Recent Therapeutic Advances for Thoracic Malignancies

Developed in collaboration

Med-IQ DukeHealth

Learning Objectives

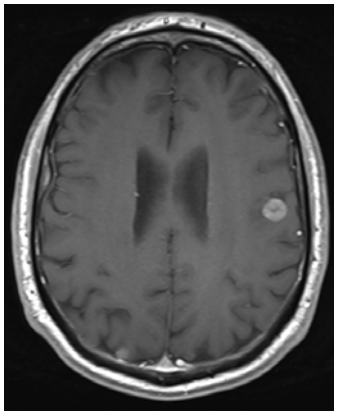
Upon completion, participants should be able to:

- Interpret new developments in the use of radiation therapy in non–small cell lung cancer
- Integrate current clinical evidence on the role of surgery in treating early and locally advanced non–small cell lung cancer into treatment decisions for appropriate patients
- Outline key current evidence that affects clinical practice and the care of patients with advanced non–small cell lung cancer

Advances in RT for Thoracic Malignancies

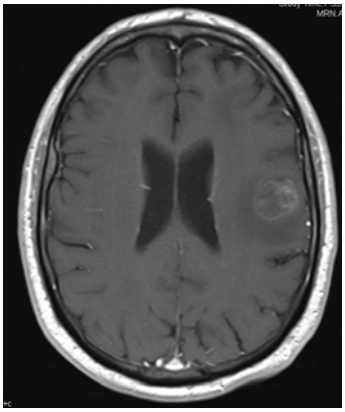
Christopher Kelsey, MD

Brain Metastases, RT, and Immune CPIs



SRS: 20 Gy X 1

2 months



Photos courtesy of Christopher Kelsey, MD.

Higher Risk of CNS-AEs After Treatment With CNS-RT Plus CPIs

- Patients with melanoma or NSCLC with brain metastases (N = 213) treated with CNS-RT (SRS or WBRT) +/- immune CPIs
  - 28 with CPIs
  - 184 without CPIs
- CNS-AEs: new or increasing edema (without disease progression), new or worsening neurologic deficits
  - Need to start or increase corticosteroids

Devitt ME, et al. *J Clin Oncol.* 2018;36(suppl; abstract 2010).

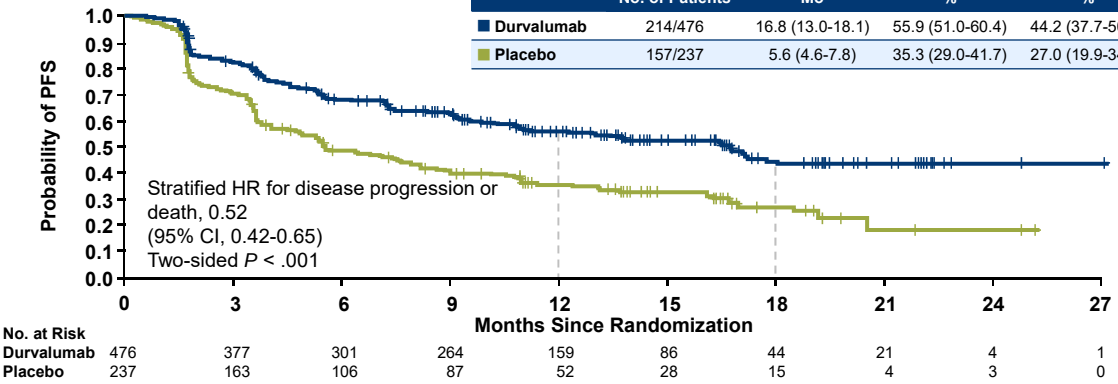
Higher Risk of CNS-AEs After Treatment With CNS-RT Plus CPIs

- NSCLC (78%), SRS (69%), median size 1.7 cm
- CNS-AEs, n = 40 (19%)
  - Neurologic deficit in 22 (55%)
- CPIs within 3 months of brain RT only factor associated with increased risk of CNS-AEs (OR, 3.9; 95% CI, 1.6-9.2; *P* = .002)
- 11/28 (39%) with CPIs vs 29/184 (16%) without CPIs

Devitt ME, et al. *J Clin Oncol.* 2018;36(suppl; abstract 2010).

