IC-ONC

Identifying Optimal Combinations of Immune-Based Therapies:

METASTATIC NSCLC

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
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IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities

Identifying Optimal Combinations of Immune-Based Therapies: Metastatic NSCLC

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PROGRAM OVERVIEW

This program will review current and emerging immunotherapies for the management of patients with advanced NSCLC.

EDUCATIONAL AUDIENCE

This activity is designed to meet the educational needs of pulmonologists, thoracic surgeons, pathologists, medical oncologists, and advanced practitioners in oncology (NP/PA/PharmD) involved in the management of patients with advanced NSCLC.

EDUCATIONAL OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Describe the anti-tumor effects of checkpoint inhibition on the pathogenesis of non-small cell lung cancer
- Apply the clinical trials data for immunotherapy regimens in advanced and metastatic NSCLC
- Examine the late stage, clinical trial data of emerging PD-1 inhibitors in the treatment of advanced non-small cell lung cancer

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NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in the care of patients with advanced NSCLC.
Credits: 1.0 ANCC Contact Hour.

CNE Accreditation Statement: Ultimate Medical Academy/Complete Conference Management (CCM) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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Dr. Sands has received consulting fees from AstraZeneca, Medtronic, Daiichi Sankyo, Blueprint Medicines, Takeda, Jazz Pharmaceuticals, and Boehringer Ingelheim.

Dr. Duma has received consulting fees from Pfizer, AstraZeneca, Bristol Myers Squibb, Neogenomics, Inivata, and Nexus.

Dr. Gubens has received consulting fees from AstraZeneca and Sanofi; his institution is also contracted for research with Amgen, Celgene, JNJ, Merck, Novartis, OncoMed, Roche, and Trizell (he serves as the study PI).

Dr. Heist has received consulting fees from Novartis, EMD Serono, and Daiichi Sankyo; her institution has also received research funds from Agios, AbbVie, Novartis, Daiichi Sankyo, Mirati, Turning Point, Corvus, and Lilly.

Dr. Kazmi has received consulting fees from Bristol Myers Squibb, Merck, Lilly, and Takeda; she has served on the speakers' bureau for Merck, Lilly, Immunomedics, Jazz, Takeda, and Eisai. She holds stock in Merck, Lilly, and Neogenomics.

Dr. Levy has received consulting fees from AstraZeneca, Pfizer, Novartis, Daiichi Sankyo, Bristol Myers Squibb, Janssen, Merck, Genentech, Eli Lilly, and Takeda.

Dr. Lisberg has received consulting fees from AstraZeneca, Bristol Myers Squibb, Leica Biosystems, Jazz Pharmaceuticals, Novocure, Pfizer, MorphoSys, Eli Lilly and Company and Oncocyte; he has also been contracted for research grants with Daiichi Sankyo, Calithera Biosciences, AstraZeneca, Dracen Pharmaceuticals, and WindMIL. Dr. Lisberg's spouse is employed by Boston Scientific and has less than 5% equity from their employer.

Dr. Liu has received consulting fees from Amgen, AstraZeneca, BeiGene, Blueprint, Bristol Myers Squibb, Daiichi Sankyo, G1 Therapeutics, Genentech, Guardant Health, Inivata, Janssen, Jazz Pharmaceuticals, Lilly, Merck, PharmaMar, Pfizer, Regeneron, and Takeda. His institution has been contracted for research with Alkermes, Bayer, Blueprint, Bristol Myers Squibb, Corvus, Debiopharm, Elevation Oncology, Genentech, Lilly, Merck, Merus, Pfizer, Rain Therapeutics, RAPT, and Turning Point Therapeutics (he serves as the study PI).

Dr. Reiss has received consulting fees from Novartis, Boehringer Ingelheim, Blueprint, Daiichi Sankyo, and EMD Serono.

Dr. Weiss has received consulting fees from Genentech, AbbVie, Azitra, Jazz Pharmaceuticals, Boehringer, and Regeneron.

CME Content Review

The content of this activity was independently peer reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.
The reviewer of this activity has nothing to disclose.

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1. Read the CME/CNE information and faculty disclosures.
2. Participate in the live virtual activity.
3. Complete the online post-test and evaluation.

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Provided by Med Learning Group

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Program Agenda

I. Tumorigenesis Primer: Immune System Dysfunction in Non–Small-Cell Lung Cancer (NSCLC)

- a. Immune surveillance processes and tumor effects
  - i. T-cell activation, proliferation, and regulation
  - ii. Tumor immune evasion and tolerance
  - iii. Function of cytotoxic T-lymphocyte-associated protein 4, programmed cell death 1 (PD-1), and PD-1 ligand 1 (PD-L1) in T-cell regulation
  - iv. ***Whiteboard animation***: depiction of the immune cellular functions and cytokine effects on tumorigenesis

II. Checkpoint Inhibitor Regimens in Treating Advanced/Metastatic NSCLC

- a. Currently available immuno-oncology treatment options
  - i. Nivolumab, ipilimumab, pembrolizumab, atezolizumab, and durvalumab
  - ii. Clinical trials overview: efficacy and safety for monotherapy and combination therapy with chemotherapy
  - iii. ***Whiteboard animation***: depiction of the complementary antitumor effects of immunotherapy and chemotherapy in NSCLC
- b. Ongoing clinical trials

III. Application of Biomarkers to Immuno-oncology Treatment

- a. Association between PD-L1 expression and clinical outcomes
  - i. PD-L1 expression measures: tumor cells, tumor proportion score
  - ii. Appropriate cutoff values for PD-L1 levels: interpretation and application
  - iii. Standardization of laboratory methods for PD-L1 testing
- b. *LKB1* mutations
- c. Tumor mutational burden: ready for prime time?
- d. Other potential biomarkers

IV. Conclusions

V. Questions and Answers

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Program Chair

Jacob Sands, MD

Physician, Dana-Farber Cancer Institute
Instructor of Medicine
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Disclosures

- Please see Program Overview for specific speaker disclosure information
- During the course of this lecture, faculty may mention the use of medications for both FDA-approved and non-approved indications

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- This educational activity is applicable for CME and CNE credits. Please complete the necessary electronic evaluation to receive credit.

Learning Objectives

- Describe the antitumor effects of checkpoint inhibition on the pathogenesis of non-small-cell lung cancer
- Apply the clinical trials data for immunotherapy regimens in advanced and metastatic NSCLC
- Examine the late-stage clinical trial data of emerging PD-1 inhibitors in the treatment of advanced non-small-cell lung cancer

Introduction of the IC-ONC Network

IC-ONC = Immunotherapy Collaborative of Oncology Networked Communities.

IC-ONC

- This program is part of the Immunotherapy Collaborative of Oncology Networked Communities (IC-ONC), a global information network in which multidisciplinary healthcare providers who are responsible for treating patients with cancer are connected via education.
- IC-ONC.org serves as the central location for educational resources and information pertinent to patients with cancer being treated with immunotherapy.
  - It is curated by global, national, and local oncology experts.
  - It provides dates and locations of upcoming live meetings.
  - It provides access to archived and enduring activities.
  - It identifies clinical articles.
  - It is a source of downloadable content and other inter-professional resources from more than 14 collaborative educational partners.
  - It provides access to our open-source immuno-oncology registry: **The Observatory**
- Its objective is to facilitate ongoing communication and collaboration among participating healthcare providers with the aim of providing optimal care for the patient with cancer.
- For more information, please visit www.ic-onc.org
- Supported by educational grants from Bristol Myers Squibb, Merck & Co., Inc., Pfizer, and Regeneron Pharmaceuticals Inc.

IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities

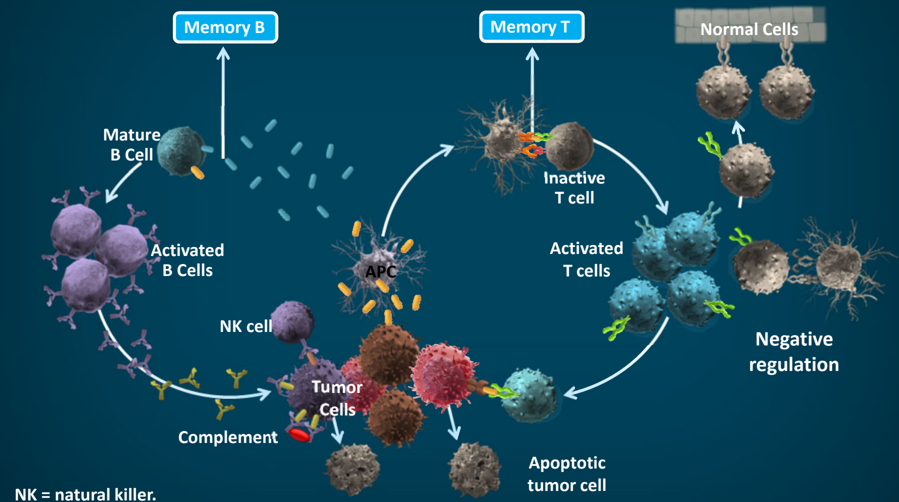
IC-ONC Observatory

- Through participation in this course, you will become a member of the IC-ONC Observatory
- Your login details will be emailed to you in the coming weeks
- For immediate information, please visit www.ic-onc.org

IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities

Tumorigenesis Primer: Immune System Dysfunction in NSCLC

Immune Response to Cancer: Very Complex Balance Between Continuous Activation and Suppression

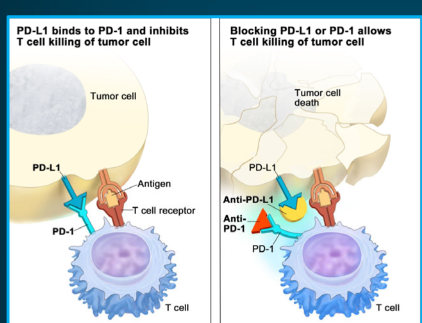


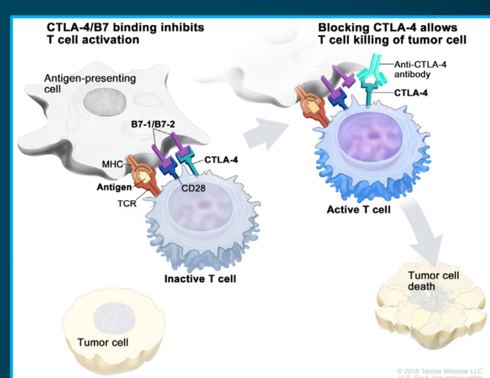
NK = natural killer.

Abbas AK, et al. *Cellular and Molecular Immunology*. 7th ed. Philadelphia, PA: Elsevier Saunders; 2012. Mellman I, et al. *Nature*. 2011;480:480-489. Boudreau JE, et al. *Mol Ther*. 2011;19:841-853. Janeway CA, et al. *Immunobiology: The Immune System in Health and Disease*. 6th ed. New York, NY: Garland Science; 2004. Pardoll DM. *Nat Rev Cancer.* 2012;12:252-264.

Interaction of PD-1 and PD-L1 With Immune System

- The interaction of PD-1 and PD-L1 downregulates the local immune response.
- This serves as a mechanism for tumors to evade a natural immune response.



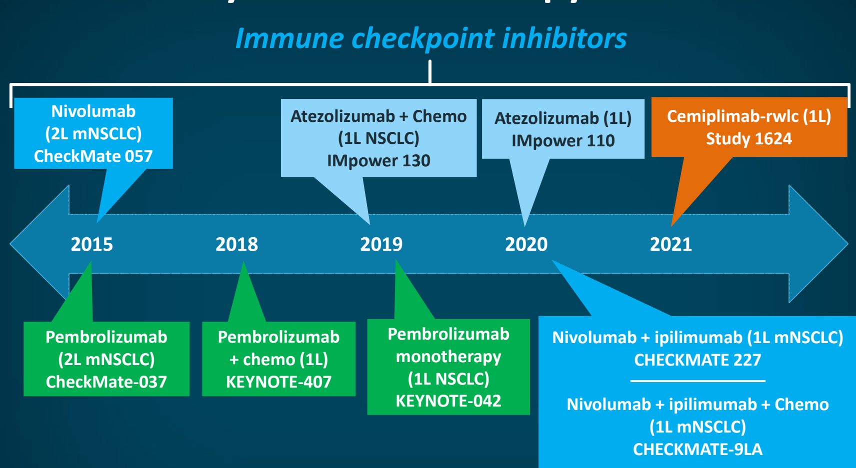


PD-1 = programmed (cell) death (protein) 1; CTLA-4 = cytotoxic T lymphocyte antigen 4; MHC = major histocompatibility complex; TCR = T cell receptor.

National Cancer Institute (NCI). Immune checkpoint inhibitor. (www.cancer.gov/publications/dictionaries/cancer-terms/def/immune-checkpoint-inhibitor) Accessed 5/10/2021.

Checkpoint Inhibitor Regimens in Treating Advanced/Metastatic NSCLC

History of Immunotherapy in NSCLC



NSCLC = non-small-cell lung cancer; mNSCLC = metastatic NSCLC; 1L = first-line; 2L = second-line; C/chemo = chemotherapy.

