DM Seminar

PD-1/PD-L1 Immune Checkpoint Inhibitors In Advanced Lung Cancer : Current Status

Dr Srikant K M

16/08/19

Overview

Immune checkpoints- PD-1/PD-L1

Immune checkpoint inhibitors mechanism of action

When to use ICI’s in Lung Cancer

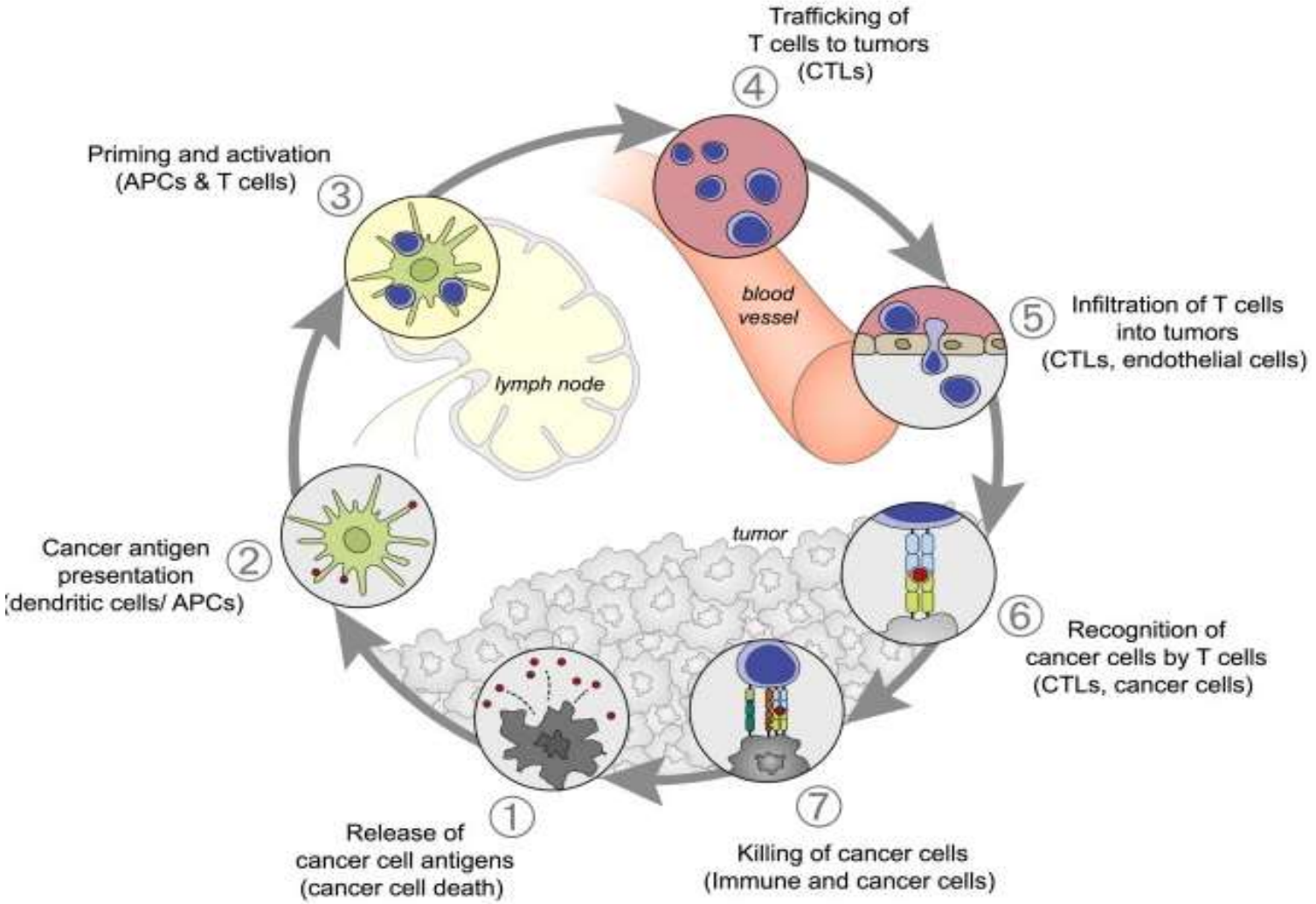
Currently available ICI’s with evidence for use

Current recommendations

Adverse effects

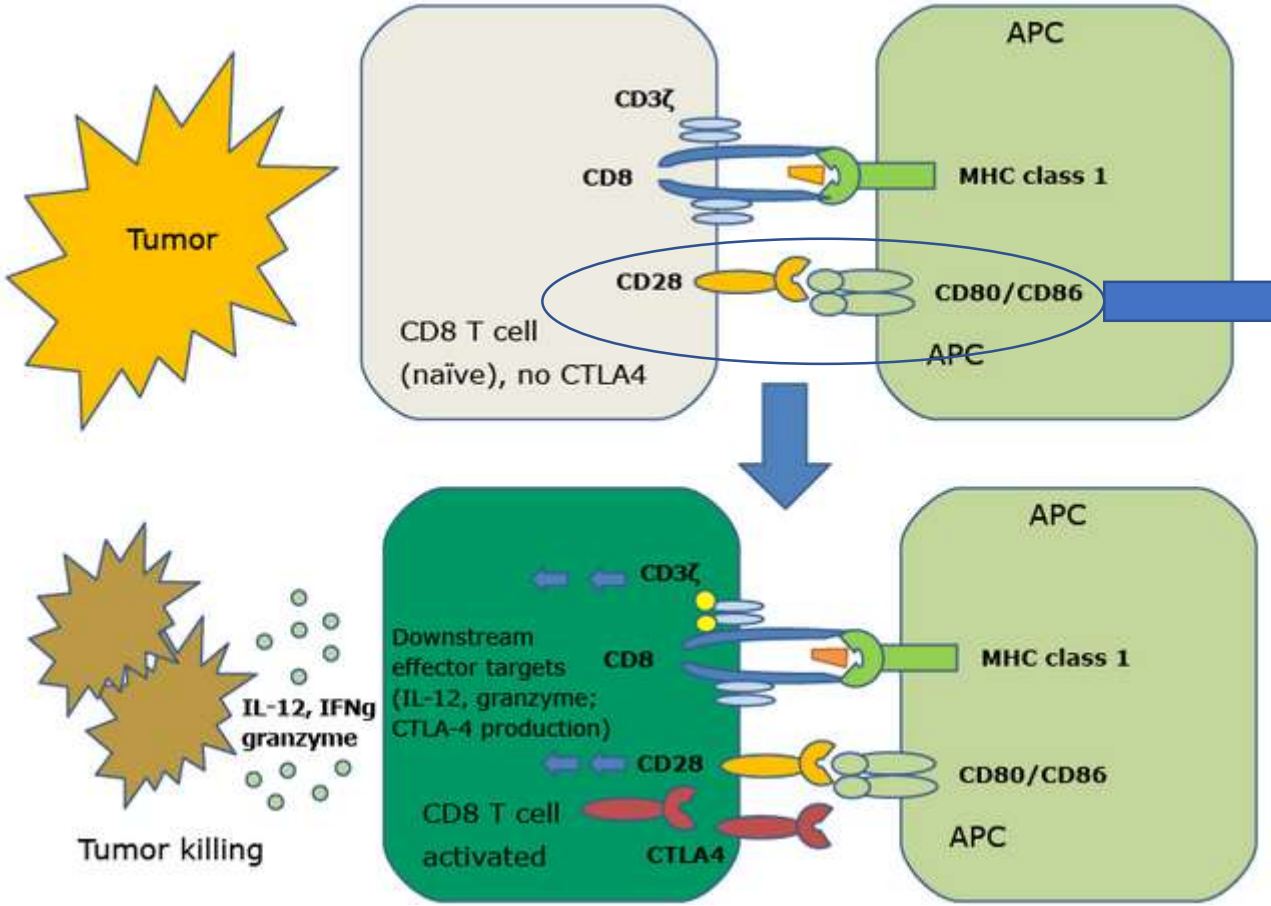
Our practice in LCC/ LCC Data

Tumour Immune System Interface- Immunosurveillance



Chen, D. S, Oncology Meets Immunology, Immunity, 39(1), 2013

TUMOR MICROENVIRONMENT- IMMUNE SURVEILLANCE IMMUNE SYNAPSE



Complex of
APC
CD8+ T CELL
COSTIMULATORY RECEPTOR
INFLUENCED BY
STIMULATORY AND INHIBITORY
SIGNALS (IMMUNE CHECKPOINT)

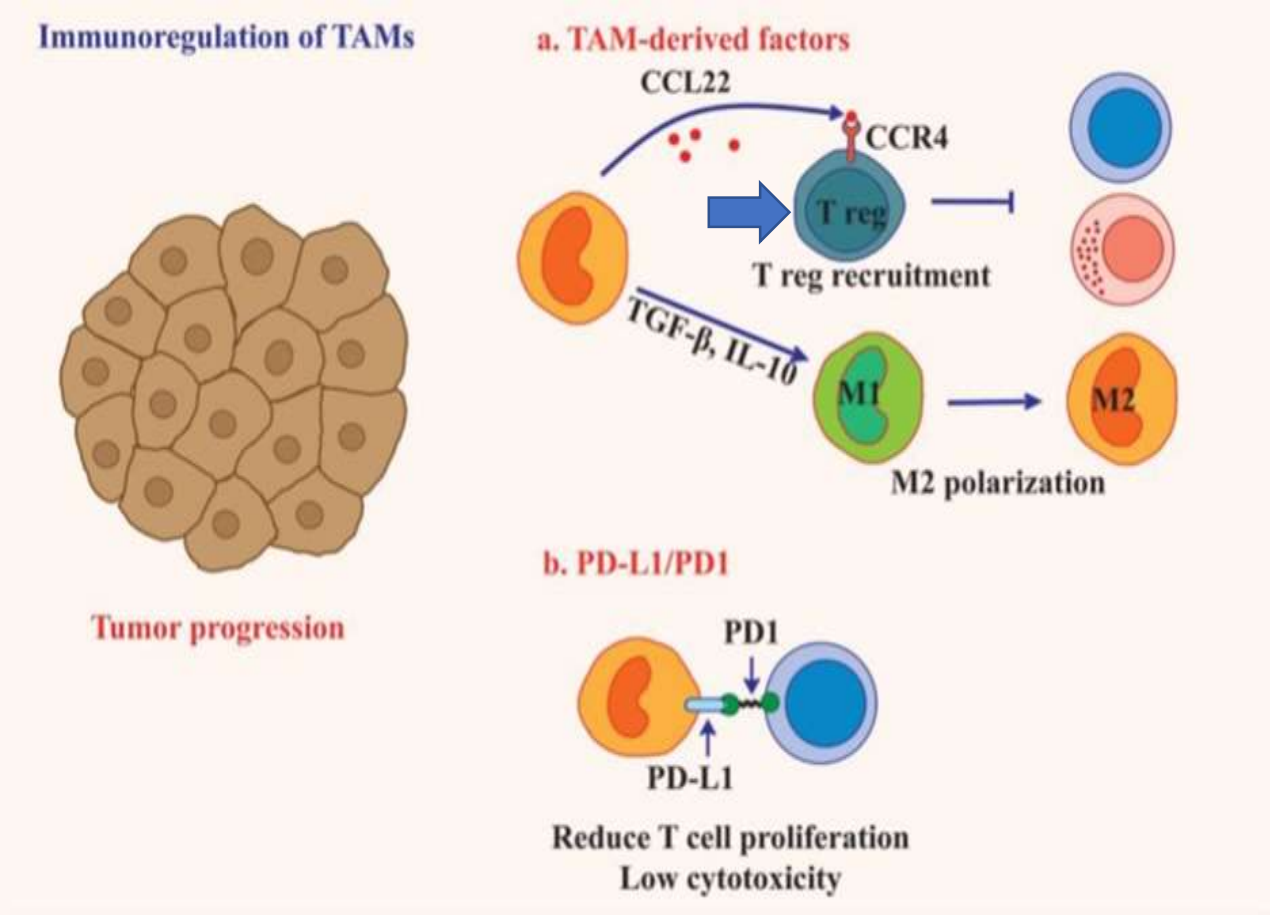
Channee T, Cancers (Basel). 2014 Sep; 6(3): 1670–1690

CANCER IMMUNOEDITING

- Interaction b/w immune system and cancer
- Three sequential phases of interaction
- Elimination : Body's immunity detects and responds to tumour antigens
- Equilibrium : balance b/w immune mediated destruction and persistence of malignant clones
- Escape : evasion of immune response by malignant clones

Schreiber R D, Cancer immunoediting, Science 2011 Mar 25;331(6024):1565-70

MECHANISMS OF ESCAPE FROM IMMUNE SURVEILLANCE



1. Inhibition of Cytotoxic T cells
2. Defective Antigen presentation
3. Immune suppressive mediators
4. Upregulation of immune checkpoint molecules

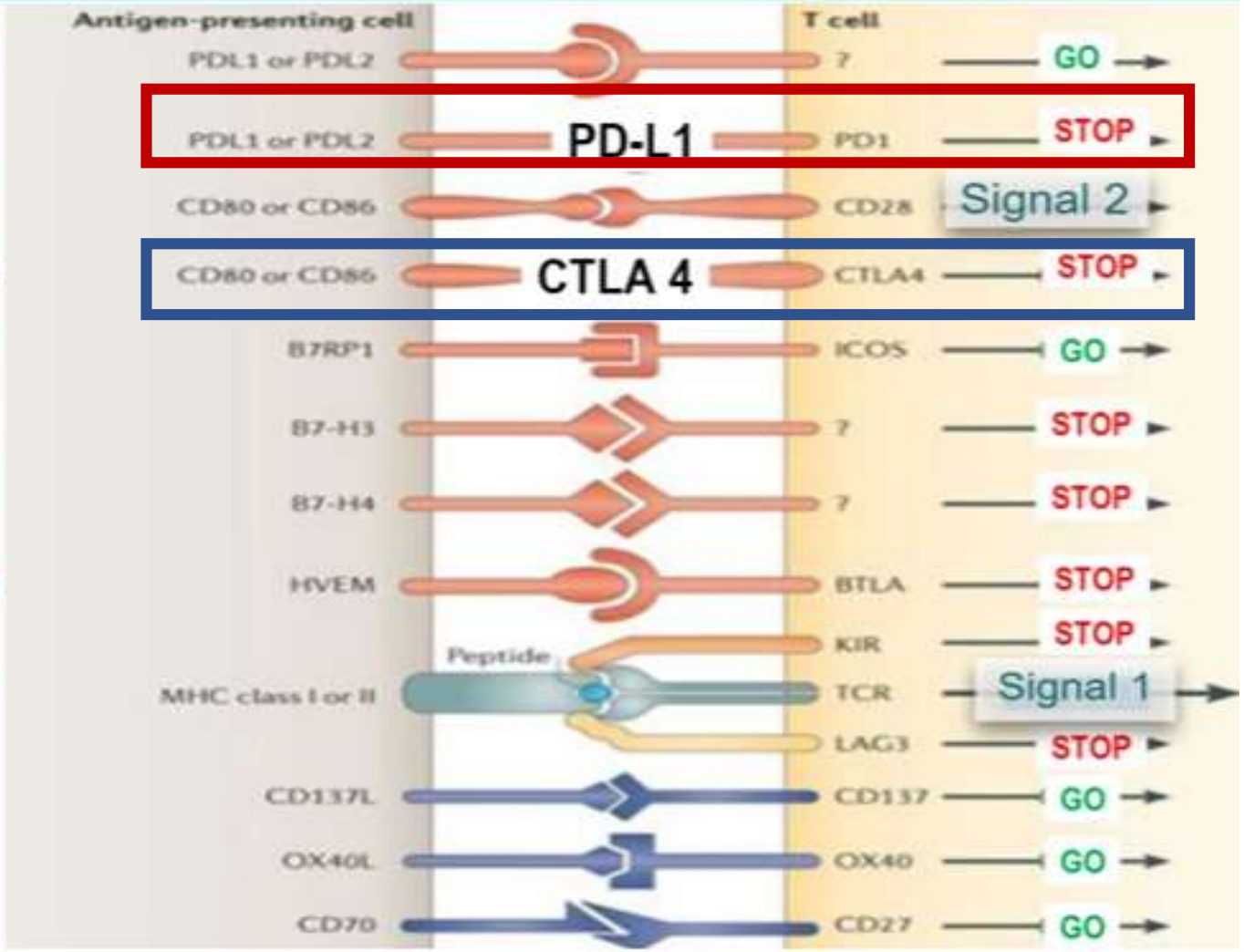
IASLC Atlas of PD-L1 IHC Testing in Lung Cancer

Immune Checkpoints

APC

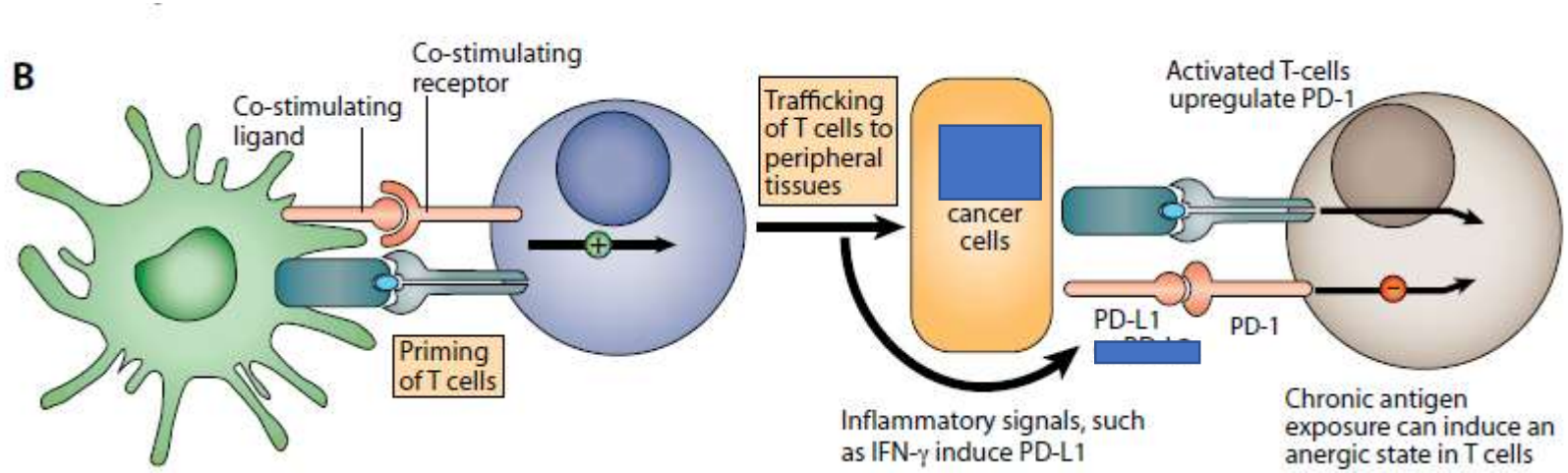
OR

TUMOUR CELL



Nat Rev Cancer 2012 Mar 22, 12(4) 252-64

PD-1/PD-L1 PATHWAY



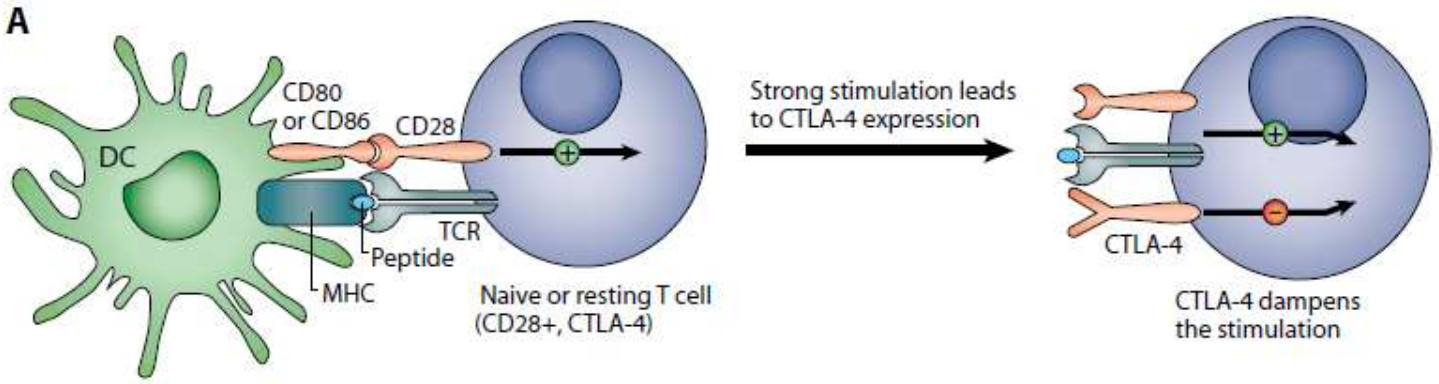
Inhibits apoptosis of tumour cells

Exhaustion of effector T cell

Conversion of T cell to Treg cells

IASLC Atlas of PD-L1 IHC Testing in Lung Cancer

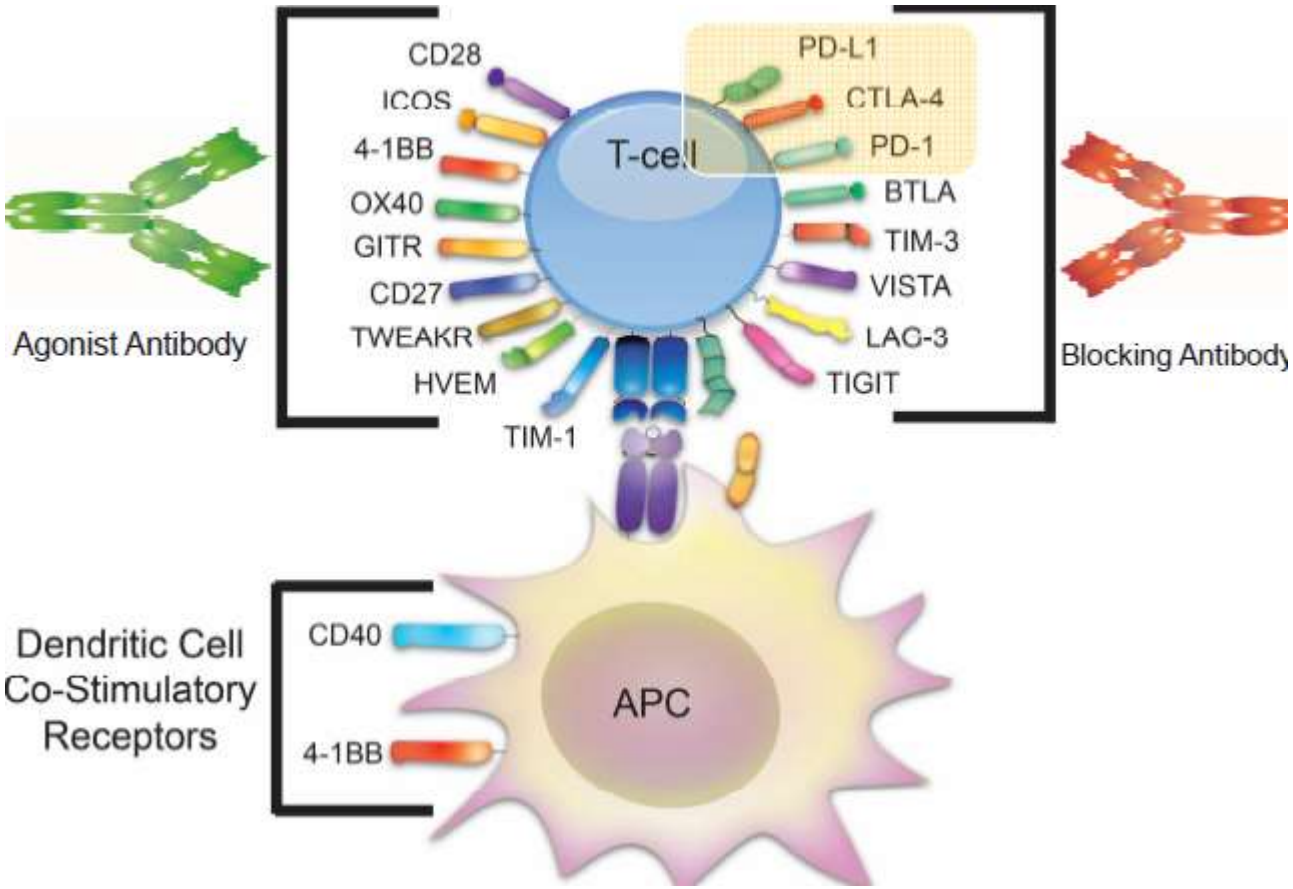
CTLA-4 PATHWAY



CTLA-4 competes with CD28, thus preventing stimulation of T cell

IASLC Atlas of PD-L1 IHC Testing in Lung Cancer

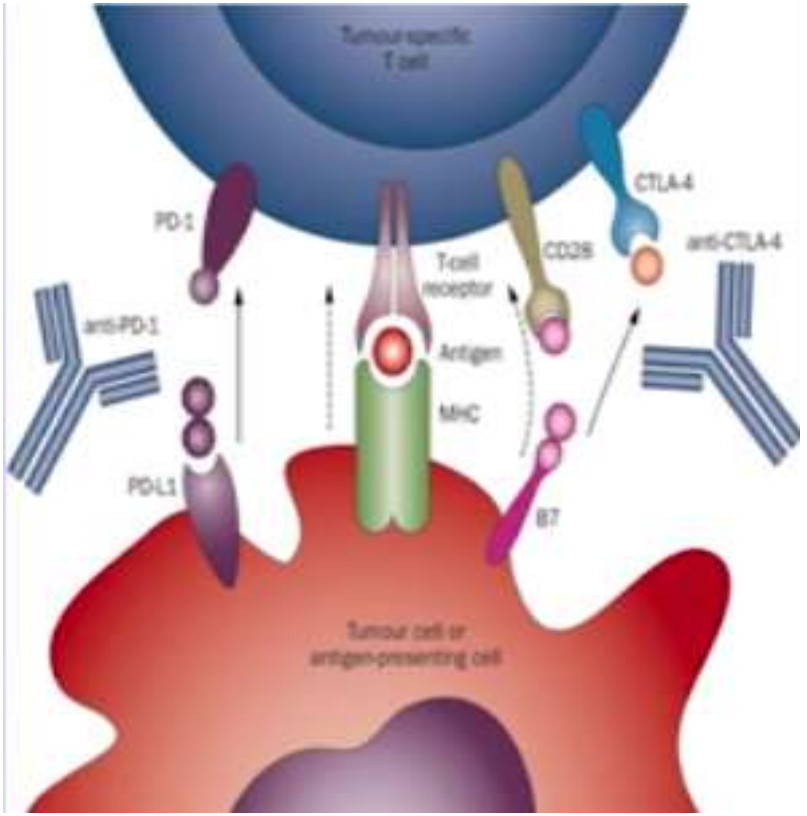
Principle of immunotherapy : Alteration of regulatory pathway



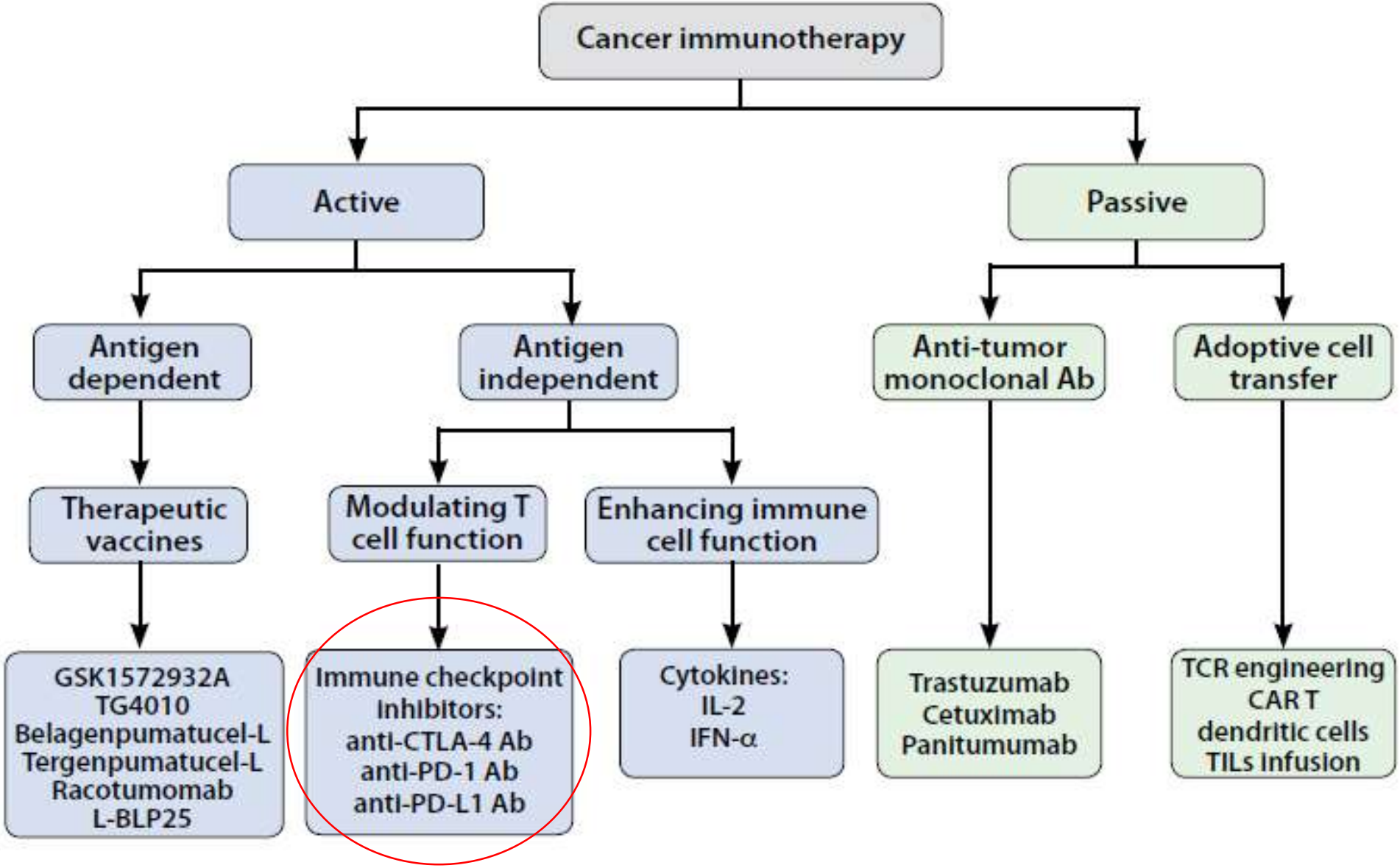
Curran M A, immune checkpoint combinations, Cancer immunology,2015

For Checkpoint blockade to work optimally - prerequisites

- T cells must express co inhibitory molecule (i.e. CTLA-4/PD-1)
- Tumour/ tumour microenvironment must express corresponding ligand(i.e. PD-L1)
- T cells on release of checkpoint blockade should act against tumour cells



Pardoll, Nat Rev Cancer, 12:252-64



IASLC Atlas of PD-L1 IHC Testing in Lung Cancer

Need for immunotherapy?

