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Immunotherapy for Lung Cancer

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Thursday, September 8, 2016

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Disclosures

- No relevant financial relationships
- There will not be discussion about the use of products for non-FDA approved indications in this presentation

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Overview

- Clinical vignette: advanced lung cancer

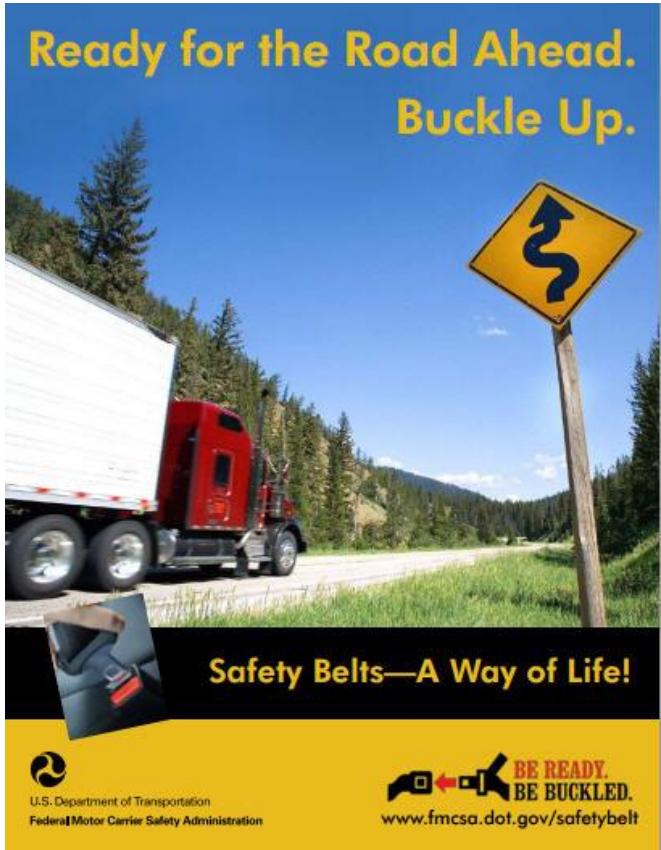
- Immune checkpoint inhibitors in advanced disease:

  -*Non-squamous* NSCLC

  -*Squamous* NSCLC

  *Focus on major phase III studies

- Conclusions & questions



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Clinical Vignette

A 65 y/o fit gentleman with an 80 pack/year tobacco hx presents with stage IV adenocarcinoma of the lung (KRAS-mutated).

- Following 4 cycles of 1st line palliative Carboplatin/Pemetrexed, he receives maintenance Pemetrexed for 6 cycles
- 8 months after initial diagnosis, he experiences disease progression in the lungs

Where do we go from here?

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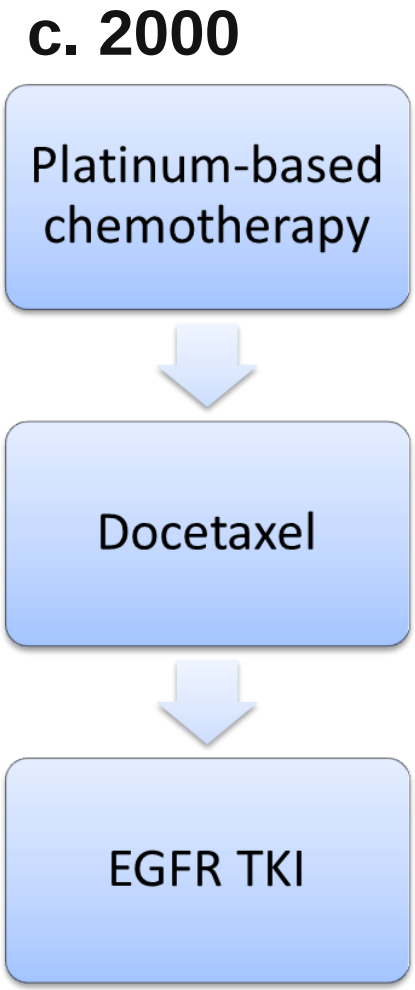
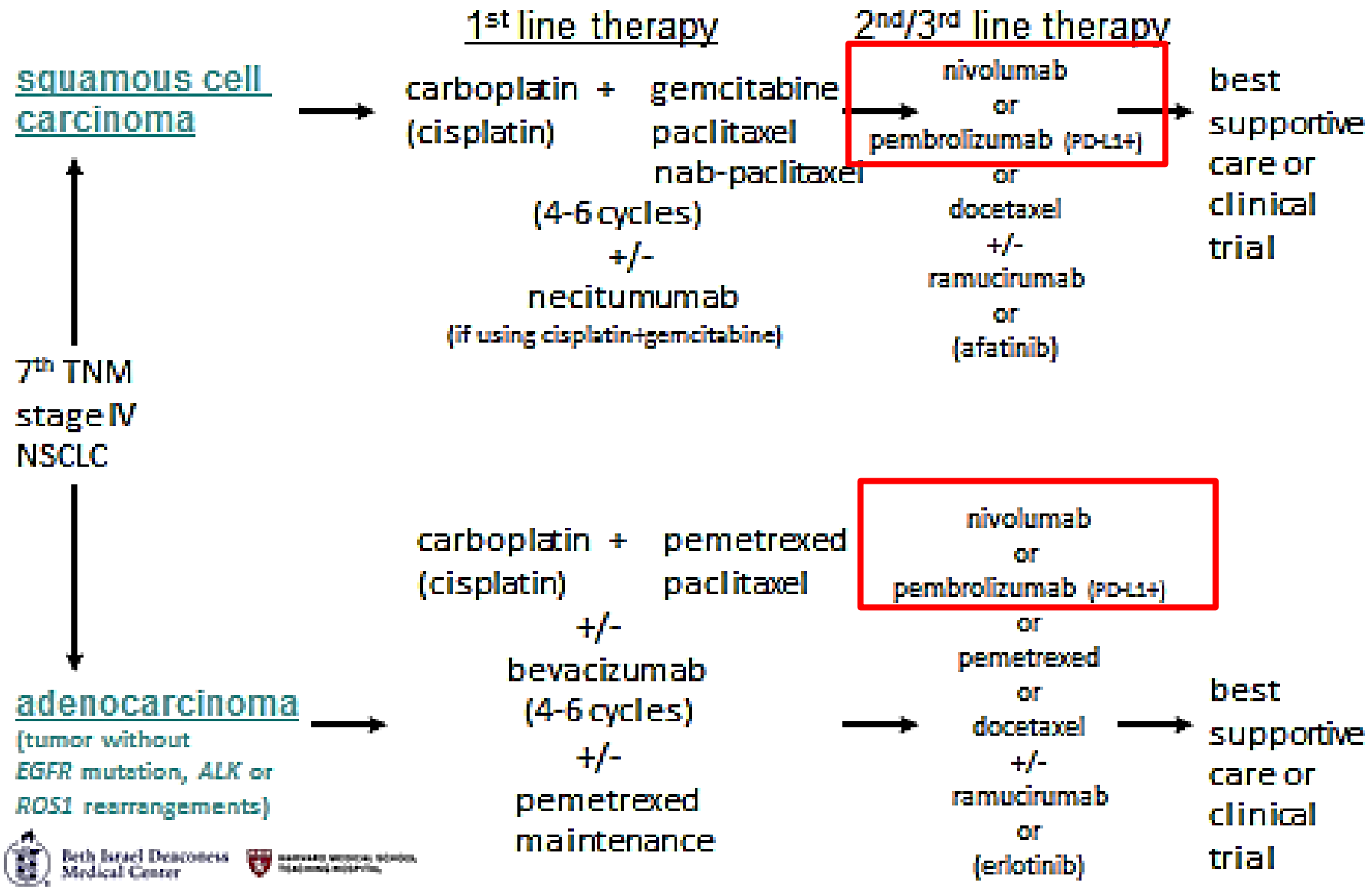
Evolving paradigms in the management of advanced NSCLC: THEN



