Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Non-Small Cell Lung Cancer Webinar

Thursday, September 13, 2018

1–2 p.m. EDT

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Brahmer *et al. Journal for ImmunoTherapy of Cancer* (2018) 6:75
https://doi.org/10.1186/s40425-018-0382-2

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC)

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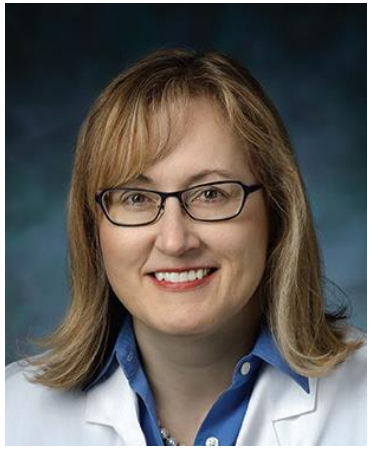
Webinar Faculty



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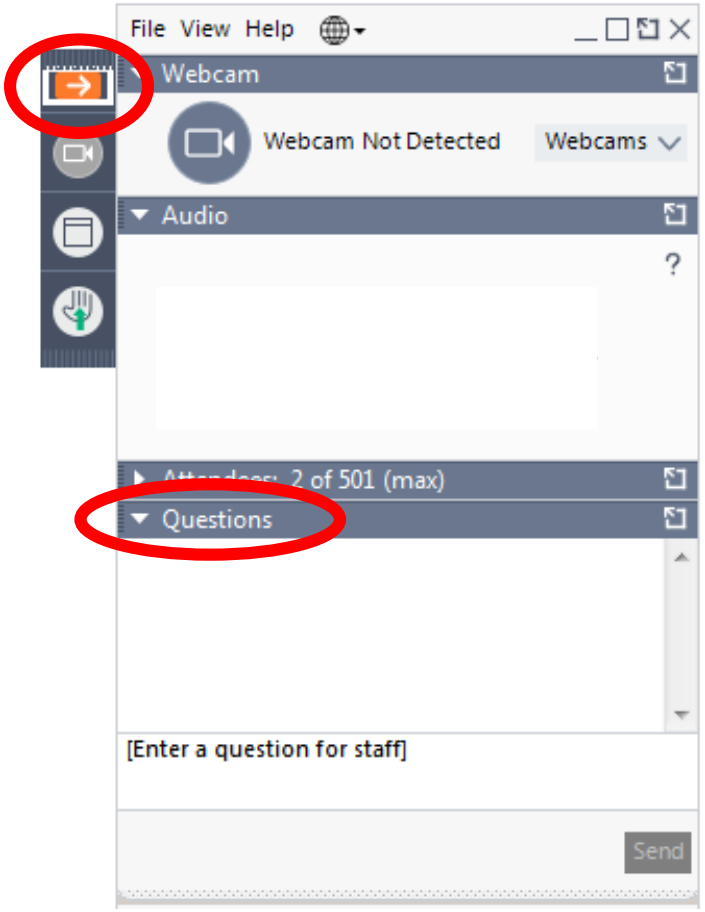
Webinar Agenda

1:00–1:05 p.m. EDT	Welcome and Introductions
1:05–1:40 p.m. EDT	Review of SITC Cancer Immunotherapy Guideline – NSCLC
1:40–1:55 p.m. EDT	Question and Answer Session
1:55–2:00 p.m. EDT	Closing Remarks

To Submit a Question

Computer



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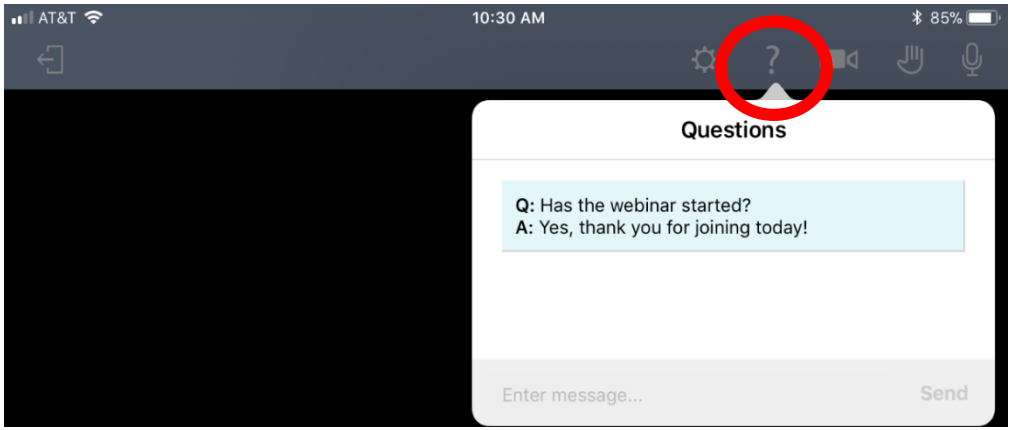

FDA-approved Checkpoint Inhibitors in NSCLC

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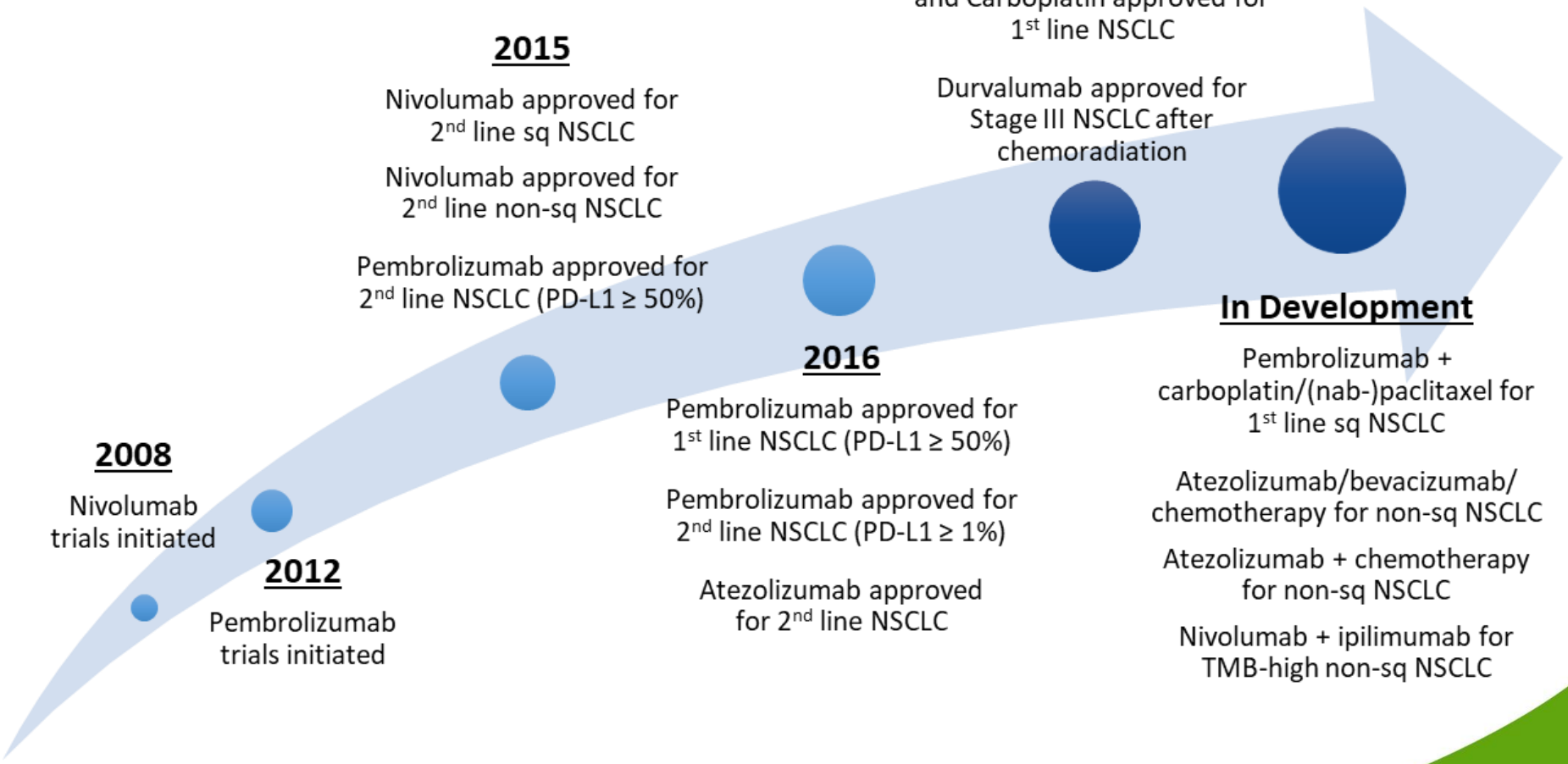

First-Line: Phase III KEYNOTE-024 Trial

Pembrolizumab vs Platinum Doublet Chemotherapy for PD-L1 ≥ 50% NSCLC (without EGFRm/ALKr)

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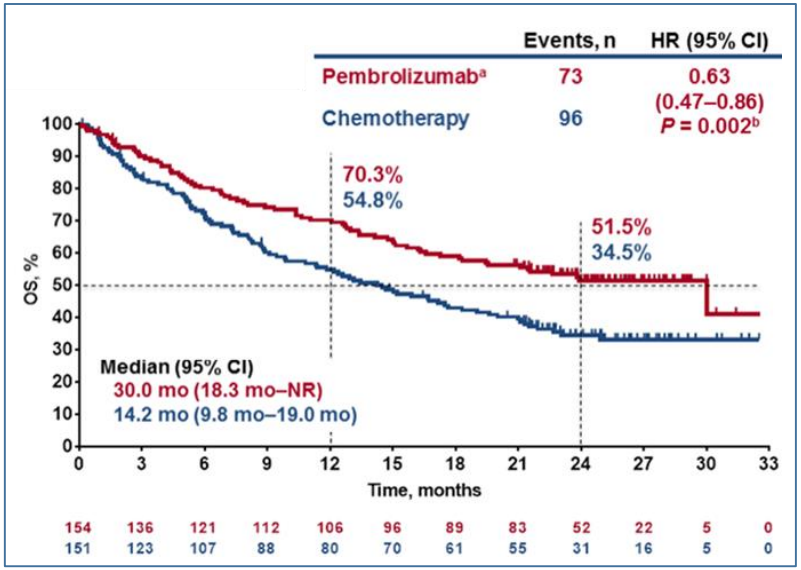

