VII Simpósio Internacional Câncer de PULMÃO

15 e 16 de março de 2019

Hotel Pullman São Paulo Vila Olímpia

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Imunoterapia de primeira linha em pacientes sem mutações dirigidoras e PD-L1 ≥ 50%

Eu recomendo imunoterapia isolada

(First line immune checkpoint inhibitor therapy in non-small-cell lung cancers with PD-L1 ≥ 50% and no actionable mutations)

I reccomend imunotherapy alone

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Cancer Center

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

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Relevant financial relationships with a commercial interest:

_ Clovis Oncology, research funding (previous 2016)
_ Boehringer Ingelheim Pharm. Inc., consulting/honoraria (previous 2016)
_ Pfizer Inc., consulting/honoraria (previous 2017)
_ Takeda/Millennium Pharmaceuticals, consulting/honoraria (previous 2016-2019)
_ AstraZeneca, consulting/honoraria/research funding (previous 2016-2019)

Non-financial support (institutional research support):

_ Merck Sharp & Dohme Corporation
_ Pfizer
_ Takeda/Millennium Pharmaceuticals
_ Astrazeneca
_ Merrimack Pharmaceuticals

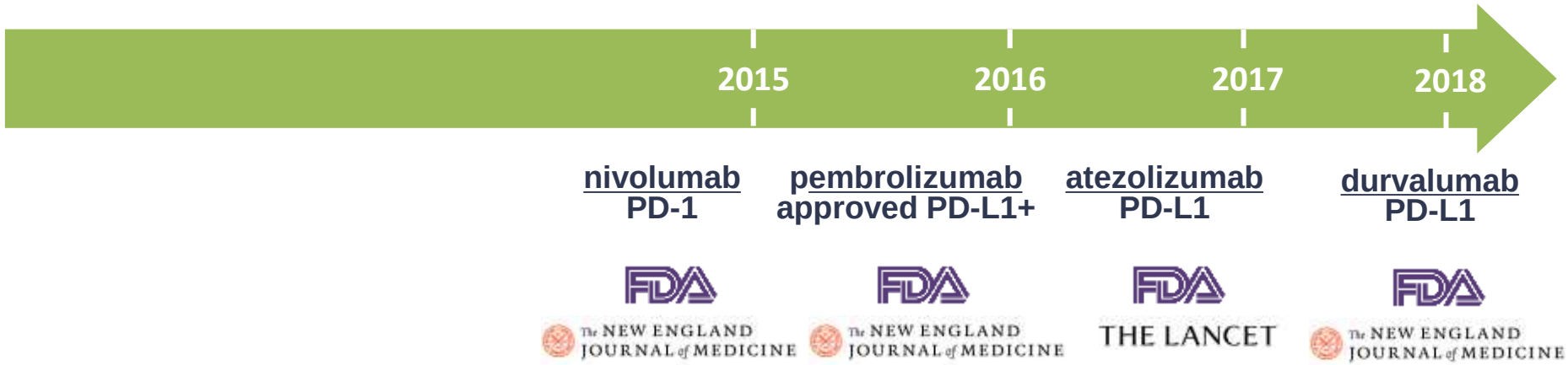
“Off-label” use disclosure relevant to my presentation:

_ none

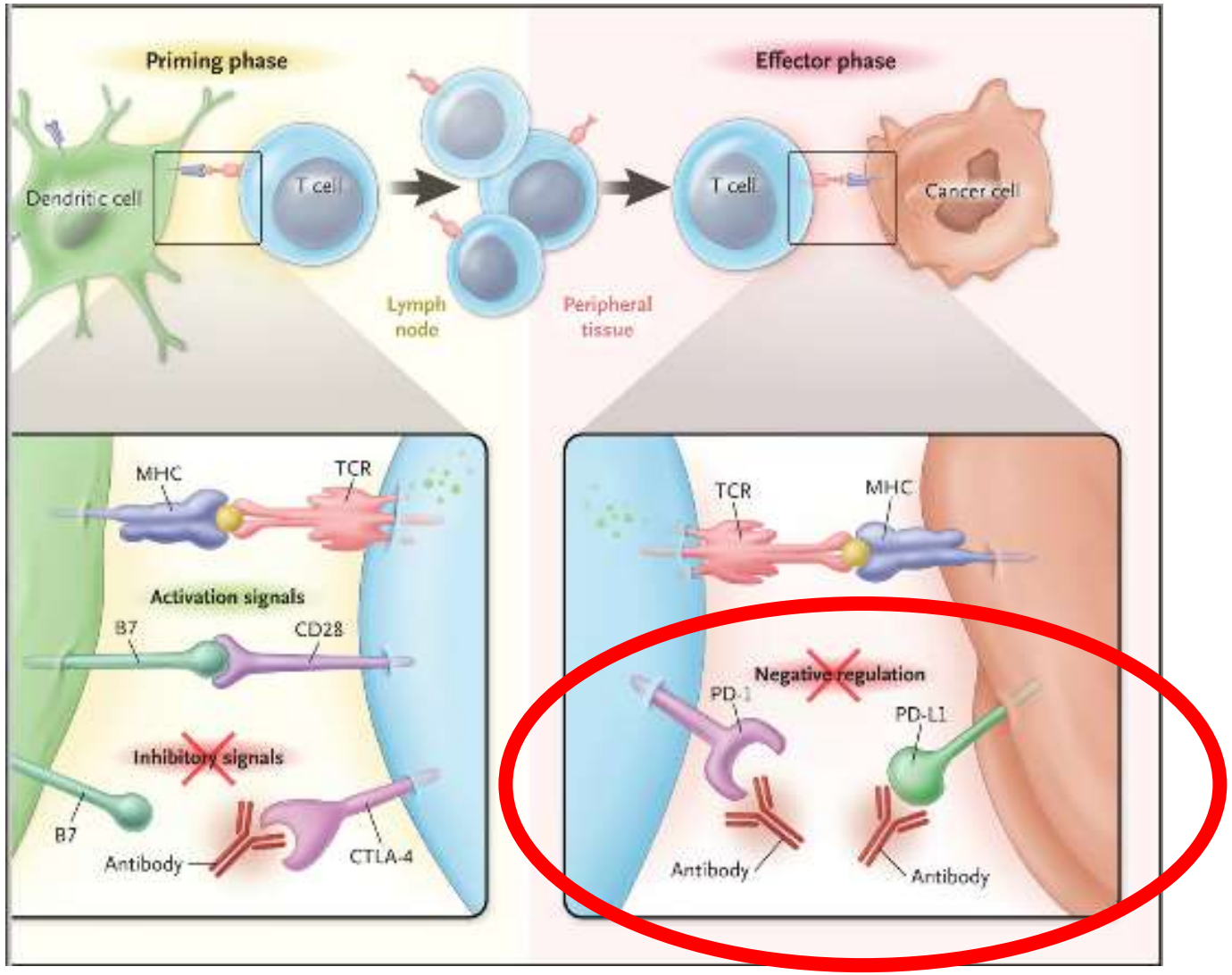
Immune checkpoint inhibitors for NSCLC (squamous cell carcinomas and adenocarcinomas)