Evolving paradigms in the management of advanced NSCLC: NOW



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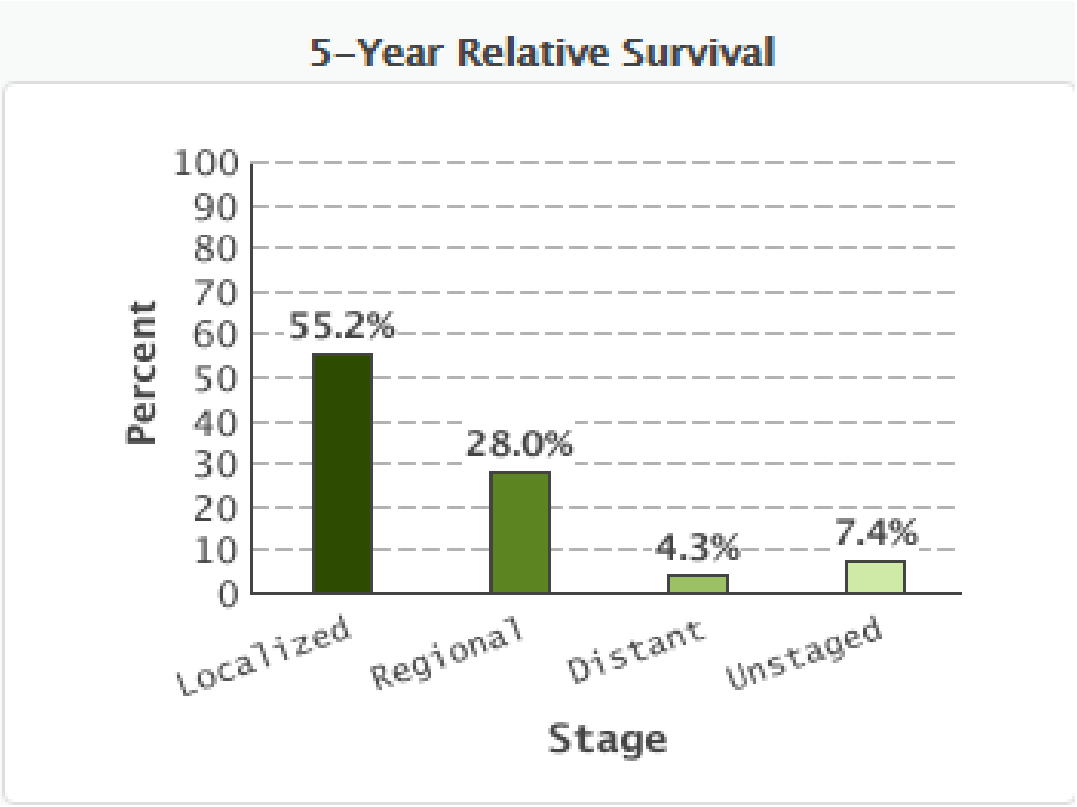
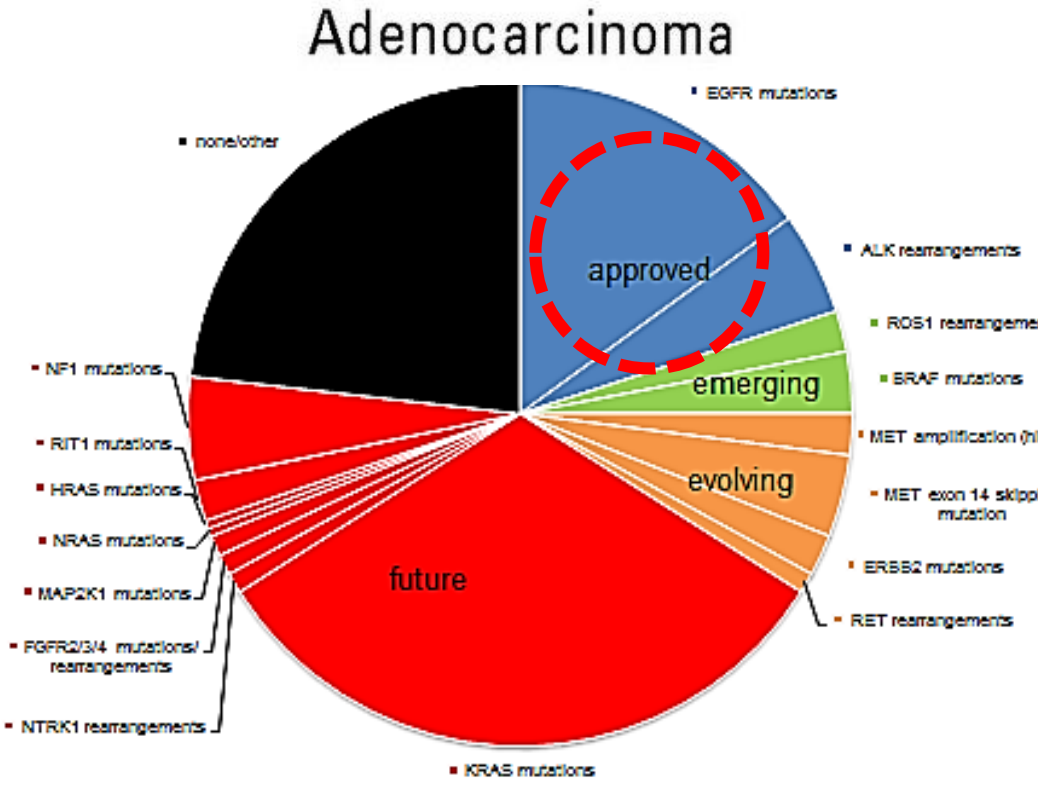
Long-term outcomes for advanced NSCLC remain poor