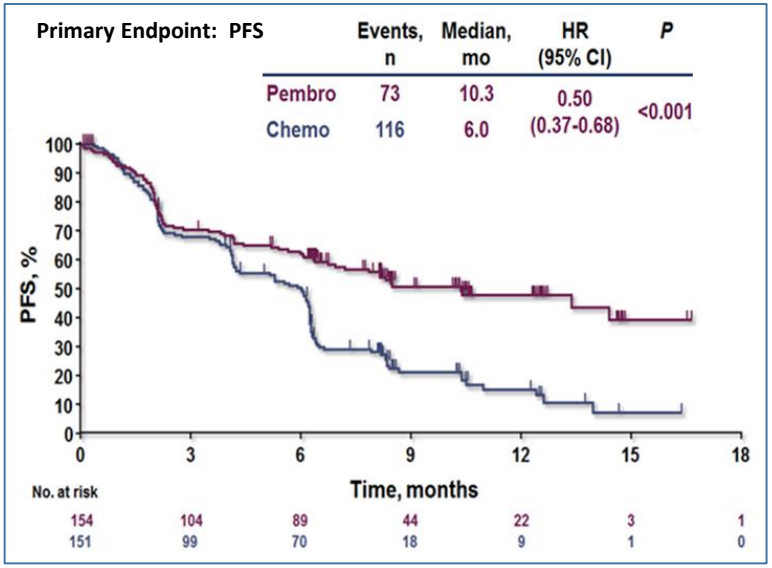

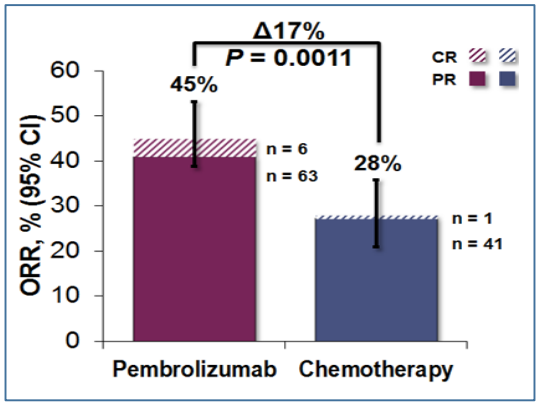

	Crossover to Pembrolizumab N = 82
Objective Response, n	17
ORR, % (95% CI)	20.7 (12.6–31.1)
Median Time to Response, mo (range)	2.0 (1.1–8.4)
Censored duration of response, n	12

Reck et al, ESMO 2016, NEJM 2016; Brahmer et al. WCLC 2017

First-Line: Phase III KEYNOTE-042 Trial

Pembrolizumab vs Platinum Doublet Chemotherapy for PD-L1 ≥ 1% NSCLC (without EGFRm/ALKr)

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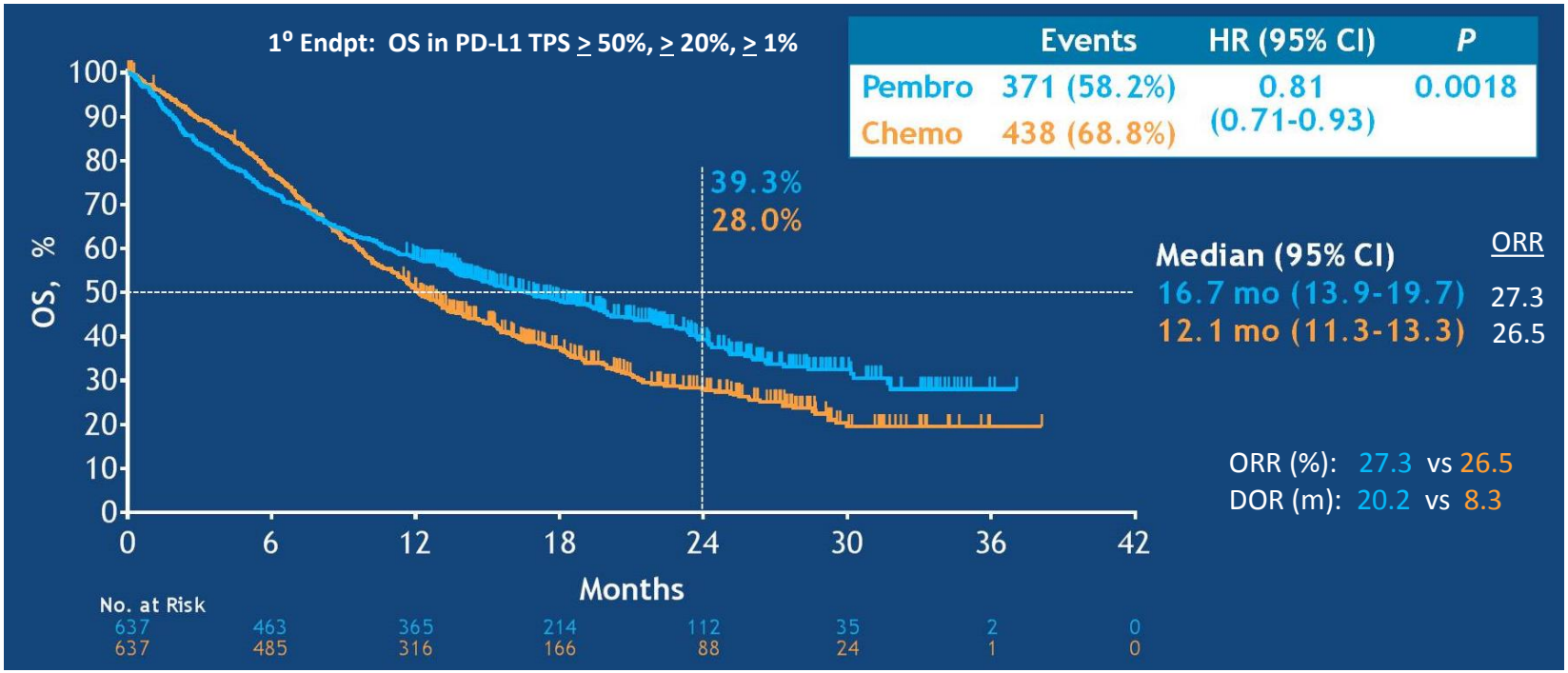

Lopes et al. ASCO 2018

First-Line: Phase III KEYNOTE-042 Trial

Pembrolizumab vs Platinum Doublet Chemotherapy for PD-L1 ≥ 1% NSCLC (without EGFRm/ALKr)

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PD-L1 TPS	≥ 1%	≥ 20%	≥ 50%	1-49%
n (P/ Chemo)	637/ 637	413/ 415	299/ 300	338/ 337
OS HR (95% CI)	**0.81** (0.71-0.93)	**0.77** (0.64-0.92)	**0.69** (0.56-0.85)	**0.92** (0.77-**1.11**)
OS (mos) Median (95% CI)	**16.7-12.1** (13.9-19.7) (11.3-13.3)	**17.7/ 13** (15.3-22.1) (11.6-15.3)	**20.2/ 12.2** (15.4-24.9) (10.4-14.2)	**13.4/ 12.1** (10.7-18.2) (11-14)
2yr OS %	**39.3/ 28**	**40.5/ 29.6**	**44.7/ 30.1**	**34.6/ 26.5**
PFS HR (95% CI)	**1.07** (0.94-**1.21**)	**0.94** (0.8-**1.11**)	**0.81** (0.67-.99)	
PFS (mos) Median (95% CI)	**5.4/ 6.5** (4.3-6.2) (6.3-7)	**6.2/ 6.6** (5.1-7.8) (6.2-7.3)	**7.1/ 6.4** (5.9-9) (6.1-6.9)	
1yr PFS %	**28/ 26.6**	**32.4/ 28.8**	**37.4/ 27.3**	
ORR	**27.3/ 26.5**	**33.4/ 28.9**	**39.5/ 32**	

Lopes et al. ASCO 2018

First-Line: Phase III KEYNOTE-189 Trial

Carboplatin/ Cisplatin with Pemetrexed +/- Pembrolizumab for Advanced, Non-squamous NSCLC (without EGFRm/ALKr)

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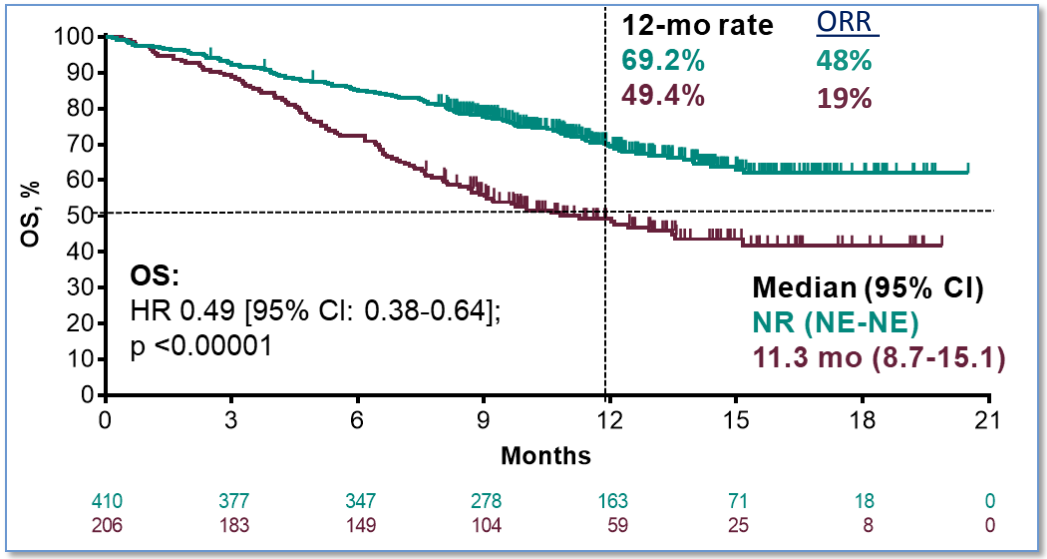
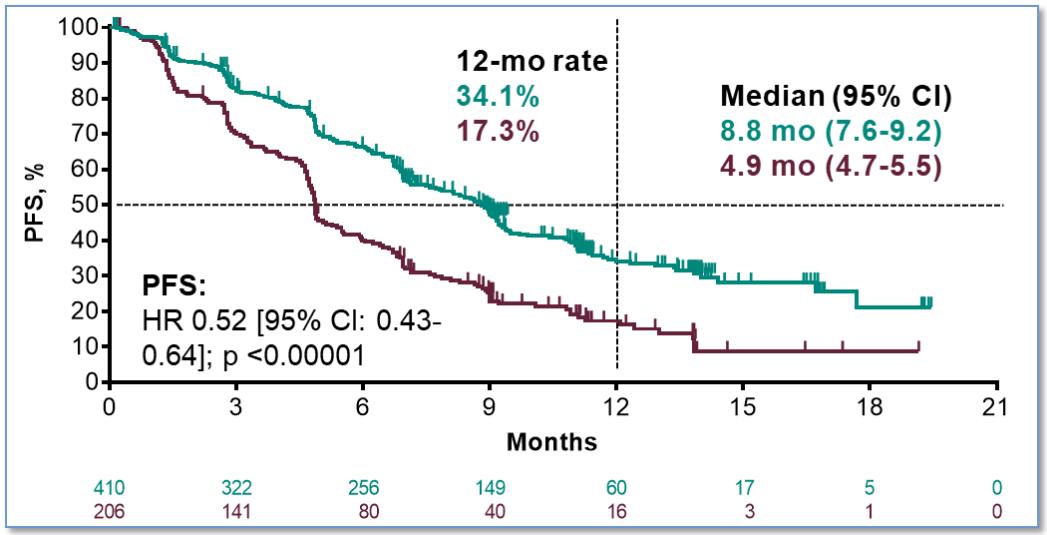
Primary Endpoints: PFS & OS





By PD-L1 TPS

	<1%	1-49%	> 50%
OS HR (95% CI)	**0.59** (0.38-0.92))	**0.55** (0.34-0.90)	**0.42** (0.26-0.68)
OS (mos) Median (95% CI)	**15.2/ 12** (12.3- NE) (7.0-NE)	**NR/ 12.9** (NE-NE) (8.7-NE)	**NR/ 10** (NE-NE) (7.5-NE)
1yr OS %	**61.7/ 52.2**	**71.5/ 50.9**	**73/ 48.1**
PFS HR (95% CI)	**0.75** (0.53- 1.05)	**0.55** (0.37-0.81)	**0.36** (0.25-0.52)
PFS (mos) Median (95% CI)	**6.1/ 5.1** (4.9-7.6) (4.5-6.9)	**9/ 4.9** (7.1-11.3)) (4.6-6.9)	**9.4/ 4.7** (9-13.8) (3.1-6)
1yr PFS %	**19.1/ 15.7**	**37.5/ 19.6**	**44.9/15.4**
ORR	**32.3/ 14.3**	**48.4/ 20.7**	**61.4/ 22.9**

