumor neoantigen presentation

2) Alterations in oncogenic signaling pathways

} Ricciuti et al.

3 and 4) Changes in tumor immune microenvironment including decreased anti-tumor inflammation and increase in protumorigenic inflammation

Paulus et al.
Zhao et al.

5) Dependence on alternate immune checkpoints

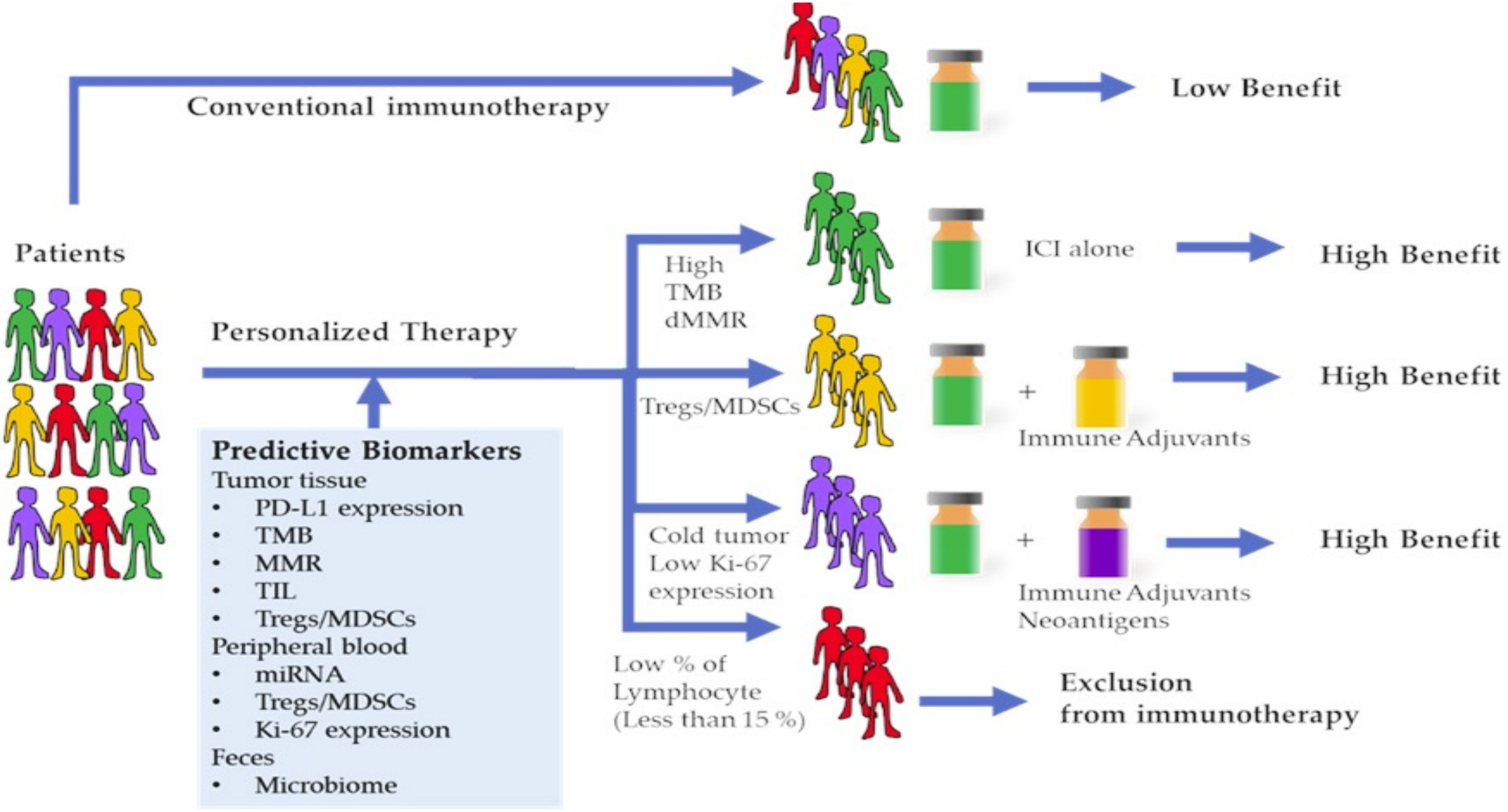
Hu-Lieskovan et al., Future Oncol 2021

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Immunotherapy resistance in NSCLC