anti-PD-1 pembrolizumab (1st line PD-L1 IHC ≥50%, 2nd line PD-L1 IHC ≥1%)
(1st line advanced, irrespective of PD-L1 IHC, with carboplatin/pemetrexed)
anti-PD-1 nivolumab (2nd line, irrespective of biomarker PD-L1 IHC)
anti-PD-L1 atezolizumab (2nd line, irrespective of biomarker PD-L1 IHC)
(1st line advanced, irrespective of PD-L1 IHC, with carboplatin/paclitaxel/bevacizumab)

anti-PD-L1 durvalumab (locally advanced after chemoradiation)



Harnessing the immune system to treat lung cancer
(PD-1 and PD-L1 antibodies [remove the *breaks* of the immune system])



Ribas A., et al. N Engl J Med 2012; 366:2417-2519.

FDA approval of anti-PD-1 pembrolizumab for second line therapy of advanced NSCLC (KEYNOTE-010 clinical trial)

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

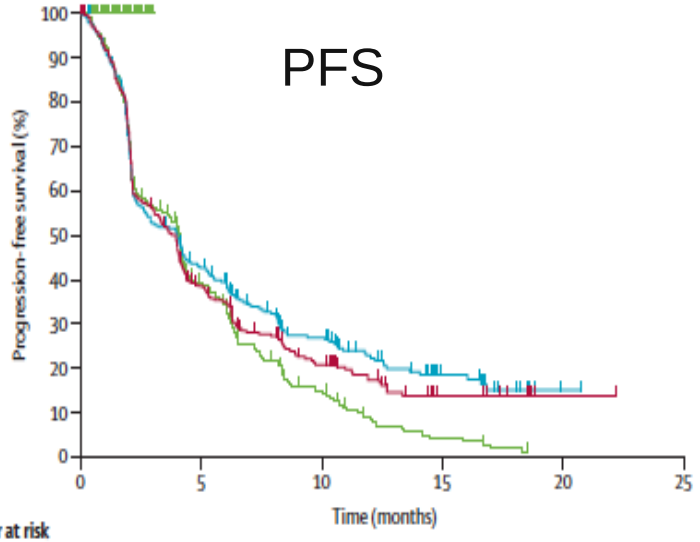
KEYNOTE -010

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

Herbst R et al. The Lancet 2016

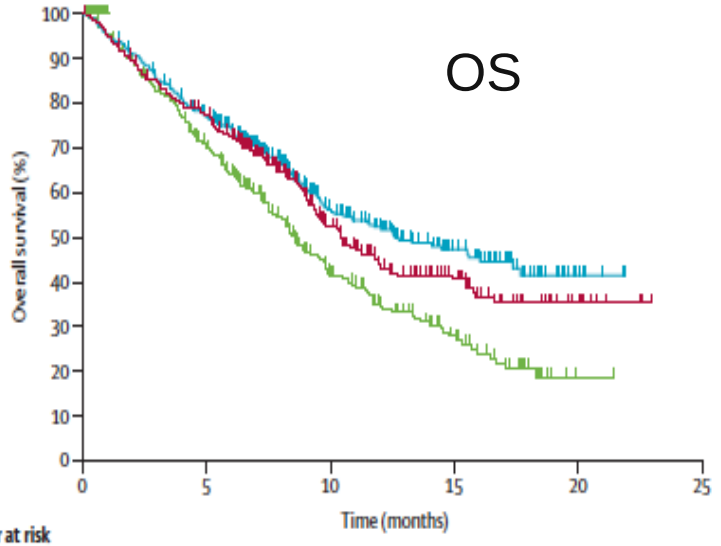
pembrolizumab - PD-L1 >1% expression using the clone 22C3 pharmDx kit
ORR 18% duration response NR (> 10-12 mths) median PFS 3.9 months median OS 10.4 months

PFS



Number at risk						
Pembrolizumab 2 mg/kg	344	122	46	12	1	0
Pembrolizumab 10 mg/kg	346	137	60	19	1	0
Docetaxel	343	103	27	6	0	0

OS



Number at risk						
Pembrolizumab 2 mg/kg	344	259	115	49	12	0
Pembrolizumab 10 mg/kg	346	255	124	56	6	0
Docetaxel	343	212	79	33	1	0

PD-L1 immunohistochemical (IHC) staining 22C3 assay using tumor proportion score (TPS)

Integrated ONCOLOGY

PD-L1 Immunohistochemistry Analysis

Patient Name [redacted]

Order # Specimen # Case #

Birth Date Age Gender [redacted]

Client Specimen ID Account #

Referring Physician Treating Physician [redacted]

Client Lab ID [redacted]
BIDMC- Integrated Oncology
330 Brookline Avenue
Finard 305
Client Hospital ID [redacted]
Boston MA 02215
USA

Container(s) Received
4 Slide Paraffin, 1 Slide Stained

Clinical Summary and Indication
Lung cancer.

