First-Line Management of Patients with Metastatic NSCLC without a Targetable Tumor Mutation

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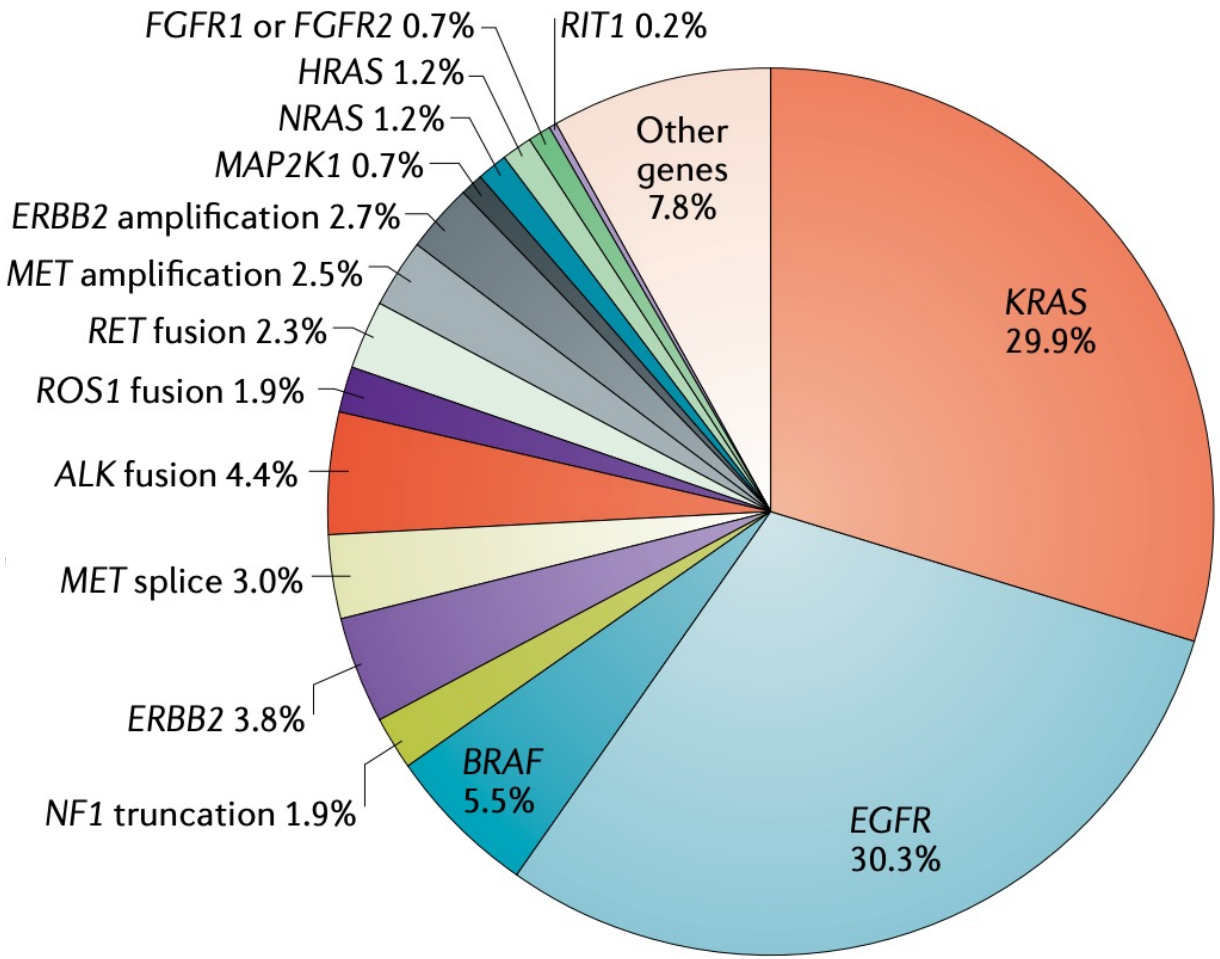
Outline

- NSCLC without a Targetable Tumor Mutation
- State of Affairs: Current Standards for Metastatic NSCLC
- Development

Courtesy of David R Spigel, MD

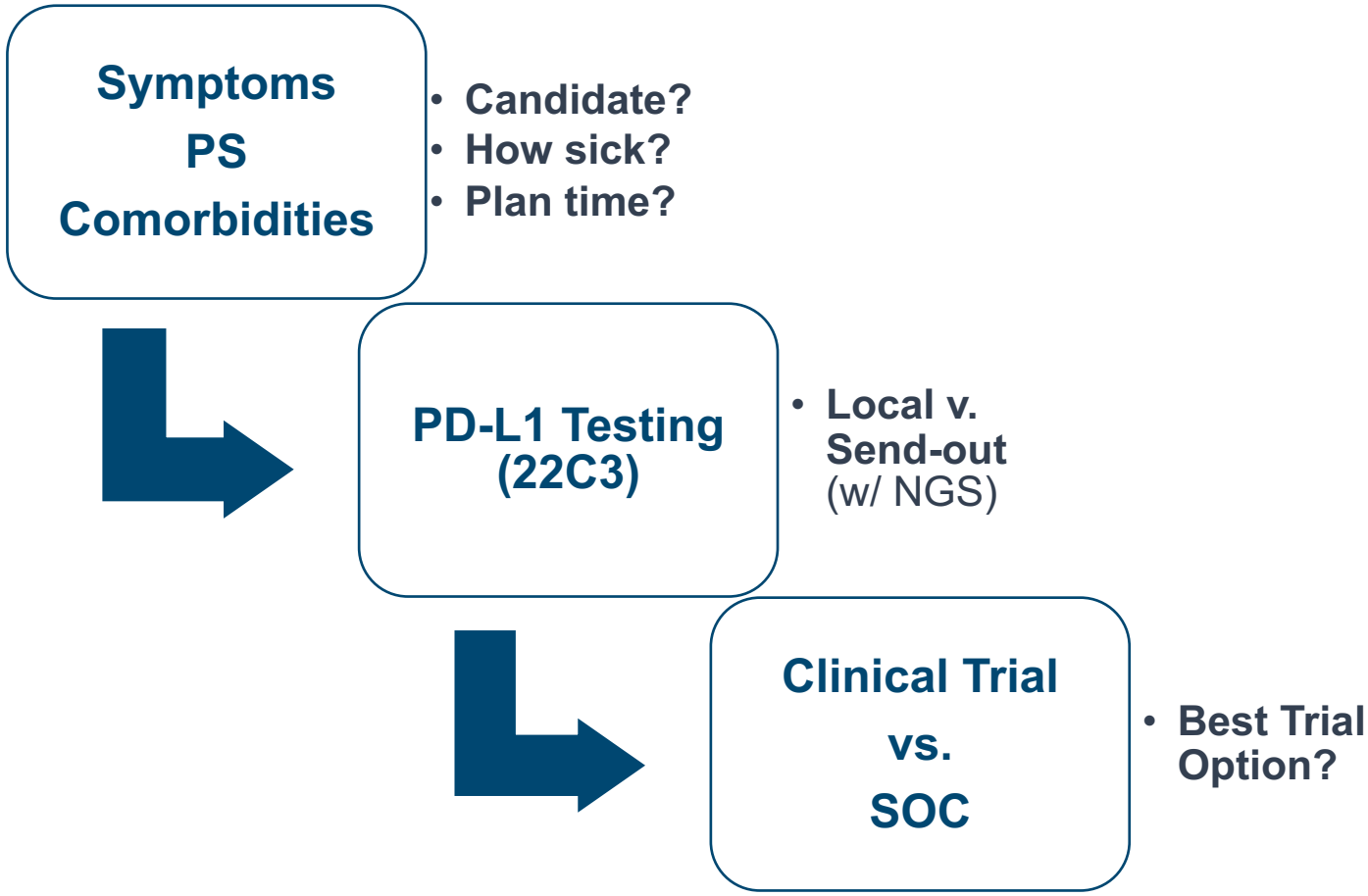
NSCLC without a (yet) Targetable Tumor Mutation



Skoulidis and Heymach, Nat Rev Ca, 2019

Courtesy of David R Spigel, MD

First-Line Decision Making (after NGS)



Courtesy of David R Spigel, MD

SOC: Mono v. Doublet v. Chemo-IO

Mono-Immunotherapy	Doublet-Immunotherapy	Chemotherapy and Immunotherapy
• Pembrolizumab • Atezolizumab • Cemiplimab	• Nivolumab and Ipilimumab	• Histology-Based Chemotherapy and Immunotherapy

Courtesy of David R Spigel, MD

Mono-Immunotherapy

Pembrolizumab

KEYNOTE-024

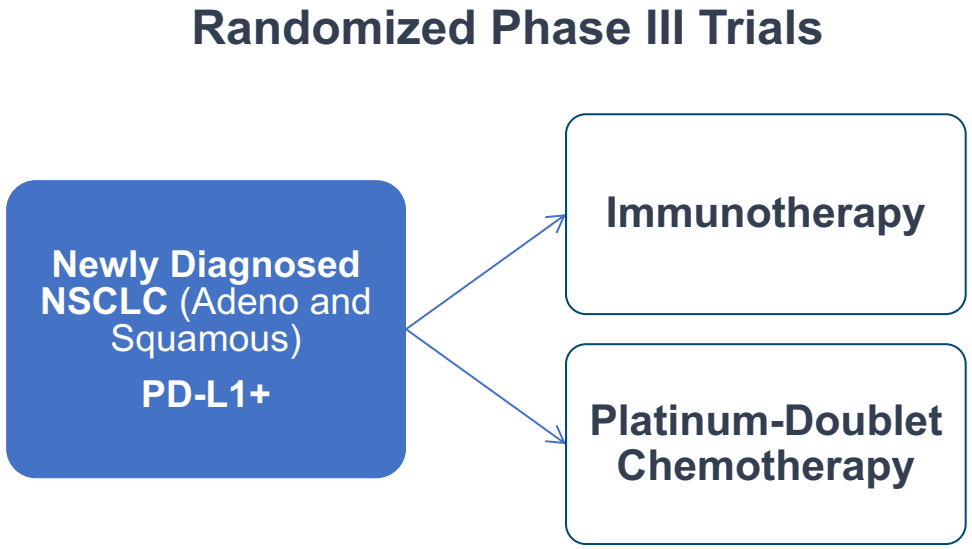
KEYNOTE-042

Atezolizumab

IMpower110

Cemiplimab

EMPOWER-Lung 1

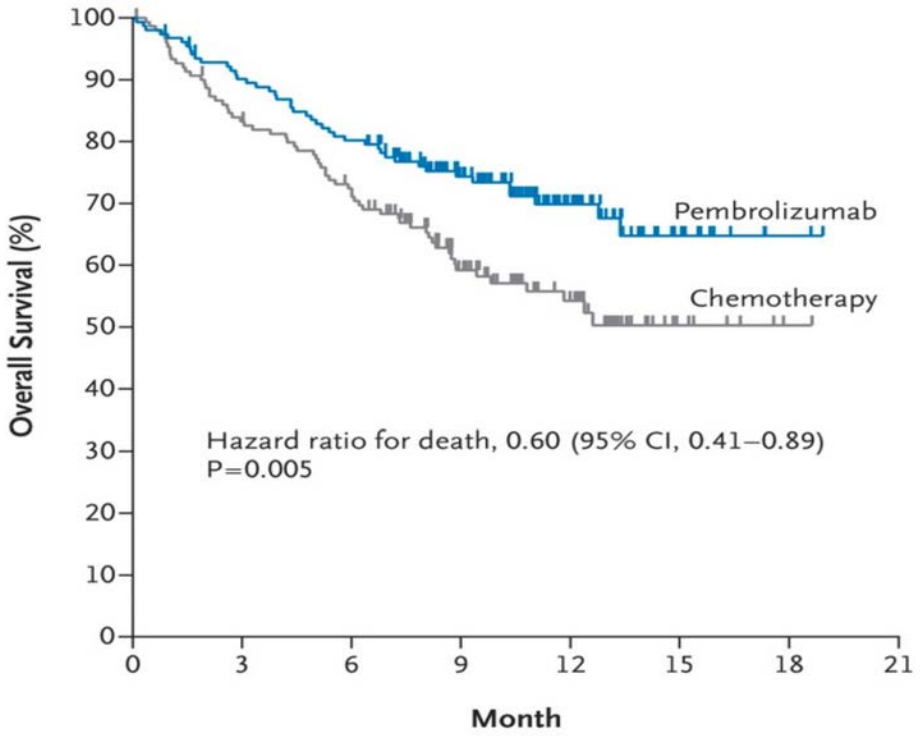


Reck, NEJM, 2016
Herbst, NEJM 2020
Mok, Lancet 2019
Cezar, Lancet 2021

Courtesy of David R Spigel, MD

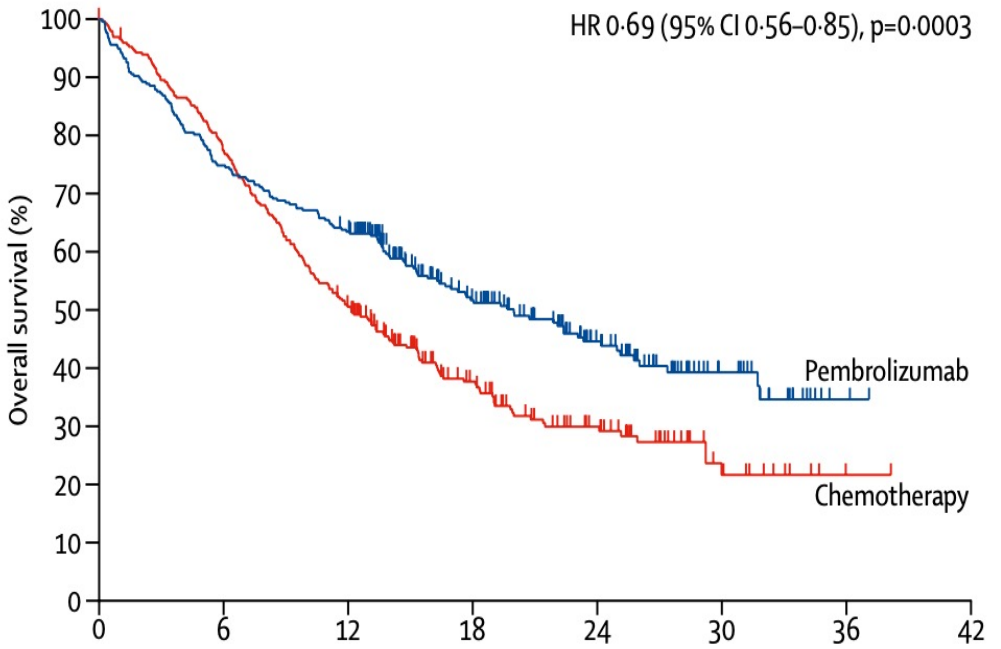
Mono-Immunotherapy: Pembrolizumab

KEYNOTE-024



No. at Risk								
Pembrolizumab	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