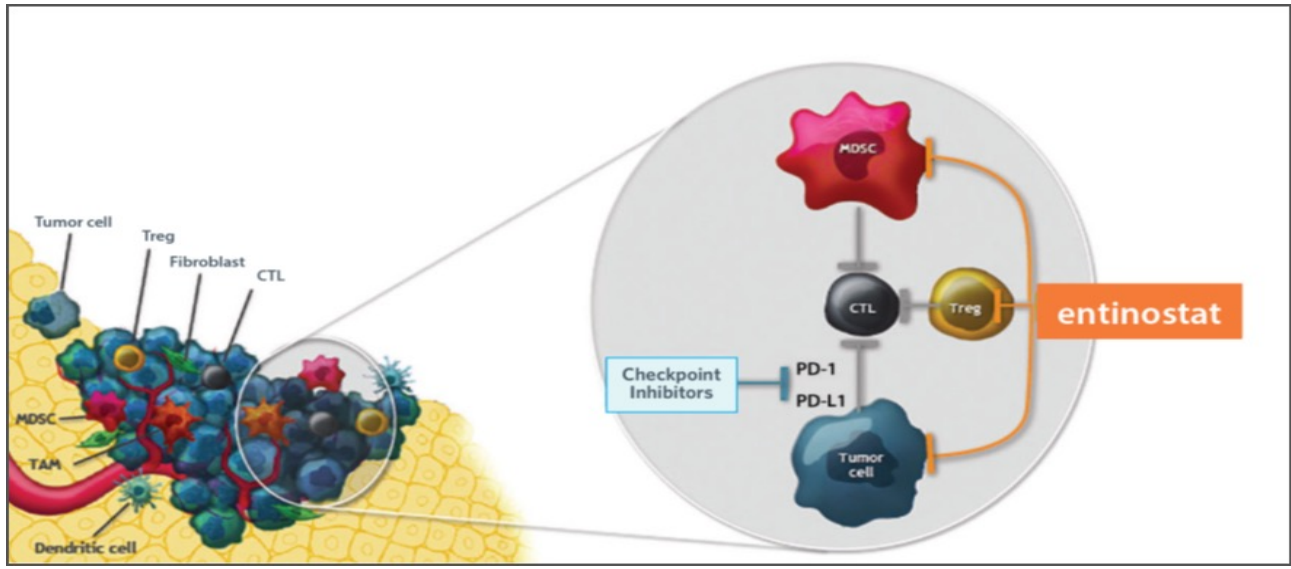
- Deacetylase Inhibitors (etinostat, vorinostat)
- Vaccines (Heat Shock Protein gp96)
- STK11/LKB1 and KEAP
- Cytokines (IL-10, IL-15)
- Adenosine pathway
- Combination checkpoints (IDO, TIM, LAG3)
- Adoptive T cell therapies (TILs, TILs + anti PD(L)-1, TCRs)
- B-catenin pathway


Conventional immunotherapy
Low Benefit
Patients
Personalized Therapy
High
TMB
dMMR
ICI alone
High Benefit
Tregs/MDSCs
+
Immune Adjuvants
High Benefit
Cold tumor
Low Ki-67
expression
+
Immune Adjuvants
Neoantigens
High Benefit
Low % of
Lymphocyte
(Less than 15 %)
Exclusion
from immunotherapy
Predictive Biomarkers
Tumor tissue
• PD-L1 expression
• TMB
• MMR
• TIL
• Tregs/MDSCs
Peripheral blood
• miRNA
• Tregs/MDSCs
• Ki-67 expression
Feces
• Microbiome