- Three special characters of immune mediated therapy
  Specificity – minimal collateral damage
  Adaptability – change/recognize any new changes in cancer cell
  Memory – prevent recurrence

- Limitations of currently available therapy
  Surgery
  Chemotherapy
  Radiation
  Molecular targeted therapy

Curran M A, immune checkpoint combinations, Cancer immunology,2015

CURRENTLY APPROVED IMMUNE CHECKPOINT INHIBITORS IN LUNG CARCINOMA

DRUG	BRAND NAME	TARGET	INDICATION	DETAILS
PEMBROLIZUMAB	KEYTRUDA	PD-1	1L. METASTATIC NSCLC WITH HIGH PD-L1 EXPRESSION	TPS≥50%
			1L. METASTATIC NSCLC	IN COMBINATION CT
			2L. METASTATIC NSCLC WITH PD-L1 EXPRESSION	TPS≥1%
			3L. METASTATIC SCLC	
NIVOLUMAB	OPDYTA	PD-1	2L. METASTATIC NSCLC	IRRESPECTIVE OF PD-L1
			3L. METASTATIC SCLC	
ATEZOLIZUMAB	TECENTRIQ	PD-L1	1L. METASTATIC NON SQUAMOUS NSCLC 1L. ED-SCLC	
			2L. METASTATIC NSCLC	IRRESPECTIVE OF PD-L1
DURVALUMAB	IMFINZI	PD-L1	MAINTAINENCE UNRESECTABLE STG III NSCLC	IRRESPECTIVE OF PD-L1

When to use immunotherapy?

- The management of advanced NSCLC is mainly palliative

- The aim being prolonging survival, preserving QOL and minimizing side effects of treatment

- Factors which affect choice of treatment are-

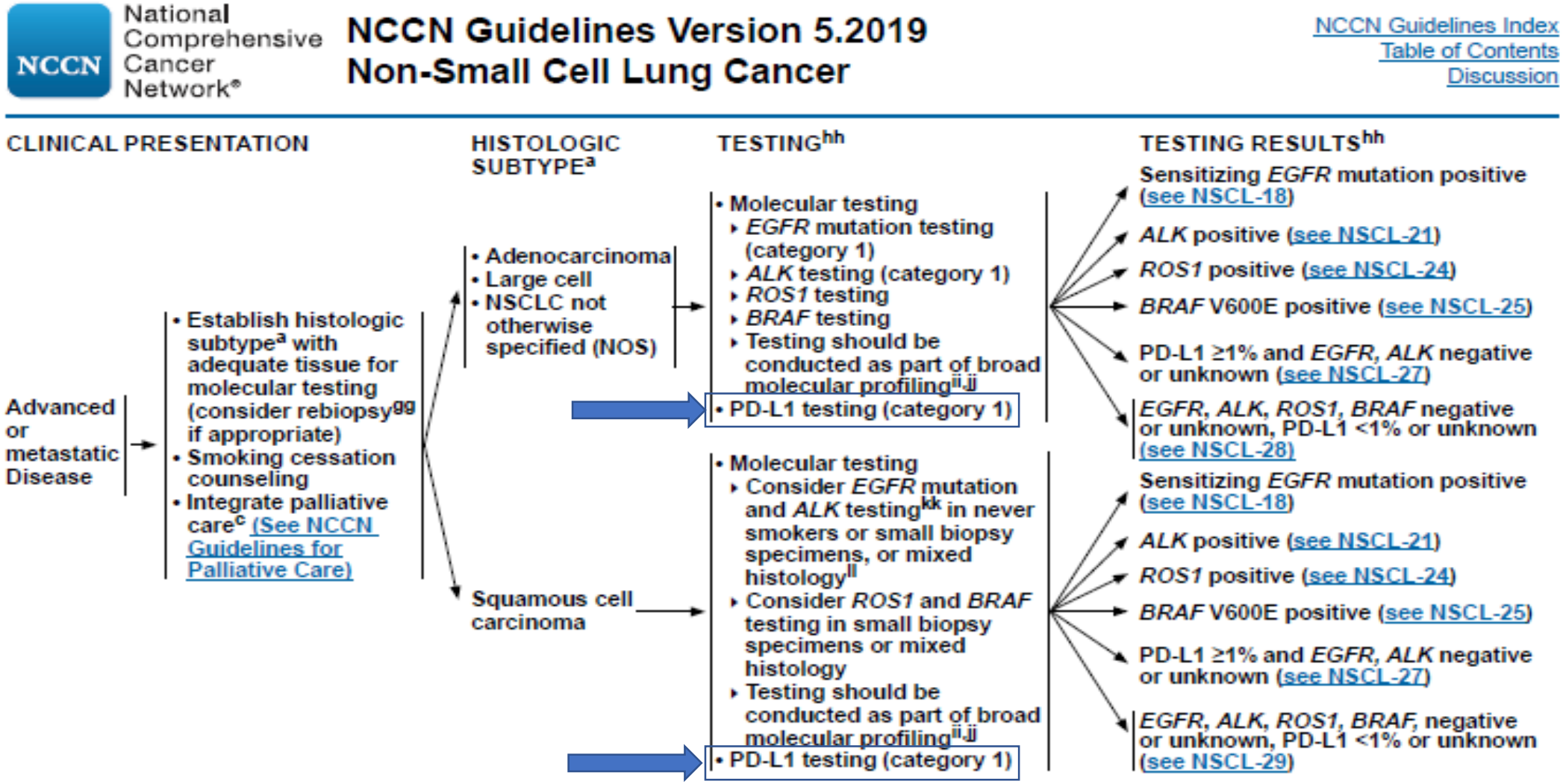
  Histology

  Driver mutation

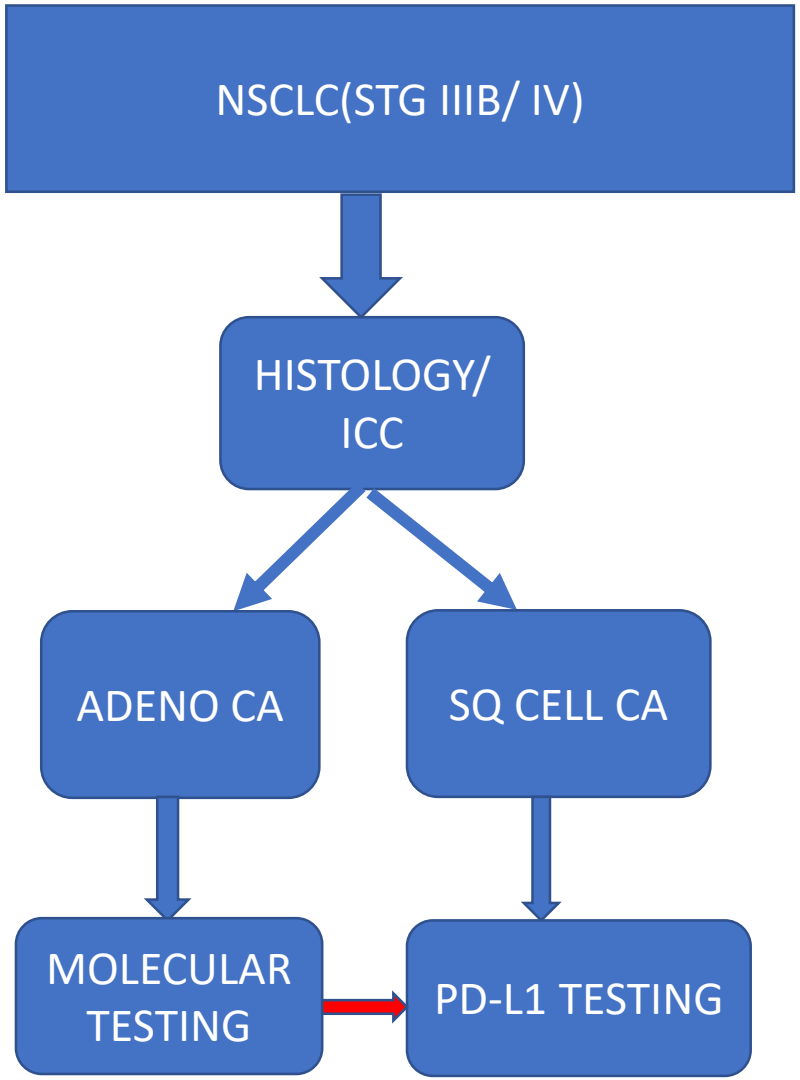
  Level of PD-L1 expression

  Extent of disease

When to use immunotherapy?



NCCN NSCLC GUIDELINES 2019



Journal of the National Comprehensive Cancer Network, 2015

PD-L1 testing in Lung Cancer

- PD-L1 expression is detected by IHC
- FFPE tissue is used for IHC (Fluid and FNAC cell blocks/ smears can be used)
- Cold ischemia time (b/w sampling and fixation should be kept minimum ~ 30min)
- Fixation time b/w 6-48hr is recommended
- If not to be immediately stained should be reviewed within 2months
- Specimen age for testing should be lesser than 3 years.

IASLC Atlas of PD-L1 IHC Testing in Lung Cancer

FDA approved antibody clones and platforms for IHC assay

Table 2. Programmed Cell Death Ligand 1 (PD-L1) Immunohistochemistry Assays According to Drugs and Diagnostic Tests

Drug	PD-L1 Diagnostic Antibody Clone	PD-L1 Binding Domain	Platform	Second- line Criteria for PD-L1 Positivity
Nivolumab (Bristol-Myers Squibb)	28-8 (rabbit)	Extracellular	Link 48 Autostainer	≥1% tumor cells
Pembrolizumab (Merck)	22C3 (mouse)	Extracellular	Link 48 Autostainer	≥50% tumor cells
Atezolizumab (Genentech/Roche)	SP142 (rabbit)	Cytoplasmic	BenchMark ULTRA	Tumor cells and/or tumor-infiltrating immune cells
Durvalumab (AstraZeneca/ MedImmune)	SP263 (rabbit)	Extracellular[a]	BenchMark	≥25% tumor cells
Avelumab (Pfizer/Merck Serono)	73-10	unknown	Dako assay	≥1% tumor cells

IASLC Atlas of PD-L1 IHC Testing in Lung Cancer

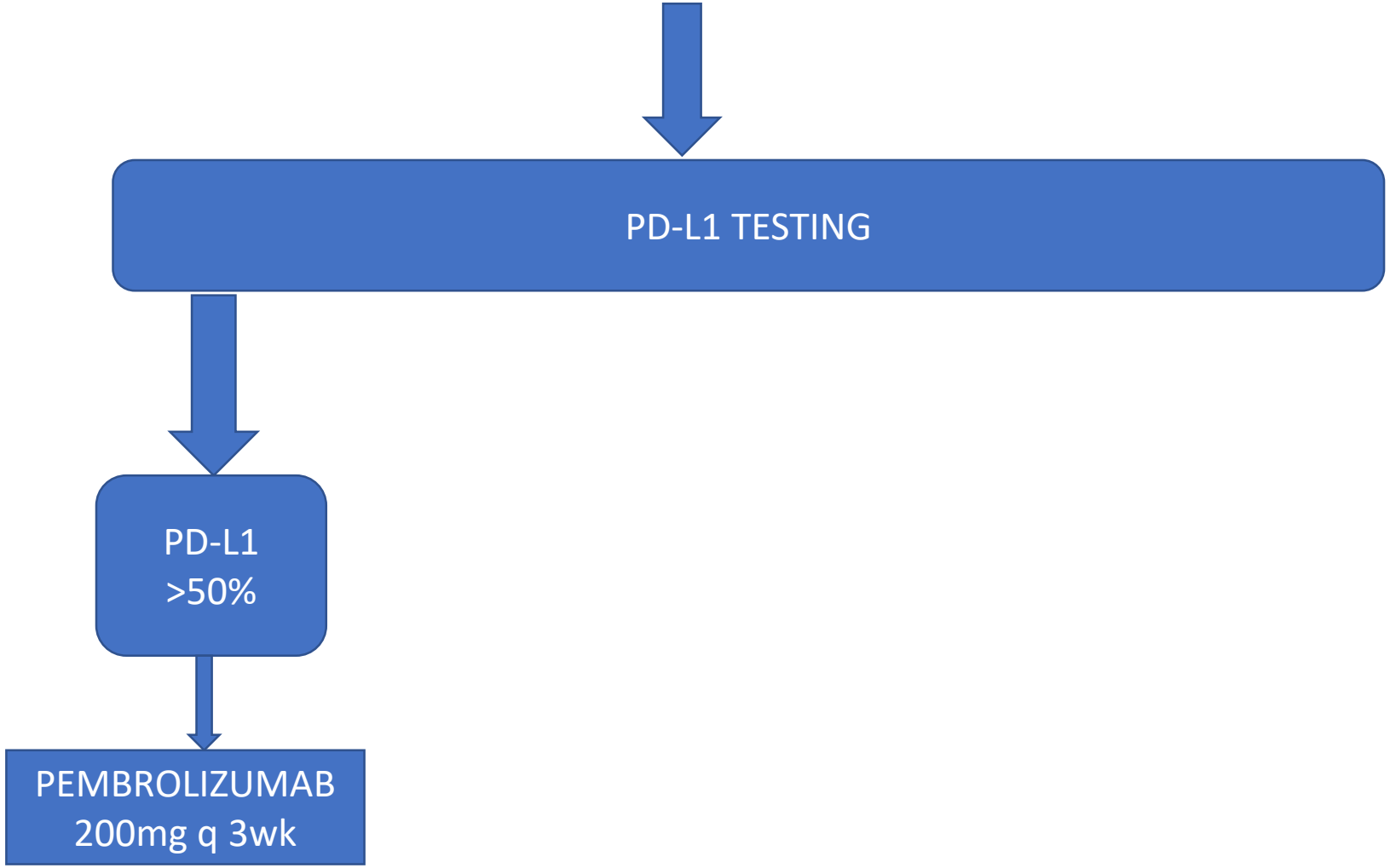
Challenges in PD-L1 testing

- Intratumoral heterogeneity
- Different antibody/platform approved for different ICI
- Interobserver variation

- Purpose of Blueprint study : information on clinical and analytic comparability of 4 IHC assays used
- >85% concordance b/w SP263/22C3/28-8 in identifying positive TC staining

Rimm DL JAMA Oncol. 2017;3(8):1051–1058

Adenocarcinoma(Stg IV)- 1ST Line Treatment



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 10, 2016 VOL. 375 NO. 19

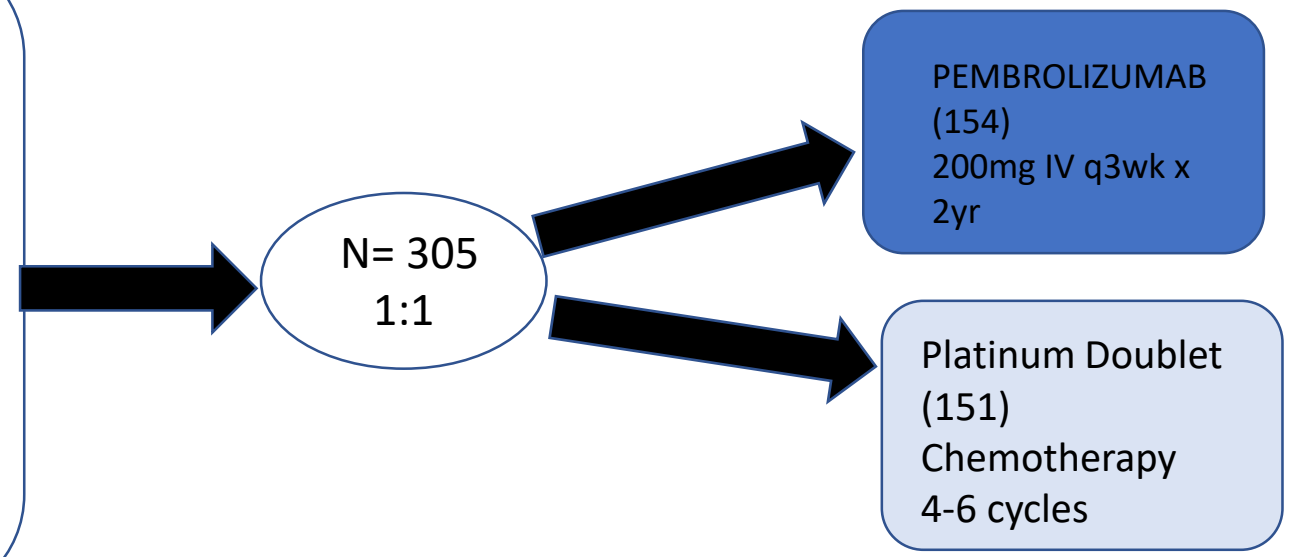
Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*

Reck M et al, N Engl J Med. 2016

Study Design

Eligibility Criteria
- Untreated stage IV NSCLC
- PD-L1 ≥ 50%
- ECOG PS 0-1
- No EGFR mutation/ALK translocation
- No active autoimmune disease
- Not on immunosuppressant
- No brain mets
- No ILD/ h/o pneumonitis

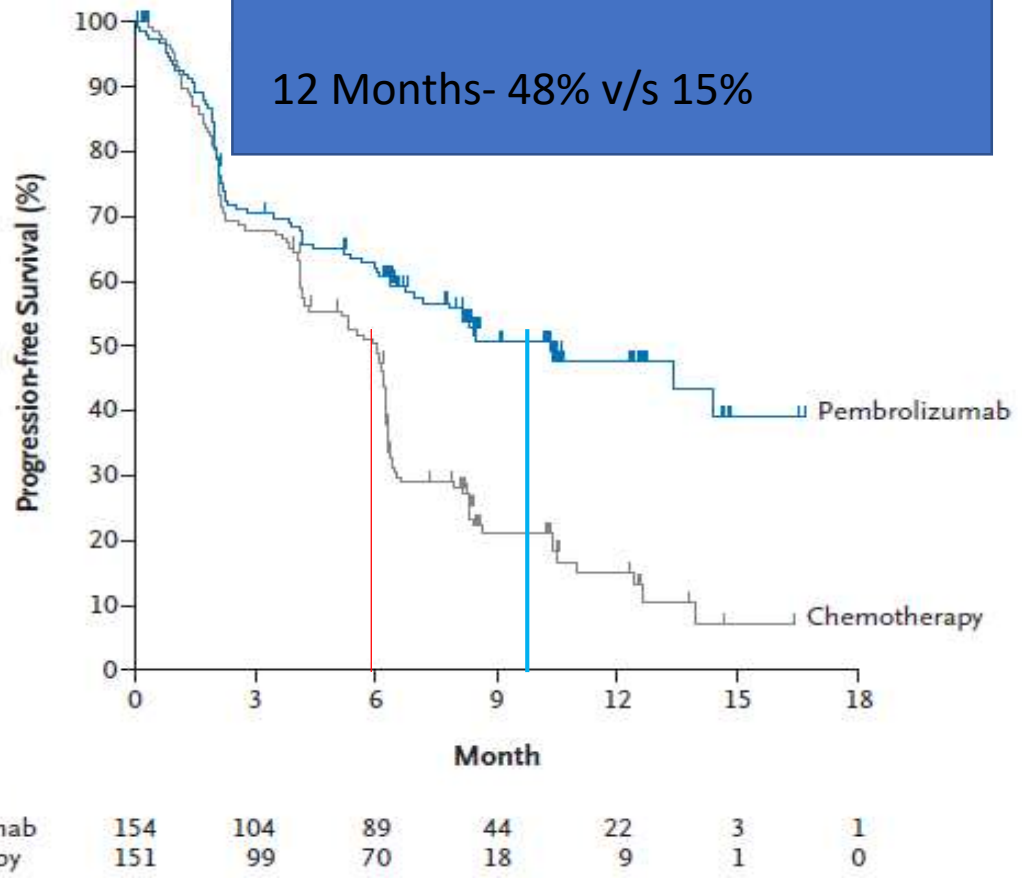


Reck M et al, N Engl J Med. 2016

Primary End Point- Progression Free Survival

6 Months- 62% v/s 50%

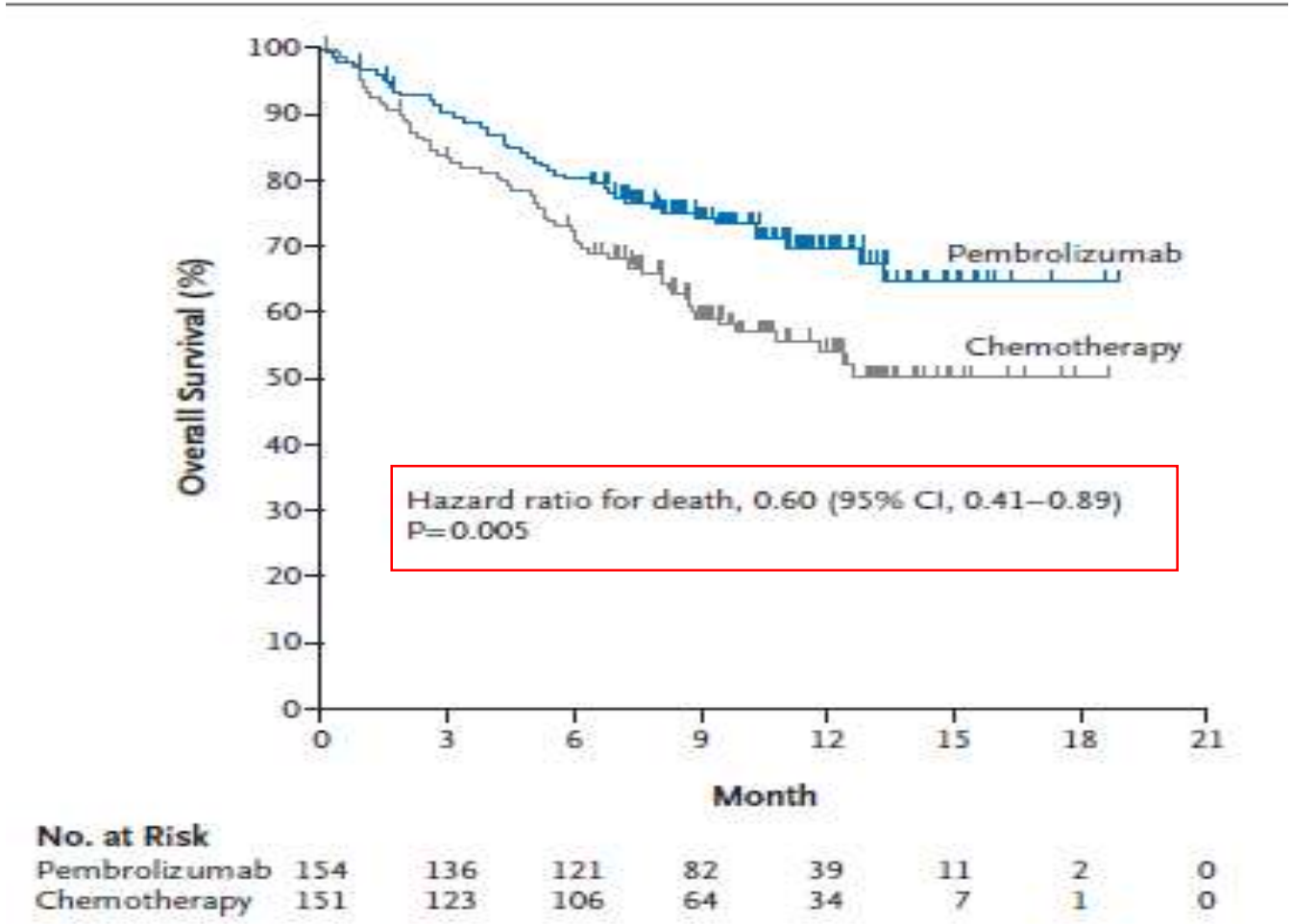
12 Months- 48% v/s 15%



	Events	Median Survival (months)	HR	P value
Pembro	73	10.3	0.5(0.37 -0.68)	<0.001
Chemo	116	6		

Reck M et al, N Engl J Med. 2016

Secondary End Point – Overall survival



At 6 months – 80% v/s 72%

At 12 months – 70% v/s 54%

Reck M et al, N Engl J Med. 2016

Secondary End Point – Objective response rate

Variable	Pembrolizumab Group (N=154)	Chemotherapy Group (N=151)
Objective response†		
No. of patients	69	42
% (95% CI)	44.8 (36.8 to 53.0)	27.8 (20.8 to 35.7)
Time to response — mo‡		
Median	2.2	2.2
Range	1.4 to 8.2	1.8 to 12.2
Duration of response — mo‡§		
Median	NR	6.3
Range	1.9+ to 14.5+	2.1+ to 12.6+

Objective response is complete/ partial response assessed by RECIST 1.1 criteria

Reck M et al, N Engl J Med. 2016

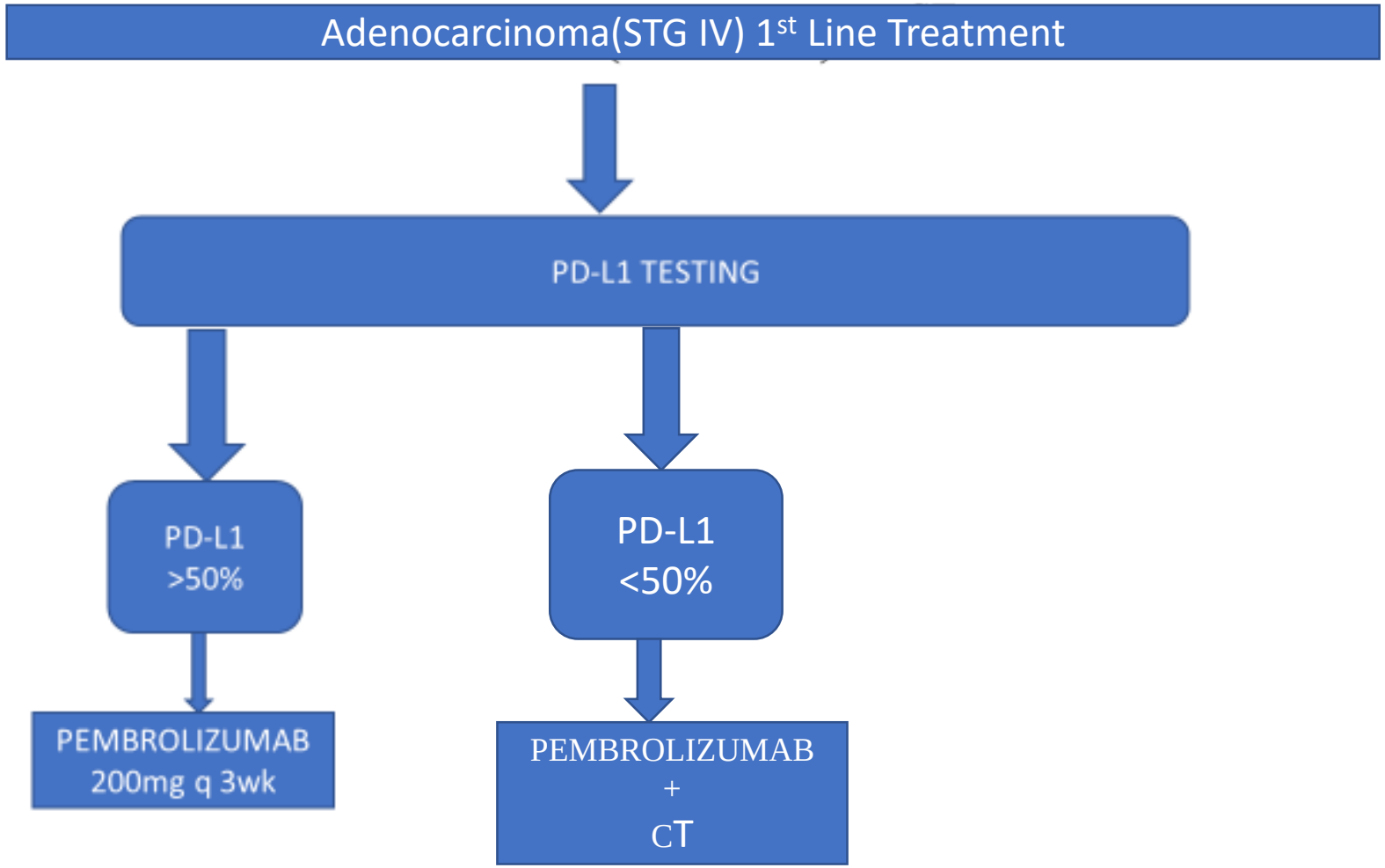
Adverse events

TABLE 2. Adverse Events in the As-Treated Population

Adverse Event	No. of Patients (%)			
	Pembrolizumab (n = 154)		Chemotherapy (n = 150)	
Treatment-related AEs†				
Any grade	118 (76.6)		135 (90.0)	
Grade 3-5	48 (31.2)		80 (53.3)	
Serious	35 (22.7)		31 (20.7)	
Led to discontinuation	21 (13.6)		16 (10.7)	
Led to death	2 (1.3)		3 (2.0)	
Treatment-related AEs occurring in ≥ 10% of patients in either arm‡	Any Grade	Grade 3 or 4*	Any Grade	Grade 3 or 4*
Diarrhea	25 (16.2)	6 (3.9)	21 (14.0)	2 (1.3)
Fatigue	22 (14.3)	3 (1.9)	43 (28.7)	5 (3.3)
Pyrexia	18 (11.7)	0	9 (6.0)	0
Pruritus	18 (11.7)	0	3 (2.0)	0
Rash	16 (10.4)	2 (1.3)	3 (2.0)	0
Nausea	15 (9.7)	0	65 (43.3)	3 (2.0)
Decreased appetite	15 (9.7)	0	39 (26.0)	4 (2.7)
Anemia	8 (5.2)	2 (1.3)	66 (44.0)	29 (19.3)
Constipation	6 (3.9)	0	17 (11.3)	0
Blood creatinine increased	5 (3.2)	0	16 (10.7)	0
Vomiting	4 (2.6)	0	30 (20.0)	0
Stomatitis	4 (2.6)	0	18 (12.0)	2 (1.3)
Neutropenia	1 (0.6)	0	33 (22.0)	20 (13.3)
Neutrophil count decreased	1 (0.6)	0	21 (14.0)	7 (4.7)
WBC count decreased	1 (0.6)	0	17 (11.3)	4 (2.7)
Dysgeusia	1 (0.6)	0	16 (10.7)	0
Platelet count decreased	0	0	18 (12.0)	10 (6.7)
Thrombocytopenia	0	0	16 (10.7)	8 (5.3)

AEs with possible immune etiology occurring in ≥ 0% of patients	Any Grade	Grade 3 or 4§	Any Grade	Grade 3 or 4§
Any	52 (33.8)	20 (13.2)	8 (5.3)	1 (0.7)
Hypothyroidism	16 (10.4)	0	3 (2.0)	0
Pneumonitis	12 (7.8)	4 (2.6)	1 (0.7)	1 (0.7)
Hyperthyroidism	11 (7.1)	0	2 (1.3)	0
Infusion reactions	8 (5.2)	1 (0.6)	2 (1.3)	0
Severe skin reactions	8 (5.2)	8 (5.2)	0	0
Colitis	6 (3.9)	3 (1.9)	0	0
Thyroiditis	4 (2.6)	0	0	0
Myositis	3 (1.9)	0	0	0
Hepatitis	1 (0.6)	1 (0.6)	0	0
Hypophysitis	1 (0.6)	1 (0.6)	0	0
Nephritis	1 (0.6)	1 (0.6)	0	0

Reck M et al, N Engl J Med. 2016


Adenocarcinoma(STG IV) 1st Line Treatment
PD-L1 TESTING
PD-L1
>50%
PD-L1
<50%
PEMBROLIZUMAB
200mg q 3wk
PEMBROLIZUMAB
+
CT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

ABSTRACT

BACKGROUND

First-line therapy for advanced non–small-cell lung cancer (NSCLC) that lacks targetable mutations is platinum-based chemotherapy. Among patients with a tumor proportion score for programmed death ligand 1 (PD-L1) of 50% or greater, pembrolizumab has replaced cytotoxic chemotherapy as the first-line treatment of choice. The addition of pembrolizumab to chemotherapy resulted in significantly higher rates of response and longer progression-free survival than chemotherapy alone in a phase 2 trial.