Body Site
Ischium, Left

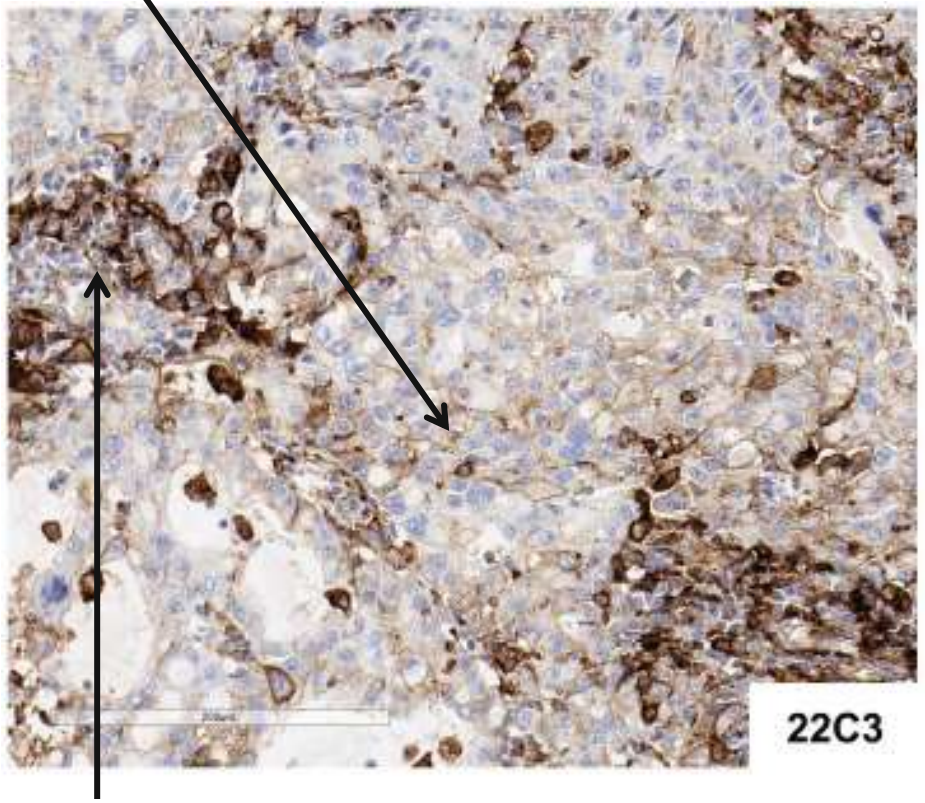
Marker	Tumor Proportion Score	Interpretation	Description
PD-L1 (KEYTRUDA)	70%	High Expression	Programmed Death Ligand 1 (PD-L1), Clone 22C3 pharmDx(TM) kit for KEYTRUDA®

PD L1

Reference Range:
TPS = Tumor Proportion Score = % of at least 100 viable tumor cells showing complete or partial membrane staining at ≥ 1+
TPS < 1% = No Expression.
TPS 1 - 49% = Low Expression. Eligible for second-line treatment with KEYTRUDA® (pembrolizumab).
TPS ≥ 50% = High Expression. Eligible for first or second-line treatment with KEYTRUDA® (pembrolizumab).

The PD-L1, 22C3 pharmDx(TM) is FDA approved for use in the detection of PD-L1 in formalin-fixed paraffin-embedded non-small cell lung carcinoma using the Dako Automated Link 48 platform. The assay is indicated as an aid in identifying NSCLC patients for treatment with KEYTRUDA® (pembrolizumab). PD-L1, 22C3 pharmDx(TM) is a trademark of Dako, an Agilent Technologies company. Reference ranges for this test in other cancer types are not approved at this time.

Membranous/cytoplasmic staining of **tumor cells** (% with *any* staining calculated)



Staining of tumor infiltrating immune cells (TIICs)

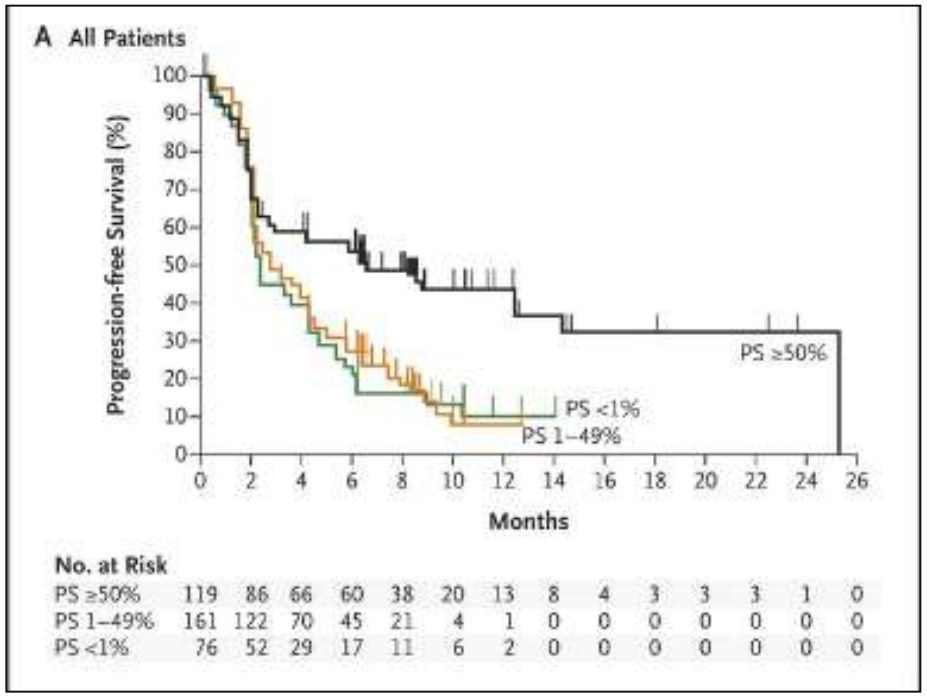
- Lymphocytes, plasma cells, histiocytes
- Only scored in some assays (SP124)