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

Entinostat plus Pembrolizumab in Patients with Metastatic NSCLC Previously Treated with Anti-PD-(L)1 Therapy

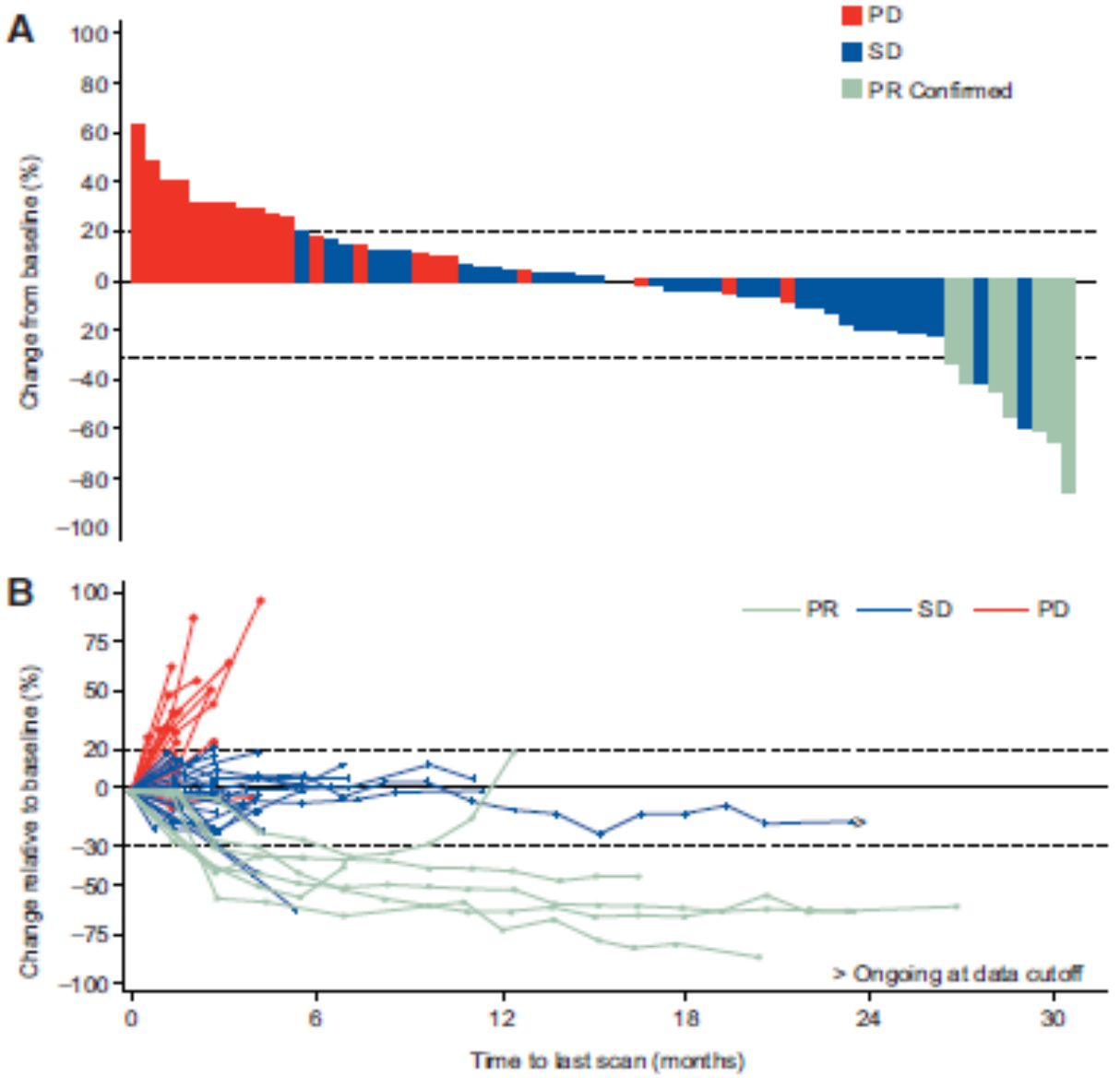
Matthew D. Hellmann[1], Pasi A. Jänne[2], Mateusz Opyrchal[3], Navid Hafez[4], Luis E. Raez[5], Dmitry I. Gabrilovich[6], Fang Wang[6], Jane B. Trepel[7], Min-Jung Lee[7], Akira Yuno[7], Sunmin Lee[7], Susan Brouwer[8], Serap Sankoh[8], Lei Wang[8], David Tamang[8], Emmett V. Schmidt[9], Michael L. Meyers[8], Suresh S. Ramalingam[10], Elaine Shum[11], and Peter Ordentlich[8]



