Optum Health Education Program
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Immunotherapy in Non-Small Cell Lung Cancer (NSCLC)

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Masonic Cancer Center
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Comprehensive Cancer Center designated by the National Cancer Institute

Disclosures (Updated April 2021)

- Research Funding: Astra-Zeneca
- Stocks
  - Fate Therapeutics, Merck, Exact Sciences, Blueprint Medicine, Gilead, Astra Zeneca, Novamax

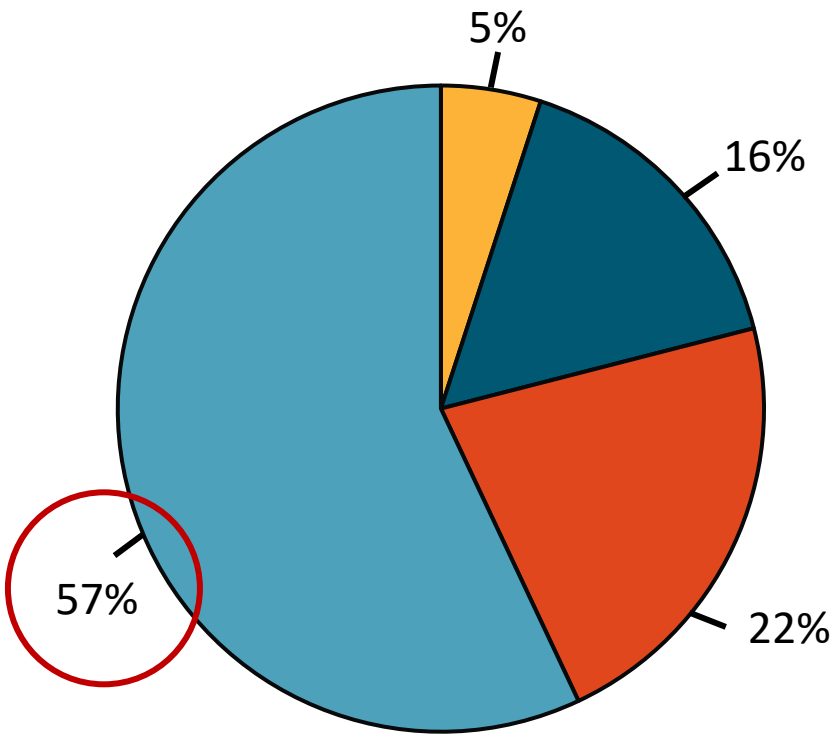
Slide credits: clinicalcareoptions.com

Learning Objectives

- Introduction
- Describe the principles of cancer immunotherapy
- Discuss the role of immunotherapy for the treatment of NSCLC
- Identify which lung cancer patients would benefit from the initial use of immunotherapy versus chemo-immunotherapy
- Immune related adverse events
- Summary

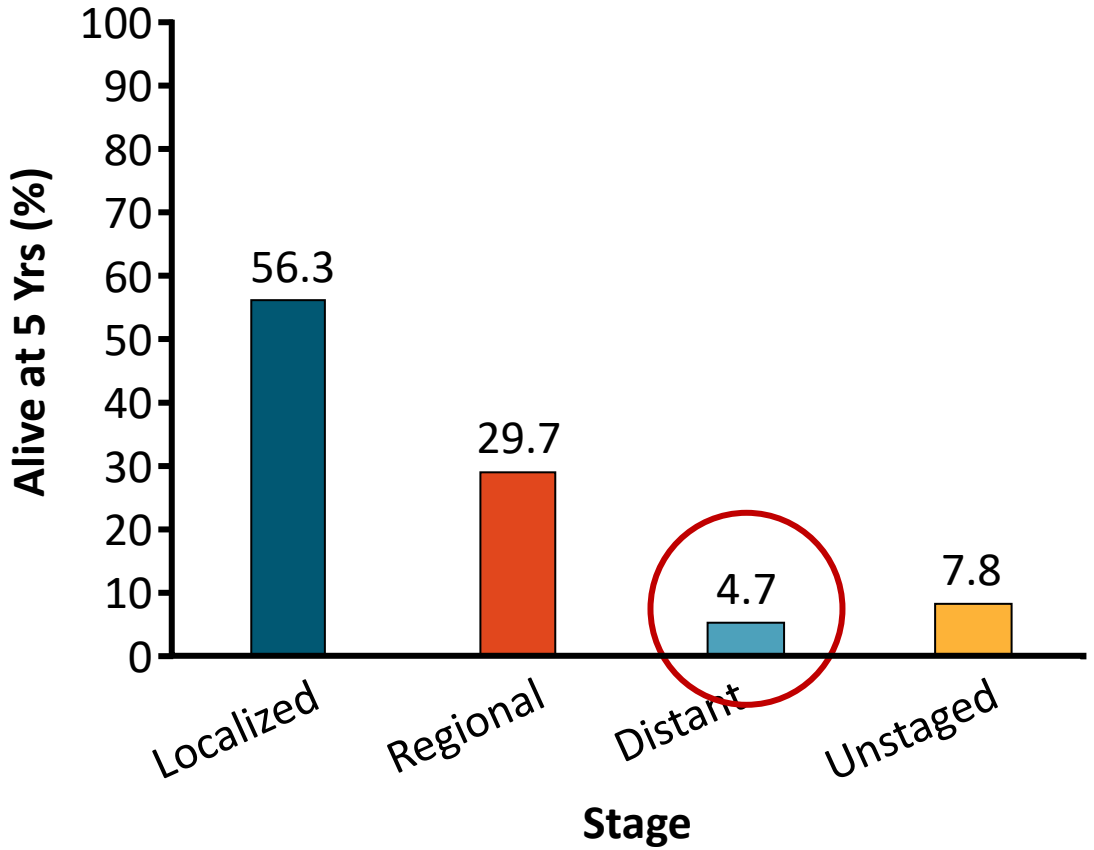
Lung Cancer: US Incidence and 5-Yr Relative Survival (2008-2014)

Percent of Cases by Stage



- **Localized:** confined to primary site
- **Regional:** spread to regional lymph nodes
- **Distant:** cancer has metastasized
- **Unknown:** unstaged

5-Yr Relative Survival by Stage



SEER 18 Cancer Statistics Review, 2008-2014. https://seer.cancer.gov/statfacts/html/lungb.html

Types of lung cancer and staging

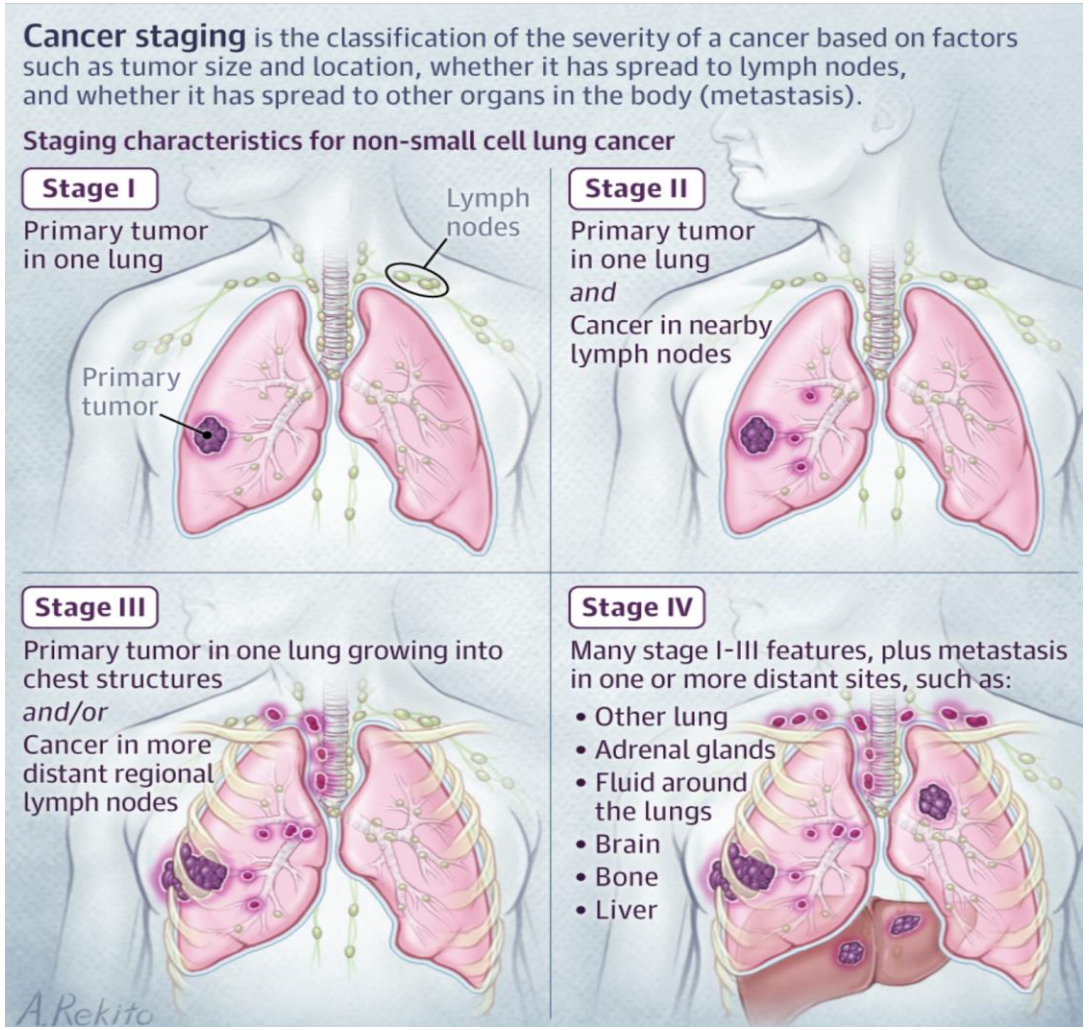
Non-small cell lung cancer (NSCLC)

80% to 85% of lung cancers are NSCLC.

- Adenocarcinoma: Current or former smokers, or non-smokers, women > men, and younger people
- Squamous cell carcinoma: linked to a history of smoking
- Large cell (undifferentiated) carcinoma

Small cell lung cancer (SCLC)

~15% of lung cancer, strong smoking Hx and more aggressive



Jama Oncology patient page, A Patel et al JAMA Oncol. 2020;6(8):1308.

Current Standard for NSCLC

Menu

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2021
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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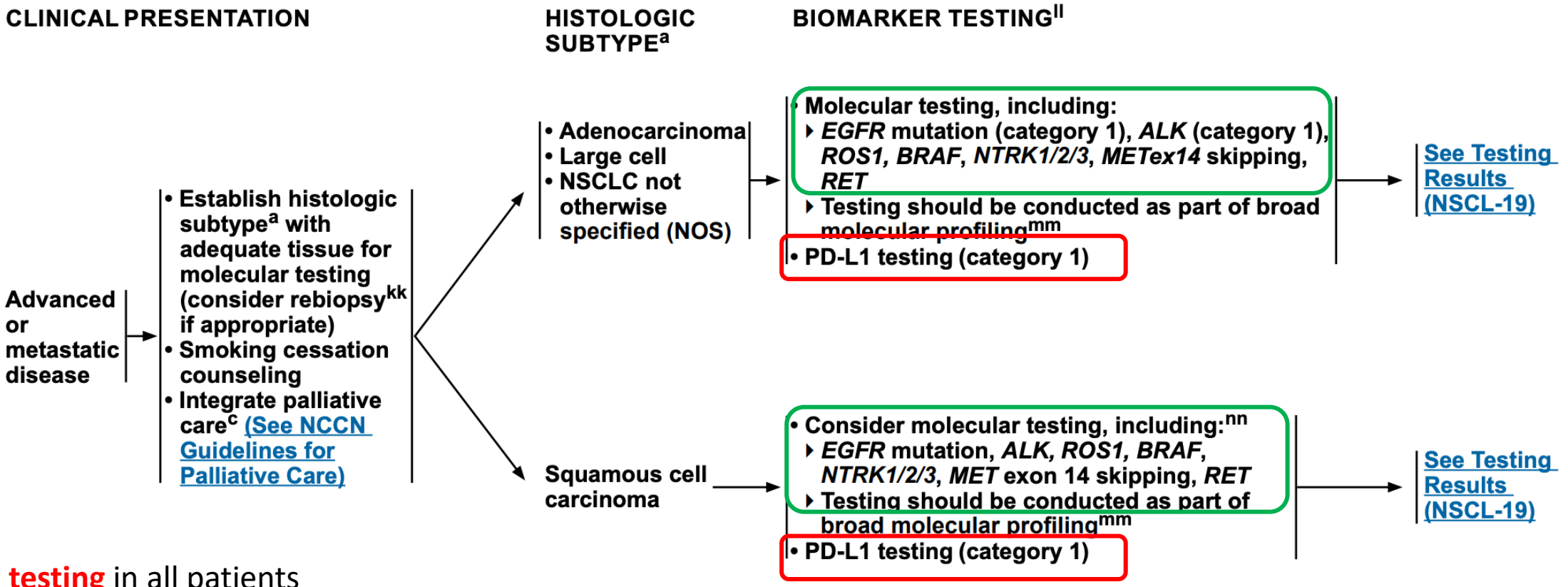
Discussion

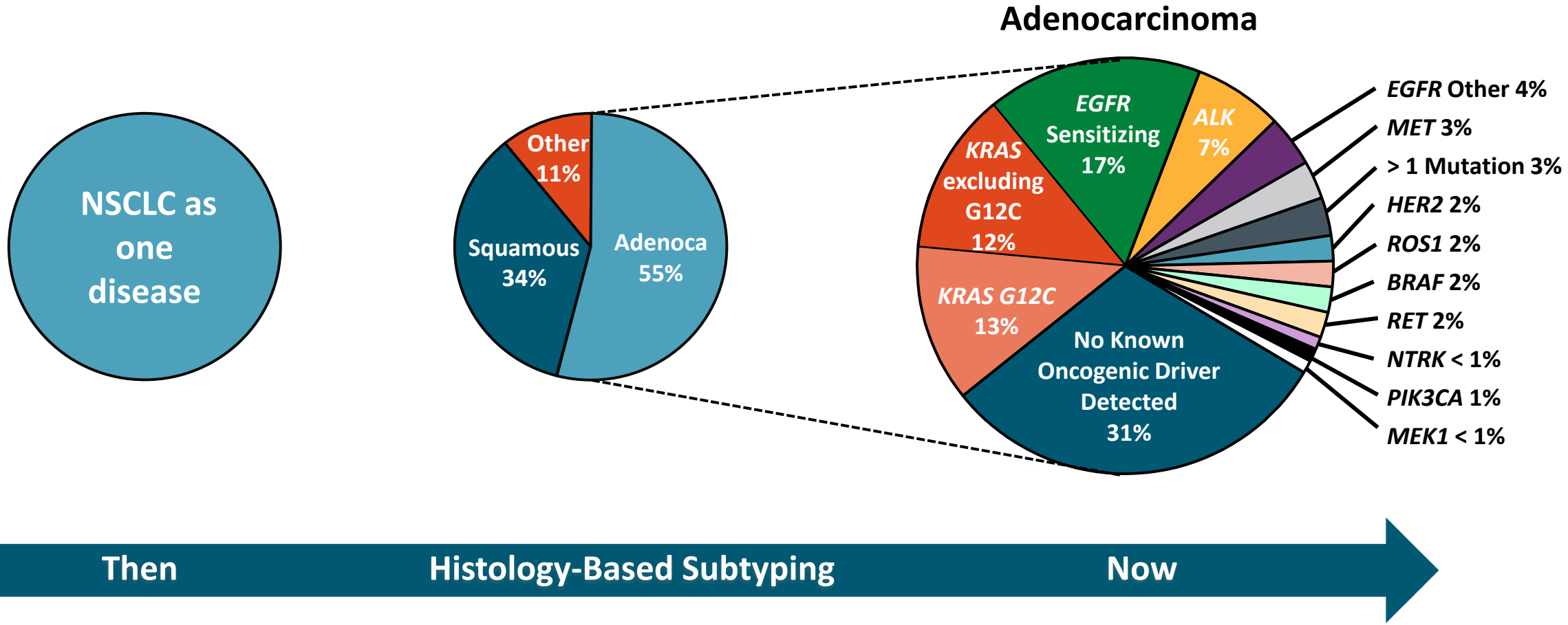


Key-

PD-L1 testing in all patients

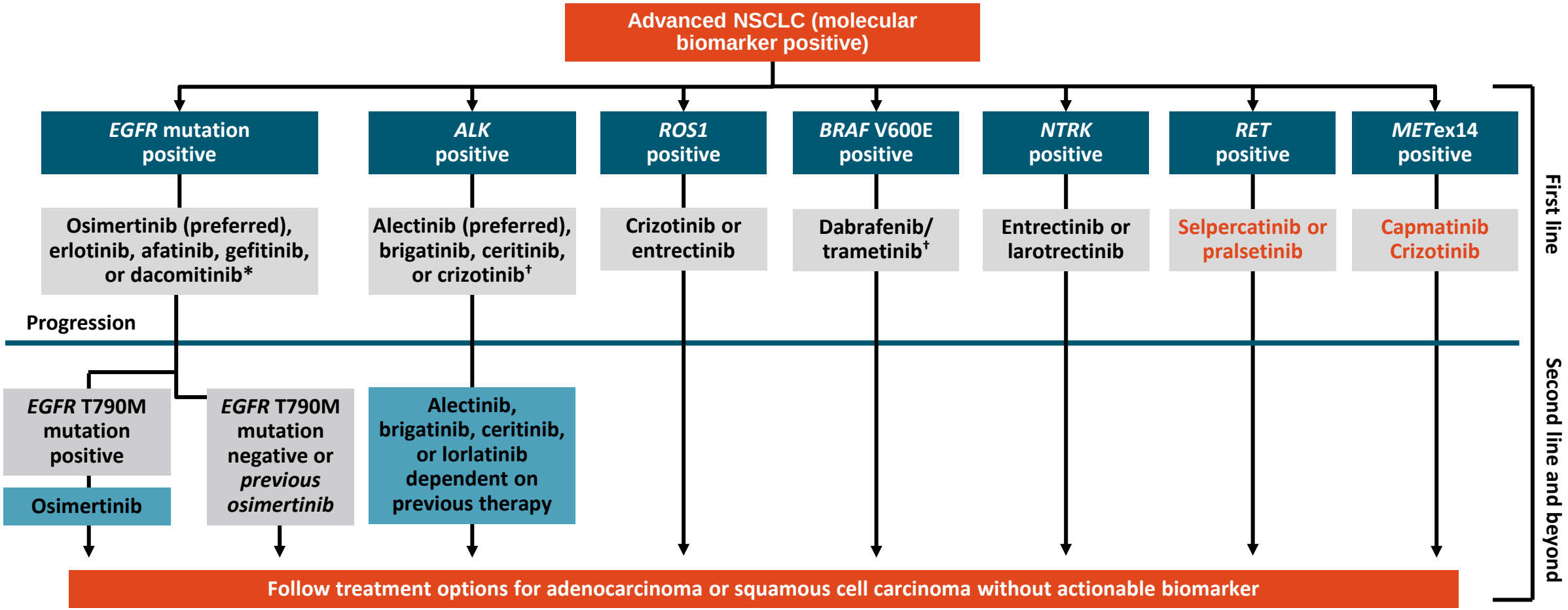
Molecular testing **(look for oncogenic driver mutations** -all adenocarcinomas, select squamous cell)

Non-Small-Cell Lung Cancer: Not One Disease, but Many!



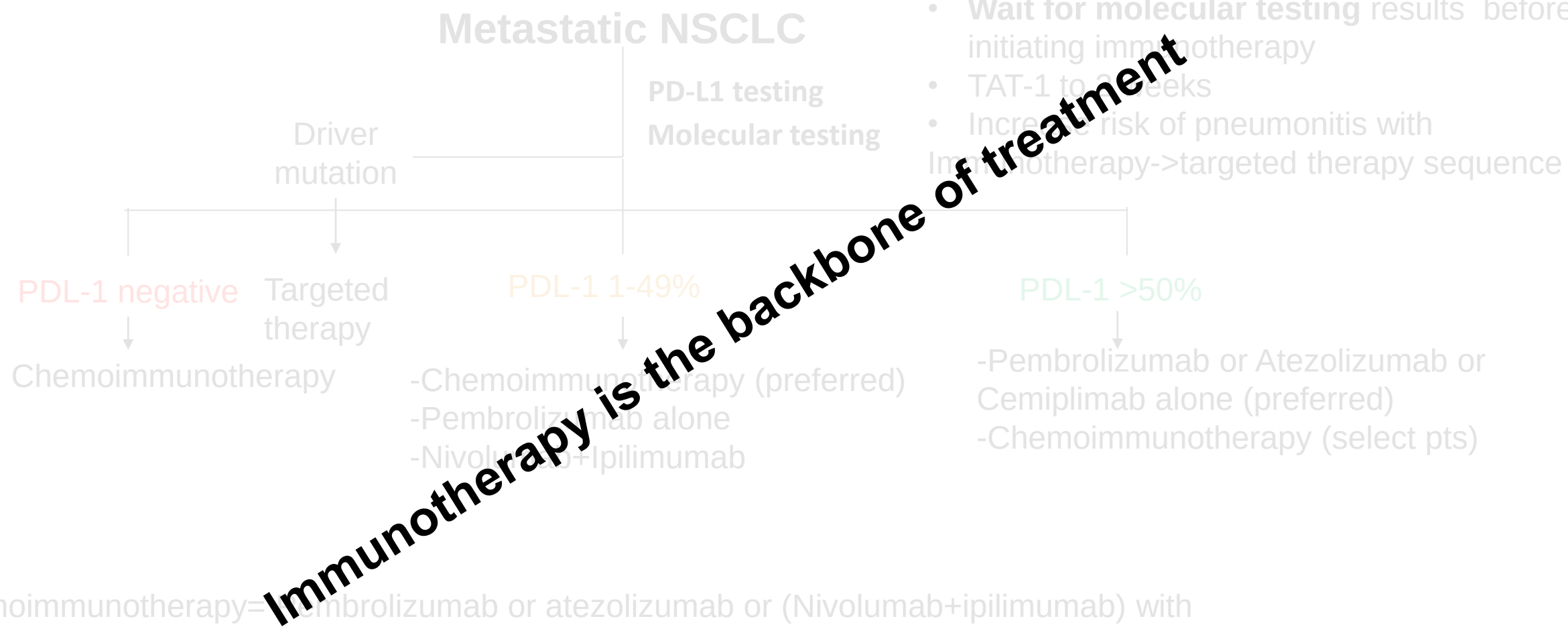
Li. JCO. 2013;31:1039. Tsao. J Thorac Oncol. 2016;11:613.