Gandhi et al. NEJM 2018

First-Line: Phase III KEYNOTE-407 Trial

Carboplatin with Paclitaxel/ (nab-)Paclitaxel +/- Pembrolizumab for Advanced, Squamous NSCLC

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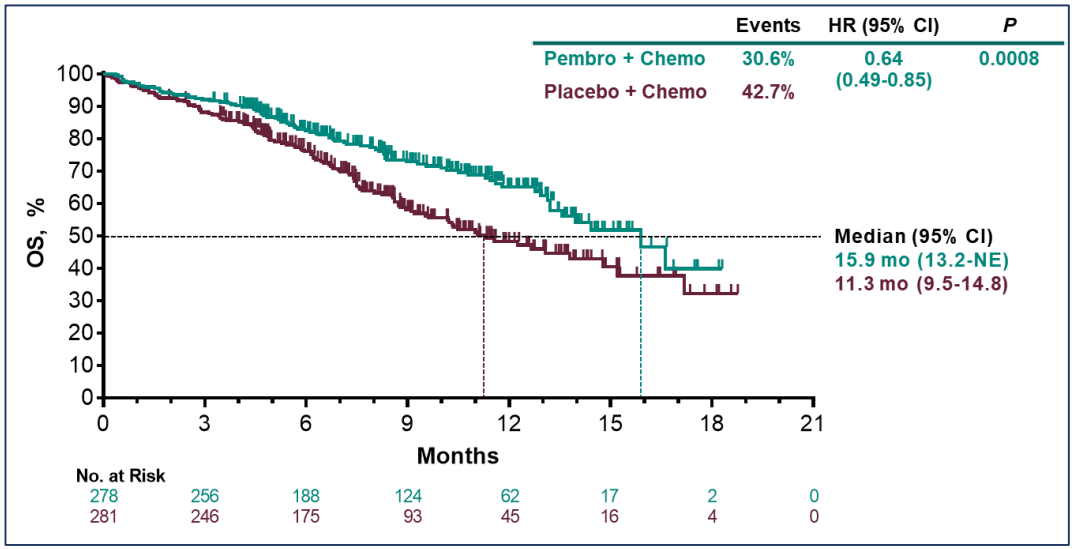
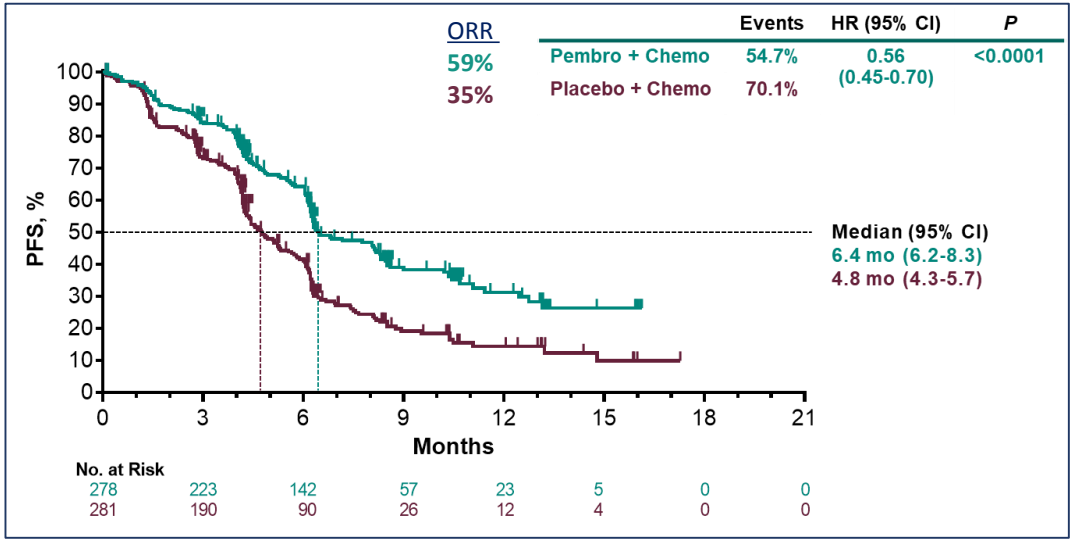
Primary Endpoints: PFS & OS





BICR, blinded, independent central review. Data cutoff date: Apr 3, 2018.

By PD-L1 TPS

	<1%	1-49%	> 50%
OS HR (95% CI)	**0.61** (0.38- 0.98)	**0.57** (0.36-0.90)	**0.64** (0.37-1.10)
OS (mos) Median (95% CI)	**15.9/ 10.2** (13.1- 6NE) (8.6-13.8)	**14.0/ 11.6** (12.8-NE) (8.9-17.2)	**NR/ NR** (11.3-NE) (7.4-NE)
PFS HR (95% CI)	**0.68** (0.47- 0.98)	**0.56** (0.39-0.80)	**0.37** (0.24-0.58)
PFS (mos) Median (95% CI)	**6.3/ 5.3** (6.1- 6.5) (4.4-6.2)	**7.2/ 5.2** (6- 11.4)) (4.2-6.2)	**8/ 4.2** (6.1- 10.3) (2.8-4.6)

Paz Ares et al. ASCO 2018

Efficacy of Anti-PD-1/PD-L1 by EGFR/ALK & PD-L1 Status

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Pembrolizumab (EGFRm and wt)

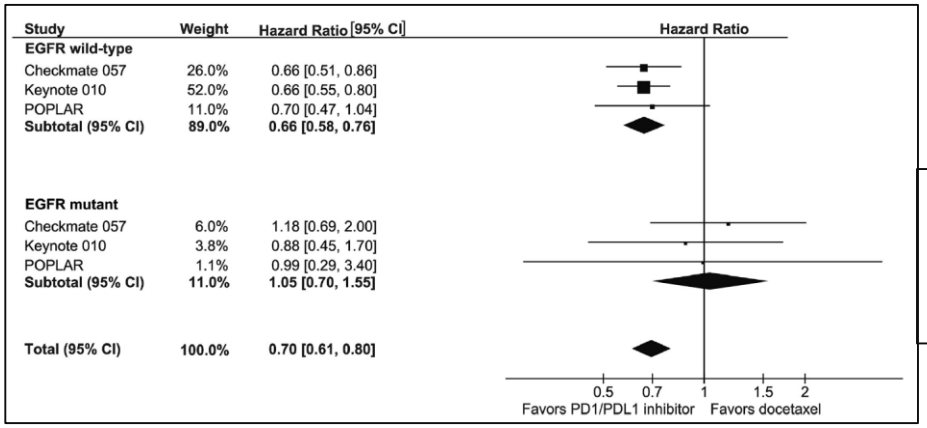
ORR	TPS ≥50%		TPS 1-49%		TPS <1%		Total[a]	
	n	ORR, % (95% CI)	n	ORR, % (95% CI)	n	ORR, % (95% CI)	N	ORR, % (95% CI)
Overall	144	38.2 (30.2-46.7)	185	11.9 (7.6-17.4)	80	10.0 (4.4-18.8)	550	20.2 (16.9-23.8)
EGFR wild type	113	39.8 (30.7-49.5)	156	12.2 (7.5-18.4)	63	12.7 (5.6-23.5)	450	21.6 (17.8-25.6)
EGFR mutant	20	20.0 (5.7-43.7)	23	8.7 (1.1-28.0)	14	0.0 (0.0-23.2)	77	7.8 (2.9-16.2)

Hellman et al, KEYNOTE 001 WCLC 2015

OS	TPS ≥50%		TPS ≥1%		TPS <1%	
Subgroup	n/N[a]	Median, months (95% CI)	n/N[a]	Median, months (95% CI)	n/N[a]	Median, months (95% CI)
EGFR mutation status						
Wild type	60/109	15.7 (11.1-NR)	152/245	13.2 (9.2-15.4)	51/71	9.1 (5.8-13.6)
Mutant	17/19	6.5 (2.0-13.7)	37/45	6.5 (4.4-12.6)	11/17	5.7 (2.2-NR)

[a]n = number of patients who died; N = number of patients in the subgroup.
NR = not reached.

Hui et al, KEYNOTE 001 ASCO 2016



Lee et al, JTO 2016

Durvalumab (EGFRm/ALKr)

Table: 820

	PD-L1 high (≥25%)	PD-L1 low/negative (<25%)
	n = 74[c]	n = 28[c]
ORR,[b] % (95% CI)	12.2 (5.7, 21.8)	3.6 (0.1, 18.3)
DCR, % (95% CI)	20.3 (11.8, 31.2)	7.1 (0.9, 23.5)
mDoR, months (95% CI)	7.4 (5.4, 9.2)	NC
	n = 77[d]	n = 30[d]
mPFS, months (95% CI)	1.9 (1.8, 3.6)	1.9 (1.8, 1.9)
mOS, months (95% CI)	13.3 (8.1, NC)	9.9 (4.2, 13.0)
1-year OS, % (95% CI)	54.8 (41.5, 66.3)	40.0 (22.1, 57.4)
mFollow-up for OS, months	6.5	8.2

Note: 4 patients had PD-L1 expression unknown or missing.
[a]Full analysis set - evaluable for response per independent central review (ICR).
[b]Confirmed response per ICR.
[c]Not calculated due to small number of responders.
[d]Full analysis set.
DCR=disease control rate (complete response, partial response or stable disease ≥24 weeks); DoR=duration of response; m=median; NC=not calculated; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

Garassino et al, ATLANTIC ESMO 2016

- Similar meta-analysis (4 studies) done by Huang et al. (OncoImmunology, 2017)
  - OS HR 1.09 (95% CI: 0.84-1.41)
  - PFS HR 1.44 (95% CI: 1.05-1.98, p=0.02)