PACIFIC

	No. of Events/Total No. of Patients	Median PFS (95% CI) Mo	12-Mo PFS (95% CI) %	18-Mo PFS (95% CI) %
Durvalumab	214/476	16.8 (13.0-18.1)	55.9 (51.0-60.4)	44.2 (37.7-50.5)
Placebo	157/237	5.6 (4.6-7.8)	35.3 (29.0-41.7)	27.0 (19.9-34.5)



No. at Risk										
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

Antonia SJ, et al. *N Engl J Med.* 2017;377:1919-29.

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ETOP NICOLAS Phase 2 Trial

- Patients (N = 62) with stage III NSCLC
- 3 cycles of platinum-based chemotherapy and definitive RT (66 Gy) with concurrent nivolumab
- Primary endpoint: grade ≥ 3 pneumonitis at 6 months post-RT with interim analysis after 21 patients
- No grade ≥ 3 pneumonitis in first 21 patients (3-month follow-up)
  - 6 (10%) grade 3 pneumonitis (2 > 6 months after RT)
- Study ongoing (1-year PFS secondary endpoint)

Peters S, et al. *J Clin Oncol.* 2018;36(suppl; abstract 8510).

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PEMBRO-RT Study (Netherlands)

- Hypothesis:
  - High-dose RT can lead to increased tumor antigen release, improved antigen presentation, and T-cell infiltration
  - SBRT to a single metastatic site preceding pembrolizumab would lead to increased tumor response in stage IV NSCLC

Theelen W, et al. *J Clin Oncol*. 2018;36(suppl; abstract 9023).

PEMBRO-RT Study (Netherlands)

- Patients (n = 64) with stage IV NSCLC (≥ 2nd line) regardless of PD-L1 status randomized to:
  - Pembrolizumab (200 mg Q3W)
  - SBRT (8 Gy X 3) to a single metastasis →pembrolizumab
- ORR (12 weeks): 21% vs 39% (*P* = .28)
- Median PFS: 2.8 months vs 7.1 months
  - Most significant improvement in PD-L1: 0%
- No increased toxicity

Theelen W, et al. *J Clin Oncol*. 2018;36(suppl; abstract 9023).

SBRT for Operable Stage I NSCLC (Japan)

- Patients (n = 64) with operable, cT1N0 NSCLC received SBRT (12 Gy X 4 at isocenter); primary endpoint: 3-year OS (80%)
- Median age: 79 years
- OS was 77% (3 years), 54% (5 years), and 24% (10 years)
- 27 failures (9 local failures, 11 regional nodal failures, 11 distant metastases)
- Grade 3 toxicity in 6 patients (9%); chest pain (n = 1), dyspnea (n = 4), hypoxia (n = 1), pneumonitis (n = 2)

Nagata Y, et al. *J Clin Oncol*. 2018;36(suppl; abstract 8512).

SBRT vs Surgery Trials

- Veterans Affairs: VALOR
  - SBRT vs lobectomy/segmentectomy
  - Watch videos followed by TSU and rad onc consults
- United Kingdom: SABRTooth
  - Initial meeting with pulmonologist
- UT Southwestern: STABLE-MATES
  - SBRT vs sublobar resection (high-risk surgical population)
  - Pre-randomization before protocol discussion

ClinicalTrials.gov. Identifier: NCT02984761; Snee MP, et al. *Pilot Feasibility Stud.* 2016;2:5; ClinicalTrials.gov. Identifier: NCT02468024.

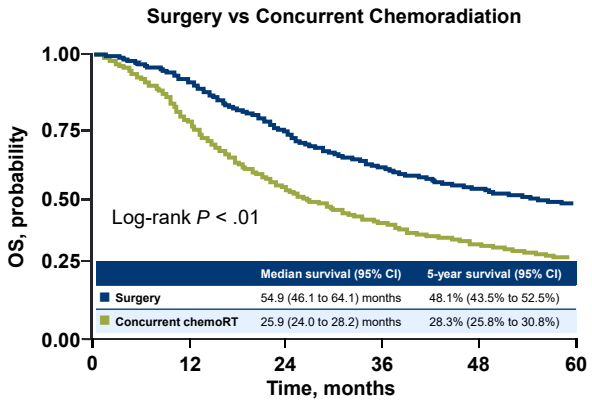
Surgical Advances in the Treatment of Lung Cancer