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

Helllman M (Raez L) Clin Can Research 2021 Feb 15;27(4):1019-1028.

- **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)**



Helllman M (Raez L) Clin Can Research 2021 Feb 15;27(4):1019-1028.

COSMIC-021 Study Design for NSCLC Cohorts

Key Eligibility Criteria

- Stage IV non-squamous NSCLC with radiographic progression on or after one prior ICI for metastatic disease
- ≤2 prior lines of systemic anticancer therapy*
- Patients with known *EGFR*, *ALK*, *ROS1*, or *BRAF* V600E tumor mutations excluded

Cohort 7†
Cabozantinib 40 mg QD PO + Atezolizumab 1200 mg Q3W IV
(N=80)

Cohort 20‡
Cabozantinib 60 mg QD PO
(N=30)

Tumor assessment per RECIST v1.1 by investigator every 6 weeks for the first year and every 12 weeks thereafter

Primary endpoint:	ORR per RECIST v1.1 by investigator
Secondary endpoint:	Safety (AEs, SAEs, AESIs)
Exploratory endpoints:	DOR, PFS per RECIST v1.1 by investigator, OS

*Prior treatment with platinum-based chemotherapy was not required. †Patients were initially enrolled to cohort 7 (n=35). Following an initial assessment of clinical activity, subsequent patients were randomized between cohorts 7 and 20. ‡Patients in cohort 20 may receive combination therapy after radiographic disease progression per RECIST v1.1 by the investigator.
SAEs, serious adverse events; AESIs, adverse events of special interest

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Efficacy Summary

	Cabozantinib + Atezolizumab (N=81)				Cabozantinib (N=31)*
	All patients (N=81)	PD-L1 <1% (n=19)	PD-L1 ≥1% (n=41)	PD-L1 unknown (n=21)	
ORR, n (%)	**15 (19)**	2 (11)	8 (20)	5 (24)	**2 (6)**
Best overall response, n (%)					
Complete response	**0**	0	0	0	**0**
Partial response	**15 (19)**	2 (11)	8 (20)	5 (24)	**2 (6)**
Stable disease	**50 (62)**	12 (63)	25 (61)	13 (62)	**18 (58)**
Progressive disease	**13 (16)**	3 (16)	8 (20)	2 (10)	**6 (19)**
Missing / not evaluable	**3 (4)**	2 (11)	0	1 (5)	**5 (16)**
Disease control rate, n (%)	**65 (80)**	14 (74)	33 (80)	18 (86)	**20 (65)**
PFS, mo (95% CI)	**4.5 (3.5–5.6)**	4.0 (2.6–5.6)	4.7 (2.7–5.6)	5.4 (2.9–10.9)	**3.4 (1.4–5.6)**
Median DOR, mo (95% CI)	**5.8 (4.2–6.9)**	3.4 (2.6–NE)	6.5 (3.5–NE)	6.2 (4.2–NE)	**10.6 (6.3–NE)†**
OS, mo (95% CI)	**13.8 (7.2–15.7)**	6.8 (5.1–15.4)	10.4 (5.9–17.1)	17.4 (9.4–NE)	**9.4 (4.5–11.7)**

*Eight patients in the cabozantinib alone cohort were crossed over to receive cabozantinib plus atezolizumab after experiencing disease progression; the efficacy data of these patients are not reported in this presentation except for OS. †The DOR of the 2 responders was 6.3 and 14.8 months.