L. Gandhi et al, N Engl J Med, May 2018

Double blind placebo controlled trial

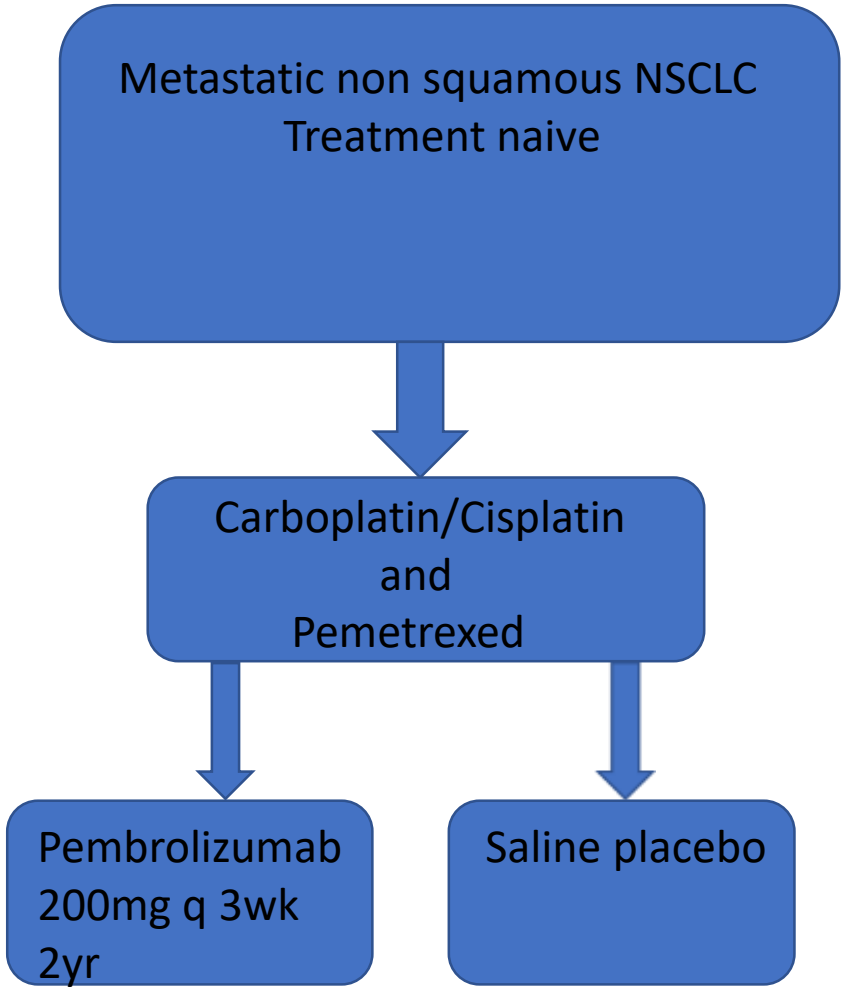


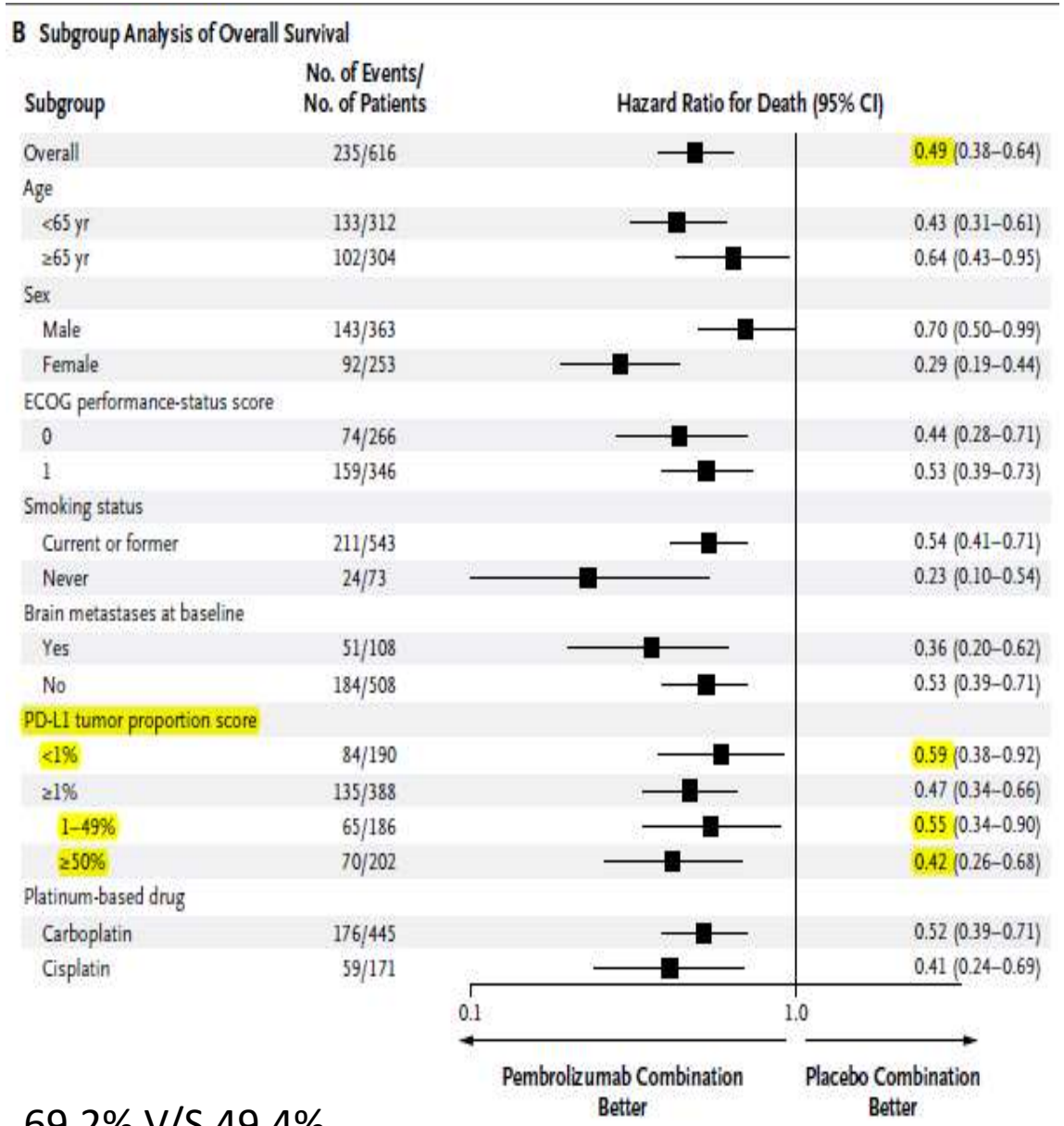
Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

Characteristic	Pembrolizumab Combination (N=410)	Placebo Combination (N=206)
Age		
Median (range) — yr	65.0 (34.0–84.0)	63.5 (34.0–84.0)
<65 yr — no. (%)	197 (48.0)	115 (55.8)
Male sex — no. (%)†	254 (62.0)	109 (52.9)
Region of enrollment — no. (%)		
Europe	243 (59.3)	131 (63.6)
North America	111 (27.1)	46 (22.3)
East Asia	4 (1.0)	6 (2.9)
Other region	52 (12.7)	23 (11.2)
ECOG performance-status score — no. (%)‡		
0	186 (45.4)	80 (38.8)
1	221 (53.9)	125 (60.7)
2	1 (0.2)	0
Smoking status — no. (%)		
Current or former	362 (88.3)	181 (87.9)
Never	48 (11.7)	25 (12.1)
Histologic features — no. (%)		
Adenocarcinoma	394 (96.1)	198 (96.1)
NSCLC not otherwise specified	10 (2.4)	4 (1.9)
Other§	6 (1.5)	4 (1.9)
Brain metastases — no. (%)	73 (17.8)	35 (17.0)
PD-L1 tumor proportion score — no. (%)¶		
<1%	127 (31.0)	63 (30.6)
≥1%	260 (63.4)	128 (62.1)
1–49%	128 (31.2)	58 (28.2)
≥50%	132 (32.2)	70 (34.0)
Could not be evaluated‖	23 (5.6)	15 (7.3)
Previous therapy for nonmetastatic disease		
Thoracic radiotherapy	28 (6.8)	20 (9.7)
Neoadjuvant therapy	5 (1.2)	6 (2.9)
Adjuvant therapy	25 (6.1)	14 (6.8)

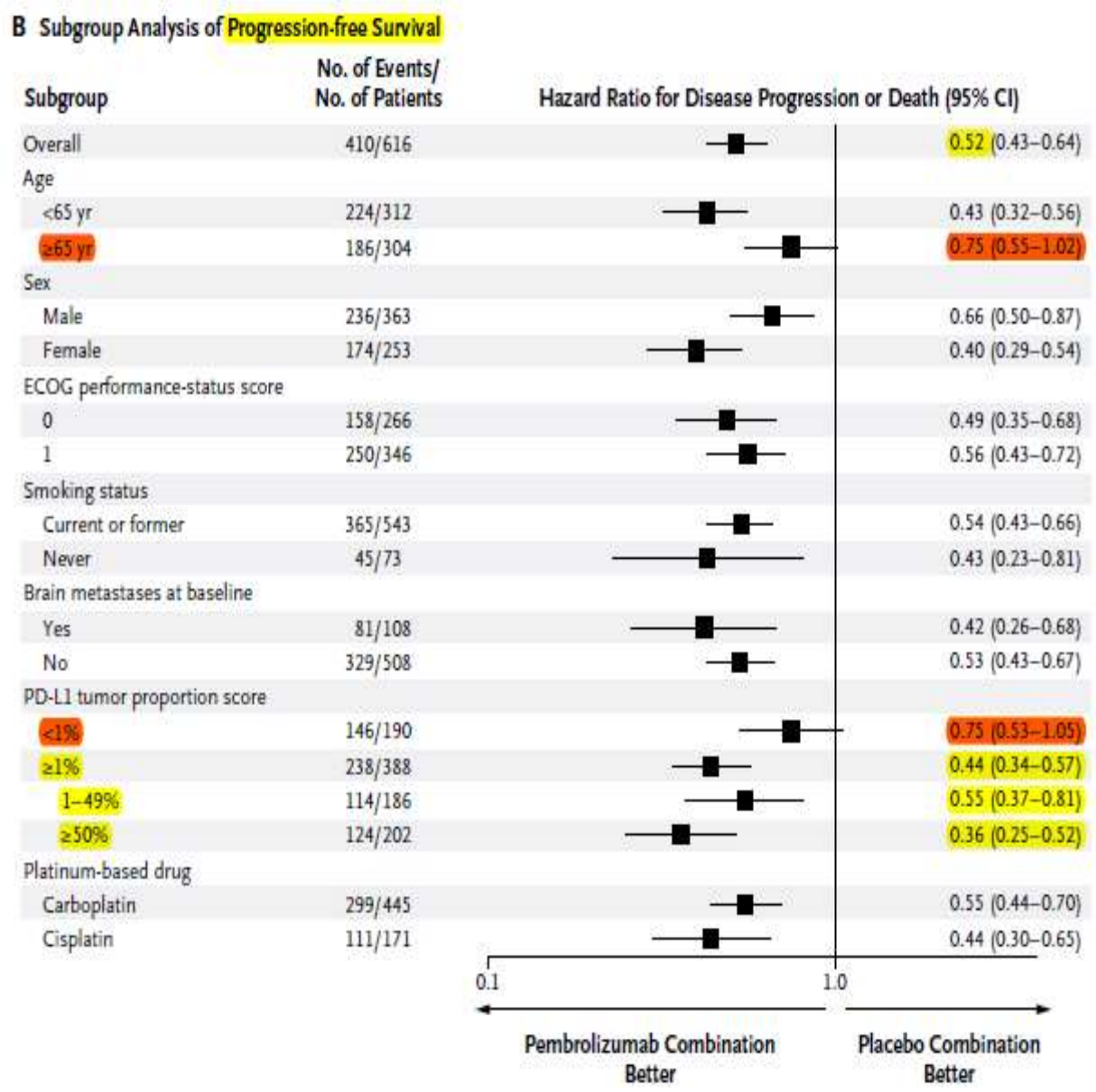
Comparable baseline characteristics

L. Gandhi et al, N Engl J Med, May 2018

Primary Endpoints



69.2% V/S 49.4%



L. Gandhi et al, N Engl J Med, May 2018

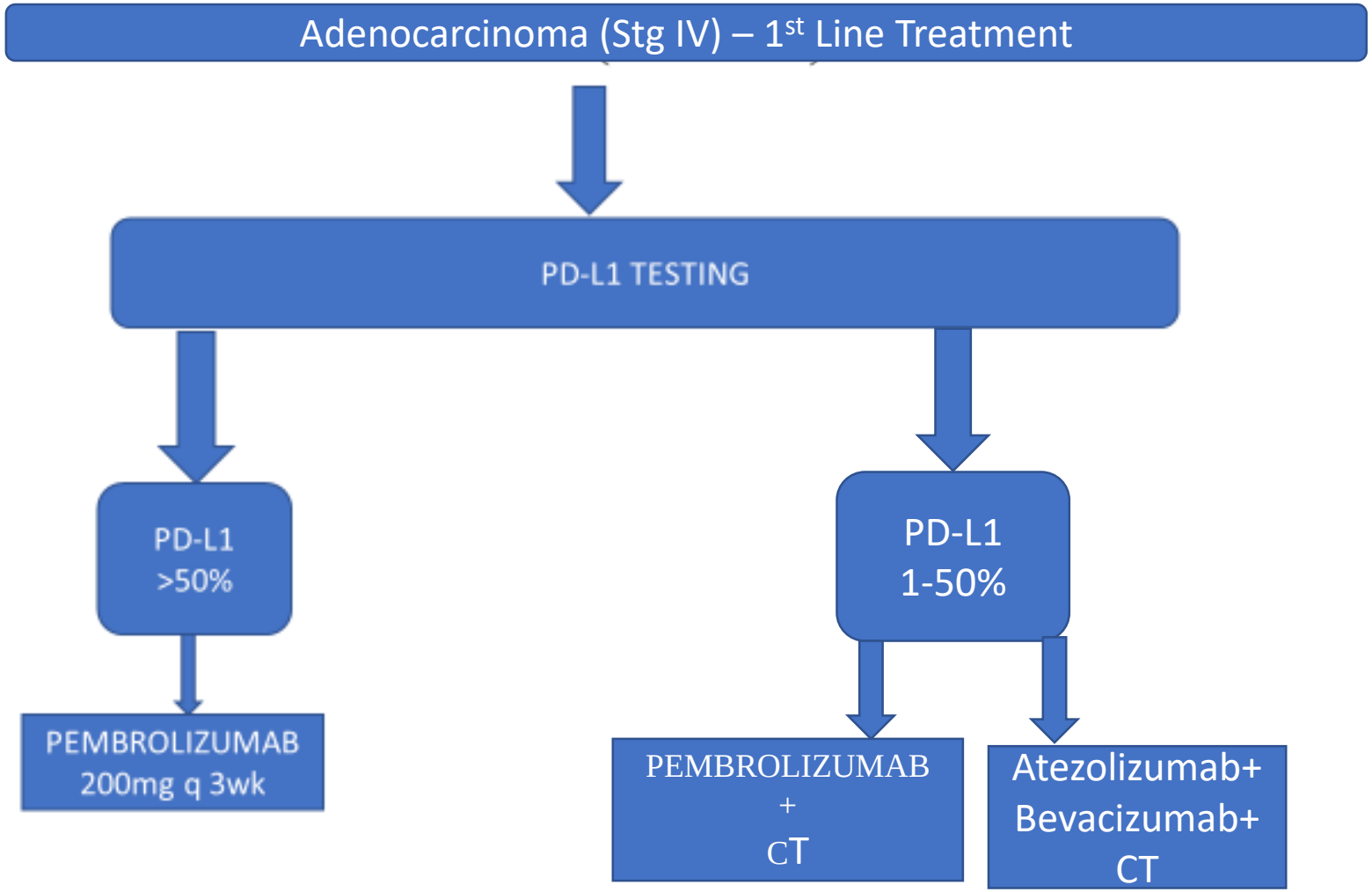
- Response rate and median duration of response was better in pembrolizumab combination group
- Adverse effects was similar in both the groups

Event	Pembrolizumab Combination (N=405)		Placebo Combination (N=202)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any event	404 (99.8)	272 (67.2)	200 (99.0)	133 (65.8)
Event leading to discontinuation of all treatment†	56 (13.8)	48 (11.9)	16 (7.9)	14 (6.9)
Event leading to discontinuation of any treatment component‡	112 (27.7)	81 (20.0)	30 (14.9)	22 (10.9)
Discontinuation of pembrolizumab or placebo	82 (20.2)	64 (15.8)	21 (10.4)	17 (8.4)
Discontinuation of pemetrexed	93 (23.0)	69 (17.0)	23 (11.4)	17 (8.4)
Discontinuation of platinum-based drug	31 (7.7)	27 (6.7)	12 (5.9)	10 (5.0)
Event leading to death§	27 (6.7)	27 (6.7)	12 (5.9)	12 (5.9)
Event occurring in ≥15% of patients in either group¶				
Nausea	225 (55.6)	14 (3.5)	105 (52.0)	7 (3.5)
Anemia	187 (46.2)	66 (16.3)	94 (46.5)	31 (15.3)
Fatigue	165 (40.7)	23 (5.7)	77 (38.1)	5 (2.5)
Constipation	141 (34.8)	4 (1.0)	64 (31.7)	1 (0.5)
Diarrhea	125 (30.9)	21 (5.2)	43 (21.3)	6 (3.0)
Decreased appetite	114 (28.1)	6 (1.5)	61 (30.2)	1 (0.5)
Neutropenia	110 (27.2)	64 (15.8)	49 (24.3)	24 (11.9)
Vomiting	98 (24.2)	15 (3.7)	47 (23.3)	6 (3.0)
Cough	87 (21.5)	0	57 (28.2)	0
Dyspnea	86 (21.2)	15 (3.7)	52 (25.7)	11 (5.4)
Asthenia	83 (20.5)	25 (6.2)	49 (24.3)	7 (3.5)
Rash	82 (20.2)	7 (1.7)	23 (11.4)	3 (1.5)
Pyrexia	79 (19.5)	1 (0.2)	30 (14.9)	0

Table 3. Adverse Events of Interest in the As-Treated Population.*

Event	Pembrolizumab Combination (N=405)		Placebo Combination (N=202)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any	92 (22.7)	36 (8.9)	24 (11.9)	9 (4.5)
Hypothyroidism	27 (6.7)	2 (0.5)	5 (2.5)	0
Pneumonitis	18 (4.4)	11 (2.7)	5 (2.5)	4 (2.0)
Hyperthyroidism	16 (4.0)	0	6 (3.0)	0
Infusion reaction	10 (2.5)	1 (0.2)	2 (1.0)	0
Colitis	9 (2.2)	3 (0.7)	0	0
Severe skin reaction	8 (2.0)	8 (2.0)	5 (2.5)	4 (2.0)
Nephritis	7 (1.7)	6 (1.5)	0	0
Hepatitis	5 (1.2)	4 (1.0)	0	0
Hypophysitis	3 (0.7)	0	0	0
Pancreatitis	3 (0.7)	2 (0.5)	0	0
Adrenal insufficiency	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.5)
Myositis	1 (0.2)	0	0	0
Thyroiditis	1 (0.2)	0	0	0
Type 1 diabetes mellitus	1 (0.2)	1 (0.2)	0	0

L. Gandhi et al, N Engl J Med, May 2018


Adenocarcinoma (Stg IV) – 1st Line Treatment
PD-L1 TESTING
PD-L1
>50%
PEMBROLIZUMAB
200mg q 3wk
PD-L1
1-50%
PEMBROLIZUMAB
+
CT
Atezolizumab+
Bevacizumab+
CT

Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC

M.A. Socinski, R.M. Jotte, F. Cappuzzo, F. Orlandi, D. Stroyakovskiy, N. Nogami, D. Rodríguez-Abreu, D. Moro-Sibilot, C.A. Thomas, F. Barlesi, G. Finley, C. Kelsch, A. Lee, S. Coleman, Y. Deng, Y. Shen, M. Kowanetz, A. Lopez-Chavez, A. Sandler, and M. Reck, for the IMpower150 Study Group*

ABSTRACT

BACKGROUND

The cancer-cell–killing property of atezolizumab may be enhanced by the blockade of vascular endothelial growth factor–mediated immunosuppression with bevacizumab. This open-label, phase 3 study evaluated atezolizumab plus bevacizumab plus chemotherapy in patients with metastatic nonsquamous non–small-cell lung cancer (NSCLC) who had not previously received chemotherapy.

METHODS

We randomly assigned patients to receive atezolizumab plus carboplatin plus paclitaxel (ACP), bevacizumab plus carboplatin plus paclitaxel (BCP), or atezolizumab plus BCP (ABCP) every 3 weeks for four or six cycles, followed by maintenance therapy with atezolizumab, bevacizumab, or both. The two primary end points were investigator-assessed progression-free survival both among patients in the intention-to-treat population who had a wild-type genotype (WT population; patients with *EGFR* or *ALK* genetic

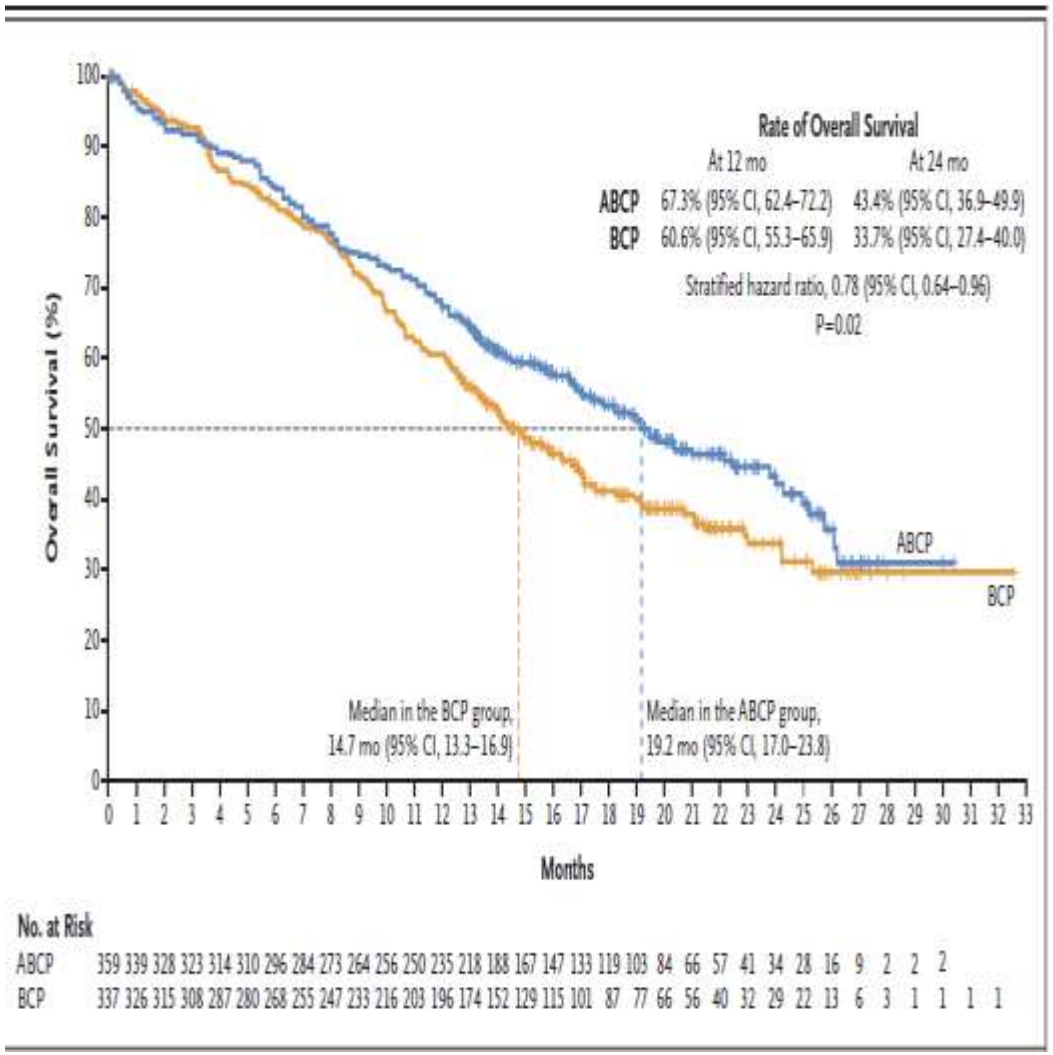
STG IV NON SQUAMOUS NSCLC

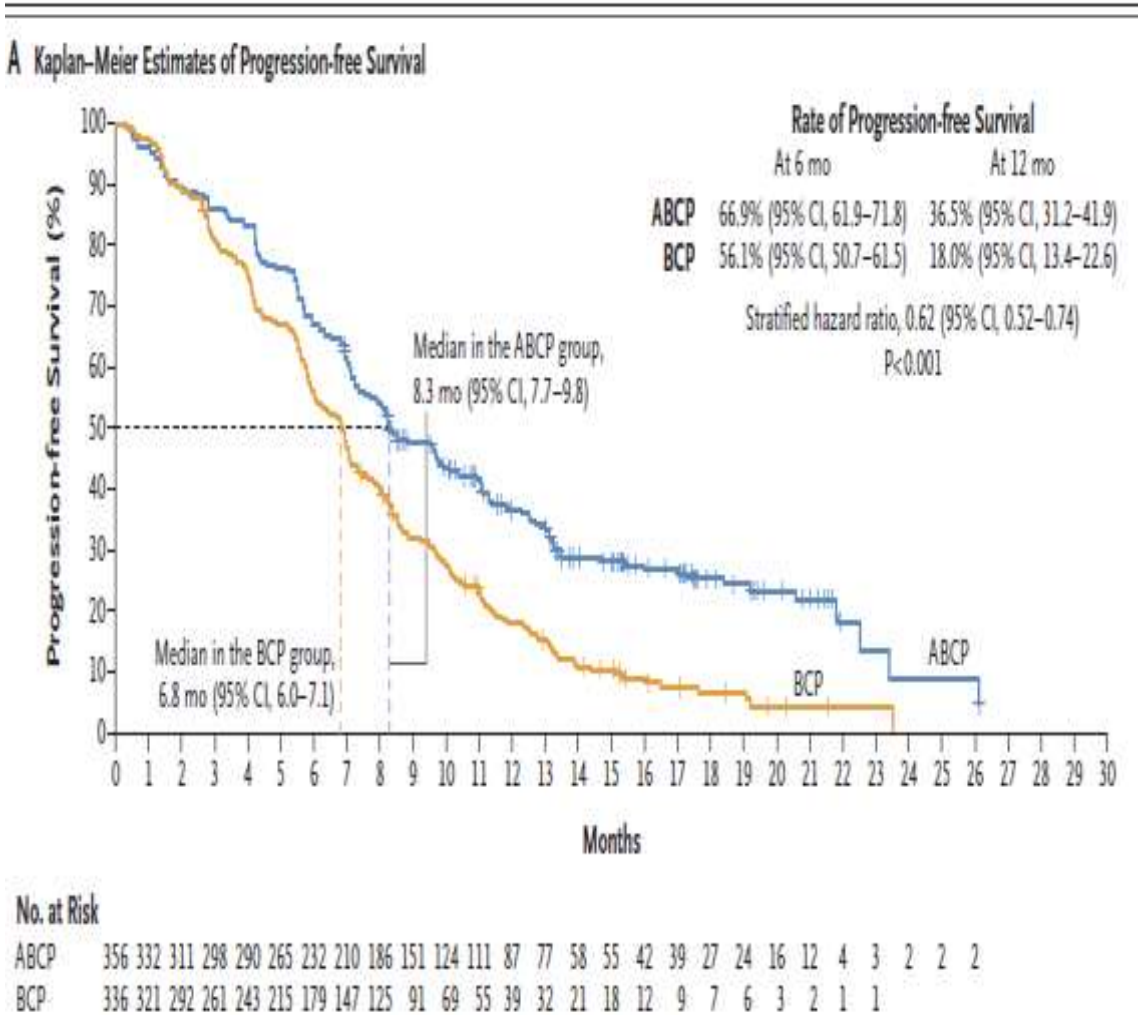
Atezo
Bevaci
Carbo
Pacli
N=400

Bevaci
Carbo
Pacli
N=400

Progression free survival
Overall survival

Socinski et al,ASCO 2018



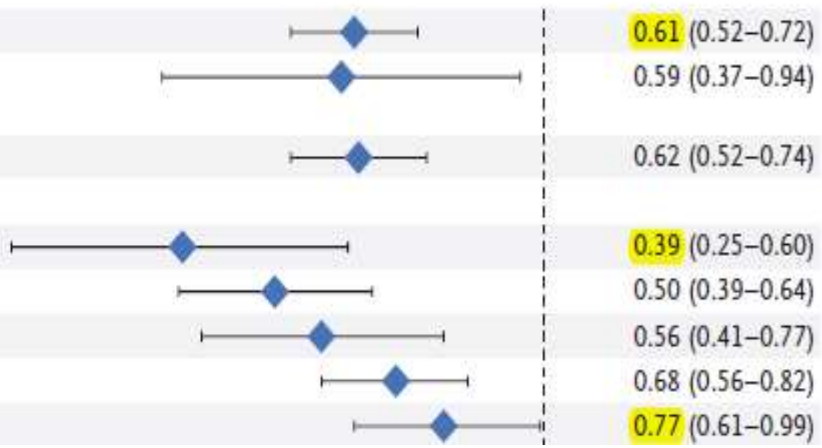


Atezolizumab with bevacizumab improved PFS and OS irrespective of PD-L1 status and EGFR/ALK rearrangement

Socinski et al,ASCO 2018

B Hazard Ratios for Disease Progression or Death in Biomarker Subgroups

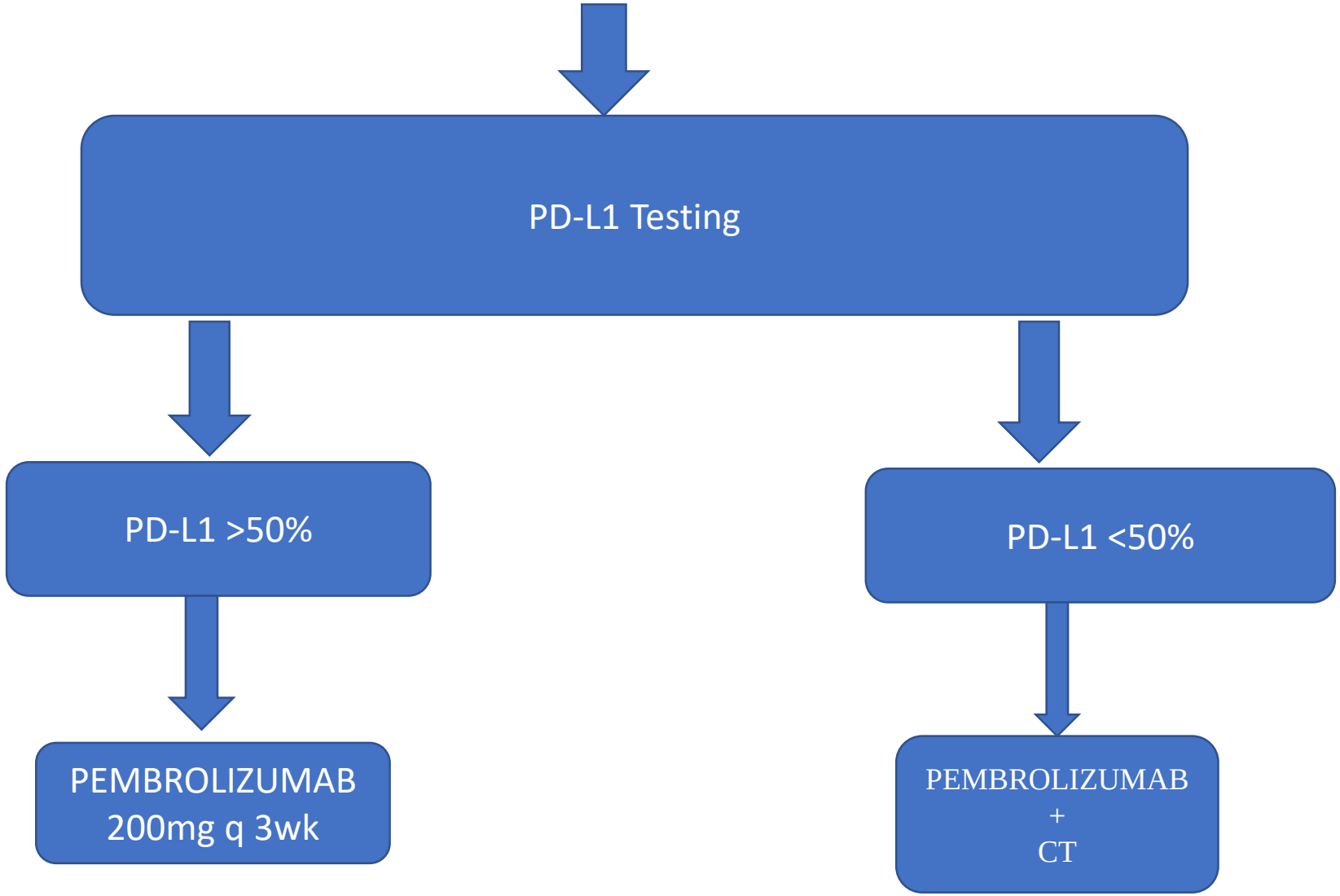
Population	No. of Patients (%)	Median Progression-free Survival (mo)		Hazard Ratio (95% CI)
		ABCP	BCP	
ITT population	800 (100)	8.3	6.8	0.61 (0.52–0.72)
Patients with *EGFR* or *ALK* genetic alternations	108 (14)	9.7	6.1	0.59 (0.37–0.94)
WT population	692 (87)	8.3	6.8	0.62 (0.52–0.74)
PD-L1 subgroups (in the WT population)				
TC3 or IC3	135 (20)	12.6	6.8	0.39 (0.25–0.60)
TC1/2/3 or IC1/2/3	354 (51)	11.0	6.8	0.50 (0.39–0.64)
TC1/2 or IC1/2	224 (32)	8.3	6.6	0.56 (0.41–0.77)
TC0/1/2 and IC0/1/2	557 (80)	8.0	6.8	0.68 (0.56–0.82)
TC0 and IC0	338 (49)	7.1	6.9	0.77 (0.61–0.99)



