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Principles and Application of Immunotherapy for Cancer: Advanced NSCLC

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Faculty Disclosures

Naiyer Rizvi, MD, has disclosed that he has received consulting fees from AstraZeneca, Bristol-Myers Squibb, Merck, Novartis, and Roche.

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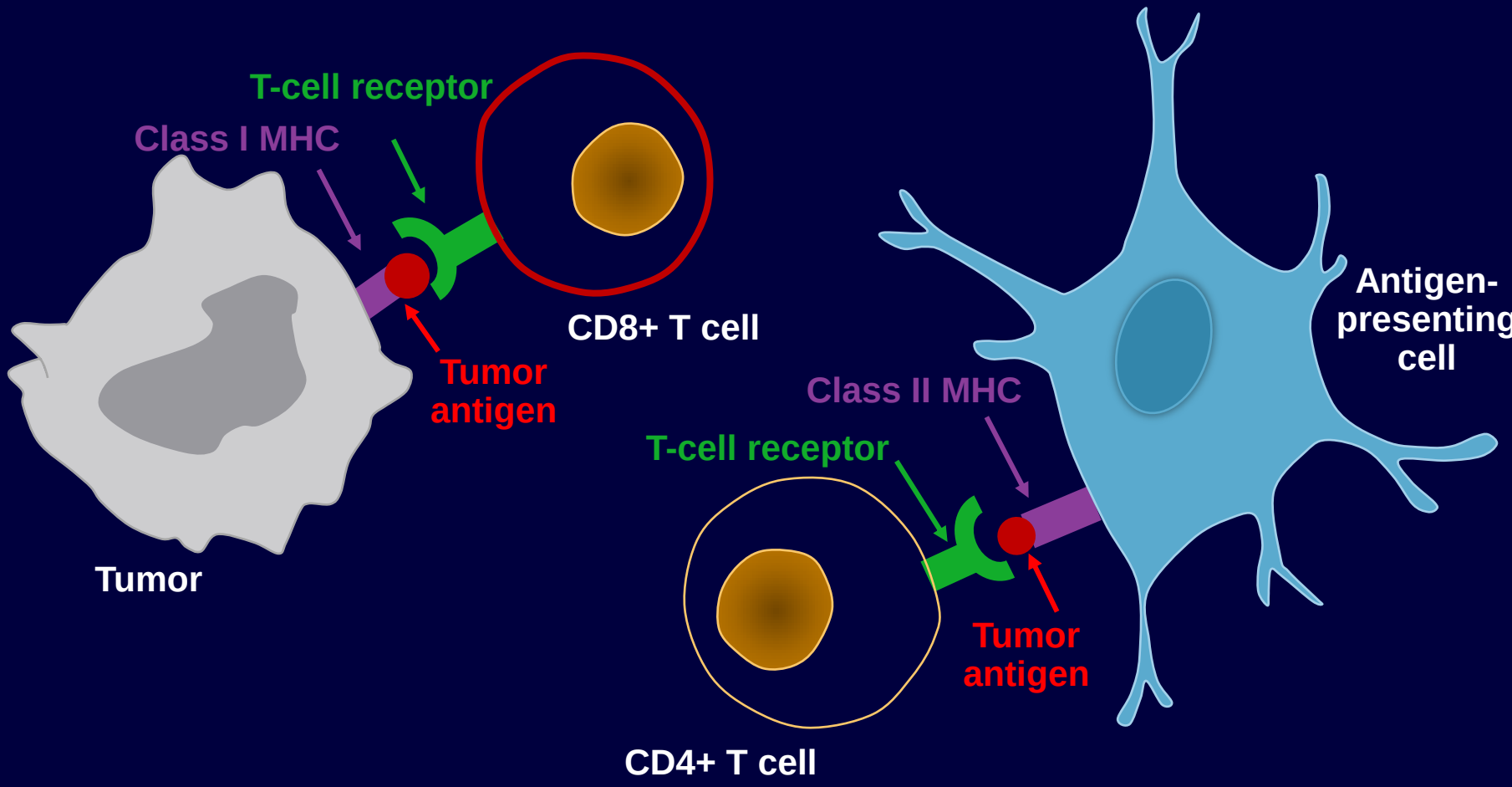
Agenda

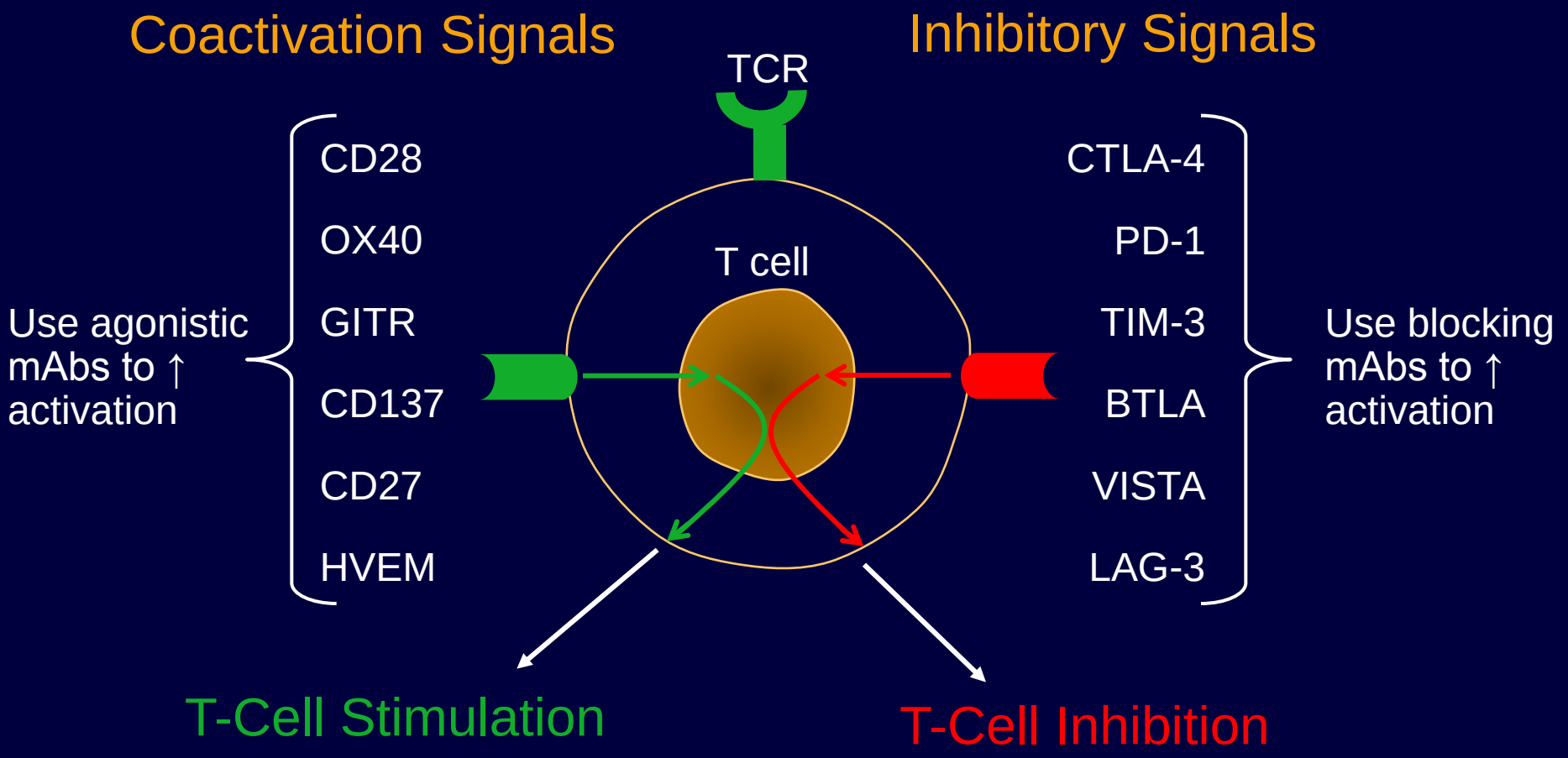
- Lung cancer and the immune system
  - Defining the role of the immune system in cancer
  - Tumor escape from immune surveillance
  - Harnessing the immune system as a treatment strategy for lung cancer
- Incorporating immunotherapeutic agents in lung cancer
  - Efficacy and safety of agents in development
  - Managing potential adverse events associated with immunotherapy
  - Educating pts about immunotherapy
- Selecting pts with lung cancer who may benefit from immunotherapy

T-Cell Response: First Signal



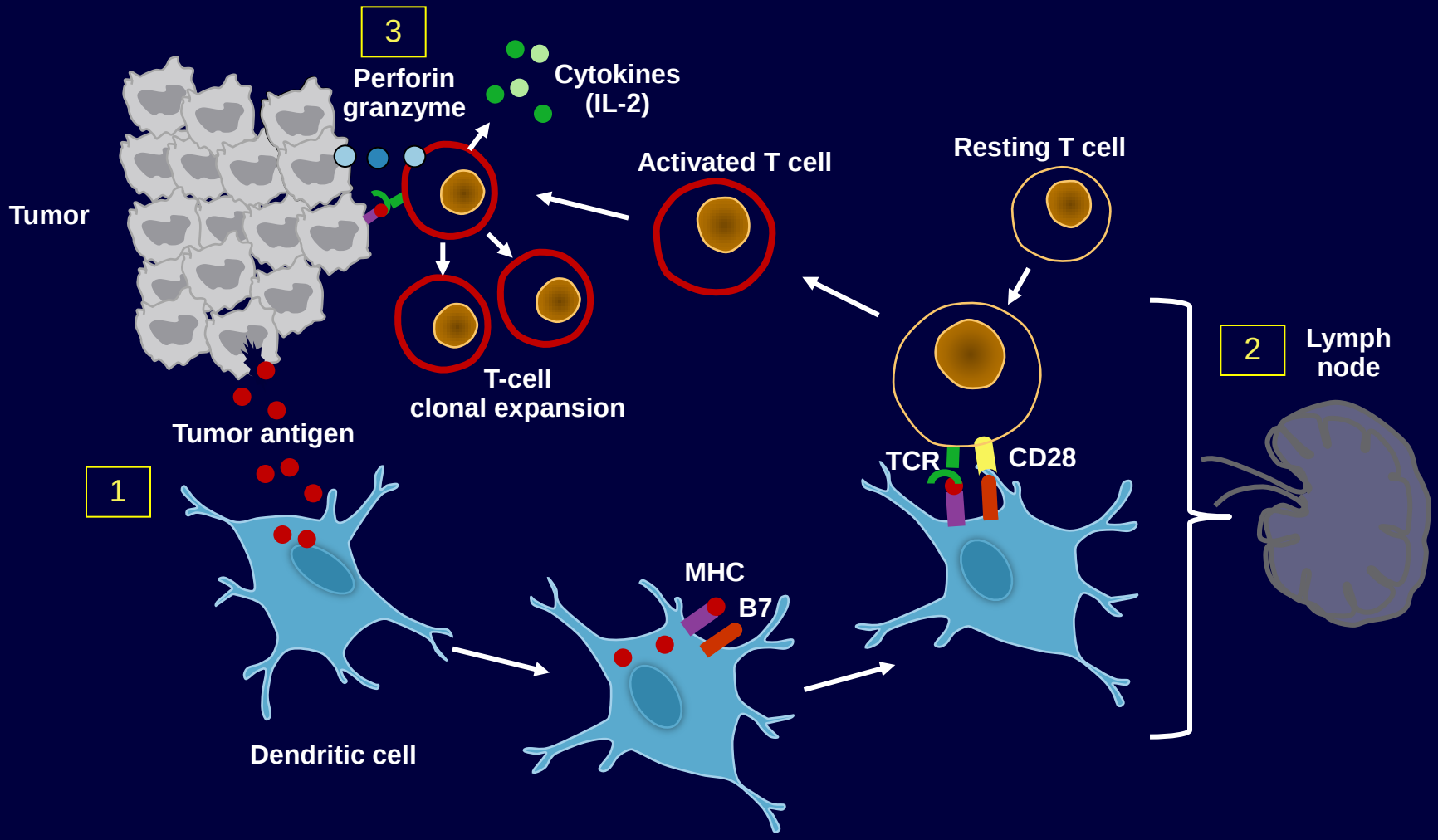
Snyder A, et al. Curr Opin Genet Dev. 2015;30C:7-16.