Treatment Paradigm for Oncogenic mutation–Positive Advanced NSCLC



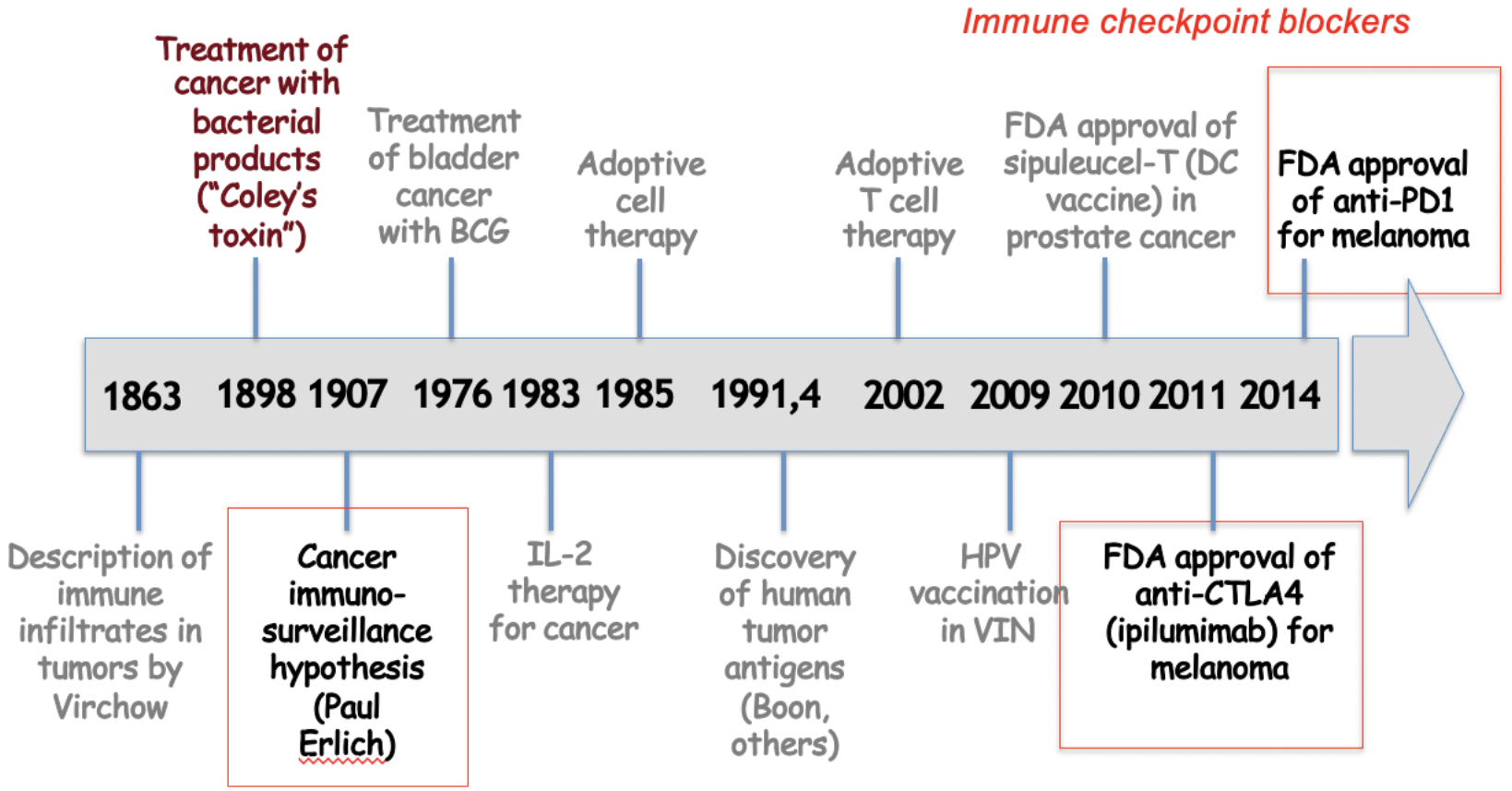
~ 35% of Patients With Advanced Nonsq NSCLC Have a Driver Mutation Targetable by an FDA-Approved Agent

Treatment Paradigm for Advanced NSCLC with no oncogenic driver mutation

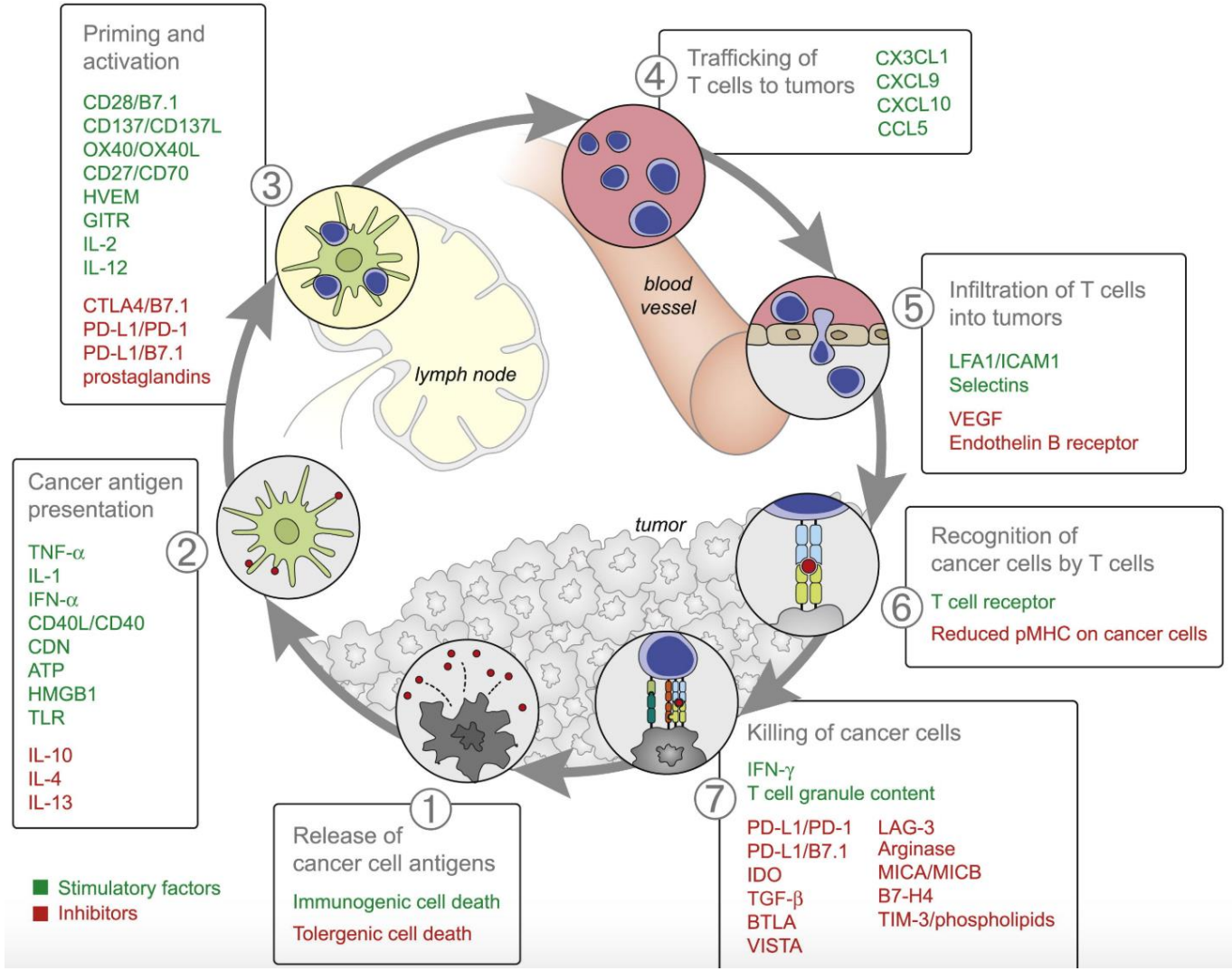


Cancer Immunotherapy

Cancer Immunotherapy is defined as the approach to treat the tumor by either inducing de novo or reactivating tumor specific immune responses

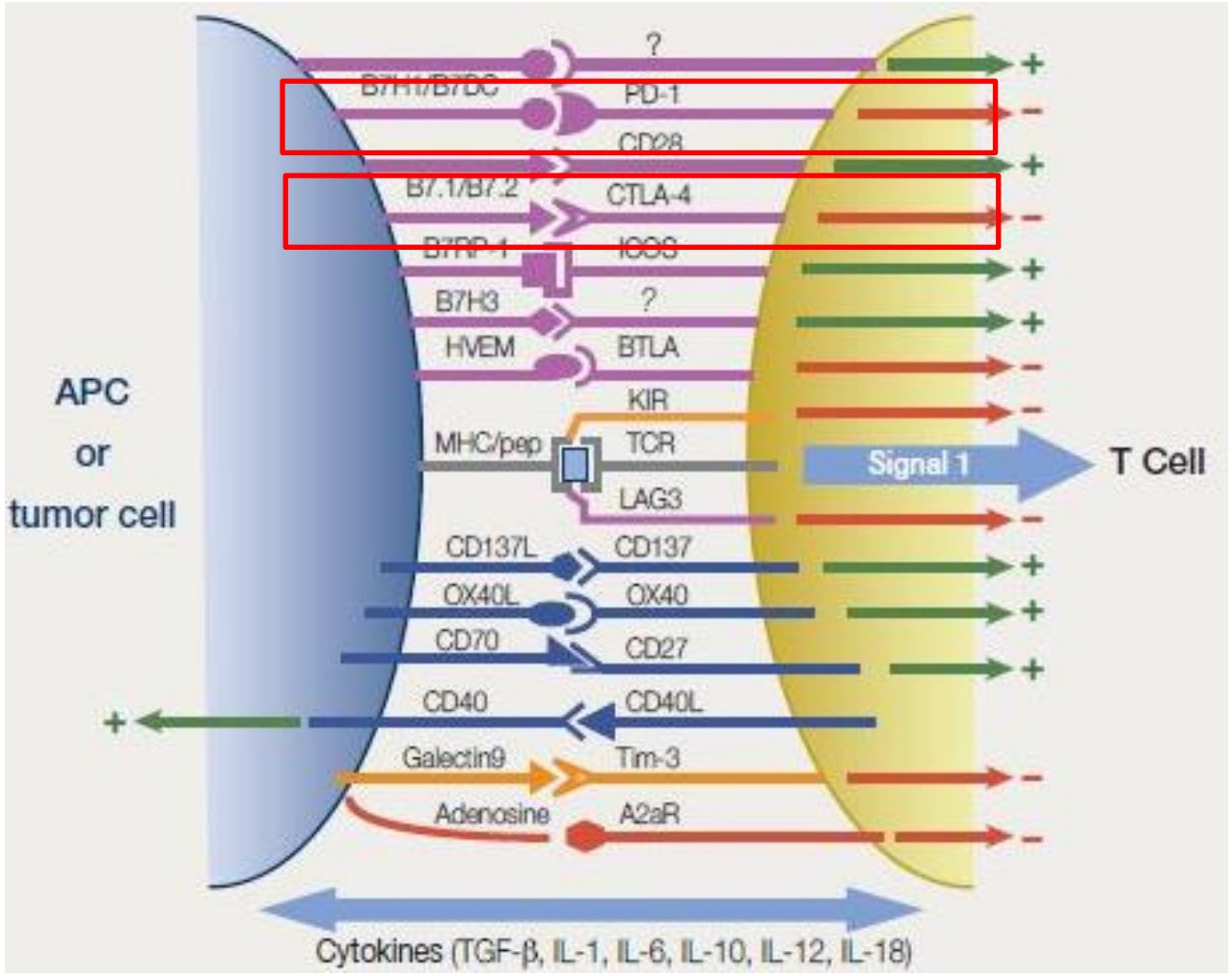


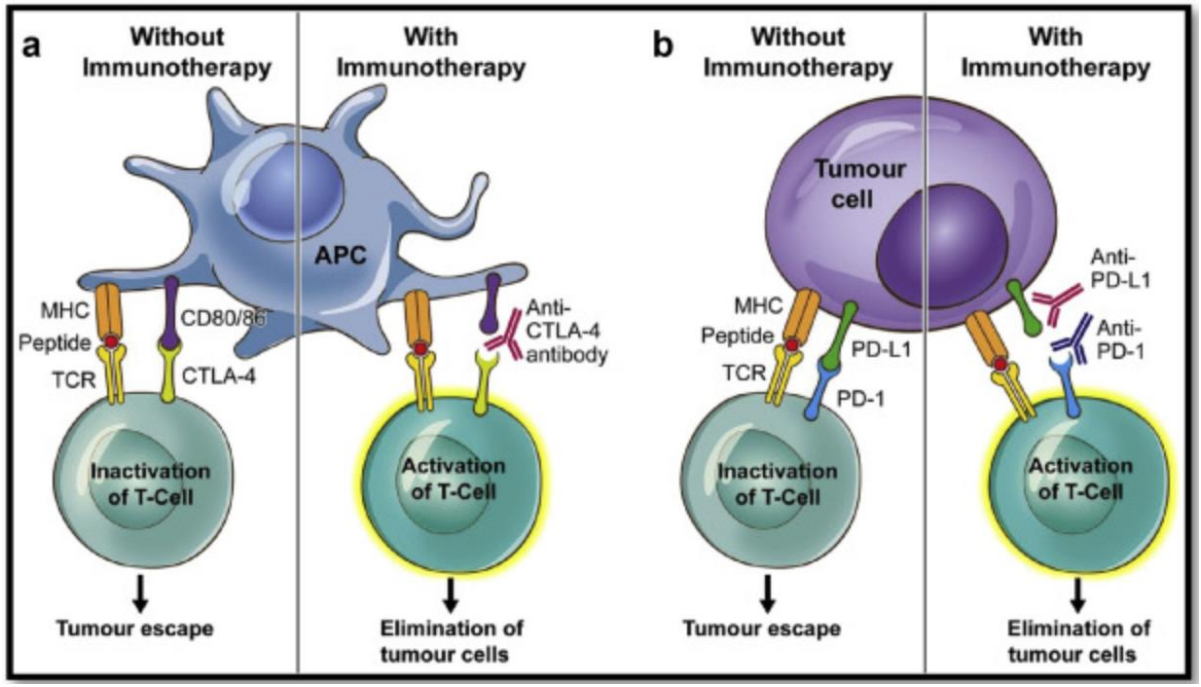
Cancer Immunosurveillance



Mellman et al Immunity 2013.

Immune checkpoints





Ipilimumab, tremilimumab — CTLA-4

atezolizumab, durvaluamb, avelumab — PD-L1

nivolumab, pembrolizumab, cemiplimab — PD-1

Discovery of immune checkpoints

Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

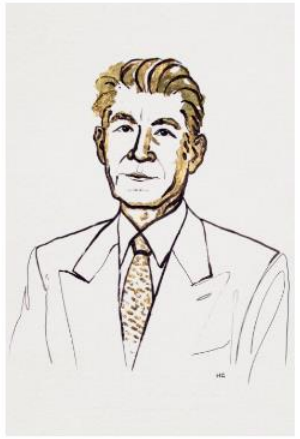
The Nobel Prize in Physiology or Medicine 2018

CTLA-4

Ill. Niklas Elmehed. © Nobel Media

James P. Allison

Prize share: 1/2



Ill. Niklas Elmehed. © Nobel Media

Tasuku Honjo

Prize share: 1/2

PD-L1

The Nobel Prize in Physiology or Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation."

Timeline of FDA approvals of immune checkpoint blockers

CANCER RESEARCH INSTITUTE®
The Anna-Maria Kellen Clinical Accelerator

Drug & Company
- Pembrolizumab, Merck & Co
- Nivolumab, Bristol Myers Squibb
- Atezolizumab, Roche
- Durvalumab, AstraZeneca
- Avelumab, EMD Serono
- Cemiplimab, Regeneron

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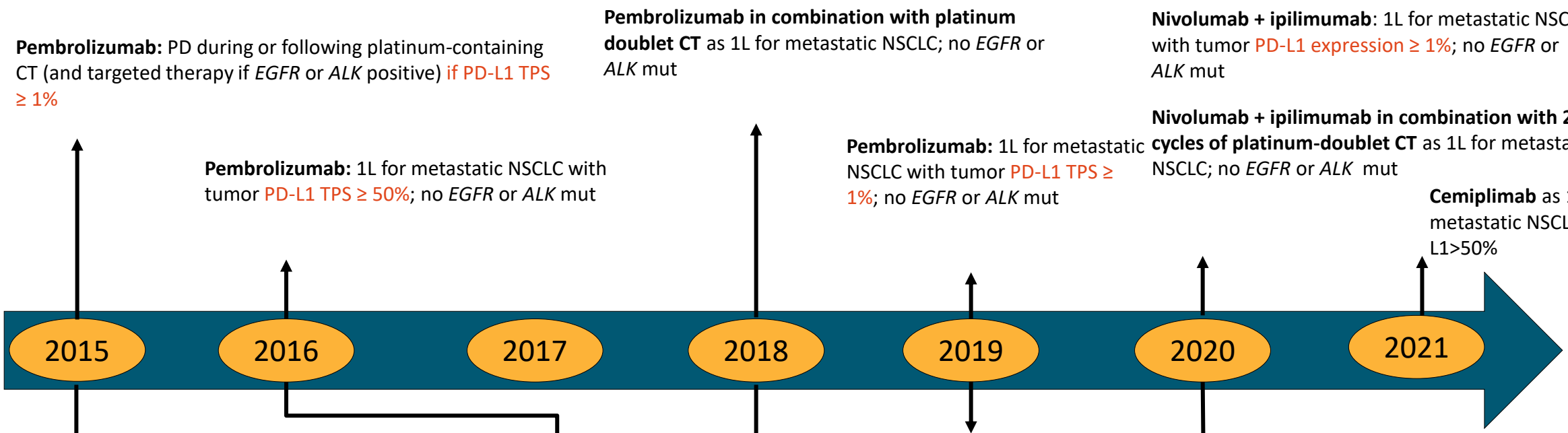
Current FDA Approvals of ICIs for Metastatic NSCLC



Pembrolizumab: PD during or following platinum-containing CT (and targeted therapy if *EGFR* or *ALK* positive) if PD-L1 TPS ≥ 1%

Pembrolizumab: 1L for metastatic NSCLC with tumor PD-L1 TPS ≥ 50%; no *EGFR* or *ALK* mut

Pembrolizumab in combination with platinum doublet CT as 1L for metastatic NSCLC; no *EGFR* or *ALK* mut

Pembrolizumab: 1L for metastatic NSCLC with tumor PD-L1 TPS ≥ 1%; no *EGFR* or *ALK* mut

Nivolumab + ipilimumab: 1L for metastatic NSCLC with tumor PD-L1 expression ≥ 1%; no *EGFR* or *ALK* mut

Nivolumab + ipilimumab in combination with 2 cycles of platinum-doublet CT as 1L for metastatic NSCLC; no *EGFR* or *ALK* mut

Cemiplimab as 1L for metastatic NSCLC; PD-L1>50%

Nivolumab: PD during or following platinum-containing CT (and targeted therapy if *EGFR* or *ALK* mut)

Atezolizumab: PD during or following platinum-containing CT (and targeted therapy if *EGFR* or *ALK* mut)

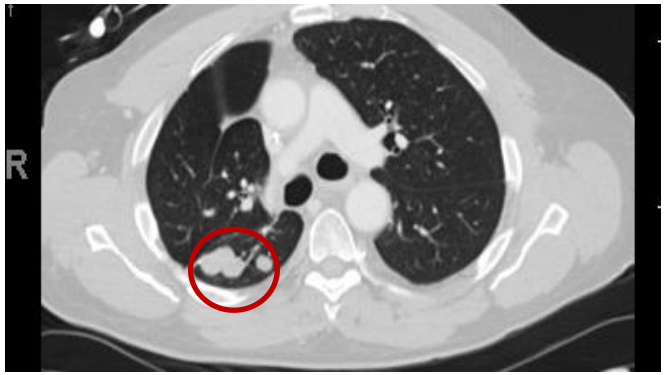
Atezolizumab in combination with bevacizumab/paclitaxel/carboplatin as 1L for metastatic, non-squamous NSCLC; no *EGFR* or *ALK* mut

Atezolizumab in combination with paclitaxel protein-bound/carboplatin as 1L for metastatic, non-squamous NSCLC; no *EGFR* or *ALK* mut

Atezolizumab: 1L for metastatic NSCLC with tumor cell PD-L1 expression (TC) ≥ 50% or PD-L1 stained tumor-infiltrating immune cells [IC] ≥ 10% of the tumor area; no *EGFR* or *ALK* mut