Improvement in PFS irrespective of PD-L1 status

Socinski et al,ASCO 2018

Squamous Cell Carcinoma – Front Line Therapy



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer

L. Paz-Ares, A. Luft, D. Vicente, A. Tafreshi, M. Gümüş, J. Mazières, B. Hermes, F. Çay Şenler, T. Csőszi, A. Fülöp, J. Rodríguez-Cid, J. Wilson, S. Sugawara, T. Kato, K.H. Lee, Y. Cheng, S. Novello, B. Halmos, X. Li, G.M. Lubiniecki, B. Piperdi, and D.M. Kowalski, for the KEYNOTE-407 Investigators*

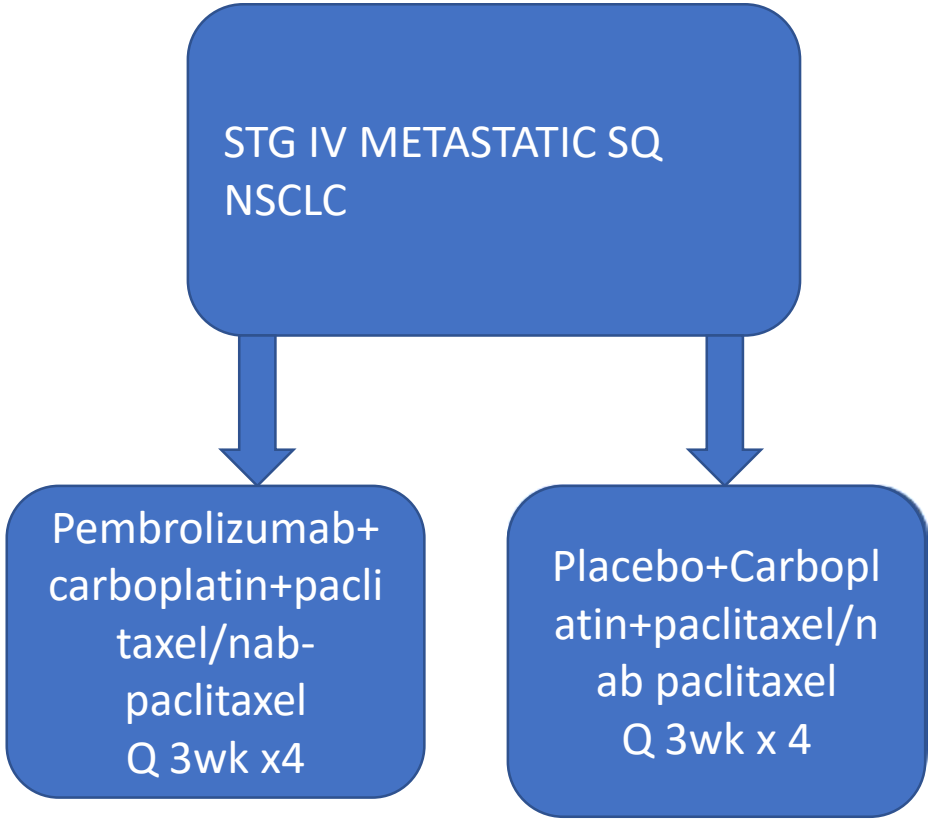
ABSTRACT

BACKGROUND

Standard first-line therapy for metastatic, squamous non–small-cell lung cancer (NSCLC) is platinum-based chemotherapy or pembrolizumab (for patients with programmed death ligand 1 [PD-L1] expression on ≥50% of tumor cells). More recently, pembrolizumab plus chemotherapy was shown to significantly prolong overall survival among patients with nonsquamous NSCLC.

METHODS

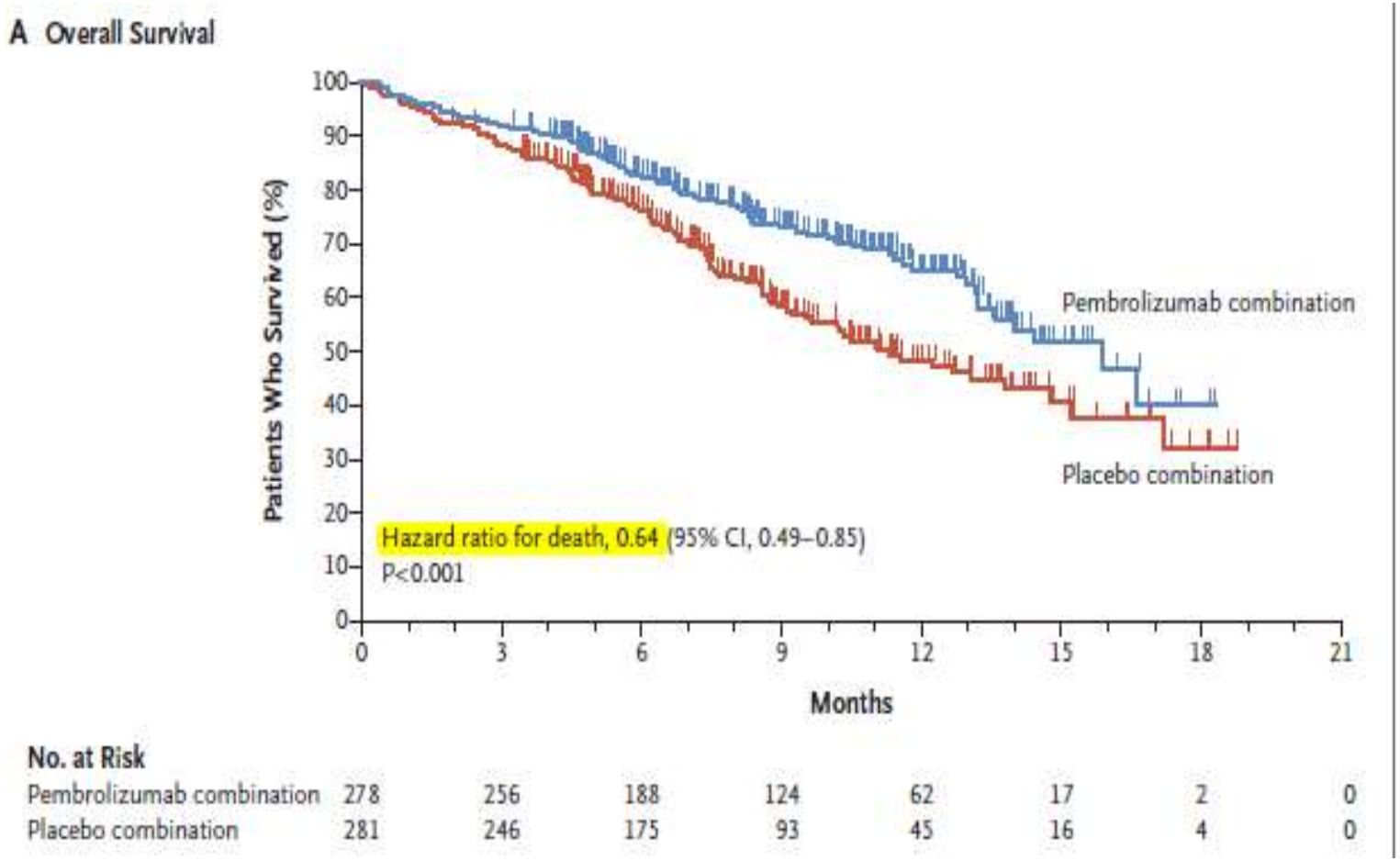
In this double-blind, phase 3 trial, we randomly assigned, in a 1:1 ratio, 559 patients with untreated metastatic, squamous NSCLC to receive 200 mg of pembrolizumab or saline placebo for up to 35 cycles; all the patients also received carboplatin and



Primary end point : PFS, OS

Secondary end point : ORR, Safety, Duration of response

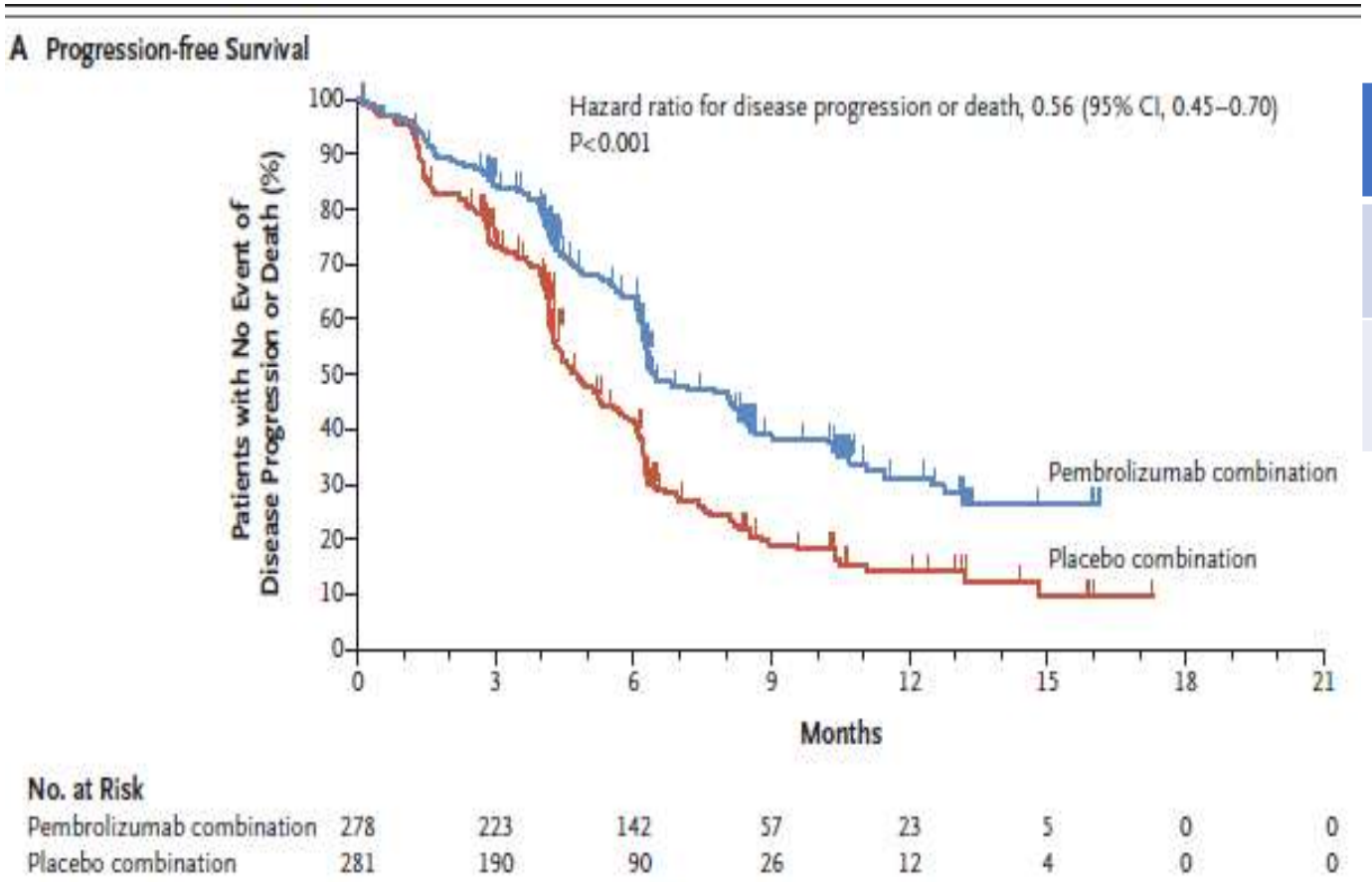
Paz ares et al, ASCO, 2018



	Pembrolizumab combination	Chemotherapy
OS	15.9	11.9
	HR- 0.64 , P<0.001	

Longer overall survival

Paz ares et al, ASCO, 2018



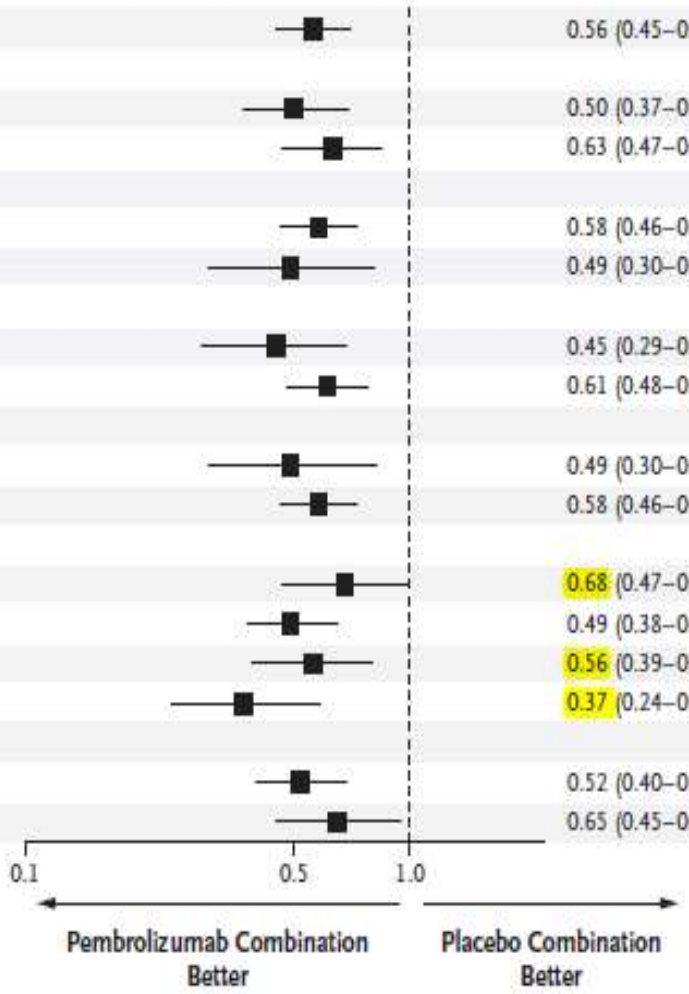
	Pembrolizumab	Chemotherapy
PFS	6.4	4.8
	HR- 0.56, p<0.001	

Longer progression free survival

Paz ares et al, ASCO, 2018

B Subgroup Analysis of Progression-free Survival

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	349/559	0.56 (0.45–0.70)
Age		
<65 yr	162/254	0.50 (0.37–0.69)
≥65 yr	187/305	0.63 (0.47–0.84)
Sex		
Male	284/455	0.58 (0.46–0.73)
Female	65/104	0.49 (0.30–0.81)
ECOG performance-status score		
0	96/163	0.45 (0.29–0.68)
1	253/396	0.61 (0.48–0.78)
Region of enrollment		
East Asia	61/106	0.49 (0.30–0.82)
Rest of the world	288/453	0.58 (0.46–0.73)
PD-L1 tumor proportion score		
<1%	122/194	0.68 (0.47–0.98)
≥1%	221/353	0.49 (0.38–0.65)
1–49%	127/207	0.56 (0.39–0.80)
≥50%	94/146	0.37 (0.24–0.58)
Taxane-based drug		
Paclitaxel	231/336	0.52 (0.40–0.68)
Nab-paclitaxel	118/223	0.65 (0.45–0.94)



Benefit of pembrolizumab was seen across all PD-L1 levels
Greatest benefit in PD-L1 > 50%

Paz ares et al, ASCO, 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D., Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M.D., Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.D., Jared K. Lunceford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, M.D., Charlotte Roach, B.S., Kenneth Emancipator, M.D., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators*

ABSTRACT

BACKGROUND

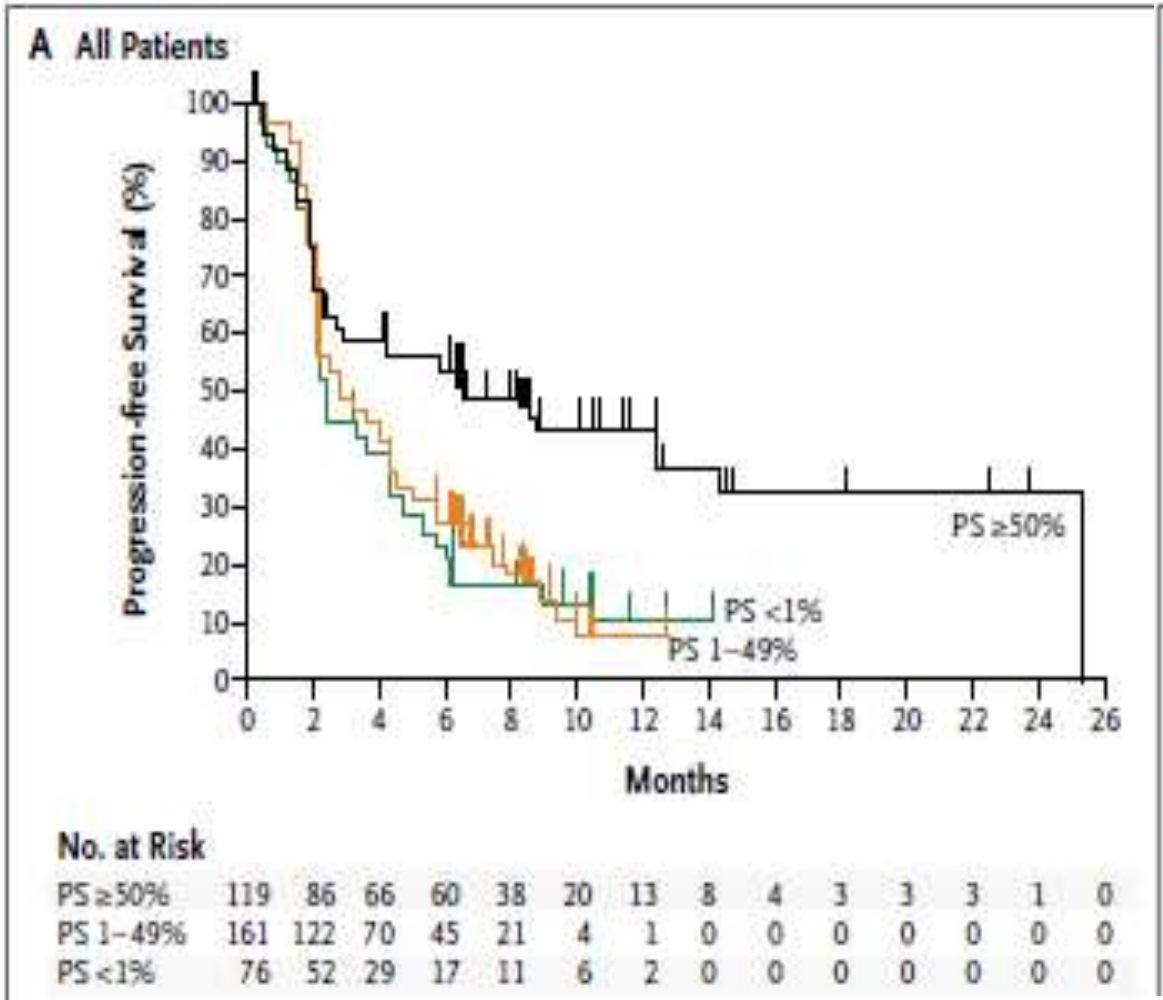
We assessed the efficacy and safety of programmed cell death 1 (PD-1) inhibition with pembrolizumab in patients with advanced non–small-cell lung cancer enrolled in a phase 1 study. We also sought to define and validate an expression level of the PD-1 ligand 1 (PD-L1) that is associated with the likelihood of clinical benefit.

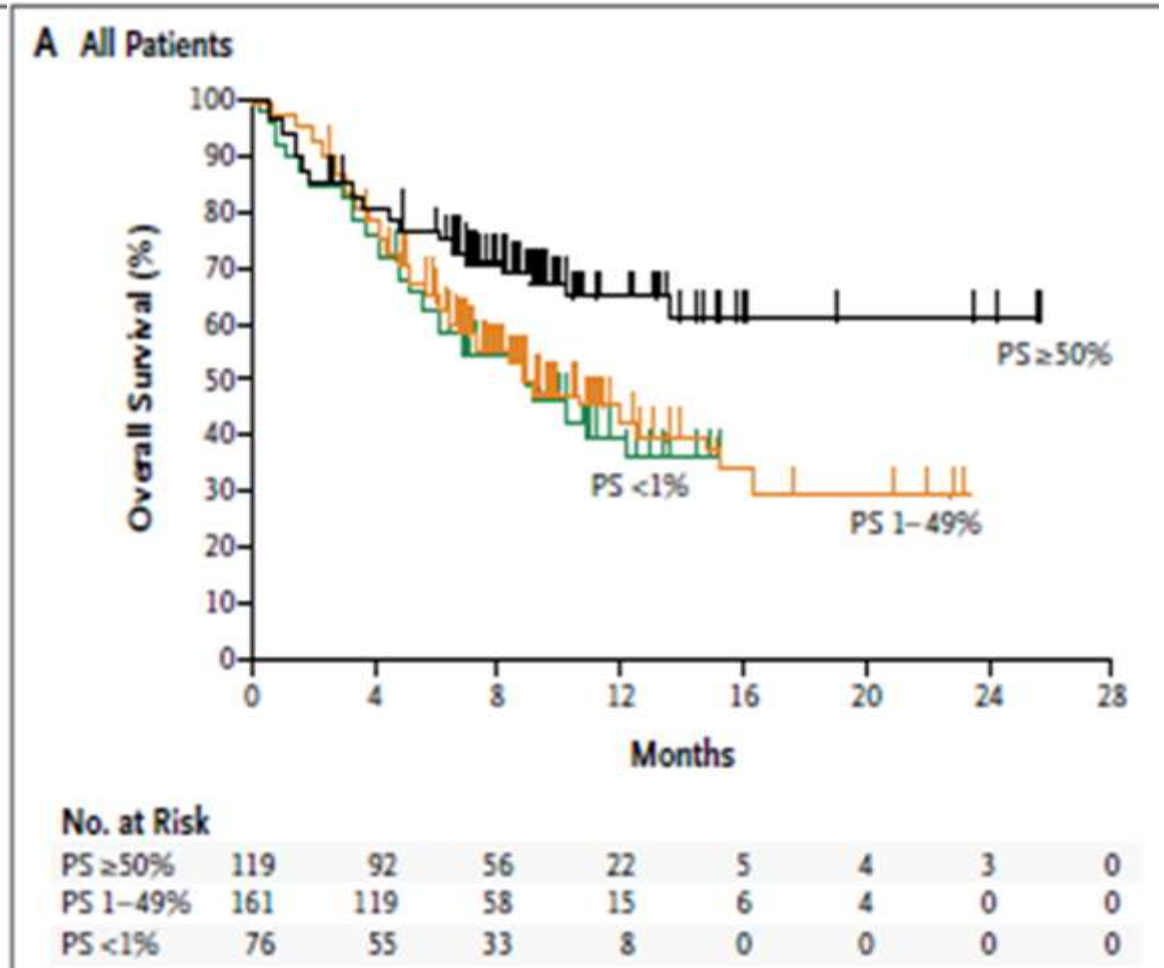
KEYNOTE 001 TRIAL

	PS>50%	PS1-49%	PS<1
ORR	45.2	16.5	10.7
PREV RX	43.9	15.6	9.1
RX NAIVE	50	19.2	16.7

- Overall response rate was 19.4%
  - 18.0% in previously treated patients
  - 24.8% in un-treated patients
- Similar response rate among dose, schedule and histology

Garon E, et al, NEJM, Apr 2015





Pembrolizumab is safe and efficacious in prev. treated and untreated advanced NSCLC
Greatest benefit was seen in patient with PD-L1 > 50%

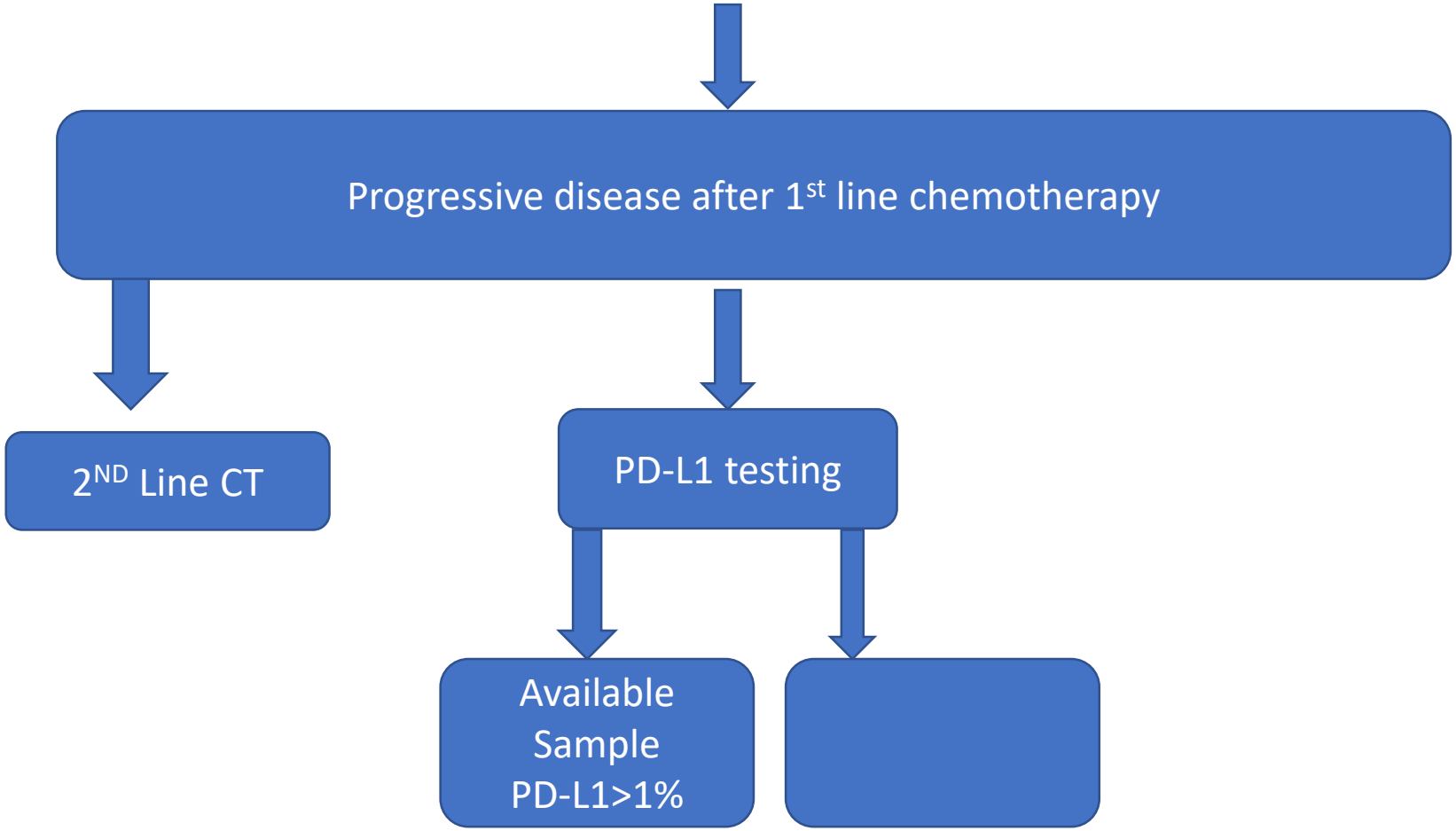
Garon E, et al, NEJM, Apr 2015

KEYNOTE 001

- Response in advanced NSCLC was independent of

1. Histology
2. Similar for both doses
3. Adverse effects were comparable
4. Response was higher in those with PS>50%

Adenocarcinoma(Stg IIIB/ IV)- 2nd Line



Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward B Garon

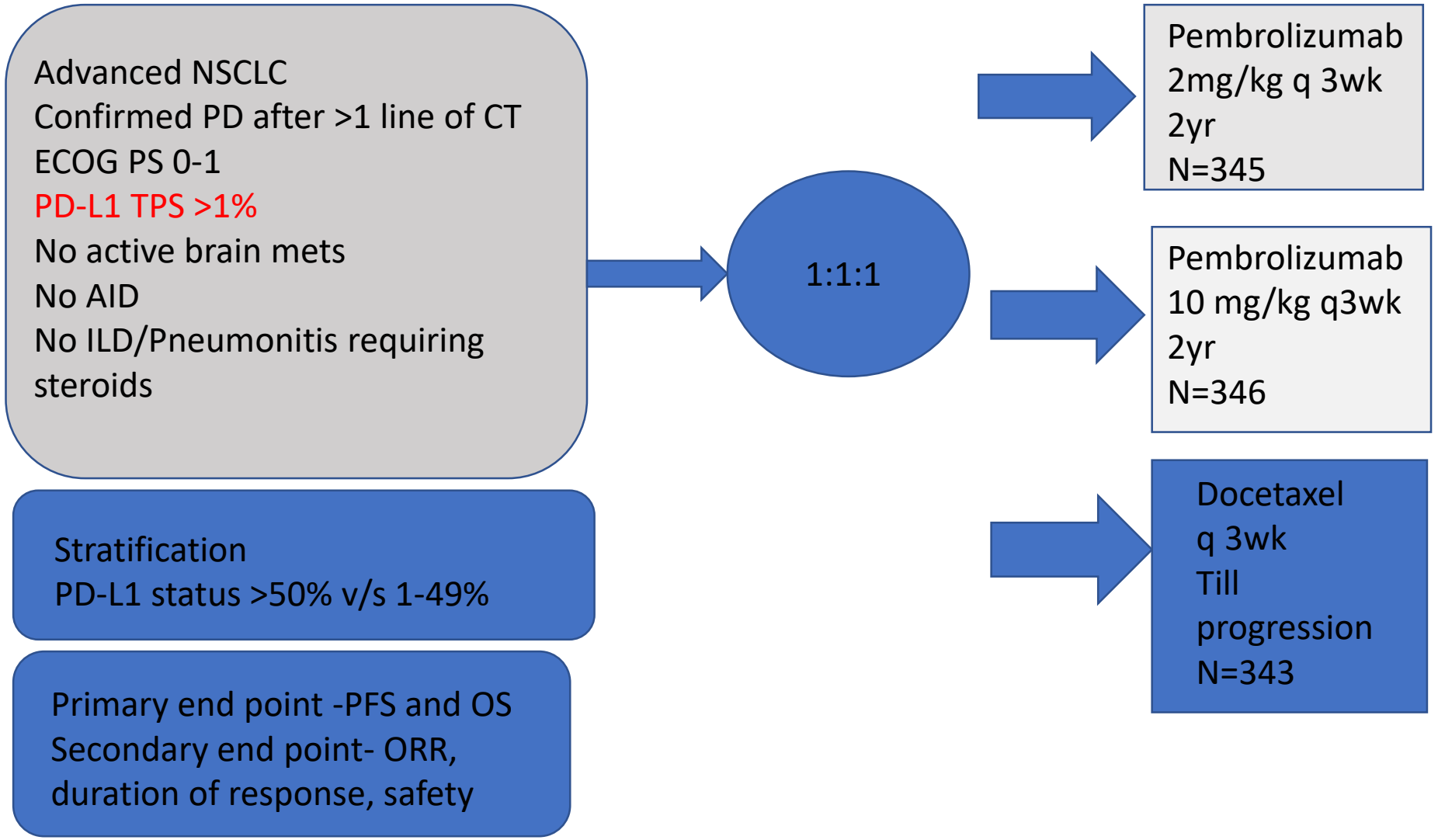
Lancet 2016; 387: 1540–50

Published Online December 19, 2015 http://dx.doi.org/10.1016/

Summary

Background Despite recent advances in the treatment of advanced non-small-cell lung cancer, there remains a need for effective treatments for progressive disease. We assessed the efficacy of pembrolizumab for patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer.