US Food and Drug Administration (FDA) press releases: (www.cancer.gov/news-events/cancer-currents-blog/2015/fda-opdivo); (www.cancer.gov/news-events/cancer-currents-blog/2015/pembrolizumab-nsclc); (https://tinyurl.com/3bhr7deu); (https://tinyurl.com/wz2vdwnt); (https://tinyurl.com/hyn3nbe9); (https://tinyurl.com/wd2rfr8); (www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-nivolumab-plus-ipilimumab-first-line-mnsclc-pd-l1-tumor-expression-1); (https://tinyurl.com/462nm9vs); (www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-cemiplimab-rwlc-non-small-cell-lung-cancer-high-pd-l1-expression).

Immunotherapy in the Second-Line Setting

	ORR	DoR (95% CI)	Median OS		1-yr OS	2-yr OS
CheckMate 017[1,2]—squamous						
Nivo, 3 mg/kg	20%	NR (2.9–20.5+)	9.2 mos	HR = 0.59 *P* <.001	42%	23%
Doc, 75 mg/m^2	9%	8.4 mos (1.4–15.2+)	6.0 mos		24%	8%
CheckMate 057[2,3]—nonsquamous						
Nivo, 3 mg /kg	19%	17.2 mos (1.8–22.6+)	12.2 mos	HR = 0.73 *P*= .002	51%	29%
Doc, 75 mg/m^2	12%	5.6 mos (1.2–15.2+)	9.4 mos		39%	16%
KEYNOTE-010[4] —all histologies, only PD-L1 tumors + ≥1% tumor cells staining positive						
Pembro, 2 mg/kg	18%	NR	10.4 mos	HR = 0.71 *P*= .0008	43.2%	Not reported
Doc, 75 mg/m^2	9%	6 mos	8.5 mos		34.6%	
OAK[5]—all histologies						**18-mo OS**
Atez, 1200 mg	14%	16.3 mos	13.8 mos	HR = 0.73 *P*= .0003	55%	40%
Doc, 75 mg/m^2	13%	6.2 mos	9.6 mos		41%	27%

ORR = overall/objective response rate; DoR = duration of response; CI = confidence interval; mo(s) = month(s); OS = overall survival; HR = hazard ratio; NR = not reached; Nivo = nivolumab; Doc = docetaxel; Pembro/Pemb = pembrolizumab; Atez = atezolizumab; yr = year.

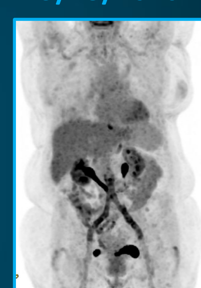
1. Brahmer J, et al. *N Engl J Med*. 2015;373:123-135. 2. Horn L, et al. J Clin Oncol. 2017;35:3924-3933. 3. Borghaei H, et al. *N Engl J Med*. 2015;373:1627-1639. 4. Herbst RS, et al. *Lancet*. 2016;387:1540-1550. 5. Rittmeyer A, et al. *Lancet*. 2017;389:255-265.

Case Study 1: Second-Line Pembrolizumab

- 78-year-old woman with adenocarcinoma of lung on second-line pembrolizumab 5/4/2016–8/21/2018
- She experienced durable response for years after stopping pembrolizumab

5/26/2015

9/23/2020



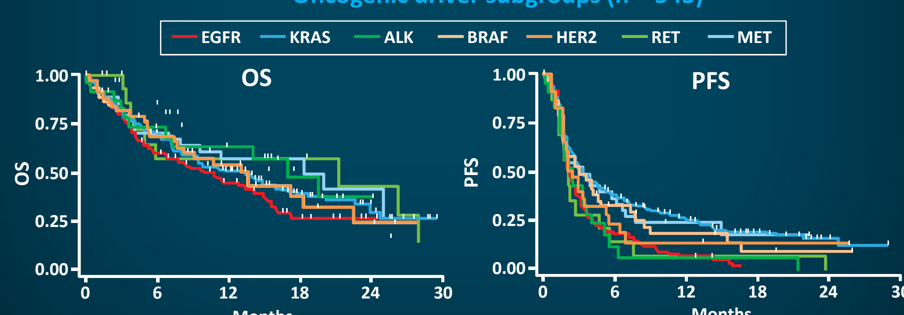
Dana-Farber Cancer Institute

First-Line Trials

Genomic Testing is Important

- Genomic testing is an important part of initial workup and should be completed before initiating immune checkpoint inhibitor (ICI) therapy
- Initiating targeted treatment after treatment with ICI may increase risk of toxicities (ie, the risk of pneumonitis risk is much higher with osimertinib

Oncogenic driver subgroups (n = 543)

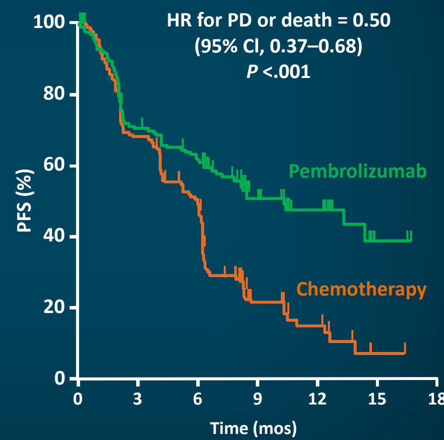


PFS = progression-free survival.

Mazieres J , et al. *Ann Oncol.* 2019;30:1321-1328.

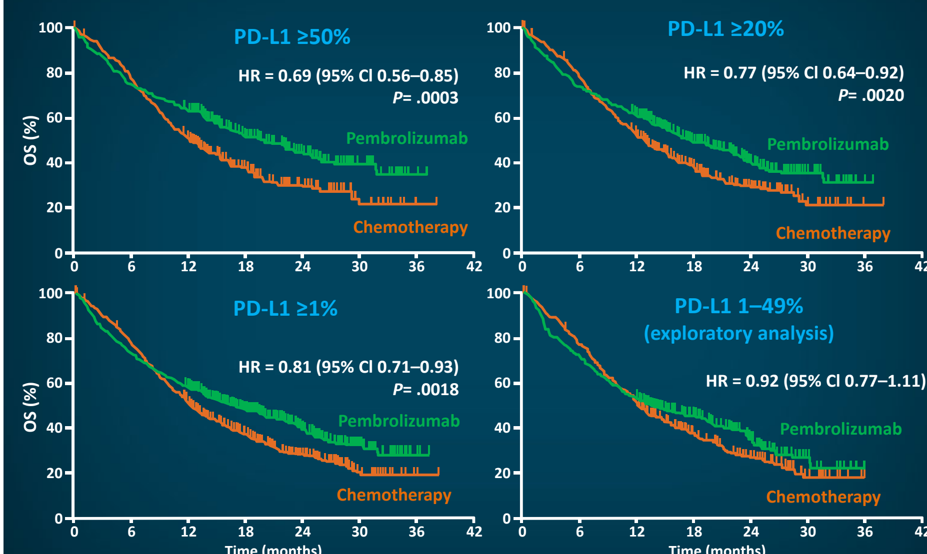
Keynote-024: Pembrolizumab as Single Agent

- Randomized 305 patients with advanced NSCLC with PD-L1 expression >50%
  - Chemotherapy
  - Pembrolizumab (single agent)
- Median PFS
  - Chemotherapy = 6.0 mos
  - Pembrolizumab = 10.3 mos
- Response rate
  - Chemotherapy = 27.8%
  - Pembrolizumab = 44.8%



Reck M, et al. *N Engl J Med.* 2016;375:1823-1833.

Keynote-042: Pembrolizumab as Single Agent

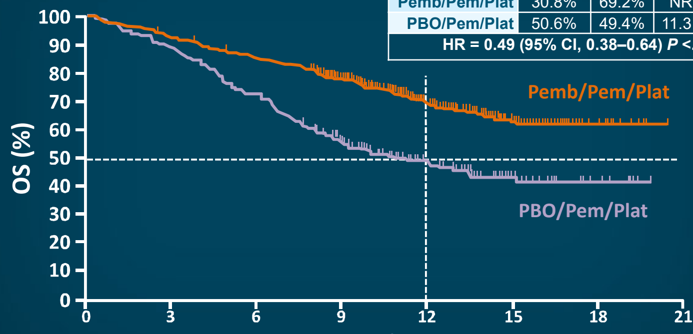


Mok TSK, et al. *Lancet.* 2019;393:1819-1830.

KEYNOTE-189: OS

Non-squamous NSCLC, ITT

PD-L1 expression of ≥1%	Events	12-mo OS	mOS, mos (95% CI)
Pemb/Pem/Plat	30.8%	69.2%	NR (NE–NE)
PBO/Pem/Plat	50.6%	49.4%	11.3 (8.7–15.1)
HR = 0.49 (95% CI, 0.38–0.64) *P* <.001			



No. at risk	0	3	6	9	12	15	18	21
Pemb/Pem/Plat	410	377	347	278	163	71	18	0
PBO/Pem/Plat	206	183	149	104	59	25	8	0

PBO = placebo; mOS = median OS; NE = not estimable.

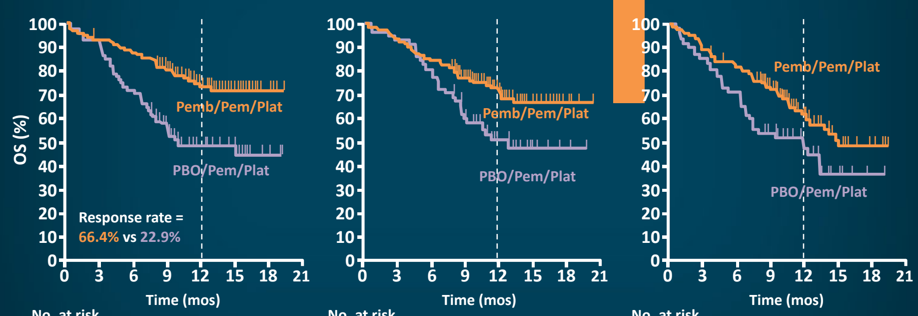
Gandhi L, et al. *N Engl J Med*. 2018;378:2078-2092. Gandhi L, et al. *Cancer Res*. 2018;78(13 suppl): abstract CT075.

KEYNOTE-189: OS by Tumor Proportion Score

TPS ≥50%	Evts	OS (95% CI) mOS	1-yr	2-yr
Pemb/Pem/Plat	43.9%	NR (20.4–NR)	73.3%	51.9%
PBO/Pem/Plat	60.0%	10.1 mos (7.5–NR)	48.6%	39.4%
HR = 0.59 (95% CI, 0.39–0.88)				

TPS 1–49%	Evts	OS (95% CI) mOS	1-yr	2-yr
Pemb/Pem/Plat	52.3%	21.8 mos (17.7–25.9)	71.7%	44.3%
PBO/Pem/Plat	69.0%	12.1 mos (8.7–19.4)	50.0%	33.0%
HR = 0.62 (95% CI, 0.42–0.92)				

TPS <1%	Evts	OS (95% CI) mOS	1-yr	2-yr
Pemb/Pem/Plat	59.1%	17.2 mos (13.8–22.8)	63.4%	38.5%
PBO/Pem/Plat	81.0%	10.2 mos (7.0–13.5)	47.6%	15.5%
HR = 0.52 (95% CI, 0.36–0.74)				



No. at risk	0	3	6	9	12	15	18	21
TPS ≥50% Pemb/P/P	132	122	114	96	56	25	6	0
TPS ≥50% PBO/P/P	70	64	50	35	19	13	4	0
TPS 1–49% Pemb/P/P	128	119	108	84	52	21	5	0
TPS 1–49% PBO/P/P	58	54	47	32	17	5	2	0
TPS <1% Pemb/P/P	127	113	104	79	42	20	6	0
TPS <1% PBO/P/P	63	54	45	32	21	6	1	0

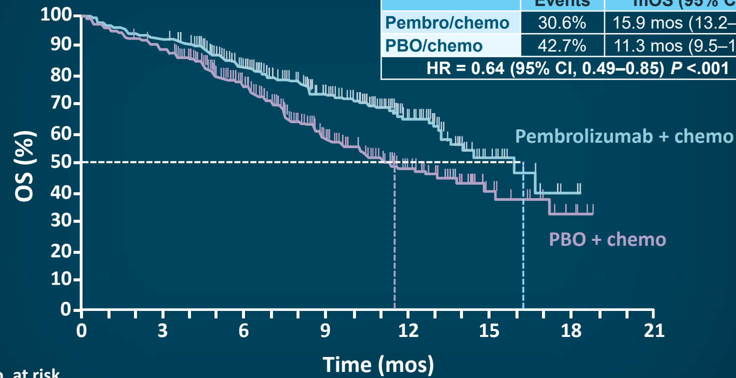
TPS = tumor proportion score; Evts = events; Pemb/P/P = pembrolizumab/pemetrexed/platinum; PBO/P/P = placebo/pemetrexed/platinum.

Gandhi L et al. *N Engl J Med*. 2018;378:2078-2092. Gadgeel S, et al. *J Clin Oncol*. 2020;38:1505-1517.