KEYNOTE-042



Number at risk (censored)								
Pembrolizumab group	299 (0)	224 (0)	189 (1)	107 (55)	59 (91)	22 (122)	2 (140)	0 (142)
Chemotherapy group	300 (0)	231 (2)	149 (4)	75 (46)	40 (67)	11 (90)	1 (100)	0 (101)

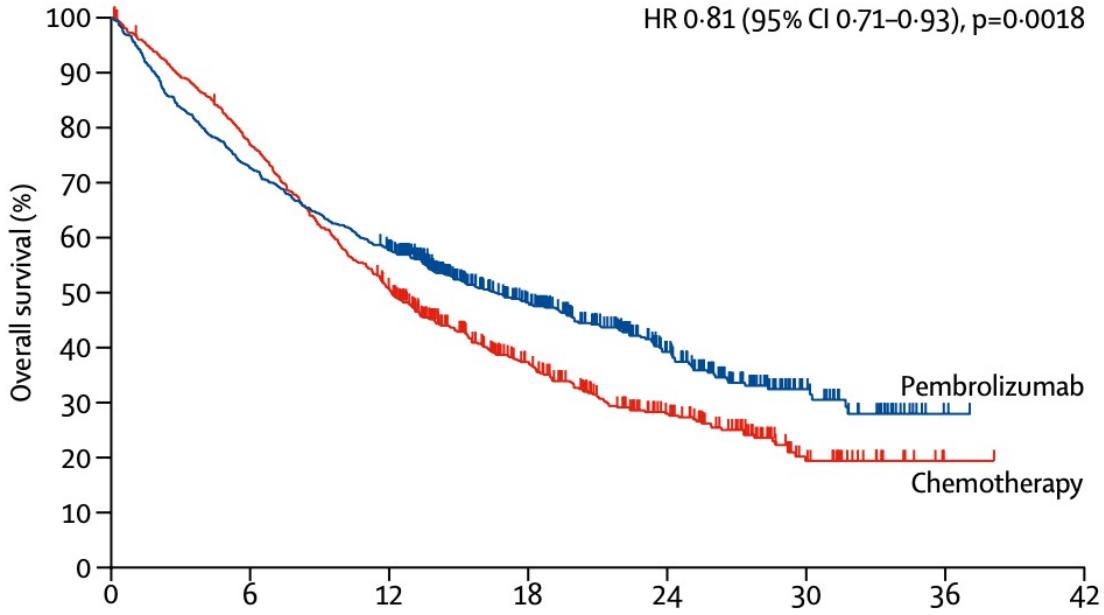
Courtesy of David R Spigel, MD

Reck NEJM, 2016
Mok, Lancet, 2019

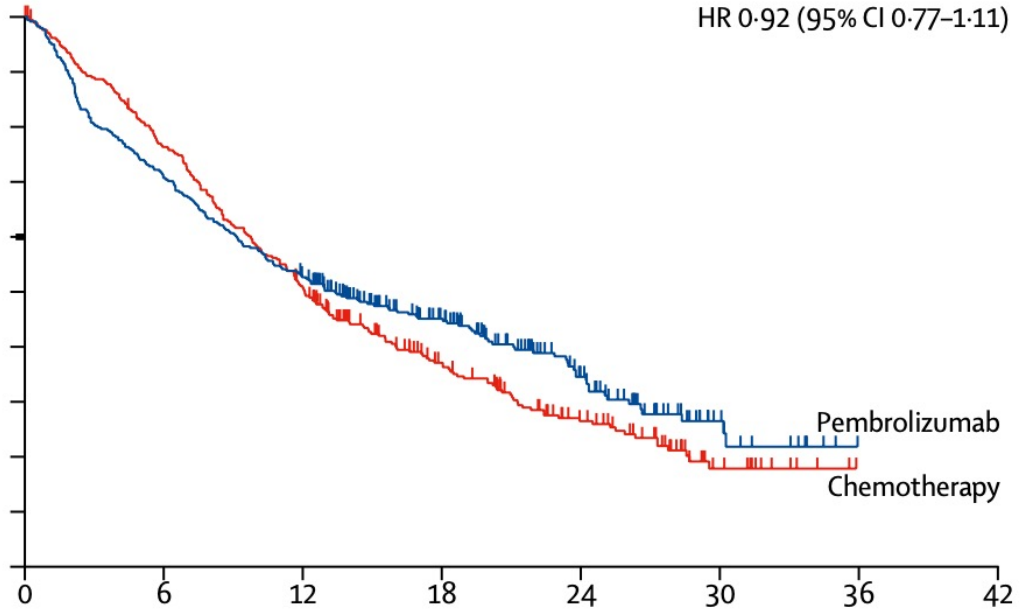
Mono-Immunotherapy: Pembrolizumab

KEYNOTE-042

PD-L1>1%



PD-L1 1-49%



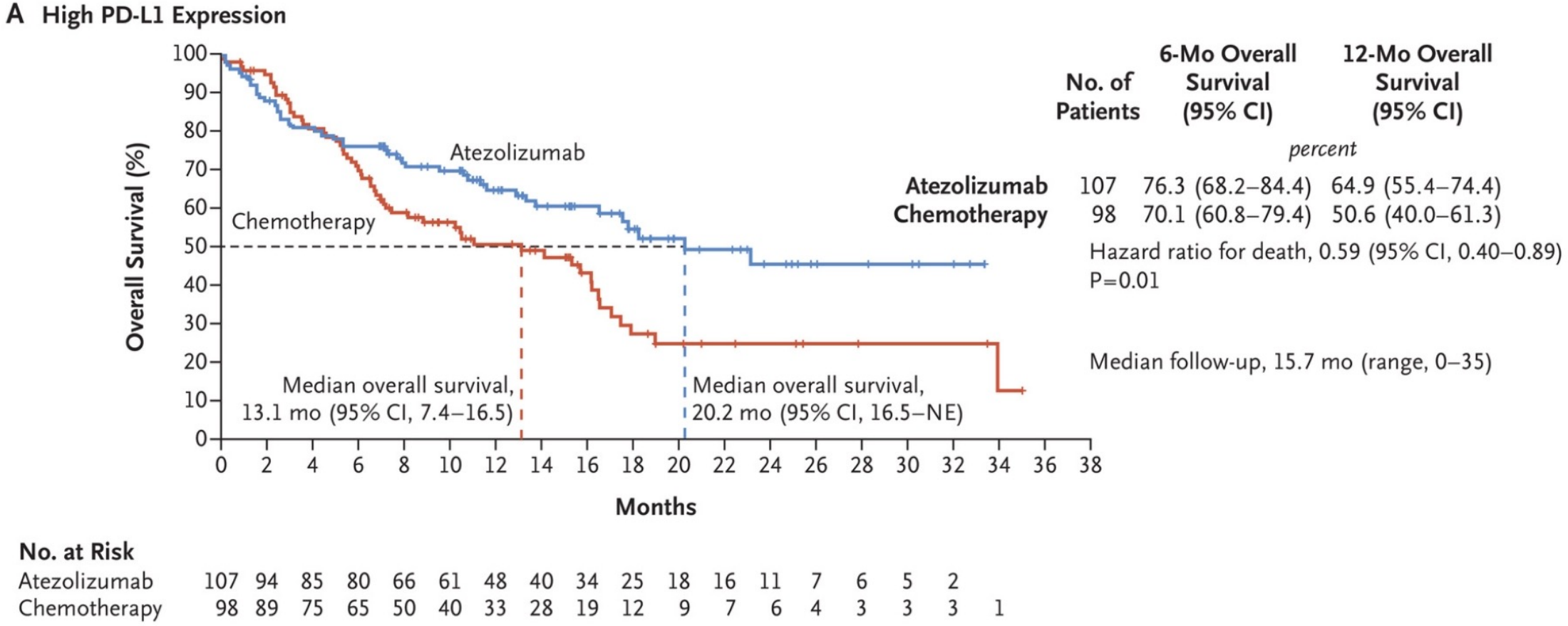
Number at risk (censored)																
Pembrolizumab group	637 (0)	463 (0)	365 (3)	214 (104)	112 (174)	35 (235)	2 (264)	0 (266)	338 (0)	239 (0)	176 (2)	107 (49)	53 (83)	13 (113)	0 (124)	0 (124)
Chemotherapy group	637 (0)	485 (6)	316 (10)	166 (88)	88 (128)	24 (175)	1 (198)	0 (199)	337 (0)	254 (4)	167 (6)	91 (42)	48 (61)	13 (85)	0 (98)	0 (98)