Herbst et al, Lancet,2016,387,1540-1550



Herbst et al, Lancet,2016,387,1540-1550

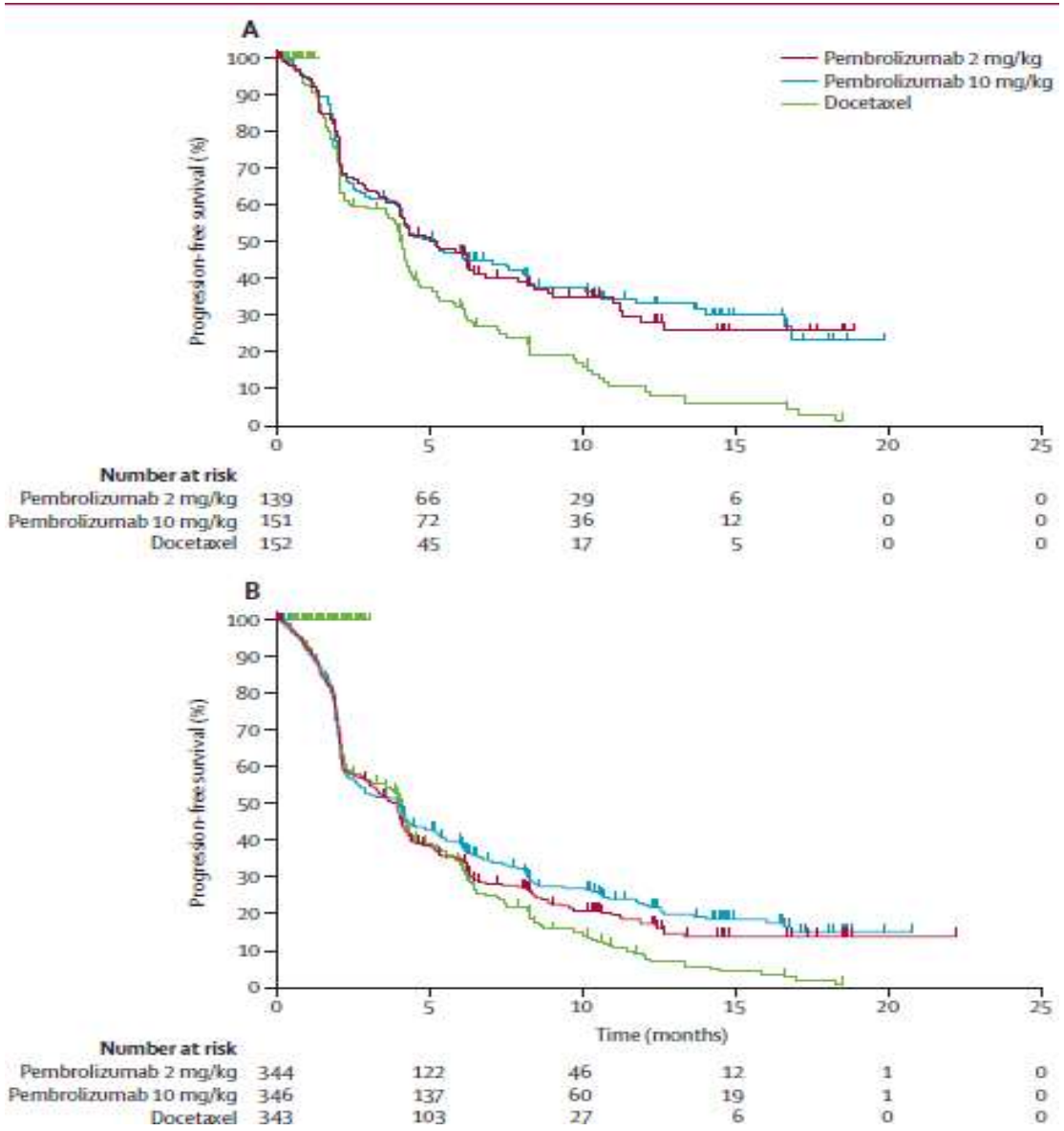
1034 (PDL 1 ≥ 1%) , 442 (PDL 1≥ 50 %)				
		Pembrolizumab 2 mg/kg	**Pembrolizumab 10 mg/kg**	**Docetaxel**
PDL 1 ≥ 1% (345/ 346/ 343)	**OS**	10·4 months HR 0·71 95% CI 0·58–0.88	12·7 months HR 0·61 95 % CI 0·49–0·75	8·5 months
	PFS	3·9 months HR 0·88, 95% CI 0·74–1·05	4·0 months HR 0·79, 95% CI 0·66–0·94	4·0 months
PDL 1 ≥ 50 % (139/ 151/ 152)	**OS**	14.9 months HR 0·54 95% CI 0·38–0.77	17.3 months HR 0·50 95 % CI 0·36–0·70	8·2 months
	PFS	5.0 months HR 0·59 95% CI 0·44–0·78	5.2 months HR 0·59 95% CI 0·45–0·78	4·1 months

OS	Pembro	Docetaxel
PD-L1>1%	11.8	8.5
PD-L1>50%	16.9	8.2

Patients with both
PD-L1 1-49%
PD-L1 >50%
Benifitted

Patients with PD-L1>50%
Showed greater benefit

Herbst et al, Lancet,2016,387,1540-1550

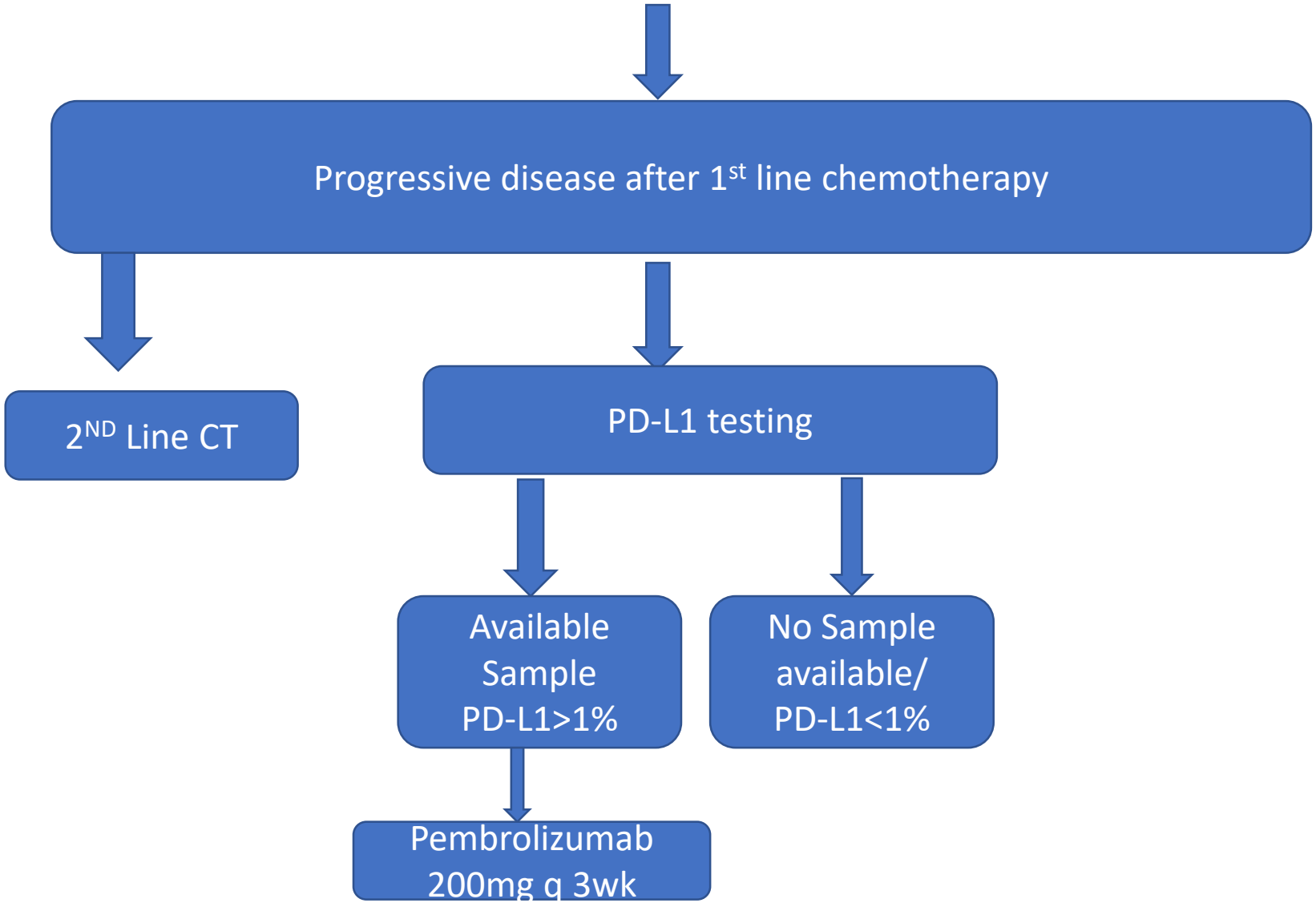


	Pembro 2mg/kg	Pembro 10mg/kg	Docetaxel
PFS	3.9	3.9	4
Adverse events	13%	16%	35%

Both doses of pembrolizumab were equally efficacious and adverse effect profile was similar

Herbst et al, Lancet,2016,387,1540-1550

Adenocarcinoma(Stg IV)- 2nd Line



CHECKMATE 057

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, and J.R. Brahmer

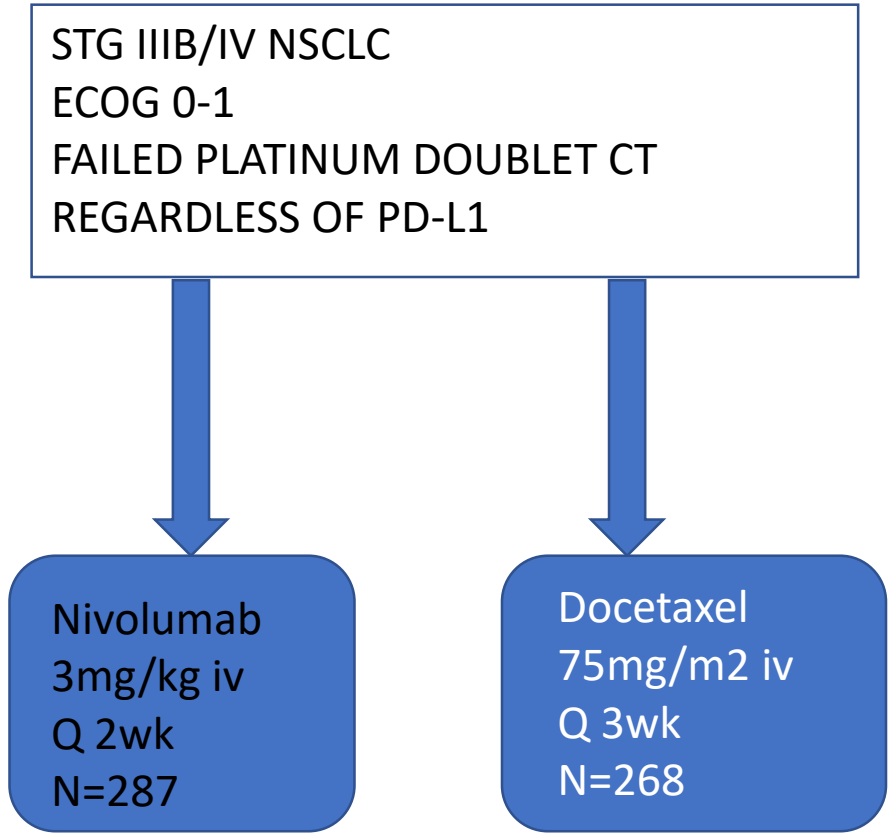
ABSTRACT

BACKGROUND

Nivolumab, a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint–inhibitor antibody, disrupts PD-1–mediated signaling and may restore antitumor immunity.

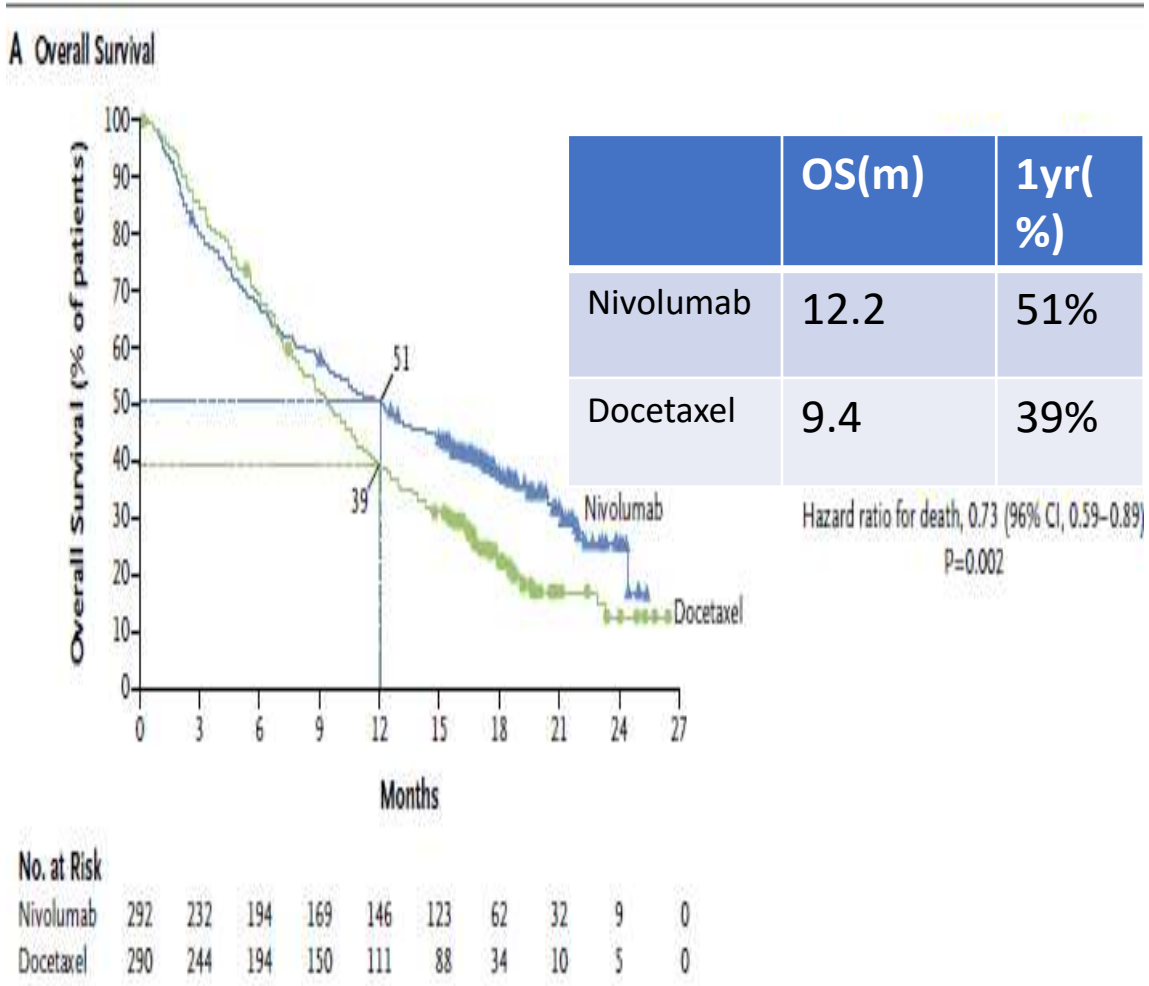
METHODS

In this randomized, open-label, international phase 3 study, we assigned patients with nonsquamous non–small-cell lung cancer (NSCLC) that had progressed during or after platinum-based doublet chemotherapy to receive nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks or docetaxel at a dose of 75 mg per square meter of body-surface area every 3 weeks. The primary end point was overall survival.



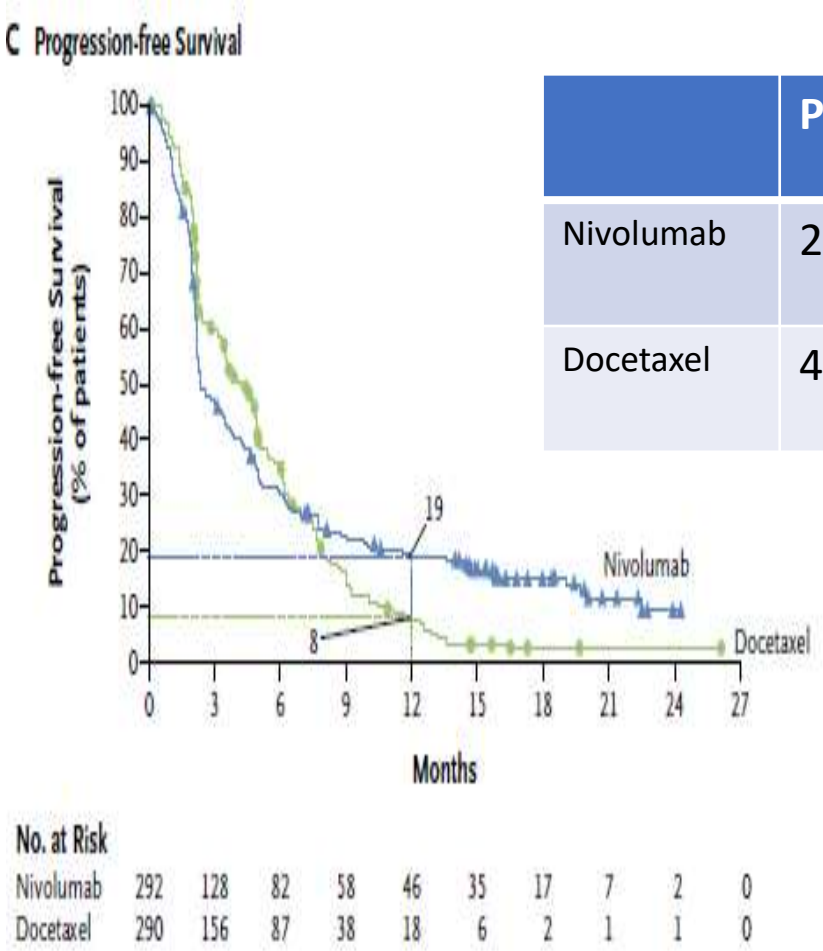
Primary end point : OS
Secondary end point : PFS, ORR, Safety, Efficacy acc to PD-L1 status

Borghaei H et al, NEJM, 2015,373,1627-1639



	OS(m)	1yr(%)
Nivolumab	12.2	51%
Docetaxel	9.4	39%

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002



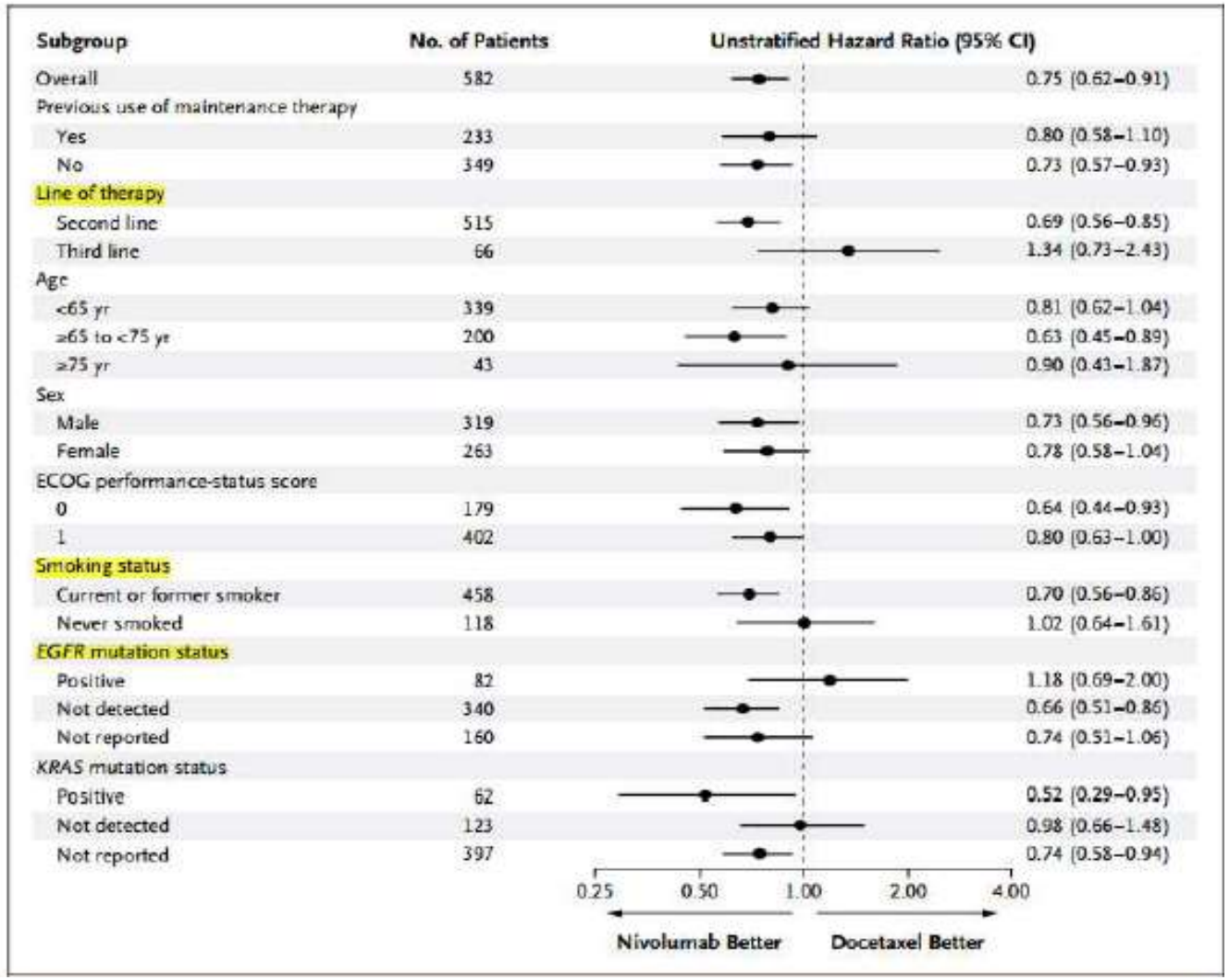
	PFS(m)	PFS rate
Nivolumab	2.3	19%
Docetaxel	4.2	8%

Hazard ratio for disease progression or death, 0.92 (95% CI, 0.77–1.11); P=0.39

Nivolumab has superior overall survival in unselected previously treated advanced non squamous NSCLC

Borghaei H et al, NEJM, 2015,373,1627-1639

Checkmate 057



Subgroup	No. of Patients	Unstratified Hazard Ratio (95% CI)
Overall	582	0.75 (0.62–0.91)
Previous use of maintenance therapy		
Yes	233	0.80 (0.58–1.10)
No	349	0.73 (0.57–0.93)
Line of therapy		
Second line	515	0.69 (0.56–0.85)
Third line	66	1.34 (0.73–2.43)
Age		
<65 yr	339	0.81 (0.62–1.04)
≥65 to <75 yr	200	0.63 (0.45–0.89)
≥75 yr	43	0.90 (0.43–1.87)
Sex		
Male	319	0.73 (0.56–0.96)
Female	263	0.78 (0.58–1.04)
ECOG performance-status score		
0	179	0.64 (0.44–0.93)
1	402	0.80 (0.63–1.00)
Smoking status		
Current or former smoker	458	0.70 (0.56–0.86)
Never smoked	118	1.02 (0.64–1.61)
EGFR mutation status		
Positive	82	1.18 (0.69–2.00)
Not detected	340	0.66 (0.51–0.86)
Not reported	160	0.74 (0.51–1.06)
KRAS mutation status		
Positive	62	0.52 (0.29–0.95)
Not detected	123	0.98 (0.66–1.48)
Not reported	397	0.74 (0.58–0.94)

Nivolumab did not improve survival in

- Age >75yr
- Never smokers
- EGFR +
- When given as 3rd line of therapy

Borghaei H et al, NEJM, 2015,373,1627-1639

OAK TRIAL

Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial

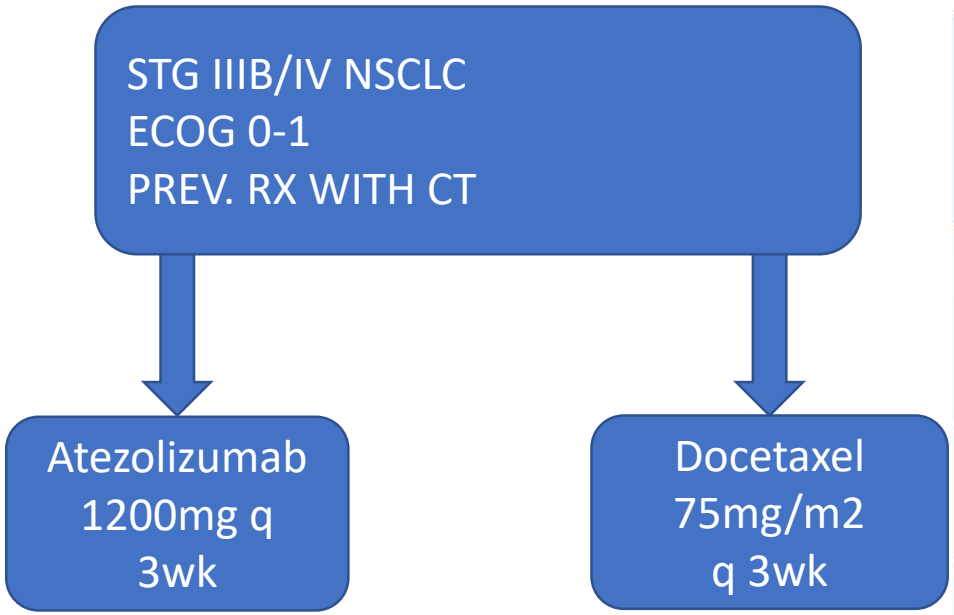
*Achim Rittmeyer, Fabrice Barlesi, Daniel Waterkamp, Keunchil Park, Fortunato Ciardiello, Joachim von Pawel, Shirish M Gadgeel, Toyoaki Hida, Dariusz M Kowalski, Manuel Cobo Dols, Diego L Cortinovis, Joseph Leach, Jonathan Polikoff, Carlos Barrios, Fairooz Kabbinavar, Osvaldo Arén Frontera, Filippo De Marinis, Hande Turna, Jong-Seok Lee, Marcus Ballinger, Marcin Kowanetz, Pei He, Daniel S Chen, Alan Sandler, David R Gandara, for the OAK Study Group**

Summary

Background Atezolizumab is a humanised antiprogrammed death-ligand 1 (PD-L1) monoclonal antibody that inhibits PD-L1 and programmed death-1 (PD-1) and PD-L1 and B7-1 interactions, reinvigorating anticancer immunity. We assessed its efficacy and safety versus docetaxel in previously treated patients with non-small-cell lung cancer.