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

2022 ASCO® ANNUAL MEETING

SWOG CANCER RESEARCH NETWORK | NCI National Clinical Trials Network | NCI Community Oncology Research Program

Overall survival from a phase II randomized study of ramucirumab plus pembrolizumab versus standard of care for advanced non-small cell lung cancer previously treated with immunotherapy—Lung-MAP non-matched sub-study S1800A

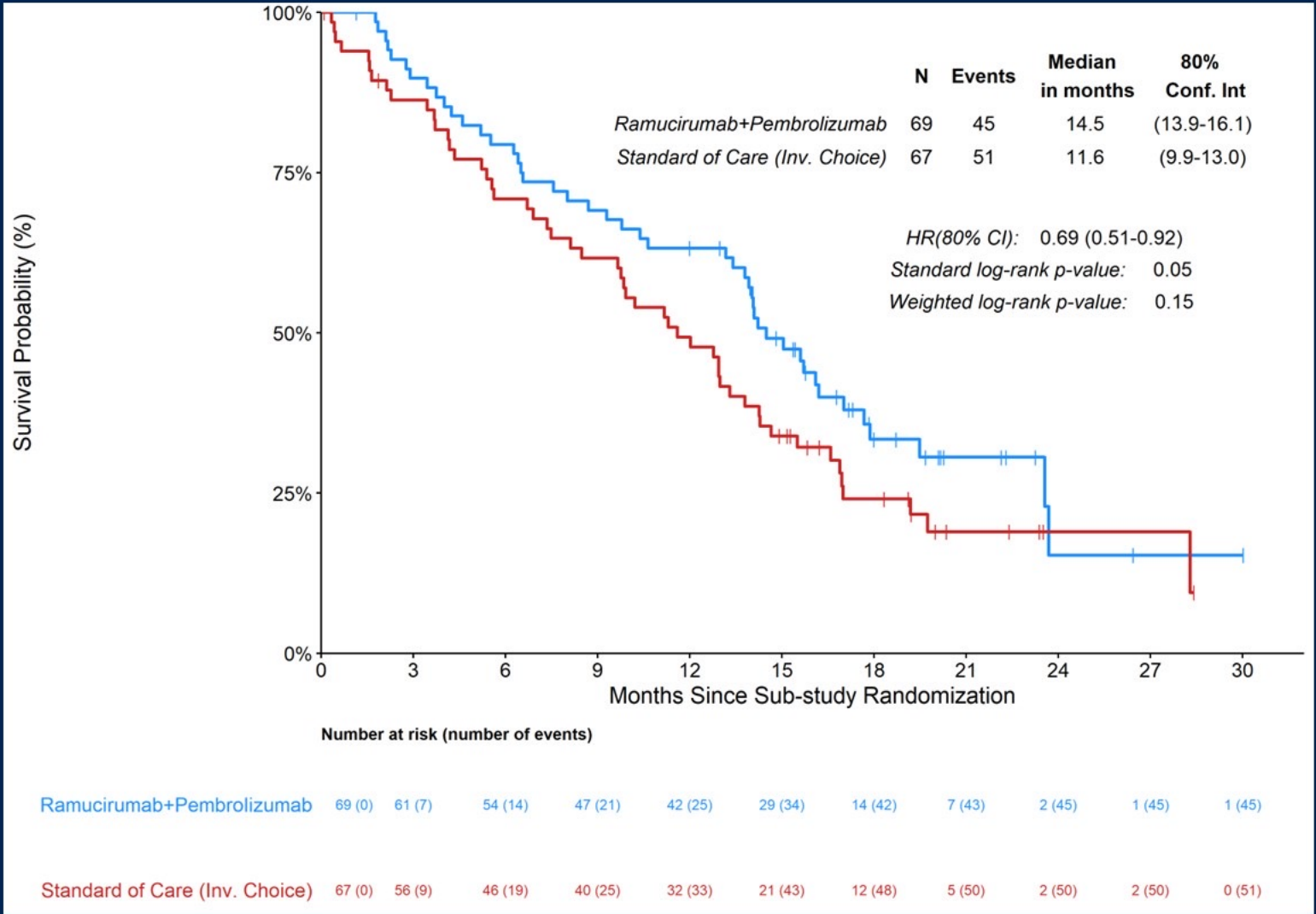
Karen L. Reckamp, M.D.[1], Mary W. Redman, PhD[2], Konstantin H. Dragnev, M.D.[3], Liza Villaruz, M.D.[4], Bryan Faller, MD[5]; Tareq Al Baghdadi, MD[6], Susan Hines, MD[7], Lu Qian, M.S.[2], Katherine Minichiello, M.S.[2], David R. Gandara, M.D.[8], Karen Kelly, MD[8], Roy S. Herbst, M.D., Ph.D.[9]