Courtesy of David R Spigel, MD

Mok, Lancet, 2019

Mono-Immunotherapy: Atezolizumab

IMpower110

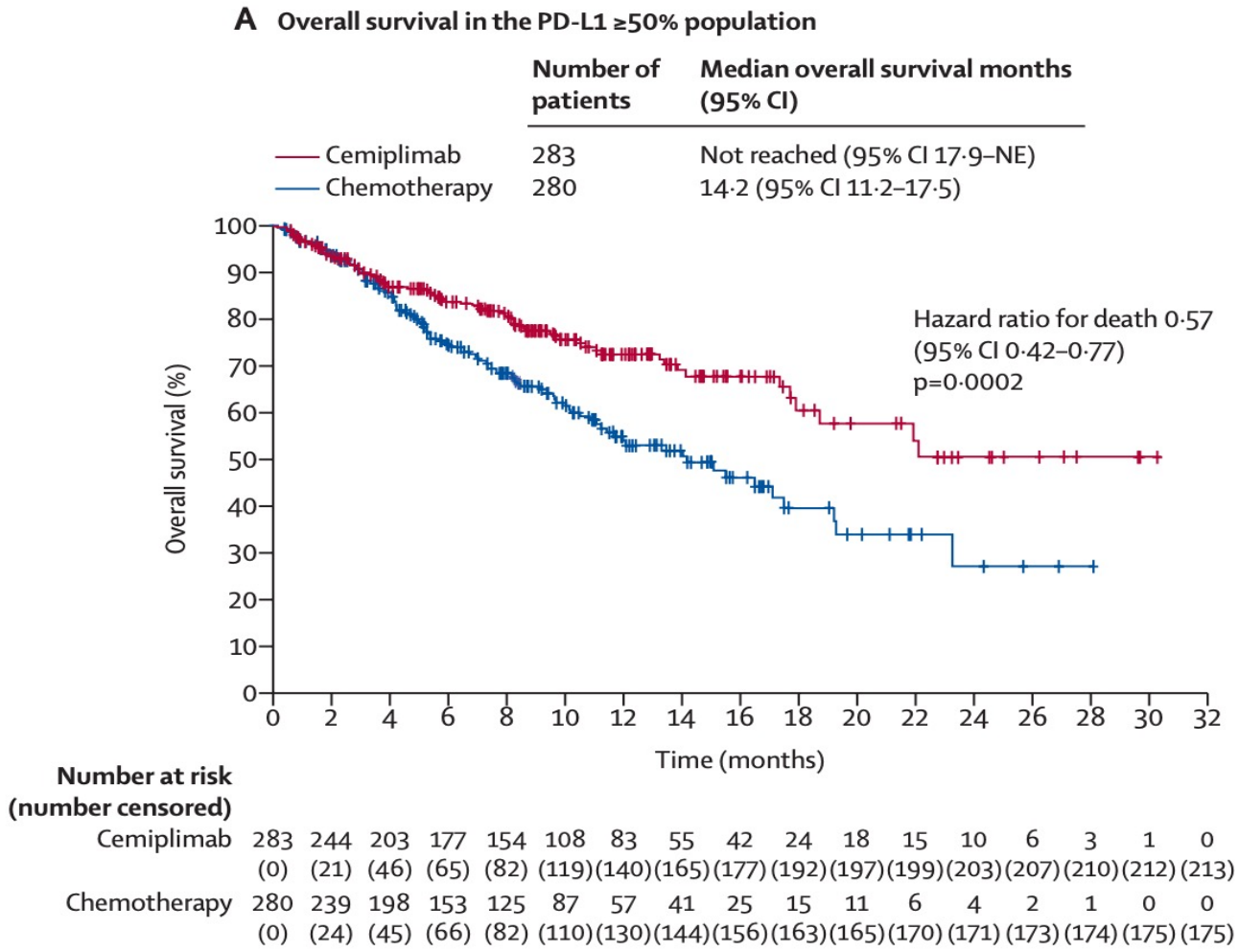


Courtesy of David R Spigel, MD

Herbst, NEJM 2020

Mono-Immunotherapy: Cemiplimab

EMPOWER-Lung 1



Courtesy of David R Spigel, MD

Cezar, Lancet 2021

Doublet-Immunotherapy

Nivolumab and Ipilimumab

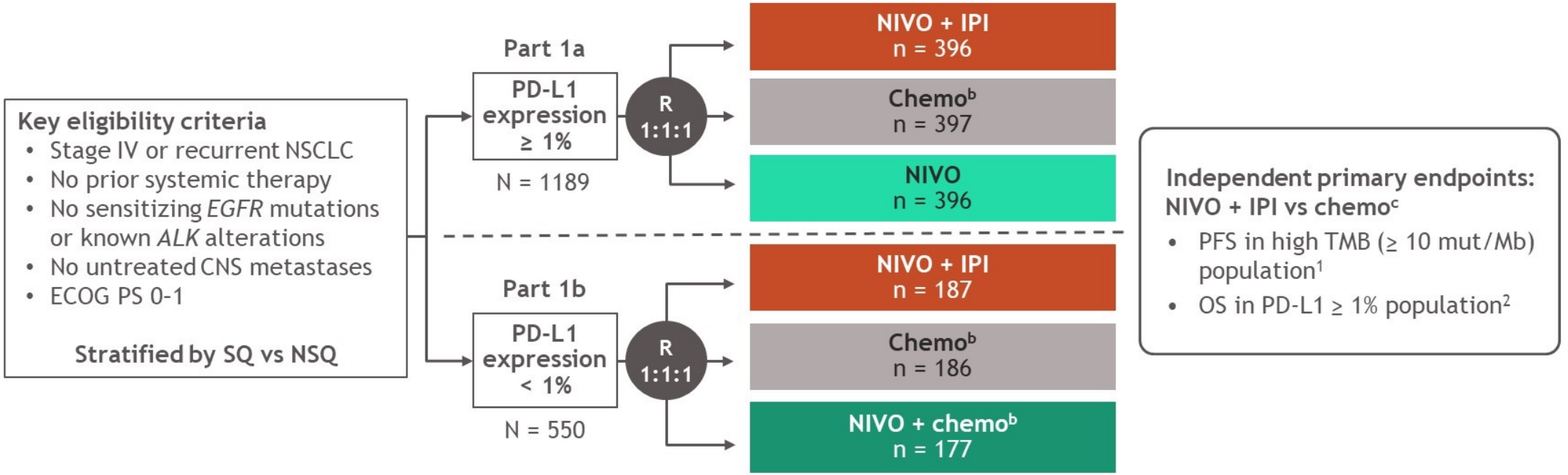
CheckMate 227

Courtesy of David R Spigel, MD

Hellmann, NEJM, 2019

Doublet Immunotherapy: Nivolumab and Ipilimumab

CheckMate 227



- Here we present updated 4-year efficacy and safety results for CheckMate 227 Part 1, and a post hoc efficacy analysis in patients who discontinued NIVO + IPI due to TRAEs

Database lock: February 18, 2021; minimum / median follow-up for OS: 49.4 months / 54.8 months.

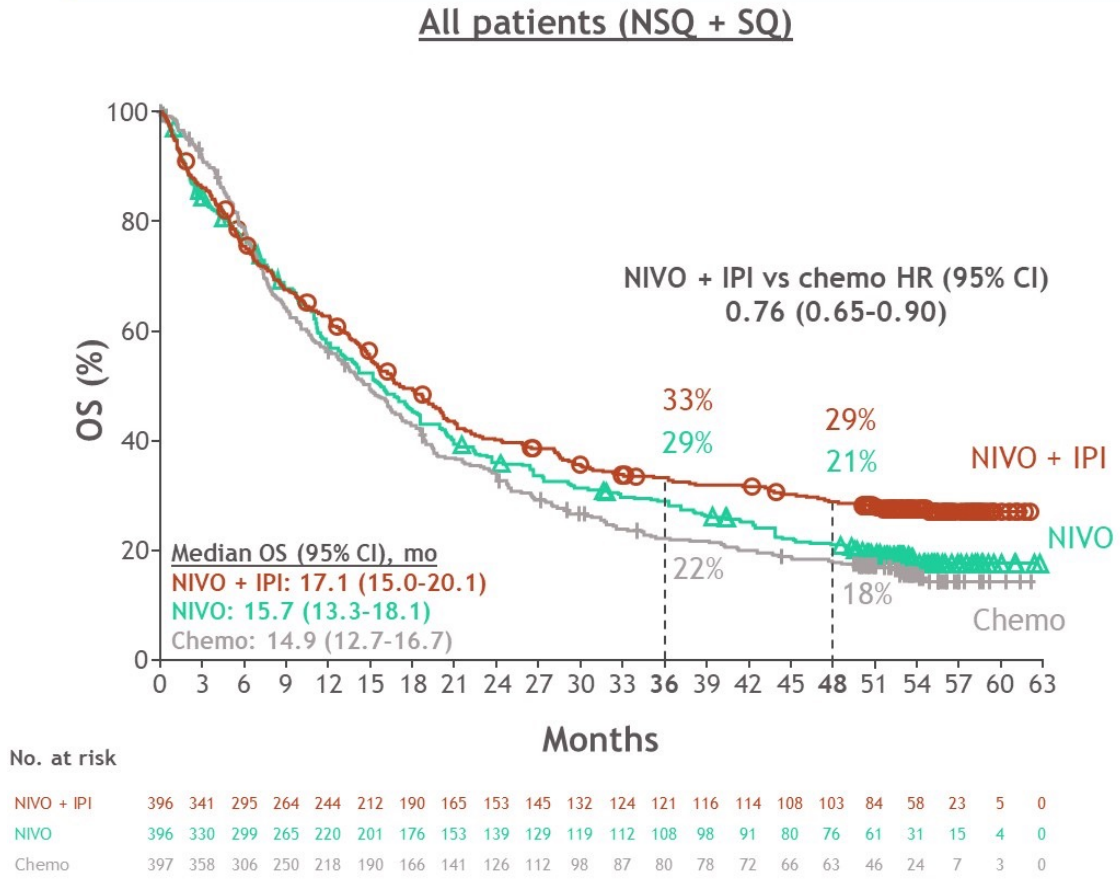
Courtesy of David R Spigel, MD

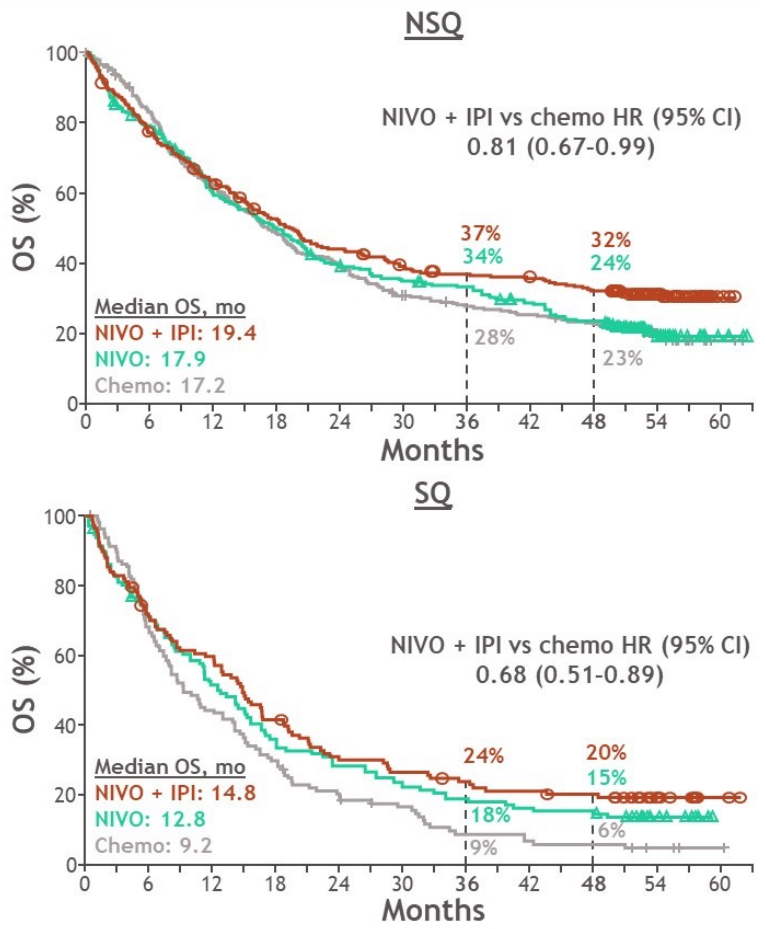
Paz-Ares, ASCO Annual Meeting Abstract 9016 2021

Doublet Immunotherapy: Nivolumab and Ipilimumab

CheckMate 227

4-year OS in patients with PD-L1 ≥ 1%





In all patients with PD-L1 ≥ 1% (NSQ + SQ) with a PFS event (per BICR), subsequent systemic therapy was received by 34% in the NIVO + IPI arm, 46% in the NIVO arm, and 49% in the chemo arm; subsequent immunotherapies by 7%, 9%, and 40%; and subsequent chemo by 32%, 45%, and 25%, respectively.

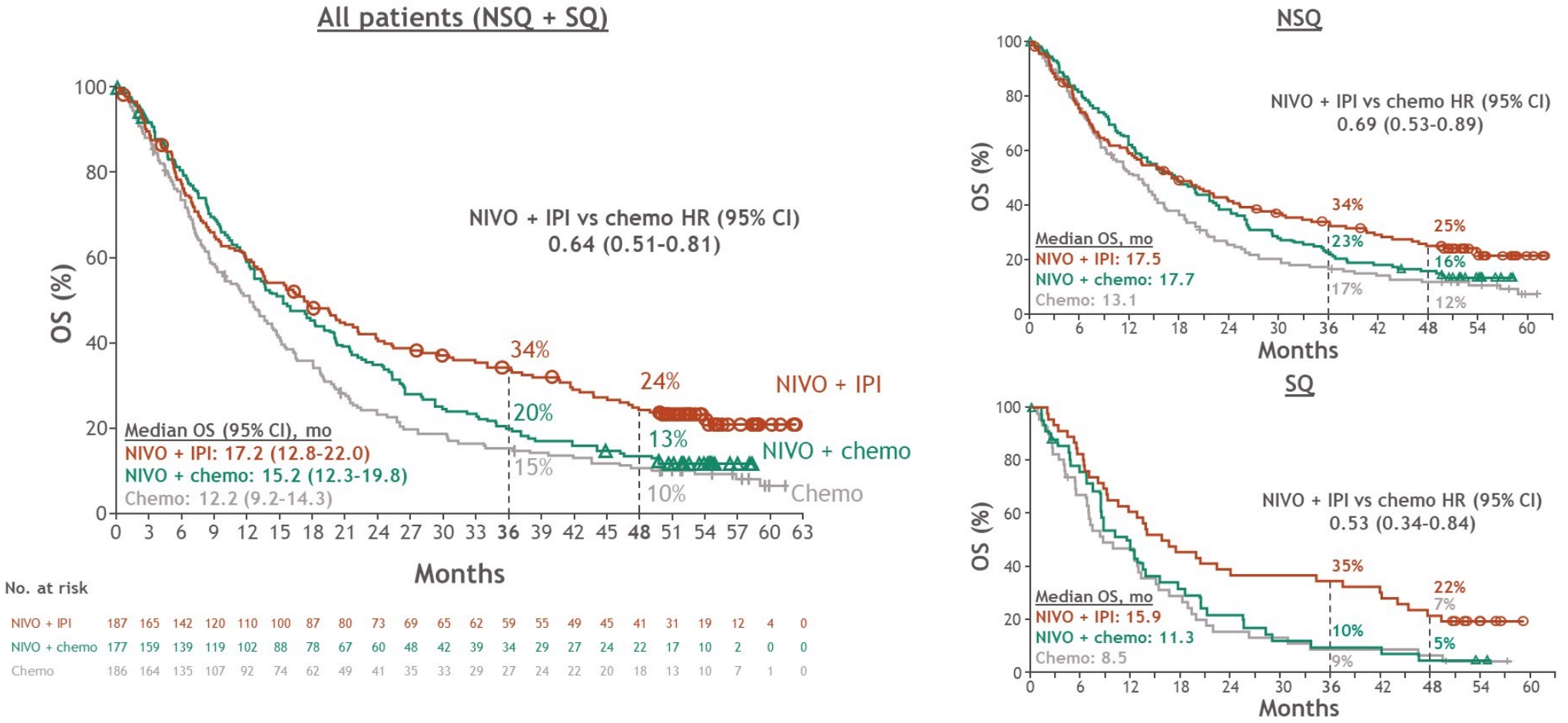
Courtesy of David R Spigel, MD

Paz-Ares, ASCO Annual Meeting Abstract 9016 2021

Doublet Immunotherapy: Nivolumab and Ipilimumab

CheckMate 227

4-year OS in patients with PD-L1 < 1%



In all patients with PD-L1 < 1% (NSQ + SQ) with a PFS event (per BICR), subsequent systemic therapy was received by 46% in the NIVO + IPI arm, 39% in the NIVO + chemo arm, and 48% in the chemo arm; subsequent immunotherapies by 9%, 5%, and 33%; and subsequent chemo by 44%, 37%, and 33%, respectively.