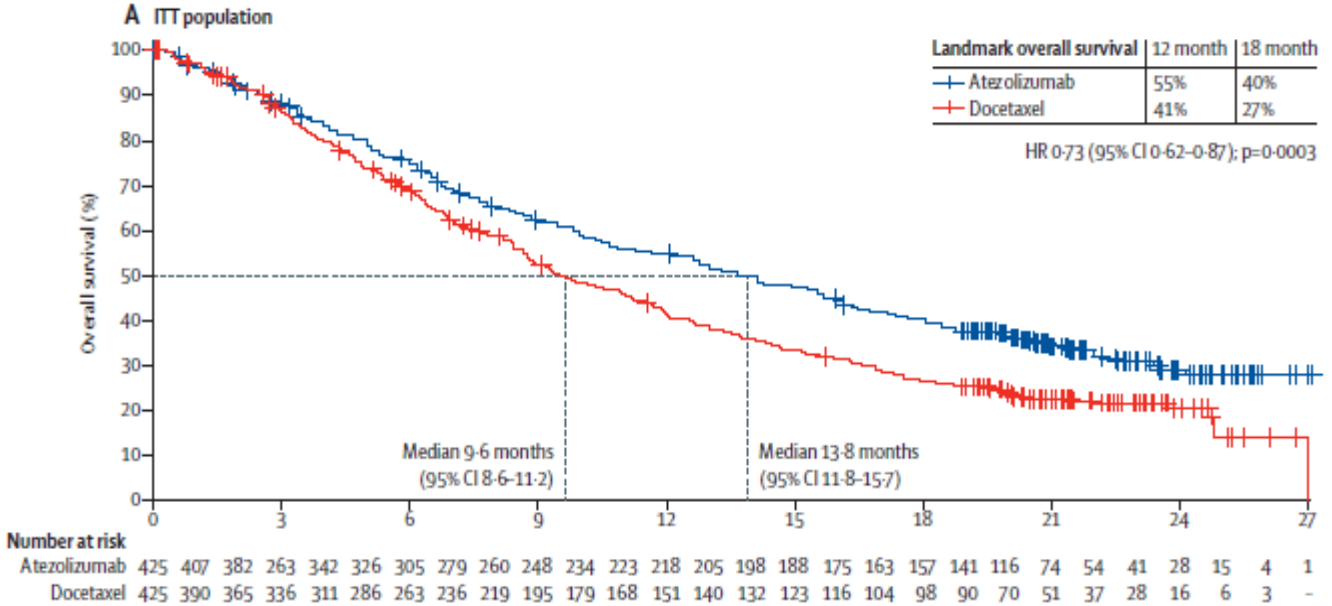
Lancet 2017; 389: 255–65
Published Online
December 12, 2016
http://dx.doi.org/10.1016/
S0140-6736(16)32517-X

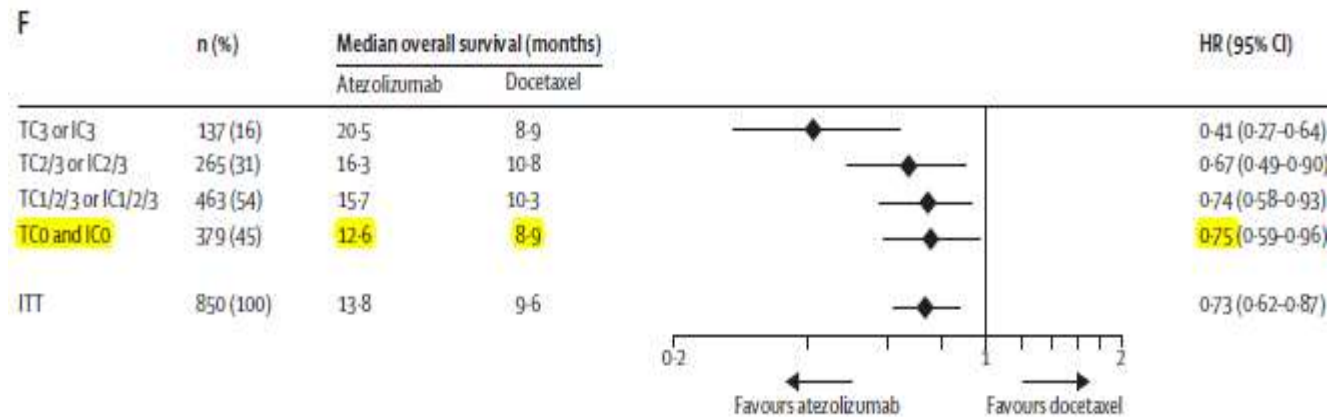
Achim Rittmeyer et al, Lancet 2017; 389: 255–65



	Atezolizumab (n = 425)	Chemotherapy (n = 425)	HR
Median PFS	2·8 months (2·6–3·0)	4·0 months (3·3–4·2)	0.95 (0·82–1·10)
Objective response rate	58 (14%)	57 (13%)	0.34 (0·21–0·55)
Objective response rate in TC3/IC3	22 /72 (31%)	7 /65 (11%)	
Median duration of response	16.3 months	6.2 months	-

Achim Rittmeyer et al, Lancet 2017; 389: 255–65



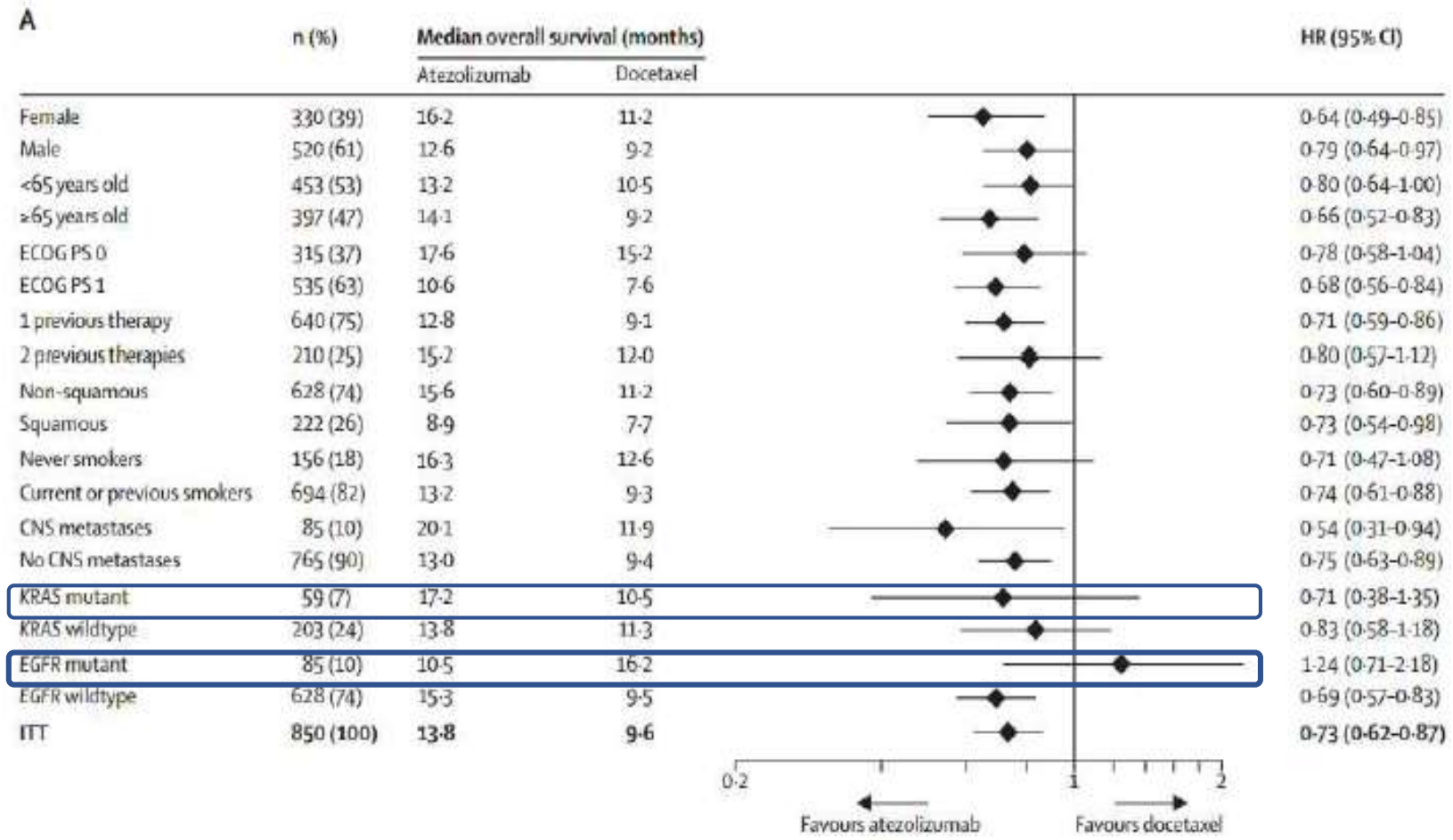


OS	Months
Atezolizumab	13.8
Docetaxel	9.6

Benefit across all lines of PD-L1 expression

Achim Rittmeyer et al, Lancet 2017; 389: 255–65

OAK trial - Atezolizumab



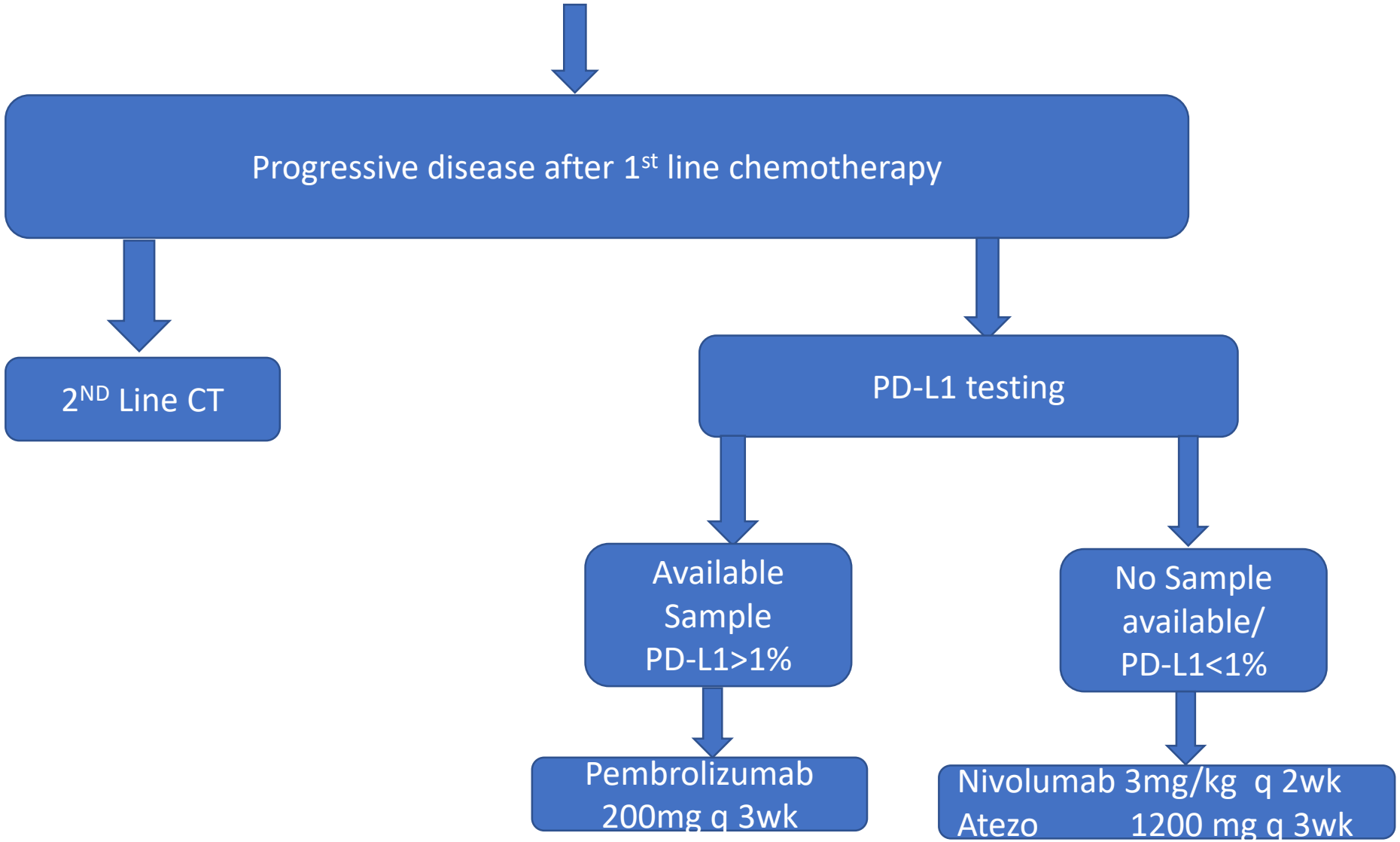
A	n (%)	Median overall survival (months)		HR (95% CI)
		Atezolizumab	Docetaxel	
Female	330 (39)	16·2	11·2	0·64 (0·49–0·85)
Male	520 (61)	12·6	9·2	0·79 (0·64–0·97)
<65 years old	453 (53)	13·2	10·5	0·80 (0·64–1·00)
≥65 years old	397 (47)	14·1	9·2	0·66 (0·52–0·83)
ECOG PS 0	315 (37)	17·6	15·2	0·78 (0·58–1·04)
ECOG PS 1	535 (63)	10·6	7·6	0·68 (0·56–0·84)
1 previous therapy	640 (75)	12·8	9·1	0·71 (0·59–0·86)
2 previous therapies	210 (25)	15·2	12·0	0·80 (0·57–1·12)
Non-squamous	628 (74)	15·6	11·2	0·73 (0·60–0·89)
Squamous	222 (26)	8·9	7·7	0·73 (0·54–0·98)
Never smokers	156 (18)	16·3	12·6	0·71 (0·47–1·08)
Current or previous smokers	694 (82)	13·2	9·3	0·74 (0·61–0·88)
CNS metastases	85 (10)	20·1	11·9	0·54 (0·31–0·94)
No CNS metastases	765 (90)	13·0	9·4	0·75 (0·63–0·89)
KRAS mutant	59 (7)	17·2	10·5	0·71 (0·38–1·35)
KRAS wildtype	203 (24)	13·8	11·3	0·83 (0·58–1·18)
EGFR mutant	85 (10)	10·5	16·2	1·24 (0·71–2·18)
EGFR wildtype	628 (74)	15·3	9·5	0·69 (0·57–0·83)
ITT	**850 (100)**	**13·8**	**9·6**	**0·73 (0·62–0·87)**

Atezolizumab response was independent of histology and PD-L1 status

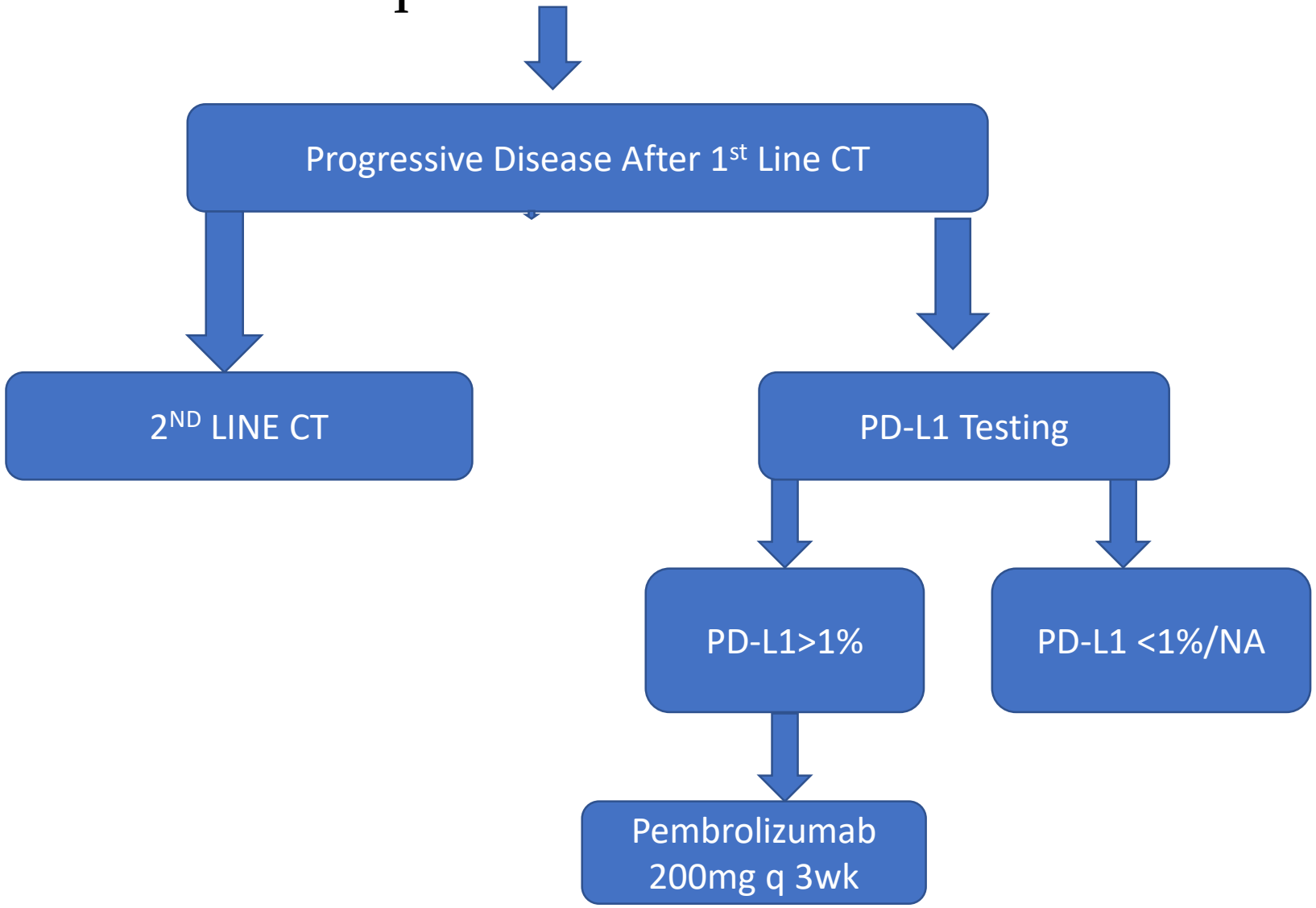
But was lesser in patients with mutant EGFR AND KRAS

Achim Rittmeyer et al, Lancet 2017; 389: 255–65

Adenocarcinoma(Stg IV)- 2nd Line



Advanced Squamous Cell Carcinoma – 2nd Line



CHECKMATE 017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

ABSTRACT

BACKGROUND

Patients with advanced squamous-cell non–small-cell lung cancer (NSCLC) who have disease progression during or after first-line chemotherapy have limited treatment options. This randomized, open-label, international, phase 3 study evaluated the efficacy and safety of nivolumab, a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint–inhibitor antibody, as compared with docetaxel in this patient population.

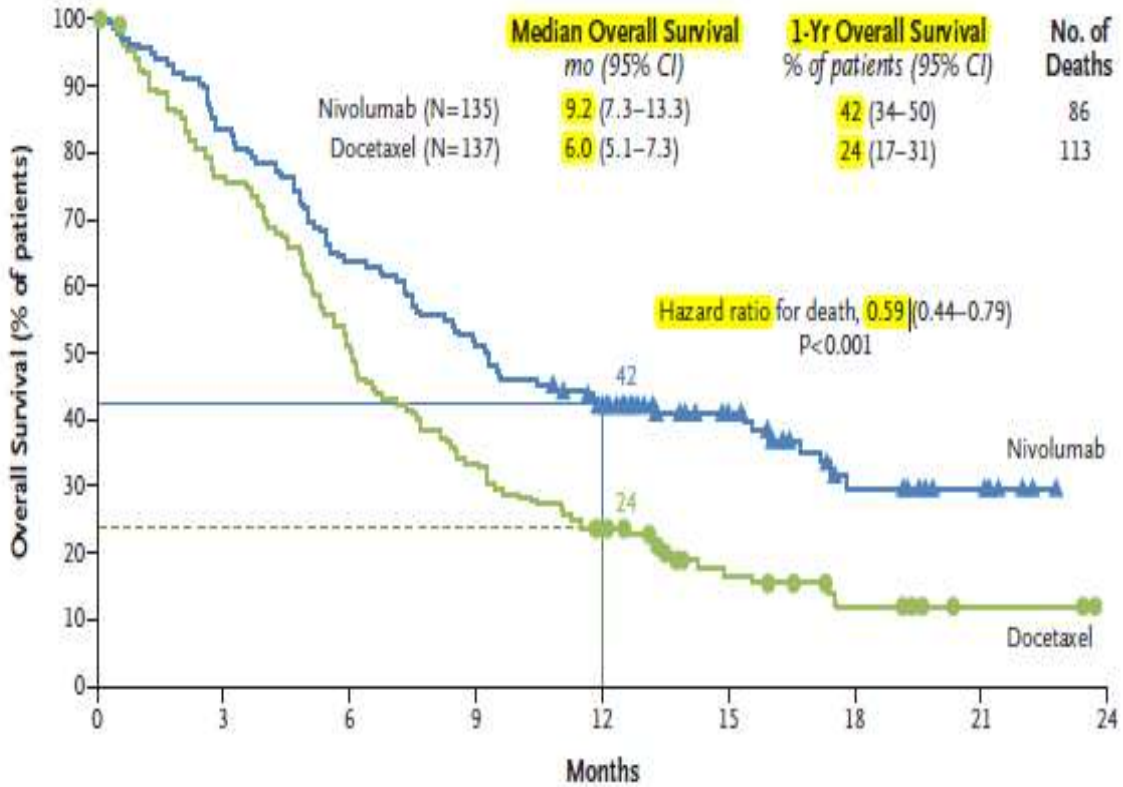
STG IIIB/IV NSCLC
ECOG 0-1
FAILED 1 previous PLATINUM containing regimen

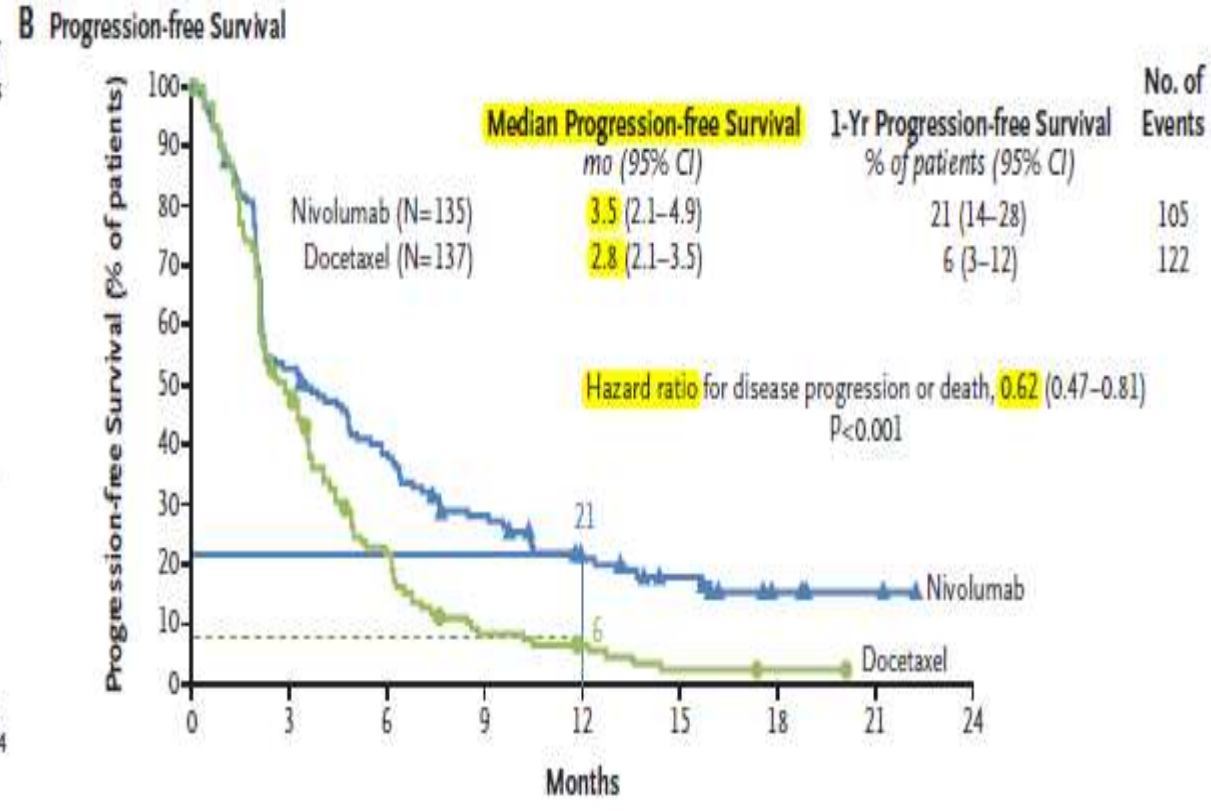
Nivolumab
3mg/kg iv
Q 2wk
N= 135

Docetaxel
75mg/m2 iv
Q 3wk
N=137

Primary end point : OS
Secondary end point : PFS, ORR, Safety, Efficacy by PD-L1 expression

Brahmer J et al, NEJM 2015, 373,123-135





No. at Risk									
Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

No. at Risk									
Nivolumab	135	68	48	33	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

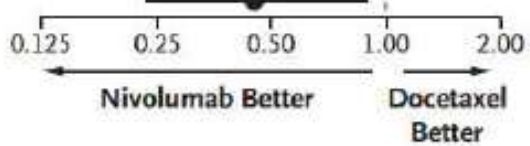
Nivolumab showed clinically meaningful survival benefit in prev. treated advanced squamous NSCLC

Brahmer J et al, NEJM 2015, 373,123-135

Checkmate 017 (PDL1 expression)

C Overall and Progression-free Survival According to PD-L1 Expression Level

PD-L1 Expression Level	Nivolumab	Docetaxel	Unstratified Hazard Ratio (95% CI)
	no. of patients		
Overall survival			
≥1%	63	56	0.69 (0.45–1.05)
<1%	54	52	0.58 (0.37–0.92)
≥5%	42	39	0.53 (0.31–0.89)
<5%	75	69	0.70 (0.47–1.02)
≥10%	36	33	0.50 (0.28–0.89)
<10%	81	75	0.70 (0.48–1.01)
Not quantifiable at baseline	18	29	0.39 (0.19–0.82)
Progression-free survival			
≥1%	63	56	0.67 (0.44–1.01)
<1%	54	52	0.66 (0.43–1.00)
≥5%	42	39	0.54 (0.32–0.90)
<5%	75	69	0.75 (0.52–1.08)
≥10%	36	33	0.58 (0.33–1.02)
<10%	81	75	0.70 (0.49–0.99)
Not quantifiable at baseline	18	29	0.45 (0.23–0.89)



PD-L1 expression did not influence survival benefit/PFS

Brahmer J et al, NEJM 2015, 373,123-135

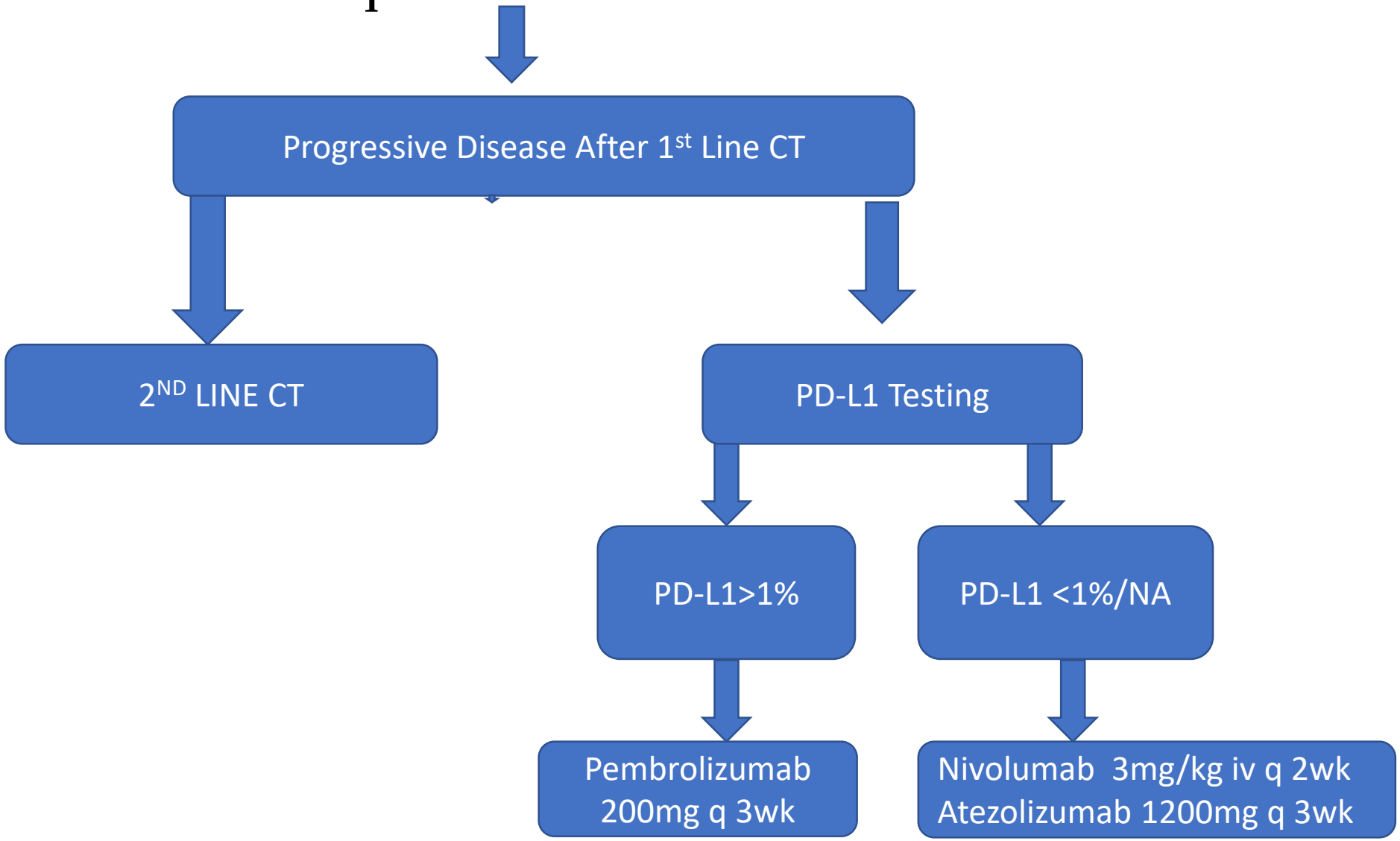
Nivolumab 2L v/s Docetaxel

	Checkmate 017 (Squamous NSCLC)	Checkmate 057 (Non Squamous NSCLC)
No of subjects	135 vs 137	292 vs 290
Dose	Nivolumab 3 mg/kg q 2 weekly vs	Docetaxel 75 mg/sq.m q 3 weekly
OS	**9.2 months** (95% CI, 7.3 to 13.3) vs **6.0 months** (95% CI, 5.1 to 7.3) **HR, 0.59**; (0.44 to 0.79; P<0.001)	**12.2 months** (95% CI, 9.7 to 15.0) vs **9.4 months** (95% CI, 8.1 to 10.7) **HR, 0.73;** (0.59 to 0.89;P=0.002)
PFS	**3.5 months** (95% CI, 7.3 to 13.3) vs **2.8 months** (95% CI, 5.1 to 7.3) **HR, 0.62**; (0.47 to 0.81; P<0.001)	2.3 months (95% CI, 2.2 to 3.3) vs 4.2 months (95% CI, 3.5 to 4.9) HR, 0.92; (0.77 to 1.1; P<0.001)

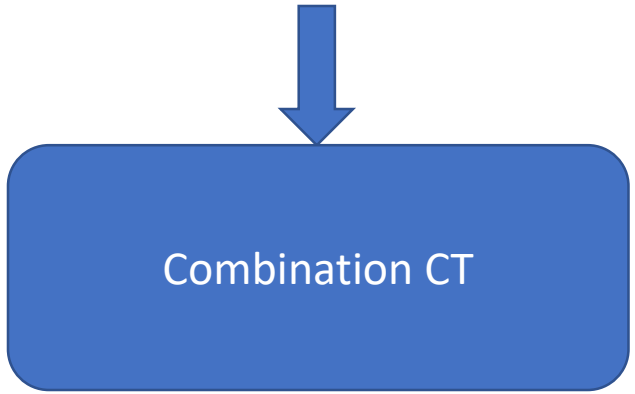
Nivolumab 2L v/s Docetaxel

	Checkmate 017 (Squamous NSCLC)	Checkmate 057 (Non Squamous NSCLC)
Overall survival rate at 1 yr	**42%** (95% CI, 34 to 50) Vs **24%** (95% CI, 17 to 31)	**51%** (95% CI, 45 to 56) Vs **39%** (95% CI, 33 to 45)
Objective response rate	**20 %** vs **9 %**	**19 %** vs **12 %**
Time to res	2.2 m vs 2.1 m	2.1 m vs 2.6 m
Duration of res	NR vs 8.4 m	17.2 m vs 5.6 m
AEs 3/4	7 % vs 55 %	10 % vs 54 %

Advanced Squamous Cell Carcinoma – 2nd Line



EXTENSIVE STAGE SMALL CELL LUNG CA



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

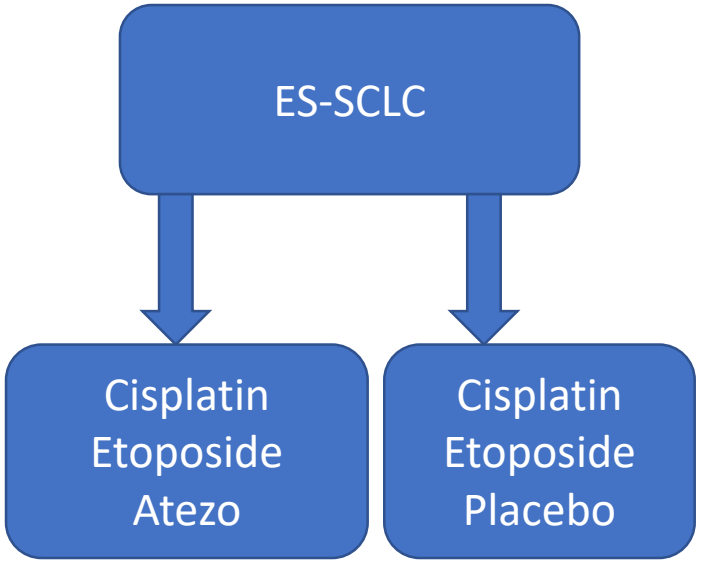
First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

L. Horn, A.S. Mansfield, A. Szczęsna, L. Havel, M. Krzakowski, M.J. Hochmair, F. Huemer, G. Losonczy, M.L. Johnson, M. Nishio, M. Reck, T. Mok, S. Lam, D.S. Shames, J. Liu, B. Ding, A. Lopez-Chavez, F. Kabbinavar, W. Lin, A. Sandler, and S.V. Liu, for the IMpower133 Study Group*

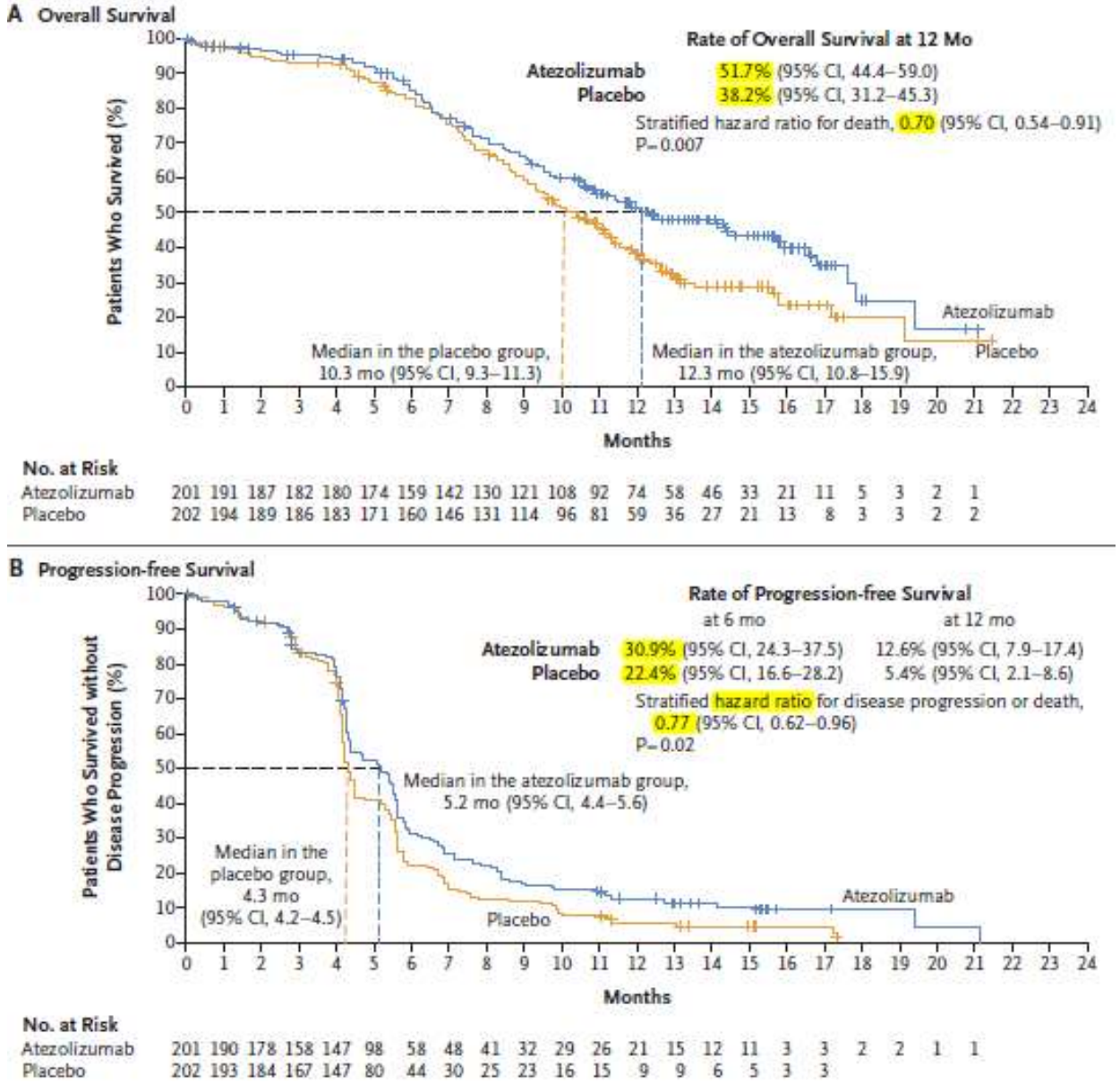
ABSTRACT

BACKGROUND

Enhancing tumor-specific T-cell immunity by inhibiting programmed death ligand 1 (PD-L1)–programmed death 1 (PD-1) signaling has shown promise in the treatment of extensive-stage small-cell lung cancer. Combining checkpoint inhibition with cytotoxic chemotherapy may have a synergistic effect and improve efficacy.