Hirsch FR et al. *J Thorac Oncol*. 2017

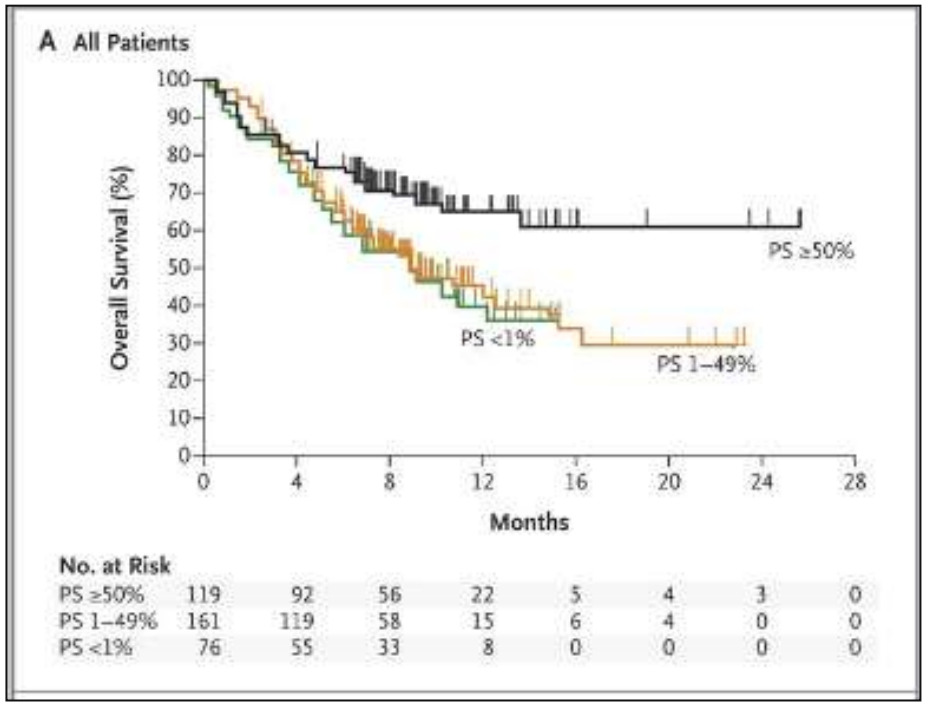
Pembrolizumab's response rate increases with PD-L1 expression using 22C3 IHC assay

Best response rates (>35%) seen in tumors with PD-L1 TPS≥50%

pembrolizumab 2mg/kg or 10 mg/kg q3 weeks
ORR 19.4% (95% confidence interval [CI], 16.0 to 23.2)
ORR 36.6% (95% CI, 22.1 to 53.1) if PD-L1 ≥50%



PFS



OS

Garon EB, et al. NEJM 2015; 372:2018.

FDA approval of anti-PD-1 pembrolizumab for first line therapy of advanced NSCLC (KEYNOTE-024 clinical trial)

The NEW ENGLAND JOURNAL of MEDICINE

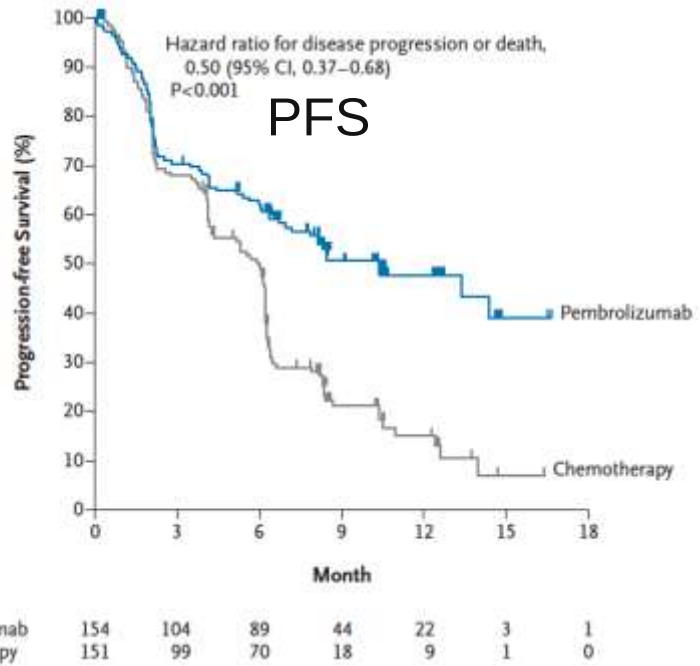
ORIGINAL ARTICLE

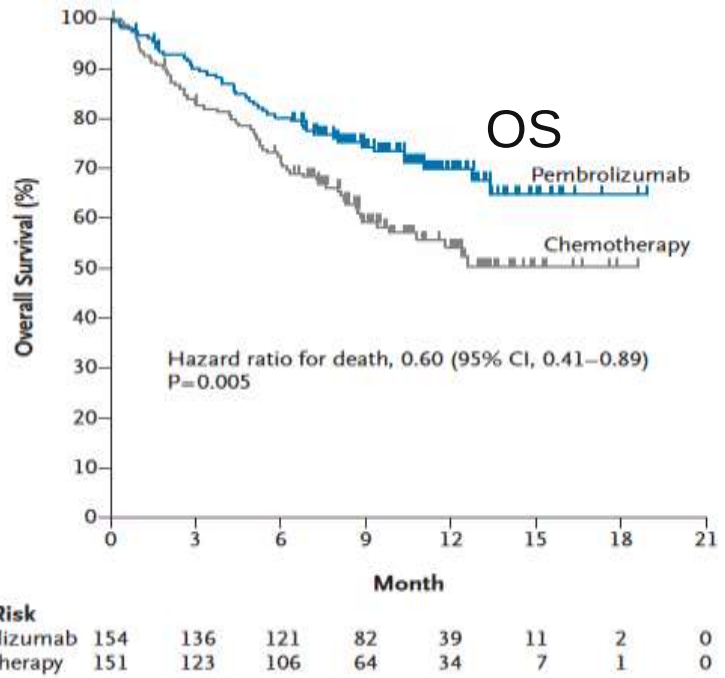
Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

KEYNOTE -024

Reck M et al. NEJM 2016

pembrolizumab - PD-L1 ≥50% expression using the clone 22C3 pharmDx kit
ORR 44.8% duration response NR (1.9-14.5 mths) median PFS 10.3 months 6-month survival 80.2%