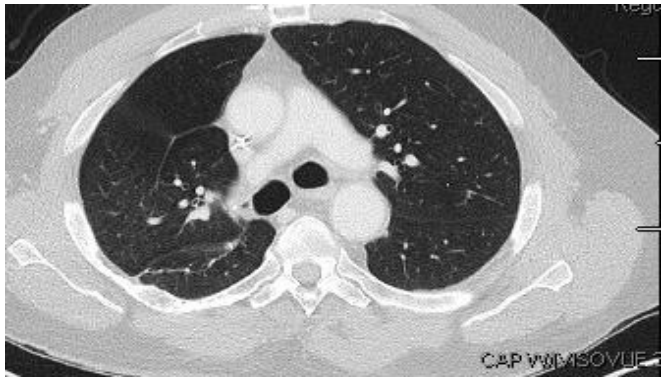
Patient example

2/2015



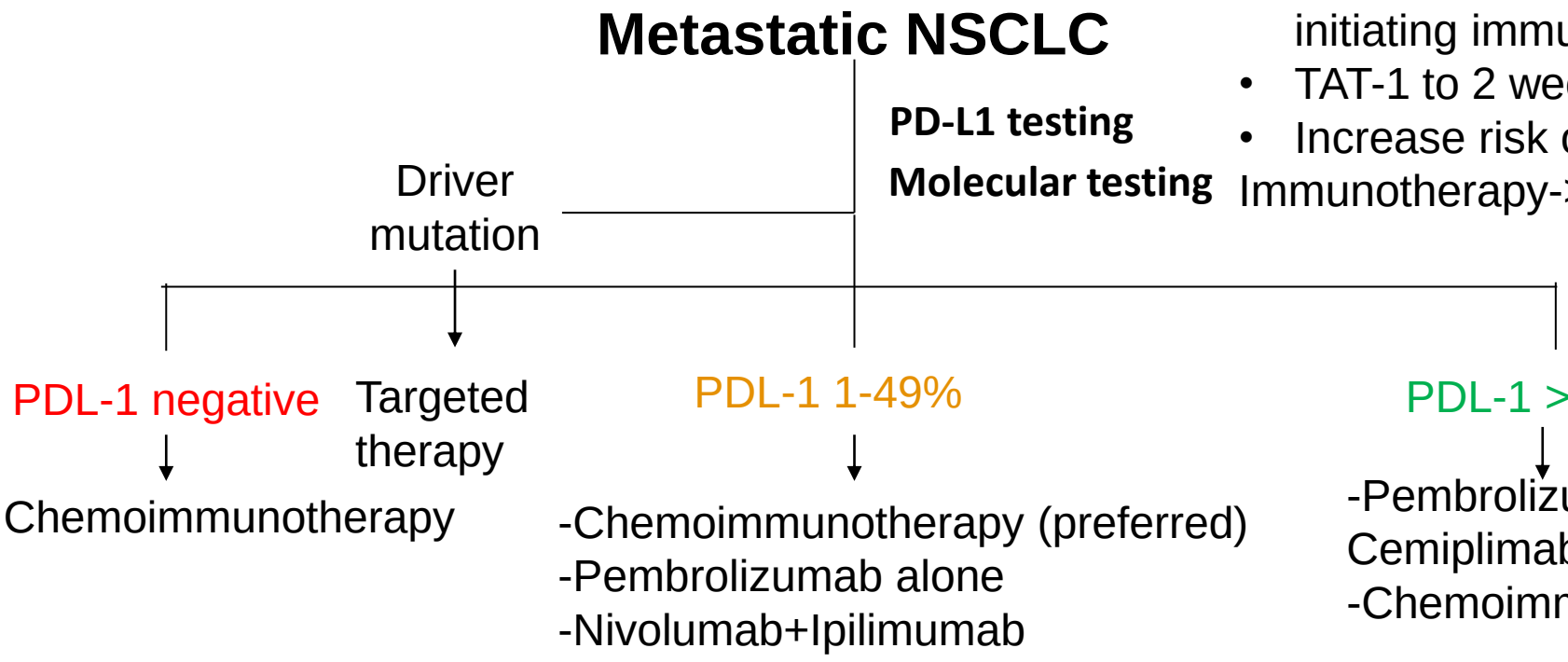
- 58 yo father of 4 girls under 16
- Had 3 prior lung cancer surgeries
- Radiation therapy
- 2 lines of prior chemotherapy for metastatic disease

3/2015 -On trial with Atezolizumab



- Complete response
- After 3 years, stopped therapy
- As of today, has no evidence of disease
- He has outlived his wife and now is the primary caregiver for his 4 daughters

Treatment Paradigm for Advanced NSCLC with no driver mutation



- **Wait for molecular testing** results before initiating immunotherapy
- TAT-1 to 2 weeks
- Increase risk of pneumonitis with Immunotherapy->targeted therapy sequence

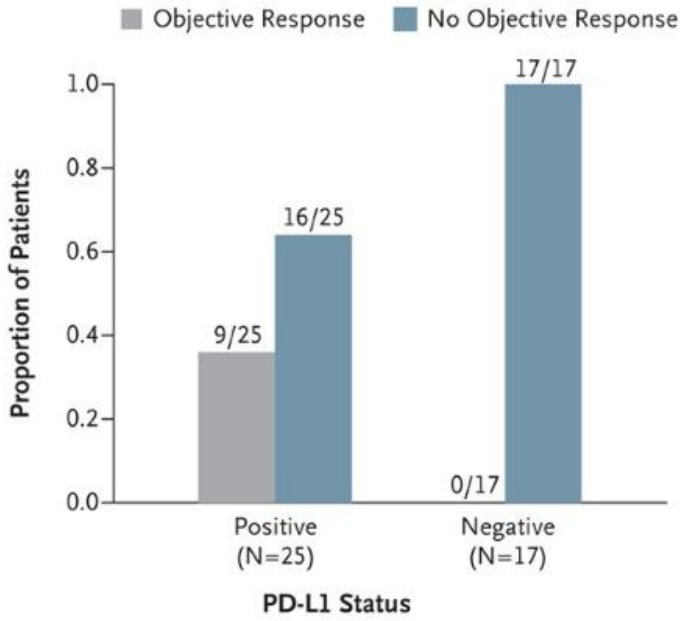
Chemoimmunotherapy= Pembrolizumab or atezolizumab or (Nivolumab+ipilimumab) with (carboplatin+paclitaxel or pemetrexed)

Importance of level of PD-L1 expression

PDL-1 tumor proportion score (TPS)

Most robust biomarker

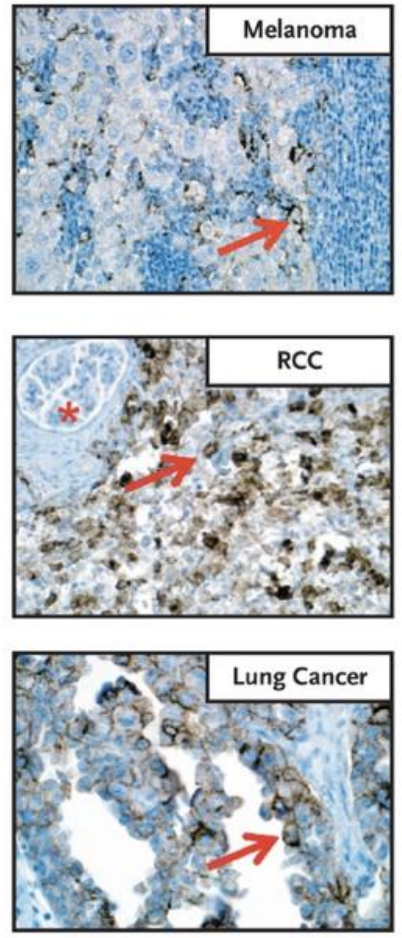
- By simple IHC
- PDL1 staining on tumor cells
- PD-L1 staining on immune cells used for atezolizumab



Association between Pretreatment Tumor PD-L1 Expression and Clinical Response

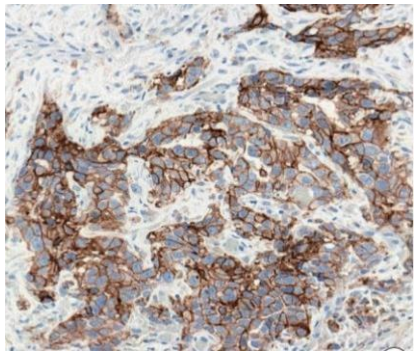
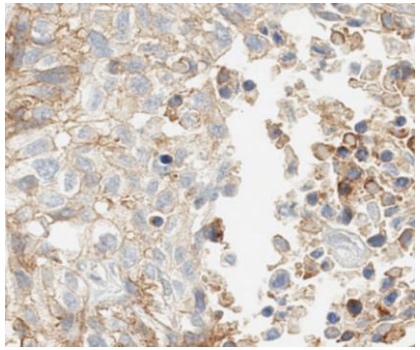
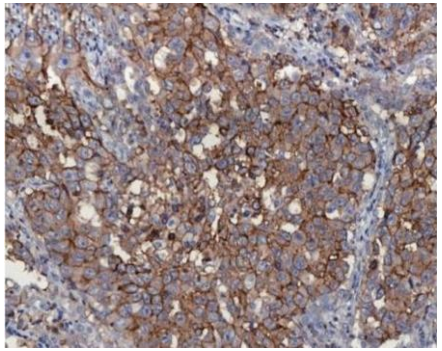
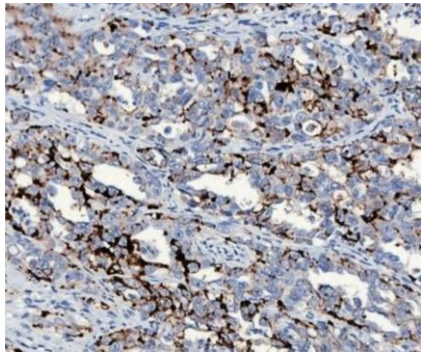
Response Status	PD-L1–Positive	PD-L1–Negative	Total
		number (percent)	
Objective response	9 (36)	0	9 (21)
No objective response	16 (64)	17 (100)	33 (79)
All	25	17	42

P=0.006 for association by Fisher's exact test



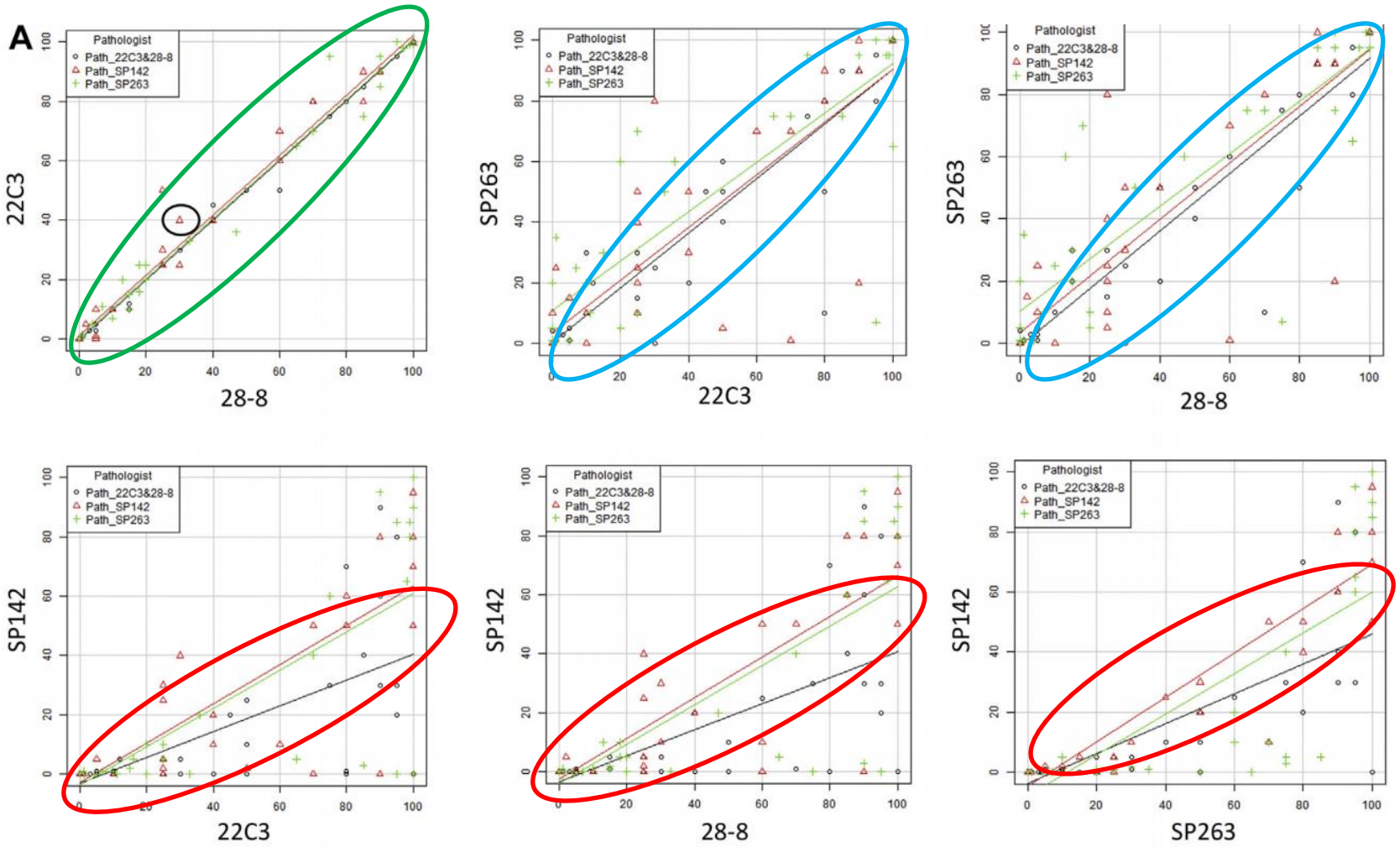
Topilan S, et al. NEJM 2012

4 drug approvals and 4 PD-L1 tests

	Dako (22C3)	Dako (28-8)	Ventana SP263	Ventana SP 142
Drug	• **Pembrolizumab**	• **Nivolumab**	• **Durvalumab**	• **Atezolizumab**
Staining pattern	• Membranous (TC)	• Membranous (TC)	• Membranous (TC)	• Membranous (**TC & IC)**
IHC Staining	• ≥50% (High) • 1-49% (Low) • <1% (Neg)	• ≥1% • ≥5% • ≥10%	• ≥25% High - (Durvalumab) • ≥10% (Nivolumab)	• TC3/IC3 PD-L1 50% on TC or 10% IC (high) • TC 1/2 or IC 1/2 PD-L1 1-50% on TC and 1-10% on IC (low) • TC 1/2/3 or IC 1/2/3 PD-L1 ≥1% (positive) • TC 0 or IC 0 PD-L1 <1% on TC or IC (negative)
				

J Pathol Transl Med. 2019 Jul; 53(4): 199–206

Pairwise comparison between assays for PD-L1 expression



22C3, 28-8, and SP263 assays demonstrated a high correlation

All comparisons that include **SP142** show lower correlation between assays

Hirsch F et al . JTO 2016

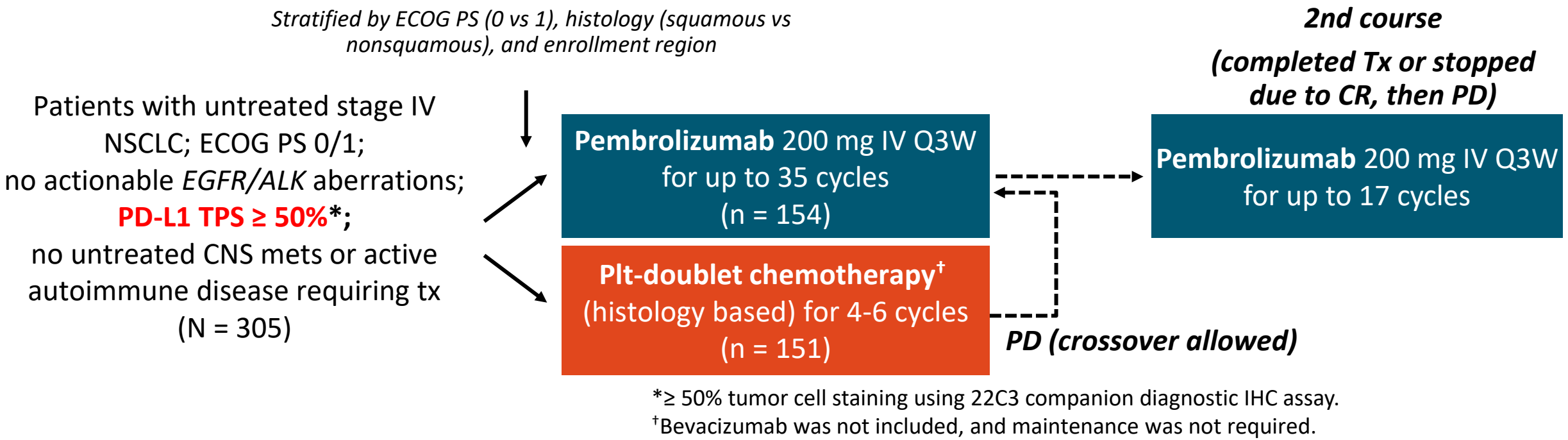
4 drug approvals and 4 PD-L1 tests

Are there differences?

Pembrolizumab

KEYNOTE-024: First-line Pembrolizumab vs Platinum Doublet Chemotherapy for Advanced NSCLC PD-L1>50%

- Open-label, randomized phase III study



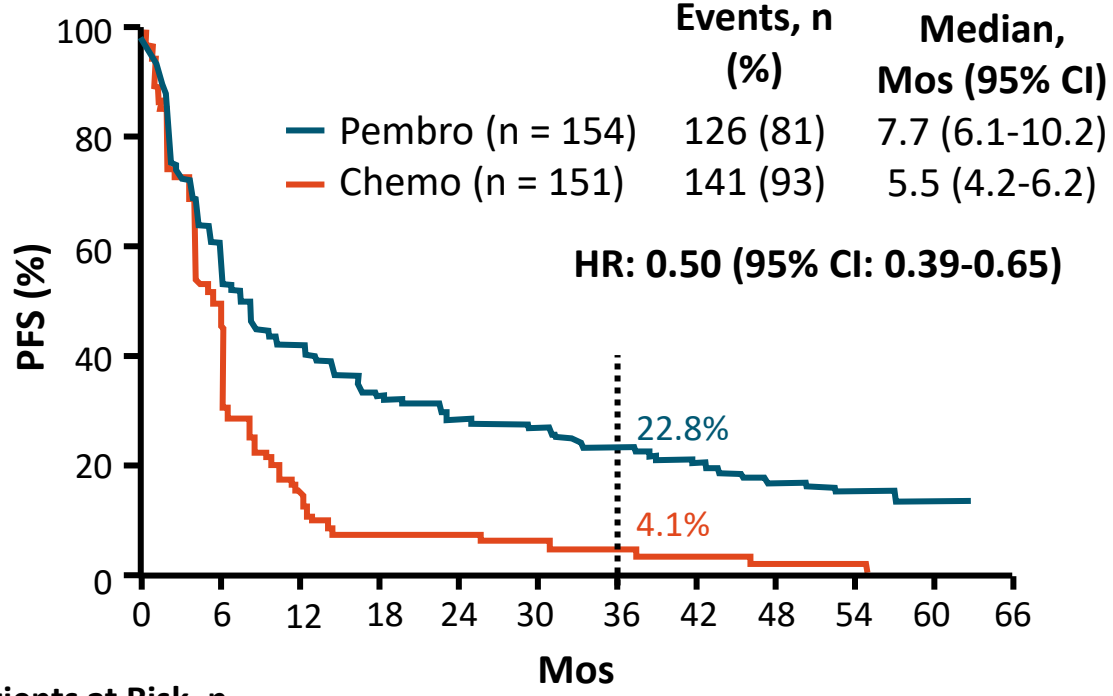
*≥ 50% tumor cell staining using 22C3 companion diagnostic IHC assay.
†Bevacizumab was not included, and maintenance was not required.

- Primary endpoint: PFS by BICR
- Secondary endpoints: ORR, OS, and safety

Reck. NEJM. 2016;375:1823. Reck. JCO. 2019;37:537.

KEYNOTE-024: Survival With First-line Pembrolizumab vs Platinum Doublet Chemotherapy

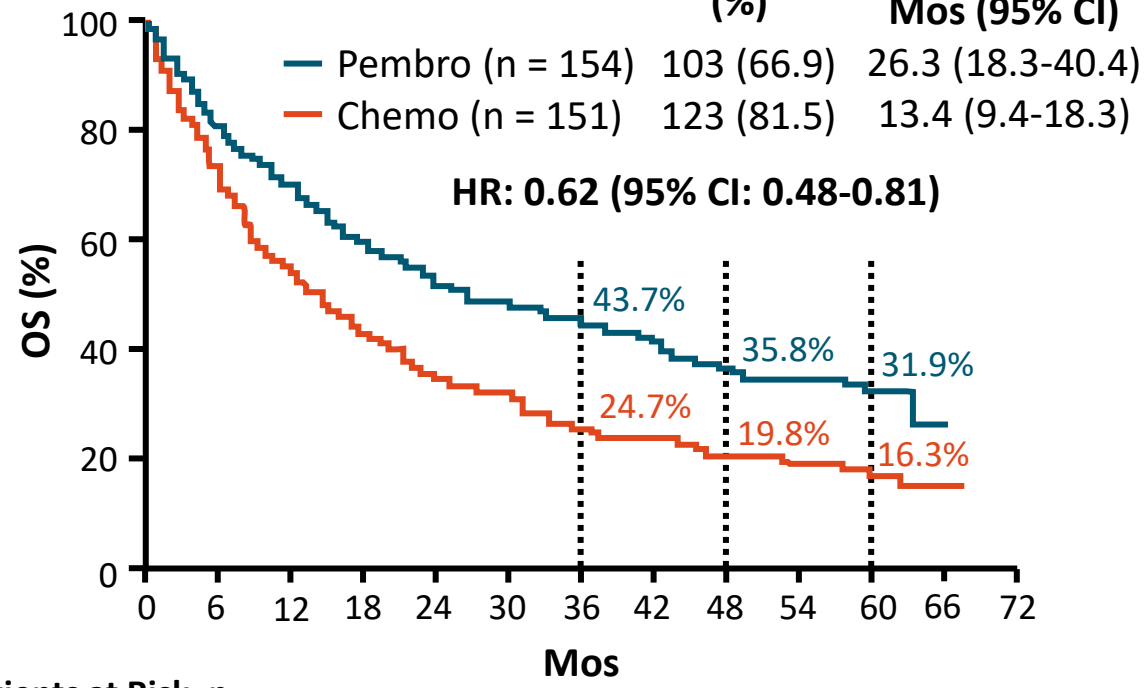
PFS



Patients at Risk, n

Pembro	154	92	62	46	38	36	30	24	20	15	3	0
Chemo	151	73	20	6	5	4	3	2	1	1	0	0

OS



Patients at Risk, n

Pembro	154	121	106	89	78	73	66	62	54	51	20	0	0
Chemo	151	108	80	61	48	44	35	33	28	26	13	3	0

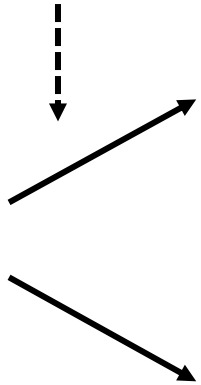
Reck. NEJM. 2016;375:1823. Reck. JCO. 2019;37:537.