Efficacy of Anti-PD-1 in Advanced EGFRm NSCLC

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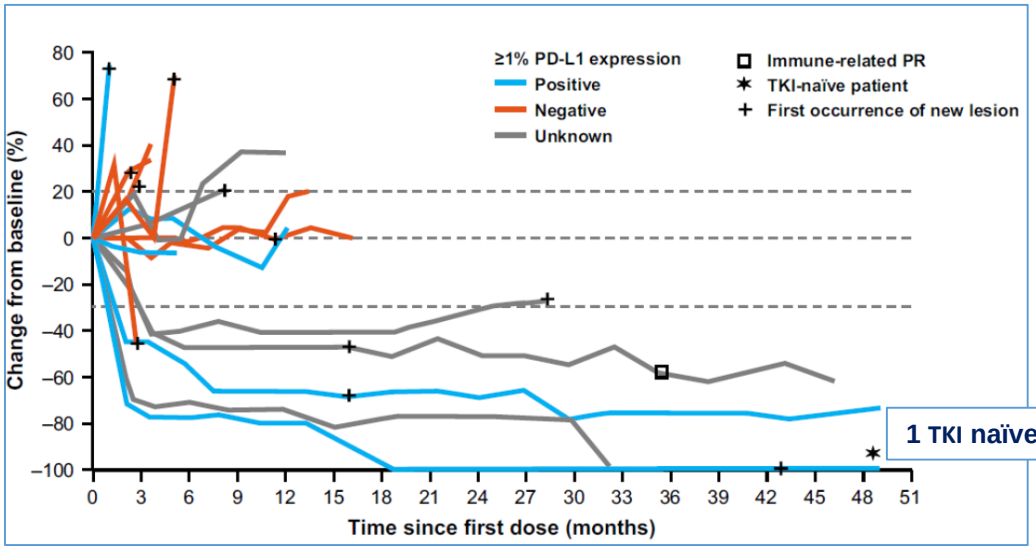
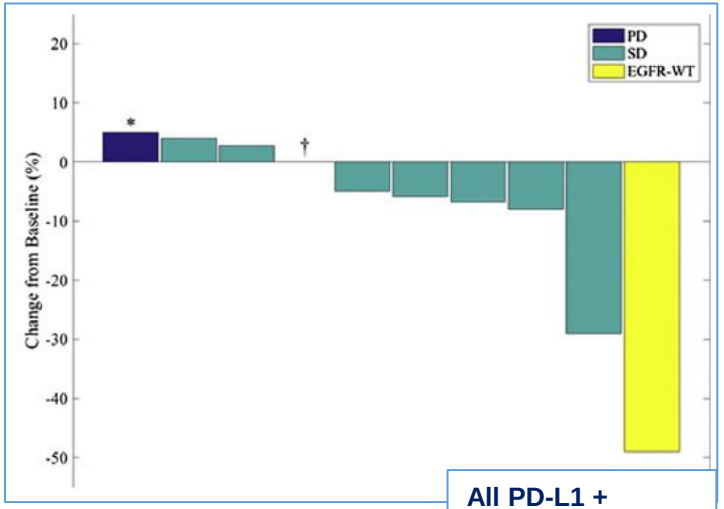
Nivolumab + erlotinib in advanced TKI treated EGFRm NSCLC (TKI last Tx)*

Gettinger et al, Cm-012 JTO 2018



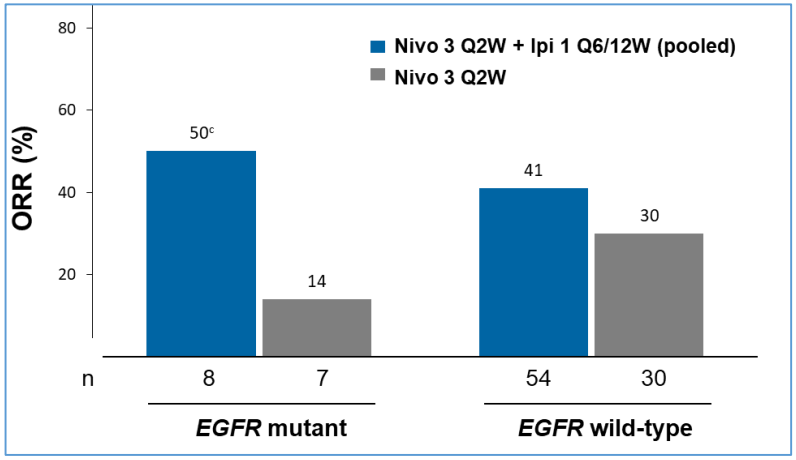
1 TKI naïve pt

Pembrolizumab in Advanced TKI naïve EGFRm NSCLC



Lisberg et al, Cm-012 JTO 2018

All PD-L1 + 7/ 10 EGFRm pts with PD-L1 ≥ 50%



Nivolumab + Ipilimumab in Advanced EGFRm NSCLC

Hellman et al, ASCO 2016, Lancet Oncol 2017

Consensus Recommendations for Advanced NSCLC

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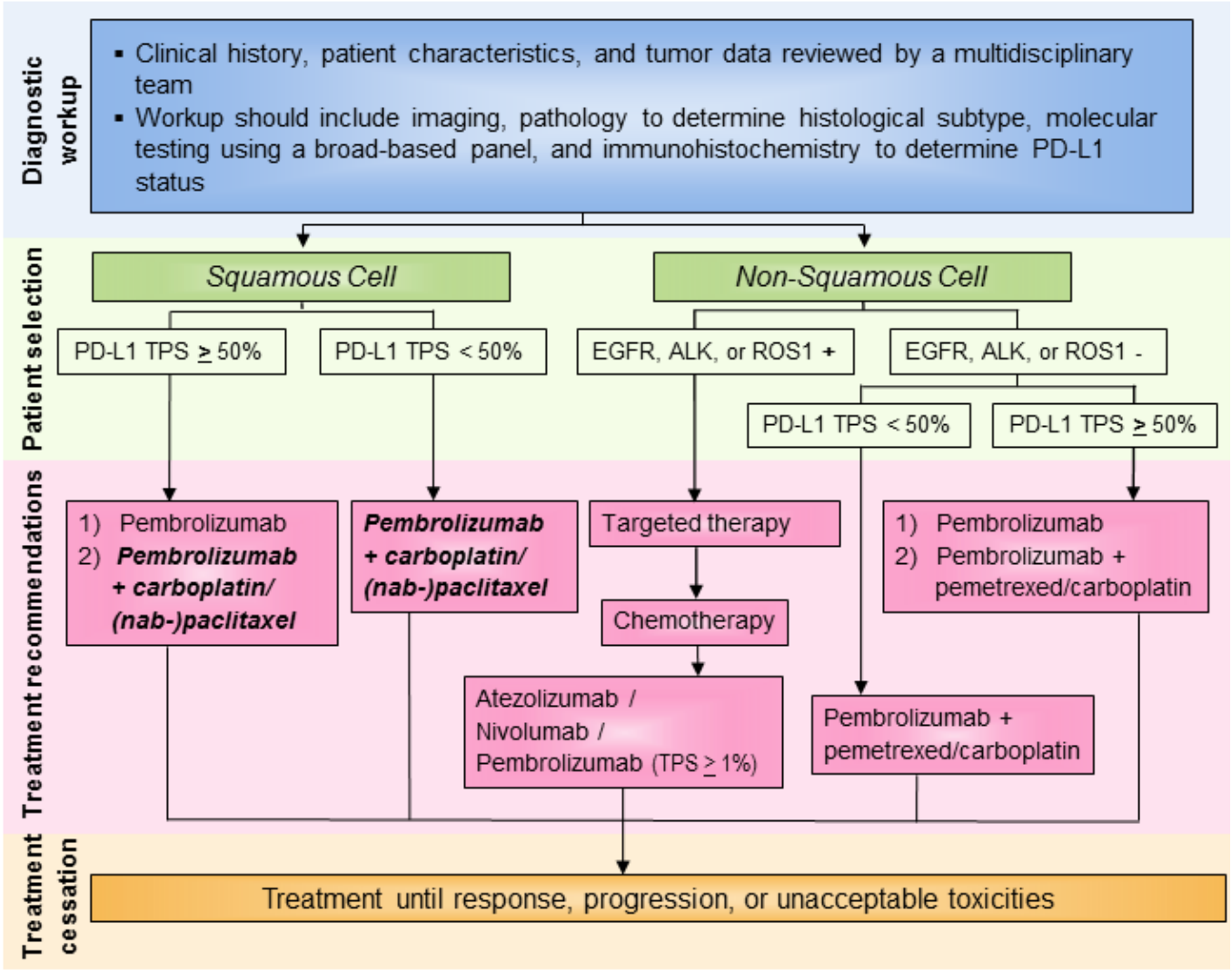

Second-Line: Phase III Trials

Improved OS with PD-1 Axis Inhibitors vs Docetaxel for Advanced NSCLC

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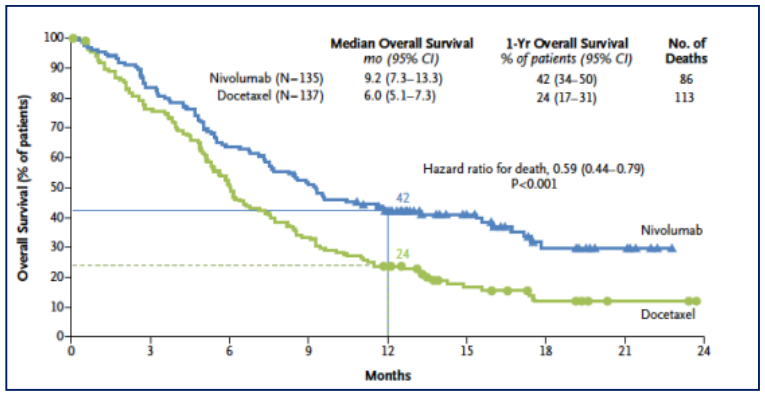
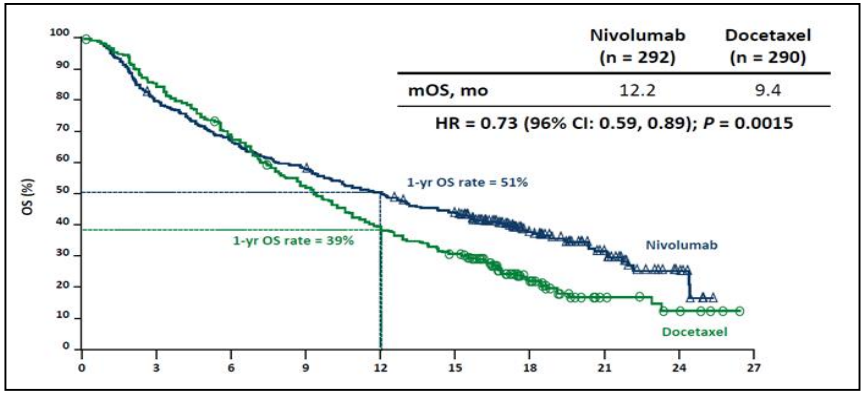
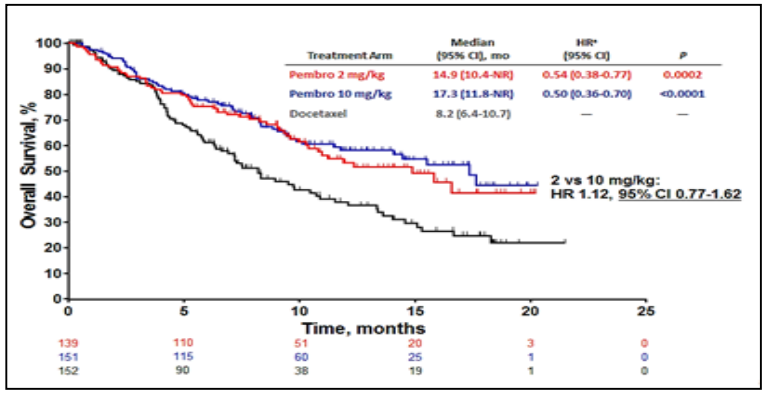
CHECKMATE 017 (Brahmer et al, NEJM 2015)



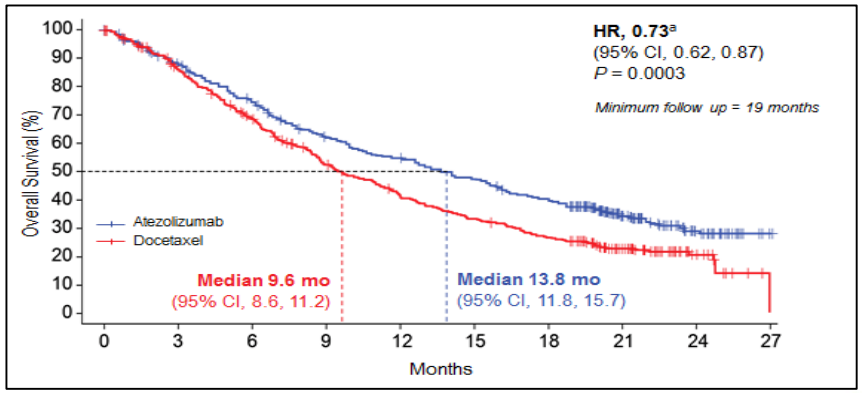
CHECKMATE 057 (Borghaei et al, NEJM 2015)