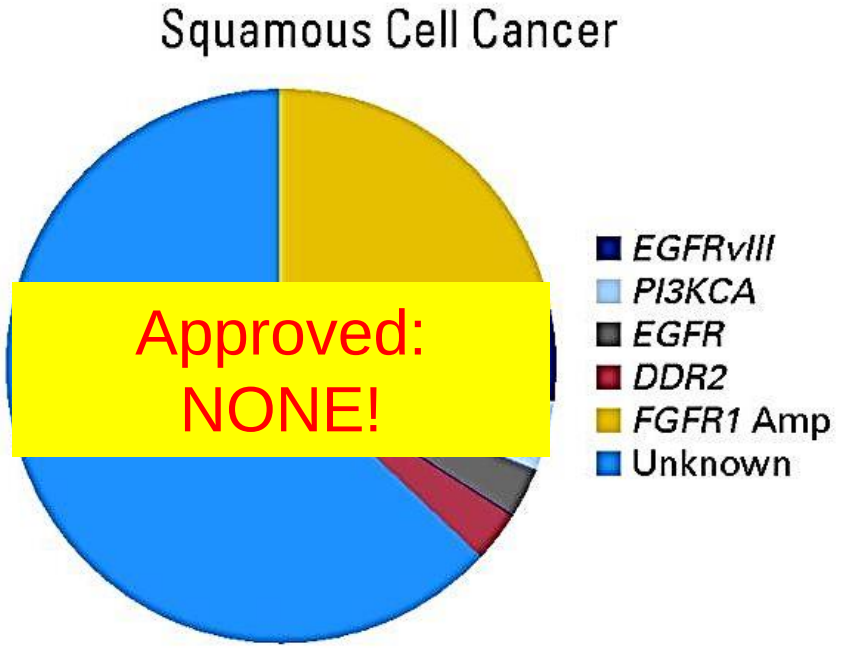


	Median Survival
1980s	4-6 mos
2000	8 mos
2005	12 mos
2020	???

Courtesy of J Brahmer
http://seer.cancer.gov/statfacts/html/lungb.html

Targeted therapies in advanced NSCLC have brought promise– but not for most





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Shea, Costa, Rangachari, Ther Adv Resp Dis, Oct 2016
Li et al, J Clin Oncol, 2013

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FDA-approved indications for immunotherapy in advanced NSCLC (as of right now…)

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

March 4, 2015

FDA News Release

FDA expands approved use of Opdivo to treat lung cancer

October 2, 2015

FDA News Release

FDA approves Keytruda for advanced non-small cell lung cancer

First drug approved in lung cancer for patients whose tumors express PD-L1

October 9, 2015

FDA News Release

FDA expands approved use of Opdivo in advanced lung cancer

Opdivo demonstrates survival benefit in squamous and non-squamous non-small cell lung cancer

NIVOLUMAB

- 2nd line
- Squamous & Non-squamous NSCLC

PEMBROLIZUMAB

- 2nd line
- Squamous & Non-squamous NSCLC
- PDL1+: ≥50%

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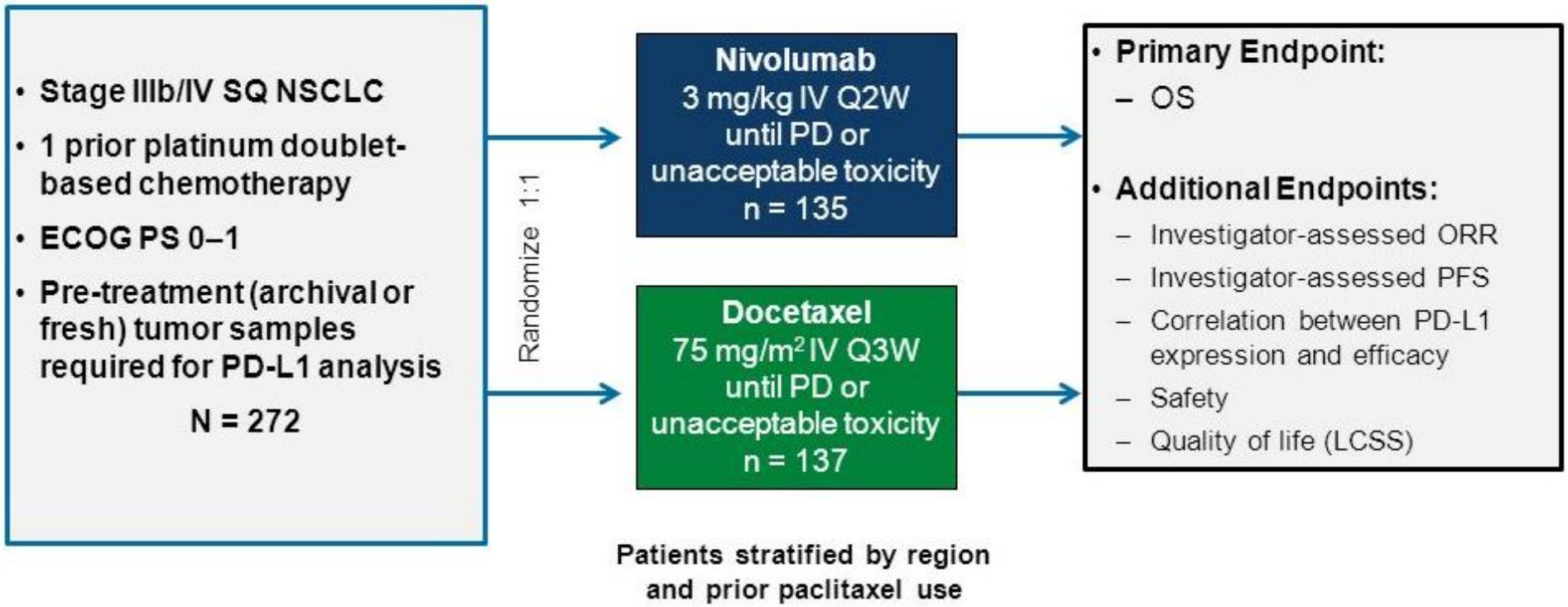
NIVOLUMAB IN SQUAMOUS NSCLC