[1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]SWOG Statistics and Data Management Center & Fred Hutchinson Cancer Research Center, Seattle, WA; [3]Dartmouth-Hitchcock Norris Cotton Cancer Center, Lebanon, NH/Alliance for Clinical Trials in Cancer; [4]University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center; [5]Missouri Baptist Medical Center, St. Louis, MO/Heartland NCORP; [6]IHA Hematology Oncology Consultants-Ann Arbor/Michigan CRC NCORP; [7]Novant Health Cancer Institute - Mount Airy/Southeast Clinical Oncology Research Consortium NCORP); [8]UC Davis Comprehensive Cancer Center, Sacramento, CA; [9]Yale University, New Haven, CT

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

ASCO® AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Overall survival



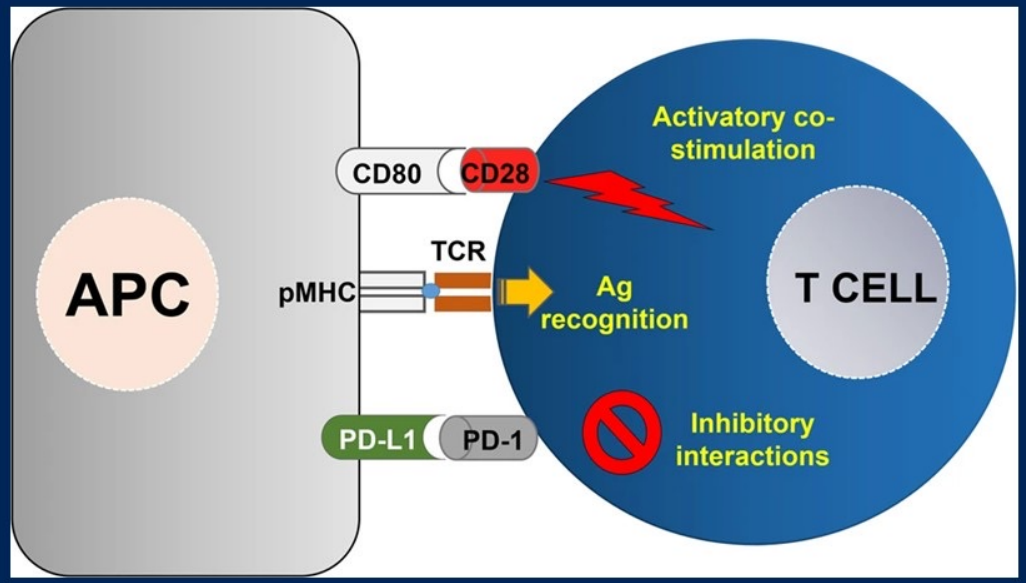
- Median OS for RP 14.5 months v. SOC 11.6 months
- HR= 0.69; SLR p-value 0.05