FDA approval-2016

KEYNOTE-042: Study Design

Stratified by region (East Asia vs rest of world, ECOG PS (0 vs 1), histology (squamous vs nonsquamous), PD-L1 TPS (≥ 50% vs 1% to 49%)

Patients with untreated, locally advanced or metastatic NSCLC (any histology); PD-L1 TPS ≥ 1%; *EGFR/ALK* neg; ECOG PS 0/1; no untreated/unstable CNS mets; no pneumonitis requiring steroids (N = 1274)



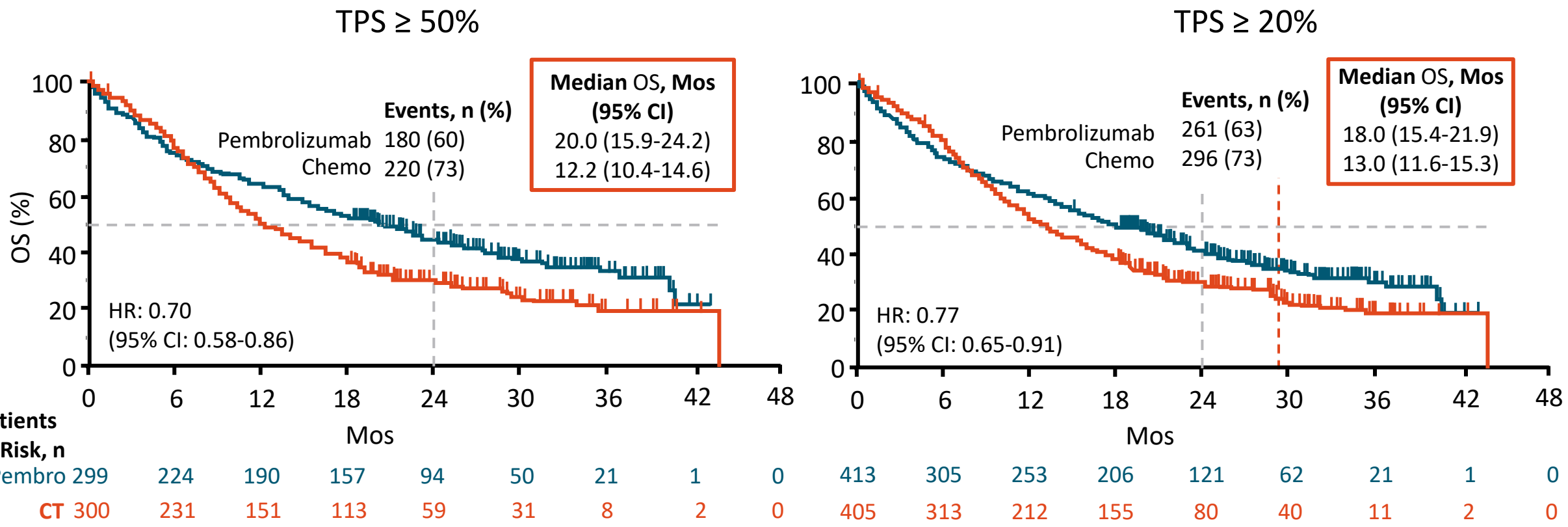
Pembrolizumab 200 mg Q3W up to 35 cycles (n = 637)

Carboplatin AUC 5 or 6 Q3W + Paclitaxel 200 mg/m² Q3W or Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m² Q3W up to 6 cycles (n = 637)

- Primary endpoint: OS in PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1%
- Secondary endpoints: PFS and ORR in PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1%; safety in ≥ 1%
- Current analysis planned for ~ 45 mos after study start

Mok. ELCC 2019. Abstr 102O. Used with permission.

KEYNOTE-042: OS in TPS ≥ 50% and TPS ≥ 20% Patient Subgroups



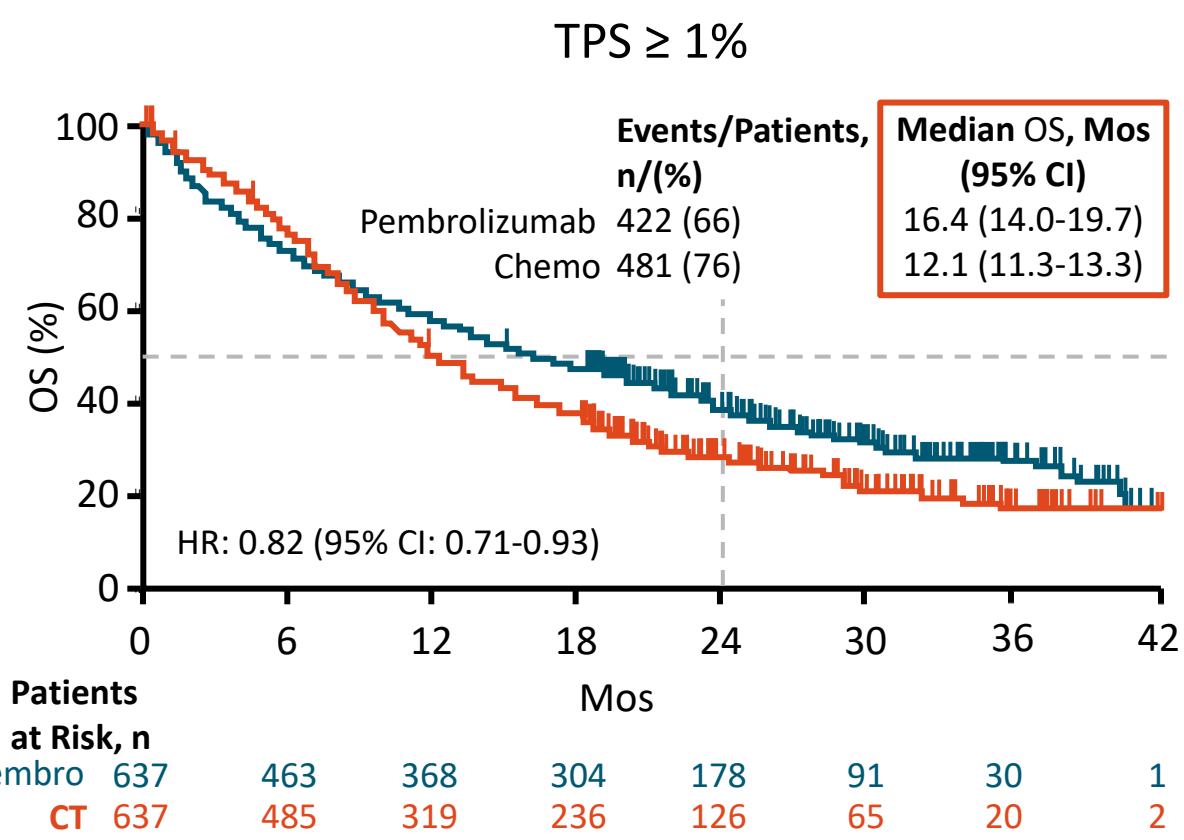
Patients at Risk, n

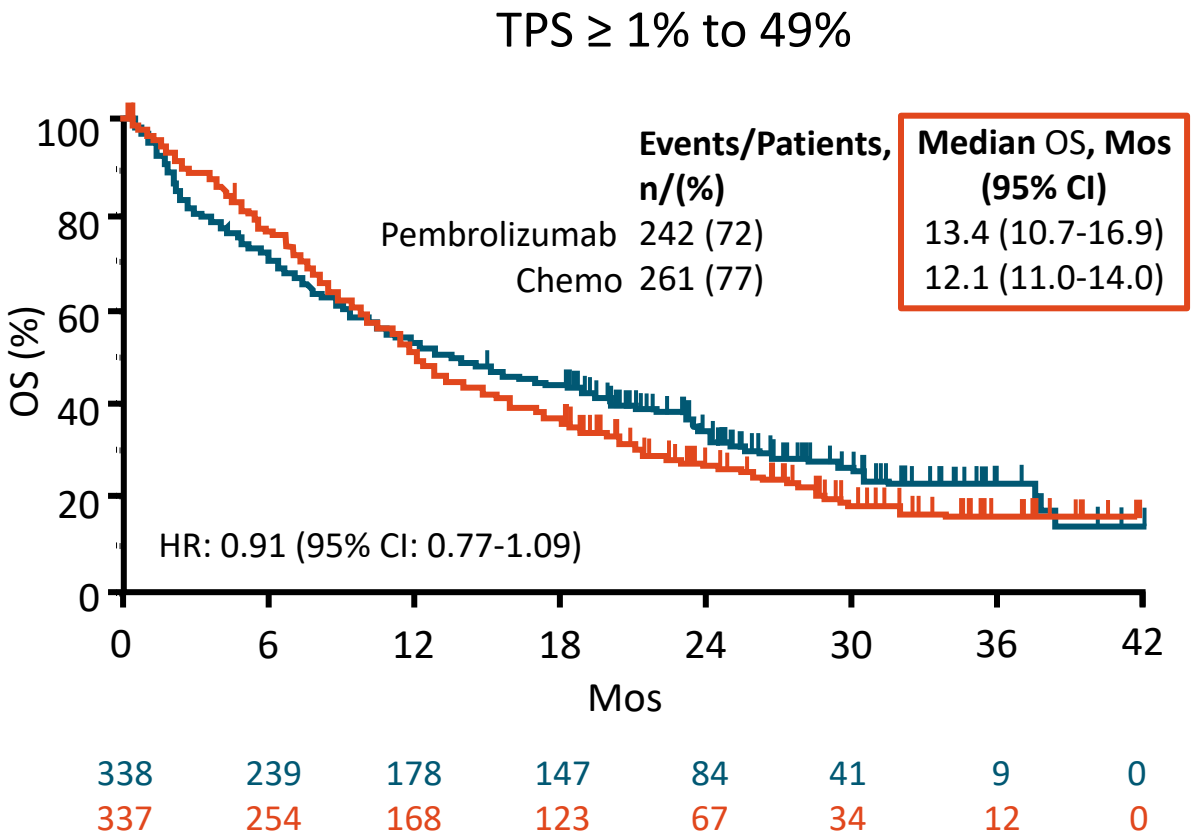
Pembro	299	224	190	157	94	50	21	1	0
CT	300	231	151	113	59	31	8	2	0

Pembro	413	305	253	206	121	62	21	1	0
CT	405	313	212	155	80	40	11	2	0

Mok. ELCC 2019. Abstr 102O. Used with permission.

KEYNOTE-042: OS in TPS ≥ 1% and TPS ≥1% to 49% Patient Subgroups





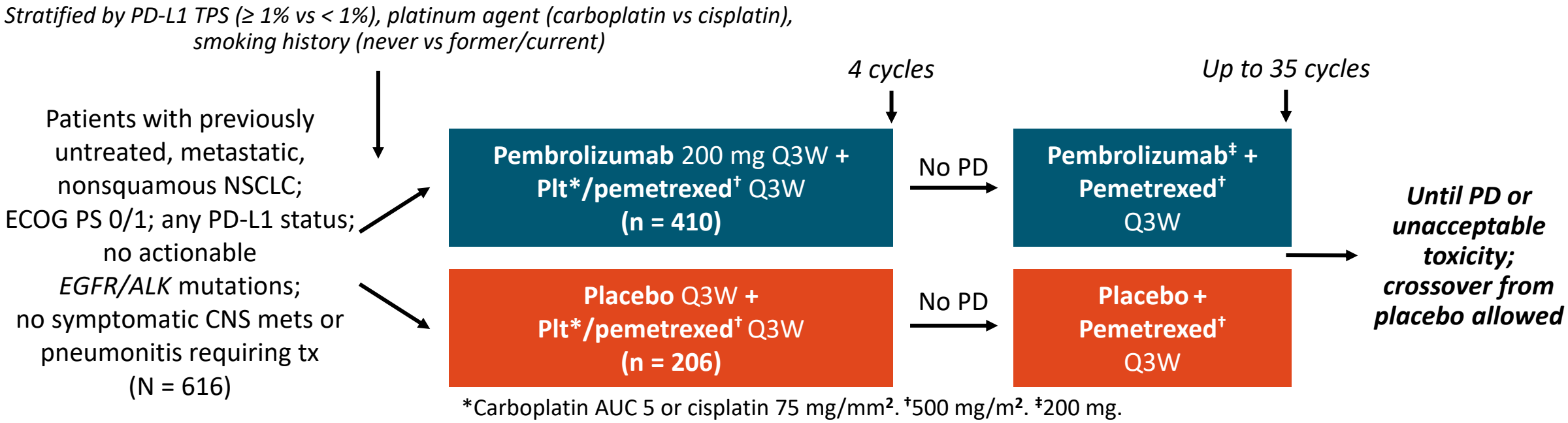
The benefit of pembrolizumab in the whole population was driven by patients with PD-L1 >50%

Mok. ELCC 2019. Abstr 102O. Used with permission.

FDA approval-2019

KEYNOTE-189: First-line Carboplatin/Pemetrexed ± Pembrolizumab in Stage IV Nonsquamous NSCLC

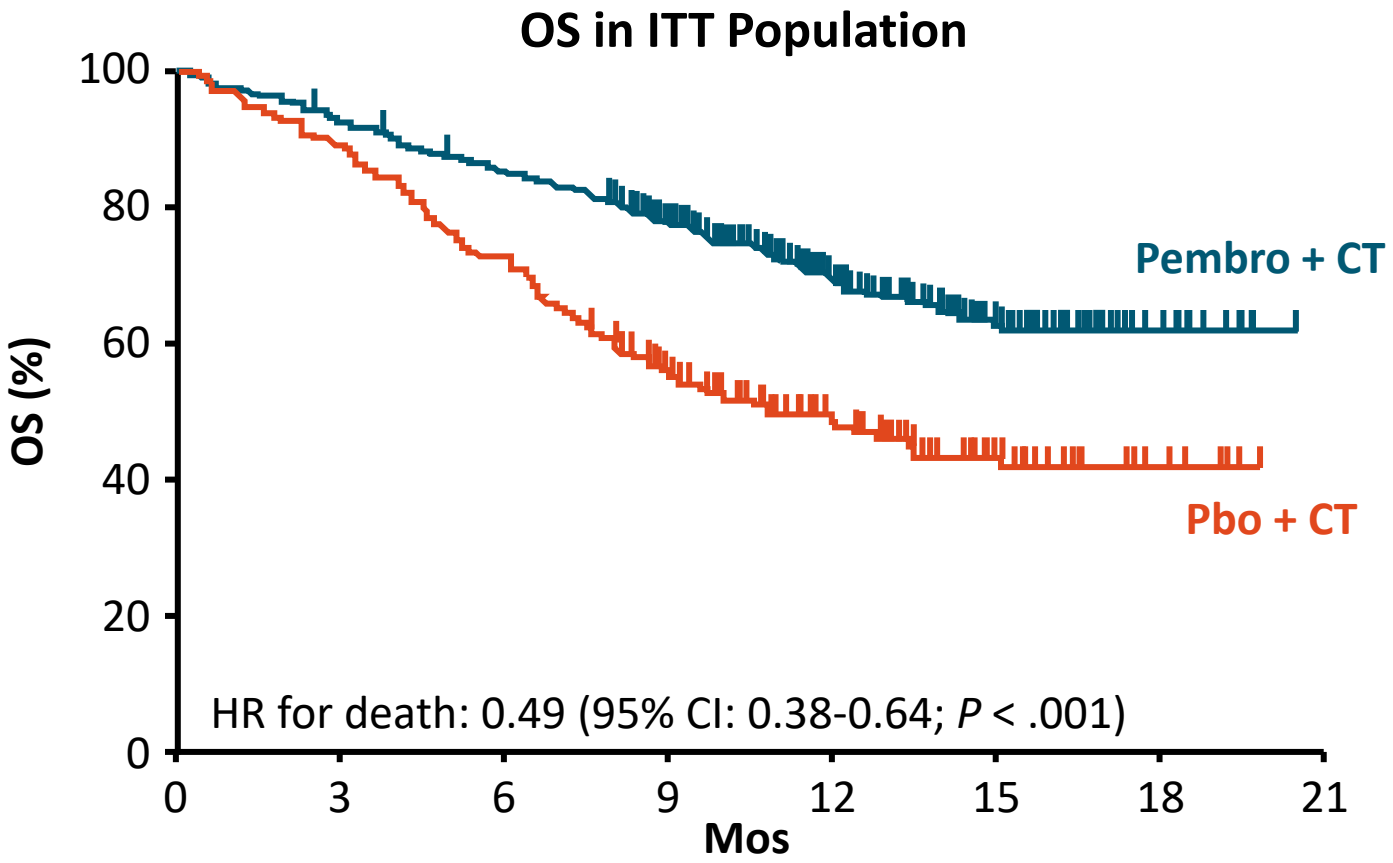
- Randomized, double-blind, international phase III study

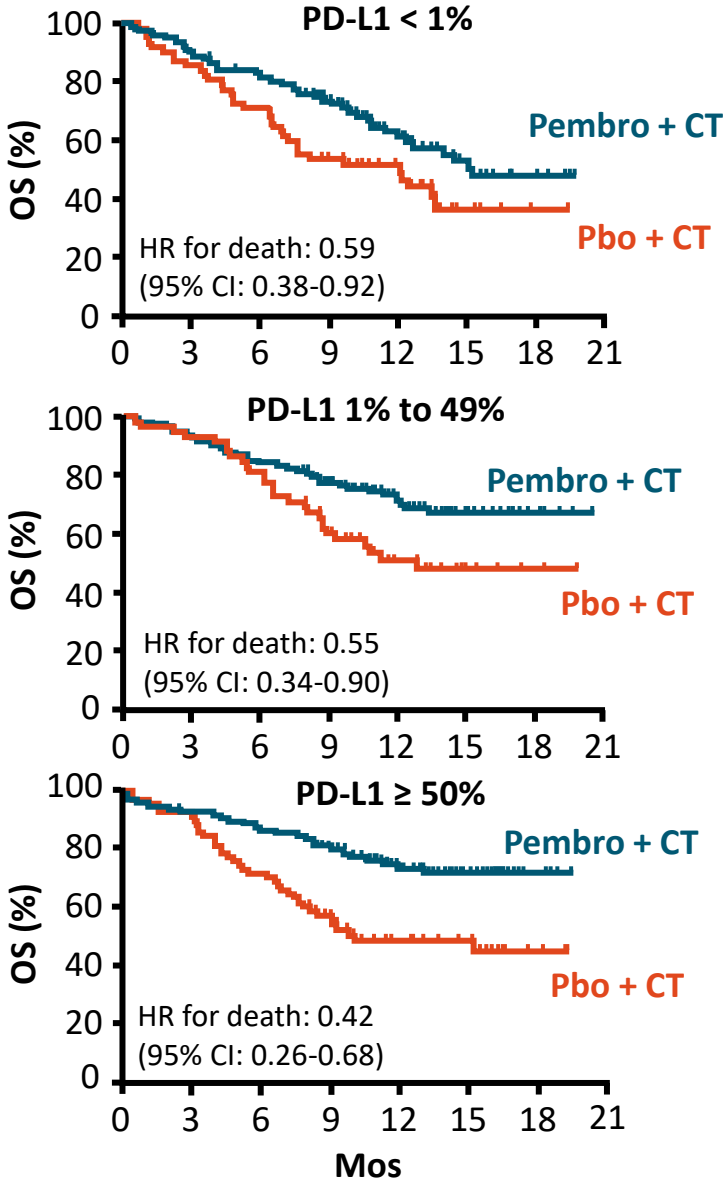


- Primary endpoints: OS, PFS by BICR
- Secondary endpoints: ORR, DoR, safety

Gandhi. NEJM. 2018;378:2078.