Checkmate-017: Nivolumab vs. Docetaxel for 2nd line tx of adv squamous NSCLC



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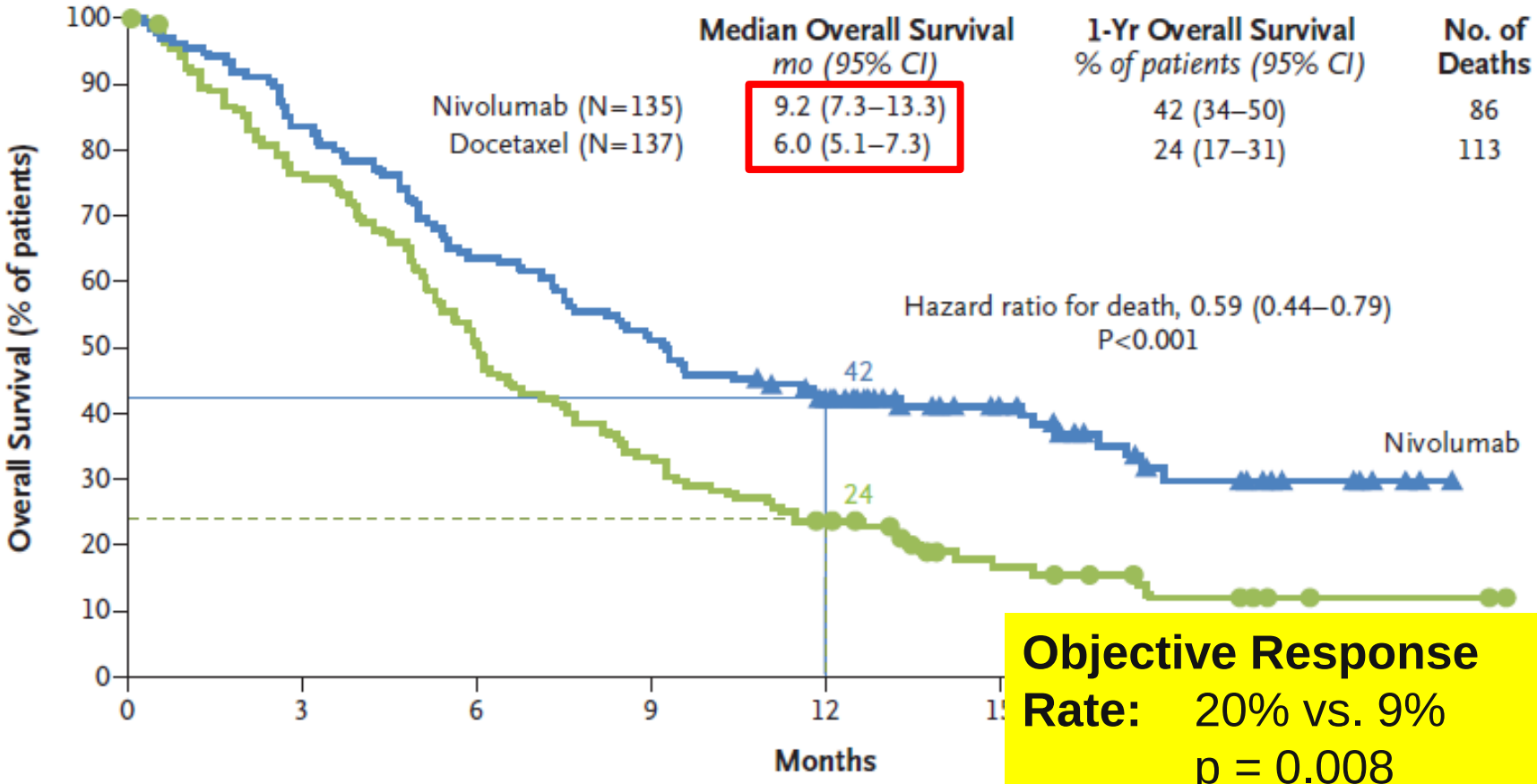
Brahmer J et al, NEJM, May 2015

Checkmate-017: Overall survival improved with Nivolumab



Objective Response Rate: 20% vs. 9%
p = 0.008

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Brahmer J et al, NEJM, May 2015

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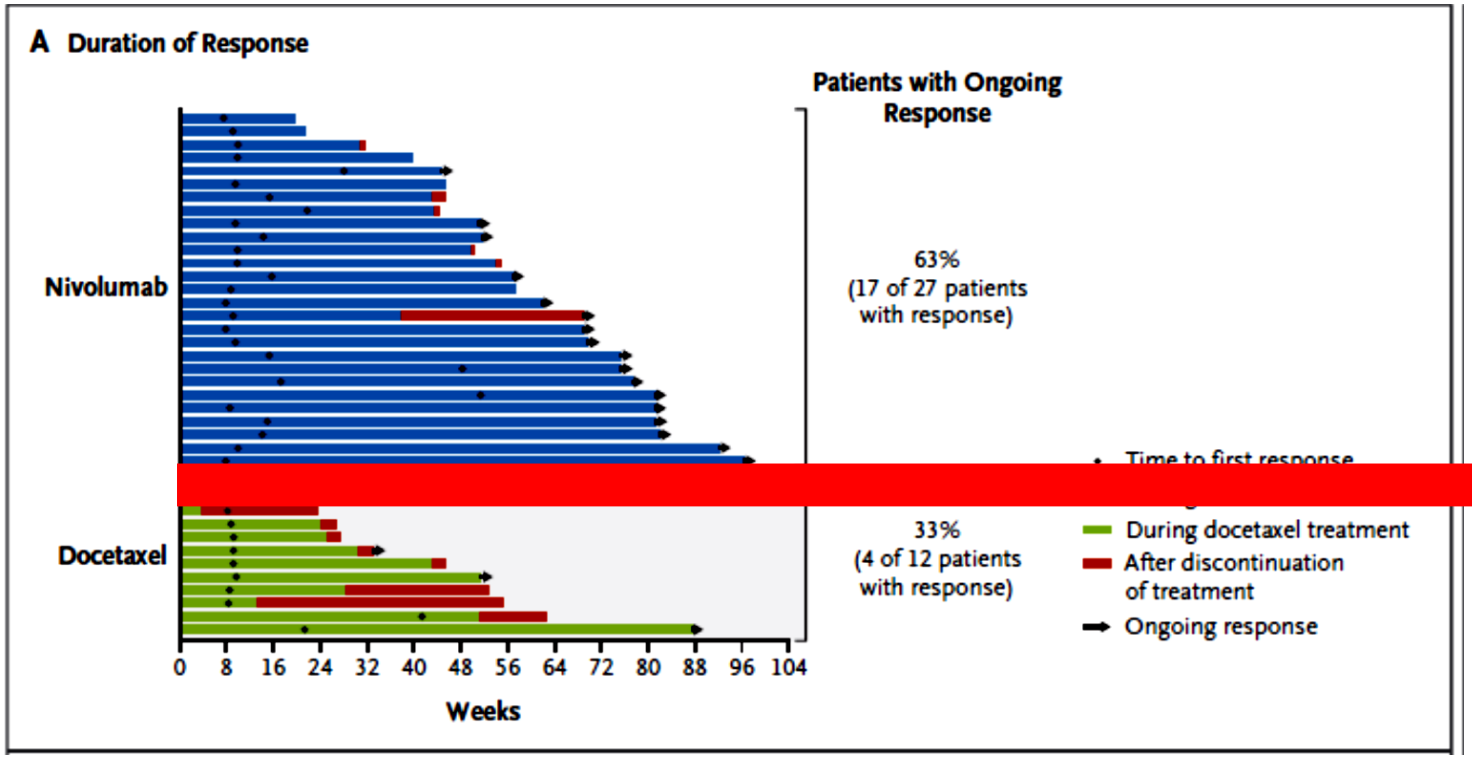
Checkmate-017: Durable responses with Nivolumab