Horn L et al,N Engl J Med 2018; 379:2220-2229

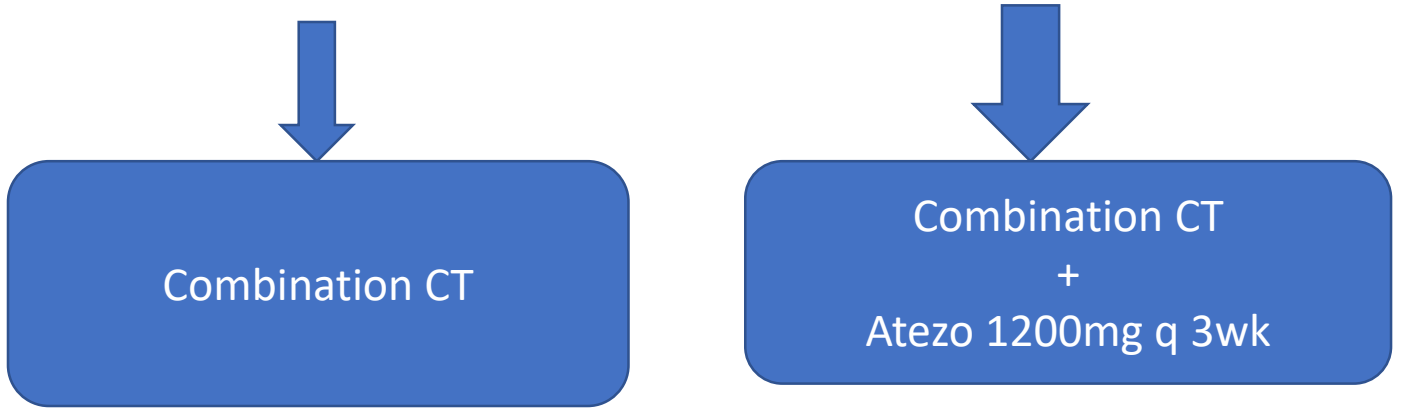


OS
12.3 V/S 10.3 months

PFS
5.2 v/s 4.3 months

Horn L et al,N Engl J Med 2018; 379:2220-2229

EXTENSIVE STAGE SMALL CELL LUNG CA



PACIFIC Trial

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

ABSTRACT

BACKGROUND

Most patients with locally advanced, unresectable, non–small-cell lung cancer (NSCLC) have disease progression despite definitive chemoradiotherapy (chemotherapy plus concurrent radiation therapy). This phase 3 study compared the anti–programmed death ligand 1 antibody durvalumab as consolidation therapy with placebo in patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy.

METHODS

We randomly assigned patients, in a 2:1 ratio, to receive durvalumab (at a dose of 10 mg per kilogram of body weight intravenously) or placebo every 2 weeks for up to 12 months. The study drug was administered 1 to 42 days after the patients had received chemoradiotherapy. The coprimary end points were progression-free survival (as assessed by means of blinded independent central review) and overall survival (unplanned for the interim analysis). Secondary end points included 12-month and 18-month progression-free survival rates, the objective response rate, the duration of response, the time to death or distant metastasis, and safety.

RESULTS

Of 713 patients who underwent randomization, 709 received consolidation therapy (473 received durvalumab and 236 received placebo). The median progression-free survival from randomization was 16.8 months (95% confidence interval [CI], 13.0 to 18.1) with durvalumab versus 5.6 months (95% CI, 4.6 to 7.8) with placebo (stratified hazard ratio for disease progression or death, 0.52; 95% CI, 0.42 to 0.65; P<0.001); the 12-month progression-free survival rate was 55.9% versus 35.3%, and the 18-month progression-free survival rate was 44.2% versus 27.0%. The response rate was higher with durvalumab than with placebo (28.4% vs. 16.0%; P<0.001), and the median duration of response was longer (72.8% vs. 46.8% of the patients had an ongoing response at 18 months). The median time to death or distant metastasis was longer with durvalumab than with placebo (23.2 months vs. 14.6 months; P<0.001). Grade 3 or 4 adverse events occurred in 29.9% of the patients who received durvalumab and 26.1% of those who received placebo; the most common adverse event of grade 3 or 4 was pneumonia (4.4% and 3.8%, respectively). A total of 15.4% of patients in the durvalumab group and 9.8% of those in the placebo group discontinued the study drug because of adverse events.

CONCLUSIONS

Progression-free survival was significantly longer with durvalumab than with placebo. The secondary end points also favored durvalumab, and safety was similar between the groups. (Funded by AstraZeneca; PACIFIC ClinicalTrials.gov number, NCT02125461.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Antonia at the H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Dr., MRC 3-E, Tampa, FL 33612, or at scott.antonia@moffitt.org.

*A complete list of the investigators of the PACIFIC study is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 8, 2017, at NEJM.org.

N Engl J Med 2017;377:1919-29.
DOI: 10.1056/NEJMoa1709937

STG III LOCALLY ADVANCED NSCLC
RECEIVED >2 CYCLES OF CRT

↓

DURVALUMAB 10mg/kg iv q 2wk
OR
PLACEBO
FOR 12 MONTHS

S.J. Antonia et al, N Eng J Med 2017

	Durvalumab (N = 443)	Placebo (N =213)	HR
Median PFS	16.8 months (13.0–18.1)	5.6 months (4.6–7.8)	0.52 (0·42–0.65)
12-month PFS rate	55.9% (51.0 to 60.4)	35.3% (29.0 to 41.7)	-
18-month PFS rate	44.2% (37.7 to 50.5)	27.0% (19.9 to 34.5)	-
ORR	28.4%	16.0% P<0.001	

Durvalumab was associated with durable PFS AND ORR

S.J. Antonia et al, N Eng J Med 2017

Phase III Trials of immunotherapy agents

	OS	PFS	ORR	PD-L1 DEPENDENCY
P-KN024	✓	✓	✓	✓
P-KN010	✓	✓	✓	✓
P-KN189	✓	✓	✓	✓
N-017	-	✓	✓	-
N-057	✓	-	✓	-
A-OAK	✓	-	✓	-
A-IM150	✓	✓	✓	-
A-IM 133	✓	✓	✓	-
D- PACIFIC	✓	✓	✓	-

PEMBROLIZUMAB(KEYTRUDA)

ICI	RECOMMENDATION	BASED ON TRIAL
PEMBROLIZUMAB 200 mg q 3wk	1L. METASTATIC NSCLC	KEYNOTE-024
	1L.METASTATIC ADENO CA	KEYNOTE-189 KEYNOTE-407
	2L.METASTATIC NSCLC	KEYNOTE-010
	3L. METASTATIC SCLC	KEYNOTE-028

SITC immunotherapy guidelines for metastatic NSCLC

NIVOLUMAB(OPDYTA)

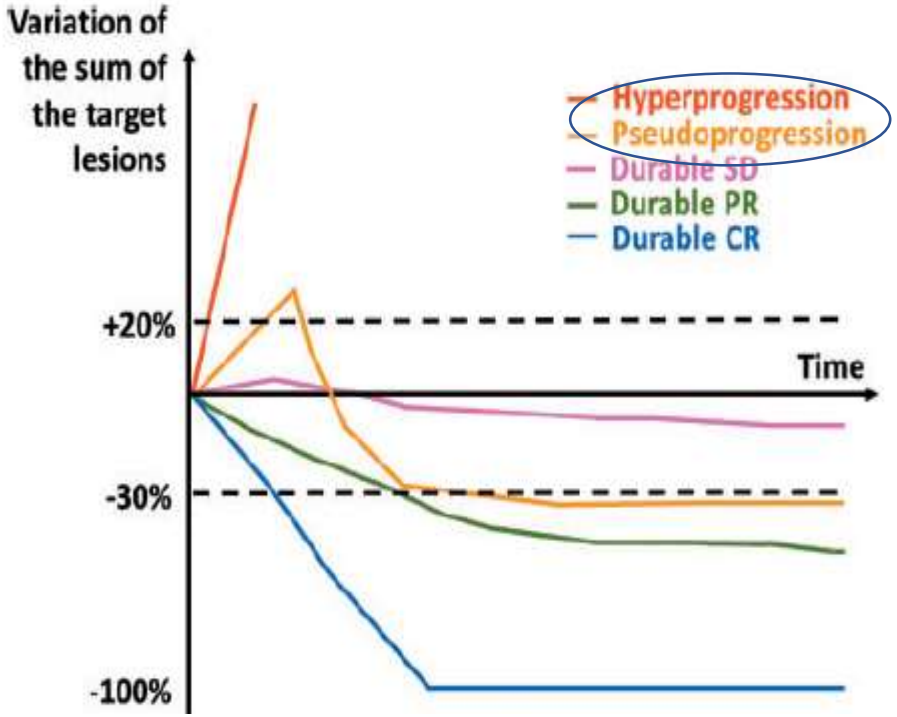
ICI	RECOMMENDATION	BASED ON TRIAL
NIVOLUMAB 3mg/kg q 2wk	2L. NSCLC NONSQUAMOUS SQUAMOUS	CHECKMATE-057 CHECKMATE-017
	3L. SCLC	CHECKMATE-032

Atezolizumab (Tecentriq)

	Recommendation	Based on trial
Atezolizumab 1200mg q 3wk	1L. Metastatic NSCLC 1L. ES-SCLC	IM POWER 150 IM POWER 133
	2L. Metastatic NSCLC	OAK trial

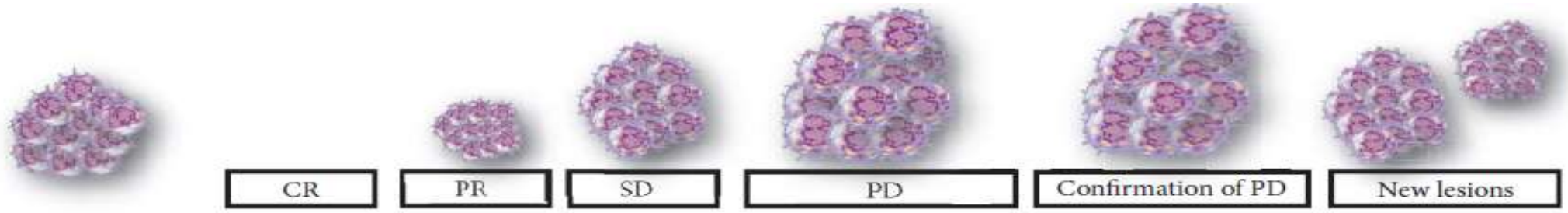
Assesment of response

- Pattern of response seen with immunotherapy differs from that seen with other modalities of treatment



Clin Cancer Res. 2009;15(23):7412

Response criteria



	CR	PR	SD	PD	Confirmation of PD	New lesions
RECIST1.1 [34] Uni-dimensional ≥10mm 5 lesions in total, 2 per organ	Disappearance of all lesions	≥ 30% decrease from baseline	Neither CR nor PD	≥ 20% increase in the nadir of the sum of target lesions (with a minimum a of 5mm)	Not applicable	PD
irRC [74] Bi-dimensional 5mm x 5mm 15 lesions in total, 5 per organ	Disappearance of all lesions	≥ 50% decrease from baseline	Neither CR nor PD	≥ 25% increase in the nadir of the sum of target lesions	At least 4 weeks later	Incorporated in the sum of measurements
irRECIST [75] Uni-dimensional ≥10mm 5 lesions in total, 2 per organ	Disappearance of all lesions	≥ 30% decrease from baseline	Neither CR nor PD	≥ 20% increase in the nadir of the sum of target lesions (with a minimum a of 5mm)	At least 4 weeks after and up to 12 weeks	Incorporated in the sum of measurements
iRECIST [76] Uni-dimensional ≥10mm 5 lesions in total, 2 per organ	Disappearance of all lesions	≥ 30% decrease from baseline	Neither CR nor PD	≥ 20% increase in the nadir of the sum of target lesions (with a minimum a of 5mm)	At least 4 weeks after and up to 8 weeks	iUPD; not incorporated in the sum becomes iCPD if confirmed
imRECIST [77] Uni-dimensional ≥10mm 5 lesions in total, 2 per organ	Disappearance of all lesions	≥ 30% decrease from baseline	Neither CR nor PD	≥ 20% increase in the nadir of the sum of target lesions (with a minimum a of 5mm)	At least 4 weeks later	Incorporated in the sum of measurements

Annals of Oncology 30: 385–396, 2019

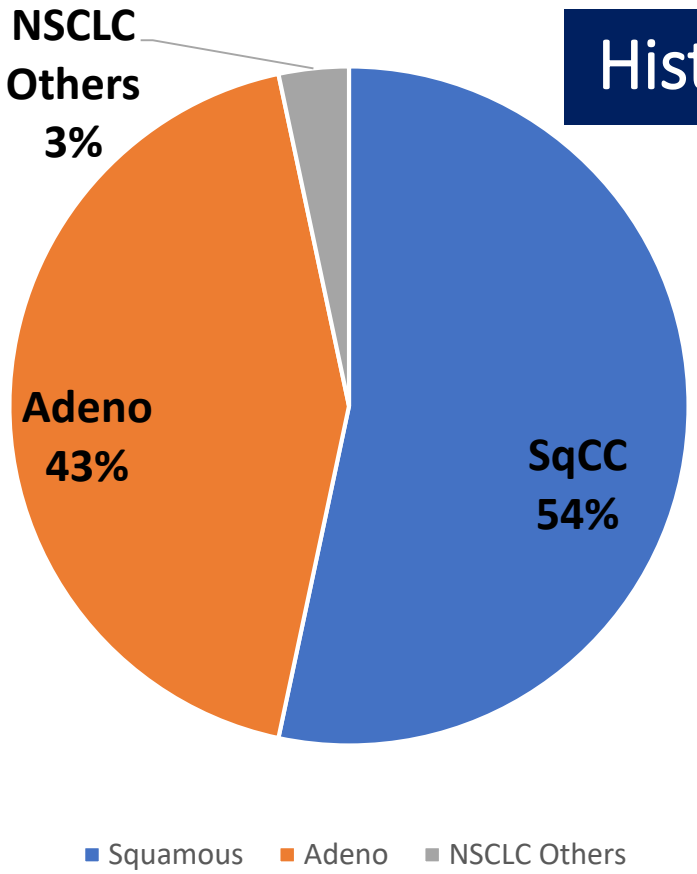
PD-1/PD-L1 ICI Rx in LC

- Patients undergoing PD-1/PD-L1 ICI Rx at Lung cancer clinic (LCC), PGIMER
- Time period: January 2017-Feb 2019
- Follow-up cutoff date: 21st February 2019

PD-1/PD-L1 ICI Rx in LC

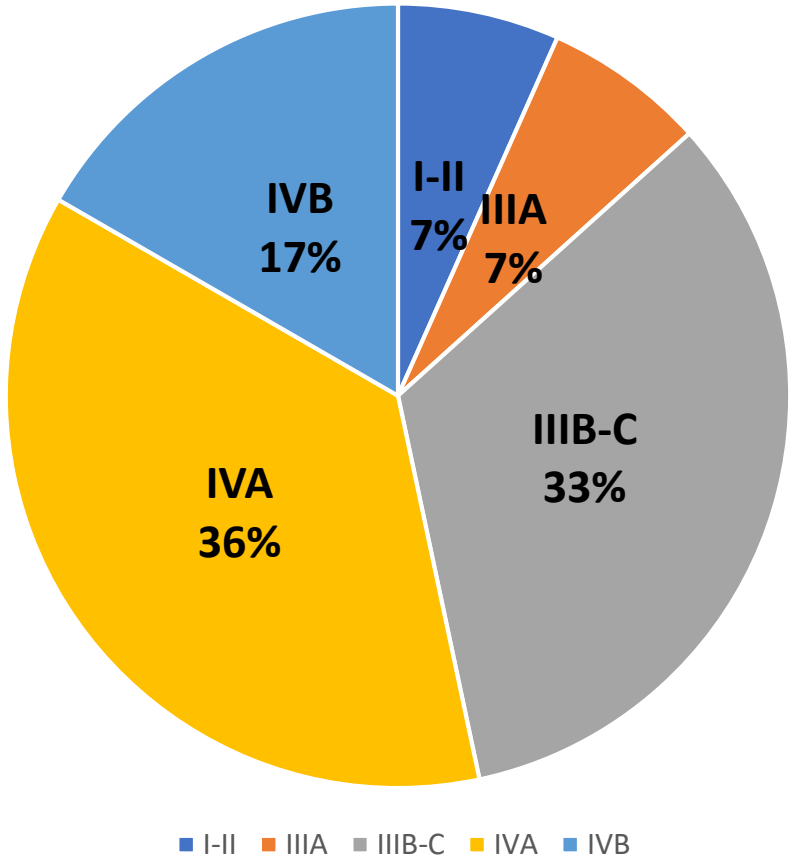
Patient characteristics (N=30)	n (%)
Age in years, mean (SD)	58.4 (12.4)
Male gender	25 (83.3%)
Current/former smokers*	19 (63.3%)
Comorbid illness	16 (53.3%)
• 1	23.3%
• 2 & ≥3	20.0% & 10.0%
Dx to ICI Rx initiation in days, median (range)	395 (151-544)
ECOG PS at ICI Rx initiation	
• 0 & 1	15.4% & 57.7%
• ≥2	26.9%

PD-1/PD-L1 ICI Rx in LC



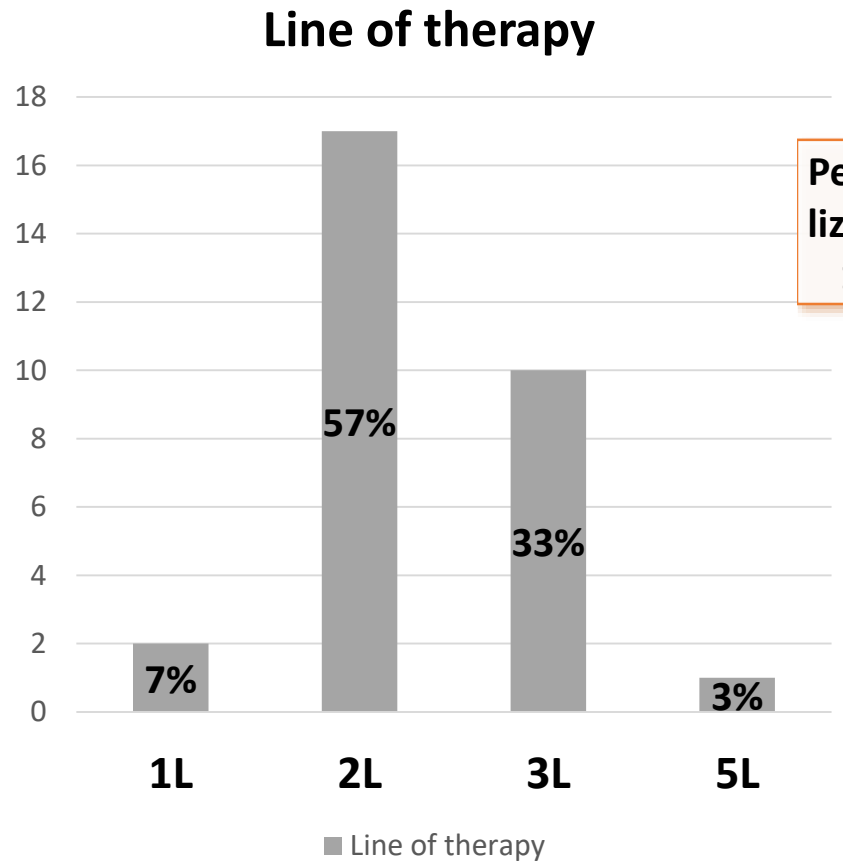
Histology

Stage at Dx

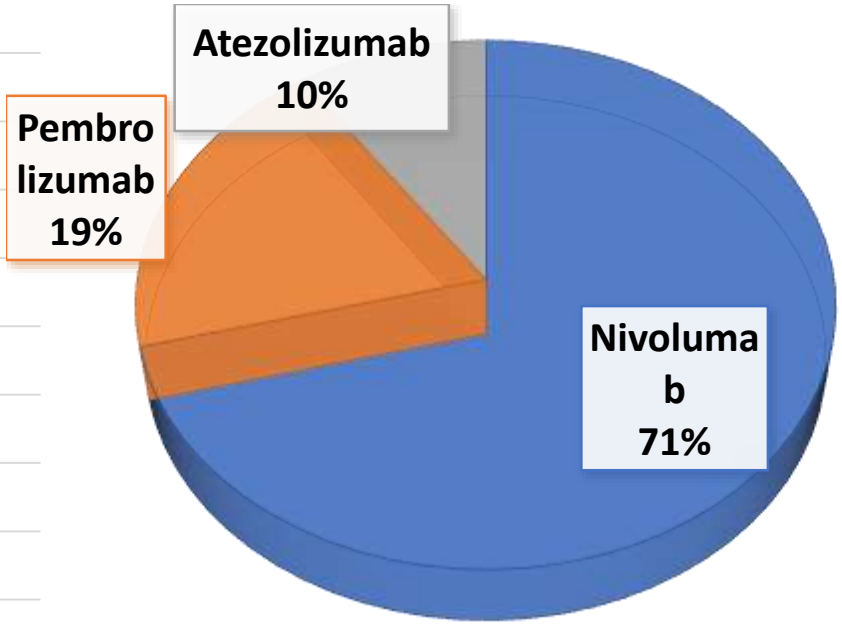


PD-1/PD-L1 ICI Rx in LC

Prior Surgery : 13% (n=4)
Radiation : 40% (n=12)



ICI used (n=31* in 30 patients)

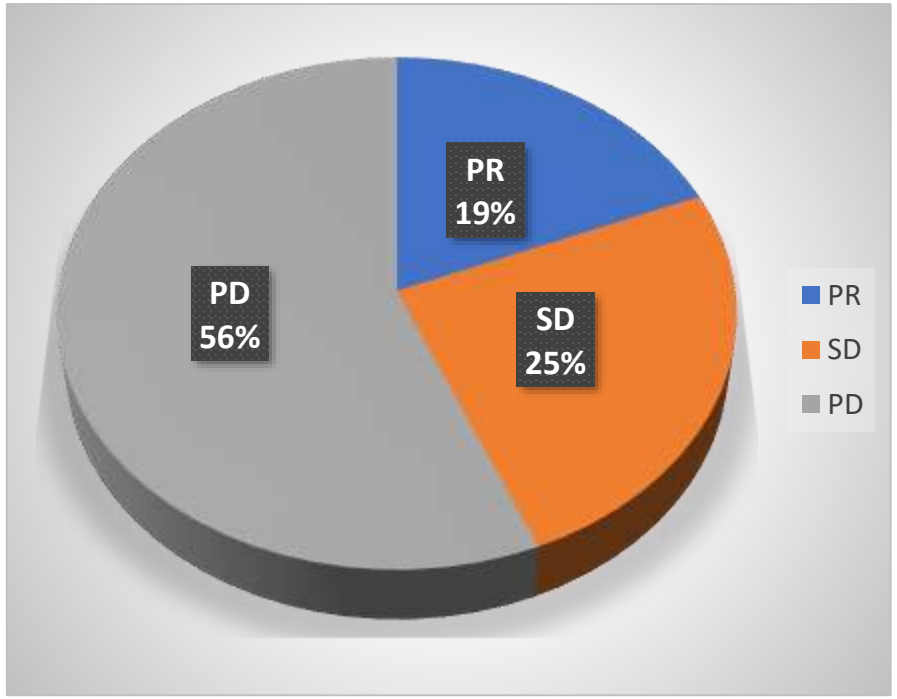


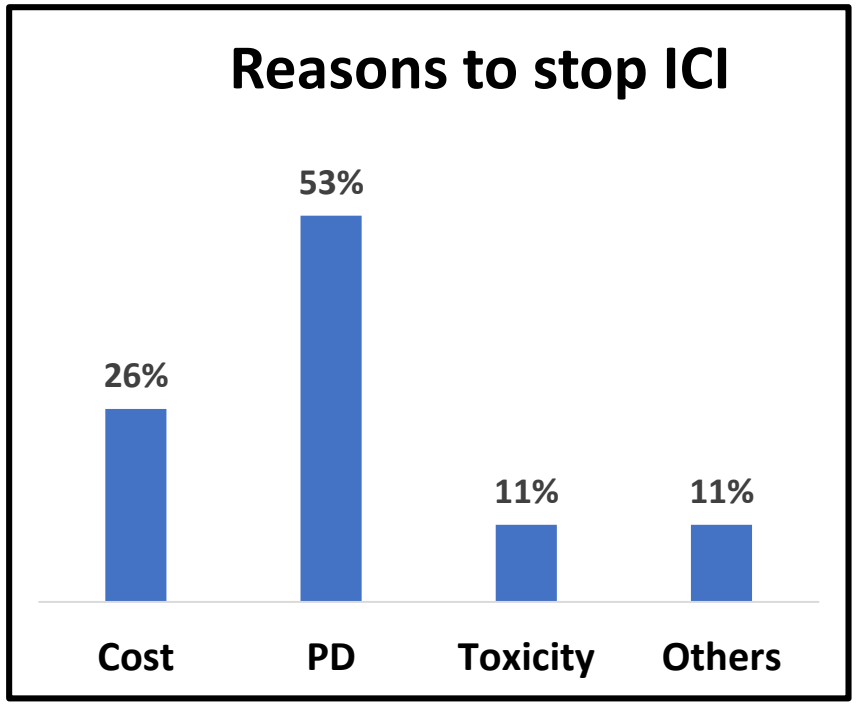
*One patient received pembrolizumab initially and later atezolizumab

PD-1/PD-L1 ICI Rx in LC

No of cycles (Median): 4

Best response to ICI Rx





PD-1/PD-L1 ICI treatment

Rx related AEs (irAEs)

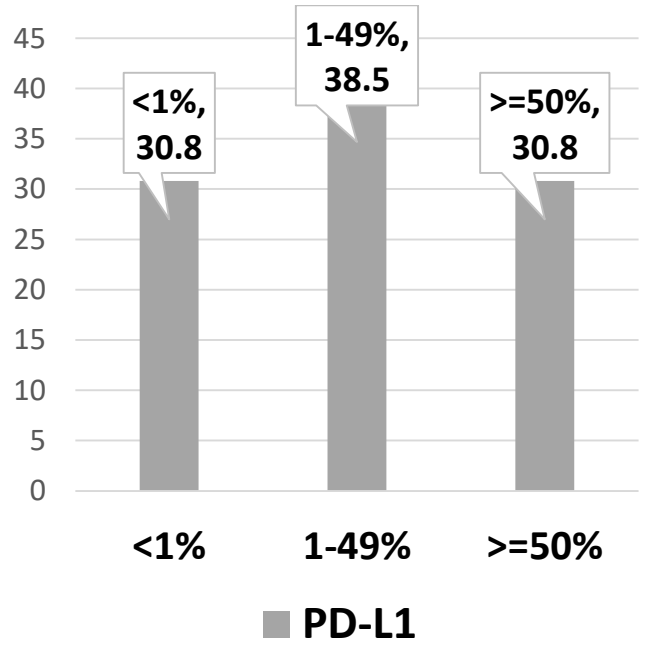
irAE	N, (%)
Any grade irAE	8 (26.7%)
Pneumonitis*	2
Hypothyroidism	2
Thrombocytopenia	1
Hepatitis	1