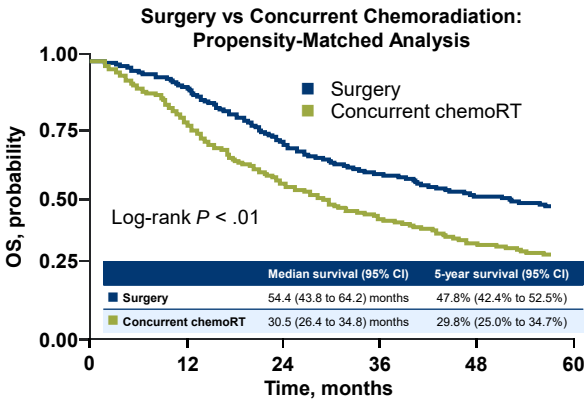
Jacob Klapper, MD

Overview

- Revisiting the role of surgery in the management of SCLC
- The debate: surgery vs radiation for stage I lung cancer
- Open surgery vs VATS and long-term OS
- Surgery in the new era of immunotherapy

Surgery Should Be Considered in Early Stage SCLC





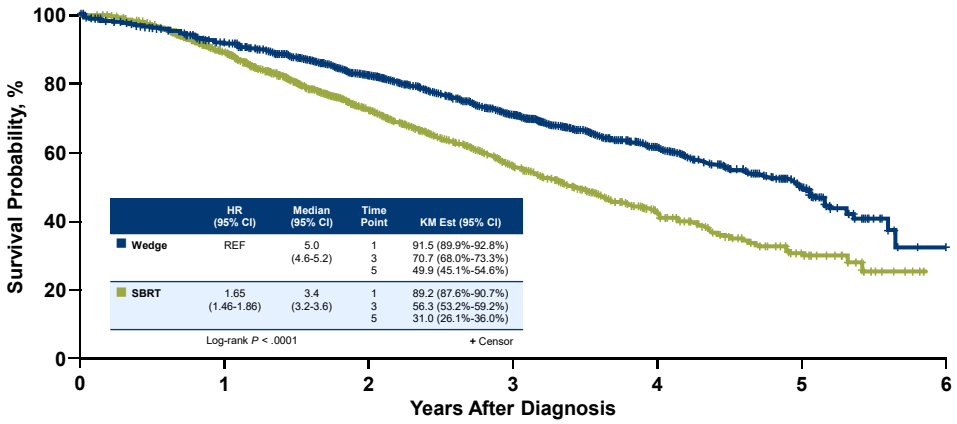
Yang CJ, et al. *Ann Surg*. 2017. [Epub ahead of print]

Surgical Resection: Safe After Induction Immunotherapy

- Neoadjuvant chemotherapy and ipilimumab followed by surgery
  - 13 patients with stage II-IIIA NSCLC
  - Zero 30-day mortalities
  - No increase in perioperative complications
    - Compared with historical cohort of patients (n = 42) who received preoperative therapy with platinum doublet
- Neoadjuvant nivolumab followed by surgery
  - 21 patients with resectable early NSCLC
  - Zero delays in surgery
  - Major pathologic response in 45% of tumors

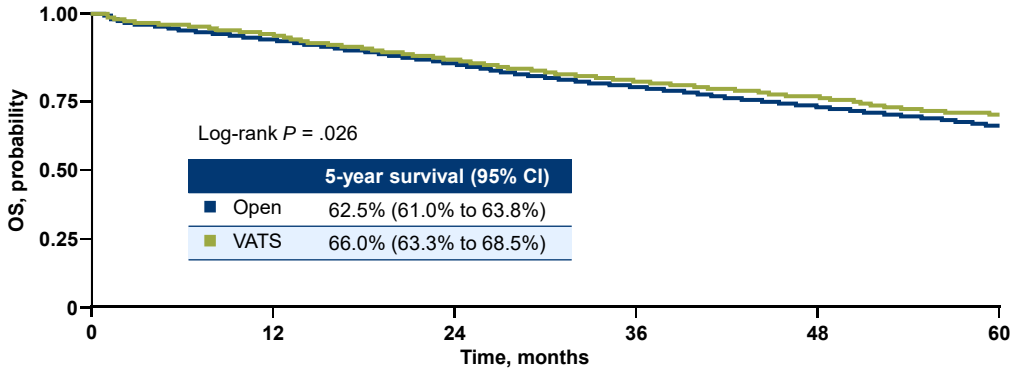
Yang CJ, et al. *Ann Thorac Surg.* 2018;105:924-29; Forde PM, et al. *N Engl J Med.* 2018;378:1976-86.