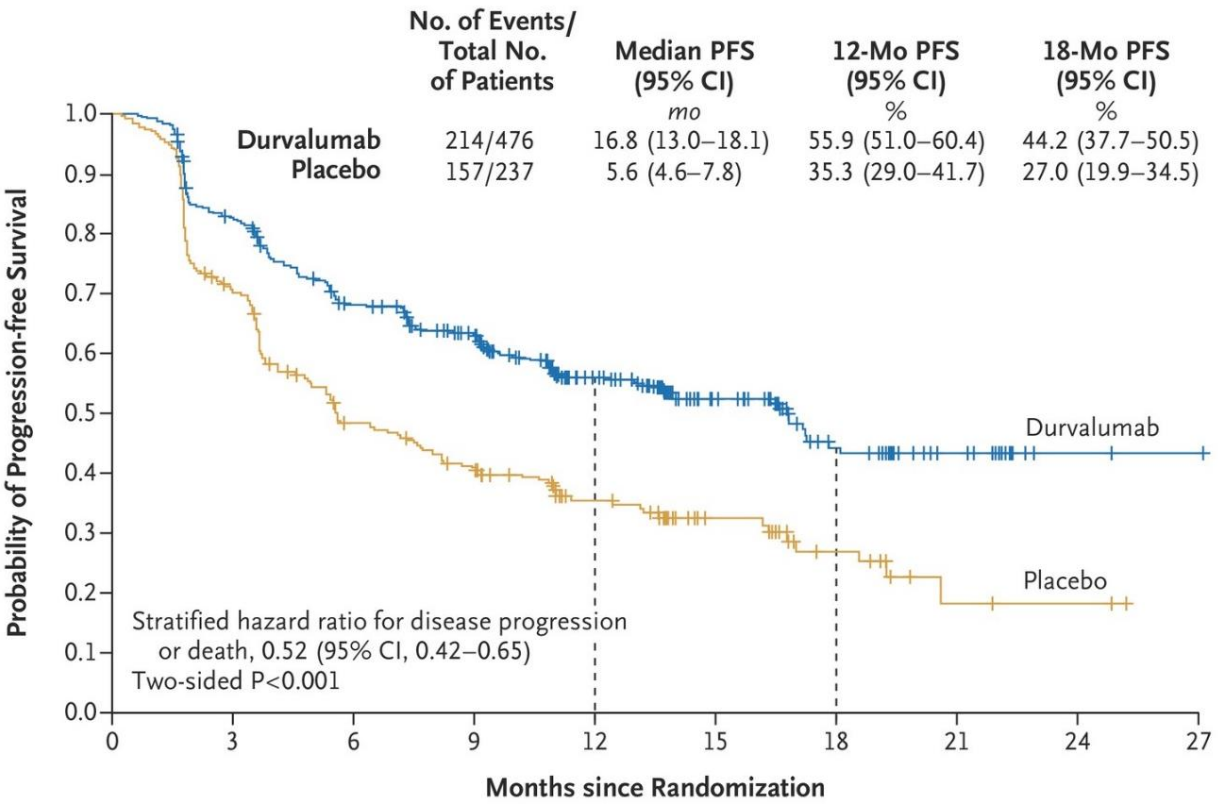
KEYNOTE 010 (TPS ≥ 1%) (Herbst et al, Lancet 2016)



OAK (Rittmeyer et al, Lancet 2017)



Stage III NSCLC: Phase III PACIFIC Trial
Durvalumab After Chemoradiotherapy



- OS primary endpoint met in May, 2018

Antonia et al. NEJM 2017

In Development: IMPOWER 131 Trial

Carboplatin/(nab-)Paclitaxel +/- Atezolizumab in Advanced Squamous NSCLC

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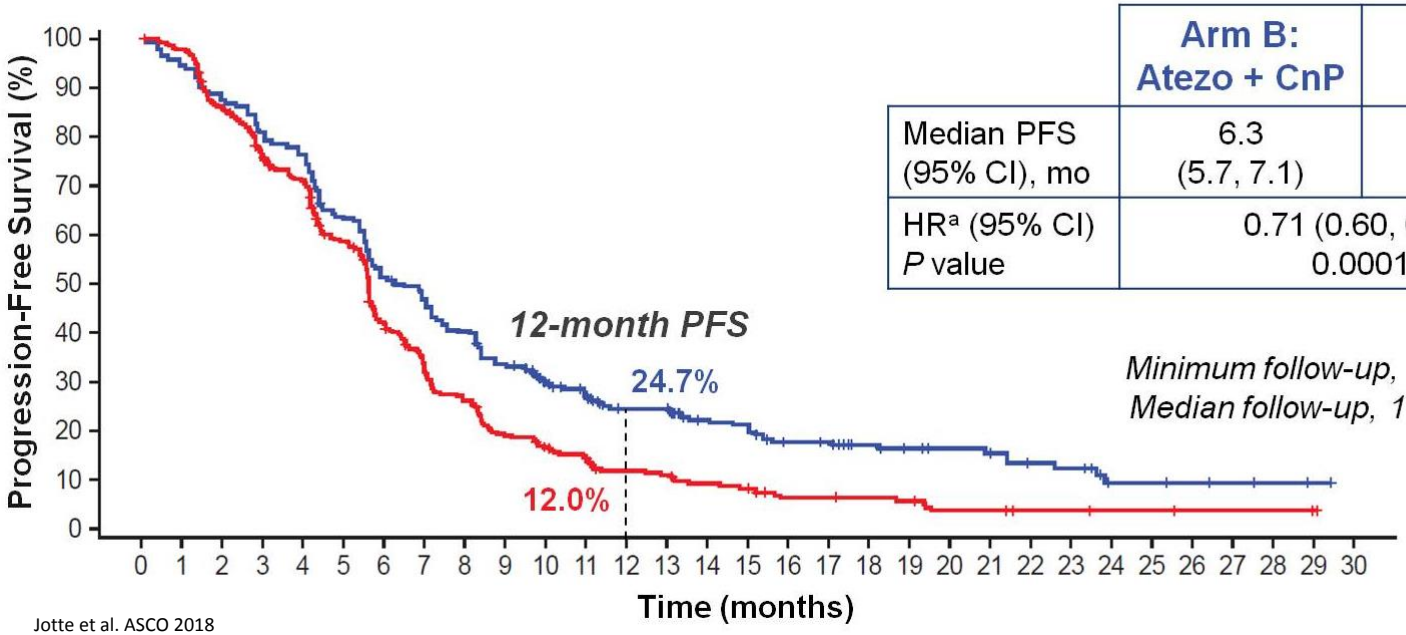

	Arm B: Atezo + CnP	Arm C: CnP
Median PFS (95% CI), mo	6.3 (5.7, 7.1)	5.6 (5.5, 5.7)
HR[a] (95% CI)	0.71 (0.60, 0.85)	
P value	0.0001	

Jotte et al. ASCO 2018

In Development: Atezolizumab/Carboplatin/nab-paclitaxel in advanced **non-squamous** NSCLC

- Phase III IMpower 130 met PFS & OS co-primary endpoints (May 2018)

In Development: IMPOWER 150 Trial

Carboplatin/Paclitaxel/Bevacizumab +/- Atezolizumab in Advanced Non-squamous NSCLC

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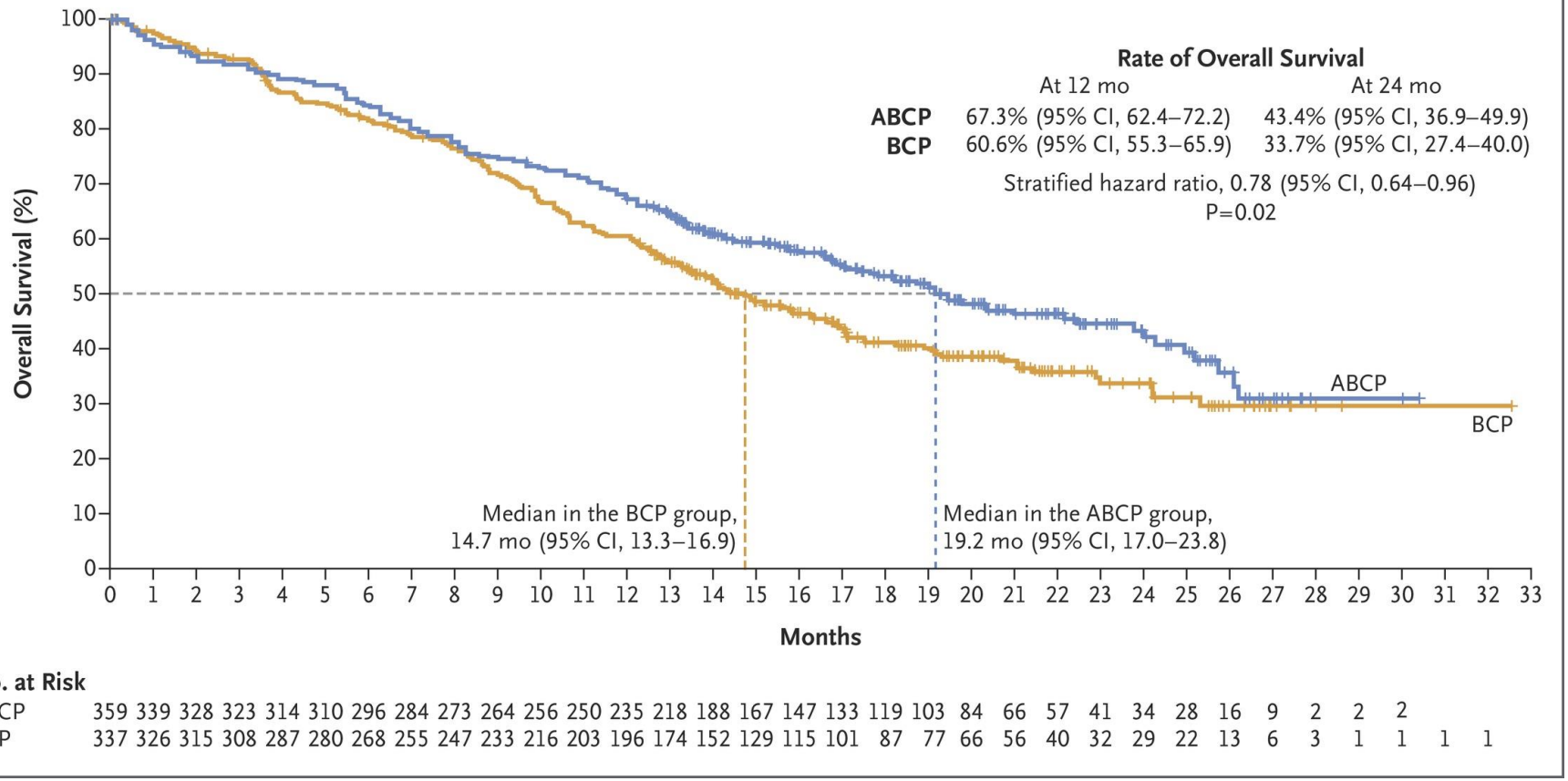