Longterm outcomes of KEYNOTE-024 clinical trial: Survival and Toxicities

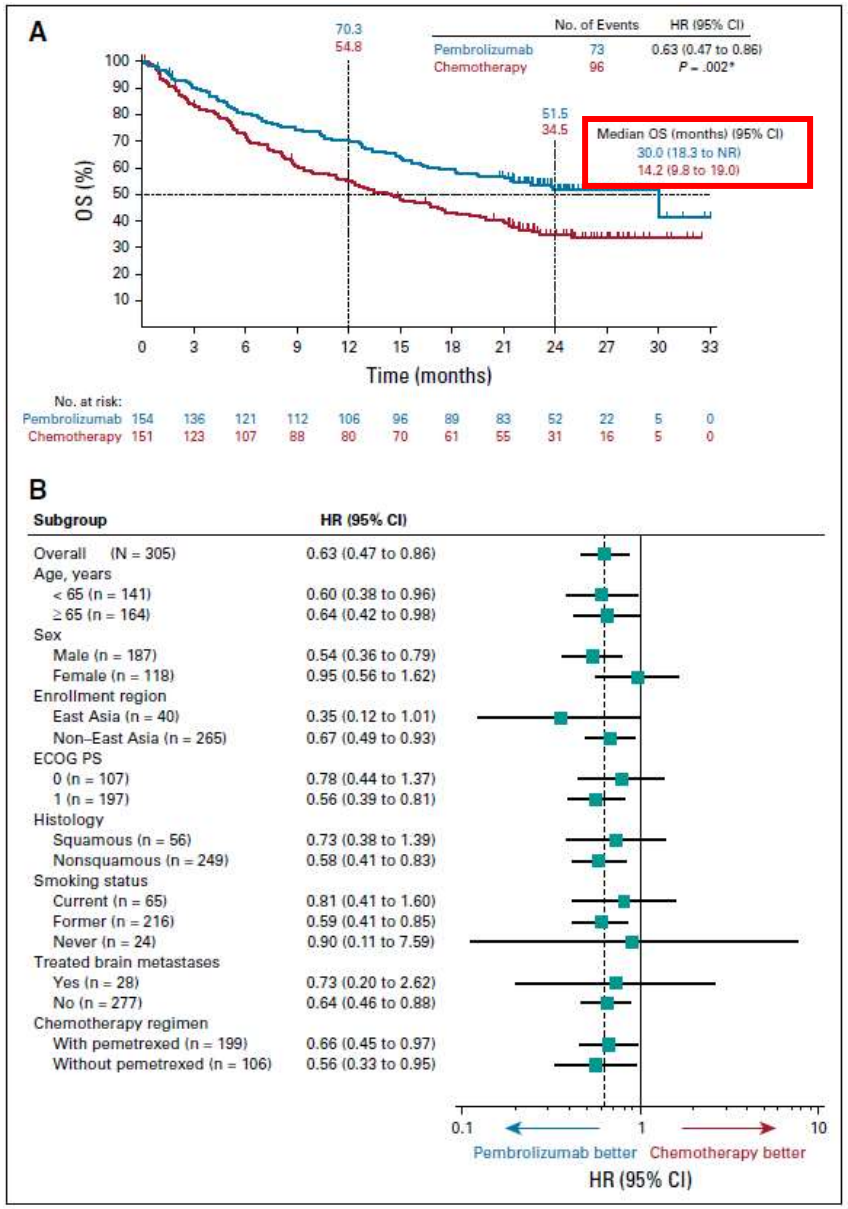


TABLE 2. Adverse Events in the As-Treated Population

	No. of Patients (%)			
Adverse Event	**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. JCO 2019; 537.

Anti-PD-1 pembrolizumab in combination with chemotherapy for first line therapy of advanced NSCLC (KEYNOTE-189 and -407 trials)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

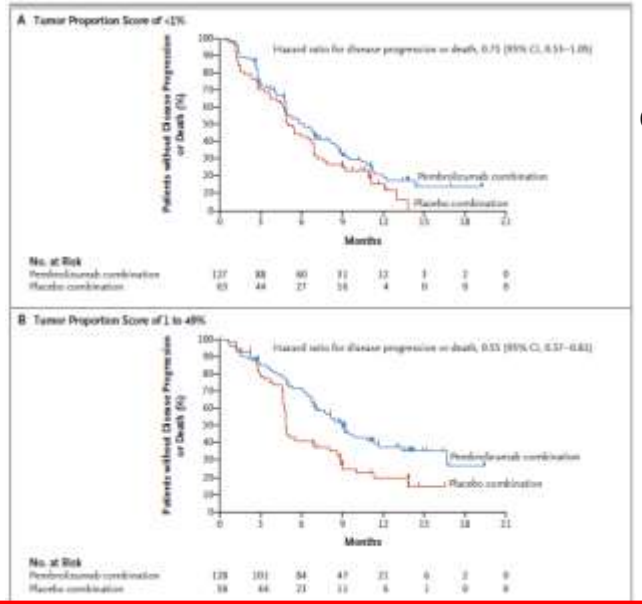
L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip,