T-Cell Response: Second Signal



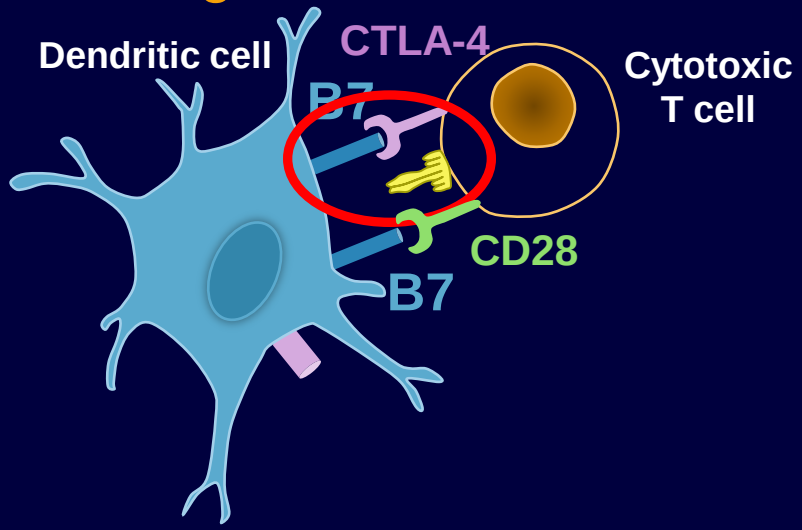
Adapted from Mellman I, et al. Nature. 2011;480:480-489.

Tumor Immunology: Overview

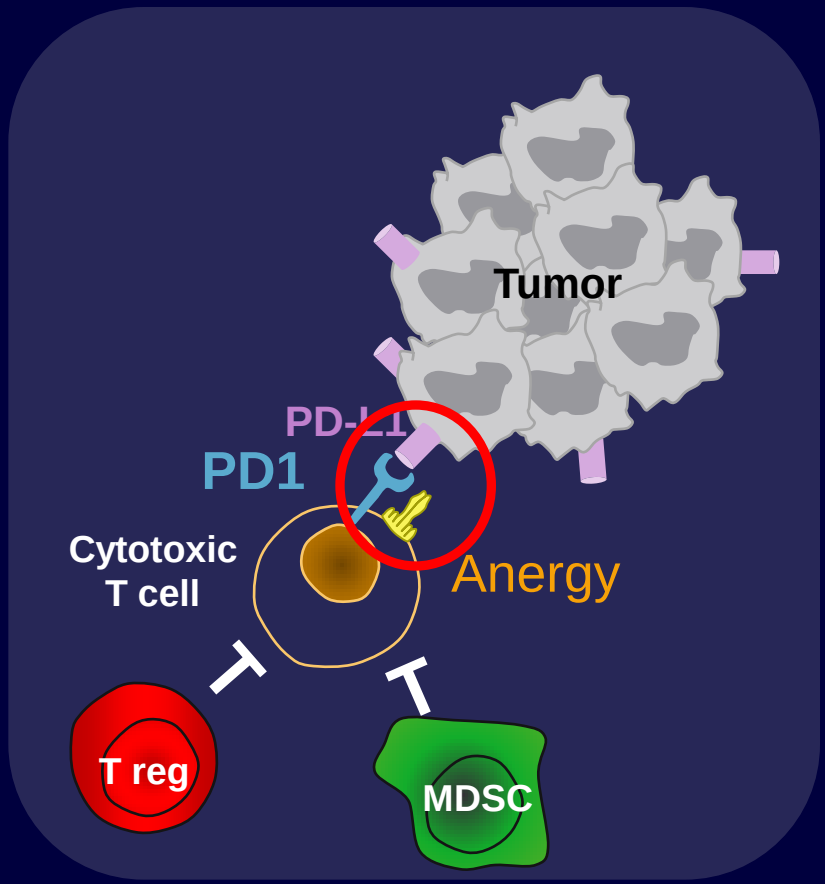


Dampening the Immune System in Cancer

Priming Phase



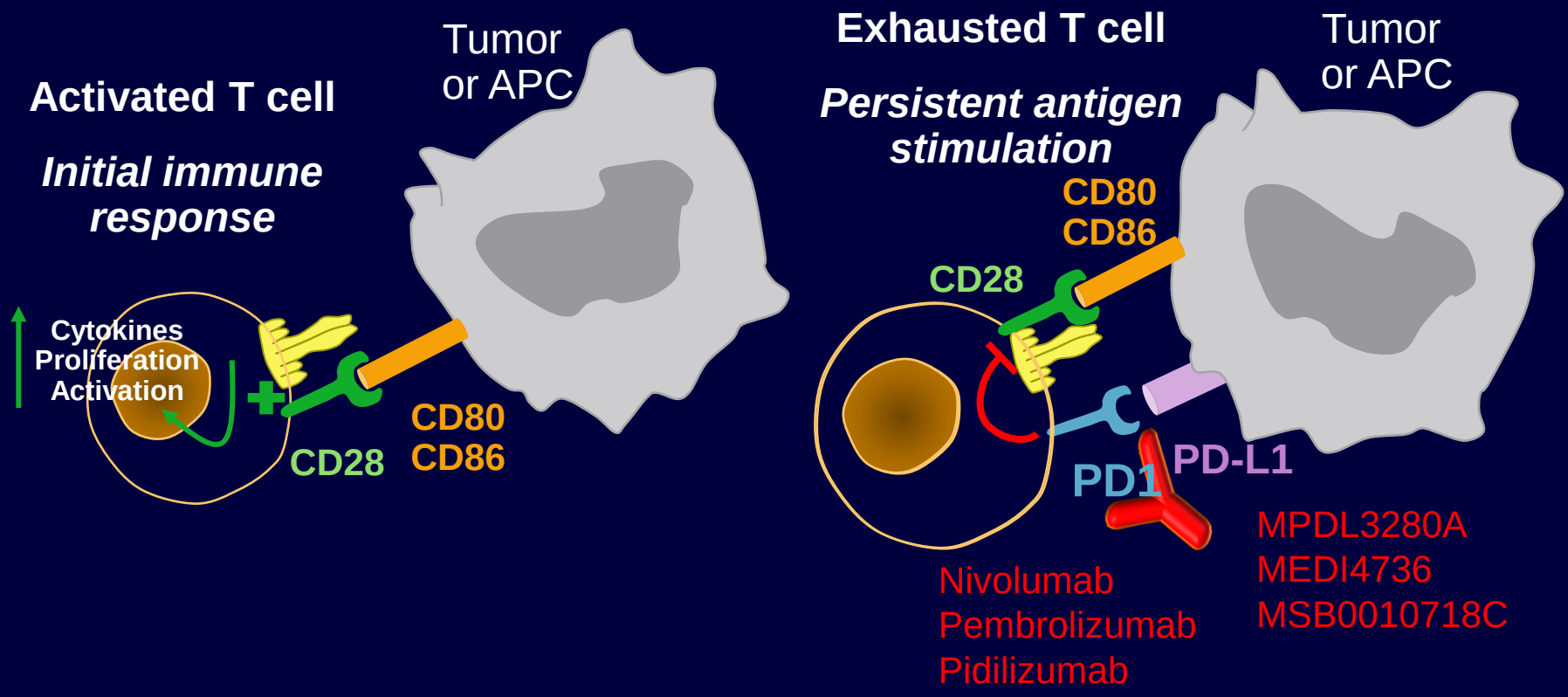
Effector Phase



- Negative immune regulators
  - Inhibitory receptors
  - Suppressive cells
  - Suppressive enzymes (IDO, arginase)

Ribas A. N Engl J Med. 2012;366:2517-2519. Spranger S, et al. J Immunother Cancer. 2013;1:16.

PD-1 as a Target in Cancer Therapy



McDermott DF, Atkins MB. Cancer Med. 2013;2:662-673.

Incorporating Immunotherapeutic Agents in Lung Cancer

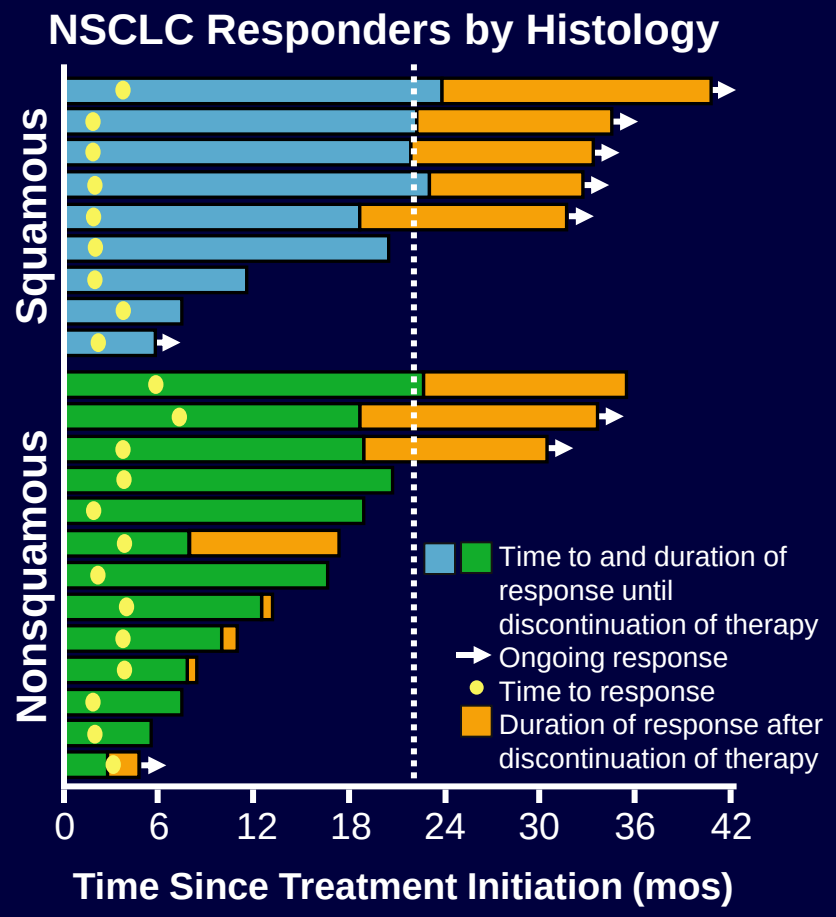
Efficacy of Nivolumab Monotherapy in Pts With NSCLC