Socinski et al. NEJM 2018

– Improved PFS and OS with addition of atezolizumab to carboplatin/paclitaxel/bevacizumab

Tumor Mutational Burden (TMB) may Determine Sensitivity to PD-1 Blockade in NSCLC

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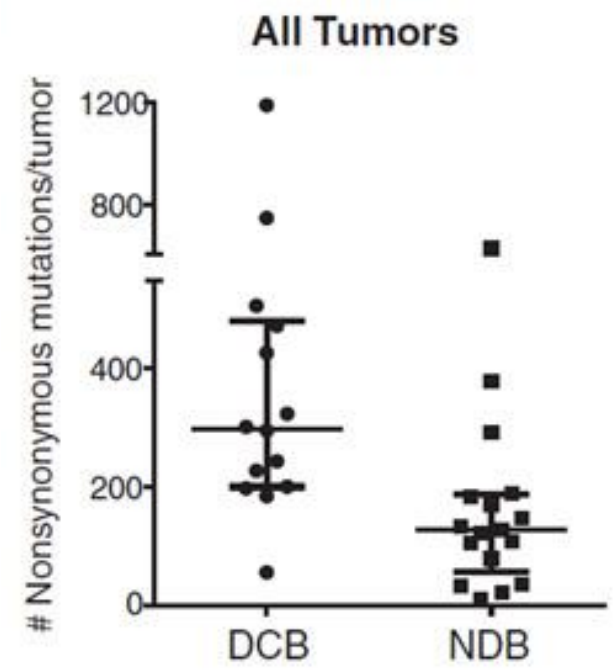

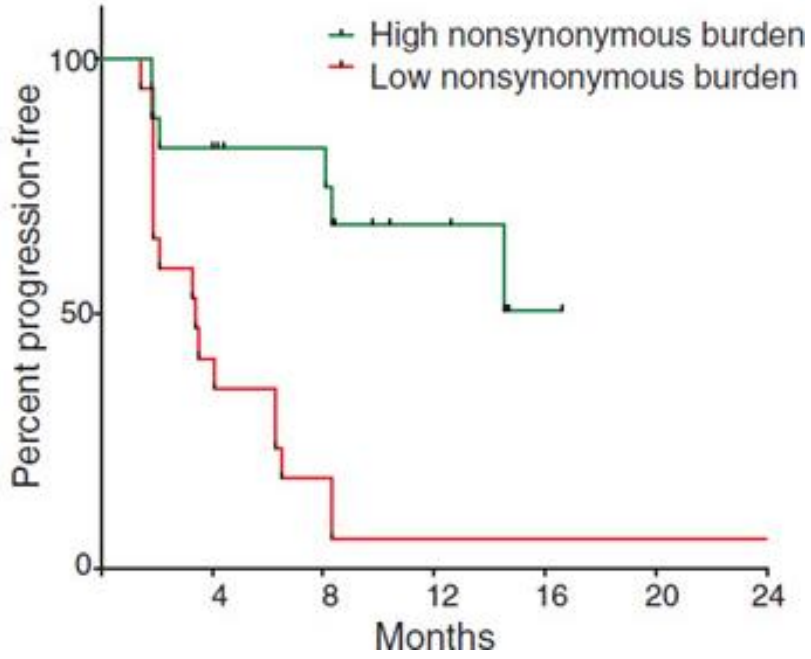

Rizvi et al. Science 2015

Patients whose tumors have higher numbers of mutations are more likely to benefit from PD-1 blockade

In Development: CheckMate 227 Trial

Ipilimumab + Nivolumab vs Chemotherapy in TMB-high NSCLC

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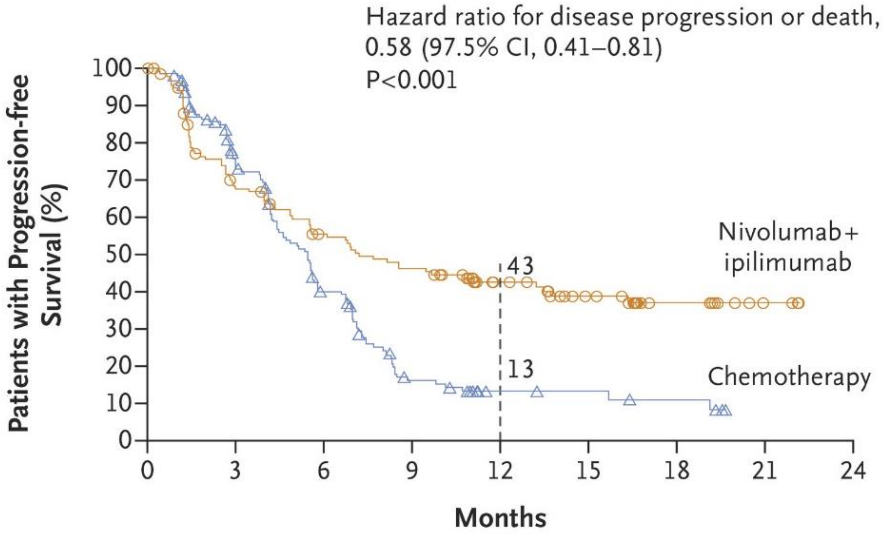

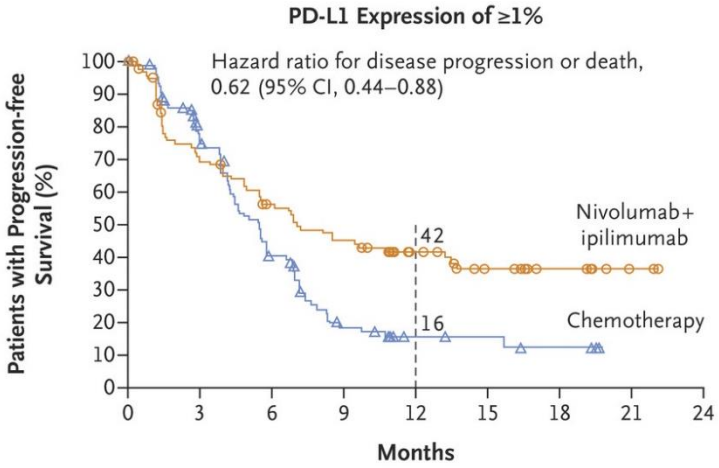

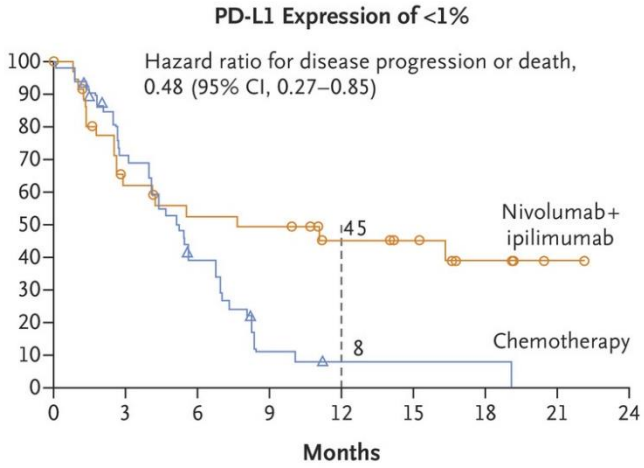

Hellmann et al. NEJM 2018

Consensus Recommendations for Biomarker Testing in NSCLC

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- Unanimous agreement that PD-L1 testing should be performed for all newly diagnosed patients with metastatic disease
  - Including those tested for *EGFR/ALK/ROS1* mutations
  - 100% of Subcommittee members reported experience with PD-L1 testing of patients with newly diagnosed metastatic NSCLC
- 100% of Subcommittee members reported waiting for PD-L1 test results before initiating first-line treatment
- 72% of Subcommittee members did not retest PD-L1-negative patients after disease progression on first-line therapy
- The Subcommittee recognizes TMB testing may be necessary/appropriate for treatment decisions in the near future

Summary of First-line Immunotherapies for Advanced NSCLC

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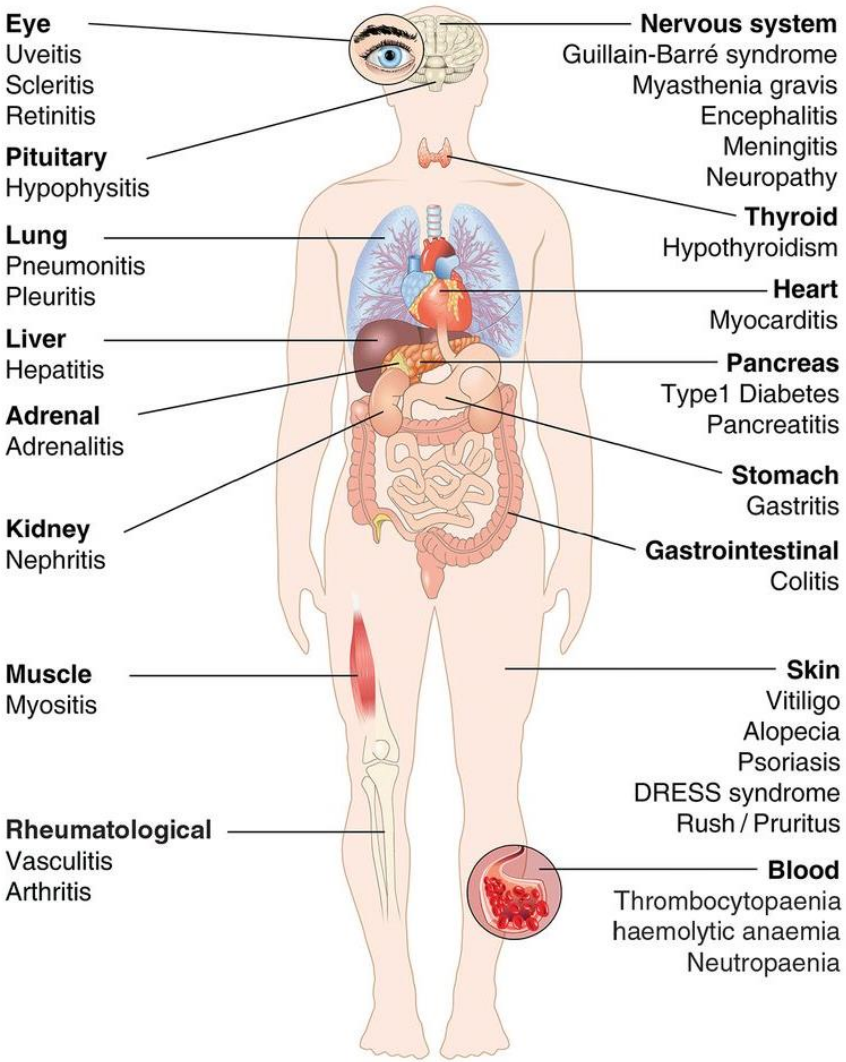
Trial		PFS / OS (months)	PFS HR in PD-L1 neg.	Toxicities Grade 3-5	ORR
KEYNOTE-024 PD-L1≥50%	Pembro Plat/Pem or Gem or Pacli	10.3 / 30 6 / 14.2	NA	27 vs 53%	**44.8%**
KEYNOTE-042 PD-L1≥1%	Pembro Plat/Pem or Pacli	5.4 / 16.7 6.5 / 12.1	NA (in 1-49%: 0.92, NS)	18 vs 41%	**27.3%**
IMPower150 Non-squamous	Atezo + Beva + Plat/Pacli Plat/Pacli	8.3 / 19.2 6.8 / 14.4	0.72	59 vs 50%	**63.5%**
KEYNOTE-189 Non-squamous	Pembro + Plat/Pem Plat/Pem	8.8 / 21.5 4.9 / 11.3	0.59	67 vs 65%	**47.6%**
KEYNOTE-407 Squamous	Pembro + Plat/Pacli or NabPacli Plat/Pacli or NabPacli	6.4 / 15.9 4.8 / 11.3	0.68	70 vs 68%	**58.4%**
CheckMate 227 TMB≥10mut/Mb	Nivo + Ipi Plat/Pem or Gem	7.2 / 23 5.4 / 16.4	0.48	31 vs 36%	**45.3%**