KEYNOTE-407: Squamous NSCLC

OS in second interim analysis (IA2)—ITT

Median OS		
	Events	mOS (95% CI)
Pembro/chemo	30.6%	15.9 mos (13.2–NR)
PBO/chemo	42.7%	11.3 mos (9.5–14.8)
HR = 0.64 (95% CI, 0.49–0.85) *P* <.001		



No. at risk								
Pembro + chemo	278	256	188	124	62	17	2	0
PBO + chemo	281	246	175	93	45	16	4	0

mOS = median OS.

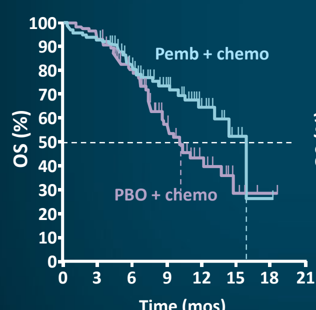
Paz-Ares L, et al. *N Engl J Med*. 2018;379:2040-2051 plus supplement.

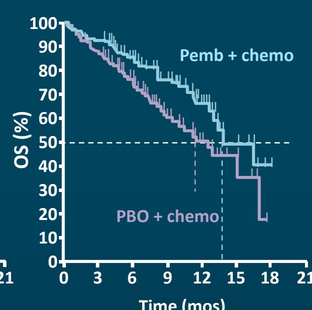
KEYNOTE-407: OS by TPS

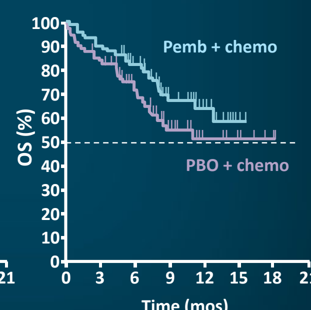
TPS <1%			
	Events	mOS (95% CI)	1-yr OS
Pemb/ chemo	30.5%	15.9 mos (13.1–NE)	64.2%
PBO/ chemo	44.4%	10.2 mos (8.6–13.8)	43.3%
HR = 0.61 (95% CI, 0.38–0.98)			

TPS 1–49%			
	Events	mOS (95% CI)	1-yr OS
Pemb/ chemo	30.1%	14.0 mos (12.8–NE)	65.9%
PBO/ chemo	43.3%	11.6 mos (8.9–17.2)	50.0%
HR = 0.57 (95% CI, 0.36–0.90)			

TPS ≥50%			
	Events	mOS (95% CI)	1-yr OS
Pemb/ chemo	31.5%	NR (11.3–NE)	63.4%
PBO/ chemo	41.1%	NR (7.4–NE)	51.0%
HR = 0.64 (95% CI, 0.37–1.10)			







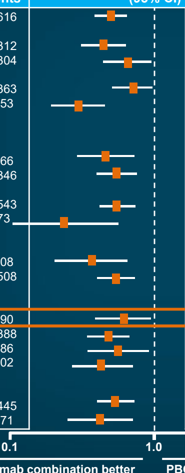
Choice of taxane: paclitaxel (HR = 0.67) or nab-paclitaxel (HR = 0.59)

Paz-Ares LG, et al. *N Engl J Med*. 2018;379:2040-2051 and supplement. Paz-Ares LG, et al. *J Clin Oncol*. 2018;36:105.

First-Line Pembrolizumab + Chemotherapy

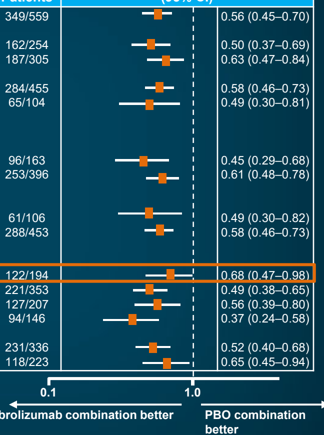
Subgroup analysis of OS (KEYNOTE-189)

Subgroup	Events/ Patients	HR for death (95% CI)
Overall	235/616	0.49 (0.38–0.64)
Age		
<65 years	133/312	0.43 (0.31–0.61)
≥65 years	102/304	0.64 (0.43–0.95)
Sex		
Male	143/363	0.70 (0.50–0.99)
Female	92/253	0.29 (0.19–0.44)
ECOG performance-status score		
0	74/266	0.44 (0.28–0.71)
1	159/346	0.53 (0.39–0.73)
Smoking status		
Current/former	211/543	0.54 (0.41–0.71)
Never	24/73	0.23 (0.10–0.54)
Brain mets at BL		
Yes	51/108	0.36 (0.20–0.62)
No	184/508	0.53 (0.39–0.71)
PD-L1 tumor proportion score		
<1%	84/190	0.59 (0.38–0.92)
≥1%	135/388	0.47 (0.34–0.66)
1–49%	65/186	0.55 (0.34–0.90)
≥50%	70/202	0.42 (0.26–0.68)
Platinum-based drug		
Carboplatin	176/445	0.52 (0.39–0.71)
Cisplatin	59/171	0.41 (0.24–0.69)



Subgroup analysis of PFS (KEYNOTE-407)

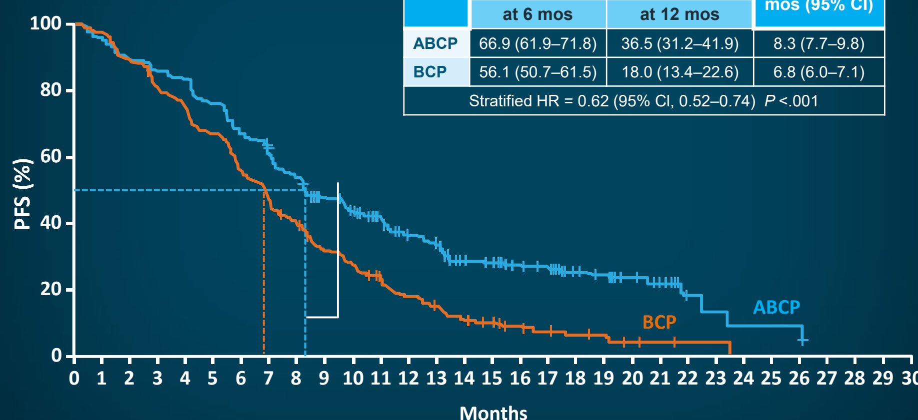
Subgroup	Events/ Patients	HR for disease progression or death (95% CI)
Overall	349/559	0.56 (0.45–0.70)
Age		
<65 years	162/254	0.50 (0.37–0.69)
≥65 years	187/305	0.63 (0.47–0.84)
Sex		
Male	284/455	0.58 (0.46–0.73)
Female	65/104	0.49 (0.30–0.81)
ECOG performance-status score		
0	96/163	0.45 (0.29–0.68)
1	253/396	0.61 (0.48–0.78)
Region of enrollment		
East Asia	61/106	0.49 (0.30–0.82)
Rest of 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)



Gandhi L, et al. *N Engl J Med.* 2018;378:2078-2092. Paz-Ares L, et al. *N Engl J Med.* 2018;379:2040-2051

IMpower150
Atezolizumab, bevacizumab, carboplatin, paclitaxel

	Rate of PFS % (95% CI)		mPFS mos (95% CI)
	at 6 mos	at 12 mos	
ABCP	66.9 (61.9–71.8)	36.5 (31.2–41.9)	8.3 (7.7–9.8)
BCP	56.1 (50.7–61.5)	18.0 (13.4–22.6)	6.8 (6.0–7.1)
Stratified HR = 0.62 (95% CI, 0.52–0.74) *P* <.001			

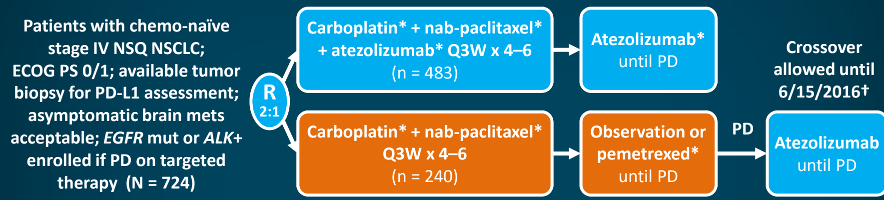


BCP = bevacizumab + carboplatin + paclitaxel; ABCP = atezolizumab + BCP.

Socinski MA, et al. *N Engl J Med*. 2018;14;378:2288-2301.

IMpower130: Carboplatin/nab-Paclitaxel + Atezolizumab in Advanced Nonsquamous NSCLC

Randomized, multicenter, open-label phase 3 study



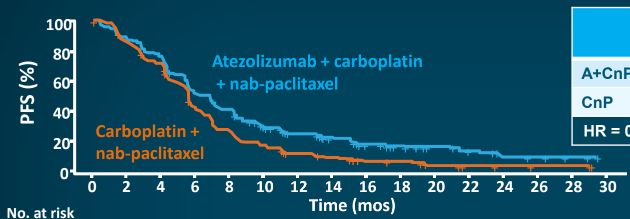
- **Primary endpoint:** PFS (investigator assessed), OS in WT EGFR/ALK patients
- **Secondary endpoints:** PFS and OS in ITT and by PD-L1 expression in ITT WT; ORR; DoR; 1-year and 2-year OS, time to deterioration in lung cancer symptoms
- **Stratification** by sex, BL liver metastases, and tumor PD-L1 expression

*Carboplatin AUC 6 Q3W, nab-paclitaxel 100 mg/m² QW, paclitaxel 200 mg/m² Q3W, atezolizumab 1200 mg Q3W, pemetrexed 500 mg/m² Q3W; †Patients in Chemo-alone arm enrolled before 6/15/2016, with confirmed PD status.

NSQ = nonsquamous; ECOG = Eastern Cooperative Oncology Group; PS = performance status; mets = metastases; mut = mutation; PD = progressive disease; PFS = progression-free survival; AUC = area under the curve; WT = wild-type; ITT = intention-to-treat (population); Q3W = every 3 weeks; QW = every week; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; BL = baseline.

West H, et al. *Lancet Oncol.* 2019;20:924-937.

IMpower130: Carboplatin/nab-Paclitaxel + Atezolizumab: PFS and OS

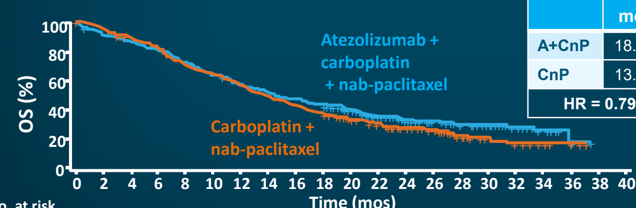


	mPFS mos (95% CI)	1-yr PFS
A+CnP	7.0 (6.2–7.3)	29.1%
CnP	5.5 (4.4–5.9)	14.1%
HR = 0.64 (95% CI, 0.54–0.77) *P* <.0001		

No. at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
A + chemo	343	294	257	172	134	88	61	44	33	24	18	12	5	4	2	0
Chemo	340	279	227	128	79	48	28	21	12	11	6	4	3	2	2	0

	mOS mos (95% CI)	OS 1-yr	OS 2-yr
A+CnP	18.6 (16.0–21.2)	63.1%	39.6%
CnP	13.9 (12.0–18.7)	55.5%	30.0%
HR = 0.79 (95% CI, 0.64–0.98) *P*= .033			



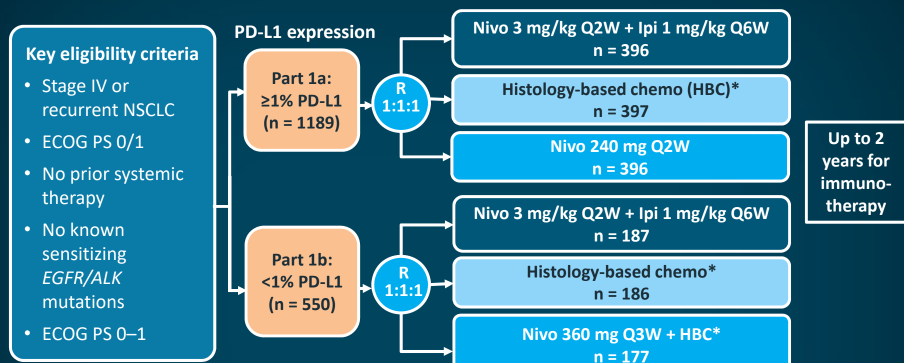
No. at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40
A + chemo	343	309	292	271	242	210	187	167	153	141	108	86	68	57	39	29	20	8	2	0	0
Chemo	340	316	293	266	29	209	184	157	138	116	85	67	49	36	22	16	11	6	2	0	0

West H, et al. *Lancet Oncol.* 2019;20:924-937. Cappuzzo F, et al. ESMO 2018: LBA53.

mPFS = median PFS; mOS = median OS.