Courtesy of David R Spigel, MD

Paz-Ares, ASCO Annual Meeting Abstract 9016 2021

Doublet Immunotherapy: Nivolumab and Ipilimumab

CheckMate 227

Table 2. Treatment-Related Adverse Events in All the Recipients of Nivolumab plus Ipilimumab or Chemotherapy.*

Adverse Event	Nivolumab plus Ipilimumab (N=576)		Chemotherapy (N=570)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
	number of patients (percent)			
Treatment-related adverse events				
All events	442 (76.7)	189 (32.8)	467 (81.9)	205 (36.0)
Reported in ≥15% of patients				
Diarrhea	98 (17.0)	10 (1.7)	55 (9.6)	4 (0.7)
Rash	98 (17.0)	9 (1.6)	30 (5.3)	0
Fatigue	83 (14.4)	10 (1.7)	108 (18.9)	8 (1.4)
Decreased appetite	76 (13.2)	4 (0.7)	112 (19.6)	7 (1.2)
Nausea	57 (9.9)	3 (0.5)	206 (36.1)	12 (2.1)
Anemia	22 (3.8)	8 (1.4)	188 (33.0)	66 (11.6)
Neutropenia	1 (0.2)	0	98 (17.2)	54 (9.5)
Treatment-related serious adverse events	141 (24.5)	106 (18.4)	79 (13.9)	61 (10.7)
Treatment-related adverse events	104 (18.1)	71 (12.3)	52 (9.1)	28 (4.9)