Adapted from Solange Peters, ASCO 2018

Immune-related Adverse Events (irAEs)



Varricchi et al. ESMO Open 2017

Single-agent Toxicities in 2/3L for NSCLC

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	Atezolizumab OAK	Nivolumab SQ: CM 017 (updated OS; 2L)	Nivolumab NSQ:CM 057 (updated OS; 2/3L)	Pembrolizumab KEYNOTE-010
Related Grade 3-5 AEs	15%	8%	11%	13-16%
Discontinuation due to related AEs	5%	6%	6%	4-5%
Pneumonitis incidence	1%	5%	3%	4-5%

Rittmeyer et al. Lancet 2017
Brahmer et al. NEJM 2015
Borghaei et al. NEJM 2015
Herbst et al. Lancet 2015

First-Line: Phase III KEYNOTE-407 Trial

Carboplatin/(nab-)Paclitaxel +/- Pembrolizumab for Advanced, Squamous NSCLC

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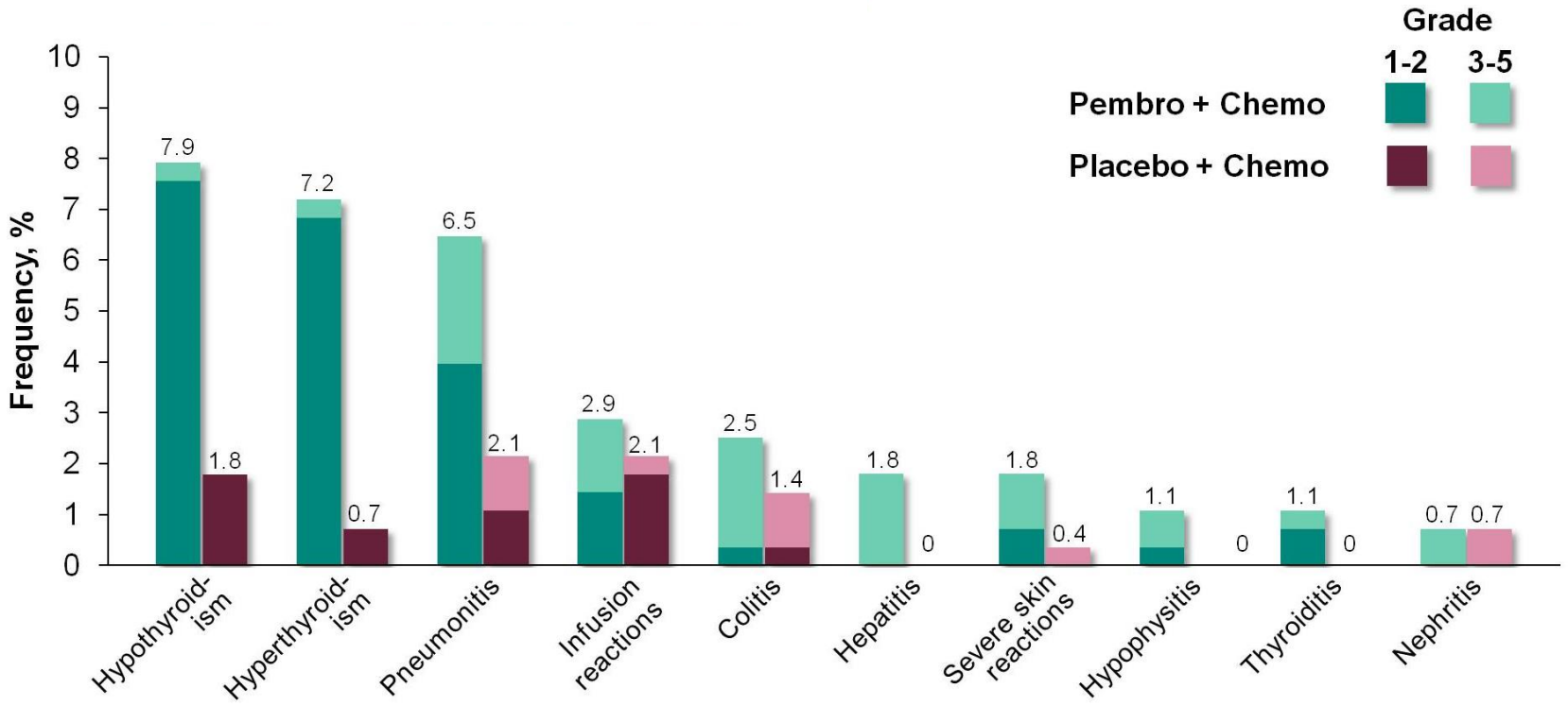

Paz-Ares et al. ASCO 2018

First-Line: Phase III KEYNOTE-189 Trial

Carboplatin/Pemetrexed +/- Pembrolizumab for Advanced, Non-squamous NSCLC (without EGFRm/ALKr)

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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

Ghandi et al. NEJM 2018

In Development: CheckMate 227 Trial

Ipilimumab + Nivolumab vs Chemotherapy in TMB-high NSCLC

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TRAE,[a] %	Nivolumab + ipilimumab (n = 576)		Chemotherapy (n = 570)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE	75	31	81	36
TRAE leading to discontinuation[b]	17	12	9	5
Most frequent TRAEs (≥15%)				
Rash	17	2	5	0
Diarrhea	16	2	10	1
Fatigue	13	1	18	1
Decreased appetite	13	<1	19	1
Nausea	10	<1	36	2
Constipation	4	0	15	<1
Anemia	4	2	32	11
Neutropenia	<1	0	17	9
Treatment-related deaths[c]	1		1	

Hellmann et al. AACR 2018
Hellmann et al. NEJM 2018

Consensus Recommendations for Treatment and Management of irAEs In NSCLC

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- Recommend close monitoring and cross-collaboration with disease specialists
  - Subcommittee members reported past collaborations with
    - Radiologists (79%)
    - Pulmonologists (71%)
    - Dermatologists (71%)
    - Rheumatologists (71%)
    - Endocrinologists (71%)

- ≥50% of Subcommittee members routinely use the following tests to monitor patients treated with immune checkpoint inhibitors
  - Thyroid function studies (93%)
  - Liver function tests (93%)
  - Blood urea nitrogen (BUN) and creatinine (86%)
  - Whole body imaging (71%)
  - Closely monitoring patients' oxygen saturation at rest and on ambulation was also noted

- The Subcommittee recommends patient monitoring and education of pneumonitis
  - All patients with radiographic and/or clinical evidence of pneumonitis should be referred to a pulmonary specialist
  - Grade 2 pneumonitis: immunotherapy should be withheld and steroids administered
  - Grade 3/4 pneumonitis: permanently discontinue immunotherapy and initiate treatment with steroids, including consideration of IV steroids and hospitalization

SITC Toxicity Management Guidelines

sitc Society for Immunotherapy of Cancer
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GUIDELINES

Puzanov et al. Journal for ImmunoTherapy of Cancer (2017) 5:95
DOI 10.1186/s40425-017-0300-z

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

CrossMark

Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

I. Puzanov[1†], A. Diab[2†], K. Abdallah[3], C. O. Bingham III[4], C. Brogdon[5], R. Dadu[2], L. Hamad[1], S. Kim[2], M. E. Lacouture[6], N. R. LeBoeuf[7], D. Lenihan[8], C. Onofrei[9], V. Shannon[2], R. Sharma[1], A. W. Silk[12], D. Skondra[10], M. E. Suarez-Almazor[2], Y. Wang[2], K. Wiley[11], H. L. Kaufman[12†], M. S. Ernstoff[1*†] and on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group

Immunotherapies in Development

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Priming and activation

Anti-CTLA4
Anti-CD137 (agonist)
Anti-OX40 (agonist)
Anti-CD27 (agonist)
IL-2
IL-12