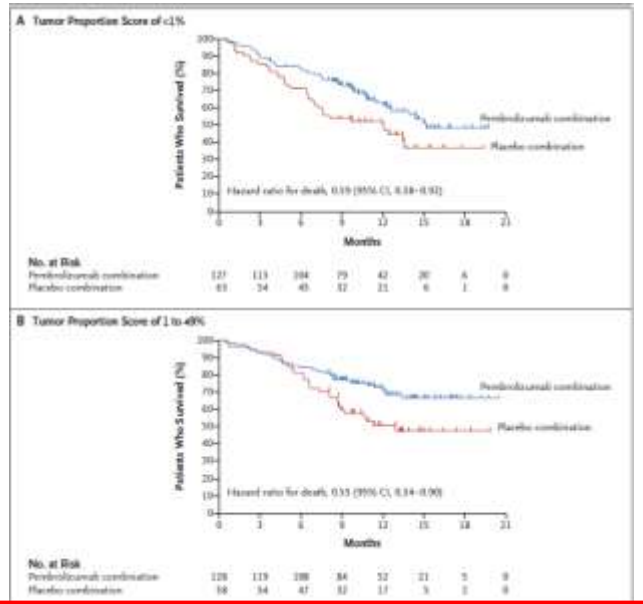
KEYNOTE -189

Gandhi L et al. NEJM 2018

Progression-free survival

Overall survival





PD-L1 IHC TPS ≥50%

ORR 61.4%

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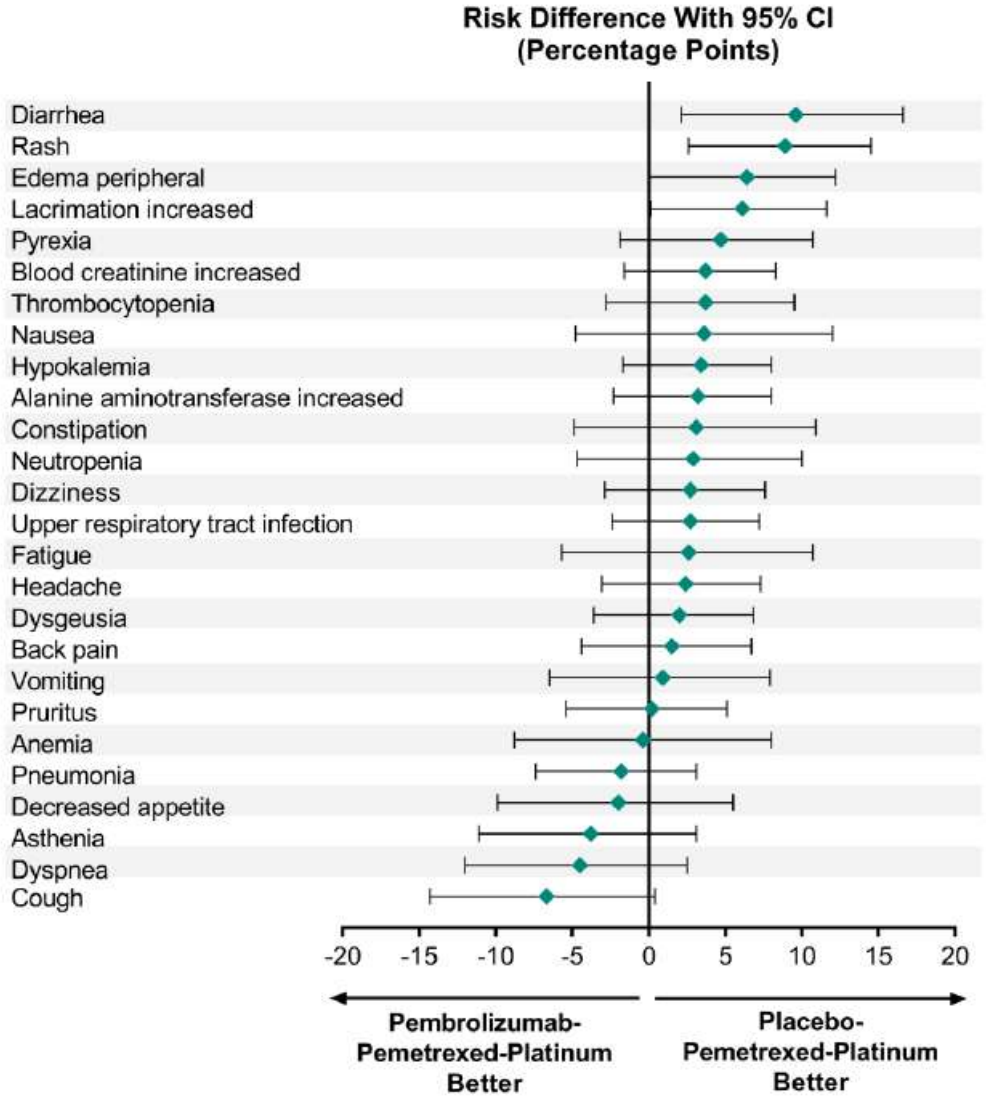
Further considerations of KEYNOTE-189 trial: Toxicities

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

* The events of interest are those with an immune-related cause and are considered regardless of attribution to a trial drug by the investigator. The events are listed in descending order of frequency in the pembrolizumab-combination group. In addition to the specific preferred terms that are listed, related terms were also included. The as-treated population included all the patients who had undergone randomization and received at least one dose of the assigned combination therapy.



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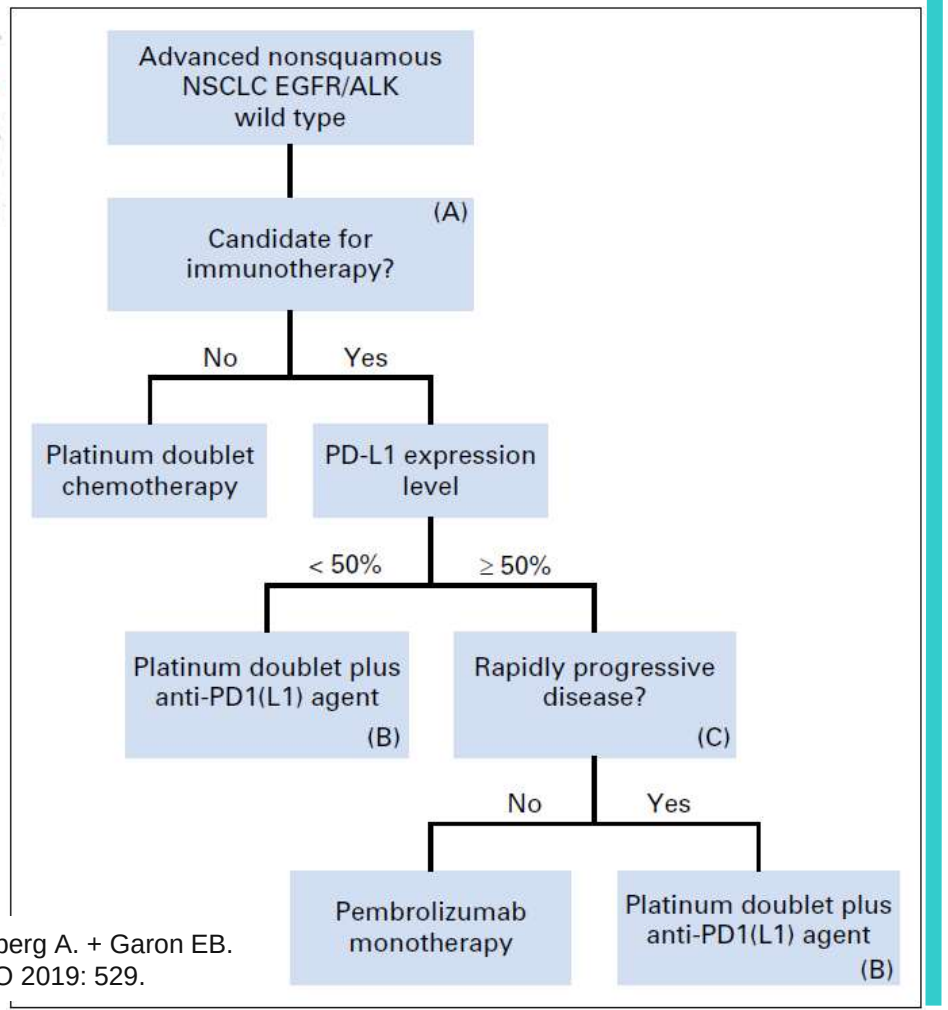
PD-L1 ≥ 50%: Why choose pembrolizumab alone versus combination pembrolizumab+carboplatin+pemetrexed (other chemo-IO-VEGF combinations)?

oncology grand rounds

Does Platinum-Based Chemotherapy Still Have a Role in First-Line Treatment of Advanced Non–Small-Cell Lung Cancer?