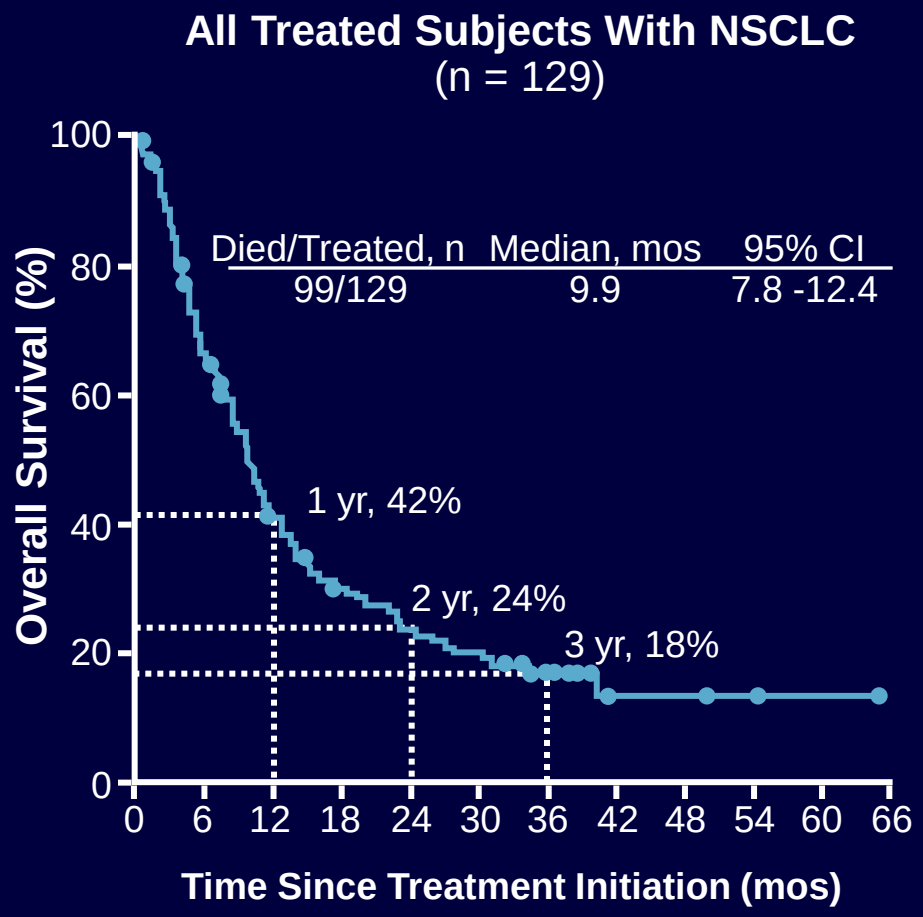
Dose, mg/kg	ORR, % (n/N)	Median DOR, Mos (Range)	1-Yr PFS, % (95% CI)	2-Yr PFS, Mos (95% CI)	Median OS, Mos (95% CI)
All	17.1 (22/129)	17.0 (1.4+ to 36.8+)	22 (15-30)	9 (4-15)	9.9 (7.8-12.4)
1	3.0 (1/33)	14.7 (14.7 to 14.7)	19 (6-38)	0	9.2 (5.3-11.1)
3	24.3 (9/37)	17.0 (3.7+ to 32.6+)	30 (16-46)	11 (3-26)	14.9 (7.3-30.3)
10	20.3 (12/59)	19.1 (1.4+ to 36.8+)	19 (9-30)	10 (4-20)	9.2 (5.2-12.4)

- Durable responses: responses are ongoing in 41% of pts (9/22)
- Rapid responses: 50% of responding pts had response at first assessment (8 wks)
- 9/18 responders who discontinued for reasons other than disease progression responded for ≥ 9 mos (range: 9.2 – 16.4+ mos)
- 6 pts with unconventional “immune-related” responses were not included as responders

Gettinger SN, et al. J Clin Oncol. 2015 Apr 20. [Epub ahead of print]

Nivolumab: Duration of Response and OS





Gettinger SN, et al. J Clin Oncol. 2015 Apr 20. [Epub ahead of print]

CA209-063 (CheckMate-063): Phase II Study Design

Stage IIIB/IV squamous NSCLC; ≥ 2 previous systemic therapies; ECOG PS 0-1 (N = 140)

→

Nivolumab 3 mg/kg IV Q2W (N = 117 treated)

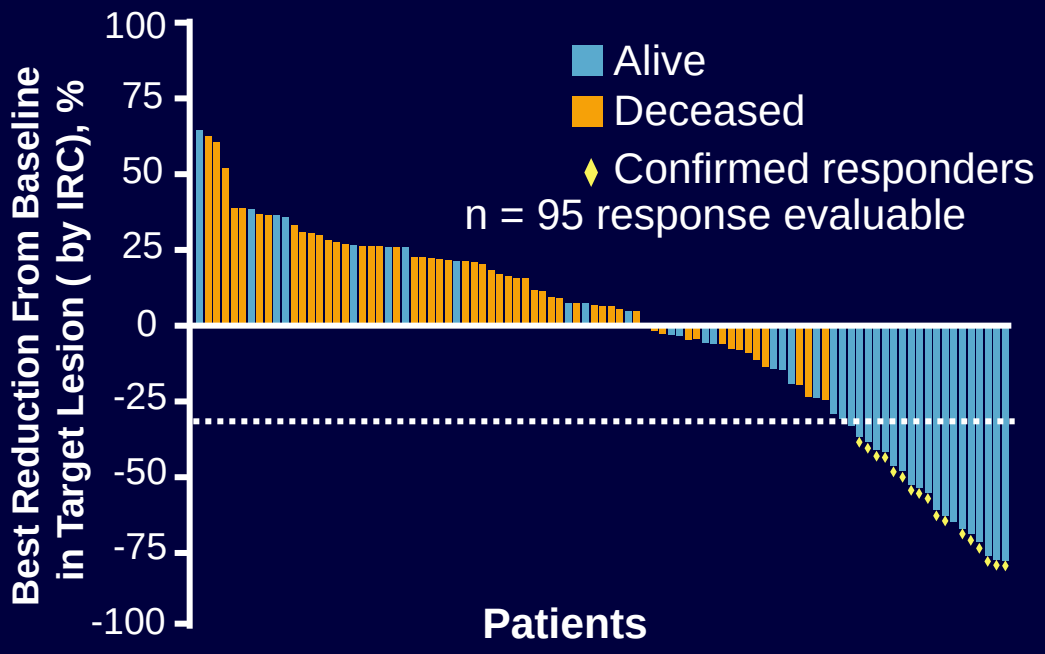
→

Treatment continues until progressive disease or unacceptable toxicity

- Planned to treat approximately 100 pts
  - Expected ORR of 10% to 50%, with 20% maximum width of exact 2-sided 95% CI
- Assessments (RECIST v1.1) performed at Wk 8 and every 6 wks
- Primary endpoint: ORR and DOR by IRC (July 2014 database lock)
- Secondary endpoint: ORR and DOR by investigator (March 2014 database lock)
- Exploratory: safety and tolerability, PFS/OS, PD-L1 expression and efficacy

Rizvi NA, et al. Lancet Oncol. 2015;[Epub ahead of print].

Response and Survival Status by Best Reduction in Target Lesion

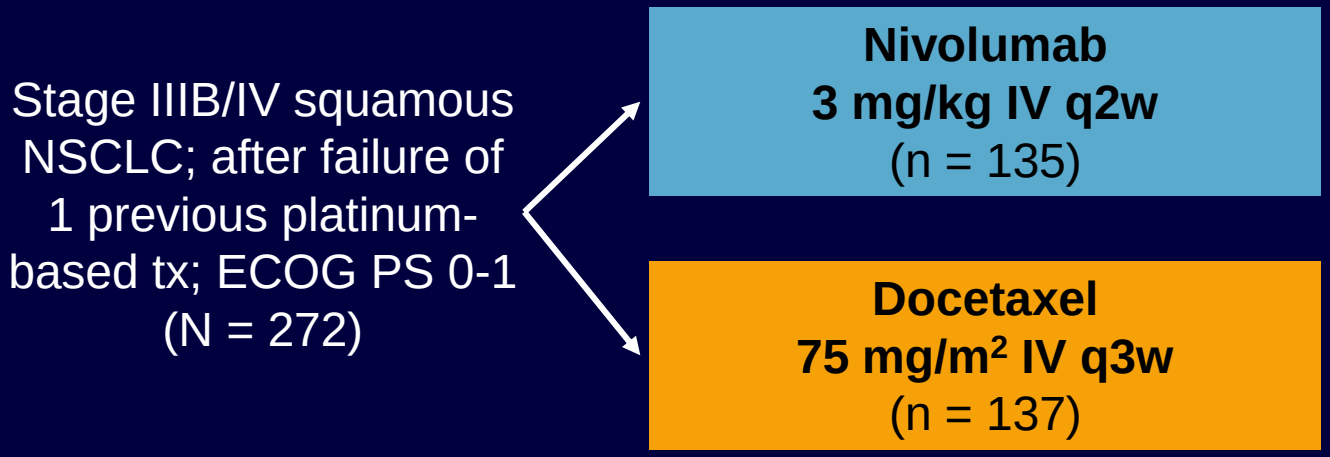


Outcome	IRC Assessment (per RECIST 1.1)
ORR, n (%) [95% CI]	17 (15) [9-22]
DCR, n (%)	47 (40)
Median DOR, mos (95% CI)	NR (8.3-NR)
Ongoing responders, n (%)	13 (77)
Median time to response, mos (range)	3.3 (2.2-4.8)
Median OS, mos (95% CI)	8.2 (6-11)
1-yr OS, % (95% CI)	41 (32-50)

Rizvi NA, et al. Lancet Oncol. 2015;16:257-265.