Median duration of response: 20.4+ vs 8.4 mos

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Brahmer J et al, NEJM, May 2015

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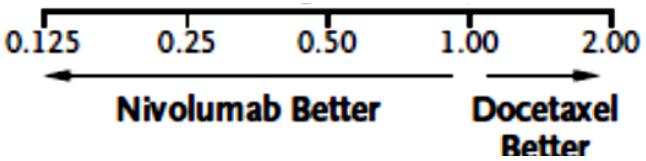
Checkmate-017: Tumor PDL1 status does not predict benefit from Nivolumab

C Overall and Progression-free Survival According to PD-L1 Expression Level

PD-L1 Expression Level	Nivolumab	Docetaxel	Unstratified Hazard Ratio (95% CI)
	no. of patients		
Overall survival			
≥1%	63	56	0.69 (0.45–1.05)
<1%	54	52	0.58 (0.37–0.92)
≥5%	42	39	0.53 (0.31–0.89)
<5%	75	69	0.70 (0.47–1.02)
≥10%	36	33	0.50 (0.28–0.89)
<10%	81	75	0.70 (0.48–1.01)
Not quantifiable at baseline	18	29	0.39 (0.19–0.82)



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Brahmer J et al, NEJM, May 2015

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Checkmate-017: Adverse events fewer and less severe with Nivolumab

- Nivolumab:
  - -7% moderate/severe toxicities
  - -fatigue, anorexia (10-16%)
  - -moderate/severe immune-related toxicities:
    - *nephritis, colitis, pneumonitis
    - *most immune events treated with systemic steroids
- Docetaxel:
  - -57% moderate/severe toxicities
  - -neutropenia, fatigue, alopecia, nausea (23-33%)