KEYNOTE-189: OS



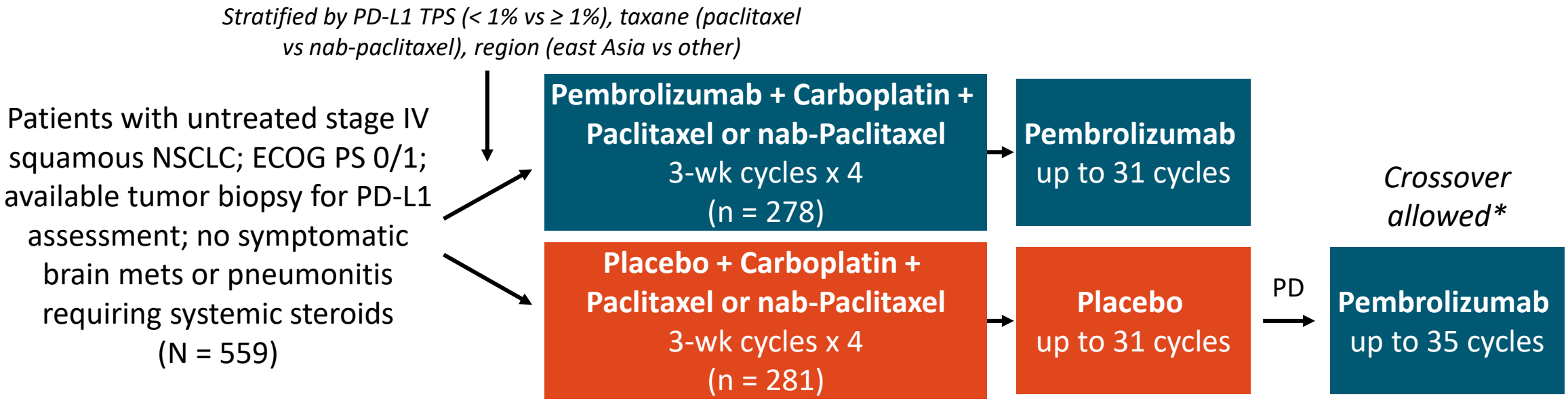


FDA approval-2018

Gandhi. NEJM. 2018;378:2078.

KEYNOTE-407: Carboplatin + Paclitaxel/nab-Paclitaxel ± Pembrolizumab in Advanced Squamous NSCLC

- Randomized, double-blind phase III trial

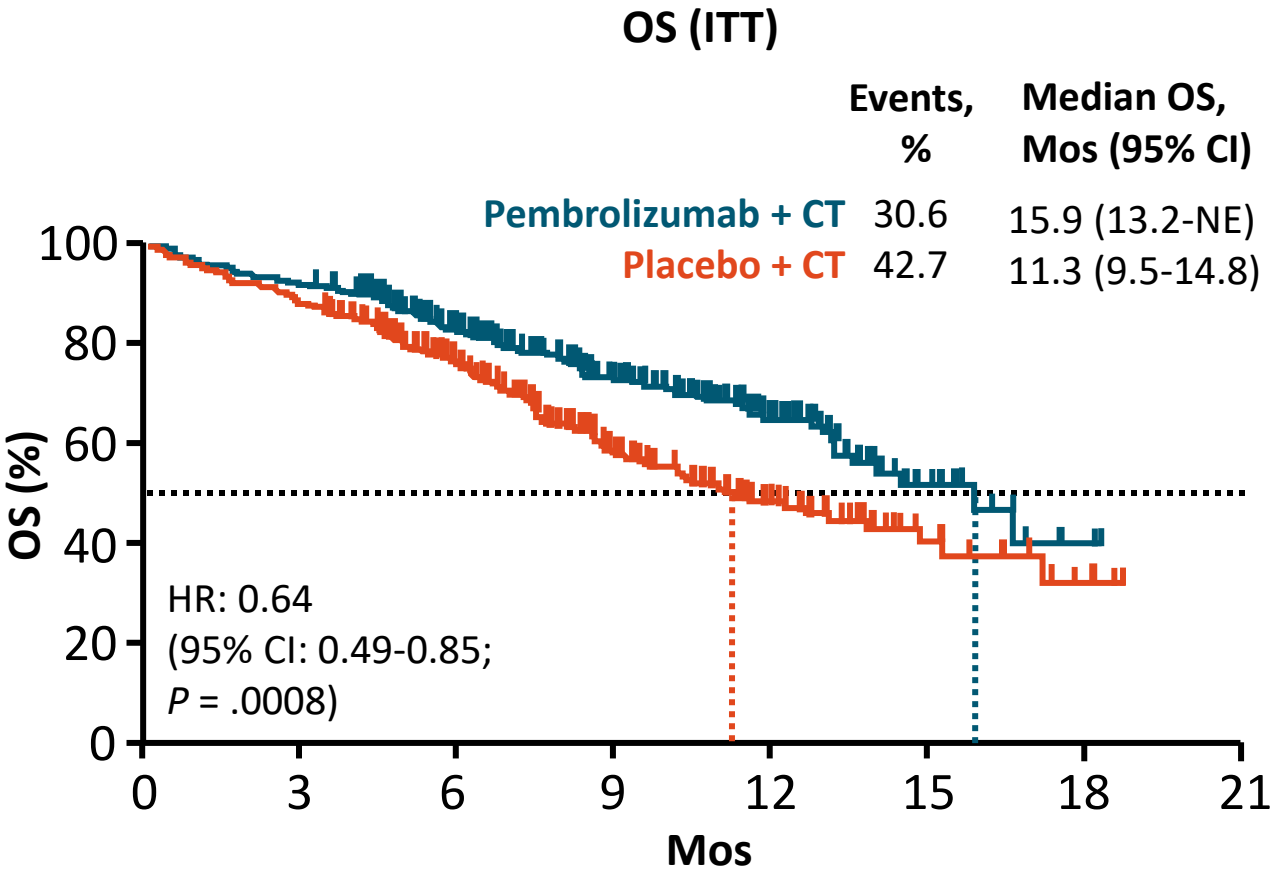


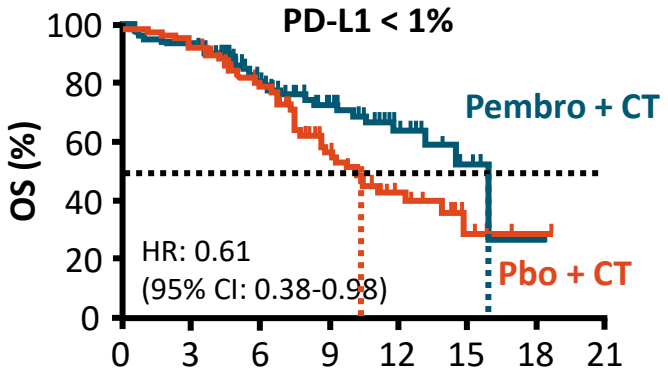
Carboplatin AUC 6 Q3W; nab-paclitaxel 100 mg/m^2 QW or paclitaxel 200 mg/m^2 Q3W; pembrolizumab 200 mg Q3W.
*Upon confirmation of PD and safety criteria by BICR, optional crossover could occur during combination or monotherapy.

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

Paz-Ares. NEJM. 2018;379:2040

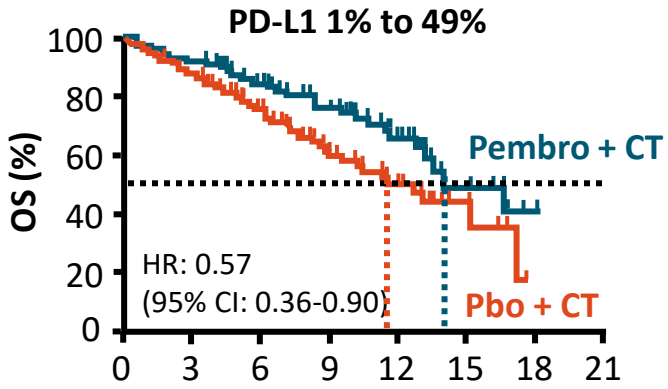
KEYNOTE 407: OS





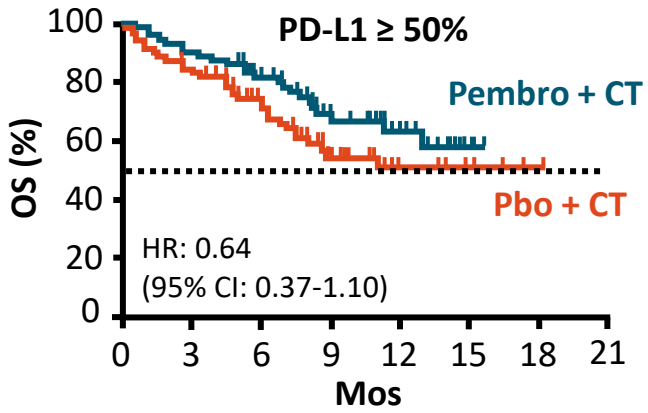
Median OS, Mos (95% CI)

15.9 (13.1-NE)
10.2 (8.6-13.8)



Median OS, Mos (95% CI)

14.0 (12.8-NE)
11.6 (8.9-17.2)



Median OS, Mos (95% CI)

NR (11.3-NE)
NR (7.4-NE)

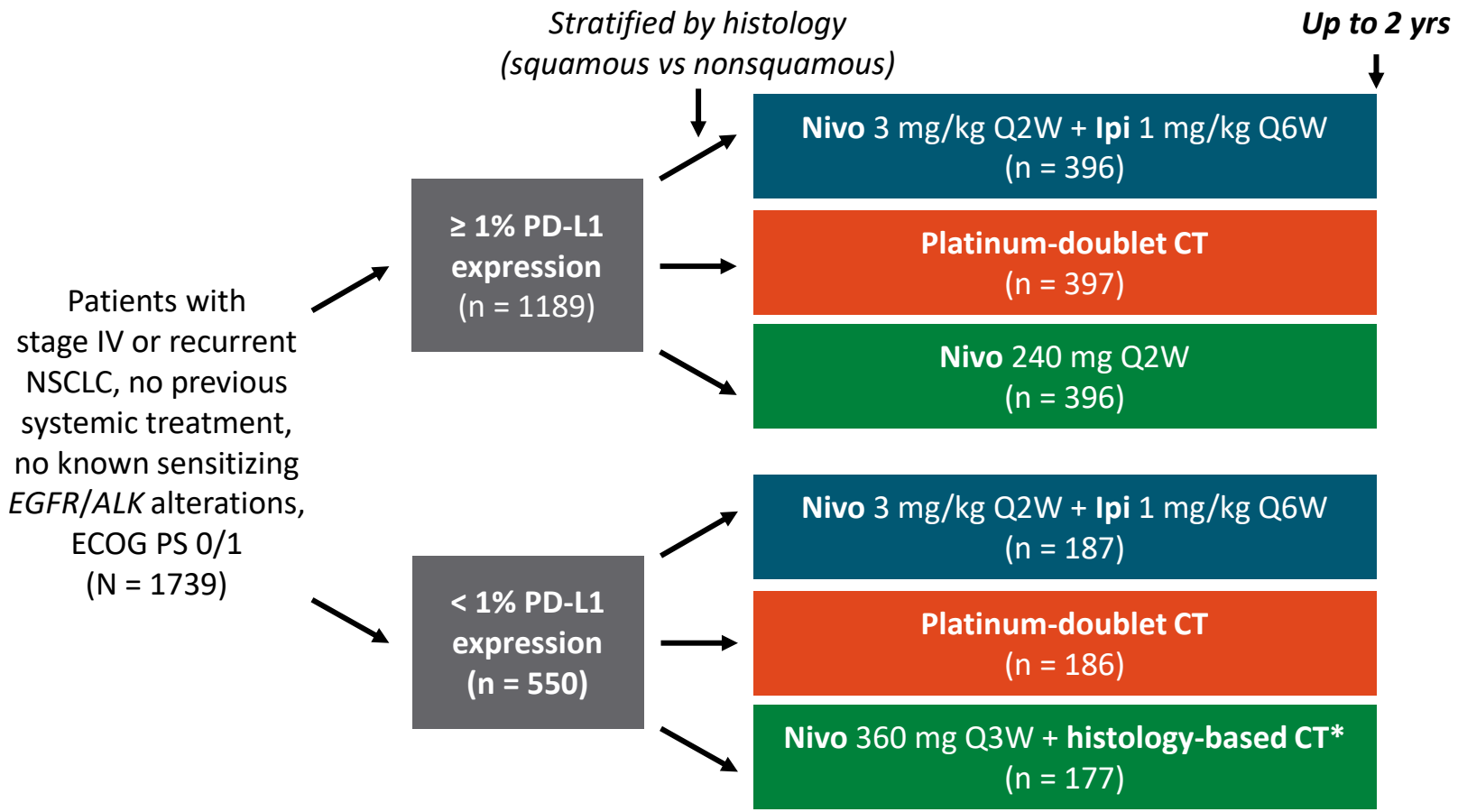
Paz-Ares. ASCO 2018. Abstract 105. Paz-Ares. NEJM. 2018;379:2040.

FDA approval-2018

Nivolumab and ipilimumab

CheckMate 227: First-line Nivolumab + Low-Dose Ipilimumab for Advanced NSCLC

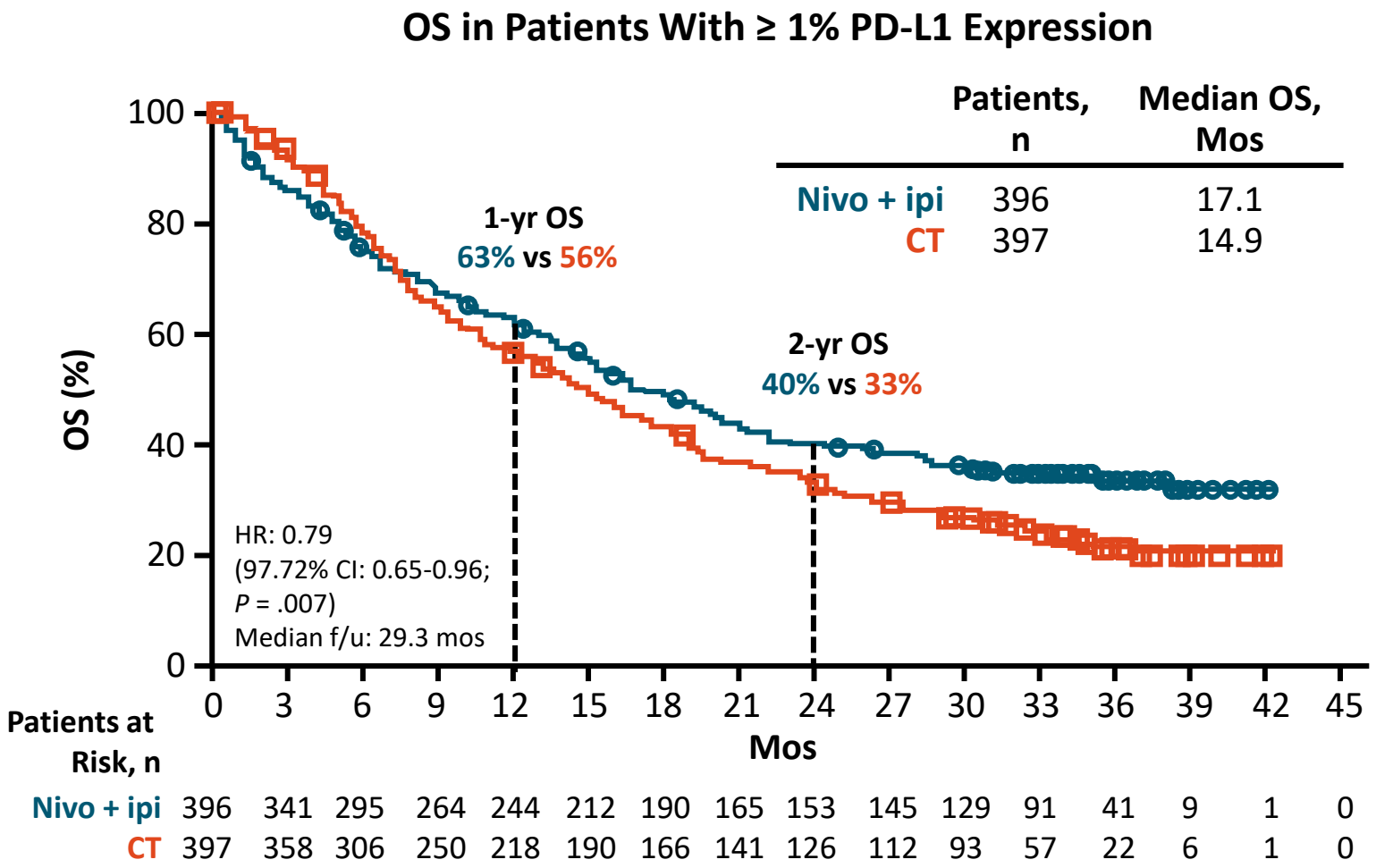
- Randomized, open-label, multipart phase III trial



- **Coprimary endpoints for nivolumab + ipilimumab vs CT:**
  - **OS in patients with ≥ 1% PD-L1 expression**
  - **PFS in high TMB population**
- Secondary endpoints: PFS and OS for nivolumab + CT vs CT in patients with PD-L1 < 1%; OS for nivolumab vs CT in patients with PD-L1 ≥ 50%

Ramalingam. ASCO 2020. Abstr 9500.

CheckMate 227: OS by Biomarker Status



Median OS, Mos	Nivo + Ipi	CT	HR*
PD-L1			
< 1% (n = 373)	17.2	12.2	0.62
1% to 49% (n = 396)†	15.1	15.1	0.94
≥ 50% (n = 397)†	21.2	14.0	0.70
TMB			
< 10 Mut/Mb (n = 380)†	16.2	12.6	0.75
≥ 10 Mut/Mb (n = 299)†	23.0	16.4	0.68

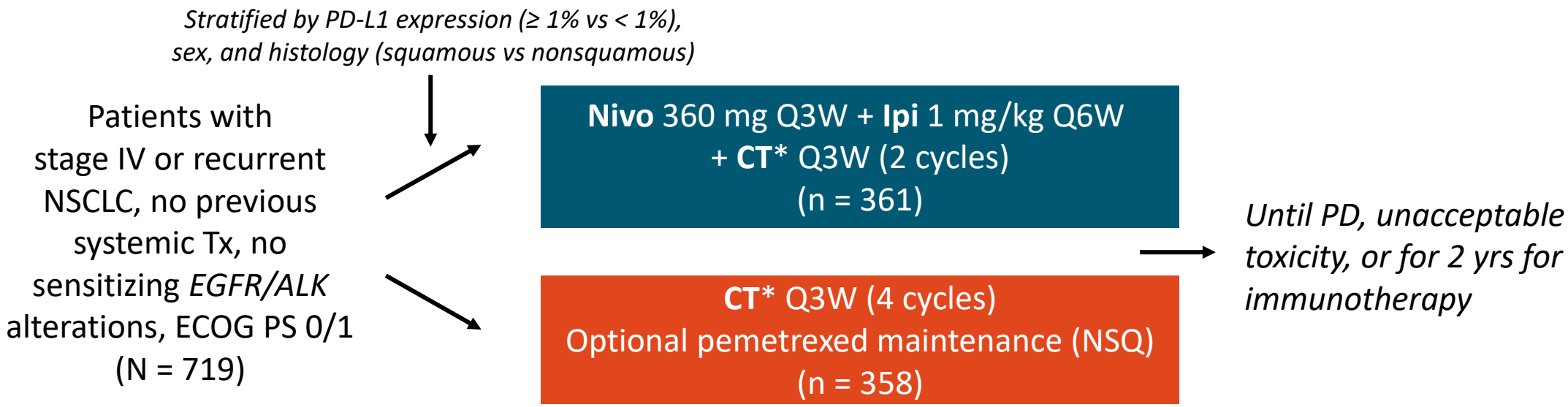
*Unstratified. †Exploratory subgroup analyses.

Peters. ESMO 2019. Abstr LBA4_PR. Hellmann. NEJM. 2019;381:2020.

FDA approval-2020; only PD-L1 positive patients

CheckMate 9LA: Study Design

- Randomized, open-label, phase III study



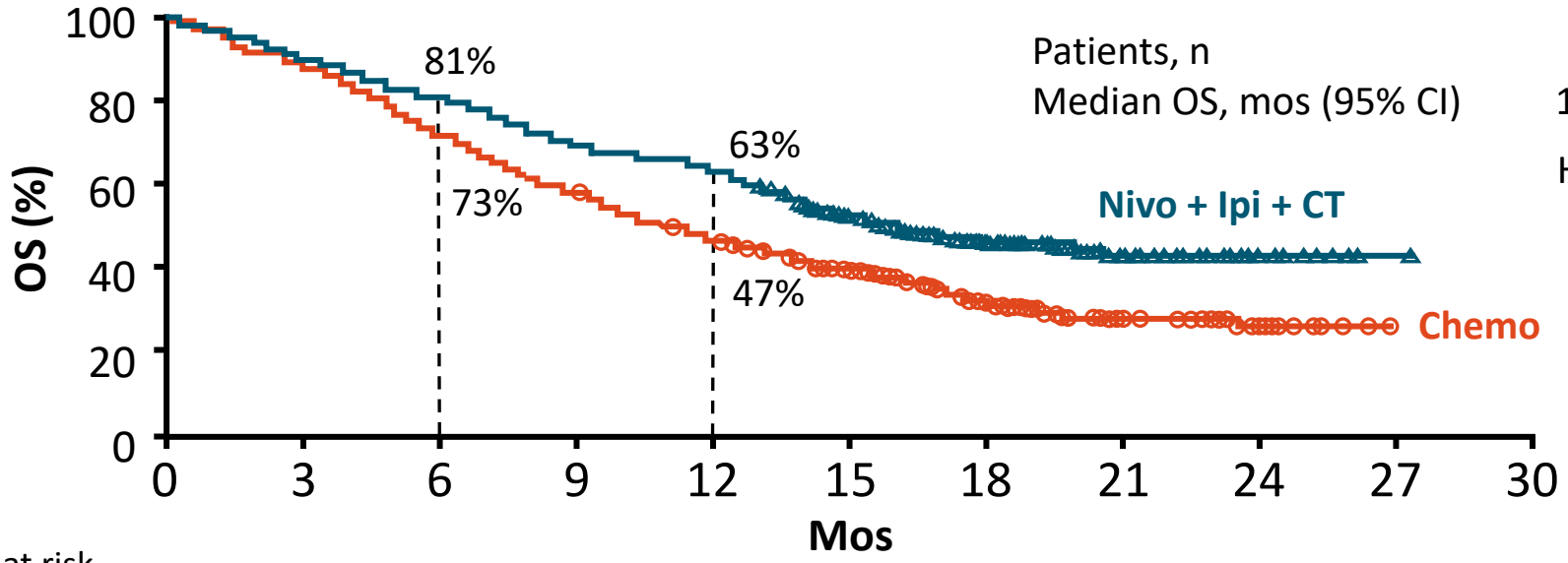
*Pts with NSQ: pemetrexed + cisplatin or carboplatin; pts with SQ: paclitaxel + carboplatin.