Courtesy of David R Spigel, MD

Hellman, NEJM, 2019

Chemotherapy and Immunotherapy

Pembrolizumab

KEYNOTE-189

KEYNOTE-407

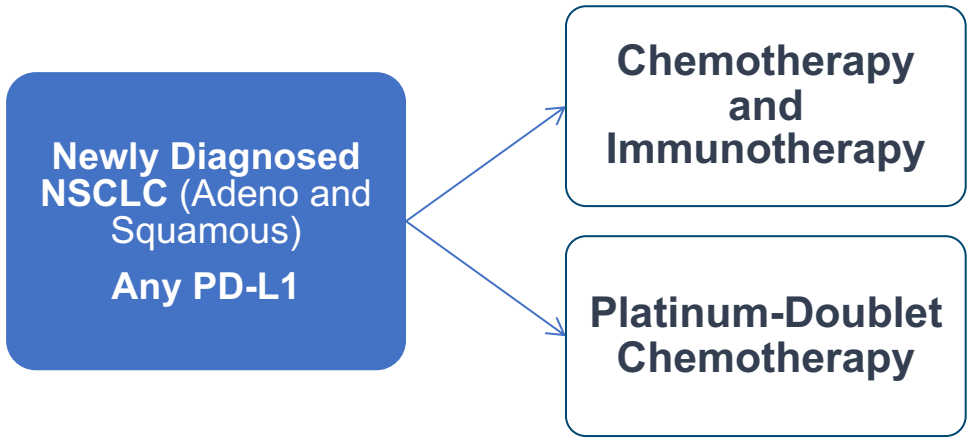
Atezolizumab

IMpower150

Nivolumab + Ipilimumab

CheckMate 9LA

Randomized Phase III Trials



Gandhi, NEJM, 2018

Socinski, NEJM 2018

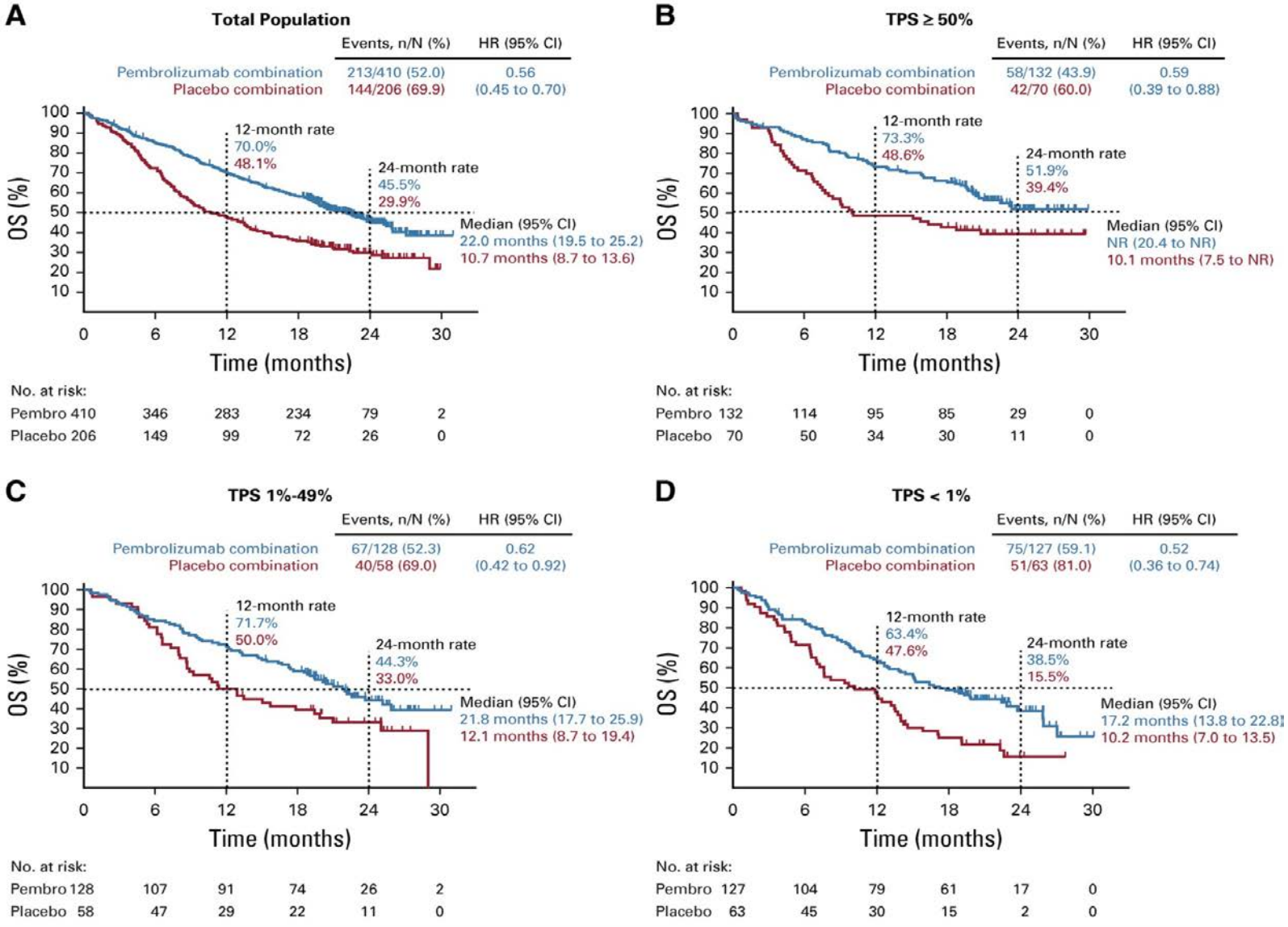
Paz-Ares, NEJM 2018

Paz-Ares, Lancet Onc 2021

Courtesy of David R Spigel, MD

Chemotherapy and Immunotherapy: Pembrolizumab

KEYNOTE-189



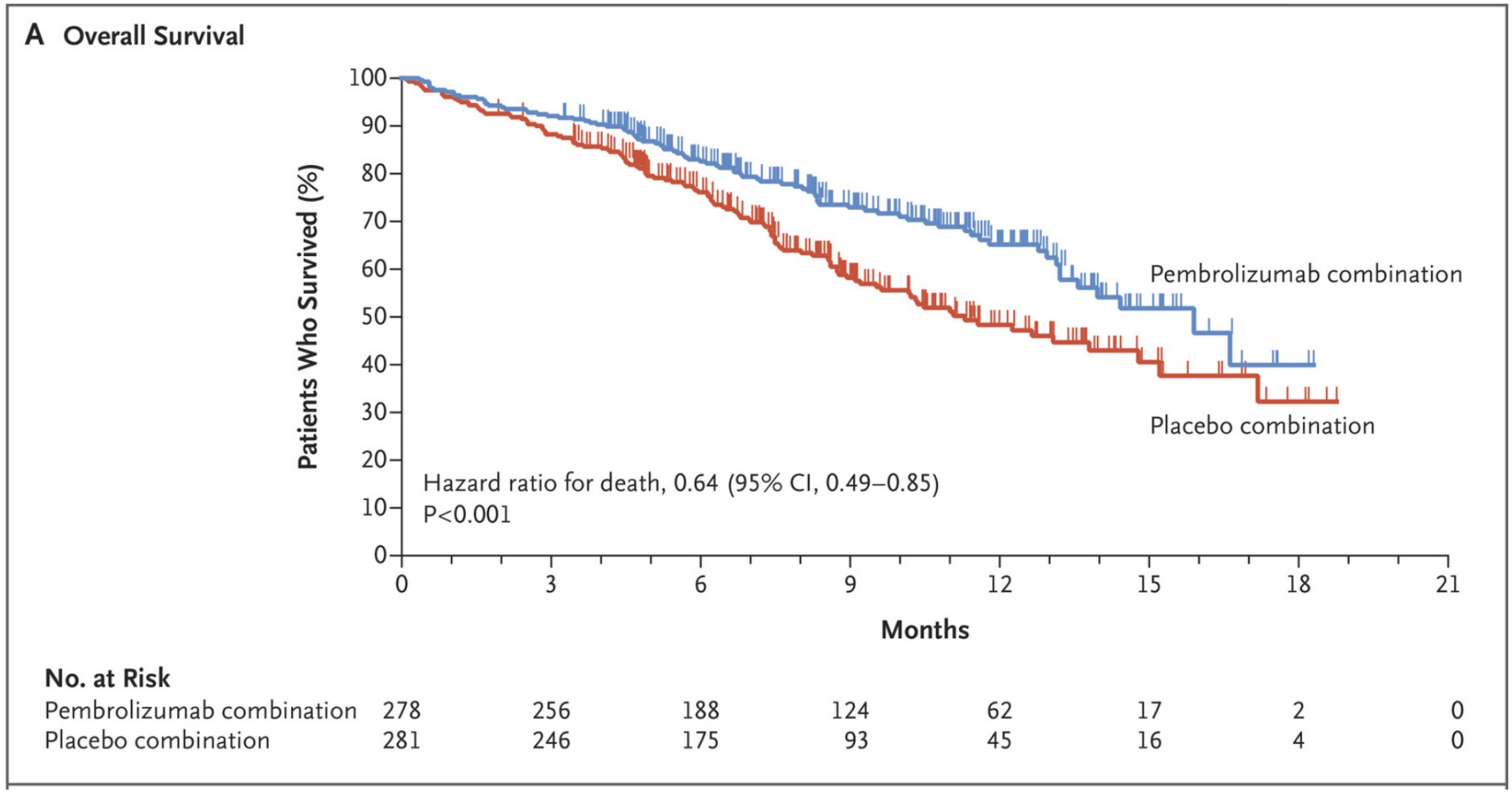
Courtesy of David R Spigel, MD

Gadgeel, JCO 2020

Chemotherapy and Immunotherapy: Pembrolizumab

KEYNOTE-407

- **Squamous NSCLC**



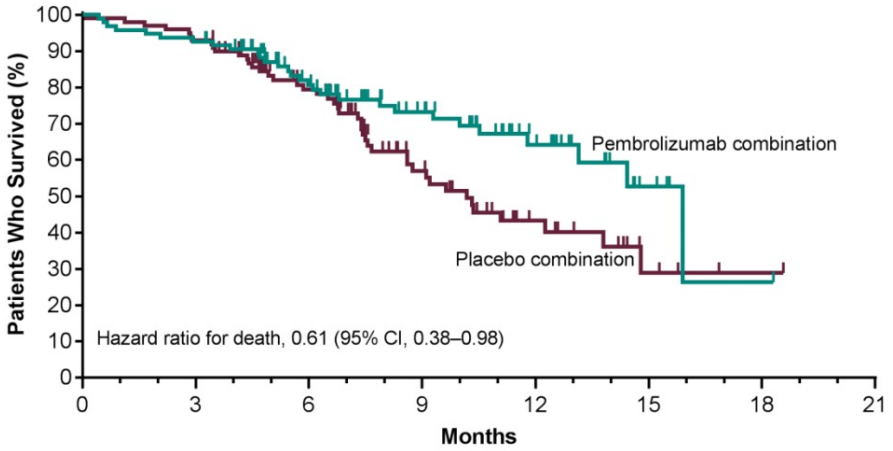
Courtesy of David R Spigel, MD

Paz-Ares, NEJM 2018

Chemotherapy and Immunotherapy: Pembrolizumab

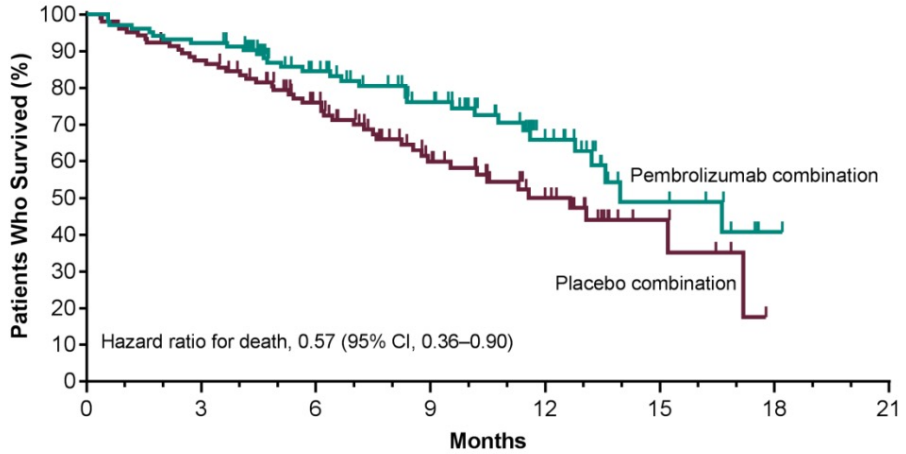
KEYNOTE-407

(A) Tumor proportion score <1%



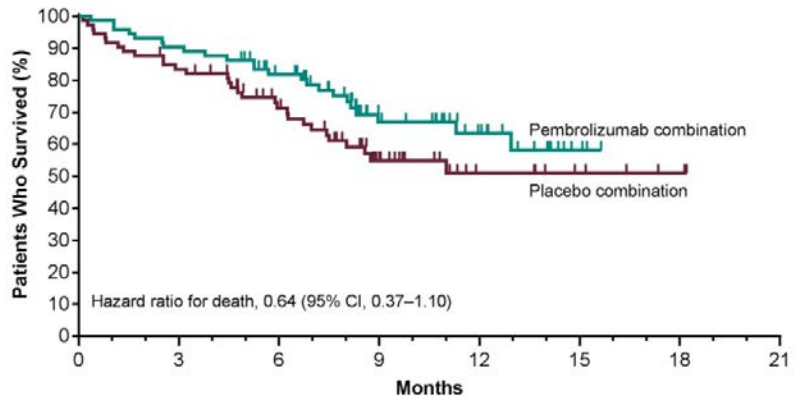
No. at Risk								
Pembrolizumab combination	95	88	62	41	20	5	1	0
Placebo combination	99	92	63	32	14	4	1	0

(B) Tumor proportion score 1-49%



No. at Risk								
Pembrolizumab combination	103	95	68	50	25	9	1	0
Placebo combination	104	90	66	37	21	6	0	0

(C) Tumor proportion score ≥50%

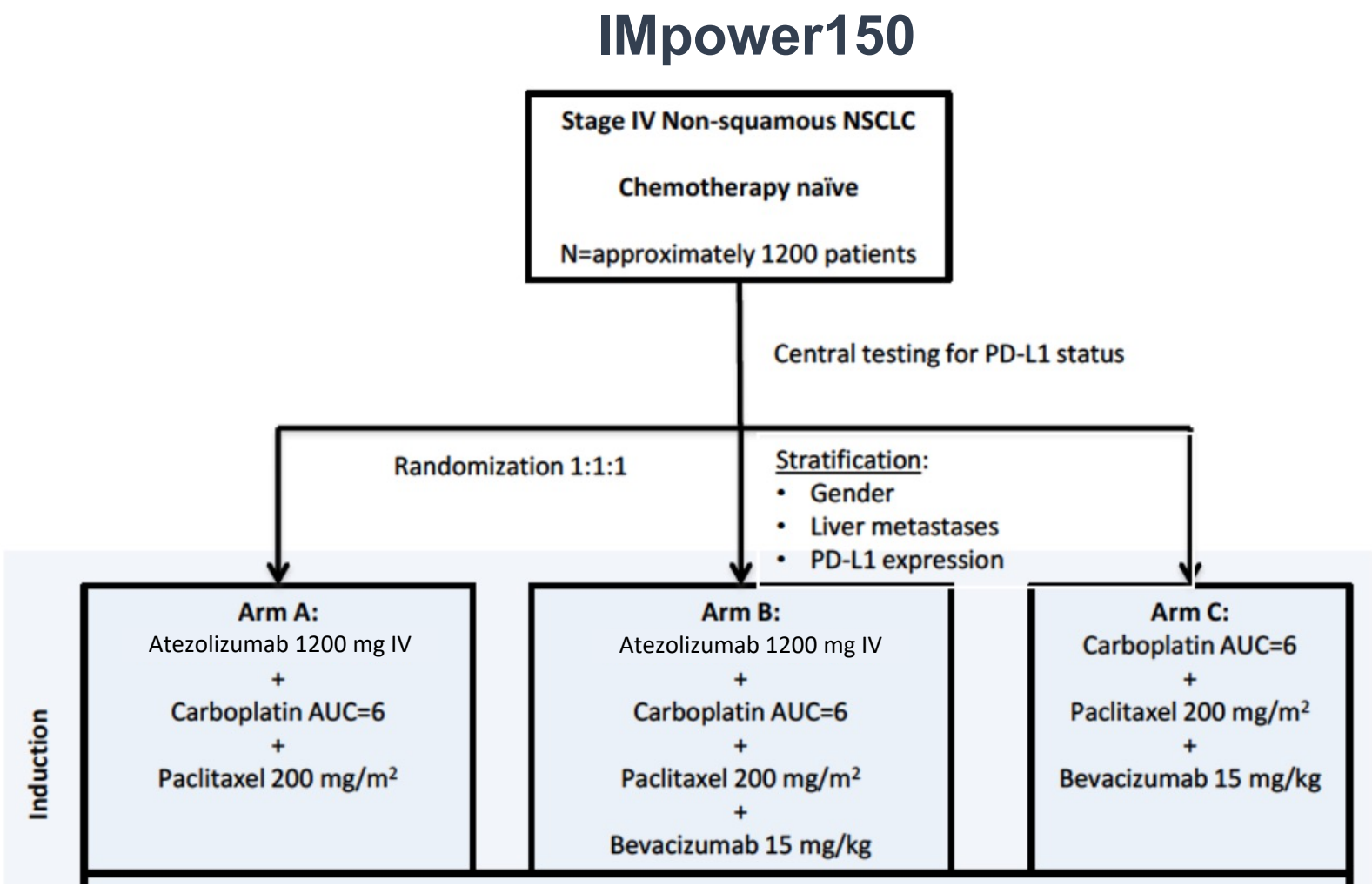


No. at Risk								
Pembrolizumab combination	73	66	53	28	15	3	0	0
Placebo combination	73	60	42	21	9	5	2	0

Courtesy of David R Spigel, MD

Paz-Ares, NEJM 2018

Chemotherapy and Immunotherapy: Atezolizumab



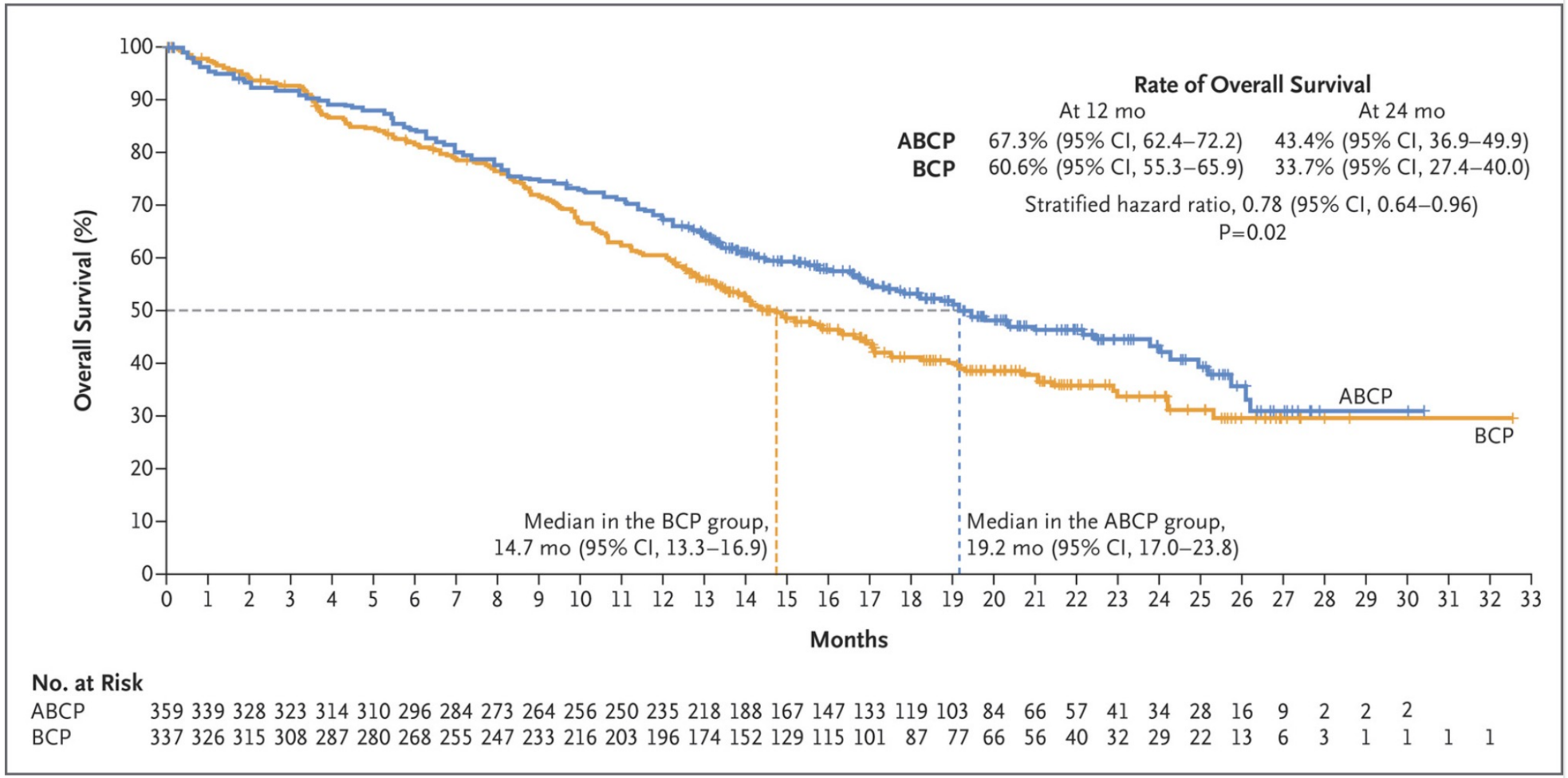
Courtesy of David R Spigel, MD

Socinski NEJM 2018

Chemotherapy and Immunotherapy: Atezolizumab

IMpower150

- **Non-Squamous NSCLC**



Courtesy of David R Spigel, MD

Socinski NEJM 2018

Chemotherapy and Immunotherapy: Atezolizumab (other Phase III Trials)

IMpower132

- Non-Squamous
- Platinum/Pemetrexed/Atezolizumab v. Platinum/Pem
- Co-Primary Endpoints: PFS (HR 0.60 favoring Atezo); OS (trend favoring Atezo, NS)

IMpower130

- Non-Squamous
- Platinum/nab-paclitaxel/Atezolizumab v. Platinum/nab-paclitaxel
- Co-Primary Endpoints: PFS (HR 0.64 favoring Atezo); OS (HR 0.79 favoring Atezo)

IMpower131

- Squamous
- Platinum/nab-paclitaxel/Atezolizumab v. Platinum/nab-paclitaxel
- Co-Primary Endpoints: PFS (HR 0.71 favoring Atezo); OS (trend favoring Atezo, NS)