Brahmer J et al, NEJM, May 2015

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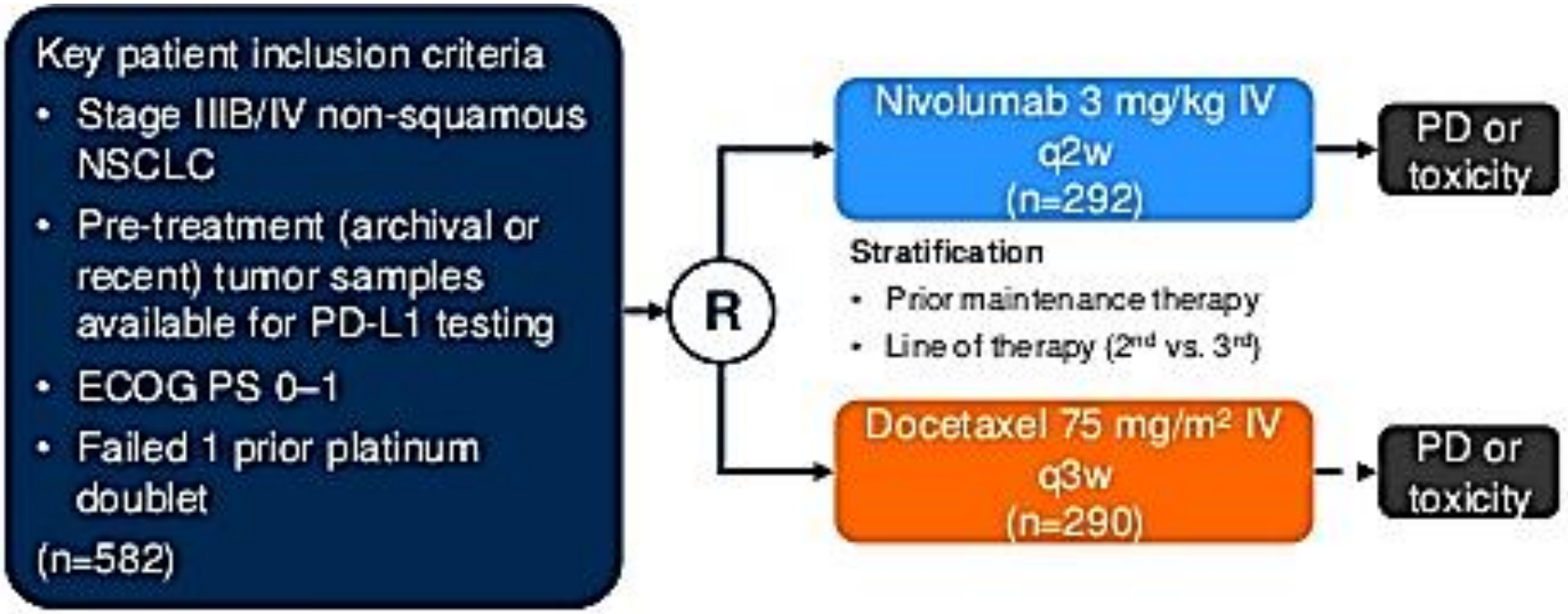
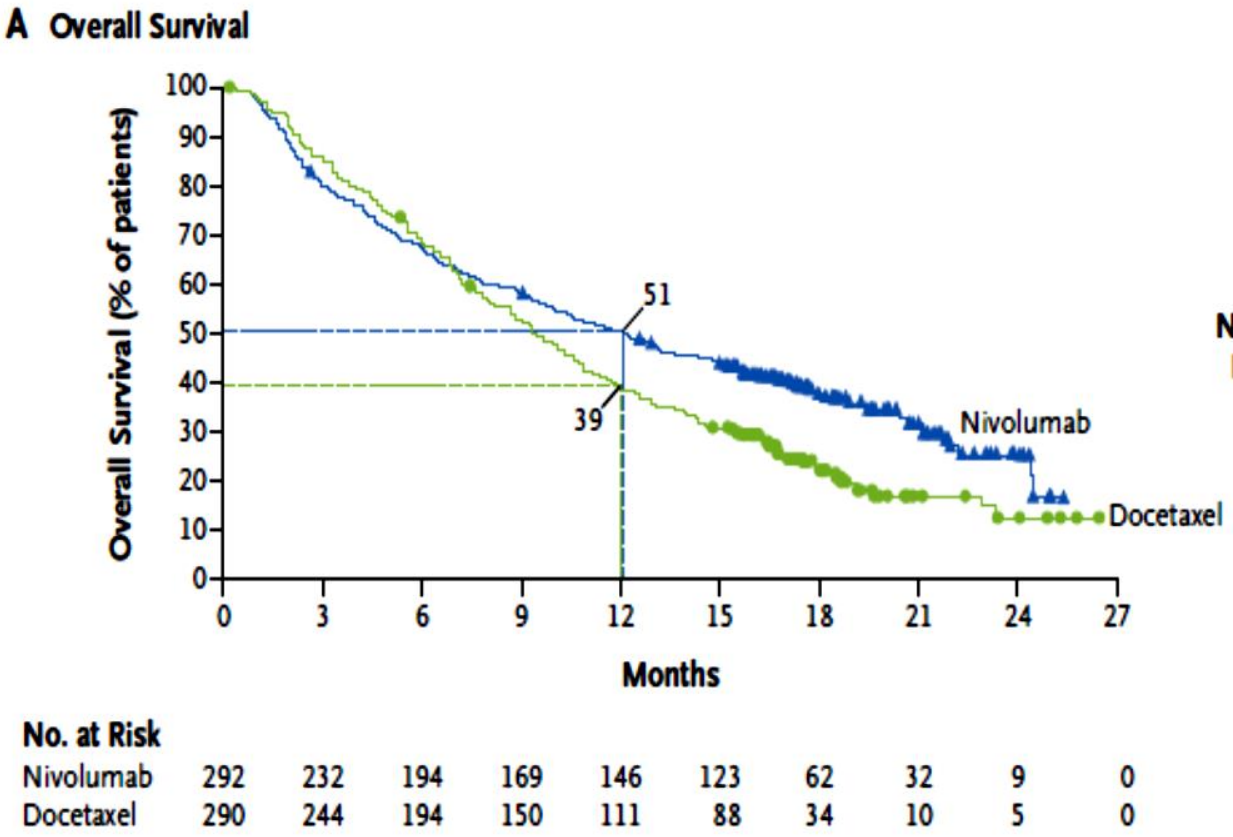
NIVOLUMAB IN NON-SQUAMOUS NSCLC

Checkmate-057: Nivolumab vs Docetaxel for 2nd line tx of adv NON-squamous NSCLC



Borghaei H et al, NEJM, Sept 2015
http://www.slideshare.net/spa718/immunooncology-in-lung-cancer

Checkmate-057: Overall survival improved with Nivolumab



	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

Objective response rate: 19% vs. 12%
p = 0.02

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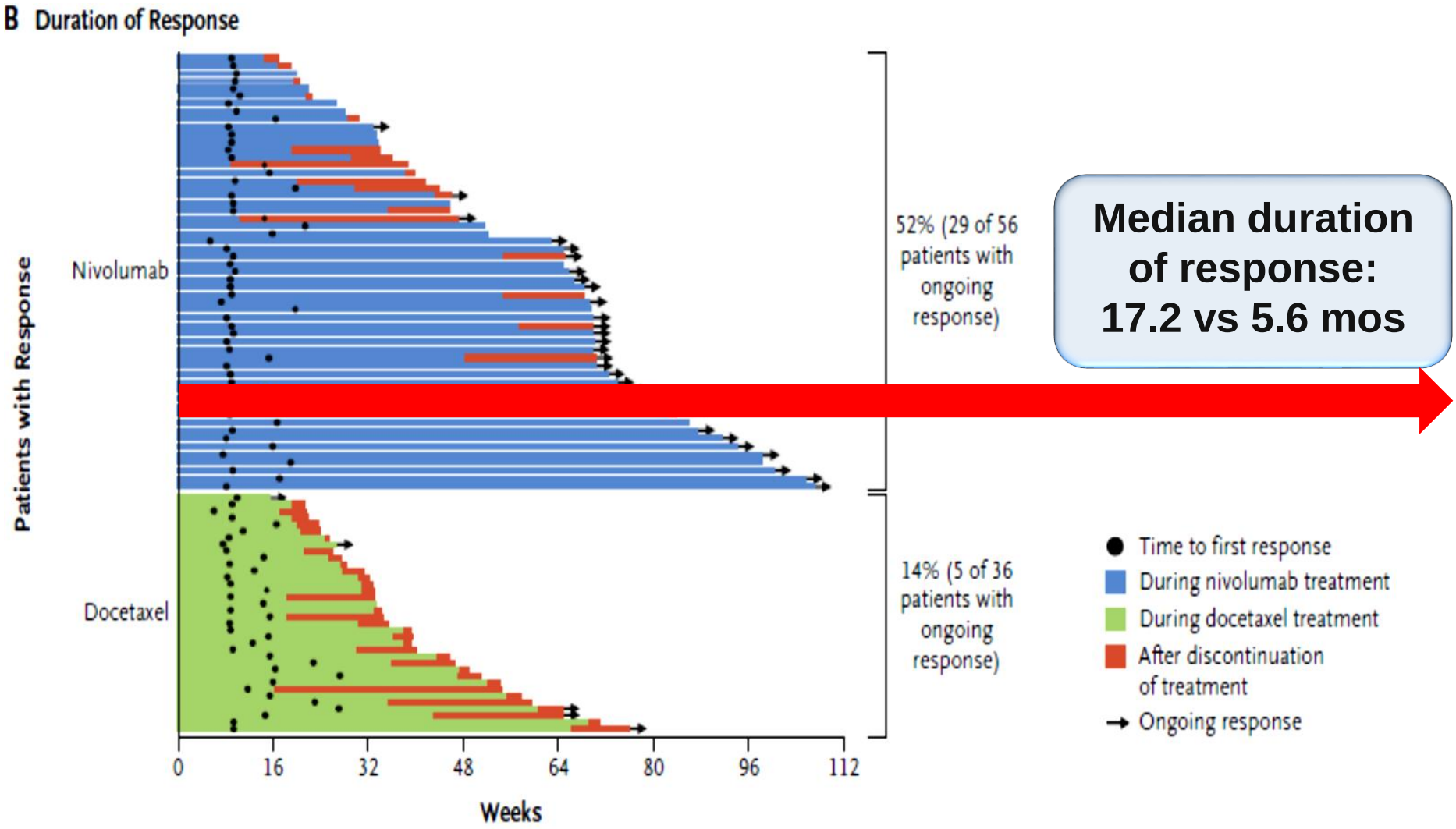
Borghaei H et al, NEJM, Sept 2015