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, efficacy by tumor PD-L1 expression

Reck. ASCO 2020. Abstr 9501.

CheckMate 9LA: Interim and Updated OS Results

- Interim analysis (minimum FU 8.1 mos) median OS, Nivo + Ipi + CT vs CT: 14.1 vs 10.7 mos; HR: 0.69 (95% CI: 0.55-0.87); *P* = .0006; met primary endpoint
- Updated results (minimum FU 12.7 mos)



	Nivo + Ipi + CT	CT
Patients, n	361	358
Median OS, mos (95% CI)	15.6 (13.9-20.0)	10.9 (9.5-12.6)

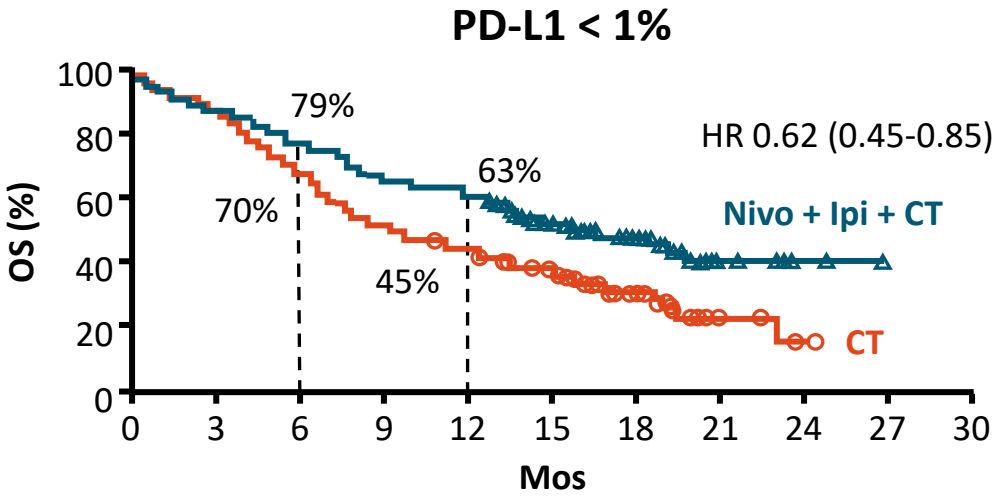
HR: 0.66 (95% CI: 0.55-0.80)

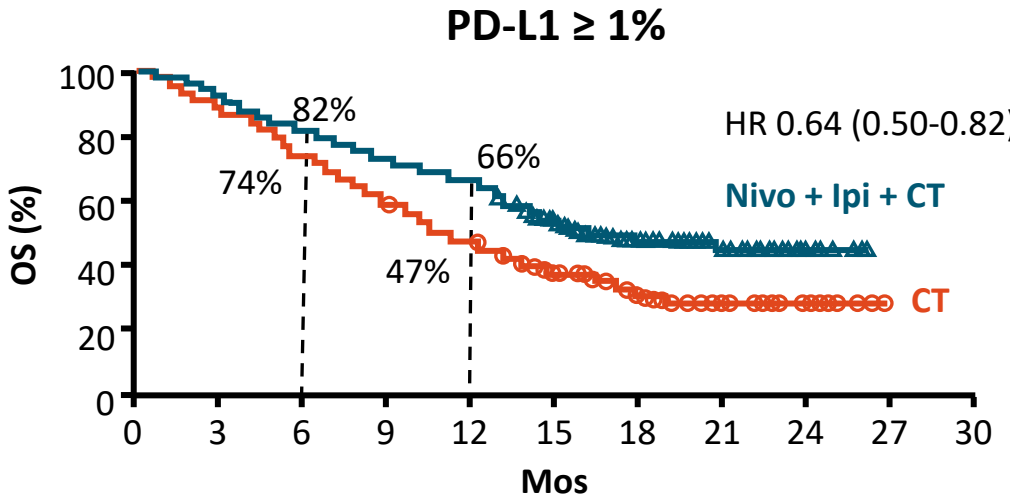
No. at risk											
Nivo + Ipi + CT	361	326	292	250	227	153	86	33	10	1	0
Chemo	358	319	260	208	166	116	67	26	11	0	0

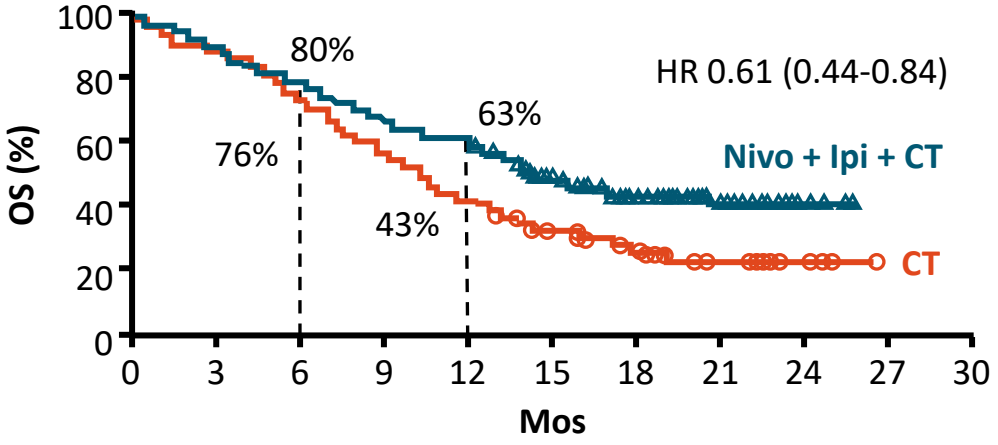
Reck. ASCO 2020. Abstr 9501. Reproduced with permission.

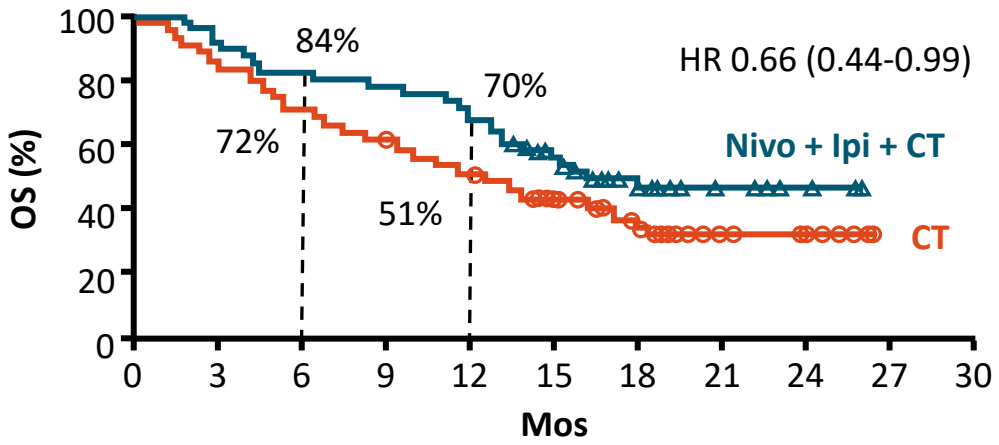
FDA approval-2020-(irrespective of PD-L1 status)

CheckMate 9LA: OS By PD-L1 Expression







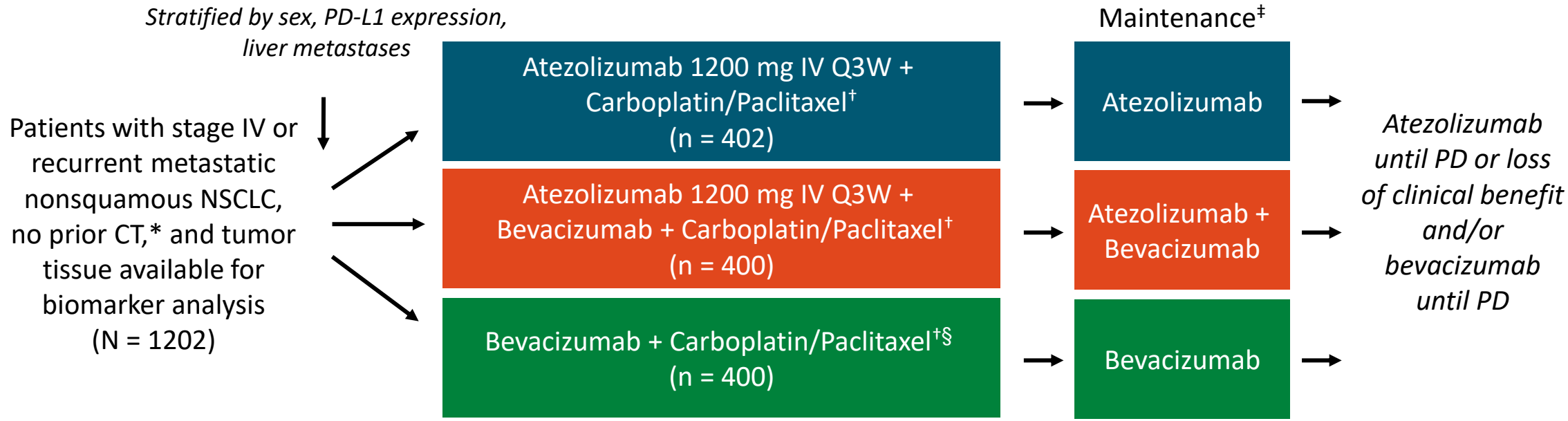


Reck. ASCO 2020. Abstr 9501. Reproduced with permission.

Atezolizumab

IMpower150

- IMpower150: Multicenter, open-label, randomized phase III trial

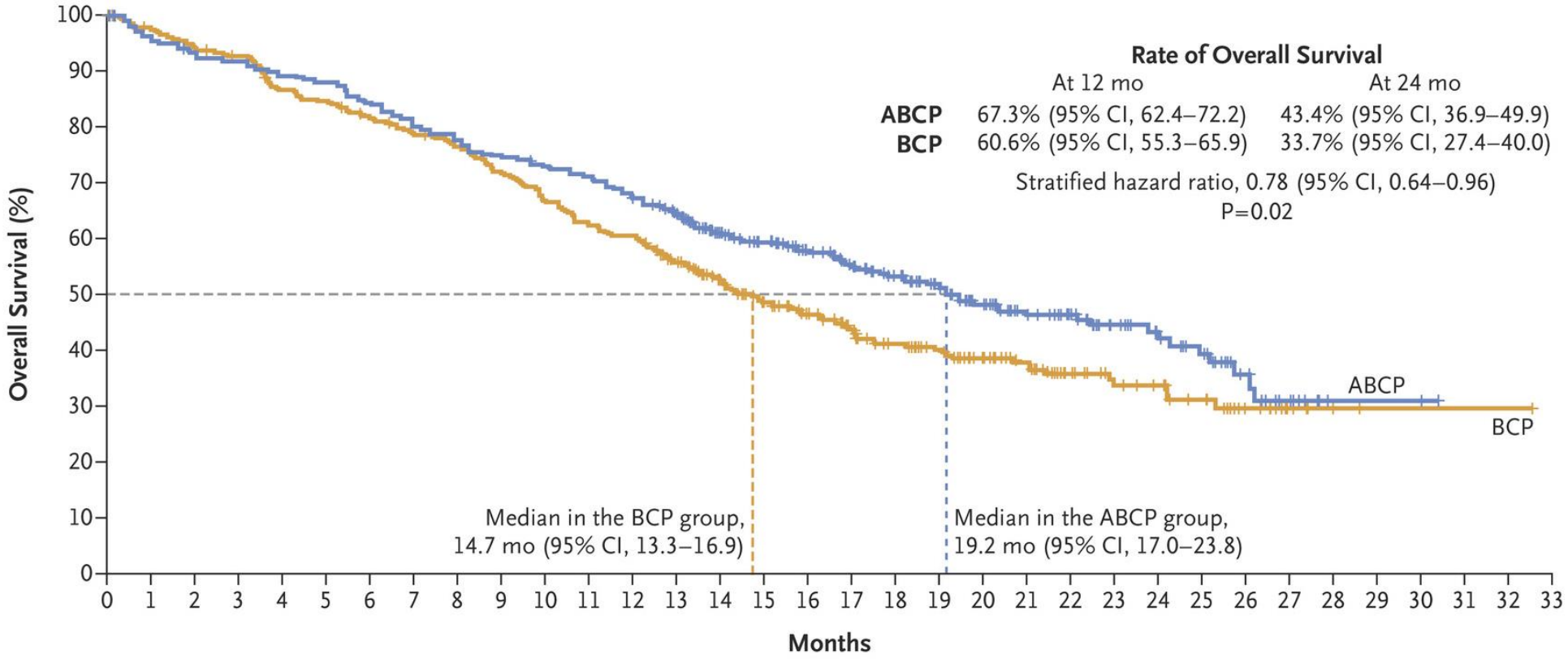


*If sensitizing *EGFR* mutation or *ALK* translocation present, must have PD on or intolerance to ≥ 1 approved targeted therapy. †Bevacizumab 15 mg/kg; carboplatin AUC 6; paclitaxel 200 mg/m^2; all given IV Q3W for 4 or 6 cycles. ‡No crossover permitted. §Control arm.

- Coprimary endpoints: investigator-assessed PFS in ITT WT, Teff-high WT; OS in ITT WT
- Secondary endpoints: investigator-assessed PFS, OS in ITT; investigator-assessed PFS in PD-L1 subgroups; IRF-assessed PFS; ORR, DoR per RECIST v1.1; safety in ITT

Socinski. NEJM. 2018;378:2288. Reck. ELCC 2019. Abstr 104O. Used with permission.

IMpower150



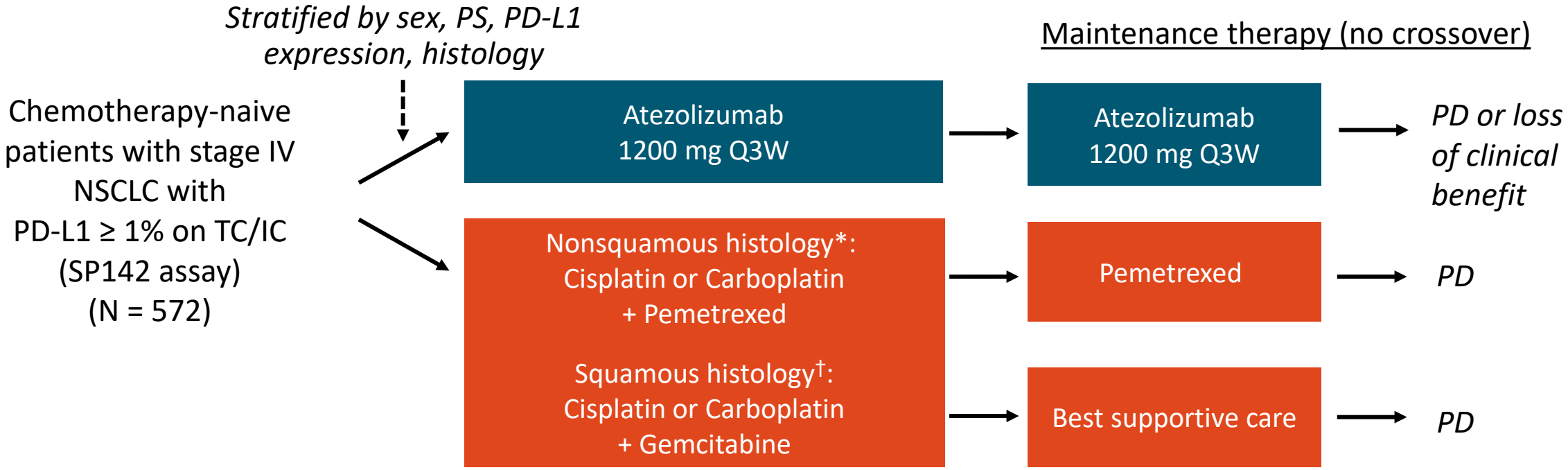
No. at Risk

ABCP	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
BCP	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

Socinski. NEJM. 2018;378:2288. Reck. ELCC 2019. Abstr 104O..

FDA approval-2019

Atezolizumab in Chemotherapy-Naive Metastatic NSCLC (IMpower110): Phase III Study Design



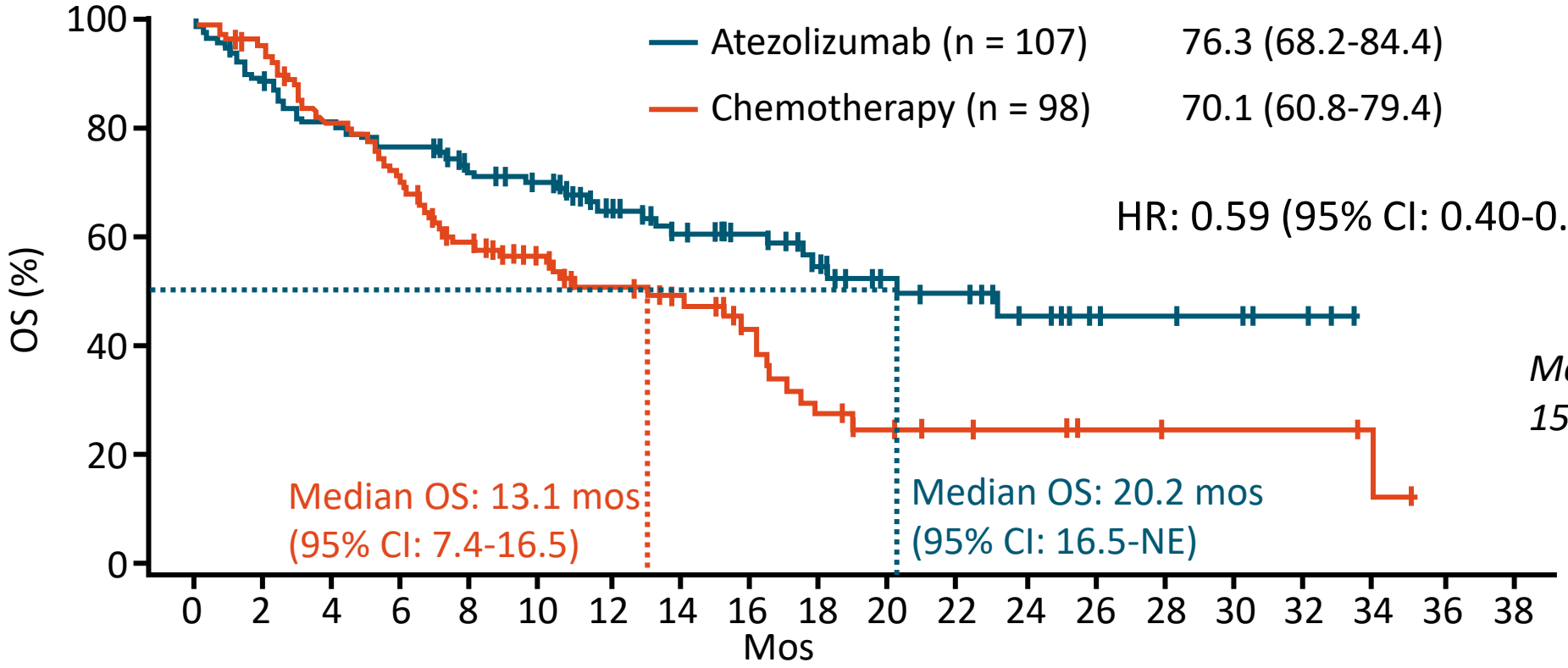
*Cisplatin 75 mg/m^2 or carboplatin AUC 6 + pemetrexed 500 mg/m^2 IV Q3W for 4 or 6 cycles.
†Cisplatin 75mg/m^2 + gemcitabine 1250 mg/m^2 IV Q3W or carboplatin AUC5 + gemcitabine 1000 mg/m^2 IV Q3W for 4 or 6 cycles.

- Primary endpoint: OS in WT population (excluding patients with *EGFR*+ and/or *ALK*+ NSCLC)
- Secondary endpoints: investigator-assessed PFS, ORR and DoR (per RECIST v1.1)

Spigel. ESMO 2019. Abstr. LBA78.