Wedge Resection vs Radiation: Better Survival With Surgery



Yerokun BA, et al. *J Thorac Cardiovasc Surg.* 2017;154:675-86.

OS: VATS Is Noninferior to Open Surgery

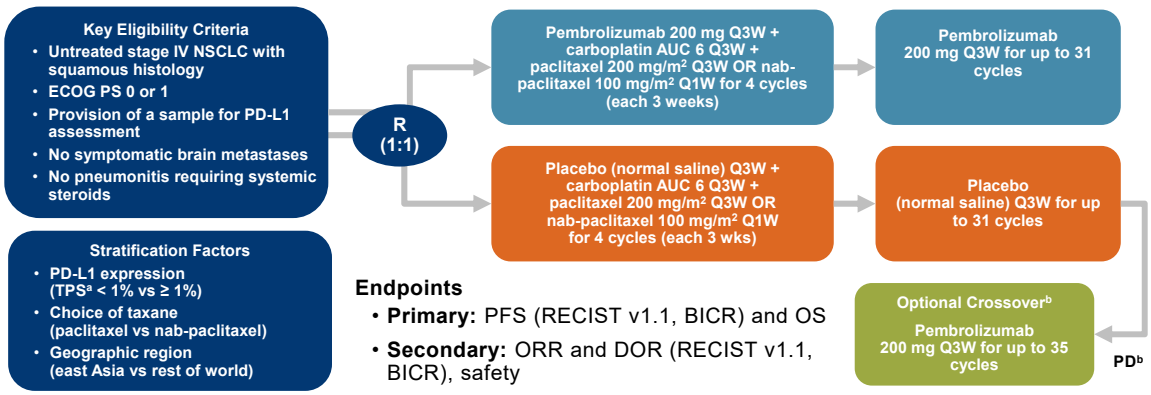


Yang CJ, et al. *Ann Surg.* 2017. [Epub ahead of print]

Phase 3 Trials of Immunotherapy for Advanced NSCLC

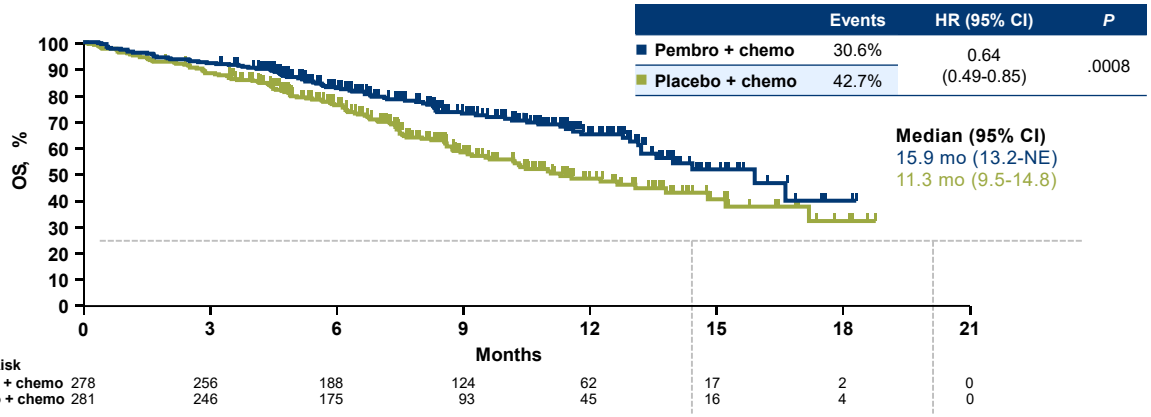
Thomas Eldridge Stinchcombe, MD

KEYNOTE-407 Study Design



[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay.
[b]Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR, and all safety criteria had to be met.
Paz-Ares LG, et al. *J Clin Oncol*. 2018;36(suppl; abstract 105).