Checkmate-057: Durable responses with Nivolumab



Median duration of response: 17.2 vs 5.6 mos

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Borghaei H et al, NEJM, Sept 2015

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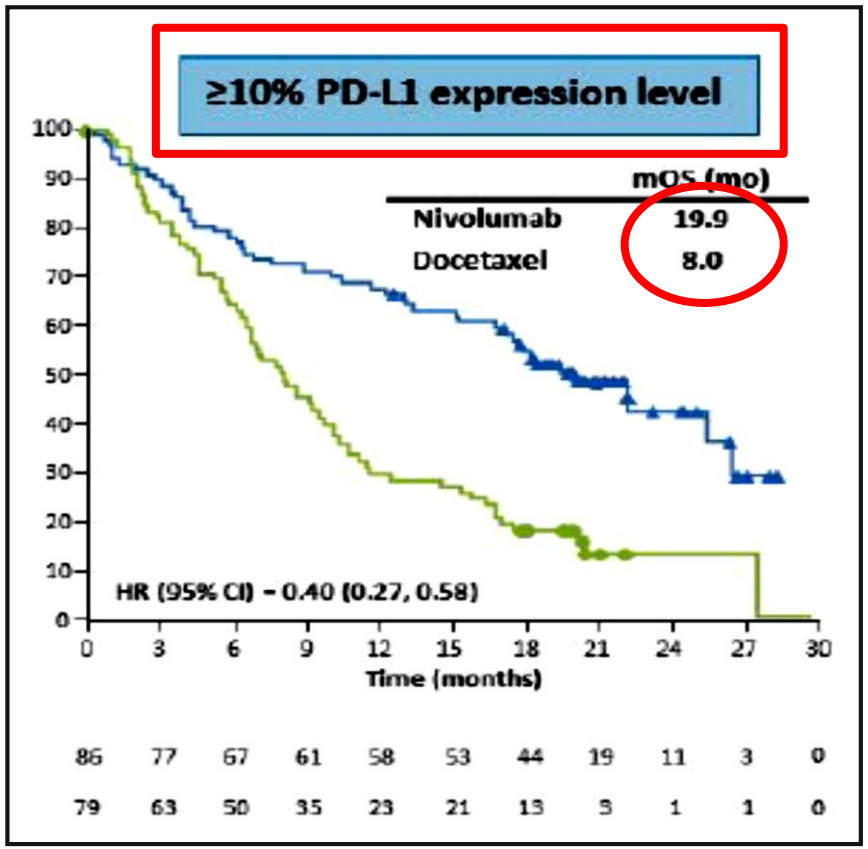
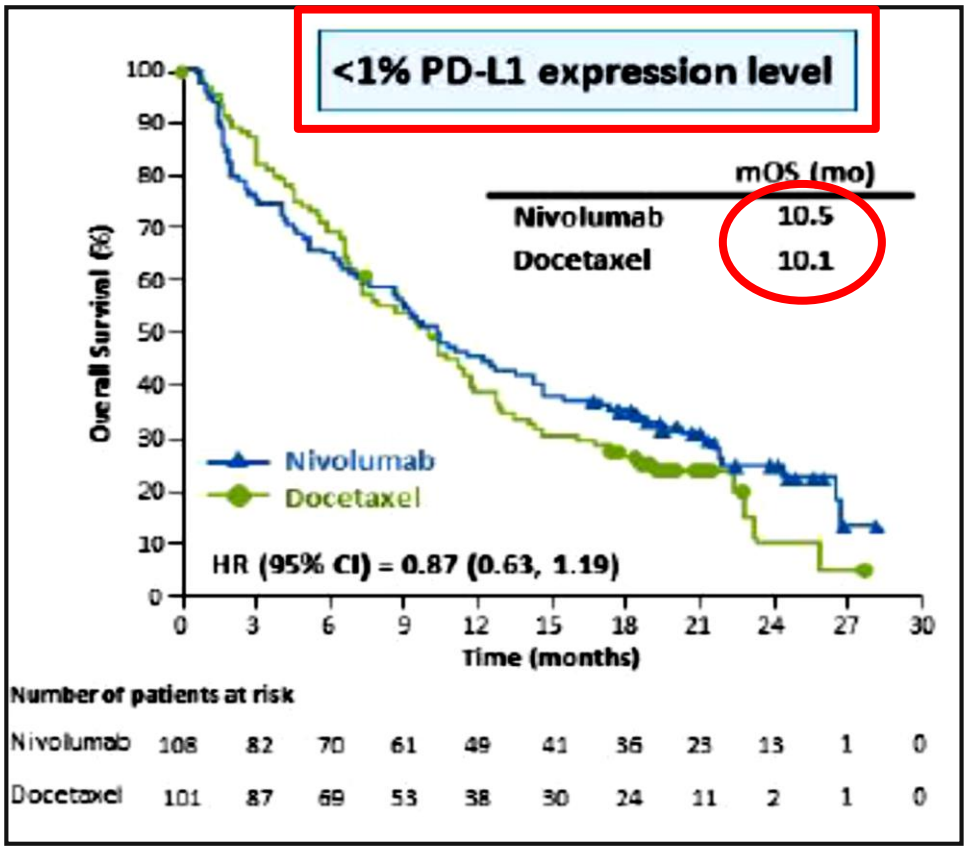
Checkmate-057: Tumor PDL1 expression associated with improved outcomes with Nivolumab