Trafficking of T cells to tumors

Infiltration of T cells into tumors

Anti-VEGF

Cancer antigen presentation

Vaccines
Anti-CD40 (agonist)
TLR agonists
HDAC inhibitors

Recognition of cancer cells by T cells

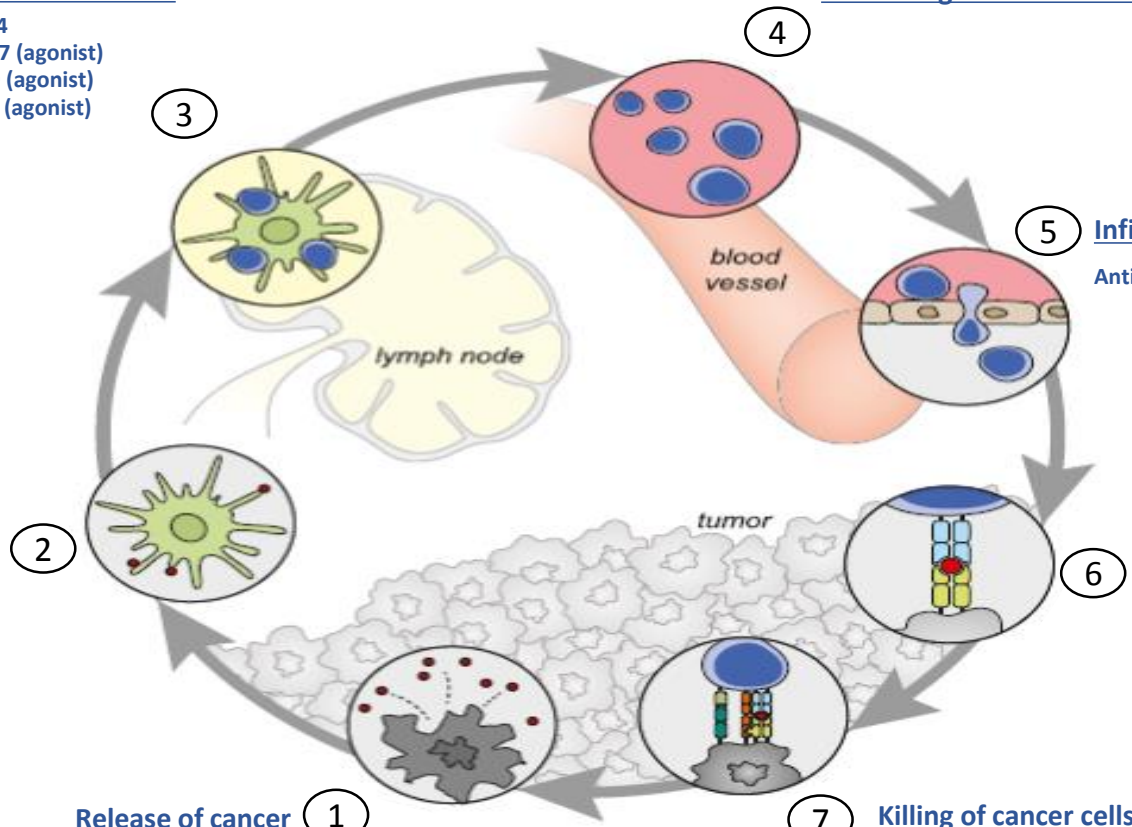
CAR Ts

Release of cancer cell antigens

Chemotherapy
Radiation therapy
Targeted therapy

Killing of cancer cells

Anti-PD-L1
Anti-PD-1
IDO inhibitors
Other Checkpoints



Chen et al. Immunity 2013
Courtesy of Dr. Michael Atkins

Consensus Recommendations for Advanced NSCLC

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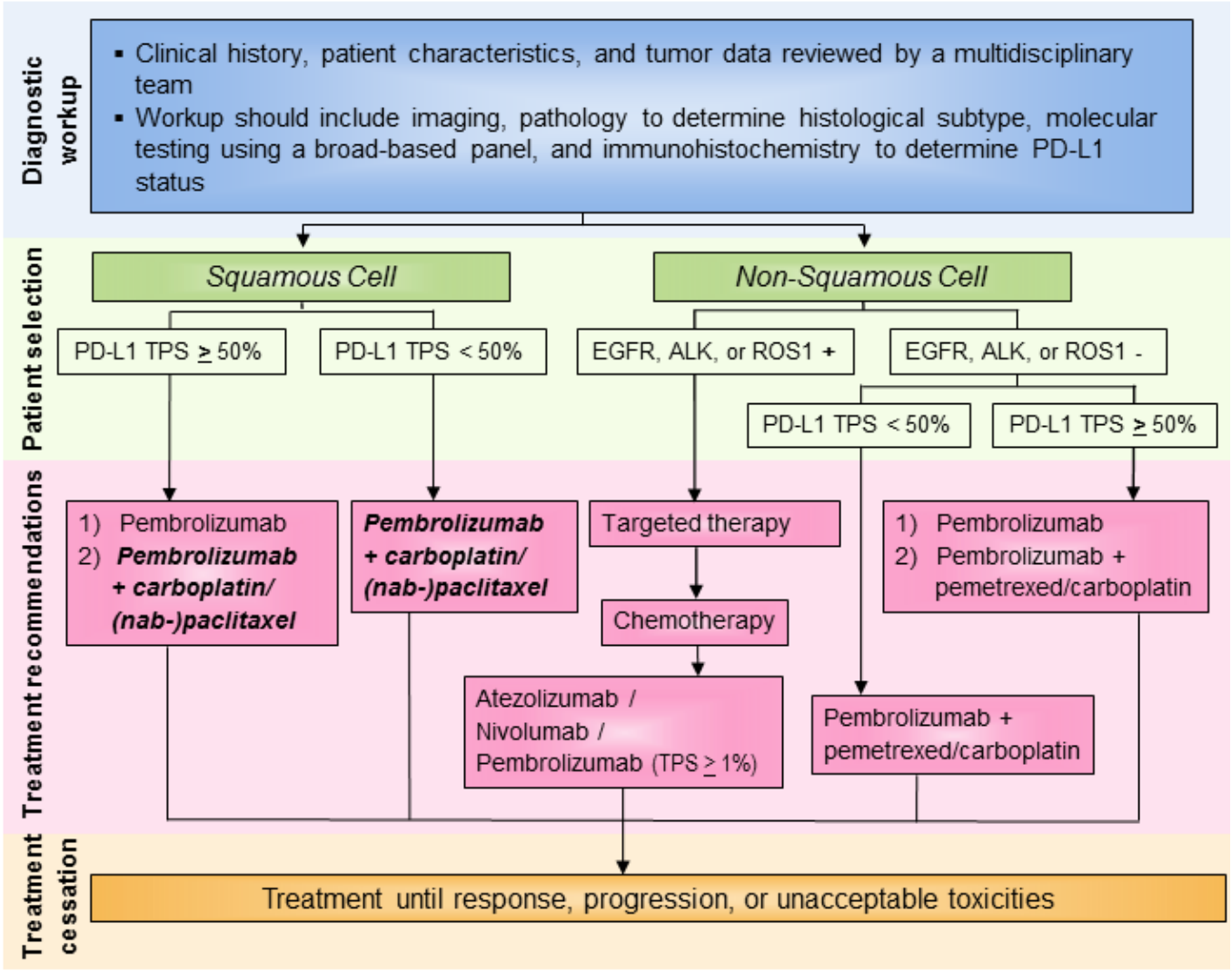

Case Study

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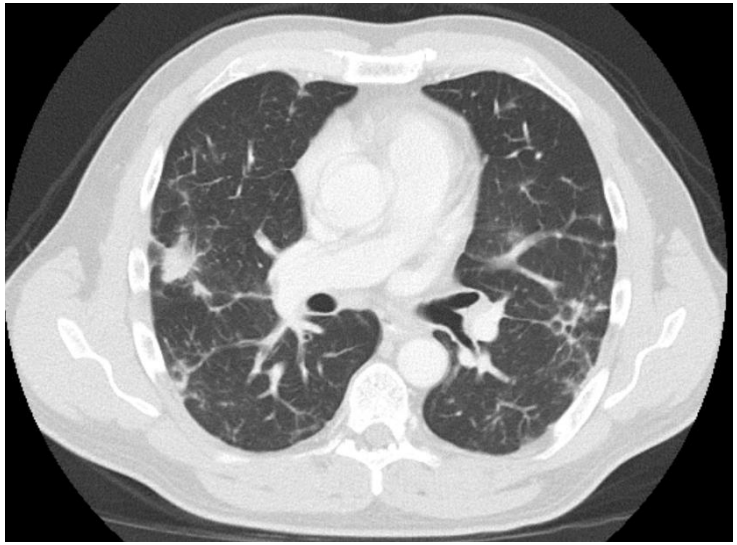
Background:

- 58 year-old male, non-smoker
- 3 month history of cough and shortness of breath, not resolved after two courses of antibiotics
- 20 lb. weight loss, night sweats, several bouts of hemoptysis
- CT scan: Bilateral lung metastases
- Biopsy
  - Adenocarcinoma
  - KRAS/p53 mutation positive
  - PD-L1 is 1%
  - TMB-intermediate of 8 mutations/MB
- Brain MRI negative for intra-parenchymal metastasis



Case Study

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For this specific patient, which regimen would be most appropriate for improved survival?

A. Pembrolizmab

B. Pembrolizumab + Carboplatin/Pemetrexed

C. Carboplatin/Pemetrexed

D. Atezolizumab with Carboplatin/Paclitaxel/Bevacizumab

E. Ipilimumab/Nivolumab

Case Study

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Conclusion/take-away: The upfront treatment of advanced NSCLC patients without an actionable mutation has evolved drastically with the incorporation of immunotherapy to platinum doublet chemotherapy. While single-agent pembrolizumab still remains the standard of care of patients whose tumor PD-L1 is greater than 50% (non-EGFR and/or ALK mutated), those patients whose TPS is between 1 and 50% should be considered for triplet therapy with Carboplatin/Pemetrexed/Pembrolizumab based on the landmark KEYNOTE-189 study. While dual checkpoint blockade with Ipilimumab/Nivolumab remains promising it has only been investigated in patients with TMB-high tumors.

To Submit a Question

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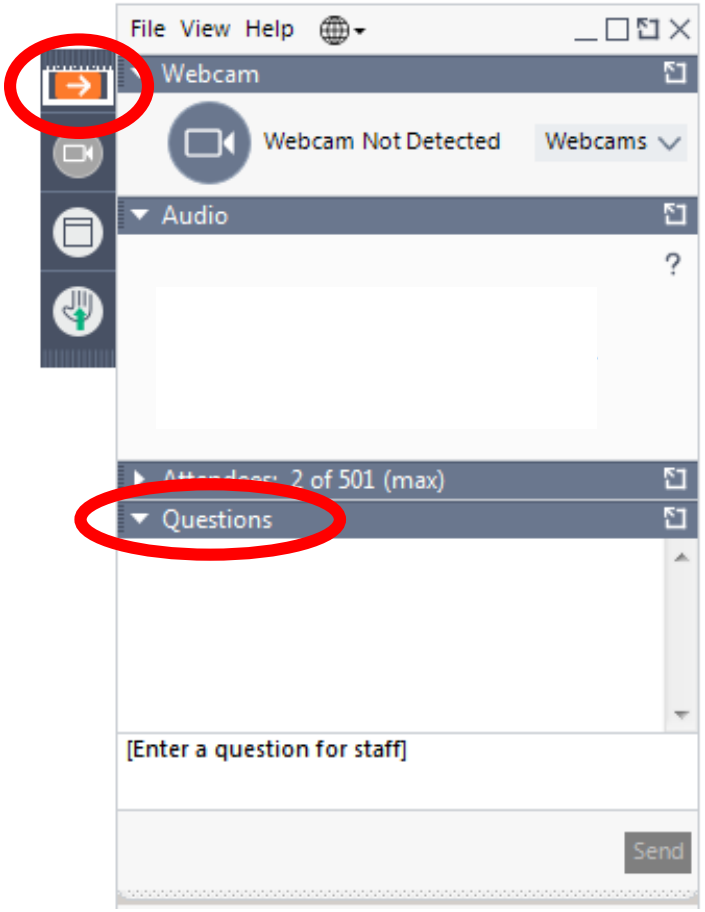
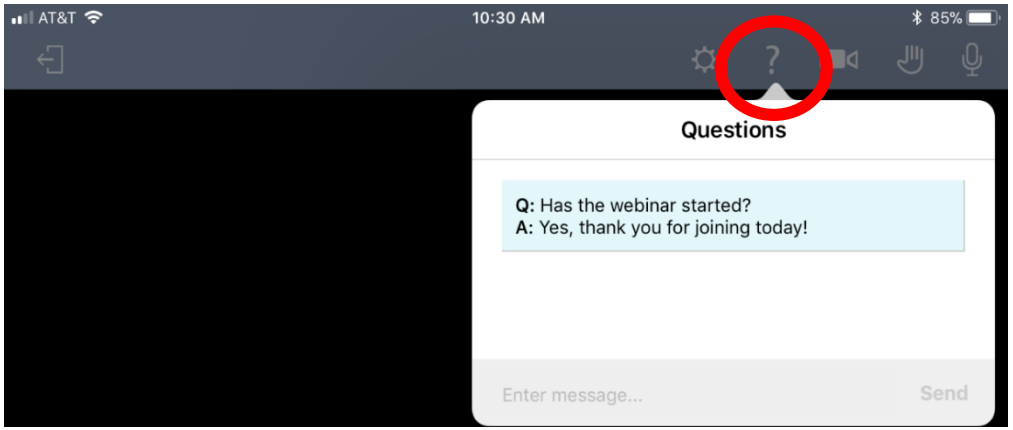
Computer



Mobile Phone



Additional Resources from SITC

Society for Immunotherapy of Cancer
Cancer Immunotherapy GUIDELINES

Cancer Immunotherapy Guidelines:

www.sitcancer.org/cancer-immunotherapy-guidelines

- Expert consensus recommendations
- On-demand webinars

Resources for healthcare providers:

www.sitcancer.org/clinicians

- Educational programs
- Online courses
- Free resources

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Continuing Education Credits are offered for physicians, PA's, NP's, RN's and pharmacists.

You will receive an email following the webinar with instructions on how to claim credit.

Questions and comments: connectED@sitcancer.org

Thank you for attending the NSCLC Webinar!