CheckMate-017: Nivolumab vs Docetaxel in Previously Treated Squamous NSCLC

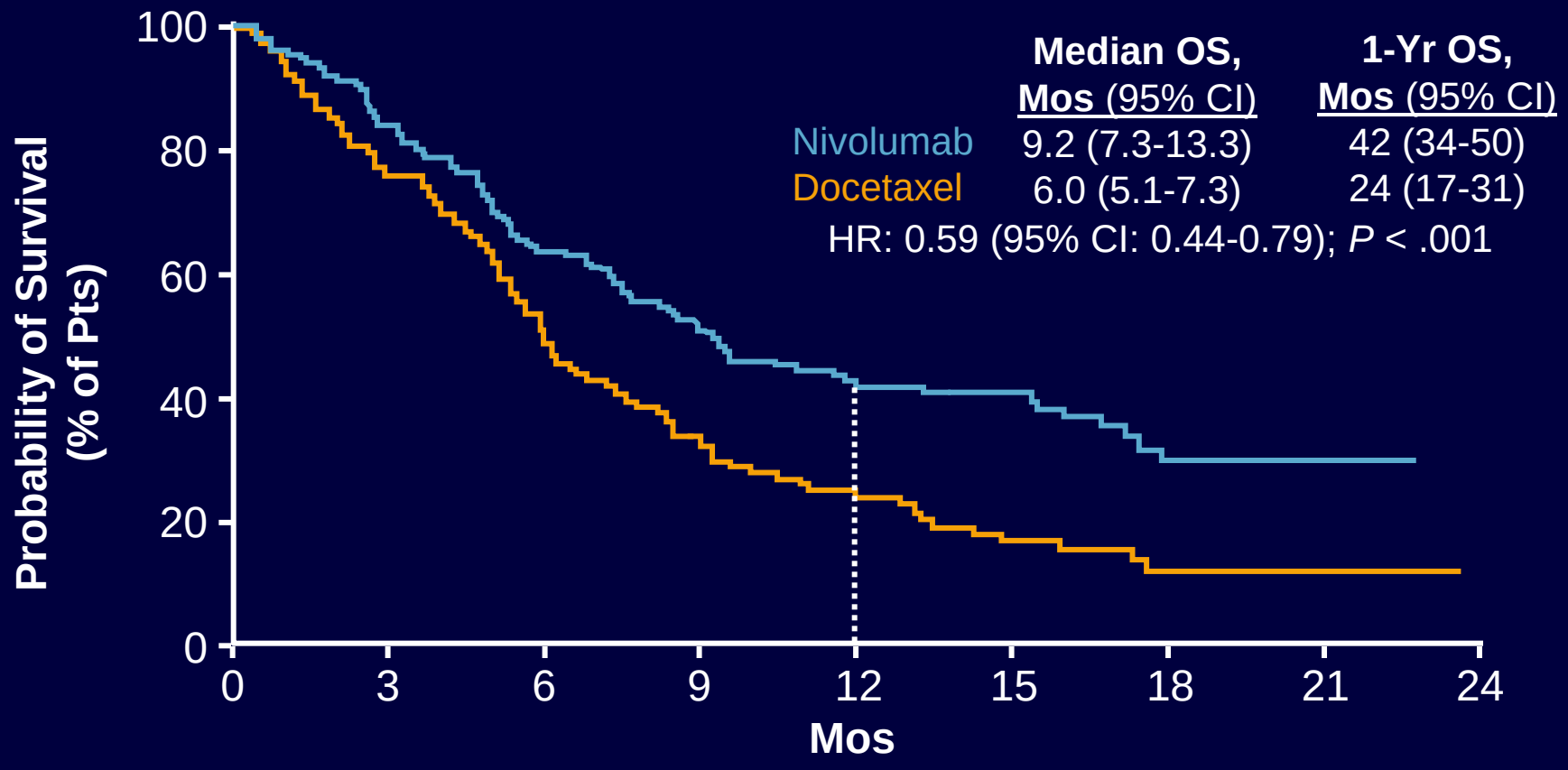
- Open-label, randomized phase III trial



- Primary endpoint: OS
- Secondary endpoint: ORR, PFS, associations with PD-L1 expression, QoL

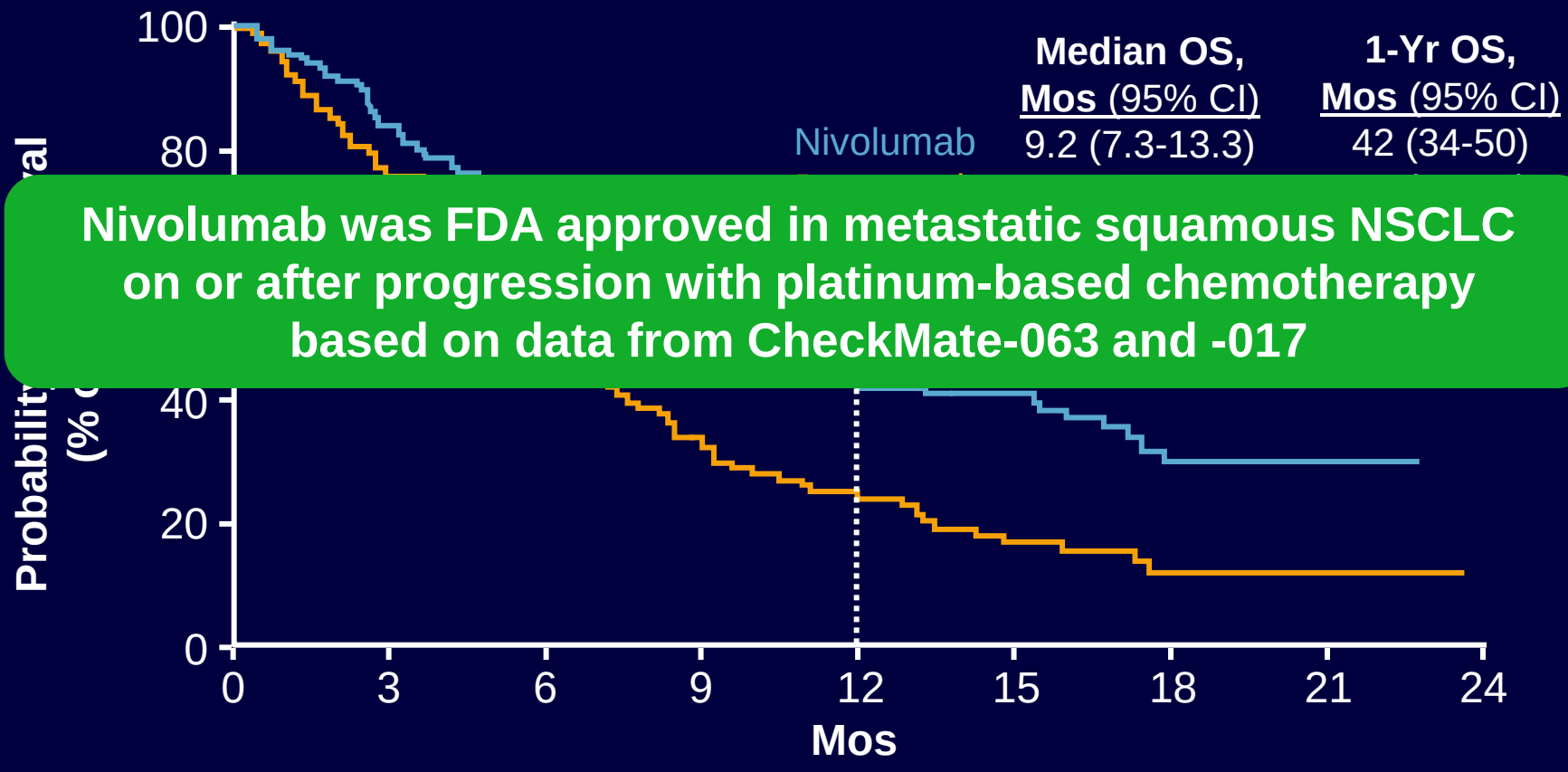
Brahmer J, et al. N Engl J Med. 2015 May 31. [Epub ahead of print]

CheckMate-017: Nivolumab vs Docetaxel Efficacy



Brahmer J, et al. N Engl J Med. 2015 May 31. [Epub ahead of print]

CheckMate-017: Nivolumab vs Docetaxel Efficacy



Nivolumab was FDA approved in metastatic squamous NSCLC on or after progression with platinum-based chemotherapy based on data from CheckMate-063 and -017

Brahmer J, et al. N Engl J Med. 2015 May 31. [Epub ahead of print]

CheckMate 057: Nivo vs Docetaxel in Previously Treated Nonsquamous NSCLC

Stratified by previous maintenance therapy (yes vs no) and line of therapy (second vs third line)

Pts with stage IIIB/IV nonsquamous NSCLC and ECOG PS 0-1 who failed 1 prior platinum doublet chemotherapy ± TKI therapy (N = 582)

Nivolumab 3 mg/kg IV q2w (n = 292)

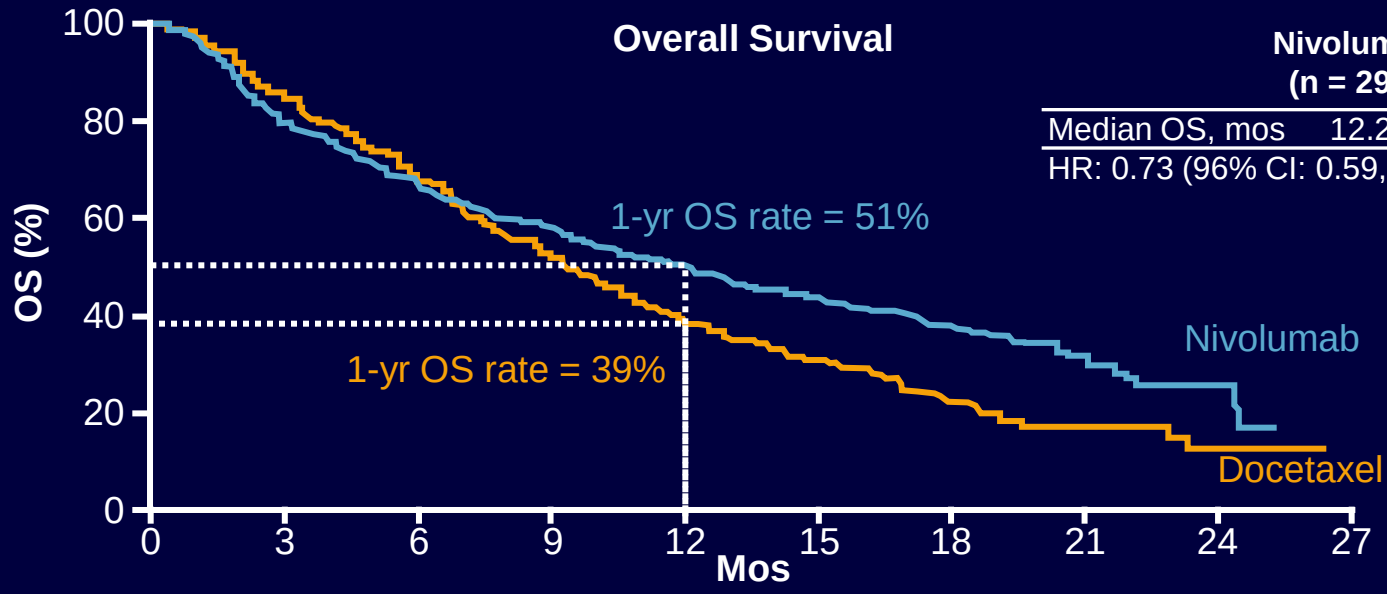
Docetaxel 75 mg/m^2 IV q3w (n = 290)

Until disease progression or unacceptable toxicity

- Primary endpoint: OS
- Secondary endpoints: ORR, PFS, efficacy by PD-L1 expression, safety, QoL

Paz-Ares L, et al. ASCO 2015. Abstract LBA109.