Standard of care therapy received:

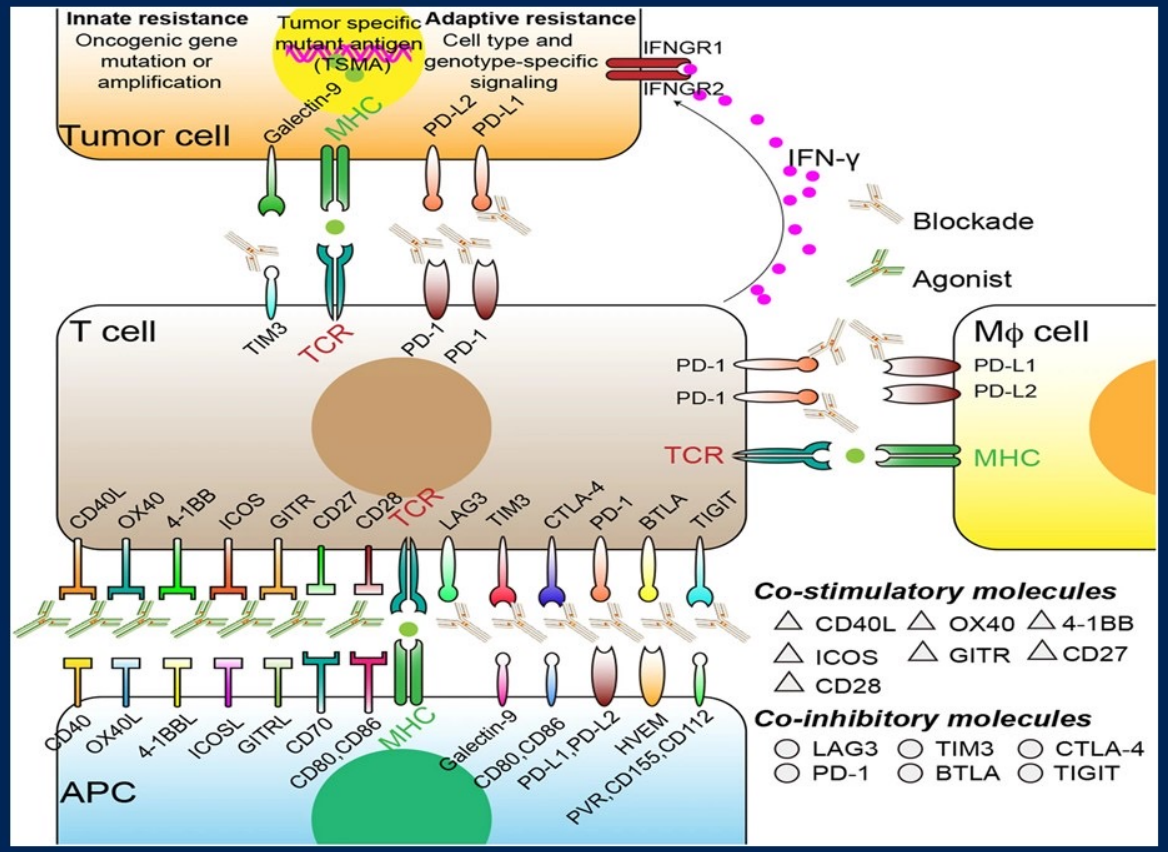
- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Co-Stimulatory and Co-Inhibitory Interactions



Escors, et al Signal Transduct Target Ther 2018



Li Cellular and Molecular Immunology 2018

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Thanks

Memorial Cancer Institute

CANCER CENTER of EXCELLENCE
Florida HEALTH