CheckMate 227: Phase 3 Study Design



- **Co-primary endpoints:** OS in PD-L1-selected populations and PFS In TMB-selected populations
- **Stratification** by histology, ie, squamous vs nonsquamous

*NSQ: pemetrexed + cisplatin or carboplatin Q3W for ≤4 cycles with optional maintenance (pemetrexed after chemo, or Nivo + pemetrexed after Nivo + chemo); SQ: gemcitabine + cisplatin or carboplatin Q3W for ≤4 cycles.

Ipi = ipilimumab; SQ = squamous; TMB = tumor mutational burden.

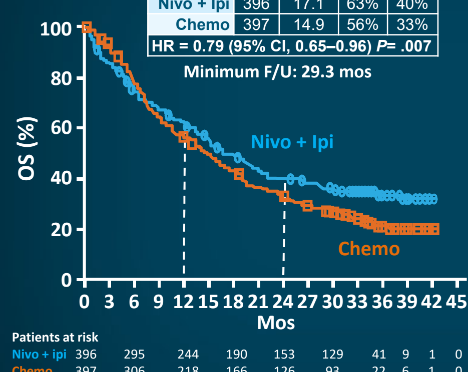
Hellmann MD, et al. *N Engl J Med*. 2018;378:2093-2104.

CheckMate 227: OS With Nivo + Ipi vs Chemo

OS in patients with tumor PD-L1 ≥1% (n = 793)

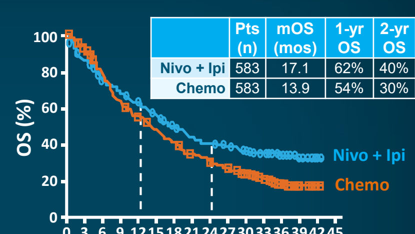
	Pts (n)	mOS (mos)	1-yr OS	2-yr OS
Nivo + Ipi	396	17.1	63%	40%
Chemo	397	14.9	56%	33%
HR = 0.79 (95% CI, 0.65–0.96) *P*= .007				

Minimum F/U: 29.3 mos



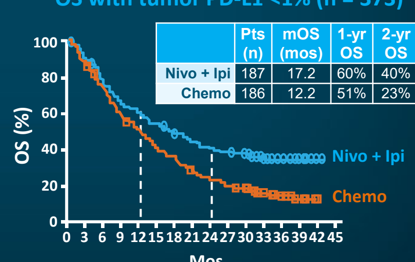
OS in all patients (N = 1166)

	Pts (n)	mOS (mos)	1-yr OS	2-yr OS
Nivo + Ipi	583	17.1	62%	40%
Chemo	583	13.9	54%	30%



OS with tumor PD-L1 <1% (n = 373)

	Pts (n)	mOS (mos)	1-yr OS	2-yr OS
Nivo + Ipi	187	17.2	60%	40%
Chemo	186	12.2	51%	23%



F/U = follow-up.

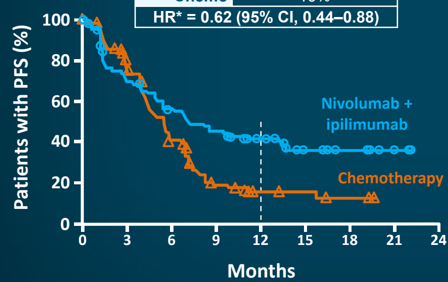
Hellman MD, et al. *N Engl J Med.* 2019;381:2020-2031.

CheckMate 227: Nivolumab plus Ipilimumab

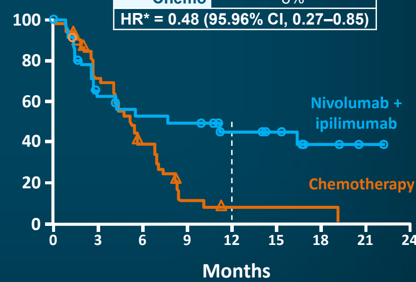
Patients with high TMB (≥10 mutations per megabase) by PD-L1 expression

Tumor PD-L1 Expression

PD-L1 expression of ≥1%	12- mo PFS
Nivo + Ipi	42%
Chemo	16%
HR* = 0.62 (95% CI, 0.44–0.88)	



PD-L1 expression of <1%	12- mo PFS
Nivo + Ipi	45%
Chemo	8%
HR* = 0.48 (95.96% CI, 0.27–0.85)	



*HR is for disease progression or death.

Hellman MD, et al. *N Engl J Med.* 2018;378:2093-2104.

CheckMate 227

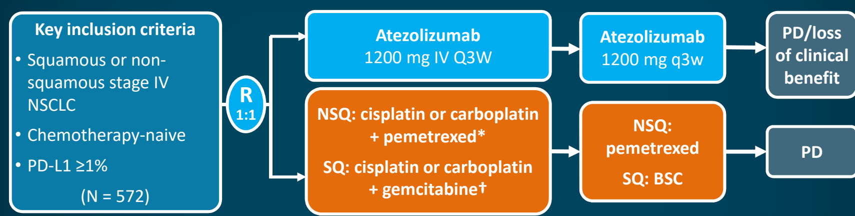
Treatment-related adverse events reported in at least 10% of patients	Nivolumab + Ipilimumab n = 576 n (%)		Nivolumab n = 391 n (%)		Chemotherapy n = 570 n (%)	
Event	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any event	433 (75.2)	180 (31.2)	251 (64.2)	74 (18.9)	460 (80.7)	206 (36.1)
Any serious event	138 (24.0)	102 (17.7)	42 (10.7)	30 (7.7)	79 (13.9)	61 (10.7)
Any event leading to discontinuation	100 (17.4)	69 (12.0)	45 (11.5)	27 (6.9)	51 (8.9)	28 (4.9)
Rash	96 (16.7)	9 (1.6)	43 (11.0)	3 (0.8)	29 (5.1)	0
Diarrhea	94 (16.3)	9 (1.6)	44 (11.3)	3 (0.8)	55 (9.6)	4 (0.7)
Pruritus	81 (14.1)	3 (0.5)	30 (7.7)	0	5 (0.9)	0
Fatigue	76 (13.2)	8 (1.4)	43 (11.0)	2 (0.5)	105 (18.4)	8 (1.4)
Decreased appetite	73 (12.7)	3 (0.5)	25 (6.4)	0	110 (19.3)	6 (1.1)
Hypothyroidism	67 (11.6)	2 (0.3)	25 (6.4)	1 (0.3)	0	0
Asthenia	56 (9.7)	7 (1.2)	29 (7.4)	2 (0.5)	72 (12.6)	5 (0.9)
Nausea	56 (9.7)	3 (0.5)	21 (5.4)	1 (0.3)	205 (36.0)	12 (2.1)
Vomiting	27 (4.7)	2 (0.3)	10 (2.6)	1 (0.3)	76 (13.3)	13 (2.3)
Constipation	23 (4.0)	0	6 (1.5)	0	86 (15.1)	2 (0.4)
Anemia	23 (4.0)	9 (1.6)	11 (2.8)	2 (0.5)	183 (32.1)	64 (11.2)
Neutrophil count decreased	4 (0.7)	0	0	0	64 (11.2)	36 (6.3)
Neutropenia	1 (0.2)	0	1 (0.3)	0	97 (17.0)	54 (9.5)

AE = adverse event; TRAE = treatment-related AE.

Hellman MD, et al. *N Engl J Med.* 2018;378:2093-2104.

IMpower110: Atezolizumab Monotherapy vs Platinum-Based Chemotherapy

Phase 3 study objective was to evaluate efficacy and safety of atezolizumab monotherapy as first-line treatment in patients with PD-L1-positive NSCLC



- **Primary endpoint:** OS (tested in hierarchical manner according to PD-L1 expression)
- **Secondary endpoints:** PFS (investigator assessed), ORR, DoR
- **Stratification** by sex, ECOG PS, PD-L1 expression, histology

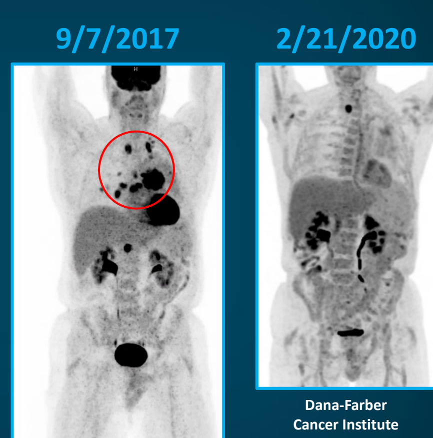
*cisplatin 75 mg/m^2 or carboplatin AUC 6 + pemetrexed 500 mg/m^2 Q3W; †cisplatin 75 mg/m^2 + gemcitabine 1250 mg/m^2 or carboplatin AUC 5 + gemcitabine 1000 mg/m^2 Q3W.

IV = intravenously; NSQ = nonsquamous; SQ = squamous; BSC = best supportive care.

Herbst RS, et al. *N Engl J Med.* 2020;383:1328-1339. Spigel D, et al. *Ann Oncol.* 2019;30(suppl 5):v915 (abstract LBA78).

Case Study 2: First-Line Pembrolizumab

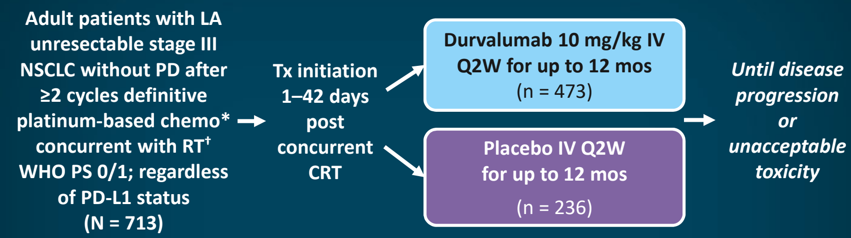
- 69-year-old man with metastatic adenocarcinoma of lung; PD-L1 = 95%
- Received pembrolizumab 9/26/2017–8/13/2019
- No evidence of disease progression >20 months after stopping treatment



PD-L1 = programmed (cell) death (protein) 1 ligand.

PACIFIC: Study Design

Randomized, double-blind, placebo-controlled phase 3 trial



- **Coprimary endpoints:** PFS by BICR per RECIST v1.1 and OS
- **Secondary endpoints:** ORR, DoR, TTDM by BICR, PFS2 by investigator, safety
- **Stratification** by age (<65 vs ≥65 years), sex, and smoking history (current/former vs never)

***Platinum-based chemo contained etoposide, vinorelbine, paclitaxel, docetaxel, vinblastine, or pemetrexed; †92% of patients received 54 Gy to 66 Gy RT dose.**

LA = locally advanced; RT = radiation therapy; WHO = World Health Organization; Tx = treatment; BICR = blinded independent central review; CRT = chemoradiotherapy; RECIST = Response Evaluation Criteria in Solid Tumors; TTDM = time to death/distant metastasis; PFS2 = time to second progression; PRO = patient-reported outcome.

Antonia SJ, et al. *N Engl J Med*. 2017;377:1919-1929. Antonia SJ, et al. *N Engl J Med*. 2018;379:2342-2350.

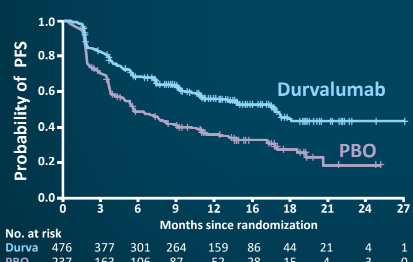
PACIFIC: Consolidation Durvalumab after CRT Improved PFS and OS

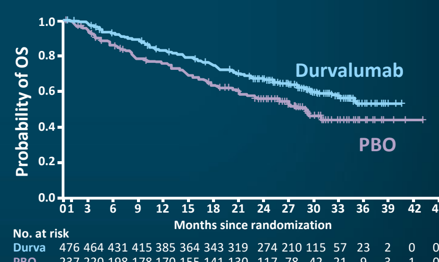
Progression-Free Survival[1]

	Events/ Total Patients	Median (95% CI) mos	12-month (95% CI) %	18-month (95% CI) %
Durva	214/476	16.8 (13.0–18.1)	55.9 (51.0–60.4)	44.2 (37.7–50.5)
PBO	157/237	5.6 (4.6–7.8)	35.3 (29.0–41.7)	27.0 (19.9–34.5)
HR (stratified for PD/death) = 0.52 (95% CI, 0.42–0.65) two-sided *P* <.001				

Overall Survival[2]

	Events/ Total Patients	Median (95% CI) mos	12-month (95% CI) %	24-month (95% CI) %
Durva	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
PBO	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)
HR (stratified for death) = 0.68 (99.73 CI, 0.47–0.997) two-sided *P* =.0025				





Durva = durvalumab.

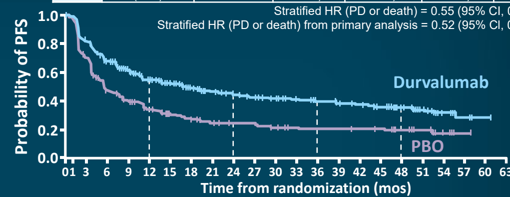
1. Antonia SJ, et al. *N Engl J Med*. 2017;377:1919-1929. 2. Antonia SJ, et al. *N Engl J Med*. 2018;379:2342-2350.