OS at IA2, ITT



	Events	HR (95% CI)	P
Pembro + chemo	30.6%	0.64 (0.49-0.85)	.0008
Placebo + chemo	42.7%		

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

Data cutoff date: April 3, 2018.
Paz-Ares LG, et al. *J Clin Oncol*. 2018;36(suppl; abstract 105).
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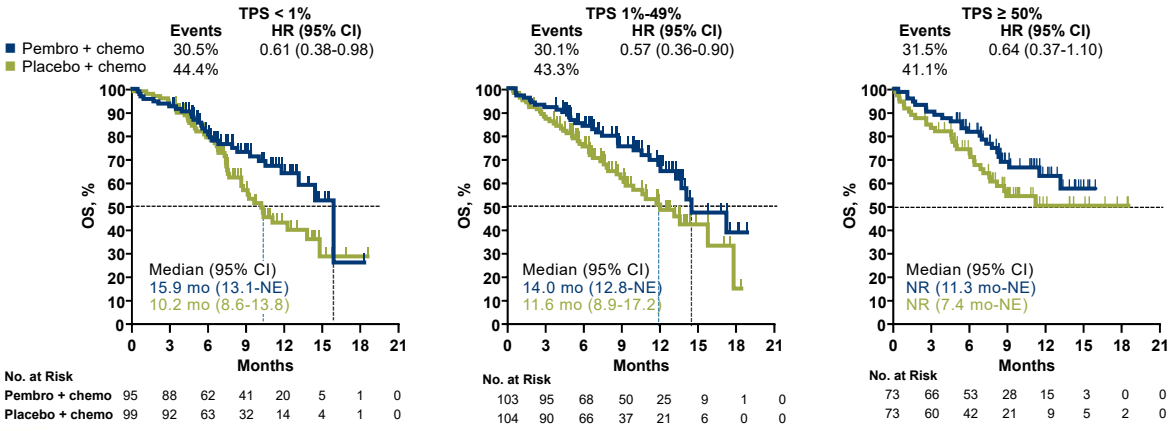
OS at IA2 by PD-L1 TPS



Paz-Ares LG, et al. *J Clin Oncol*. 2018;36(suppl; abstract 105).
Please see full prescribing information for warnings, efficacy, risk, and safety

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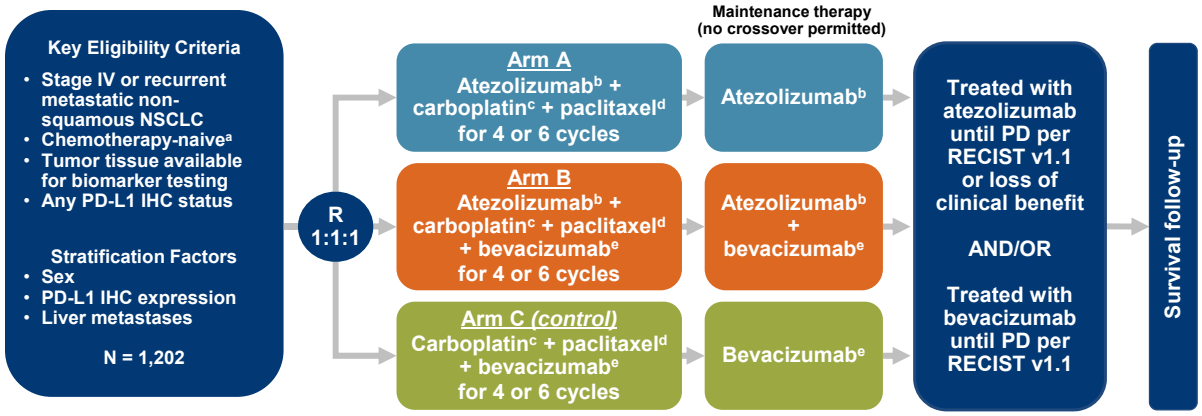
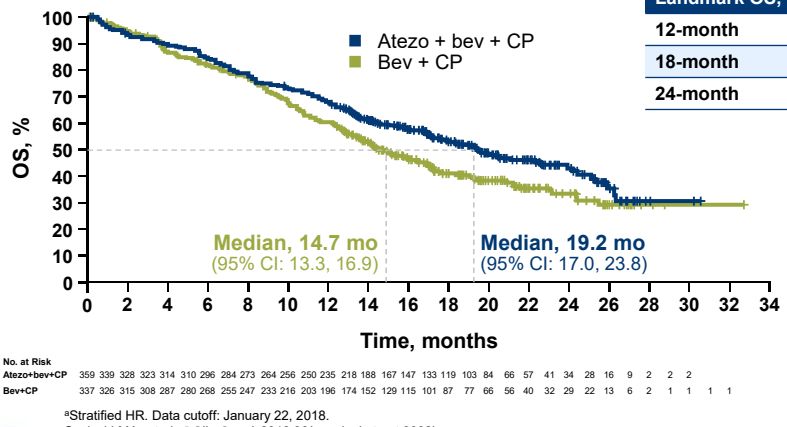
IMpower150 Study Design