IMpower110: OS for TC3 or IC3 WT Patients

	6-Mo OS, % (95% CI)	12-Mo OS, % (95% CI)
Atezolizumab (n = 107)	76.3 (68.2-84.4)	64.9 (55.4-74.4)
Chemotherapy (n = 98)	70.1 (60.8-79.4)	50.6 (40.0-61.3)



HR: 0.59 (95% CI: 0.40-0.89; *P* = .0106)

Median follow-up:
15.7 mos (range: 0-35)

Patients at Risk, n

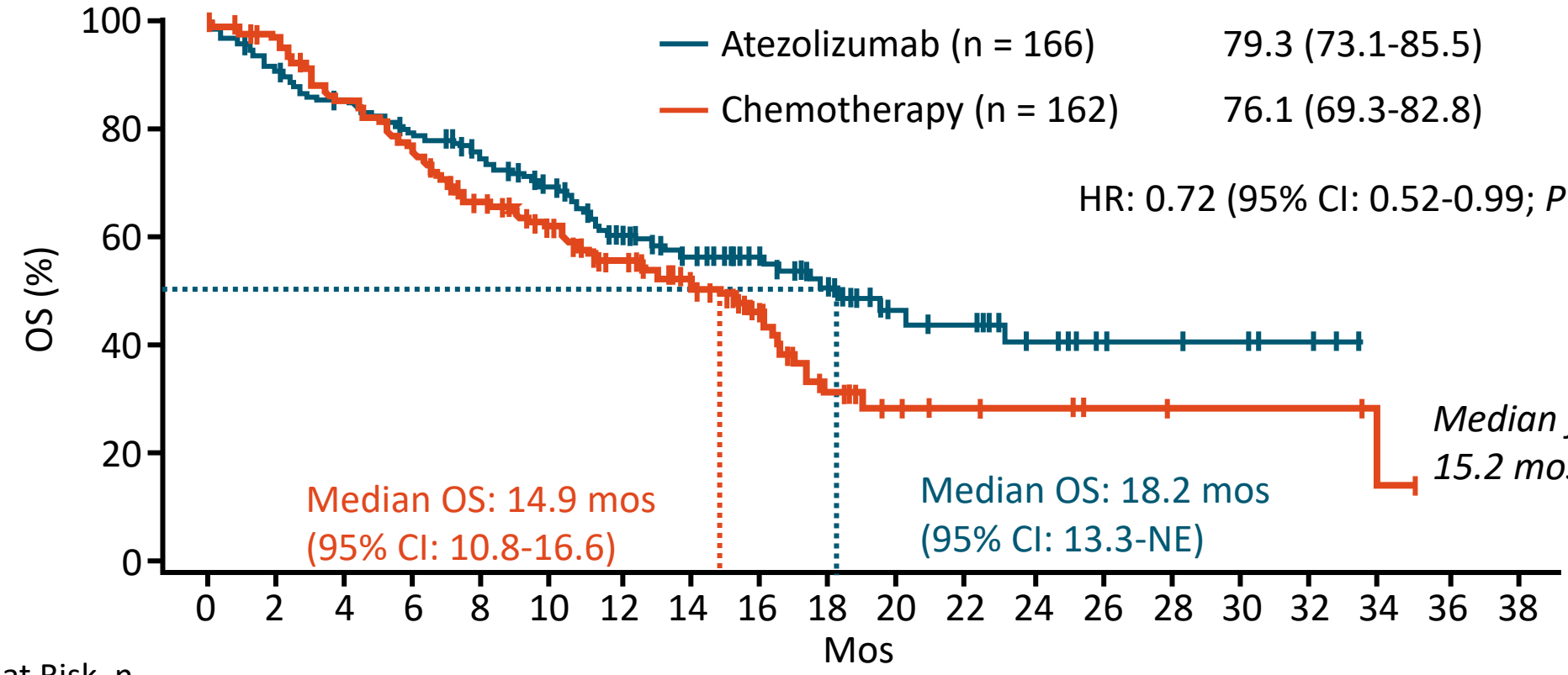
Atezolizumab	107	94	85	80	66	61	48	40	34	25	18	16	11	7	6	5	2
Chemotherapy	98	89	75	65	50	40	33	28	19	12	9	7	6	4	3	3	3	1

Spigel. ESMO 2019. Abstr. LBA78. Reproduced with permission.

IMpower110: OS for TC2/3 or IC2/3 WT Patients

	6-Mo OS (95% CI)	12-Mo OS (95% CI)
Atezolizumab (n = 166)	79.3 (73.1-85.5)	60.7 (52.6-68.7)
Chemotherapy (n = 162)	76.1 (69.3-82.8)	56.0 (47.7-64.3)

HR: 0.72 (95% CI: 0.52-0.99; *P* = .0416)



Patients at Risk, n

Atezolizumab	166	151	139	128	108	92	66	54	42	30	19	17	11	7	6	5	2
Chemotherapy	162	150	131	117	95	75	57	46	32	17	9	7	6	4	3	3	3	1

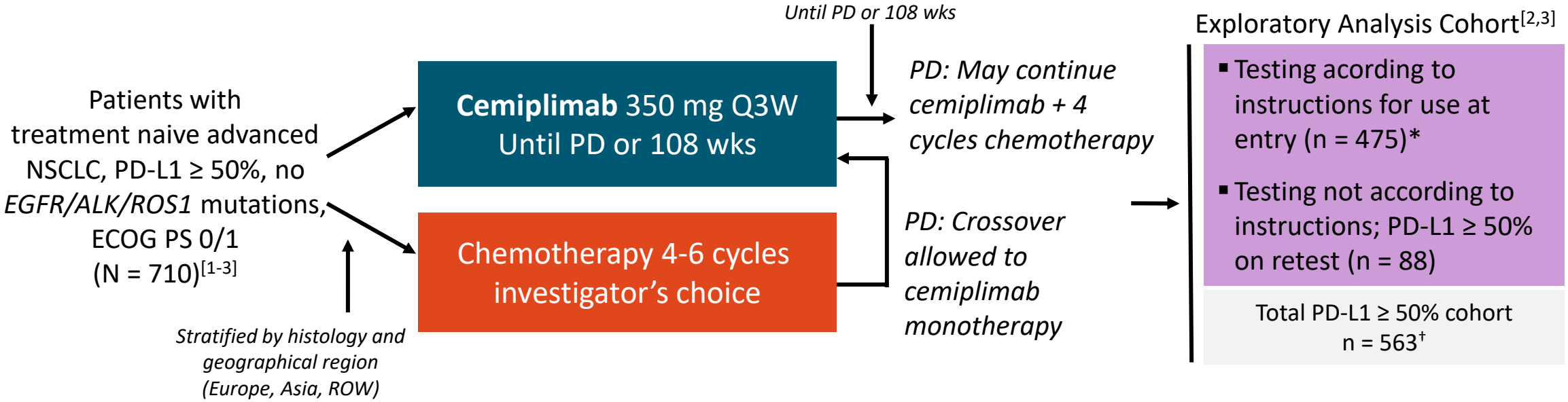
Spigel. ESMO 2019. Abstr. LBA78. Reproduced with permission.

FDA approval-2020-(only in high-PD-L1)

Cemiplimab

EMPOWER-Lung 1: Exploratory Analysis of Outcomes by PD-L1 Expression

- In phase III EMPOWER-Lung 1 trial, first-line cemiplimab monotherapy showed superior median OS and PFS, higher ORR and longer DoR vs standard chemotherapy in advanced NSCLC patients with PD-L1 ≥ 50%[1]
  - Exploratory analysis examined clinical outcomes by PD-L1 expression level in prespecified PD-L1 ≥ 50% cohort[2,3]



- Primary endpoints: OS and PFS[1-3]
- Secondary endpoints: ORR, DoR, HRQoL, and safety[1-3]

*Enrolled after August 2018 and not subject to PD-L1 retesting because initial test performed according to the assay's instructions for use.
†Prespecified cohort consisting of patients with testing according to instructions and patients with PD-L1 ≥ 50% on retest.

1. Sezer. ESMO 2020. Abstr LBA52. 2. Kilickap. WCLC 2020. Abstr OA01.03. 3. Sezer. Lancet. 2021;397:592.

EMPOWER-Lung 1 in PD-L1 ≥ 50% NSCLC: Efficacy

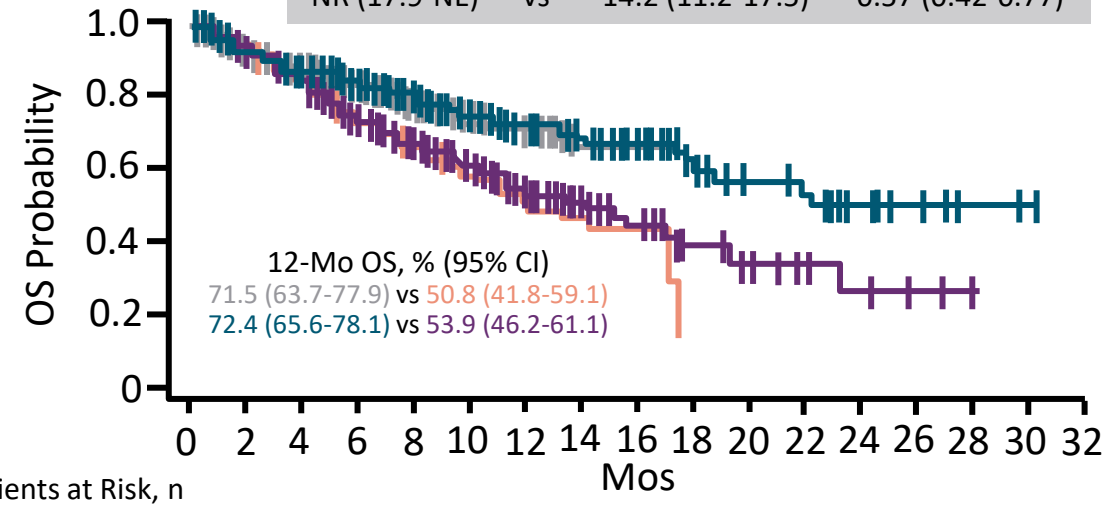
- Cemiplimab monotherapy: superior median OS/PFS vs chemotherapy in PD-L1 ≥ 50% subpopulation

PD-L1 Tested at Study Entry
All PD-L1 ≥ 50%

Cemiplimab (N=475)
Cemiplimab (N=563)
Chemotherapy (N=475)
Chemotherapy (N=563)

OS

	Median, Mos (95% CI)			HR (95% CI)
NR (NE-NE)	vs	12.1 (10.2-17.5)		0.57 (0.40-0.80)
NR (17.9-NE)	vs	14.2 (11.2-17.5)		0.57 (0.42-0.77)

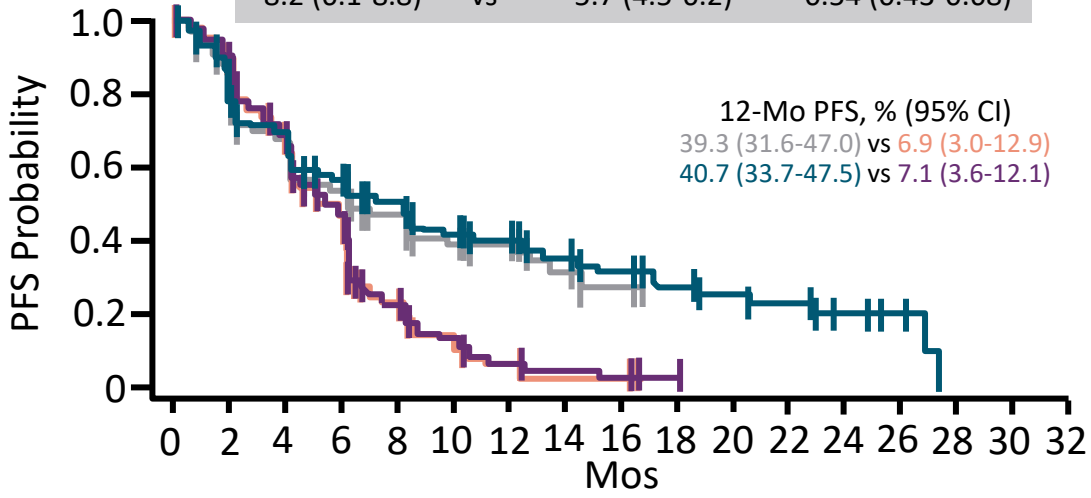


Patients at Risk, n

Cemiplimab	238	200	165	141	120	76	53	26	14	0	0	0	0	0	0	0	0
Chemotherapy	237	200	163	123	98	62	36	20	8	0	0	0	0	0	0	0	0
Cemiplimab	283	244	203	177	154	103	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

PFS

	Median, Mos (95% CI)			HR (95% CI)
6.3 (4.5-8.5)	vs	5.6 (4.3-6.2)		0.60 (0.47-0.77)
8.2 (6.1-8.8)	vs	5.7 (4.5-6.2)		0.54 (0.43-0.68)



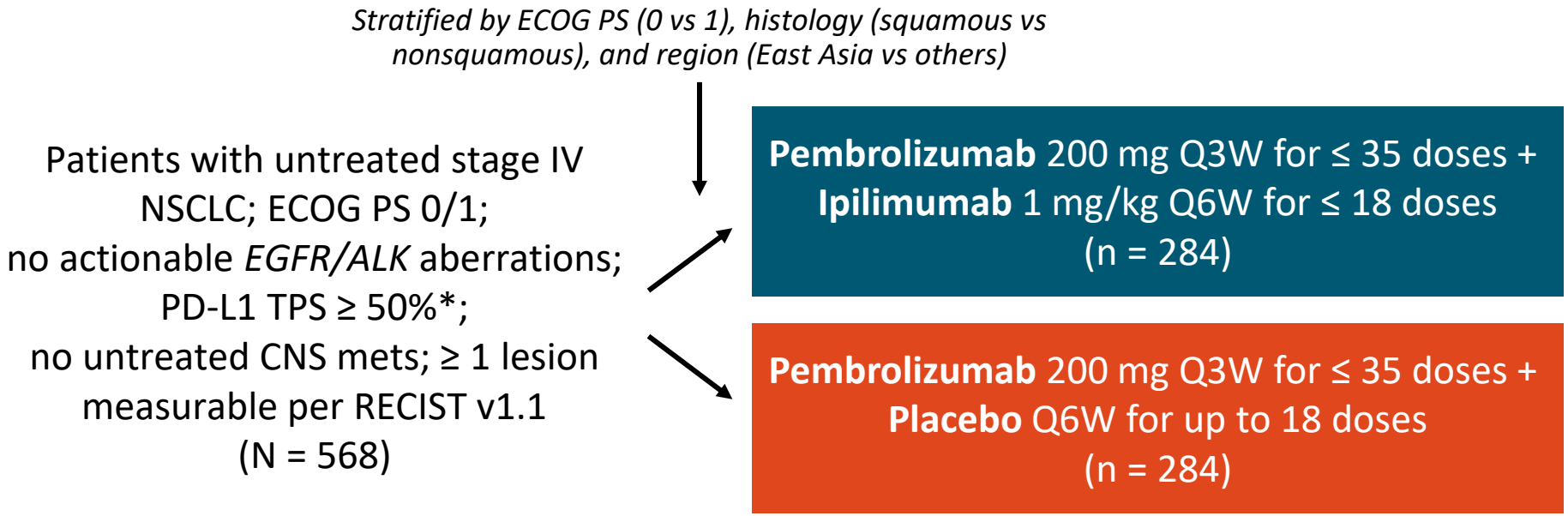
	238	181	130	93	67	38	24	10	4	0	0	0	0	0	0	0	0
	237	183	128	84	33	15	5	1	1	0	0	0	0	0	0	0	0
	283	221	162	123	92	59	43	28	20	14	11	9	5	3	0	0	0
	280	220	157	104	42	20	8	4	3	0	0	0	0	0	0	0	0

Kilickap. WCLC 2020. Abstr OA01.03. Reproduced with permission.

FDA approval-2021-(PD-L1 > 50%)

KEYNOTE-598: First-line Pembrolizumab ± Ipilimumab for Metastatic NSCLC With PD-L1 TPS ≥ 50%

- Double-blind, randomized phase III study



*Assessed centrally using the PD-L1 IHC 22C3 pharmDx assay.

- **Primary endpoints:** OS and PFS per RECIST v1.1 by BICR
- **Key secondary endpoints:** ORR and DoR per RECIST v1.1 by BICR, safety

Boyer. WCLC 2020. Abstr PS01.09.

KEYNOTE-598: OS and PFS

Outcome	Pembrolizumab + Ipilimumab (n = 284)	Pembrolizumab + Placebo (n = 284)	HR (95% CI)
Median OS, mos	21.4	21.9	1.08 (0.85-1.37; *P* = .74)
▪ 12-mo rate, %	63.6	67.9	
▪ Patients with event, %	48.2	47.5	
▪ RMST at 24 mos, mos	16.09	16.61	
▪ RMST at maximum time, mos	18.76	19.32	
Median PFS, mos	8.2	8.4	1.06 (0.86-1.30; *P* = .72)
▪ 12-mo rate, %	41.3	42.1	
▪ Patients with event, %	66.2	64.8	

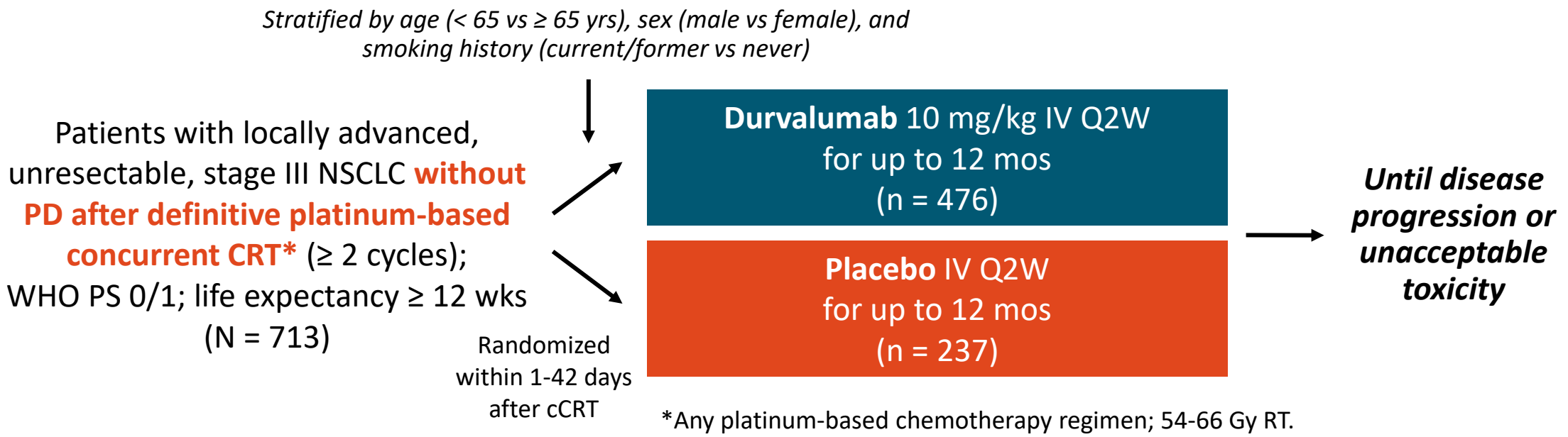
No benefit of adding ipilimumab to pembrolizumab in PD-L1 >50%

Boyer. WCLC 2020. Abstr PS01.09.

Immune Checkpoint Inhibitors in Stage III NSCLC

PACIFIC: Consolidation Durvalumab After Concurrent CRT for Locally Advanced, Unresectable, Stage III NSCLC

- Randomized, double-blind, placebo-controlled phase III trial



- Primary endpoints: PFS by BICR per RECIST v1.1, OS
- Secondary endpoints including ORR, DoR, TTDM, PFS2, safety/tolerability, PROs

Antonia. NEJM. 2018;379:2342. Antonia. WCLC 2018. Abstr PL02.01. Antonia. NEJM. 2017;377:1919. Paz-Arez. ESMO 2017. Abstr LBA1_PR.