Aaron Lisberg, MD[1] and Edward Brian Garon, MD[1]



Lisberg A. + Garon EB. JCO 2019: 529.

- **Long-term efficacy (outside response rate) may be similar**
  - ORR 45% (pembrolizumab) vs 61% (combination)
  - Duration of response > 15-18 months (pembrolizumab alone)
  - 12-month OS 70% (Keynote-024 pembrolizumab)
  - 12-month OS 73% (Keynote-189 pembrolizumab)
- **Toxicities are lower with single agent therapy**
  - Grade 3-5 CTCAE toxicities 31% pembrolizumab (mostly immune-mediated)
  - Grade 3-5 CTCAE toxicities 53% chemotherapy (+ add 31% from pembrolizumab)
- **Lower costs for health system / Patient satisfaction**
  - Infusion times
  - Management of toxicities
  - Cost of drug(s)
- **Ability to switch to cytotoxic chemotherapy at progression**
  - Outcomes of chemotherapy after initial PD-1/PD-L1 antibody IO are similar if not improved when compared to 1st line chemotherapy alone

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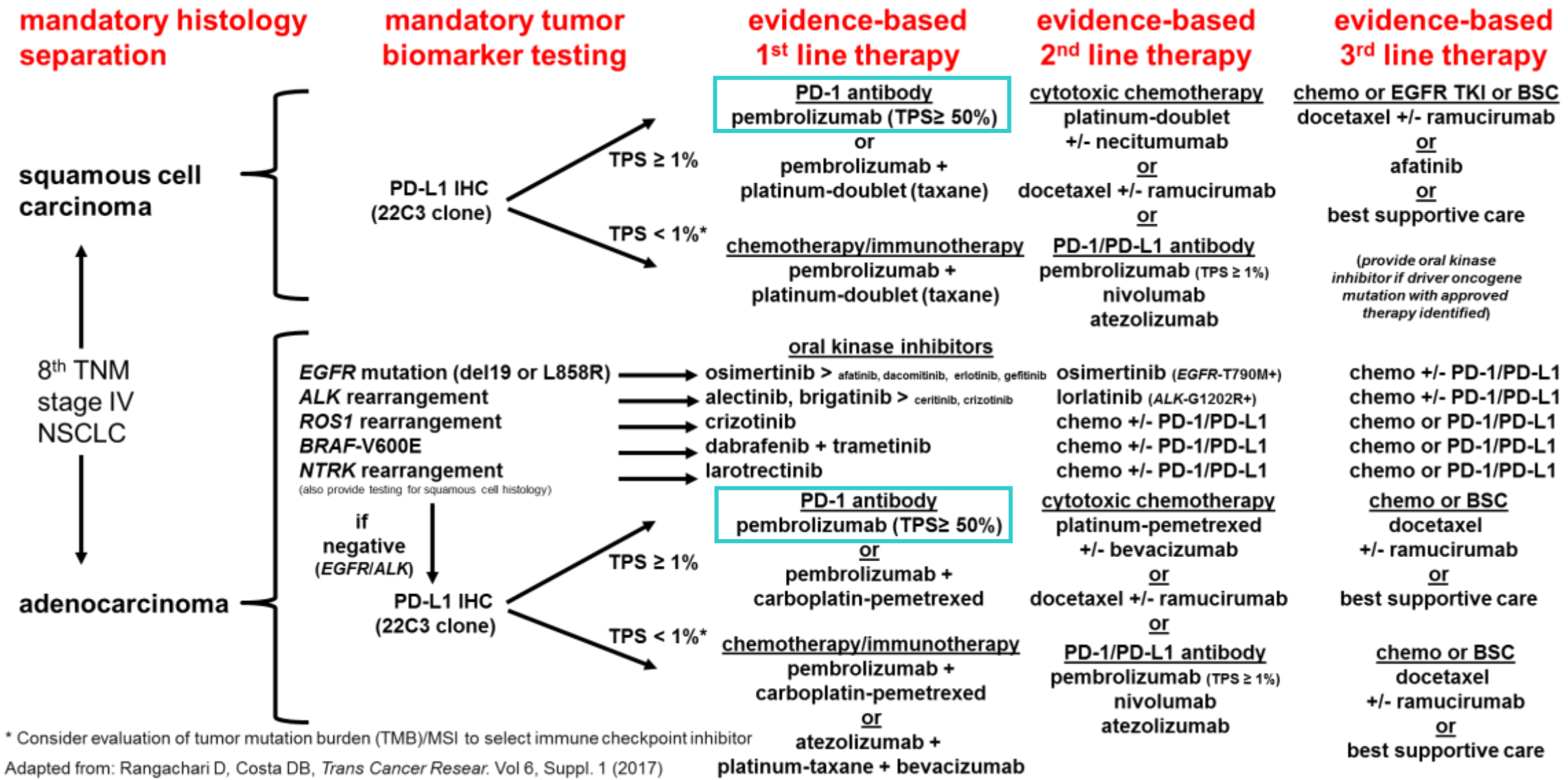
Medical Oncology management of evidence-based therapies for advanced non-small-cell lung cancer - *March 2019 (BIDMC)*



* Consider evaluation of tumor mutation burden (TMB)/MSI to select immune checkpoint inhibitor

Adapted from: Rangachari D, Costa DB, *Trans Cancer Resear.* Vol 6, Suppl. 1 (2017)