PACIFIC: Updated Durvalumab Data

- Durvalumab for ≤1 year after completing concurrent chemotherapy and radiation improves PFS and OS
- Median OS
  - Durva = 47.5 mos
  - PBO = 29.1 mos
- 48-month PFS rate
  - Durva = 35.3%
  - PBO = 19.5%

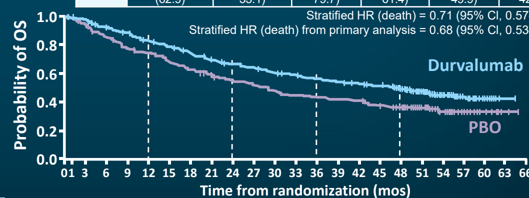
	Events/ Patients (%)	mPFS, mos (95% CI)	PFS rate (95% CI) %			
			12 mos	24 mos	36 mos	48 mos
Durva	266/476 (55.9)	17.2 (12.3–23.8)	55.3 (50.5–59.8)	44.8 (39.8–49.6)	39.8 (34.8–44.8)	35.3 (30.3–40.4)
PBO	174/237 (73.4)	5.6 (4.6–7.7)	34.4 (28.2–40.7)	24.8 (19.1–31.0)	20.5 (15.0–26.6)	19.5 (14.1–25.7)

Stratified HR (PD or death) = 0.55 (95% CI, 0.44–0.67)
Stratified HR (PD or death) from primary analysis = 0.52 (95% CI, 0.42–0.65)



	Events/ Patients (%)	mOS, mos (95% CI)	OS rate (95% CI) %			
			12 mos	24 mos	36 mos	48 mos
Durva	247/476 (51.9)	47.5 (38.4–52.6)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	56.7 (52.1–61.1)	49.6 (44.9–54.1)
PBO	149/237 (62.9)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.6 (37.1–49.9)	36.3 (30.1–42.6)

Stratified HR (death) = 0.71 (95% CI, 0.57–0.88)
Stratified HR (death) from primary analysis = 0.68 (95% CI, 0.53–0.87)



Faivre-Finn C, et al. *J Thor Oncol*. 2021;16:860-867.

Emerging Data in Monotherapy and Earlier-Stage NSCLC

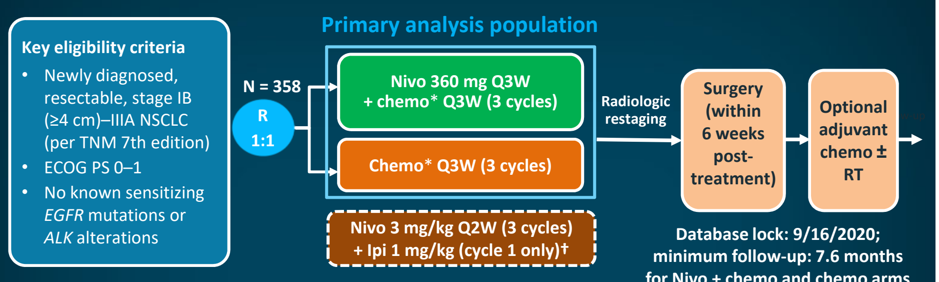
Neoadjuvant And Adjuvant Trials

Neoadjuvant trials
- LCMC3 atezolizumab
- NEOSTAR nivolumab ± ipilimumab
- NADIM II
- AEGEAN
- CheckMate 816

Adjuvant trials
- ANVIL
- KEYNOTE-091/PEARLS
- IMpower 010
- A081801 (ACCIO)

Provencio M, et al. *Lancet Oncol.* 2020;21:P1413-1422. Sands JM, et al. *Fut Med.* 2021;Apr 21: Epub ahead of print (https://doi.org/10.2217/imt-2021-0019). Accessed 5/10/2021. Clinical study reports (www.clinicaltrials.gov) for NCT02927301, NCT02259621, NCT03838159, NCT03800134, NCT02998528, NCT02595944, NCT02504372, NCT02486718, and NCT04267848.

CheckMate 816 study design



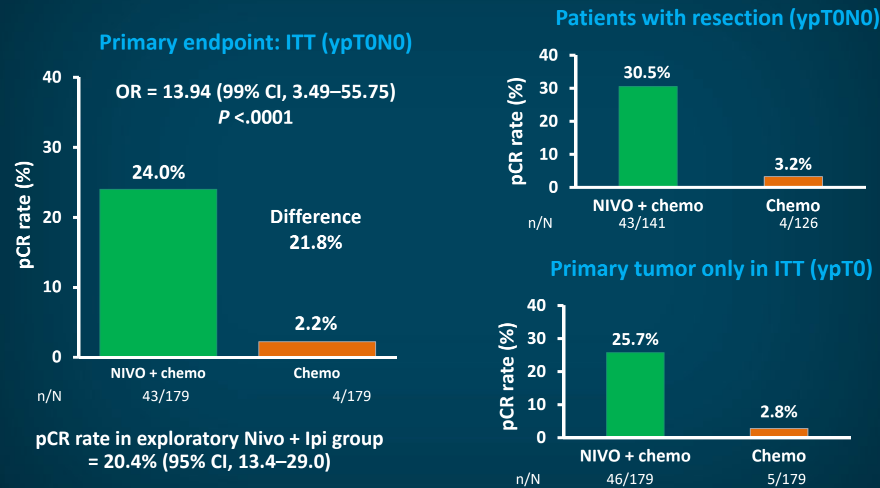
- Primary endpoints: pCR by BIPR and EFS by BICR
- Secondary endpoints: MPR by BIPR, OS, time to death or distant mets
- Exploratory endpoints: ORR by BICR, predictive biomarkers (PD-L1, TMB, ctDNA)
- Stratification by stage (IB/II vs IIIA), PD-L1 (≥1% vs <1%), and gender

*NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; eVinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin; †Randomized exploratory arm terminated early.

TNM = tumor, nodes, metastasis; Q2W = every 2 weeks; pCR = pathological complete response; BIPR = blinded independent pathological review; EFS = event-free survival; BICR = blinded independent central review; MPR = major pathological response; ORR = objective response rate; ctDNA = circulating tumor deoxyribonucleic acid.

Forde PM, et al. American Association for Cancer Research (AACR) 2021 (www.abstractsonline.com/pp8/#!/9325/presentation/5134). NCT02998528 (https://clinicaltrials.gov/ct2/show/NCT02998528). Accessed 5/10/2021.

CheckMate 816: Primary Endpoint
pCR Rate With Neoadjuvant Nivo + Chemo vs Chemo



pCR rate in exploratory Nivo + Ipi group = 20.4% (95% CI, 13.4–29.0)

OR = odds ratio.

Forde PM, et al. AACR 2021 (www.abstractsonline.com/pp8/#!/9325/presentation/5134). Accessed 5/10/2021.

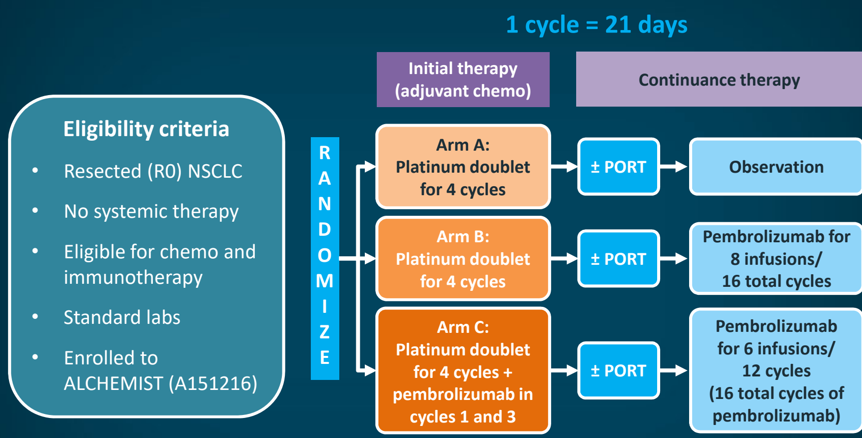
CheckMate 816: Treatment and Surgery Summary

Patients, n (%)	NIVO + chemo (n = 179)	Chemo (n = 179)
Patients receiving neoadjuvant treatment	176 (98)	176 (98)
Reason off neoadjuvant treatment		
Completed (3 cycles)	165 (94)	149 (85)
Study drug toxicity	10 (6)	12 (7)
Disease progression	1 (1)	2 (1)
Other	0	13 (7)
Patients with definitive surgery	149 (83)	135 (75)
Type of surgery		
Lobectomy	115 (77)	82 (61)
Pneumonectomy	25 (17)	34 (25)
Other	29 (19)	35 (26)
R0 resection (negative margins)	124 (83)	105 (78)
Patients with cancelled definitive surgery	28 (16)	38 (21)
Disease progression	12 (7)	17 (9)
Adverse event	2 (1)	2 (1)
Other	14 (8)	19 (11)
Patients with delayed surgery	31 (21)	24 (18)
Administrative reason	17 (11)	8 (6)
Adverse event	6 (4)	9 (7)
Other	8 (5)	7 (5)

Forde PM, et al. AACR 2021 (www.abstractsonline.com/pp8/#!/9325/presentation/5134). Accessed 5/10/2021.

40

ALCHEMIST Chemo-IO (ACCIO)

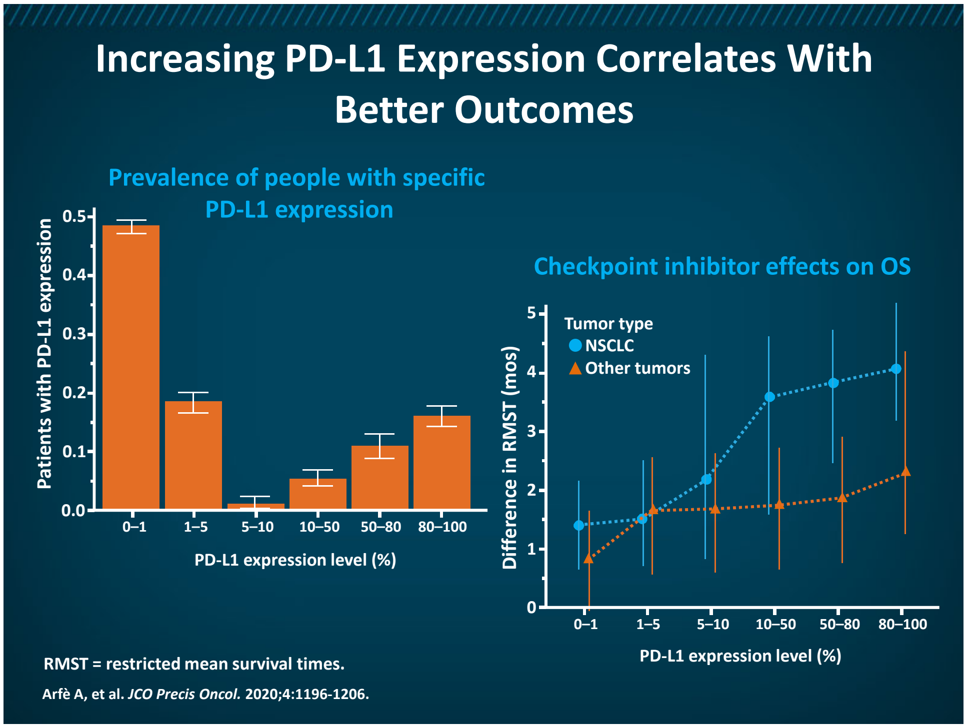


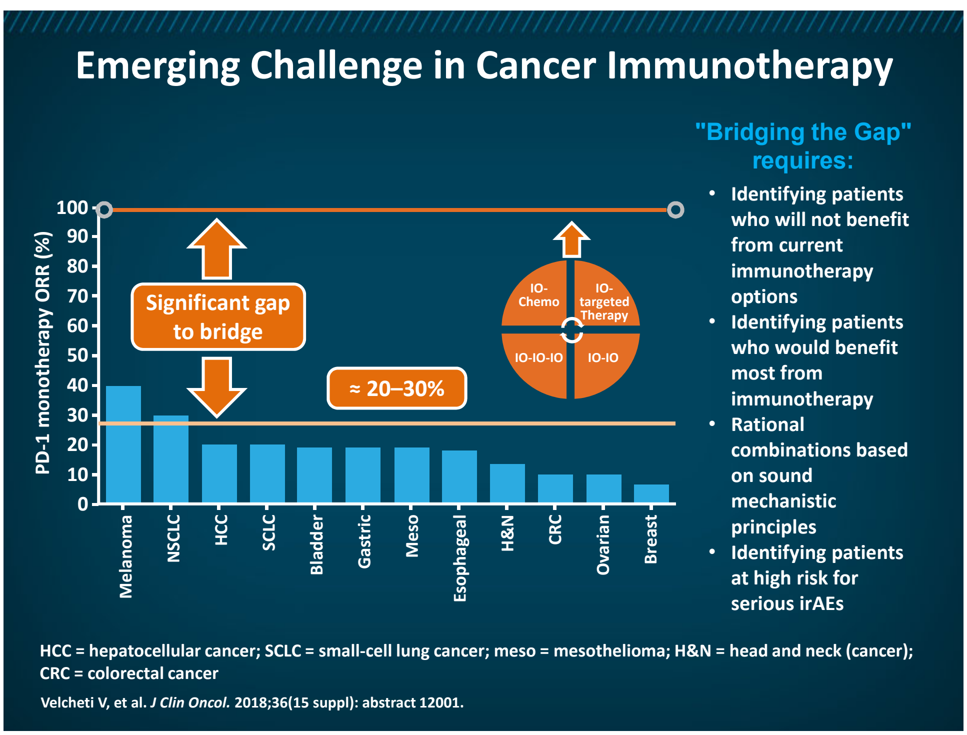
Schema of ACCIO trial includes 3 arms. Pembrolizumab dosing is every 6 weeks. Sequential and concurrent arms each include about 1 year of pembrolizumab.