CheckMate 057: Increased Efficacy of Nivo vs Docetaxel in Nonsquamous NSCLC



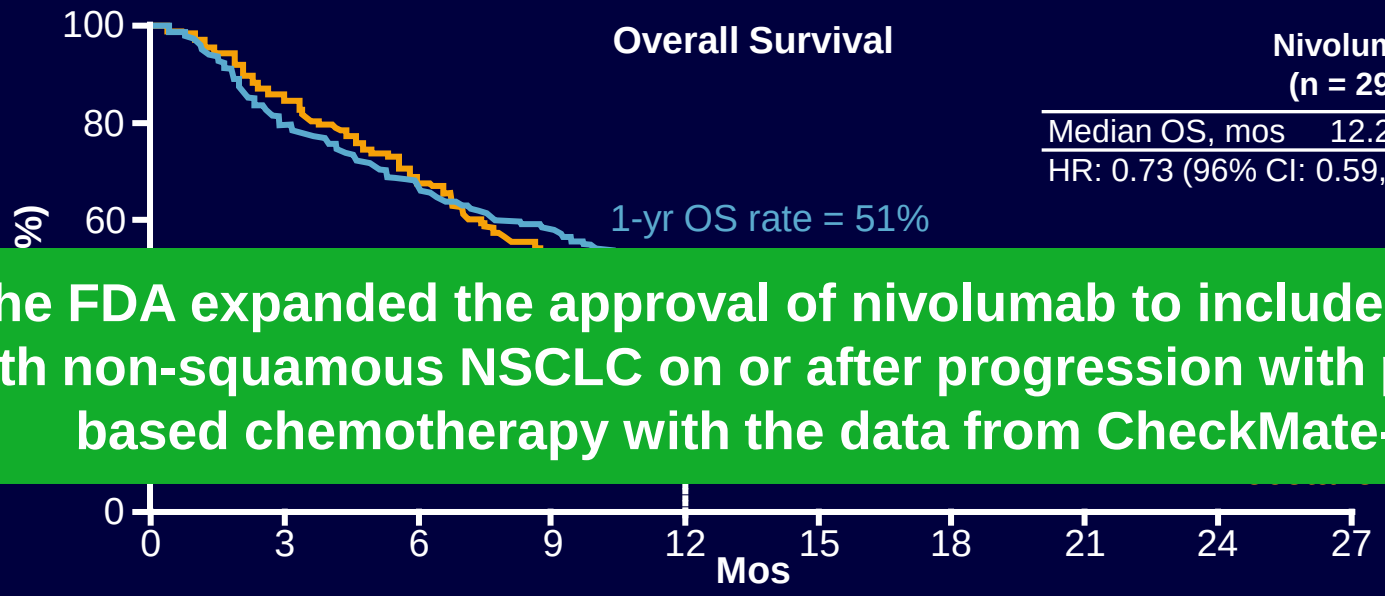
	Nivolumab (n = 292)	Docetaxel (n = 292)
Median OS, mos	12.2	9.4

HR: 0.73 (96% CI: 0.59, 0.89); *P* = .0015

PD-L1 Expression Level	Median OS Nivolumab, mos	Median OS Docetaxel, mos	Unstratified HR (95% CI)	Interaction *P* Value
≥ 1% < 1%	17.2 10.4	9.0 10.1	0.59 (0.43-0.82) 0.90 (0.66-1.24)	.0646
≥ 5% < 5%	18.2 9.7	8.1 10.1	0.43 (0.30-0.63) 1.01 (0.77-1.34)	.0004
≥ 10% < 10%	19.4 9.9	8.0 10.3	0.40 (0.26-0.59) 1.00 (0.76-1.31)	.0002

Paz-Ares L, et al. ASCO 2015. Abstract LBA109.

CheckMate 057: Increased Efficacy of Nivo vs Docetaxel in Nonsquamous NSCLC



	Nivolumab (n = 292)	Docetaxel (n = 292)
Median OS, mos	12.2	9.4

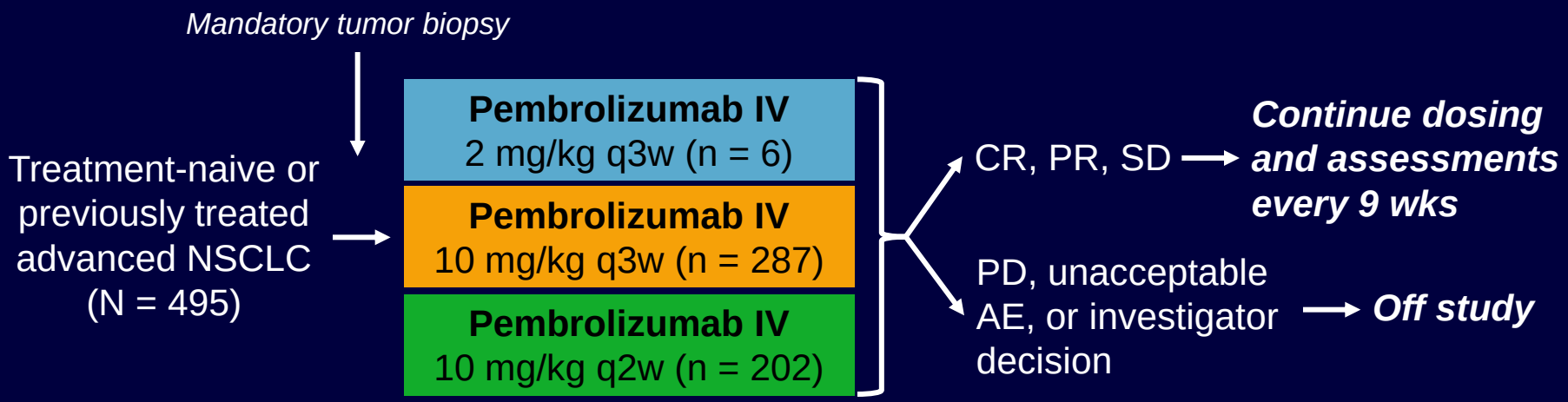
HR: 0.73 (96% CI: 0.59, 0.89); *P* = .0015

The FDA expanded the approval of nivolumab to include patients with non-squamous NSCLC on or after progression with platinum-based chemotherapy with the data from CheckMate-057

PD-L1 Expression Level	Median OS Nivolumab, mos	Median OS Docetaxel, mos	Unstratified HR (95% CI)	Interaction *P* Value
≥ 1% < 1%	17.2 10.4	9.0 10.1	0.59 (0.43-0.82) 0.90 (0.66-1.24)	.0646
≥ 5% < 5%	18.2 9.7	8.1 10.1	0.43 (0.30-0.63) 1.01 (0.77-1.34)	.0004
≥ 10% < 10%	19.4 9.9	8.0 10.3	0.40 (0.26-0.59) 1.00 (0.76-1.31)	.0002

Paz-Ares L, et al. ASCO 2015. Abstract LBA109.

KEYNOTE-001: Subanalysis of Phase I Pembrolizumab Trial in NSCLC

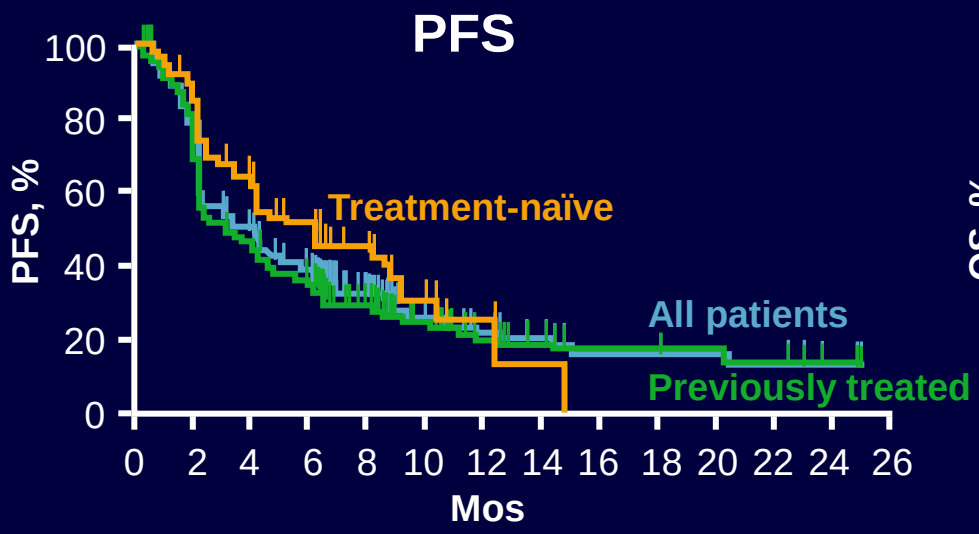


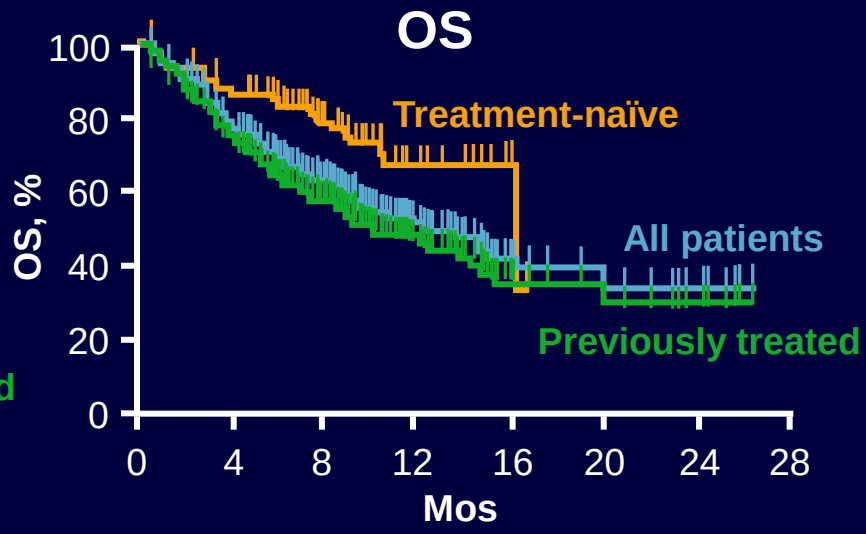
- Administered tumor assessment: imaging every 9 wks
  - Primary: RECIST v.1.1 (independent central review)
  - Secondary: immune-related response criteria (irRC; investigator assessed)
- Tumor biopsy
  - Tumor biopsy within 60 days prior to first dose of pembrolizumab required
  - Tumor PD-L1 expression determined by prototype assay to inform enrollment; Samples were independently reanalyzed using clinical trial IHC assay