* one patient had ‘radiation recall’ pneumonitis

Grade 3 pneumonitis in 2 patients
Grade 4 hepatitis in 1 patient

Other relevant details:

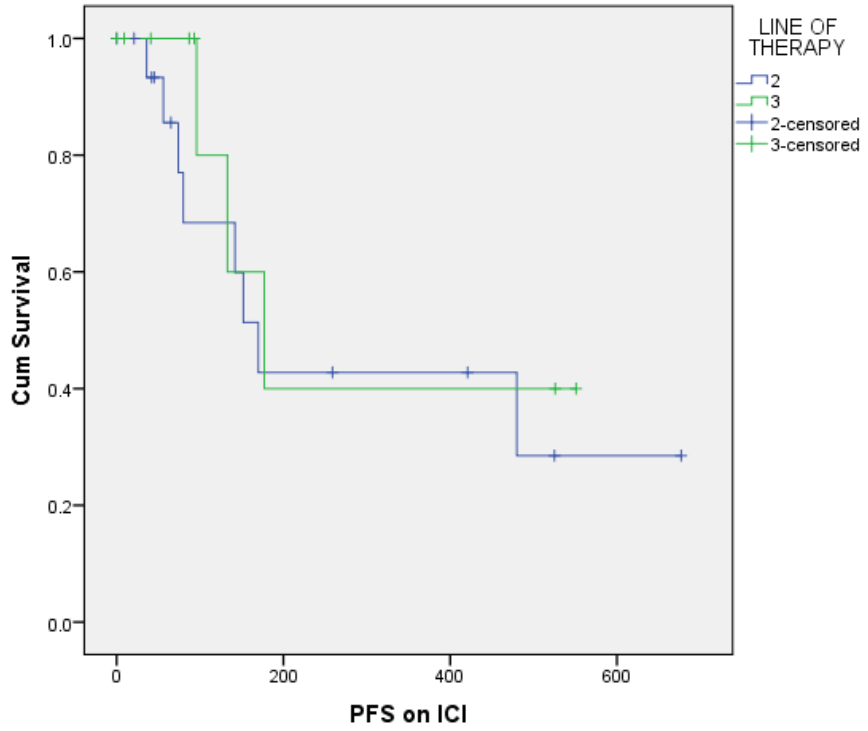
- PD-L1 status available in 43% (n=13)

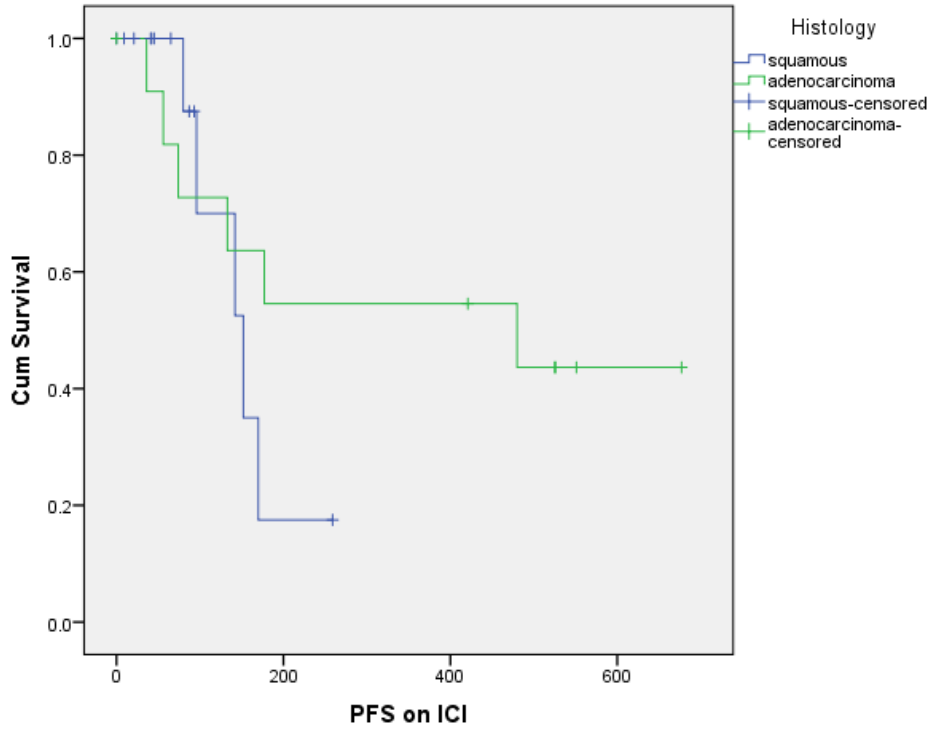


PFS with ICI Rx in 2L/3L setting

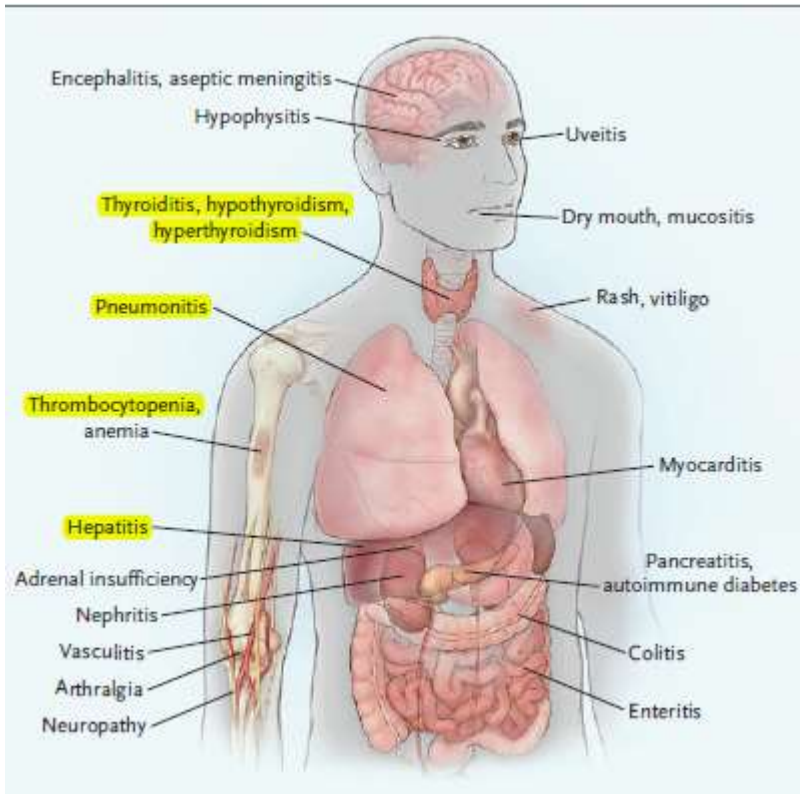
Median PFS 170 days (95% CI = 122 – 218)

OS data immature (median NR)





Immune related adverse events(irAE)



Systemic	Organ Specific
Fatigue(40%)	Dermatological(Most common) 30-40%, 3wk
	Transaminitis,<5%, 8wk
Infusion reaction(25%)	Pneumonitis,<5%
	Thyroiditis
	Thrombocytopenia

Occur due to block of normal regulators of immune system

N Engl J Med 2018;378:158-68.

Questions about Immune-Related Adverse Events	Comments
Why do they occur?	The precise pathophysiology is unknown. Translational studies in patients with immune-related adverse events have shown that T-cell, antibody, and cytokine responses may be involved.
How are they generally treated?	No prospective trials have defined the best treatment approaches, and recommendations are based on consensus opinion. Immunosuppression is used to reduce the excessive state of temporary inflammation. Glucocorticoids are usually the first-line immunosuppressive agent. Additional immunosuppressive agents can be used if glucocorticoids are not initially effective.
When do they occur?	Immune-related adverse events usually start within the first few weeks to months after treatment but can occur anytime, even after treatment discontinuation. Dermatologic adverse events are usually the first to appear.
Why do they occur in some patients and not others?	The reason for the occurrence of immune-related adverse events only in certain patients is unknown. Some studies are investigating whether such factors as germline genetics and the composition of host microbiota are related to risk.
Are they associated with the efficacy of immune checkpoint blockade?	Conflicting data are available regarding whether the occurrence of immune-related adverse events is associated with improved treatment efficacy. The development of immune-related adverse events is not required for treatment benefit. Specific adverse events (e.g., vitiligo) may be more clearly associated with treatment efficacy.
Does immunosuppression to treat such adverse events reduce the antitumor efficacy of treatment?	Clinical outcomes are similar in patients who require immunosuppression to treat immune-related adverse events and in those who do not require such treatment. Beneficial responses can persist despite the use of immunosuppression to treat immune-related adverse events.
Are there unintended effects of immunosuppression to treat adverse events?	Side effects of glucocorticoid use (e.g., hyperglycemia, edema, anxiety, and iatrogenic adrenal insufficiency) can occur. Immunosuppression is a risk factor for subsequent opportunistic infections.
Is it safe to restart treatment after a major adverse event?	Retrospective studies have shown that immune-related adverse events associated with one class of agent (e.g., anti–CTLA-4) may not necessarily recur during subsequent treatment with another agent (e.g., anti–PD-1). The safety of retreatment probably depends on the severity of the initial immune-related adverse event.

N Engl J Med 2018;378:158-68

Transaminitis

Grade	AST/ALT , TB	Mgt
1 Asymptomatic	<3x , <1.5x	Continue ICI, Monitor q wk
2 Asymptomatic	>3x, >1.5x	W/H ICI, Monitor q 3d
2 Symptomatic	>3x, >1.5x	Prednisone 1mg/kg/d
3 Symptomatic	5-20x, 3-10x	MP 2mg/kg/d AZP/MMF
4 Decompensated	>20x, >10x	MP 2mg/kg/d AZP/MMF Steroid x 4-6 wk f/b taper

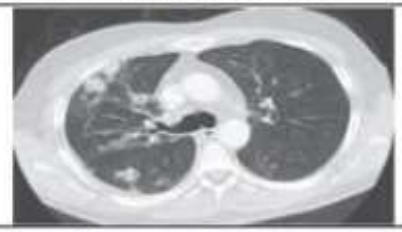
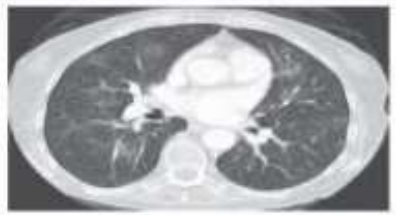
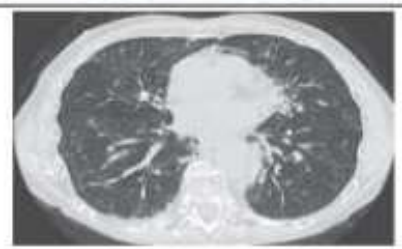
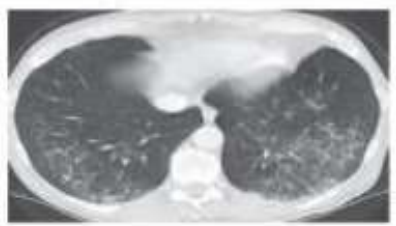
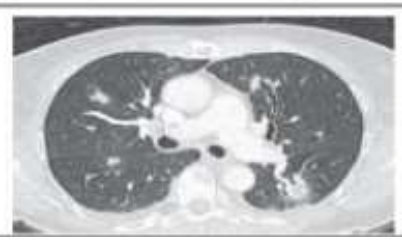
Brahmer JR, et al. American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018

Pneumonitis

- Diagnosis of exclusion(No characteristic feature)
- Overall incidence is 5%
- More common with combination therapy

Grade	Feature	Management
1. Asymptomatic	Confined to one lobe <25% of parenchyma	W/H ICI Observe repeat CT in 4wk Resume Rx if improvt.
2. Symptomatic	>1 lobe 25-50% of parenchyma	W/H ICI Empirical AB/Sputum w/u/BAL Prednisolone 1mg/kg/d Taper over 6 wk If resolves ICI can be restarted
3. Severe Symptomatic	All lobes >50% of parenchyma	D/C ICI Empirical AB/BAL/Sputum w/u Inj MP 1mg/kg/d No improvt. In 48 hr
4. Life threatening		MMF/CPD/IVig

Brahmer JR, et al. American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018

Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

Naidoo J eta l, J Clin Oncol 2016

4.1 Thyroid

4.1.1 Primary hypothyroidism

Definition: Elevated TSH, normal or low FT4

Diagnostic work-up

TSH and FT4 every 4-6 weeks as part of routine clinical monitoring on therapy or for case detection in symptomatic patients

Grading	Management
G1: TSH < 10 mIU/L and asymptomatic	Should continue ICPi with close follow-up and monitoring of TSH, FT4
G2: Moderate symptoms; able to perform ADL; TSH persistently > 10 mIU/L	May hold ICPi until symptoms resolve to baseline Consider endocrine consultation Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist > 10 mIU/L (measured 4 weeks apart) Monitor TSH every 6-8 weeks while titrating hormone replacement to normal TSH FT4 can be used in the short term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low Once adequately treated, should monitor thyroid function (at least TSH) every 6 weeks while on active ICPi therapy or as needed for symptoms to ensure appropriate replacement; repeat testing annually or as indicated by symptoms once stable
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate supplementation Endocrine consultation May admit for IV therapy if signs of myxedema (bradycardia, hypothermia) Thyroid supplementation and reassessment as in G2

Additional considerations

- For patients without risk factors, full replacement can be estimated with an ideal body weight–based dose of approximately 1.6 μg/kg/d
- For elderly or fragile patients with multiple comorbidities, consider titrating up from low dose, starting at 25-50 μg
- Extreme elevations of TSH can be seen in the recovery phase of thyroiditis and can be watched in asymptomatic patients to determine whether there is recovery to normal within 3-4 weeks
- Under guidance of endocrinology, consider tapering hormone replacement and retesting in patients with a history of thyroiditis (initial thyrotoxic phase)
- Adrenal dysfunction, if present, must always be replaced before thyroid hormone therapy is initiated

Brahmer JR, et al. American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018

4.1.2 Hyperthyroidism

Definition: Suppressed TSH and high normal or elevated FT4 and/or triiodothyronine

Diagnostic work-up

- Monitor TSH, FT4 every 4-6 weeks from the start of therapy or as needed for case detection in symptomatic patients
- Consider TSH receptor antibodies if there are clinical features and suspicion of Grave disease (eg, ophthalmopathy)
- Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch transition to hypothyroidism in patients with thyroiditis and hyperthyroidism

Grading	Management
G1: Asymptomatic or mild symptoms	Can continue ICPi with close follow-up and monitoring of TSH, FT4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism (see below) or hypothyroidism (see 4.1.1)
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until symptoms return to baseline Consider endocrine consultation β-Blocker (eg, atenolol, propranolol) for symptomatic relief Hydration and supportive care Corticosteroids are not usually required to shorten duration For persistent hyperthyroidism (> 6 weeks) or clinical suspicion, work-up for Graves disease (TSI or TRAb) and consider thionamide (methimazole or PTU) Refer to endocrinology for Graves disease
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate therapy Endocrine consultation β-Blocker (eg, atenolol, propranolol) for symptomatic relief For severe symptoms or concern for thyroid storm, hospitalize patient and

Brahmer JR, et al. American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018

8.6 Immune thrombocytopenia

Definition: An autoimmune disorder characterized by immunologic destruction of otherwise normal platelets

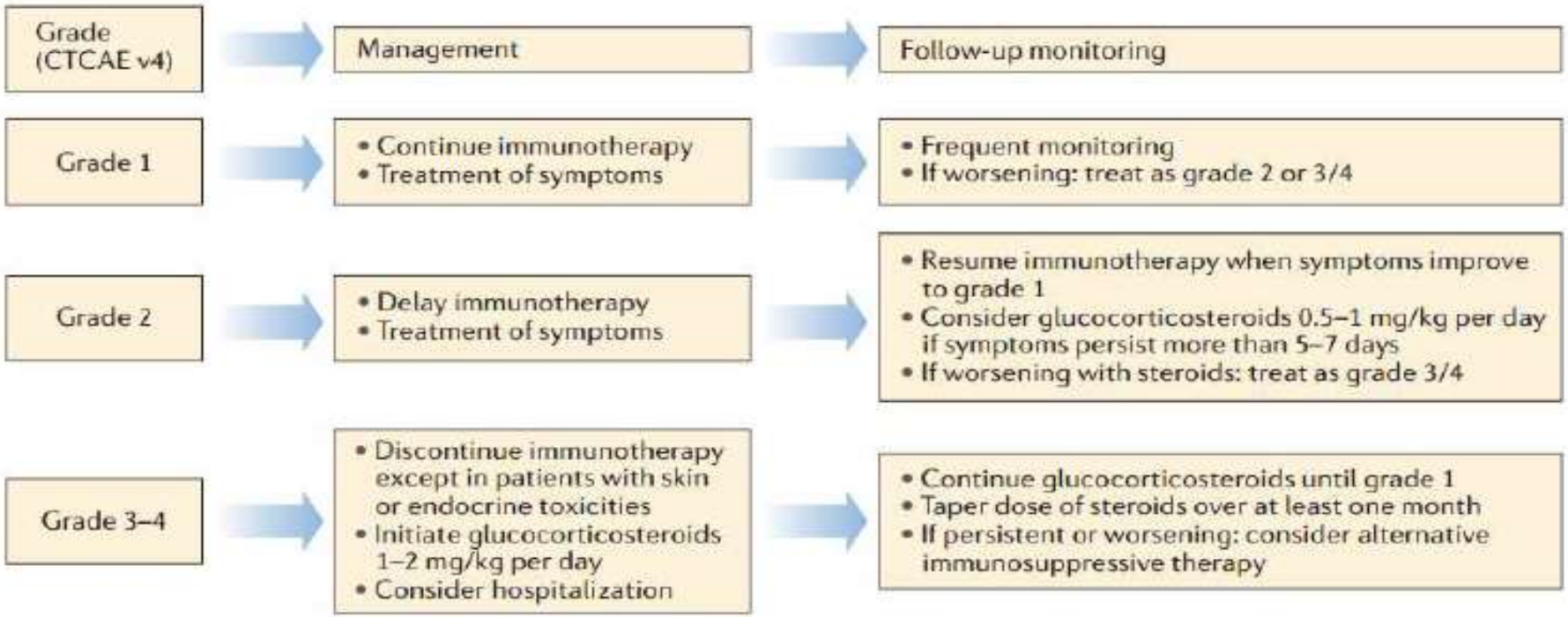
Diagnostic work-up

- History and physical examination (special attention for lymphocyte-depleting therapy, such as fludarabine, ATG, corticosteroids, cytotoxic therapy)
- Family history of autoimmunity or personal history of autoimmune disease
- History of viral illness
- CBC
- Peripheral blood smear, reticulocyte count
- Bone marrow evaluation only if abnormalities in the above test results and further investigation is necessary for a diagnosis
- Patients with newly diagnosed immune thrombocytopenia should undergo testing for HIV, hepatitis C virus, hepatitis B virus, and *Helicobacter pylori*
- Direct antigen test should be checked to rule out concurrent Evan syndrome
- Nutritional evaluation
- Bone marrow evaluation if other cell lines affected and concern for aplastic anemia

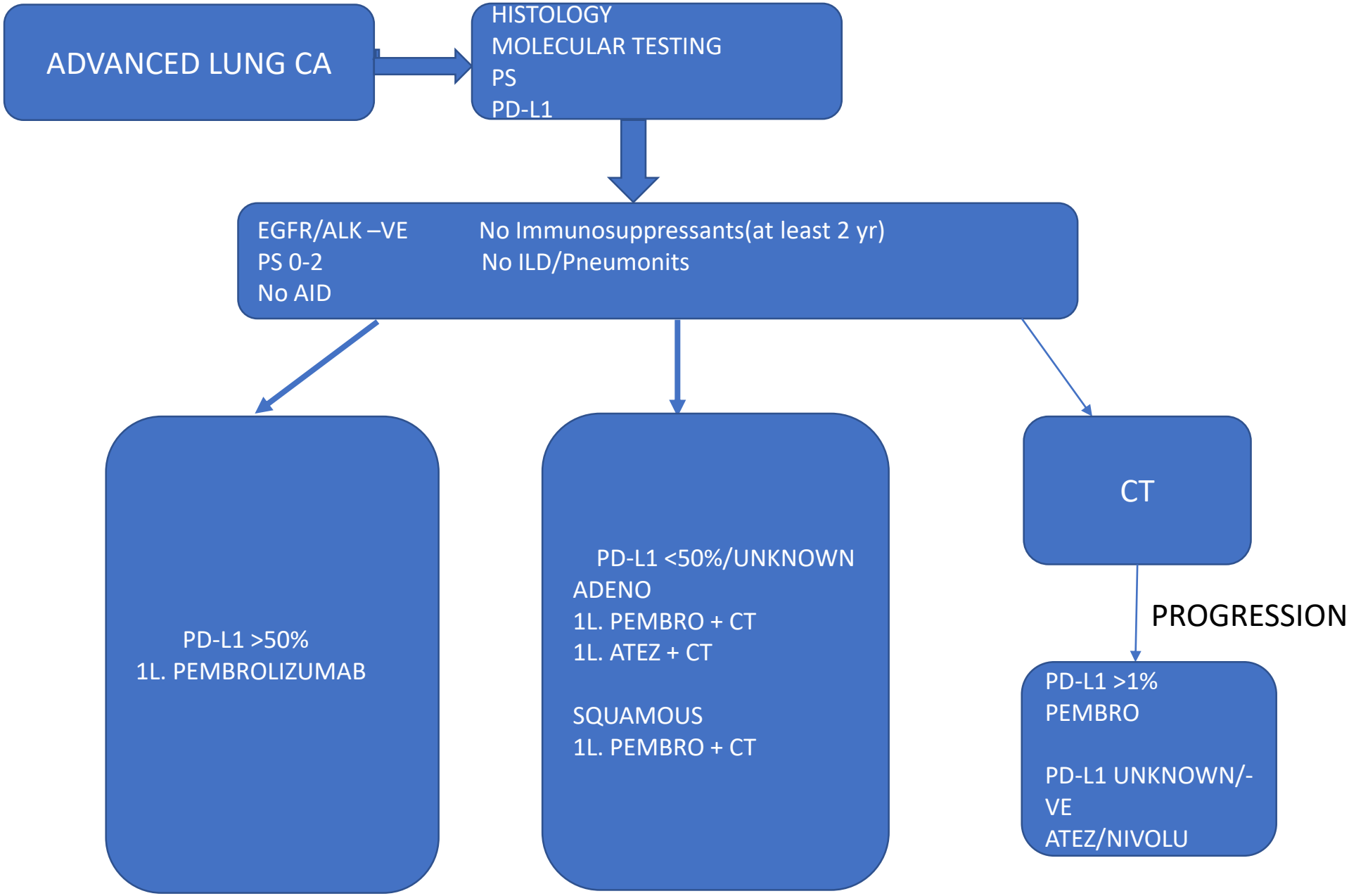
Grading	Management
G1: Platelet count < 100/μL	Continue ICPi with close clinical follow up and laboratory evaluation
G2: Platelet count < 75/μL	Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1 Administer prednisone 1 mg/kg/d (dosage range, 0.5-2 mg/kg/d) orally for 2-4 weeks after which time this medication should be tapered over 4-6 weeks to the lowest effective dose IVIG may be used in conjunction with corticosteroids if a more-rapid increase in platelet count is required.
G3: Platelet count < 50/μL	Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1
G4: Platelet count < 25/μL	Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue treatment IVIG used with corticosteroids when a more-rapid increase in platelet count is required If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary If previous treatment with corticosteroids and/or IVIG unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more-potent immunosuppression (From American Society of Hematology guideline on immune thrombocytopenia[97]; consult for further details)

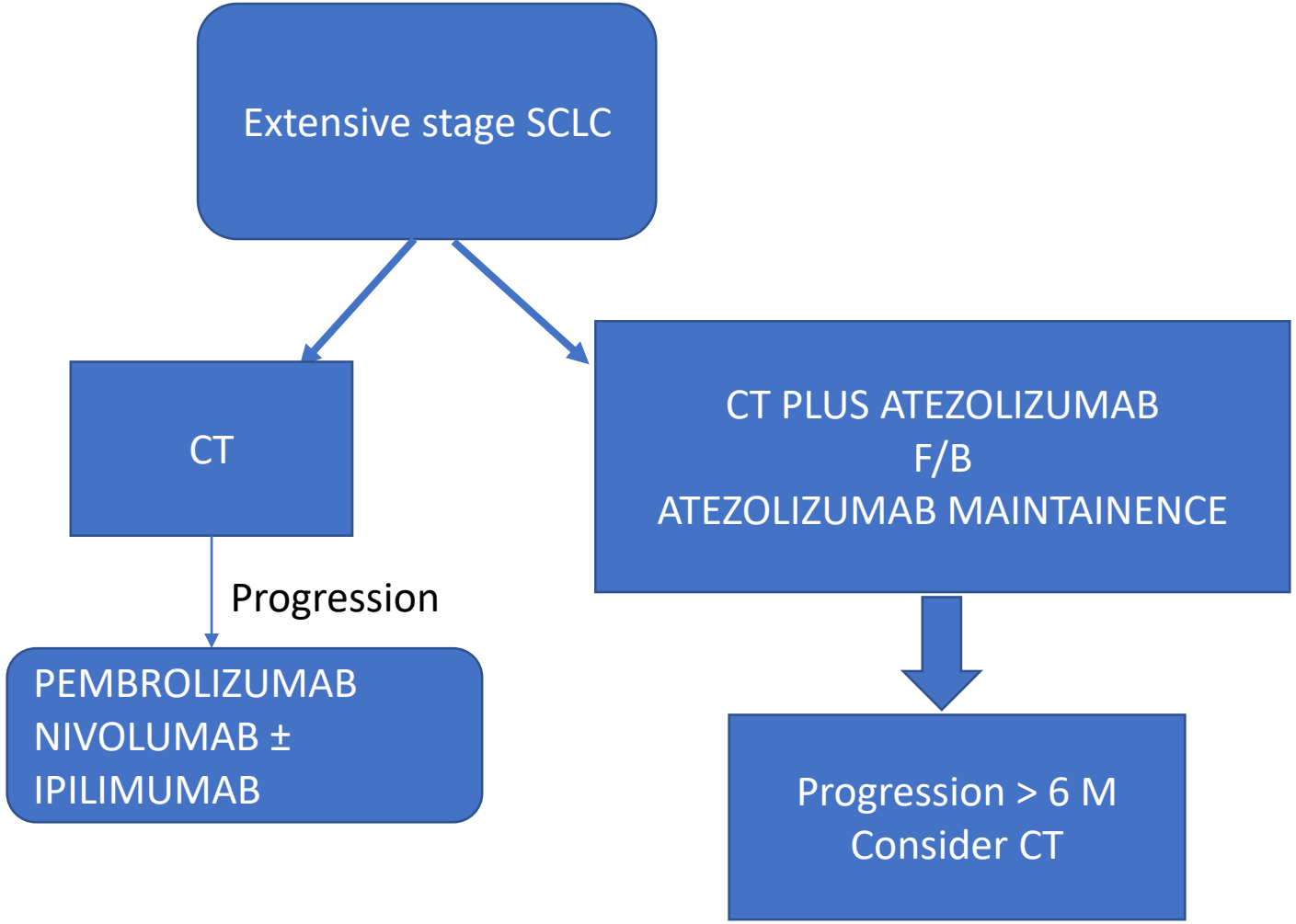
Brahmer JR, et al. American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018

Toxicities (ICPis)



Celine Boutros et al; Nat Rev Clin Oncol vol 13, 2016


ADVANCED LUNG CA
HISTOLOGY
MOLECULAR TESTING
PS
PD-L1
EGFR/ALK –VE
PS 0-2
No AID
No Immunosuppressants(at least 2 yr)
No ILD/Pneumonits
PD-L1 >50%
1L. PEMBROLIZUMAB
PD-L1 <50%/UNKNOWN
ADENO
1L. PEMBRO + CT
1L. ATEZ + CT
SQUAMOUS
1L. PEMBRO + CT
CT
PROGRESSION
PD-L1 >1%
PEMBRO
PD-L1 UNKNOWN/-VE
ATEZ/NIVOLU


Extensive stage SCLC
CT
Progression
PEMBROLIZUMAB
NIVOLUMAB ±
IPILIMUMAB
CT PLUS ATEZOLIZUMAB
F/B
ATEZOLIZUMAB MAINTAINENCE
Progression > 6 M
Consider CT

PEMBROLIZUMAB	Every 3 wk	2L/dose
NIVOLUMAB	Every 2 wk	0.85L/dose
ATEZOLIZUMAB	Every 2 wk	1.1L/dose

Conclusion

ICI have provided new alternatives for treatment of advanced lung cancer

PD-L1 testing is recommended for advanced lung cancer
Predicts response to immunotherapy agents

Monotherapy and Combination therapy regimens have shown better outcomes compared to current standard of care treatments

Immune related adverse events should be screened for prior to every cycle of immunotherapy

Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater

Martin Reck, MD, PhD[1]; Delvys Rodríguez-Abreu, MD[2]; Andrew G. Robinson, MD[3]; Rina Hui, MBBS, PhD[4]; Tibor Csőszi, MD[5]; Andrea Fülöp, MD[6]; Maya Gottfried, MD[7]; Nir Peled, MD, PhD[8]; Ali Tafreshi, MD[9]; Sinead Cuffe, MD[10]; Mary O'Brien, MD[11]; Suman Rao, MD[12]; Katsuyuki Hotta, MD, PhD[13]; Kristel Vandormael, MSc[14]; Antonio Riccio, PhD[15]; Jing Yang, PhD[15]; M. Catherine Pietanza, MD[15]; and Julie R. Brahmer, MD[16]

PURPOSE In the randomized, open-label, phase III KEYNOTE-024 study, pembrolizumab significantly improved progression-free survival and overall survival (OS) compared with platinum-based chemotherapy in patients with previously untreated advanced non–small-cell lung cancer (NSCLC) with a programmed death ligand 1 tumor proportion score of 50% or greater and without *EGFR/ALK* aberrations. We report an updated OS and tolerability analysis, including analyses adjusting for potential bias introduced by crossover from chemotherapy to pembrolizumab.

PATIENTS AND METHODS Patients were randomly assigned to pembrolizumab 200 mg every 3 weeks (for up to 2 years) or investigator's choice of platinum-based chemotherapy (four to six cycles). Patients assigned to chemotherapy could cross over to pembrolizumab upon meeting eligibility criteria. The primary end point was progression-free survival; OS was an important key secondary end point. Crossover adjustment analysis was done using the following three methods: simplified two-stage method, rank-preserving structural failure time, and inverse probability of censoring weighting.

RESULTS Three hundred five patients were randomly assigned (pembrolizumab, n = 154; chemotherapy, n = 151). At data cutoff (July 10, 2017; median follow-up, 25.2 months), 73 patients in the pembrolizumab arm and 96 in the chemotherapy arm had died. Median OS was 30.0 months (95% CI, 18.3 months to not reached) with pembrolizumab and 14.2 months (95% CI, 9.8 to 19.0 months) with chemotherapy (hazard ratio, 0.63; 95% CI, 0.47 to 0.86). Eighty-two patients assigned to chemotherapy crossed over on study to receive pembrolizumab. When adjusted for crossover using the two-stage method, the hazard ratio for OS for pembrolizumab versus chemotherapy was 0.49 (95% CI, 0.34 to 0.69); results using rank-preserving structural failure time and inverse probability of censoring weighting were similar. Treatment-related grade 3 to 5 adverse events were less frequent with pembrolizumab compared with chemotherapy (31.2% *v* 53.3%, respectively).

CONCLUSION With prolonged follow-up, first-line pembrolizumab monotherapy continues to demonstrate an OS benefit over chemotherapy in patients with previously untreated, advanced NSCLC without *EGFR/ALK* aberrations, despite crossover from the control arm to pembrolizumab as subsequent therapy.