ALCHEMIST = Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial; IO = immuno-oncology; PORT = postoperative radiation therapy.

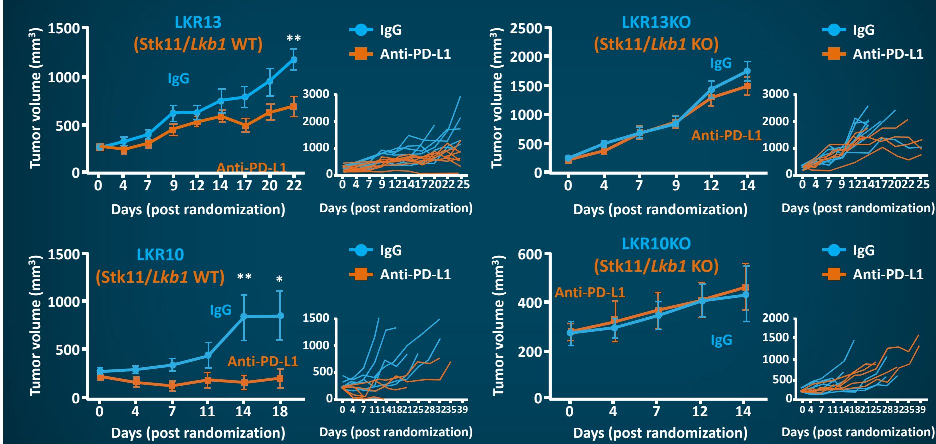
Sands JM, et al. *Fut Med.* 2021;Apr 21: Epub ahead of print (https://doi.org/10.2217/imt-2021-0019). Accessed 5/10/2021.

Using Biomarkers to Determine Immuno-oncology Treatment


Increasing PD-L1 Expression Correlates With Better Outcomes
Prevalence of people with specific PD-L1 expression
Patients with PD-L1 expression
0.5
0.4
0.3
0.2
0.1
0.0
0–1
1–5
5–10
10–50
50–80
80–100
PD-L1 expression level (%)
Checkpoint inhibitor effects on OS
Difference in RMST (mos)
5
4
3
2
1
0
Tumor type
NSCLC
Other tumors
0–1
1–5
5–10
10–50
50–80
80–100
PD-L1 expression level (%)
RMST = restricted mean survival times.
Arfè A, et al. JCO Precis Oncol. 2020;4:1196-1206.


Emerging Challenge in Cancer Immunotherapy
PD-1 monotherapy ORR (%)
100
90
80
70
60
50
40
30
20
10
0
Significant gap to bridge
≈ 20–30%
IO-Chemo
IO-targeted Therapy
IO-IO-IO
IO-IO
Melanoma
NSCLC
HCC
SCLC
Bladder
Gastric
Meso
Esophageal
H&N
CRC
Ovarian
Breast
"Bridging the Gap" requires:
• Identifying patients who will not benefit from current immunotherapy options
• Identifying patients who would benefit most from immunotherapy
• Rational combinations based on sound mechanistic principles
• Identifying patients at high risk for serious irAEs
HCC = hepatocellular cancer; SCLC = small-cell lung cancer; meso = mesothelioma; H&N = head and neck (cancer); CRC = colorectal cancer
Velcheti V, et al. J Clin Oncol. 2018;36(15 suppl): abstract 12001.

Stk11/*LKB1* Loss Promotes Resistance to PD-L1/PD-1 Blockade In Immune-Competent Models of *KRAS*-Mutant LUAC



*P ≤.05; †P ≤.01

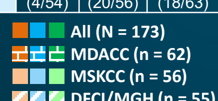
LUAC = lung adenocarcinoma; IgG = immunoglobulin G; KO = knockout.

Skoulidis F, et al. *Cancer Discov.* 2018;8:822-835.

LKB1 Mutations Associated With Worse Outcomes in LUAC Patients Treated With PD-1 Inhibitors

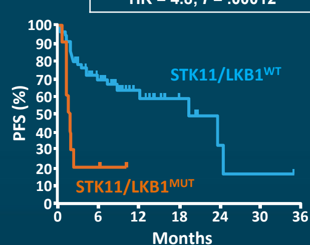
KRAS+ LUAC patients

	KL	KP	K-only
ORR	7.4% (4/54)	35.7% (20/56)	28.6% (18/63)

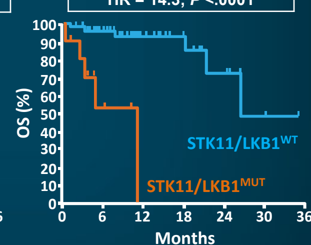


PD-L1+ LUAC patients

Group	mPFS
STK11/LKB1^{MUT}	1.7 mos
STK11/LKB1^{WT}	19.3 mos
HR = 4.8; *P*= .00012	



Group	mOS
STK11/LKB1^{MUT}	11.1 mos
STK11/LKB1^{WT}	25.6 mos
HR = 14.3; *P* <.0001	



KL = STK11/LKB1; KP = TPS3; PR = partial response; CR = complete response; BoR = best overall response; MDACC = MD Anderson Cancer Center; MSKCC = Memorial Sloan Kettering Cancer Center; DFCI/MGH = Dana-Farber Cancer Institute/Massachusetts General Hospital; mPFS = median PFS.

Skoulidis F, et al. *Cancer Discov.* 2018;8:822-835.

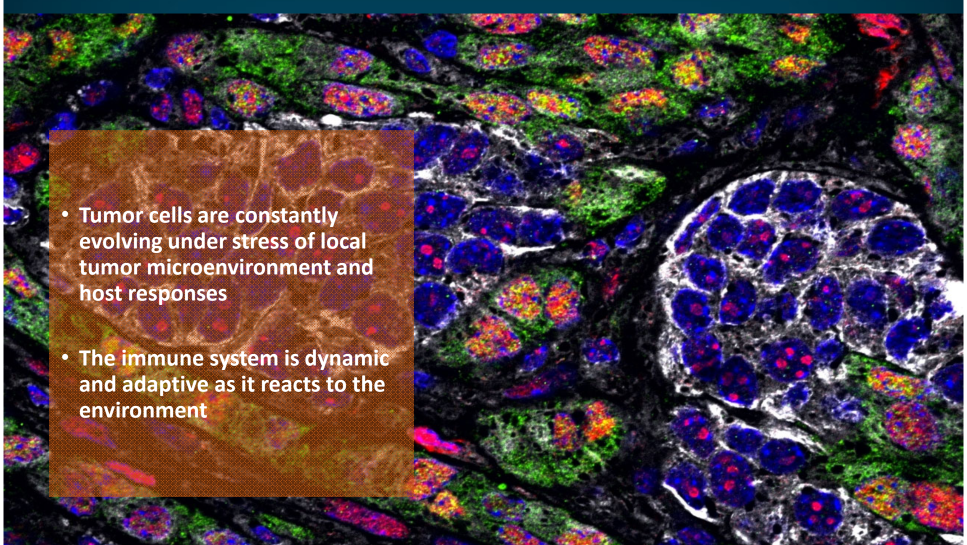
FDA-Approved and Investigational Biomarkers for IO Diagnostics

Phenotype markers	PD-L1 IHC	Topalian et al, *N Engl J Med* 2012; Herbst et al, *Nature* 2014; Garon et al, *N Engl J Med* 2015; Tumeh et al, *Nature* 2014; Weber et al, *Lancet* 2015
	TILs	Taube et al, *Clin Cancer Res* 2014; Tumeh et al, *Nature* 2014; Le et al, *N Engl J Med* 2015
	Th1/IFN-γ	Seiwert et al, ASCO 2015; Shankaran et al, ASCO 2015; Powles et al, SITC 2015; Ribas et al, ASCO 2015
	Microbiome	Vetizou et al, *Science* 2015; Sivan et al, *Science* 2015
	Other: IPRES/MDSC	Kitano et al, *Cancer Immunol Res* 2014; Hugo et al, *Cell* 2016
Genomic markers	MSI	Le et al, *N Engl J Med* 2015; Overman et al, *J Clin Oncol* 2017
	Mutational burden	Snyder et al, *N Engl J Med* 2014; Van Allen et al, *Science* 2015; Rizvi et al, *Science* 2015; Hugo et al, *Cell* 2016
	APM/IFN mut	Zaretzky et al, *N Engl J Med* 2016; Gao et al, *Cell* 2016; Shin et al, *Cancer Discov* 2017
	DNA FISH	Ansell et al, *N Engl J Med* 2014
	TCRβ clonality	Tumeh et al, *Nature* 2014; Robert et al, *Clin Cancer Res* 2014

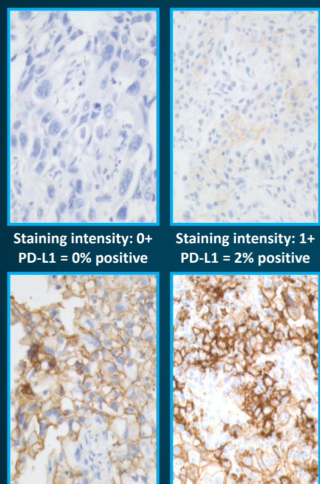
Th1 = T-helper 1 (cell);IFN = interferon; IPRES = innate anti-PD-1 resistance; MDSC = myeloid-derived suppressor cell; MSI = MS instability; APM = antigen processing and presentation machinery; FISH = fluorescence in situ hybridization.

Schalper K. ASCO symposium, 2017.

Personalized Immunotherapy: Finding a Needle in a Haystack?



The Story of PD-L1 as a Biomarker
PD-L1+ NSCLC (>50%)—KEYNOTE Studies

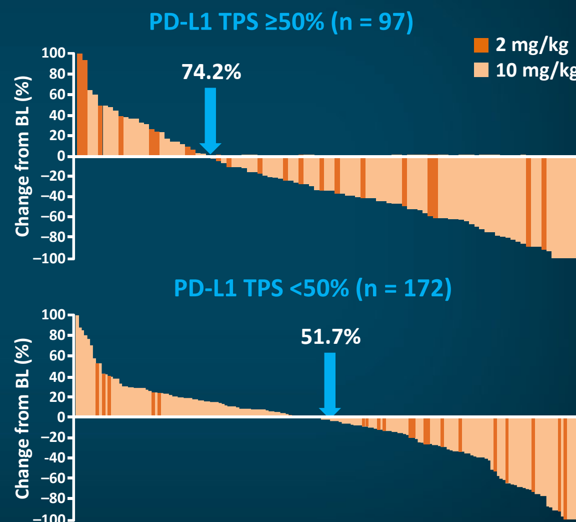


Staining intensity: 0+ PD-L1 = 0% positive

Staining intensity: 1+ PD-L1 = 2% positive

Staining intensity: 2+ PD-L1 = 100% positive

Staining intensity: 3+ PD-L1 = 100% positive

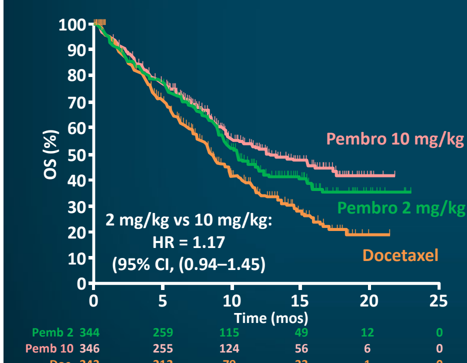


Soria JC, et al. *Eur J Cancer.* 2015;51(suppl 3):abstract 33LBA.