[a]Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[b]Atezolizumab: 1,200 mg IV Q3W. [c]Carboplatin: AUC 6 IV Q3W. [d]Paclitaxel: 200 mg/m^2 IV Q3W. [e]Bevacizumab: 15 mg/kg IV Q3W.
Socinski MA, et al. *J Clin Oncol*. 2018;36(suppl; abstract 9002).

OS in the ITT-WT



Landmark OS, %	Arm B: Atezo + bev + CP	Arm C: Bev + CP
12-month	67%	61%
18-month	53%	41%
24-month	43%	34%

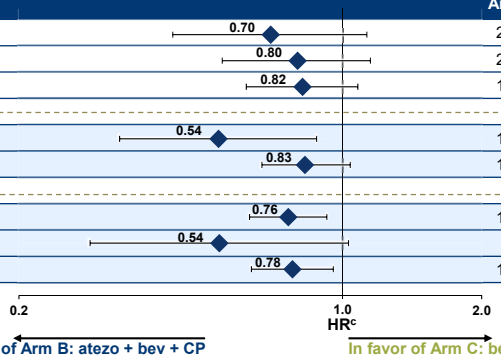
HR[a], 0.78
(95% CI: 0.64, 0.96)
P = .0164
Median follow-up: ~20 mo

No. at Risk																										
Atezo+bev+CP	359	339	328	323	314	310	296	284	273	264	256	250	235	218	188	167	147	133	119	103	84	66	57	41	34	28	16	9	2	2	2
Bev+CP	337	326	315	308	287	280	268	255	247	233	216	203	196	174	152	129	115	101	87	77	66	56	40	32	29	22	13	6	2	1	1	1	1

[a]Stratified HR. Data cutoff: January 22, 2018.
Socinski MA, et al. *J Clin Oncol*. 2018;36(suppl; abstract 9002).
Please see full prescribing information for warnings, efficacy, risk, and safety.

OS in Key Subgroups

Subgroup	n (%)[a]	Median OS, mo: Arm B	Median OS, mo: Arm C
PD-L1–high (TC3 or IC3) WT	136 (20%)	25.2	15.0
PD-L1–low (TC1/2 or IC1/2) WT	226 (32%)	20.3	16.4
PD-L1–negative (TC0 and IC0) WT	339 (49%)	17.1	14.1
Liver metastases WT	94 (14%)	13.2	9.1
No liver metastases WT	602 (86%)	19.8	16.7
ITT (including *EGFR/ALK*+)	800 (100%)	19.8	14.9
EGFR/ALK+ only	104[b] (13%)	NE	17.5
ITT-WT	696 (87%)	19.2	14.7



[a]Prevalence % for PD-L1 IHC and liver metastases subgroups out of ITT-WT (n = 696); prevalence of ITT, *EGFR/ALK*+, and ITT-WT out of ITT (n = 800). [b]One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab. [c]Stratified HR for ITT and ITT-WT; unstratified HR for all other subgroups. Data cutoff: January 22, 2018.
Socinski MA, et al. *J Clin Oncol*. 2018;36(suppl; abstract 9002).