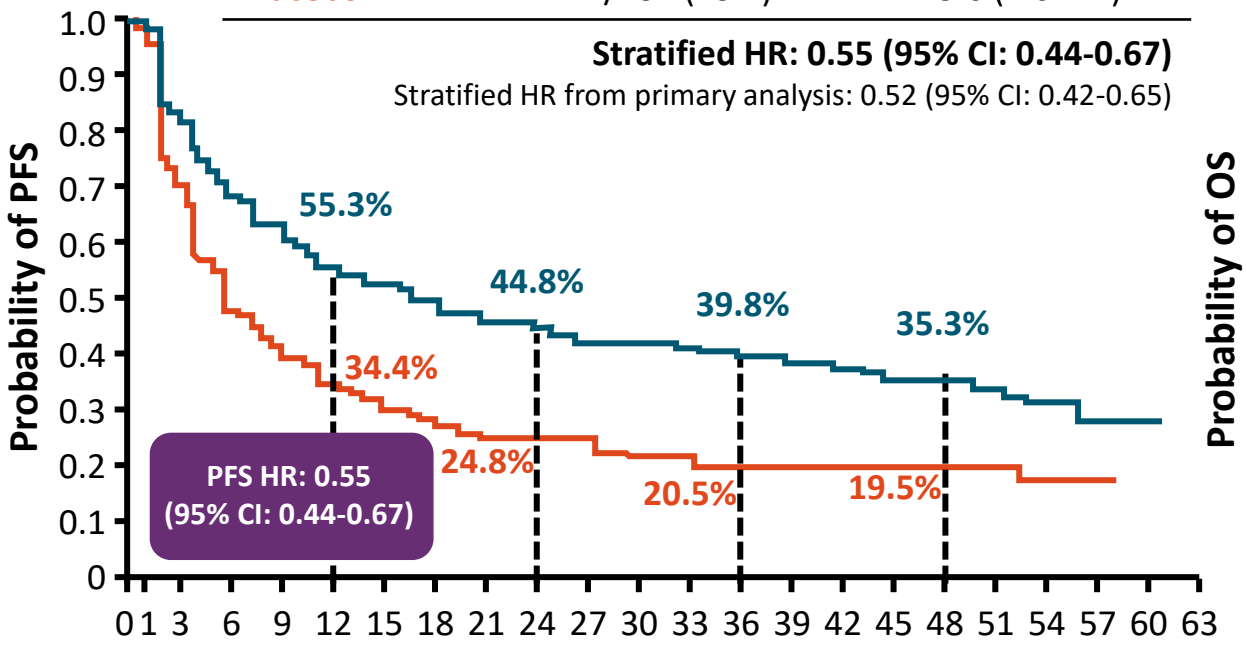
PACIFIC: PFS and OS with Durvalumab at 4 Yrs

Updated PFS (BICR; ITT)

	No. of Events/Total No. of Patients (%)	Median PFS, Mos (95% CI)
Durvalumab	266/476 (55.9)	17.2 (12.3-23.8)
Placebo	174/237 (73.4)	5.6 (4.6-7.7)

Stratified HR: 0.55 (95% CI: 0.44-0.67)

Stratified HR from primary analysis: 0.52 (95% CI: 0.42-0.65)



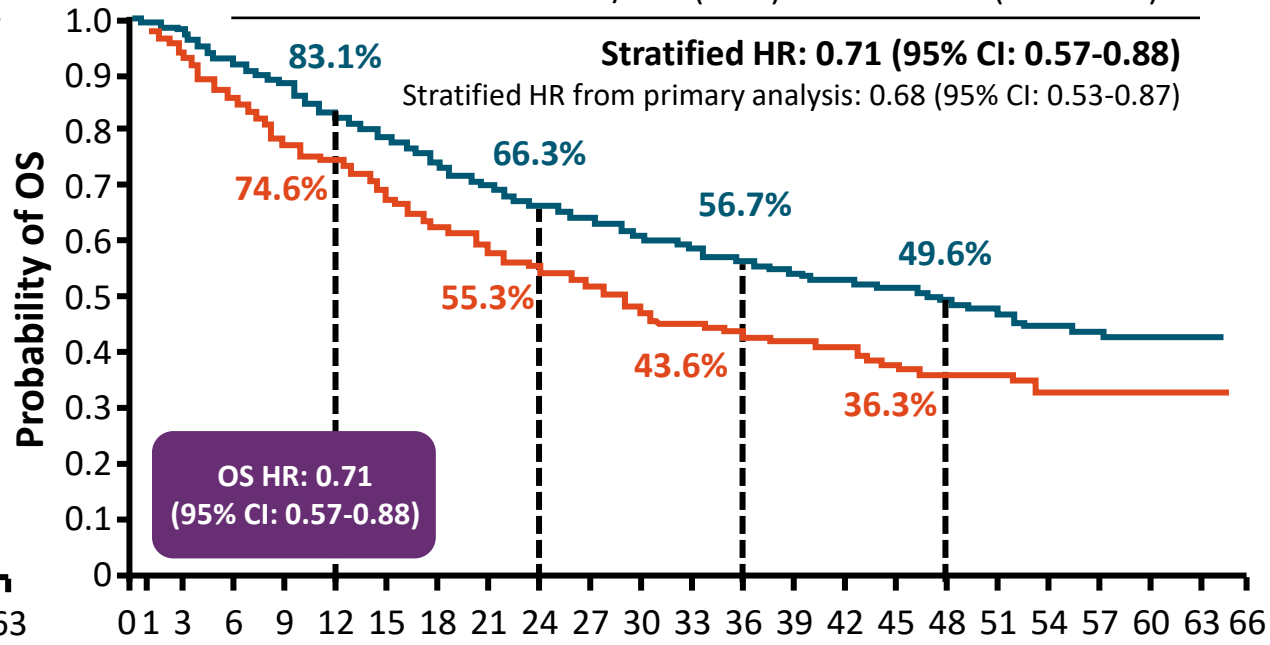
Patients at Risk, n																							
Durvalumab	476	377	301	266	213	189	165	146	136	127	119	110	103	97	92	80	59	37	18	8	1	0
Placebo	237	163	105	86	67	55	47	40	36	35	29	26	25	24	23	22	16	11	5	1	0	0

Updated OS (ITT)

	No. of Events/Total No. of Patients (%)	Median OS, Mos (95% CI)
Durvalumab	247/476 (51.9)	47.5 (38.4-52.6)
Placebo	149/237 (62.9)	29.1 (22.1-35.1)

Stratified HR: 0.71 (95% CI: 0.57-0.88)

Stratified HR from primary analysis: 0.68 (95% CI: 0.53-0.87)



476	464	431	414	385	364	343	319	299	290	274	265	252	241	235	225	195	138	75	36	15	2	0
237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	75	53	29	15	7	2	0

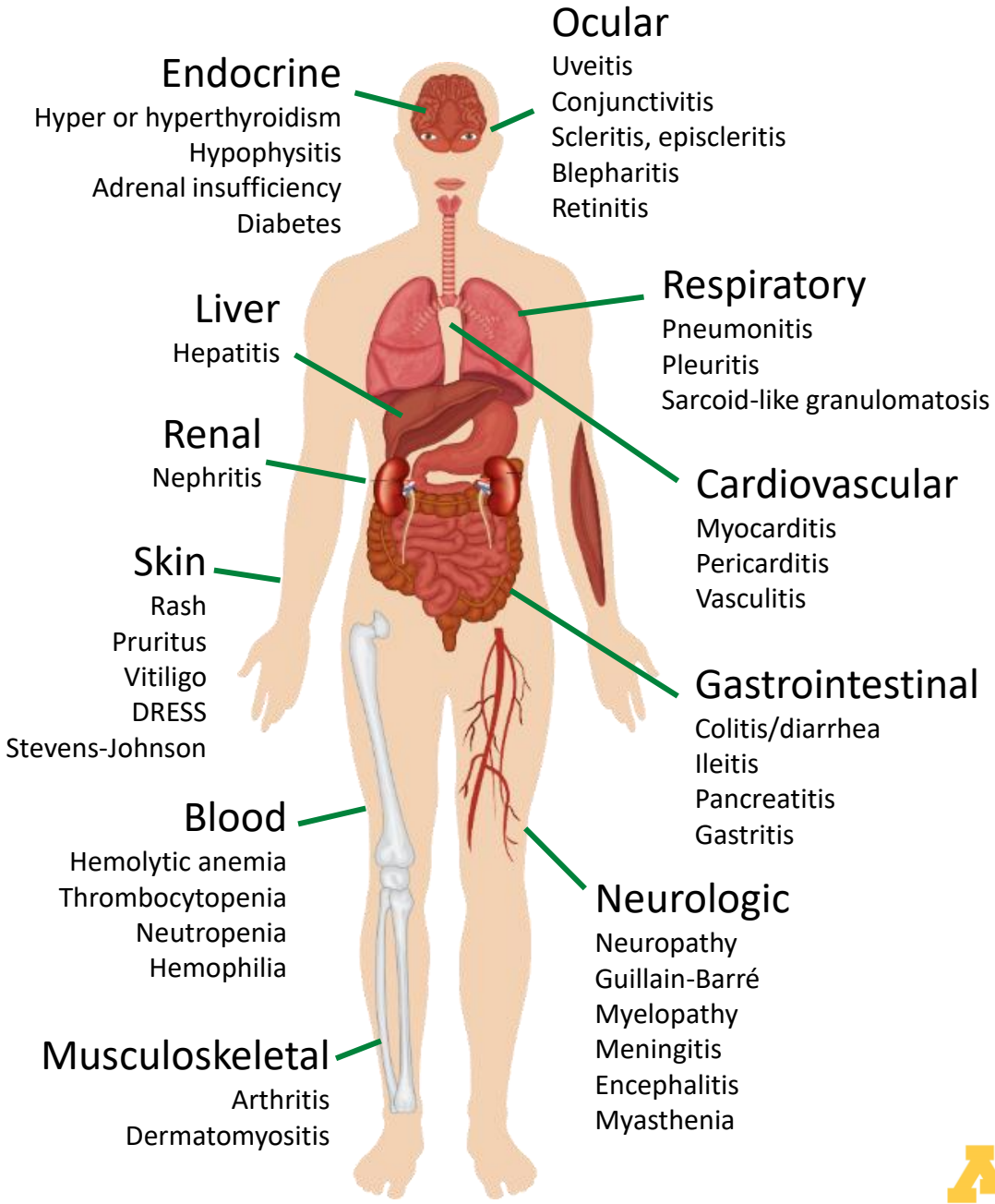
Faivre-Finn. ESMO 2020. Abstr LBA49.

FDA approval-2018

Immune related adverse events (irAE)

Immune-Related AEs Throughout the Body

- There are unique AEs associated with immune checkpoint inhibitor therapy
- These represent a new spectrum of AEs that differ in important ways from those associated with chemotherapy and targeted agents
  - Immune-related AEs occur through an imbalance of tolerance and drug-induced immunity (auto-immunity)



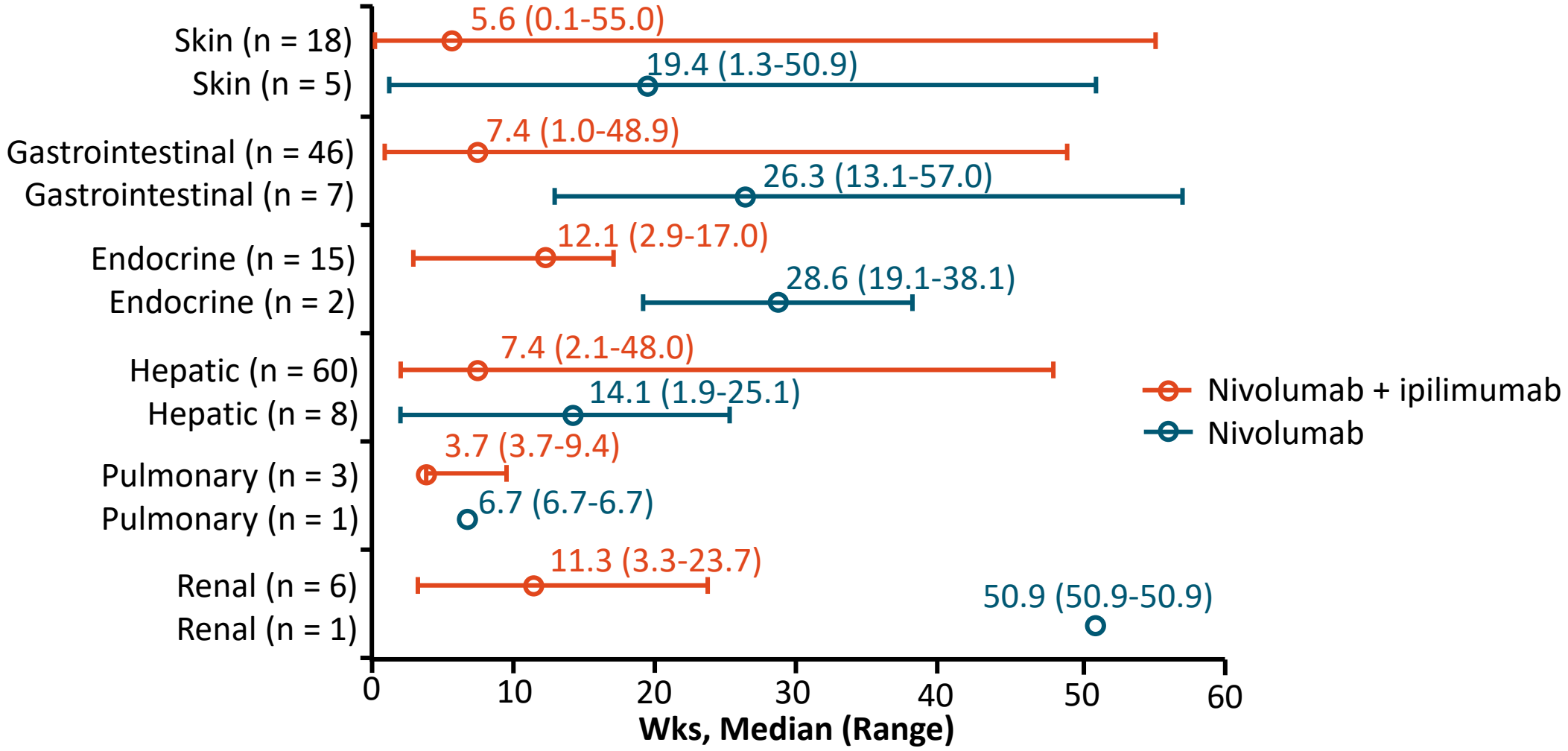
Champiat. Ann Oncol. 2016;27:559.

ICI Treatment and irAEs: Basic Issues

- Most but not all irAEs occur during the first 12 wks of therapy (ie, during induction therapy)
- Early recognition and treatment is the key
- Steroids can be used to manage almost all irAEs
- Prolonged steroid tapers are usually required
- irAEs can wax and wane, particularly colitis or hepatitis
- Late irAEs can occur: even months after drug is stopped

Davies. Immunotargets Ther. 2017;6:51. Puzanov. J Immunother Cancer. 2017;5:95. Martins. Nat Rev Clin Oncol. 2019;16:563.

Onset of Grade 3/4 Immune-Related AEs With Nivolumab + Ipilimumab vs Nivolumab



Haanen. Ann Oncol. 2017;28(suppl 4);iv119. Larkin. Eur J Cancer. 2015;51(suppl 3):S664.

General Management of irAEs Associated With Immune Checkpoint Inhibitors

Grade	Steroids	Treatment	Persistent/Recurring
1	▪ Treat symptomatically; no systemic steroids	▪ Can continue	
2	▪ Steroids for selected irAEs and for recurrent irAEs	▪ Continue ▪ Hold for selected irAEs	▪ Systemic steroids ▪ Consider withholding; discontinue if ≥ 12 wks
3	▪ Systemic steroids, prolonged tapers	▪ Withhold or discontinue*	▪ Systemic steroids and discontinue
4	▪ High-grade systemic steroids, prolonged tapers	▪ Discontinue (unless endocrine irAE)	▪ Add other immune suppressants

*Discontinue for grade 3 irAEs renal toxicity, pneumonitis, and infusion reactions; question for grade 3 hepatotoxicity.

Selected AEs: colitis, pneumonitis, liver/renal toxicity, hypophysitis, neurologic

Systemic steroids (PO or IV): 1-2 mg/kg/day prednisone or equivalent
- Slow taper over ≥ 4 wks recommended
- Several courses may be necessary if symptoms worsen when dose decreased

Trinh. Asia Pac J Oncol Nurs. 2019;6:154. Brahmer. JCO. 2018;36:1714.
NCCN Guidelines for Management of Immunotherapy-Related Toxicities. v1.2021.

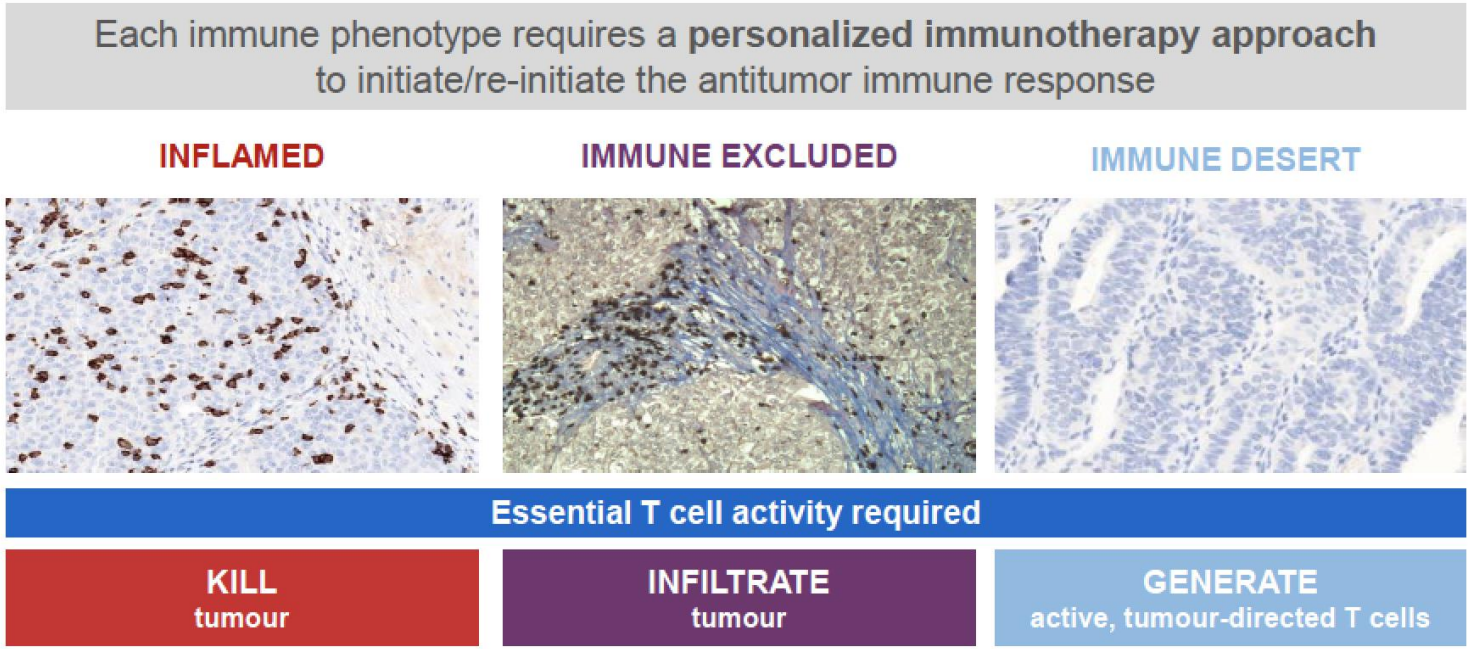
Immunotherapy in challenging populations

These patients are usually excluded from clinical trials

- Patients with oncogenic driver mutations (some date in EGFR/ALK+, IMPOWER 150)
- Patients with active auto-immune disorders
- Patients on chronic immunosuppressives (organ transplant patients)
- Poor performance status (ECOG PS 3, 4)
- Pregnancy (Category D)

What if immunotherapy does not work?

- Response rates can vary from 30% to 60%
- 75-80% of patients will ultimately progress
- How to stimulate/reinvigorate immune response?



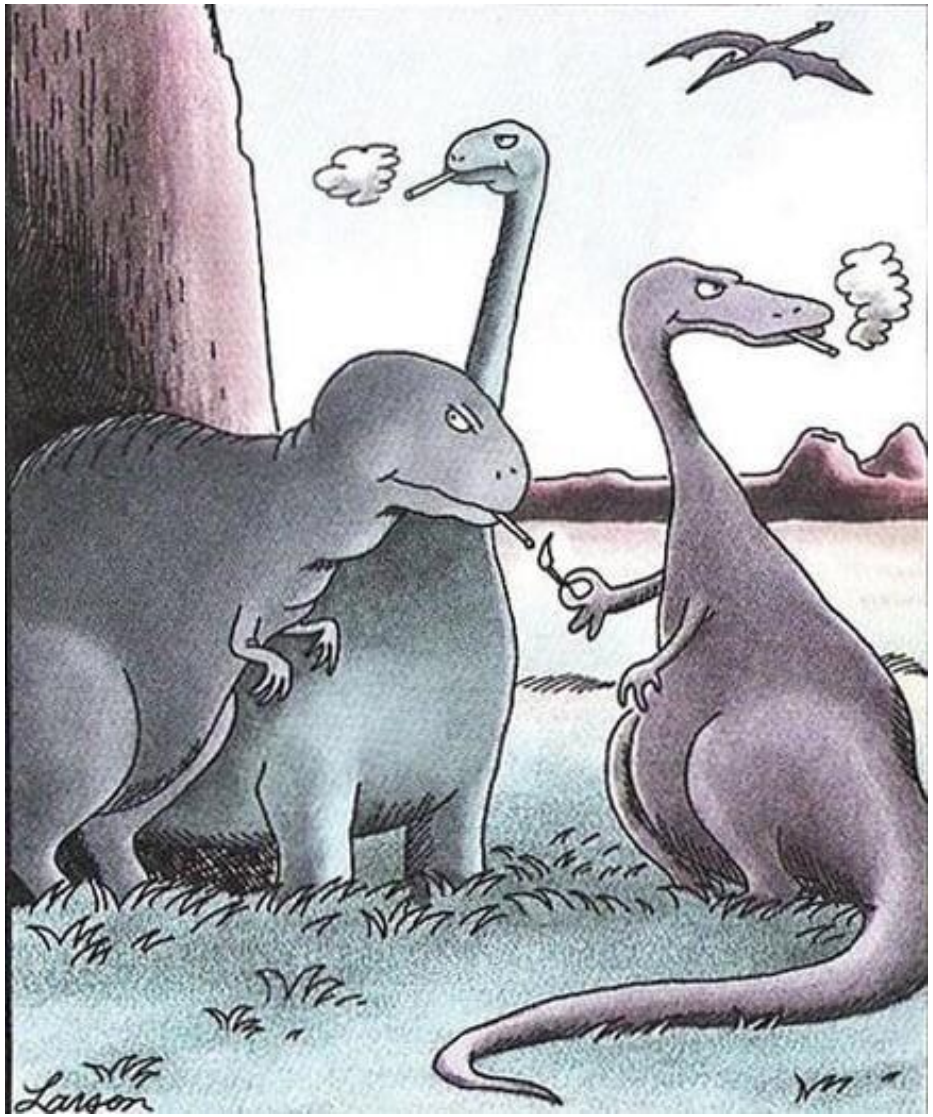
Adapted from Chen and Mellman. Immunity 2013; Hegde, et al. Clin Cancer Res 2016; Kim and Chen. Ann Oncol 2016; Chen, Herbst et al Nature 2014, and Mellman. Nature 2017

Summary

- Immunotherapy is the backbone of treatment in patients with advanced NSCLC with no oncogenic driver mutations
- PD-L1 ≥50%- Single agent immunotherapy is appropriate
- PD-L1 1-49% or <1%- addition of chemotherapy has best outcomes
- Immune related side-effects are common, early recognition is the key
- Ongoing studies to integrate immunotherapy in localized NSCLC
- Resistance mechanisms to immunotherapy is an active area of research

Thoracic Oncology at UMN

Bob Kratzke



The real reason dinosaurs became extinct

Naomi Fujioka

Manish Patel

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