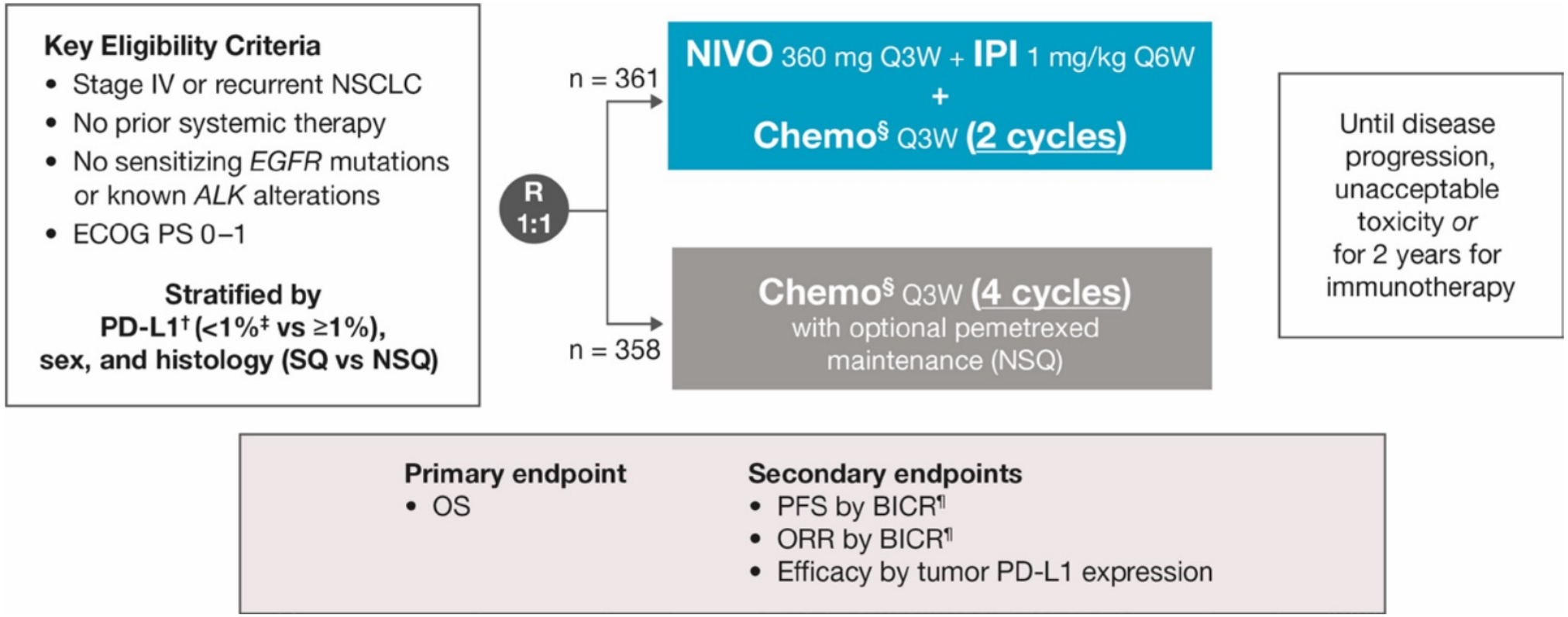
Courtesy of David R Spigel, MD

Nishio, JTO 2020
Jotte, JTO 2020

West, Lancet Onc 2019

Chemotherapy and Immunotherapy: Nivolumab and Ipilimumab

CheckMate 9LA



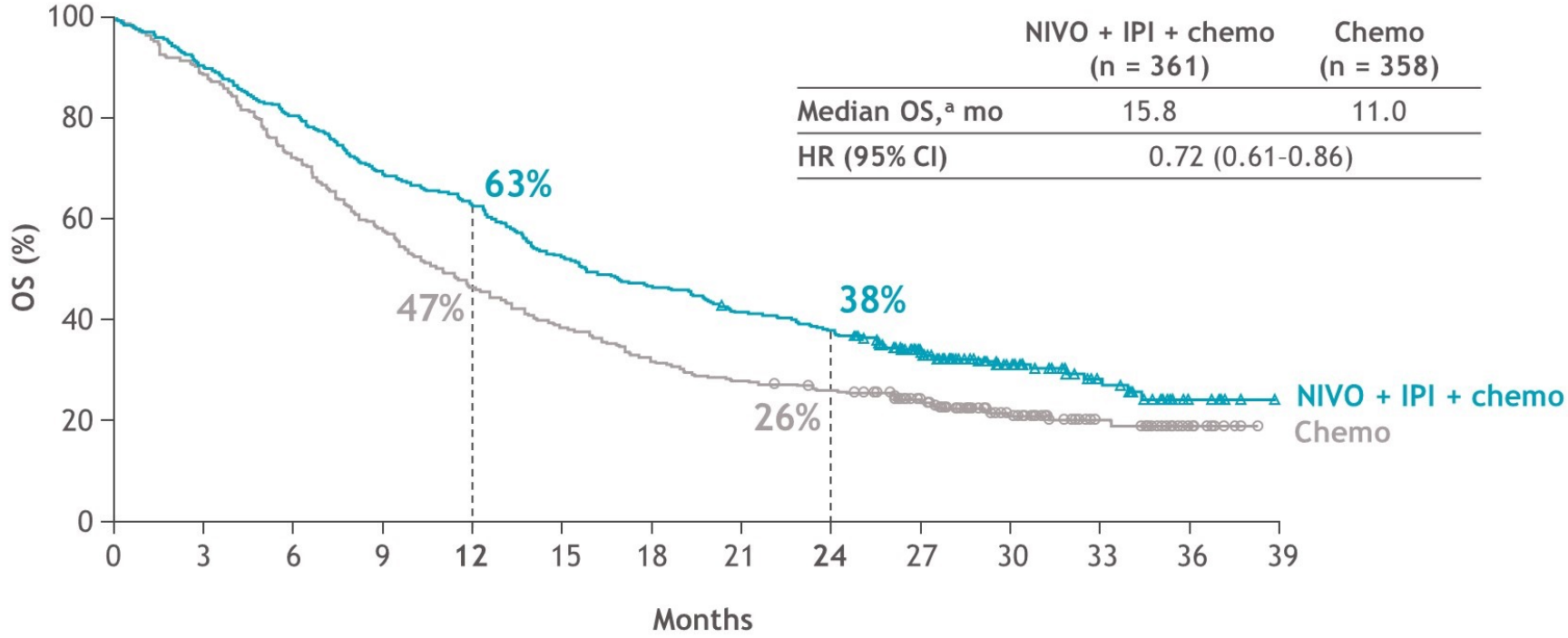
Courtesy of David R Spigel, MD

Paz-Ares, Lancet Onc 2021

Chemotherapy and Immunotherapy: Nivolumab and Ipilimumab

CheckMate 9LA

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

Courtesy of David R Spigel, MD

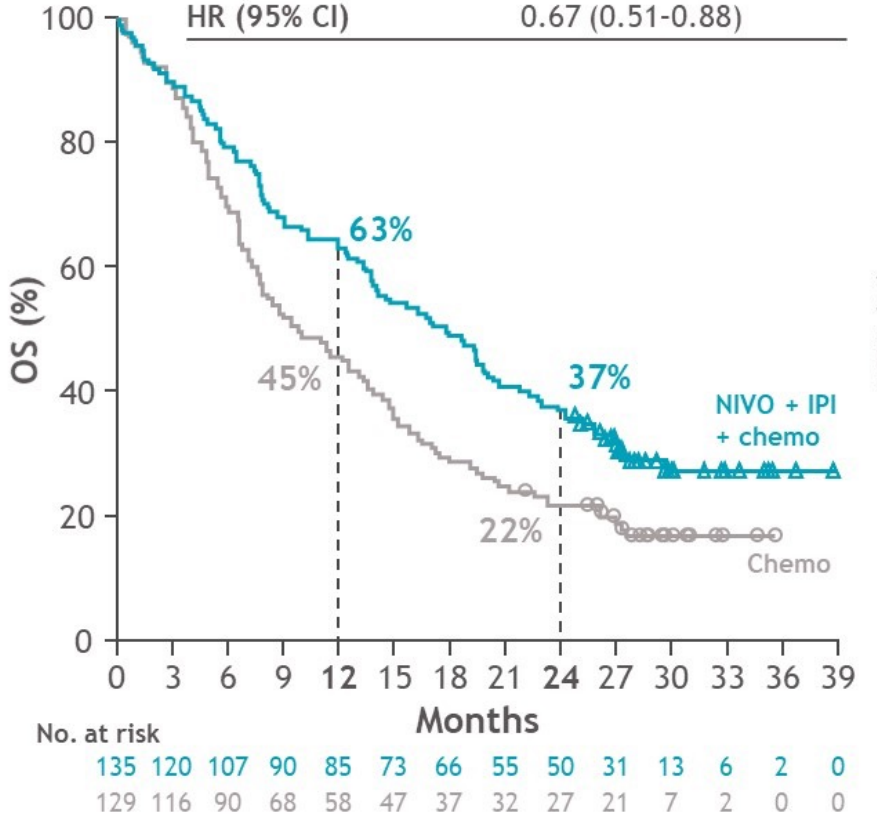
Reck, ASCO Annual Meeting Abstract 9000 2021

Chemotherapy and Immunotherapy: Nivolumab and Ipilimumab

CheckMate 9LA

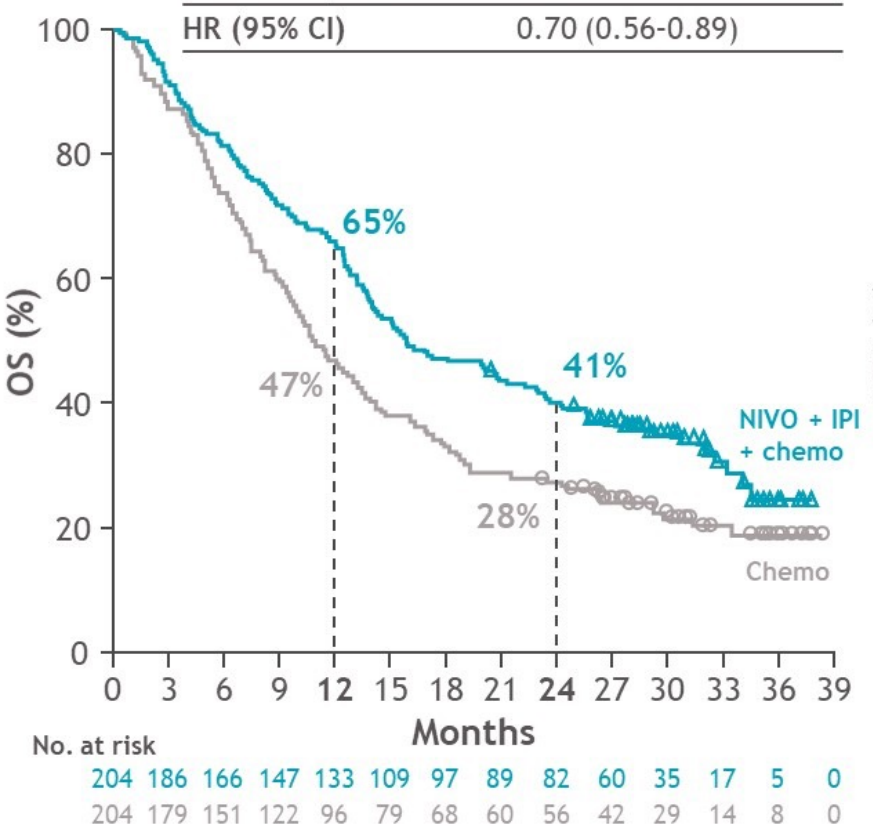
PD-L1<1%

	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)
Median OS,[b] mo	17.7	9.8
HR (95% CI)	0.67 (0.51-0.88)	



PD-L1>1%

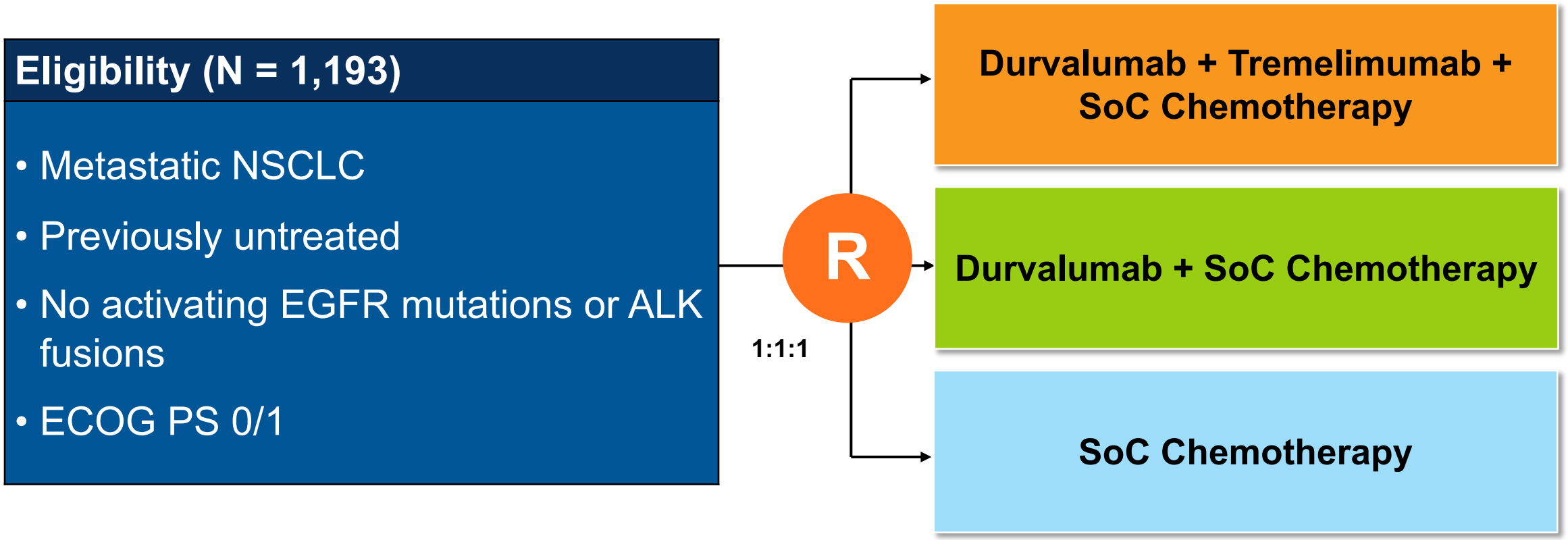
	NIVO + IPI + chemo (n = 204)	Chemo (n = 204)
Median OS,[b] mo	15.8	10.9
HR (95% CI)	0.70 (0.56-0.89)	



Courtesy of David R Spigel, MD

Reck, ASCO Annual Meeting Abstract 9000 2021

Ongoing Phase III POSEIDON Trial Design



Co-primary endpoints: Overall survival and Progression-free survival

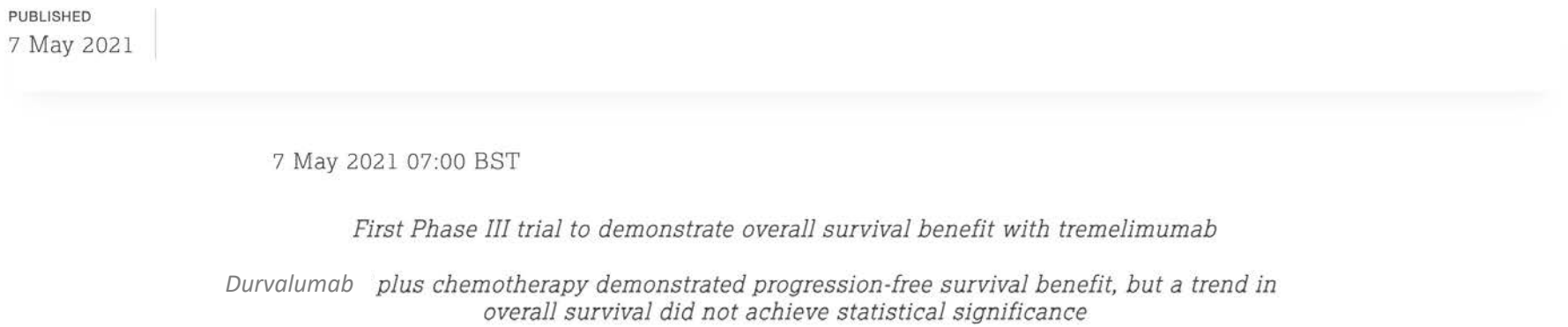
Secondary endpoints include: Objective response rate, health-related quality of life and Safety

www.clinicaltrials.gov (NCT03164616). Accessed July 2021.