KEYNOTE 010: PD-L1 Status and Overall Survival

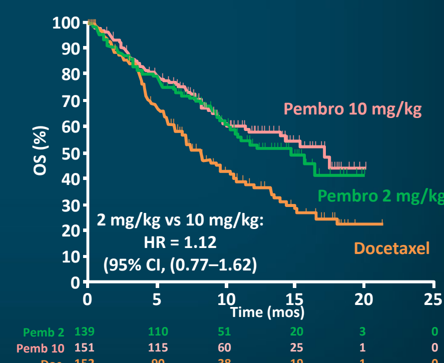
PD-L1 TPS ≥1% (total population)

Treatment arm	mOS, mos (95% CI)	OS at 1 yr	HR (95% CI)	*P*-value
Pembro 2 mg/kg	10.4 (9.4–11.9)	43.2%	0.71 (0.58–0.88)	.0008
Pembro 10 mg/kg	12.7 (10.0–17.3)	52.3%	0.61 (0.49– 0.75)	<.0001
Docetaxel	8.5 (7.5–9.8)	34.6%	—	—



PD-L1 TPS ≥50% subgroup

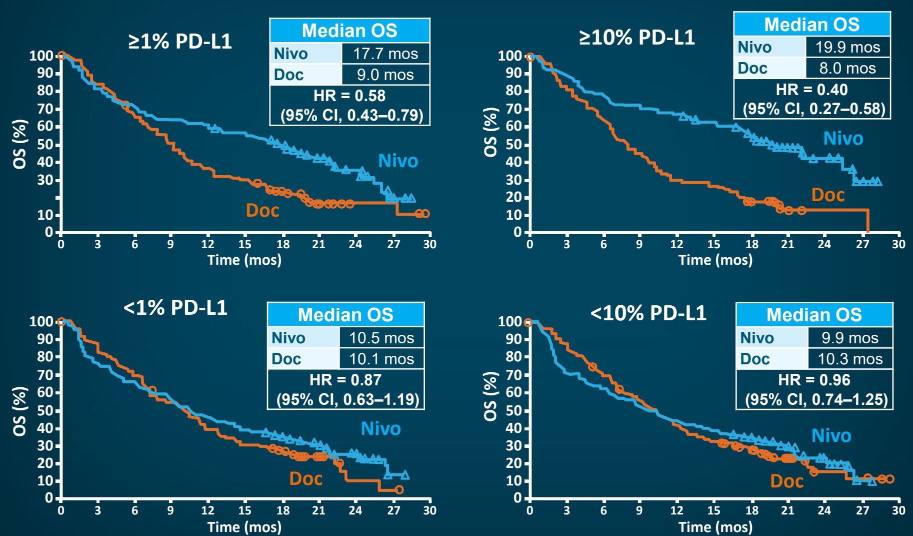
Treatment arm	mOS, mos (95% CI)	HR (95% CI)	*P*-value
Pembro 2 mg/kg	14.9 (10.4–NR)	0.54 (0.38–0.77)	.0002
Pembro 10 mg/kg	17.3 (11.8–NR)	0.50 (0.36–0.70)	<.0001
Docetaxel	8.2 (6.4–10.7)	—	—



Herbst RS, et al. *Lancet*. 2016;387:1540-1550.

Nivolumab: Survival by PD-L1 Status

OS by PD-L1 expression levels in Checkmate 057



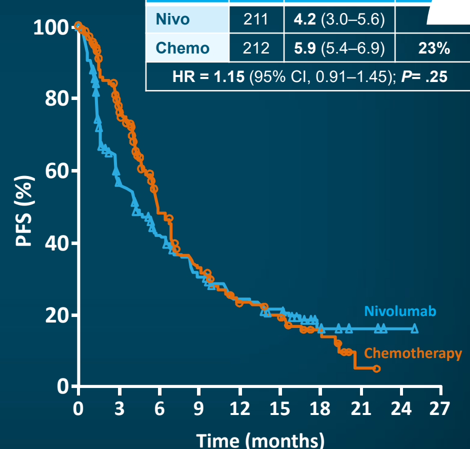
Borghaei H, et al. *N Engl J Med*. 2015;373:1627-1639 plus supplement.

CheckMate-026

Nivolumab vs chemotherapy

- PFS = 4.2 vs 5.9 mos (HR [PD/death) = 1.15, *P*= .25)
- ORR (PD-L1 ≥5%) = 26% vs 33%
- OS = 14.4 vs 13.2 mos (HR [death]= 1.02)
- No difference in patients with PD-L–expression ≥50%
- TRAE grade 3/4 = 18% vs 51%
- Exploration of novel biomarker (TMB)
- Inhomogeneities in patient populations

	Pts	mPFS (95% CI)	1-... PF...
Nivo	211	**4.2** (3.0–5.6)	
Chemo	212	**5.9** (5.4–6.9)	23%
HR = 1.15 (95% CI, 0.91–1.45); ***P*= .25**			



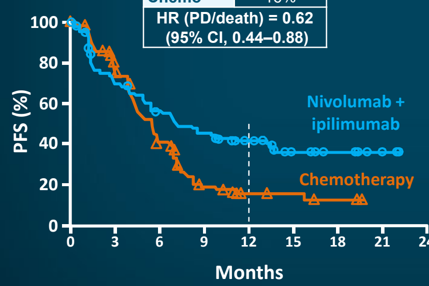
Carbone DP, et al. *N Engl J Med*. 2017;376:2415-2426.

CheckMate 227: Nivolumab + Ipilimumab

- Patients with high TMB by PD-L1 expression
- High TMB defined as >10 mutations per megabase

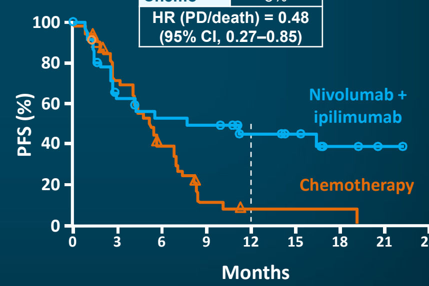
PD-L1 Expression of ≥1%

PFS at 1 year	
Nivo + Ipi	42%
Chemo	16%
HR (PD/death) = 0.62 (95% CI, 0.44–0.88)	



PD-L1 Expression of <1%

PFS at 1 year	
Nivo + Ipi	45%
Chemo	8%
HR (PD/death) = 0.48 (95% CI, 0.27–0.85)	



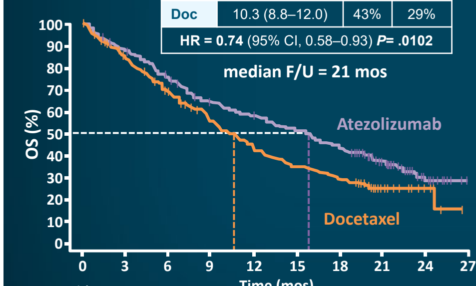
Hellmann MD, et al. *N Engl J Med.* 2018;378:2093-2104.

OAK: Atezolizumab vs Docetaxel
OS by PD-L1 Expression

PD-L1 ≥1% TC or IC
TC1/2/3 or IC1/2/3; 54% of patients

	mOS (95% CI)	1 yr	1.5 yr
Atez	15.7 (12.6–18.0)	58%	44%
Doc	10.3 (8.8–12.0)	43%	29%
HR = 0.74 (95% CI, 0.58–0.93) *P*= .0102			

median F/U = 21 mos

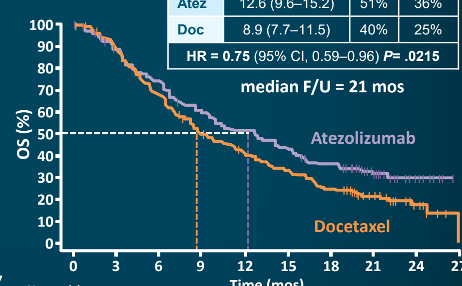


No. at risk	0	3	6	9	12	15	18	21	24	27
Atez	241	207	176	145	131	115	96	47	19	1
Doc	222	172	136	105	81	65	55	28	8	0

PD-L1 <1% TC or IC
TC0 and IC0; 45% of patients

	mOS (95% CI)	1 yr	1.5 yr
Atez	12.6 (9.6–15.2)	51%	36%
Doc	8.9 (7.7–11.5)	40%	25%
HR = 0.75 (95% CI, 0.59–0.96) *P*= .0215			

median F/U = 21 mos



No. at risk	0	3	6	9	12	15	18	21	24	27
Atez	180	152	125	100	86	64	53	17	9	0
Doc	199	161	124	89	70	54	39	19	8	0

PD-L1-expression population TC1/2/3 or IC1/2/3 = ≥1% PD-L1 on tumor cells or tumor-infiltrating immune cells.
TC = tumor cell; IC = tumor-infiltrating immune cell.

Rittmeyer A, et al. *Lancet.* 2017;389:255-265.

Challenges with PD-L1 Biomarker Evaluation When Choosing Patients for Immunotherapy

1. How different are PD-L1 IHC assays in terms of staining characteristics?
2. Can these assays be used interchangeably to determine the tumor's PD-L1 status?
3. Is PD-1 status reproducible, ie, is there spatial and temporal heterogeneity?

IHC = immunohistochemistry.

Are All PD-L1 Tests Created Equal?

Agents	Assay	Patient selection	Cut-offs used in Trials
Nivolumab	28-8	None	Tumor cells: 1%, 5%
Pembrolizumab	22C3	Tumor cells >50% 1st line, 1% 2nd line, or none with chemo	Tumor cells: 1%, 5%, 50%
Atezolizumab	SP142	None	Tumor cells: 1%, 5%, 10% Immune cells: 1%, 5%, 10%
Durvalumab	SP263	?	Tumor cells: >25%

Modified from Tsao MS. ESMO 2016 (https://cslide.ctimeetingtech.com/library/esmo/browse/search/BJX#2z9t02f). Accessed 5/13/2021.

Real-World Distribution of PD-L1 Tumor Expression by Assay Type

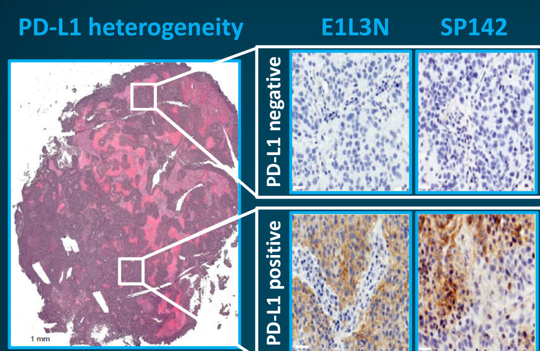
PD-L1 Biomarker IHC Assay Results (N = 1728*)

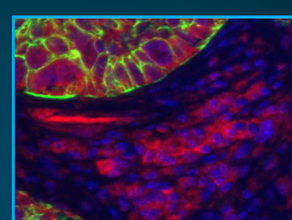
PD-L1 tumor expression, categories†	FDA-approved IHC assay, n (%)			Laboratory-developed tests, n (%) (N = 323)
	Dako 22C3 (N = 1335)	Dako 28-8 (N = 90)	Ventana SP142 (N = 75)‡	
<1%	478 (35.8)	37 (41.1)	46 (61.3)	127 (39.3)
1–49%	376 (28.2)	25 (27.8)	16 (21.3)	107 (33.1)
≥50%	481 (36.0)	28 (31.1)	13 (17.3)	89 (27.6)

*Some patients had >1 test and are represented in >1 column; †*P* <.0001 for χ^2 test comparing results across 4 assay types, and *P*= .053 for χ^2 test comparing results across 3 assay types, excluding the Ventana SP142; ‡percentage of tumor cells staining for PD-L1.

Velcheti V, et al. *J Thorac Oncol.* 2017; 12(supp 2): S1779-S1780 (abstract OA 13.02).

Tumor PD-L1 Heterogeneity





Immunofluorescence shows stroma and epithelial staining are often concordant and adjacent
Green = cytokeratin; Blue = nuclei; Red = PD-L1 (SP142)

- Heterogeneity—multiple tumors and multiple passes within a tumor
- Interval between biopsy and treatment
- Primary vs metastatic disease
- Antibody and staining conditions

Defining a positive result (cut-offs):
- Cell type expressing PD-L1 (immune cell vs tumor or both)
- Location of expression—cell surface vs intracellular vs stromal
- Intensity, percent of “positive” cells
- Distribution—patchy vs diffuse, intratumoral vs peripheral

McLaughlin J, et al. *JAMA Oncol*. 2016;2:46-54.

Distribution of PD-L1 Tumor Expression by Assay Type in Patients with Metastatic NSCLC (MNSCLC)

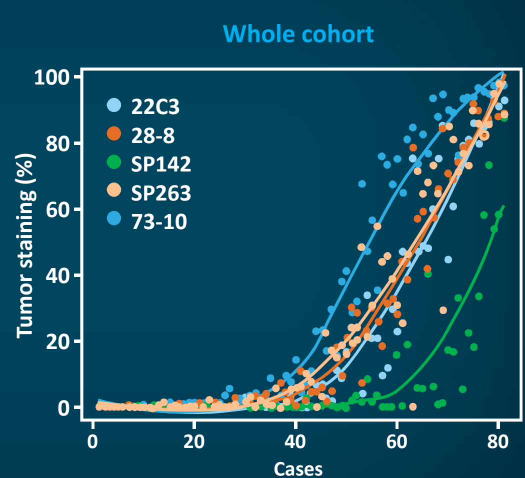
PD-L1 biomarker immunohistochemical (IHC) assay results for 1728 patients with mNSCLC whose tumors were tested from October 2015 through March 2017, by assay type*

PD-L1 tumor expression, categorized‡	FDA-approved IHC assay, n (%)			Laboratory-developed tests. n (%) (N=323)
	Dako 22C3 (N=1335)	Dako 28-8 (N=90)	Ventana SP142† (N=75)	
<1%	478 (35.8)	37 (41.1)	46 (61.3)	127 (39.3)
1-49%	376 (28.2)	25 (27.8)	16 (21.3)	107 (33.1)
≥50%	481 (36.0)	28 (31.1)	13 (17.3)	89 (27.6)

*Some patients had more than one test and are represented in more than one column.
†Ventana SP142 results represent percentage of tumor cells staining for PD-L1.
‡p<0.0001 for χ^2 test comparing results across the four assay types, and p=0.053 for χ^2 test comparing results across three assay types, excluding the Ventana SP142 assay.
FDA, Food and Drug Administration
Velcheti V, et al. *World Conference on Lung Cancer (WCLC).* 2017.