KEYNOTE-042 Study Design

Key Eligibility Criteria
- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS ≥ 1%
- No sensitizing *EGFR* or *ALK* alterations
- ECOG PS 0 or 1
- No untreated or unstable CNS metastases
- No history of pneumonitis that required systemic corticosteroids

Stratification Factors
- Region (east Asia vs rest of the world)
- ECOG PS (0 vs 1)
- Histology (squamous vs nonsquamous)
- PD-L1 TPS (≥ 50% vs 1%-49%)

Randomize 1:1

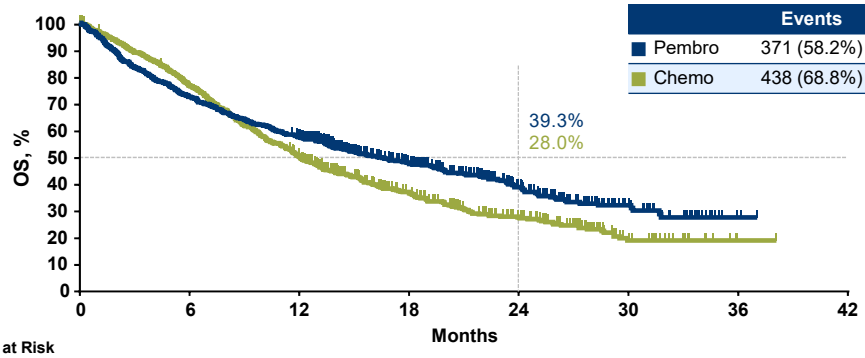
n = 637: Pembrolizumab 200 mg Q3W for up to 35 cycles

n = 637: Carboplatin AUC 5 or 6 Q3W + paclitaxel 200 mg/m² Q3W[a] OR carboplatin AUC 5 or 6 Q3W + pemetrexed 500 mg/m² Q3W[a] for up to 6 cycles

Endpoints
- **Primary:** OS in PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1%
- **Secondary:** PFS and ORR in TPS ≥ 50%, ≥ 20%, and ≥ 1%; safety in TPS ≥ 1%

[a]Pemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology.
Lopes G, et al. *J Clin Oncol*. 2018;36(suppl; abstract LBA4).

OS: TPS ≥ 1%



	Events	HR (95% CI)	*P*
Pembro	371 (58.2%)	0.81 (0.71-0.93)	.0018
Chemo	438 (68.8%)		

Median (95% CI)
16.7 mo (13.9-19.7)
12.1 mo (11.3-13.3)

No. at Risk								
Pembro	637	463	365	214	112	35	2	0
Chemo	637	485	316	166	88	24	1	0

Data cutoff date: February 26, 2018.
Lopes G, et al. *J Clin Oncol*. 2018;36(suppl; abstract LBA4).
Please see full prescribing information for warnings, efficacy, risk, and safety.

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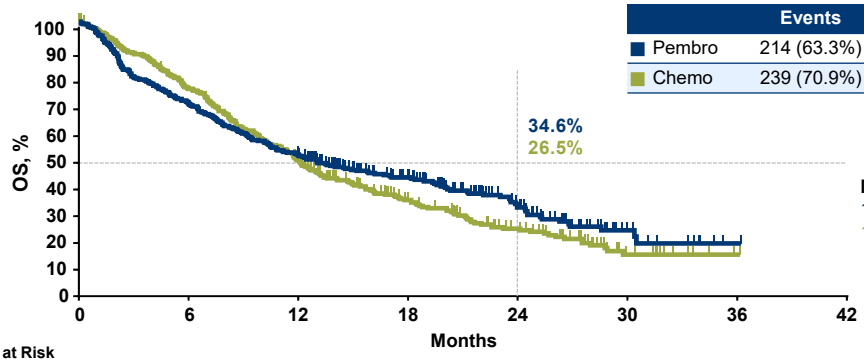
OS: TPS ≥ 1%-49% (Exploratory Analysis[a])



	Events	HR (95% CI)
Pembro	214 (63.3%)	0.92 (0.77-1.11)
Chemo	239 (70.9%)	

Median (95% CI)
13.4 mo (10.7-18.2)
12.1 mo (11.0-14.0)