Garon EB, et al. N Engl J Med. 2015 Apr 19. [Epub ahead of print]

Keynote-001: Pembrolizumab Efficacy in Overall Population

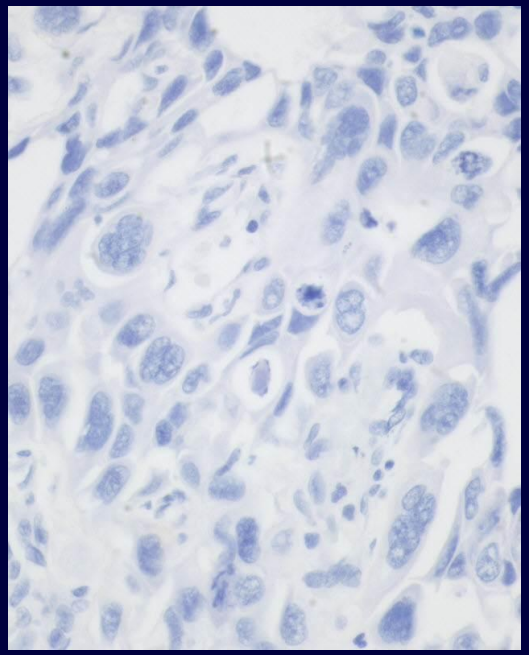
ORR by RECIST, % (95% CI)	N	All Cohorts
Total	495	19.4 (16.0-23.2)
▪ Treatment naive	101	24.8 (16.7-34.4)
▪ Previously treated	394	18.0 (14.4-22.2)
▪ Nonsquamous	401	18.7 (15.0-22.9)
▪ Squamous	85	23.5 (15.0-34.0)





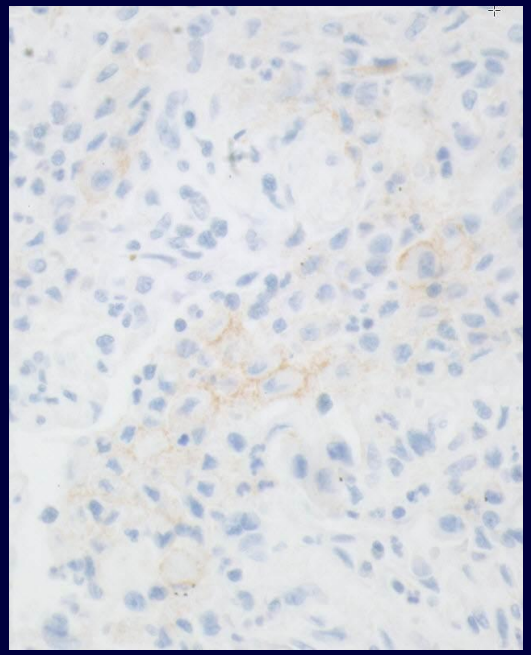
Garon EB, et al. N Engl J Med. 2015;372:2018-2028.

PD-L1 NSCLC Sample IHC Staining



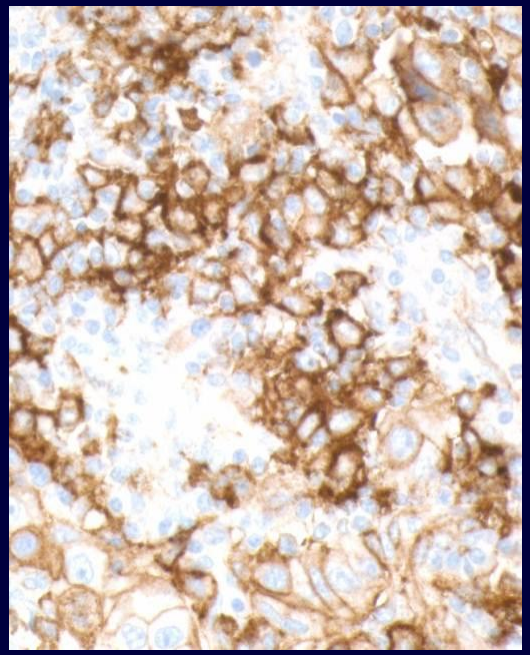
PD-L1 = 0% positive

Negative



PD-L1 = 2% positive

Weak positive (1% to 49%)



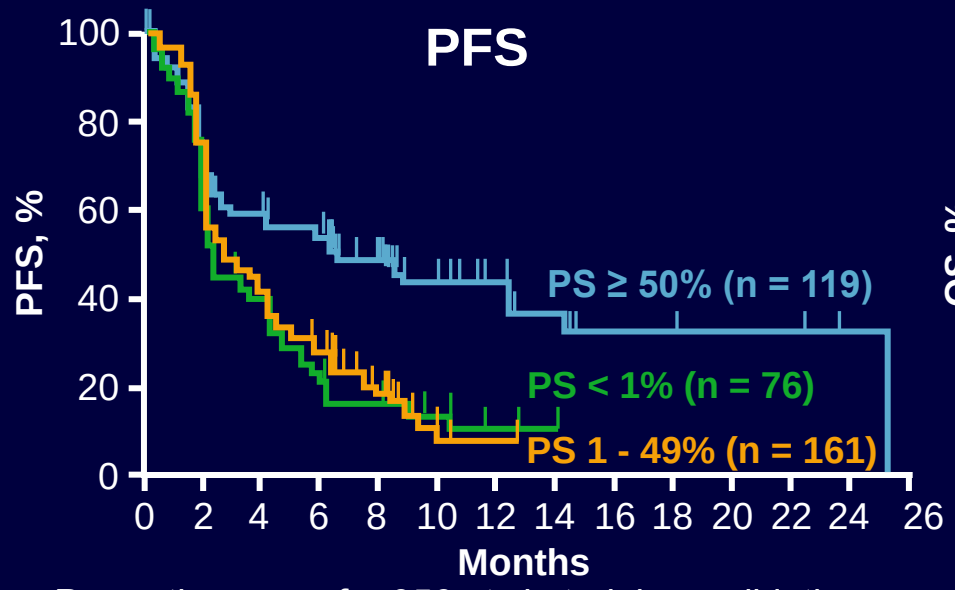
PD-L1 = 100% positive

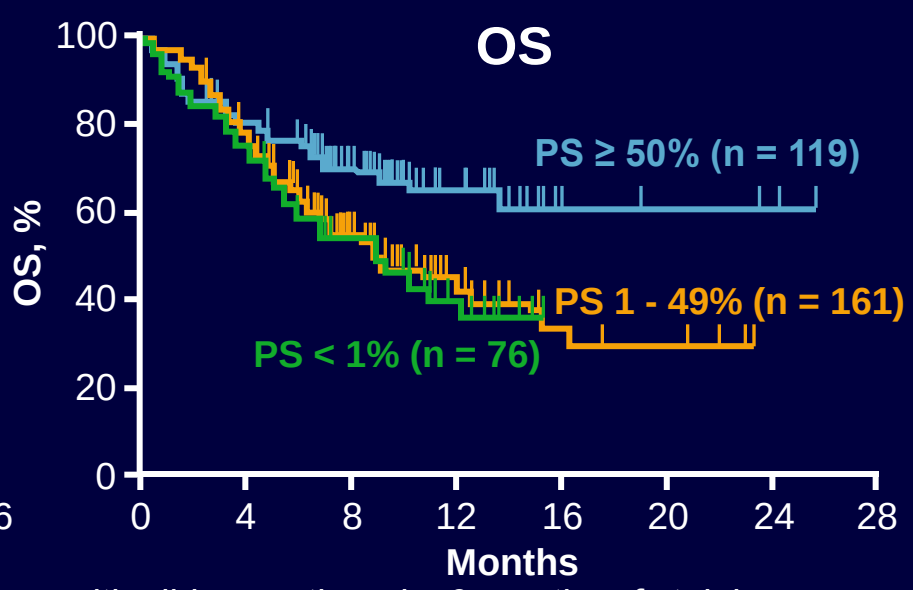
Strong positive (50% to 100%)

Gandhi L, et al. AACR 2014. Abstract CT105.

Keynote-001: Pembrolizumab Efficacy by PD-L1 Expression

ORR by RECIST, % (95% CI)	N	All Cohorts
Percent PD-L1 staining		
▪ ≥ 50%	73	45.2 (33.5-57.3)
▪ 1% - 49%	103	16.5 (9.9-25.1)
▪ < 1%	28	10.7 (2.3-28.2)





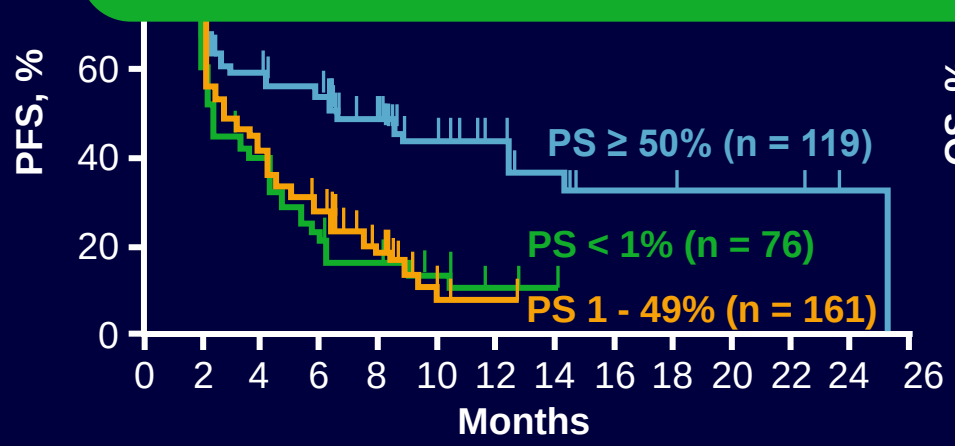
Proportion score for 356 pts in training, validation groups with slides sectioned ≤ 6 months of staining

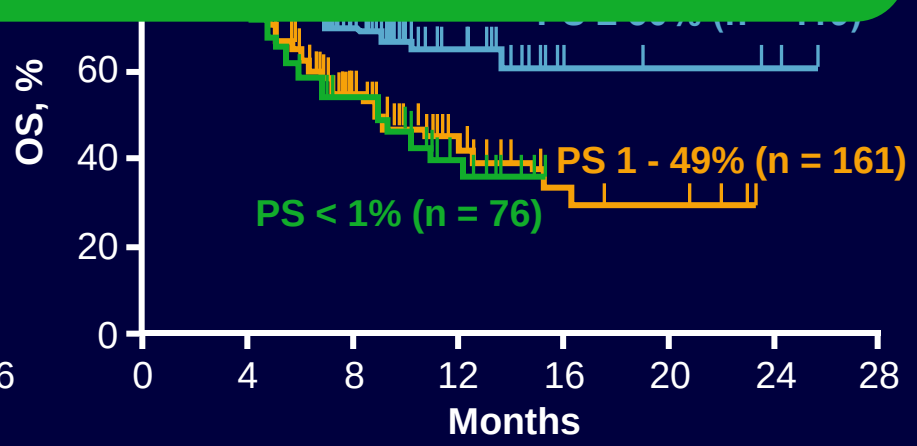
Garon EB, et al. N Engl J Med. 2015;372:2018-2028.