Predictive Molecular Markers in Era of Immunotherapy

- 22C3, 28-8, and SP263 show comparable staining across specimens
- SP142 has less sensitivity
- E1L3N also shows comparable staining



Tsao MS, et al. *J Thorac Oncol.* 2018;13:1302-1311. Hodgson A, et al. *Am J Surg Pathol.* 2018;42:1059-1066. Nagaria TS, et al. *J Pancreatology.* 2020;3:132-138.

Next Steps for PD-L1 Testing

PD-L1 expression

- Core needle biopsy/excisional biopsy/resected tissue
- FFPE tissue: at least 100 tumor cells
- PD-L1 IHC 22C3 pharmDx (Dako)
- Role for PD-L1 testing on cytology samples unknown

1934 patients entered screening
↓
1729 submitted samples for PD-L1 assessment
↓
1653 samples evaluable for PD-L1
↓
500 TPS ≥50% (30%) | 1153 TPS <50%

ATLAS of PD-L1 testing in NSCLC

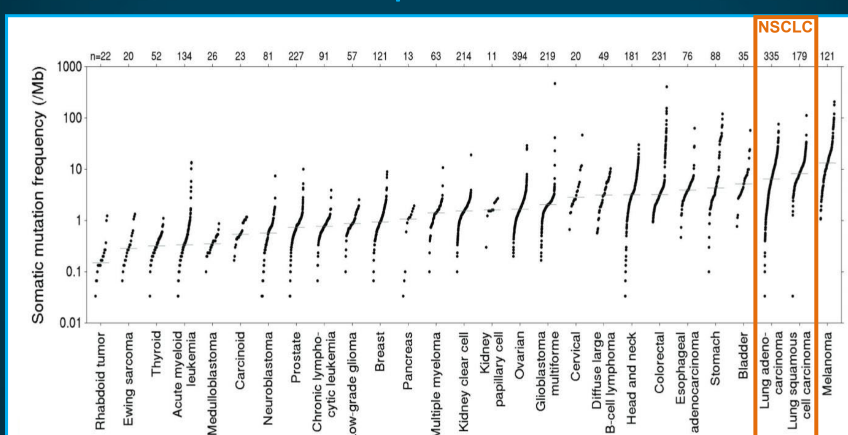
- Blueprint phase 2 project
- Validation of phase 1 assay comparability in different sample types (resection, biopsy, cytology)
- Inter-observer concordance among 20 pulmonary pathologists
- Comparability of needle biopsy vs resection sample vs cytology aspirate in same tumor

FFPE = Formalin-fixed paraffin-embedded.

Reck M, et al. *N Engl J Med.* 2016;375:1823-1833 plus supplement. Modified from Tsao MS. ESMO 2016. (https://cslide.ctimeetingtech.com/library/esmo/browse/search/BJX#2z9t02f). Accessed 5/13/2021.

Beyond PD-L1: Tumor Mutation Burden (TMB)

Somatic mutation frequencies in different tumors

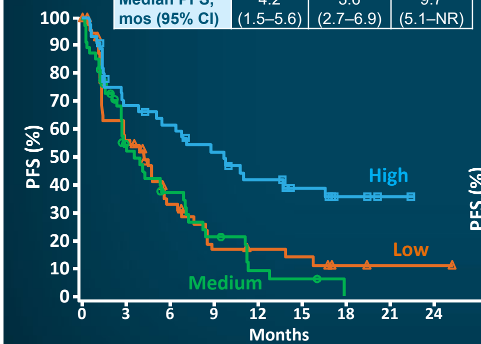


Lawrence MS, et al. *Nature.* 2013;499:214-218.

NSCLC TMB-Associated Clinical Benefit With First-Line Nivolumab

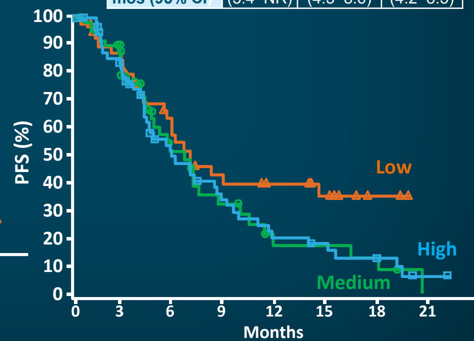
Nivolumab arm

	Tumor mutation burden		
	Low n = 62	Medium n = 49	High n = 47
Median PFS, mos (95% CI)	4.2 (1.5–5.6)	3.6 (2.7–6.9)	9.7 (5.1–NR)



Chemotherapy arm

	Tumor mutation burden		
	Low n = 41	Medium n = 53	High n = 60
Median PFS, mos (95% CI	6.9 (5.4–NR)	6.5 (4.3–8.6)	5.8 (4.2–8.5)



Low tertile = 0–99 mutations; medium tertile = 100–242 mutations; high tertile = ≥243 mutations.

Carbone DP, et al. *N Engl J Med.* 2017;376:2415-2426 and supplement. Peters S, et al *Cancer Res.* 2017;77(13 suppl): abstract CT082.

Summary of Biomarker Testing

- **Now:** PD-L1
  - Utility in first line to determine appropriateness of single-agent immunotherapy
  - Multiple PD-L1 IHC assay options; questions remain about SP142
- **Next:** tumor mutation burden
  - High TMB is distinct population from PD-L1 and may predict for immunotherapy benefit
  - Some complexity in analysis and cutoff. Blood-based assays may be an option. Further study is required
- **Future:** multidimensional...and serial
  - Identify dynamic changes in tumor, tumor microenvironment, and host
  - Identify resistance strategies

Lung-Cancer Screening

Lung-Cancer Screening

- The most effective way to dramatically improve outcomes in NSCLC is early detection
- Multiple trials have shown a significant improvement in lung-cancer survival with lung screening, despite screening at limited time points throughout the trials

Sands J, et al. *J Thorac Oncol*. 2021;16:37-53.

Lung Cancer Screening: LDCT vs CXR

- NLST
  - LDCT vs CXR
  - 3 annual screenings
- Results
  - 20% relative reduction in lung cancer deaths
  - 6.7% relative reduction death from any cause (*P*= .02)

NLST = National Lung Screening Trial; LDCT = low-dose computed tomography; CXR = chest x-ray.

Low-dose computed tomography

	During Screening, n (%)			No Screen	
Stage	Screen Detected	Negative Screening	Total Screening	(Most During Follow-up)	Overall
IA	329 (52%)	5 (11%)	334 (49%)	82 (23%)	416 (40%)
IB	71 (11%)	2 (5%)	73 (11%)	31 (9%)	104 (10%)
IIA	26 (4%)	2 (5%)	28 (4%)	7 (2%)	35 (3%)
IIB	20 (3%)	3 (7%)	23 (3%)	15 (4%)	38 (4%)
IIIA	59 (9%)	3 (7%)	62 (9%)	37 (10%)	99 (10%)
IIIB	49 (8%)	15 (34%)	64 (9%)	58 (16%)	122 (12%)
IV	81 (13%)	14 (32%)	95 (14%)	131 (36%)	226 (22%)
Total	635	44	679	361	1040
Early (1 & 2)	446 (70%)	12 (27%)	458 (67%)	135 (37%)	593 (57%)
Late (3 & 4)	189 (30%)	32 (73%)	221 (33%)	226 (63%)	447 (43%)

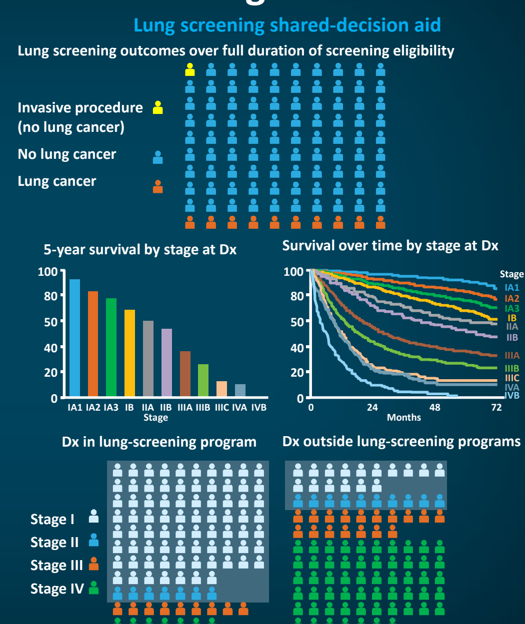
Chest x-ray

	During Screening, n (%)			No Screen	
Stage	Screen Detected	Negative Screening	Total Screening	(Most During Follow-up)	Overall
IA	90 (33%)	16 (12%)	106 (26%)	90 (17%)	196 (21%)
IB	41 (15%)	6 (4%)	47 (12%)	46 (9%)	93 (10%)
IIA	14 (5%)	2 (2%)	16 (4%)	16 (3%)	32 (3%)
IIB	11 (4%)	8 (4%)	17 (4%)	25 (5%)	42 (5%)
IIIA	35 (13%)	21 (16%)	56 (14%)	53 (10%)	109 (12%)
IIIB	27 (10%)	24 (18%)	51 (12%)	71 (14%)	122 (13%)
IV	57 (21%)	60 (44%)	117 (29%)	218 (42%)	335 (36%)
Total	275	135	410	519	929
Early (1 & 2)	156 (57%)	30 (22%)	186 (45%)	117 (34%)	363 (39%)
Late (3 & 4)	119 (43%)	105 (78%)	224 (55%)	342 (66%)	566 (61%)

Aberle DR, et al; National Lung Cancer Screening Trial Research Team. *N Engl J Med.* 2011;365:395-409.

Lung Cancer Screening

- Given the potential for regular screening to prevent death from lung cancer, it is important to discuss screening with patients
- A shared-decision aid can serve as a valuable tool for discussing risks and benefits with patients



Dx = diagnosis.

Sands J, et al. *J Thorac Oncol*. 2021;16:37-53.

Key Takeaways

- Genomic testing is a critical part of the initial workup and should be completed before initiating immunotherapy treatment.
- Immunotherapy has become an important standard of care option in the management of NSCLC, with some of the most durable results among responders.
- PD-L1 status should drive decision-making about first-line therapy options for NSCLC.
- Lung cancer screening for eligible individuals is the standard of care and significantly increases the likelihood of diagnosing NSCLC when it is still potentially curable.

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Animations

IC-ONC

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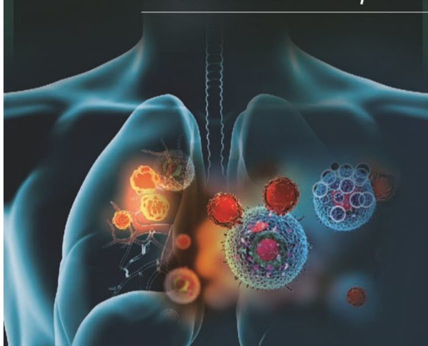

Immune cellular functions and cytokine effects on tumorigenesis
https://youtu.be/6tG5uvdM-oA

Complementary antitumor effects of immunotherapy and chemotherapy in NSCLC
https://youtu.be/LifxoPuZhrM

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Thank you!

Immunotherapy and Immune-Related Adverse Events:

HOW DOES IT AFFECT ME?

WELCOME TO AUGMENTED REALITY...

a tour in the palm of your hand!

This augmented reality application was designed using images and animations to highlight aspects of immunotherapy and its role in the treatment of cancer. Specifically, the video focuses on immune-related adverse events (IRAEs), which can occur when these therapies turn on the immune system to fight cancer. This tool will take you through the various therapies available; identification, types, grading and management of IRAEs; and ways in which the patient can become more involved.

The images and animations that are brought to reality can be manipulated and controlled by YOU, allowing you to focus on specific areas and be truly engaged in the learning tool.

ANDROID APP ON Google play | Available on the App Store

To use this augmented reality application, please download the "IRAE-AR" app from the Apple App Store or Google Play Store on your phone or tablet.

- Press the start button, and slowly move your device to scan the area around you
- Once a flat surface has been found, you will see a marker appear
- Move your device to reposition the marker, and tap the screen when you are ready to begin
- Try rotating your device to landscape mode for a wider view

This activity is provided by Med Learning Group.
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This activity is supported by an educational grant from Merck & Co., Inc.

<u>**Identifying Optimal Combinations of Immune-Based Therapies: Metastatic NSCLC**</u>

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