Courtesy of David R Spigel, MD

Chemotherapy and Immunotherapy: Durvalumab and Tremelimumab

Durvalumab and tremelimumab with chemotherapy demonstrated overall survival benefit in POSEIDON trial for 1st-line Stage IV non-small cell lung cancer



PUBLISHED
7 May 2021

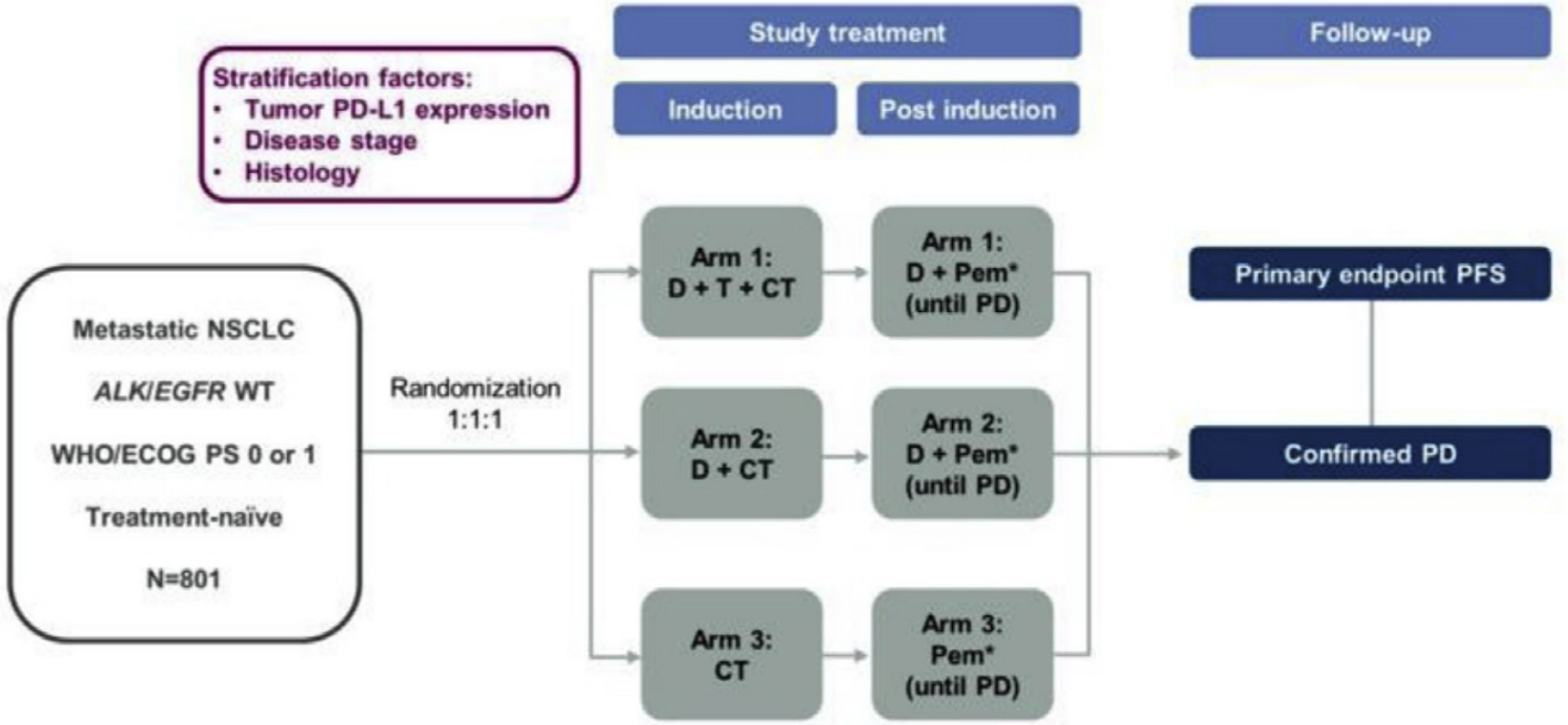
7 May 2021 07:00 BST

First Phase III trial to demonstrate overall survival benefit with tremelimumab

Durvalumab plus chemotherapy demonstrated progression-free survival benefit, but a trend in overall survival did not achieve statistical significance

Courtesy of David R Spigel, MD

Chemotherapy and Immunotherapy: Durvalumab and Tremelimumab

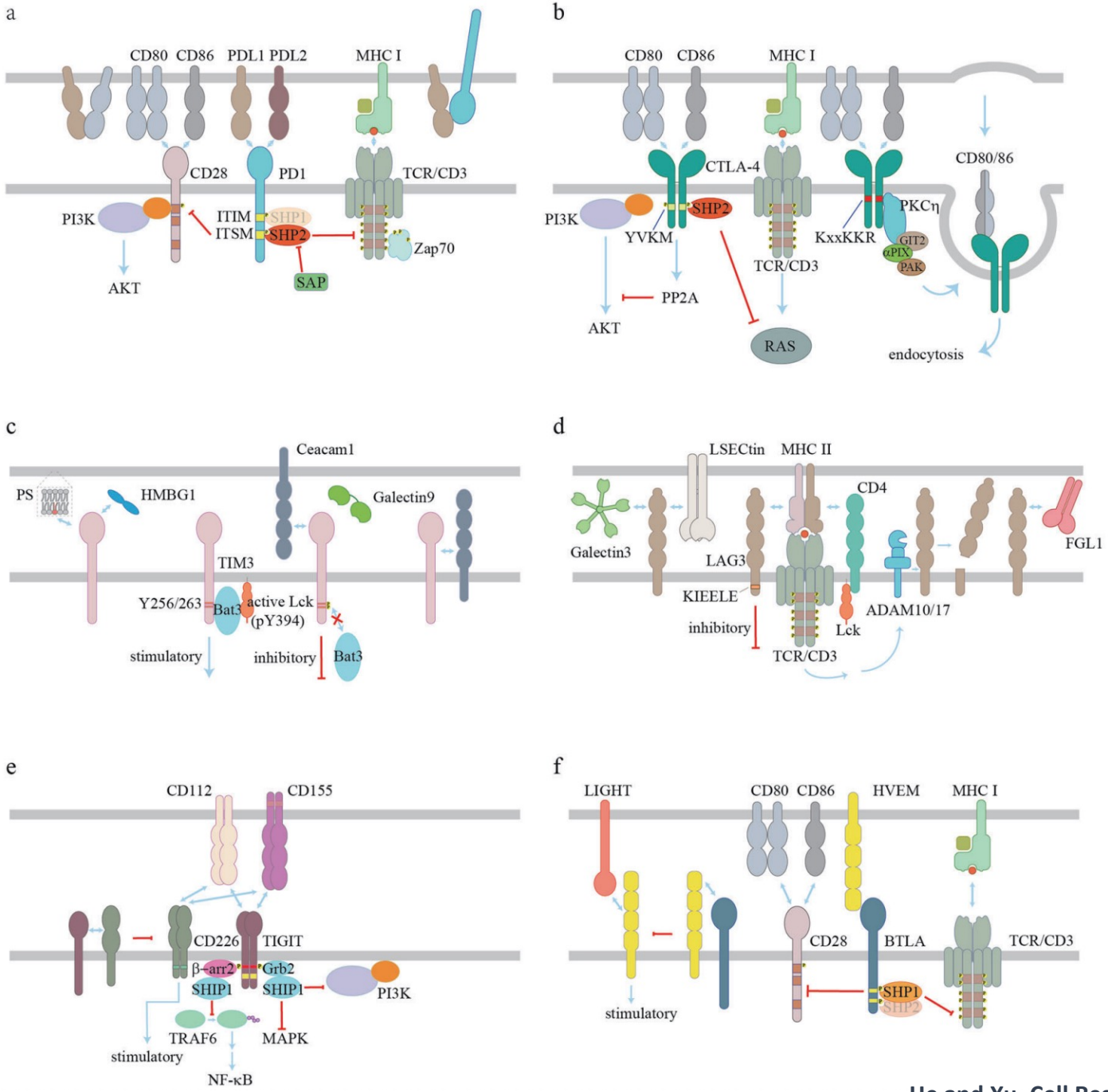


*Patients with non-squamous histology who initially received pemetrexed during induction will receive pemetrexed maintenance therapy in the post induction phase if eligible. CT, chemotherapy; D, durvalumab; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; OS, overall survival; PD, progressive disease; Pem, pemetrexed; PFS, progression-free survival; PS, performance status; T, tremelimumab; WHO, World Health Organization; WT, wild-type

Courtesy of David R Spigel, MD

Mok, JTO 2017 (Abstract P1.04-008)

Other Checkpoint Targets

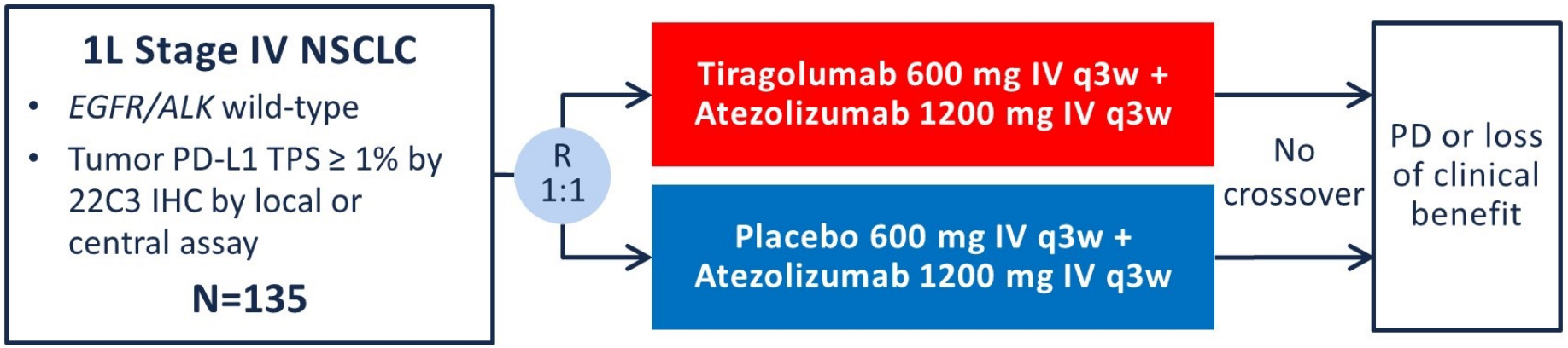


Courtesy of David R Spigel, MD

He and Xu, Cell Research 2020

Targeting the TIGIT Checkpoint

CITYSCAPE Study Design



Stratification Factors:

- PD-L1 TPS (1-49% vs ≥ 50%)
- Histology (Non-Squamous vs Squamous)
- Tobacco use (yes vs no)

- **Co-Primary Endpoints: ORR** and **PFS**
- **Key Secondary Endpoints: Safety**, DOR, OS, Patient-reported outcomes (PROs)
- **Exploratory Endpoints:** Efficacy analysis by PD-L1 status