No. at Risk								
Pembro	338	239	176	107	53	13	0	0
Chemo	337	254	167	91	48	13	0	0

[a]No alpha allocated to this comparison. Data cutoff date: February 26, 2018.
Lopes G, et al. *J Clin Oncol*. 2018;36(suppl; abstract LBA4).
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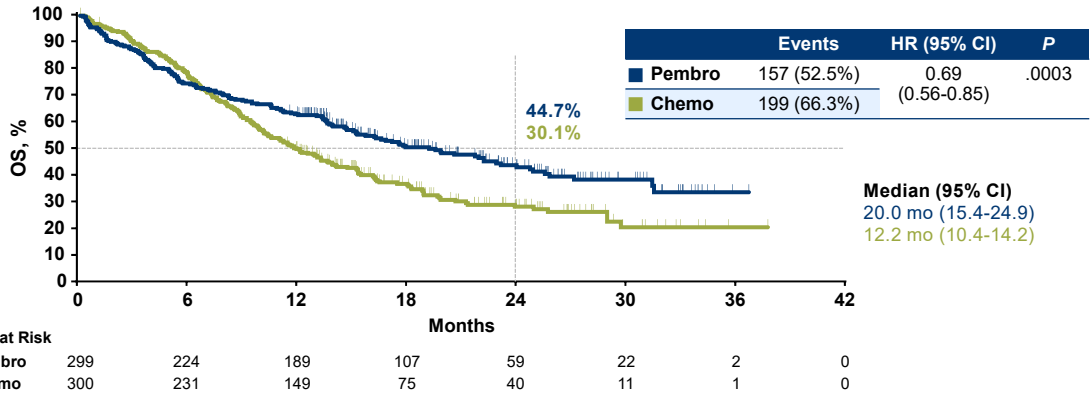
OS: TPS ≥ 50%



	Events	HR (95% CI)	P
Pembro	157 (52.5%)	0.69 (0.56-0.85)	.0003
Chemo	199 (66.3%)		

Median (95% CI)
20.0 mo (15.4-24.9)
12.2 mo (10.4-14.2)

No. at Risk								
Pembro	299	224	189	107	59	22	2	0
Chemo	300	231	149	75	40	11	1	0

Data cutoff date: February 26, 2018.
Lopes G, et al. *J Clin Oncol*. 2018;36(suppl; abstract LBA4).
Please see full prescribing information for warnings, efficacy, risk, and safety.

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Summary

- Carboplatin, paclitaxel, and pembrolizumab will become an option for patients with advanced NSCLC with squamous histology
- Carboplatin, paclitaxel, bevacizumab, and atezolizumab will become an option for patients with advanced NSCLC with nonsquamous histology
- Pembrolizumab was superior to chemotherapy for patients with PD-L1 ≥ 1%; my practice will be to use single-agent pembrolizumab in patients with PD-L1 ≥ 50%

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Contact Information

Call (toll-free) 866 858 7434
Email info@med-iq.com

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Thoracic Malignancies: Abbreviations and Acronyms

AE = adverse event
ALK = anaplastic lymphoma kinase
AUC = area under the curve
BICR = blinded independent central radiologic review
chemoRT = chemoradiation
CNS = central nervous system
CNS-RT = central nervous system radiation therapy
CP = carboplatin + paclitaxel
CPI = checkpoint inhibitor
DOR = duration of response
ECOG = Eastern Cooperative Oncology Group
EGFR = epidermal growth factor receptor
IA2 = second interim analysis
IHC = immunohistochemistry
ITT = intention to treat
IV = intravenous
KM = Kaplan Meier
NE = not estimable
NR = not reached
NSCLC = non–small cell lung cancer
ORR = objective response rate
OS = overall survival
PD = progressive disease
PD-L1 = programmed death-ligand 1
PFS = progression-free survival
PS = Performance Status
RT = radiation therapy
SBRT = stereotactic body radiotherapy
SCLC = small cell lung cancer
SRS = stereotactic radiosurgery
TPS = tumor proportion score
TSU = thoracic surgeons
VATS = video-assisted thoracoscopic surgery
WBRT = whole-brain radiation therapy
WT = wild type