Keynote-001: Pembrolizumab Efficacy by PD-L1 Expression

ORR by RECIST, % (95% CI)	N	All Cohorts
Percent PD-L1 staining		
▪ ≥ 50%	73	45.2 (33.5-57.3)

Pembrolizumab was FDA approved in metastatic NSCLC expressing PD-L1, as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy based on data from KEYNOTE-001





Proportion score for 356 pts in training, validation groups with slides sectioned ≤ 6 months of staining

Garon EB, et al. N Engl J Med. 2015;372:2018-2028.

Managing Potential Adverse Events Associated With Immunotherapy

Summary of PD-1/PD-L1 Blockade Immune-Mediated Toxicities

Occasional (5% to 20%)

- Fatigue
- Rash: maculopapular and pruritus
  - Topical treatments
- **Diarrhea/colitis**
  - Initiate steroids early, taper slowly
- Hepatitis/liver enzyme abnormalities
- Infusion reactions
- Endocrinopathies: thyroid, adrenal, hypophysitis

Infrequent (< 5%)

- **Pneumonitis**
- Grade 3/4 toxicities uncommon

Topalian SL, et al. N Engl J Med. 2012;366:2443-2454. Patnaik A, et al. ASCO 2012. Abstract 2512. Brahmer JR, et al. N Engl J Med. 2012;366:2455-2465. Herbst RS, et al. ASCO 2013. Abstract 3000.

Immune Adverse Events

- Onset:
  - Average is 6-12 wks after initiation of therapy
  - Can occur within days of the first dose, after several mos of treatment, and after discontinuation of therapy
- Pt complaints are autoimmune and drug related until proven otherwise
  - Rule out infections, metabolic causes, tumor effects, etc
- Early recognition, evaluation, and treatment are critical

PD-1/PD-L1 Inhibition: Managing for Treatment-Related Adverse Events

Any grade 1 AE or
Isolated hypothyroidism

↓

Symptom management or replacement therapy for hypothyroidism

↓

Continue PD-1 tx and monitor

Grade 2 pneumonitis, nephritis, colitis, hepatitis
Symptomatic hypophysitis
Any grade 3 AE

↓

Hold PD-1 tx and administer steroids
After improvement to ≤ grade 1, taper steroids over at least 1 mo

Resume if:
AE remains at grade 0/1 after steroid taper

Permanently discontinue if:

- No improvement to ≤ grade 1 with in 12 wks
- Cannot taper steroids to ≤ 10 mg/day of prednisone or equivalent within 12 wks

Pembrolizumab adverse reaction management guide. Nivolumab adverse reaction management guide.

PD-1/PD-L1 Inhibition: Managing for Treatment-Related Adverse Events

Grade 3/4 pneumonitis
Grade 3/4 nephritis
Grade 3/4 infusion-related reaction
Any life-threatening or grade 4 AE
Any severe or grade 3 recurrent AE

Hepatitis associated with
- AST/ALT > 5 x ULN
- AST/ALT ≥ 50% ↑ from baseline lasting ≥ 1 wk*
- Total bilirubin > 3 x ULN

→ Initiate steroid therapy

→ Permanently discontinue PD-1 tx

*In pts with liver metastasis who begin treatment with grade 2 elevation of AST/ALT.

Pembrolizumab adverse reaction management guide. Nivolumab adverse reaction management guide.

Key to Optimal Pt Management

- All members of the healthcare team should be educated about potential AEs
- Rapid and timely diagnostic and therapeutic intervention is imperative for optimal control of irAEs
  - Persistent grade 2 irAEs and grade 3/4 irAEs are treated with steroids
  - Early discontinuation of steroids may predispose to relapse
- Reinitiation of treatment may be possible with optimal management
- Approximately 5% to 10% of patients experience evidence of enlarging tumor lesions prior to a response
  - Pseudoprogression can be managed by continuing treatment and monitoring closely

Optimal management is attainable through continued communication between all members of the healthcare team and individual patients

Pt Education on Novel Therapies

- Pt education should include information on:
  - Adverse reaction profiles that differs from standard chemotherapy
  - Early recognition of irAEs essential for effective treatment
  - irAEs are infrequent, treatable and respond well to steroids
  - Who and when to call for adverse reactions
- Reinforce teaching points at every point of contact, office and treatment visits, and phone contact
  - Notify your healthcare team if you are admitted to another hospital

Pt and Family Education

- Assess for both pt and caregiver
  - Knowledge of therapy and the disease process
  - Educational level and preferred learning methods
- Provide information on:
  - Administration schedule of therapy
  - Time to response
    - Time required to mount antitumor response
  - Tumor assessment
    - May demonstrate early progression or new lesions, prior to demonstrating response

Future Directions for Immunotherapy in NSCLC

Phase II POPLAR Trial: Atezolizumab vs Docetaxel in Previously Treated NSCLC

Stratified by PD-L1 immune cell expression (0 vs 1 vs 2 vs 3), histology (squamous vs nonsquamous), and line of therapy (second vs third line)

Pts with locally advanced or metastatic NSCLC and ECOG PS 0-1 who failed prior platinum-containing chemotherapy (N = 287)

- **Atezolizumab 1200 mg IV q3w** (n = 144)
- **Docetaxel 75 mg/m^2 IV q3w** (n = 143)

- Primary endpoint: OS in PD-L1–selected and ITT populations
- Secondary endpoints: overall safety as well as PFS, ORR, DoR in PD-L1–selected and ITT populations

Spira AI, et al. ASCO 2015. Abstract 8010.

POPLAR: Efficacy of Atezolizumab Increased With Higher PD-L1 Expression

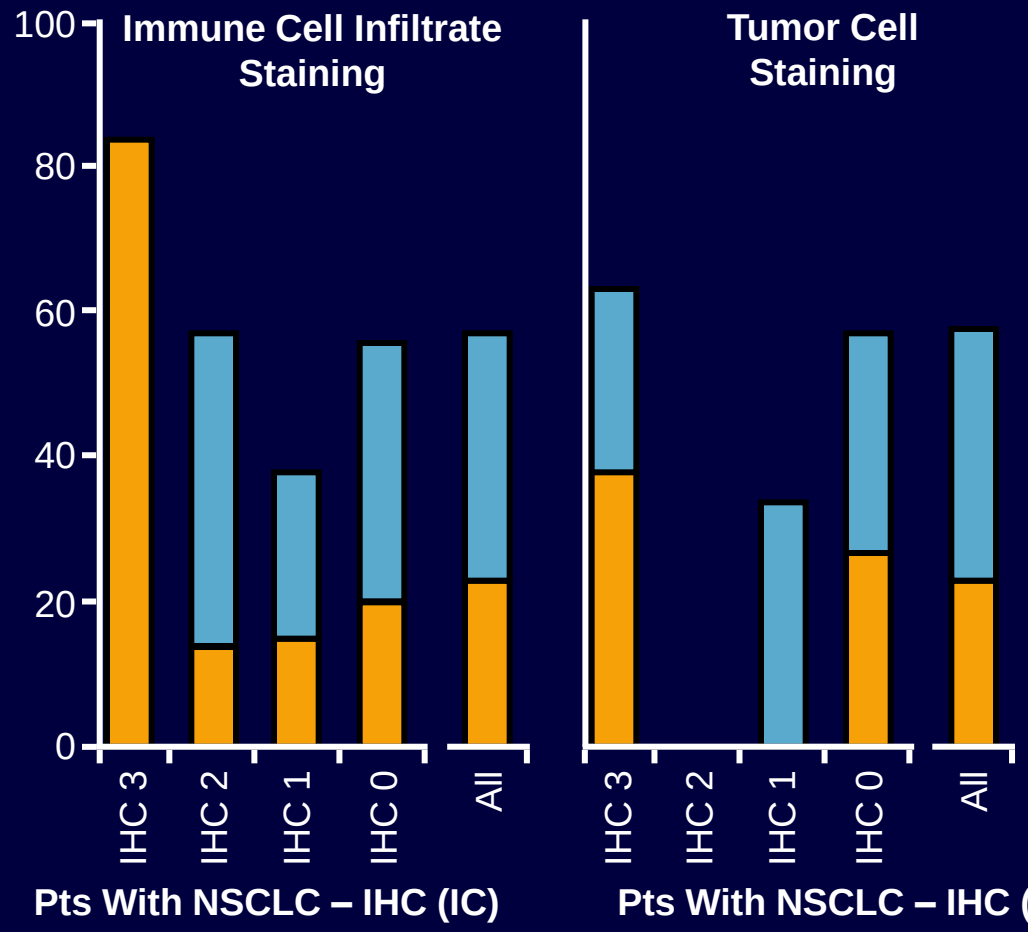
Interim Median OS Outcomes	Atezolizumab (n = 144)	Docetaxel (n = 143)	HR (95% CI)	*P* Value
ITT population (N = 287)	11.4	9.5	0.77 (0.55-1.06)	.11
Subgroups based on PD-L1 expression*				
▪ TC0 and IC0 (n = 92)	9.7	9.7	1.12 (0.64-1.93)	.70
▪ TC1/2/3 or IC1/2/3 (n = 195)	NR	9.1	0.63 (0.42-0.94)	.024
▪ TC2/3 or IC2/3 (n = 105)	13.0	7.4	0.56 (0.33-0.94)	.026
▪ TC3 or IC3 (n = 47)	NR	11.1	0.46 (0.19-1.09)	.070

*PD-L1 expression measured by SP142 IHC assay (low expression – TC0/IC0, high expression - TC3/IC3).

- PFS and ORR: similar trends in outcome for atezolizumab vs docetaxel based on PD-L1 expression
  - Median PFS in ITT population: 2.8 vs 3.4 mos (HR: 0.98)
  - Median PFS in TC3 or IC3 population: 7.8 vs 3.9 mos (HR: 0.57)
  - ORR in ITT population: 15% vs 15%
  - ORR in TC3 or IC3 population: 38% vs 13%
- Interim data based on minimum of 10 mos of follow-up

Spira AI, et al. ASCO 2015. Abstract 8010.