Medical Oncology management of evidence-based therapies for advanced non-small-cell lung cancer - *circa 2004 (BIDMC)*

mandatory histology separation (none)	mandatory tumor biomarker testing (none)	evidence-based 1st line therapy	evidence-based 2nd line therapy	evidence-based 3rd line therapy
squamous cell carcinoma ↑ 6th TNM stage IV NSCLC ↓ adenocarcinoma		cytotoxic chemotherapy with platinum-doublet	docetaxel or gefitinib (provisional approval that was revoked in 2005)	best supportive care

Internal Data - BIDMC

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PD-L1 ≥ 50%: Example of a case with superb outcome with pembrolizumab alone

Complete and Sustained Response of Brain Metastases to Programmed Death 1 Antibody Monotherapy in Treatment-naive Programmed Death Ligand 1-Positive Lung Cancer

To the Editor:

Brain metastases (BM) are a common complication of advanced NSCLC. Most trials of immune checkpoint inhibitors in advanced NSCLC have excluded patients with untreated BM.[1] However, with the expanded approvals for anti-programmed death 1 (anti–PD-1) therapy, more recent studies have begun to allow enrollment of patients with asymptomatic, treated BM following either primary surgical excision and/or radiotherapy. In a recent study, Goldberg et al.[2] showed that the anti–PD-1 agent pembrolizumab had clinical activity and an acceptable safety profile in patients with advanced NSCLC and untreated or progressive asymptomatic BM. Here, we present a case of NSCLC with multiple BM with complete intracranial response following frontline palliative pembrolizumab. A 65-year-old Chinese man with 40-pack-year history of tobacco use presented with hemoptysis and absence of neurologic symptoms. Staging studies showed a primary right upper lobe mass with additional intrapulmonary and skeletal metastases. Brain imaging showed multiple BM ranging from 4 to 8 mm in size and accompanied by significant vasogenic edema (Fig. 1A). Biopsy of the lung mass was consistent with adenocarcinoma. Comprehensive tumor molecular profiling (FoundationOne, Foundation Medicine, Cambridge, Massachusetts) showed no actionable genetic events, no microsatellite instability, and tumor mutation burden of 19 mutations/megabase. Programmed death ligand 1 tumor proportion score was 90%. The patient was commenced on pembrolizumab 200 mg intravenously every 3 weeks without any significant adverse effects. Brain imaging performed after 12 weeks of therapy showed resolution of multiple previously noted enhancing BM and associated intracranial edema (Fig. 1B). No new lesions were identified. These findings were associated with concurrent intrathoracic response (not shown). At the time of this report, the patient has been maintained on first-line palliative pembrolizumab monotherapy for more than 15 months with sustained complete intracranial and partial intrathoracic response, without need for any other intervening therapies.

Our case adds to the accumulating evidence that immune checkpoint inhibitors can lead to intracranial responses through systemic and central nervous system

Address for correspondence: Daniel S. Costa, MD, PhD, Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, 330 Brookline Ave., Boston, Massachusetts 02215. Email: dcosta@bidmc.harvard.edu

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https://doi.org/10.1016/j.jtho.2018.10.157

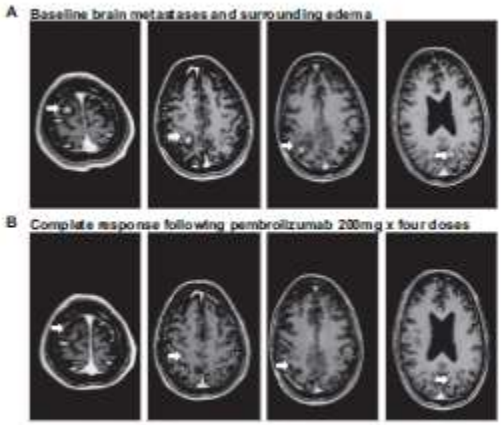

Figure 1. Magnetic resonance imaging (MRI) illustrating response of brain metastases to pembrolizumab. (A) Multiple MRI series cuts highlighting brain lesions at the gray-white junction ranging from 4-8 mm in the right frontal, right parietal, and left parietal lobes. The white arrows highlight lesions and their surrounding vasogenic edema. (B) Complete response of lesions after 12 weeks (4 doses) of single-agent pembrolizumab 200 mg. The white arrows highlight prior lesional areas in which response occurred.

_65-year-old Chinese man with 40-pack-year history of tobacco use presented with hemoptysis and absence of neurologic symptoms.

_Staging studies showed a primary right upper lobe mass with additional intrapulmonary and skeletal metastases. Brain imaging showed multiple brain metastases (BM) ranging from 4-8 millimeters in size and accompanied by significant vasogenic edema (Figure 1A).

_Biopsy of the lung mass was consistent with adenocarcinoma.

_Comprehensive tumor molecular profiling (FoundationOne, Foundation Medicine, Cambridge MA) showed no actionable genetic events (NF1, CDKN2A and TP53 mutations), no microsatellite instability, and tumor mutation burden (TMB) of 19 mutations/megabase.

_ Programmed death ligand 1 (PD-L1) tumor proportion score (TPS) was 90%.

_Started pembrolizumab 200 mg intravenously every three weeks without any non-immune or immune significant adverse effects to date (ECOG PS 0).

_Brain imaging performed after 12 weeks of therapy demonstrated resolution of multiple previously noted enhancing BM and associated intracranial edema (Figure 1B). No new lesions were identified. These findings were associated with concurrent intrathoracic response (not shown).

_Maintained on pembrolizumab monotherapy for more than 20 months with sustained complete intracranial and partial intrathoracic response, without need for any other intervening therapies. Plan to stop PD-1 antibody at 24 months.

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Q&A

- Mitigating factors to consider when deciding between pembrolizumab alone versus combination pembrolizumab+carboplatin+pemetrexed (other chemo-IO-VEGF combinations)?
  - Rapid progressive disease burden/symptomatic patient
  - Use of steroids and antibiotics in the pre anti-cancer therapy timeframe
  - Other predictive biomarkers for anti-PD-1/PD-L1
    (TMB, MSI-H, *KRAS*/*STK11*[*LKB1*] co-mutations, smoking history etc)
  - Availability of clinical trials that use backbone of anti-PD-1/PD-L1 monotherapy versus combination chemo-immunotherapy
  - Costs and insurance coverage (pending country/health system)