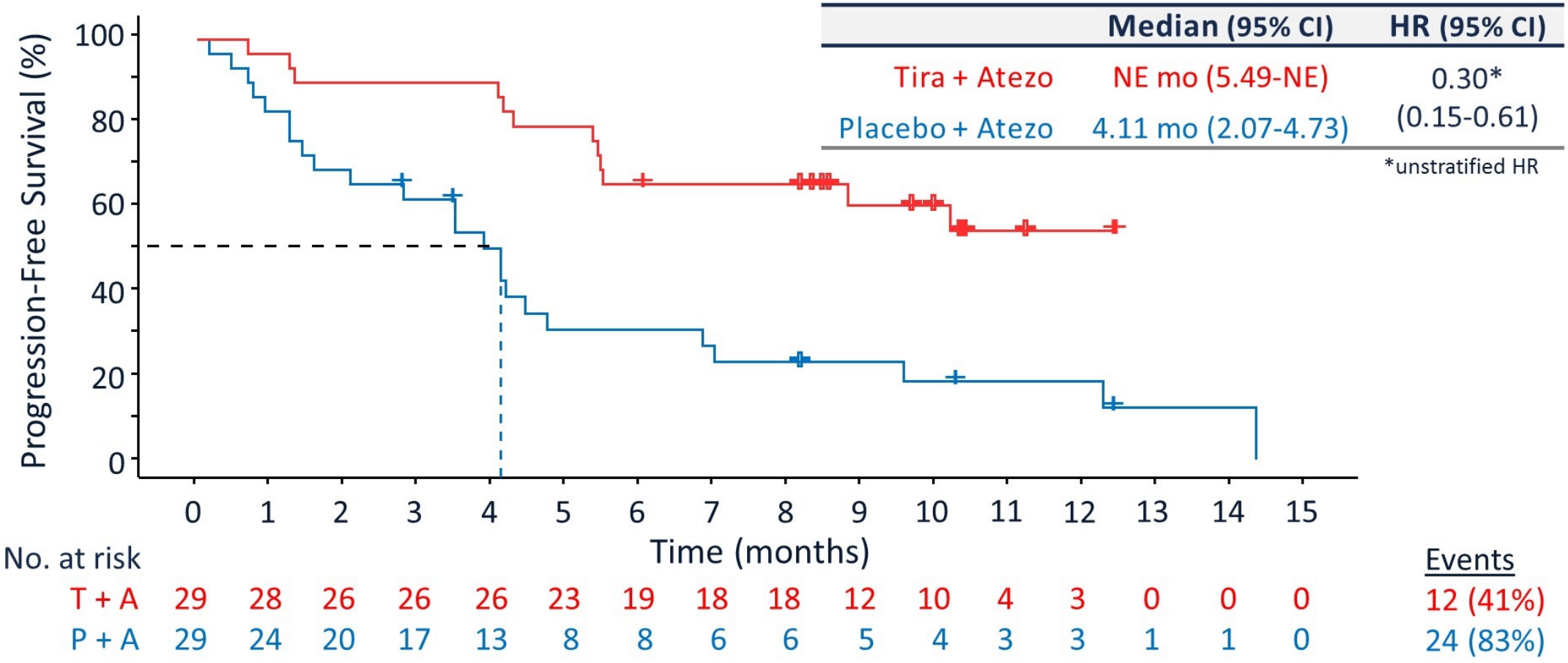
DOR = duration of response; IHC = immunohistochemistry; ORR = confirmed overall response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival ; q3w = every 3 weeks; R = randomized; TPS = tumor proportion score

Courtesy of David R Spigel, MD

Johnson, ASCO Annual Meeting Abstract 9503 2020

CITYSCAPE

Updated Investigator-Assessed PFS: PD-L1 TPS ≥ 50%



	Median (95% CI)	HR (95% CI)
Tira + Atezo	NE mo (5.49-NE)	0.30* (0.15-0.61)
Placebo + Atezo	4.11 mo (2.07-4.73)	

*unstratified HR

No. at risk																Events
T + A	29	28	26	26	26	23	19	18	18	12	10	4	3	0	0	0	12 (41%)
P + A	29	24	20	17	13	8	8	6	6	5	4	3	3	1	1	0	24 (83%)

NE = non-evaluable; P+A = placebo + atezolizumab; T+A = tiragolumab + atezolizumab; TPS = tumor proportion score

Follow data cutoff: 02 December 2019

Courtesy of David R Spigel, MD

Johnson, ASCO Annual Meeting Abstract 9503 2020

Immunotherapy Duration

Mono-Immunotherapy	Doublet-Immunotherapy	Chemotherapy and Immunotherapy
• Pembrolizumab (2 years) • Atezolizumab (indefinite) • Cemiplimab (2 years)	• Nivolumab and Ipilimumab (2 years)	• Histology-Based Chemotherapy and Immunotherapy: Pembrolizumab Nivolumab/Ipilimumab (2yrs) Atezolizumab Durvalumab (indefinite)

Courtesy of David R Spigel, MD

Summary

- **Patients with Newly Diagnosed Metastatic NSCLC who do not have Targeted Therapy Options – are candidates for:**

  Mono-Immunotherapy (Pembrolizumab, Atezolizumab, Cemiplimab)

  Doublet-Immunotherapy (Nivolumab/Ipilimumab)

  Chemotherapy and Immunotherapy (Pembrolizumab, Atezolizumab, Nivolumab/Ipilimumab)

- **Immune Regimen Selection should be based on Clinical Factors and PD-L1 Expression**

- **Newer Immune Strategies are in Development**

  (Durvalumab/Tremelimumab, Tiragolumab, etc)

Courtesy of David R Spigel, MD

Case 1

HPI

A 43yo gentleman who presented to an OSH 12/2018 w/ L-pleural effusion - diagnosed NS-NSCLC (VATS). Presented to our facility for additional opinion with neck pain, weight loss, odynophagia 3/2019.

PMH

GCT 1992 – s/p surgery and adjuvant CE (?)

Type B Aortic dissection/Graft

L-CEA - stent

HTN

SH

Identical twin (with JRA)

Single father

Works in a factory

Smoker – quit 2007

Courtesy of David R Spigel, MD

Case 1 Continued

Evaluation:

ECOG PS 1

Limited neck movement d/t pain

CT/PET/MRI revealed lesions in C1, right humerus, and LLL/pleura

Path: adenocarcinoma (pleura), outside 'hotspot' sequencing (*EGFR, ALK, BRAF, KRAS, ROS* WT), PD-L1 50% (22C3)

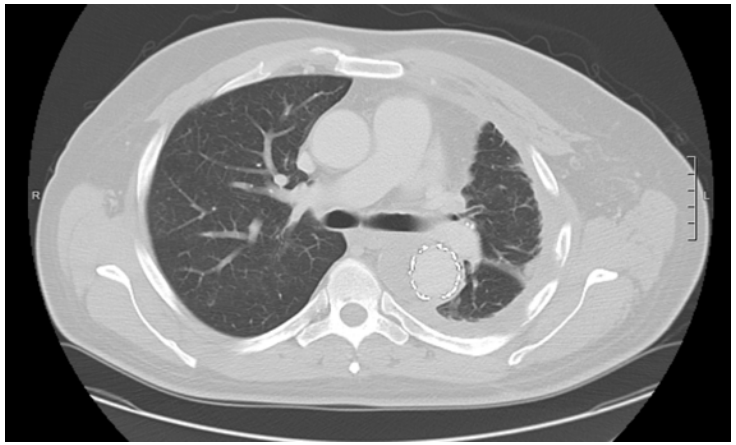
Treatment:

Pembrolizumab (3wk dosing, 4/2019)

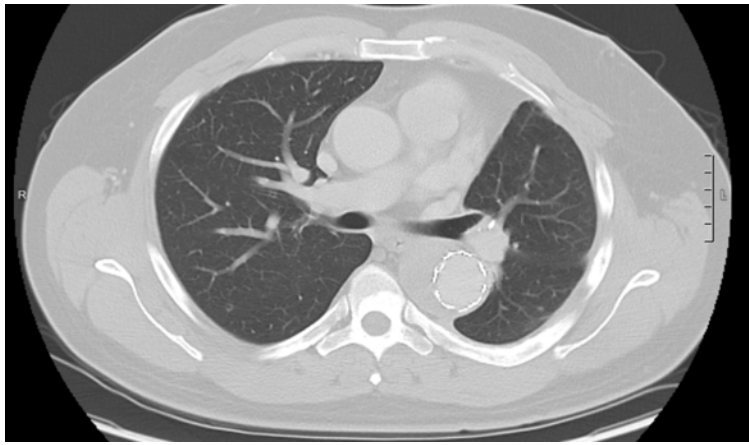
RT to the C-spine 4/2019

Denosumab

Narcotics



May 2019

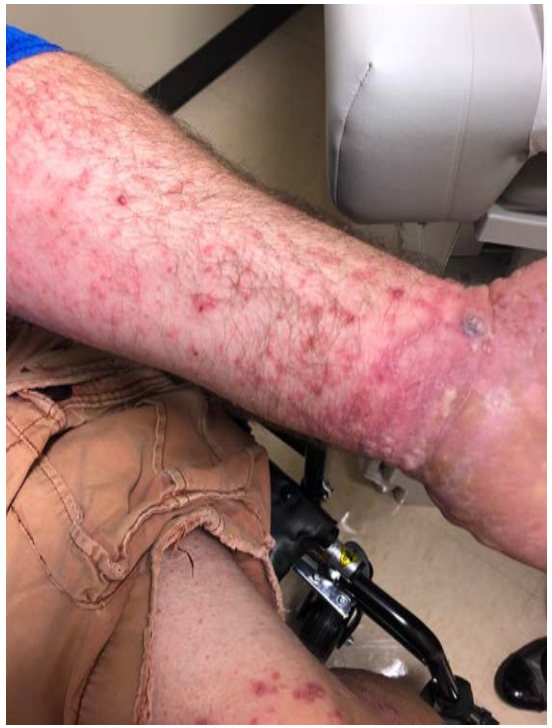


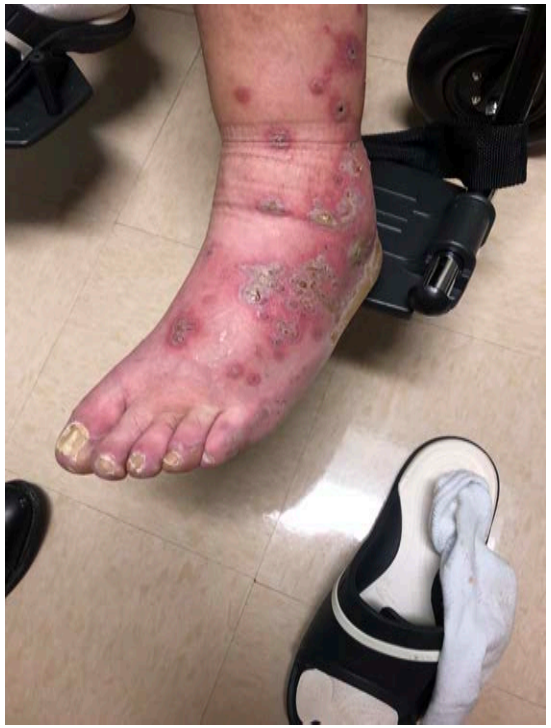
May 2020

Courtesy of David R Spigel, MD

Case 1 Continued

Moved to 6 wk dosing June 2020 – s/p 2 doses (400mg)





Therapy stopped 7/2020
Skin healed (steroids and time)
NED 6/2021

Courtesy of David R Spigel, MD

Case 2

HPI

A 52yo gentleman who presented to an OSH 8/2017 with CP.

PMH

Psoriasis

SH

Married
Realtor
Smoker - quit 2014

Courtesy of David R Spigel, MD

Case 2 Continued

Evaluation:

ECOG PS 0

CT/PET/MRI revealed lesions in lungs, LAN, bones

Path: adenocarcinoma (SCV node), FM1 NGS (*MAP2K1, STK11, MYCN, CCNE1, INPP4B, MCL1, MYCL1;* MSS, TMB 21 Mut/Mb), PD-L1 30% (22C3)

Treatment:

Treated on study with nivolumab/ipilimumab 9/2017 – 9/2019

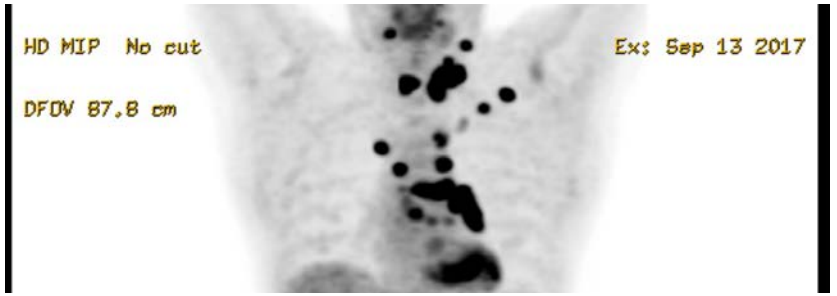
Local lung recurrence 6/2020. Resumed nivolumab/ipilimumab (off study)

RT to the Mediastinum 9/2020

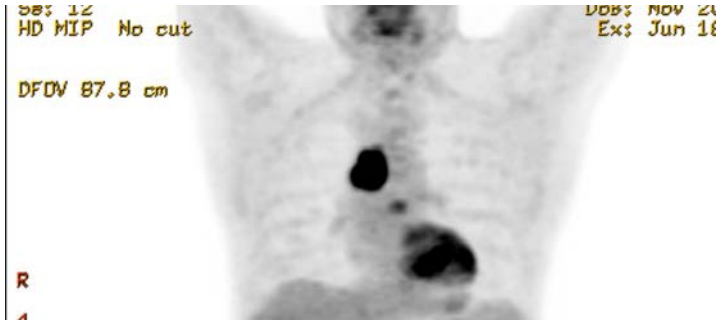
Denosumab/zoledronic acid

Prednisone 10mg/d (psoriasis)

Doing well – Cruise this summer



Sept 2017



June 2020

Courtesy of David R Spigel, MD

Case 3

HPI

A 67yo woman who heard her back ‘pop’ upon getting out of bed 8/2019.

PMH

Asthma
HTN

SH

Widow
Supportive children
Smoker - quit 2016

Courtesy of David R Spigel, MD

Case 3 Continued

Evaluation:

ECOG PS 2

CT/PET/MRI revealed lesion at L4, RUL, LAN

Path: adenosquamous carcinoma with spindle features (L4 and MED nodal biopsies), Tempus NGS (*NRAS, TP53, TERT, CDC73;* MSS, TMB 6.8 Mut/Mb), PD-L1 95% (22C3)

Treatment:

Kyphoplasty (L4)

RT to L4

Carboplatin/paclitaxel/pembrolizumab 1/2020 x 4 cycles – then pembro alone

Narcotics

Denosumab

Doing well on pembrolizumab alone (400mg dosing)

Courtesy of David R Spigel, MD