Activity of Atezolizumab by Immune Cell or Tumor PD-L1 Expression



- Specimens scored by % of cells PD-L1+ per area:
- IHC 0: < 1%
- IHC 1: 1% to < 5%
- IHC 2: 5% to < 10%
- IHC 3: ≥ 10%

Best response: CR or PR
Best response: SD

Herbst RS, et al. Nature. 2014;515: 563-567.

Activity of Atezolizumab by Immune Cell PD-L1 IHC

Diagnostic Population	IHC 3 (n = 6)	IHC 2 (n = 7)	IHC 1 (n = 13)	IHC 0 (n = 20)	Unknow n (n = 7)	All Pts (N = 53)
ORR (RECIST), n (%)	5 (83)	1 (14)	2 (15)	4 (20)	0	12 (23)
SD (best response), n (%)	0	3 (43)	3 (23)	7 (35)	5 (71)	18 (34)
SD ≥ 24 wks, n (%)	0	0	1 (8)	4 (20)	4 (57)	9 (17)
PD (best response), n (%)	1 (17)	2 (29)	7 (54)	9 (45)	2 (29)	21 (40)
24-wk PFS, %	83.3	14.3	25.6	45.0	71.4	44.7
Median PFS, wks (95% CI)	NE (5-NE)	11 (1-17)	6 (5-43)	13 (6-37)	NE (6-NE)	15 (6-43)

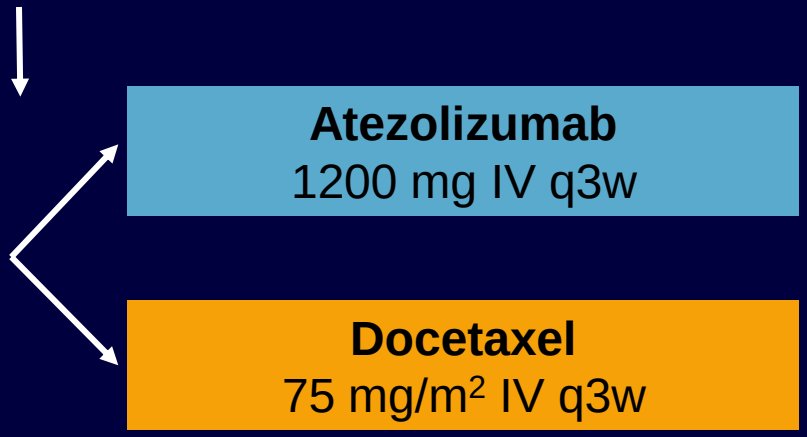
Herbst RS, et al. Nature. 2014;515: 563-567.

Phase III OAK Trial: Atezolizumab vs Docetaxel in Previously Treated NSCLC

Stratified by tumor PD-L1 status (IHC), prior chemo regimens (1 vs 2), and histology (nonsquamous vs squamous)

Stage IIIB/IV or recurrent NSCLC; 1-2 prior regimens, including 1 previous platinum-based treatment

(estimated N = 1100)



- Primary endpoint: OS
- Secondary endpoint: ORR, PFS, DoR, Safety

ClinicalTrials.gov. NCT02008227.

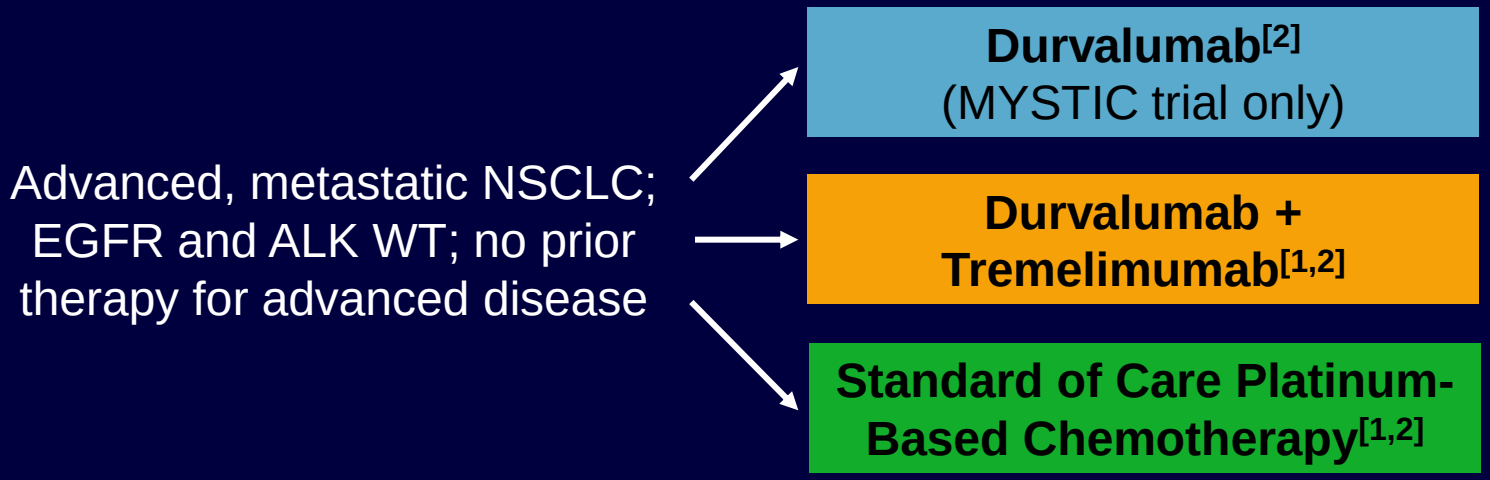
Recent Early Phase Trials in NSCLC

Agent	Population	Efficacy	Tolerability
Durvalumab (Anti-PD-L1)[1]	Squamous (n = 88) Nonsquamous (n = 112)	ORR: 16% ▪ 27% in PD-L1+ ▪ 5% in PD-L1- Squamous: 21% Nonsquamous: 13%	Tx-related AEs: ▪ Any: 50% of pts ▪ Grade 3/4: 8% ▪ Leading to d/c: 5% No tx-related colitis or hyperglycemia, no grade 3/4 pneumonitis
Durvalumab + tremelimumab (Anti-CTLA-4)[2]	Advanced NSCLC (n = 102)	ORR: 27% ▪ 33% PD-L1+ ▪ 27% PD-L1-	Tx-related AEs: ▪ Any: 63%-89% of pts by cohort ▪ Grade 3/4: 29%-78% by cohort ▪ Leading to d/c: 7%-44% by cohort Grade 3/4 immune-related AEs: colitis (9%), pneumonitis (4%), and hypothyroidism (1%)
Pembrolizumab + ipilimumab (KEYNOTE-021)[3]	Recurrent NSCLC after ≤ 2 regimens (n = 18)	ORR: 39%	Tx-related AEs: ▪ Any: 83% of pts ▪ Grade 3/4: 17% (adrenal insufficiency, maculopapular rash, drug eruption) ▪ Leading to d/c: 11%

1. Rizvi NA, et al. ASCO 2015. Abstract 8032. 2. Antonia SJ, et al. ASCO 2015. Abstract 3014.
3. Patnaik A, et al. ASCO 2015. Abstract 8011.

Phase III Trials: Durvalumab ± Tremelimumab vs SoC in Advanced NSCLC

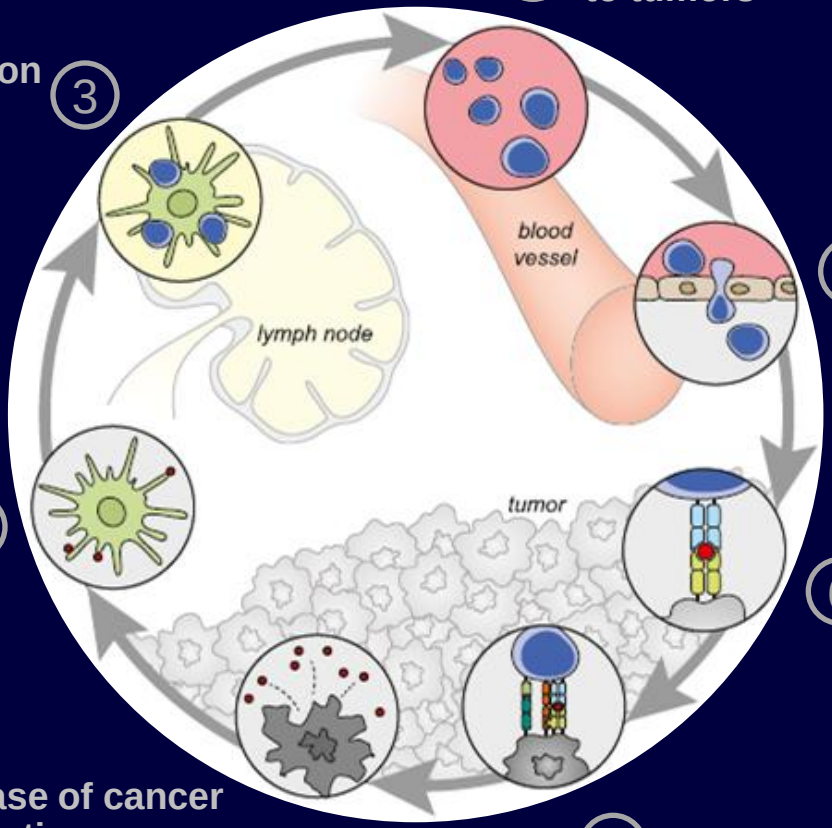
- Randomized, open-label, multi-center, global phase III trials: NEPTUNE[1] and MYSTIC[2]



- Primary endpoint: PFS, OS
- Secondary endpoint: ORR, PFS, DoR, Safety

1. ClinicalTrials.gov. NCT02542293. 2. ClinicalTrials.gov. NCT02453282.

A Roadmap of Immunotherapy-Tumor Interactions



4 Trafficking of T cells to tumors

Priming and activation 3
- Anti-CTLA4
- Anti-CD137 (agonist)
- Anti-OX40 (agonist)
- Anti-CD27 (agonist)
- IL-2
- IL-12

5 Infiltration of T cells into tumors
- Anti-VEGF

Cancer antigen presentation 2
- Vaccines
- IFN-α
- GM-CSF
- Anti-CD40 (agonist)
- TLR agonists

6 Recognition of cancer cells by T cells
- CARs

Release of cancer cell antigens 1
- Chemotherapy
- Radiation therapy
- Targeted therapy

7 Killing of cancer cells
- Anti–PD-L1
- Anti–PD-1
- IDO inhibitors

Chen DS, et al. Immunity. 2013;39:1-10.

Conclusions

- Immunotherapy for lung cancer can induce durable responses and can result in prolonged OS
- Different patterns of response with checkpoint inhibition require ongoing education for pts
- Immune-related adverse events are a unique spectrum of adverse events with checkpoint inhibition that require learning new ways to manage toxicity
- Improved understanding of the immune system and ongoing clinical trials with immunotherapy will likely result in an ongoing evolution in treatment for pts with NSCLC

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