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Borghaei H et al, NEJM, Sept 2015

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Checkmate-057: Adverse events fewer and less severe with Nivolumab

- Nivolumab:
  - -10% moderate/severe
  - -fatigue, nausea, anorexia (10-16%)
  - -moderate/severe immune-related toxicities:
    - *rash, colitis, abnl LFT's, pneumonitis
    - *most immune events treated with systemic steroids
- Docetaxel:
  - -54% moderate/severe
  - -neutropenia, fatigue, alopecia, nausea (25-31%)

Brahmer J et al, NEJM, May 2015

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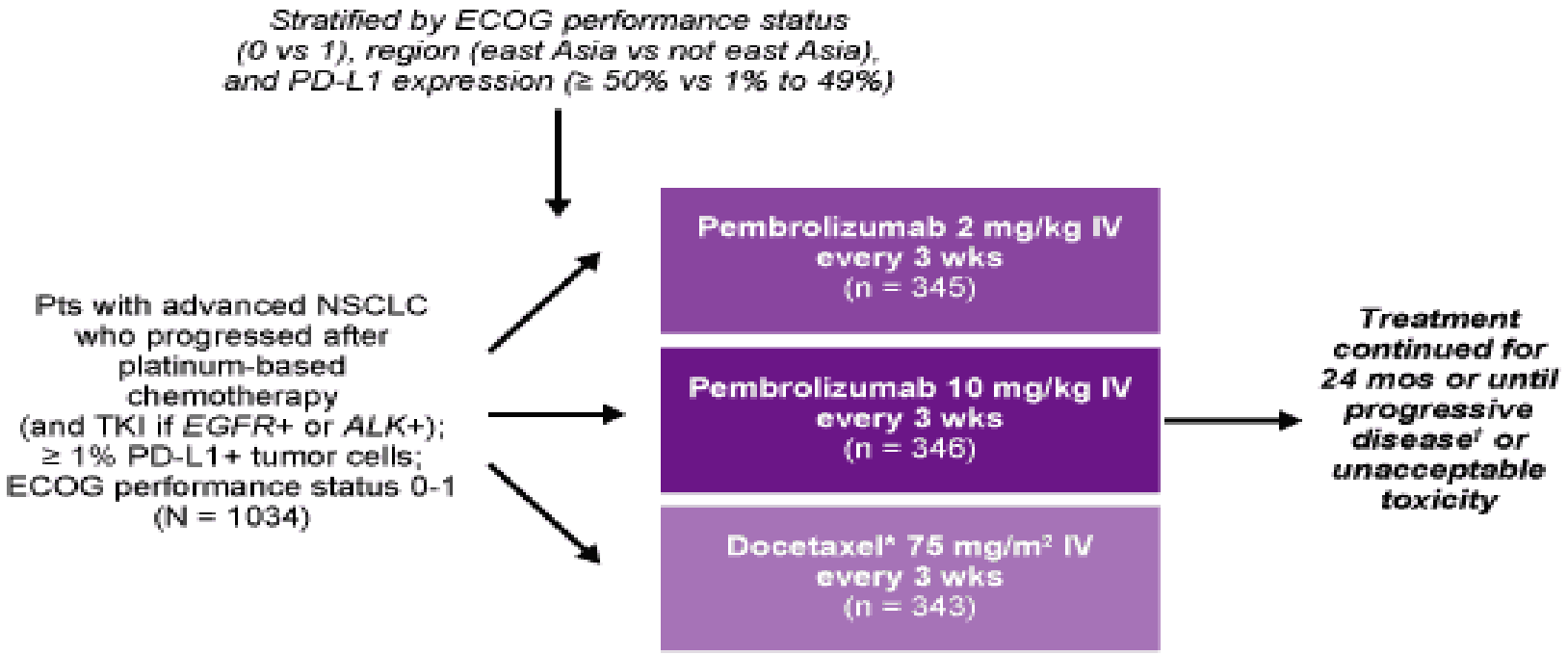
PEMBROLIZUMAB IN NSCLC

KEYNOTE-010: Pembrolizumab vs. Docetaxel for previously treated adv NSCLC

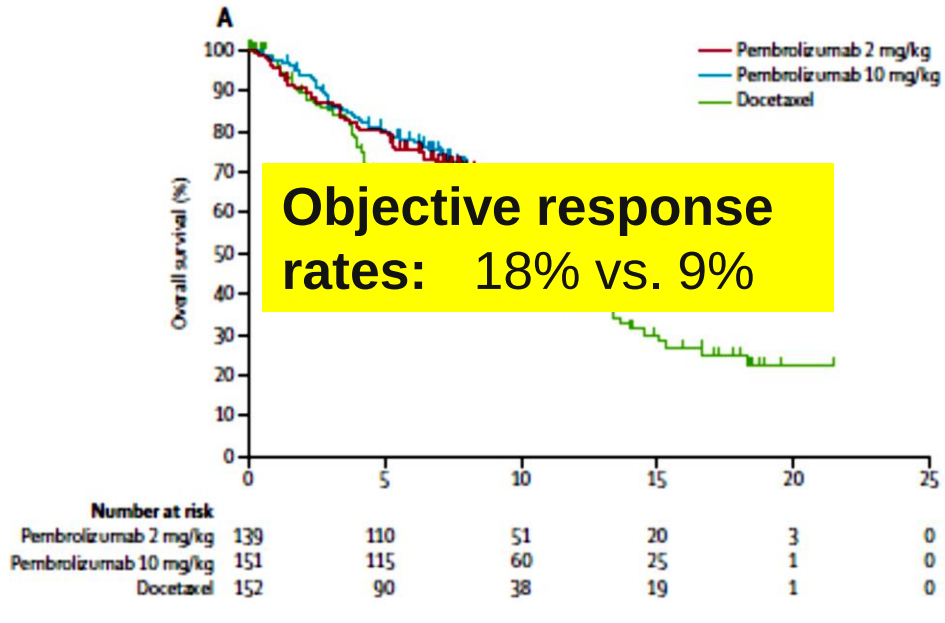


Pembrolizumab given at 2 different doses; Patients stratified by tumor PDL1 status

Herbst R et al, Lancet, 2016
http://www.clinicaloptions.com/Oncology

KEYNOTE-010: Overall survival improved with Pembrolizumab in all groups/dose levels

PD-L1 ≥ 1%

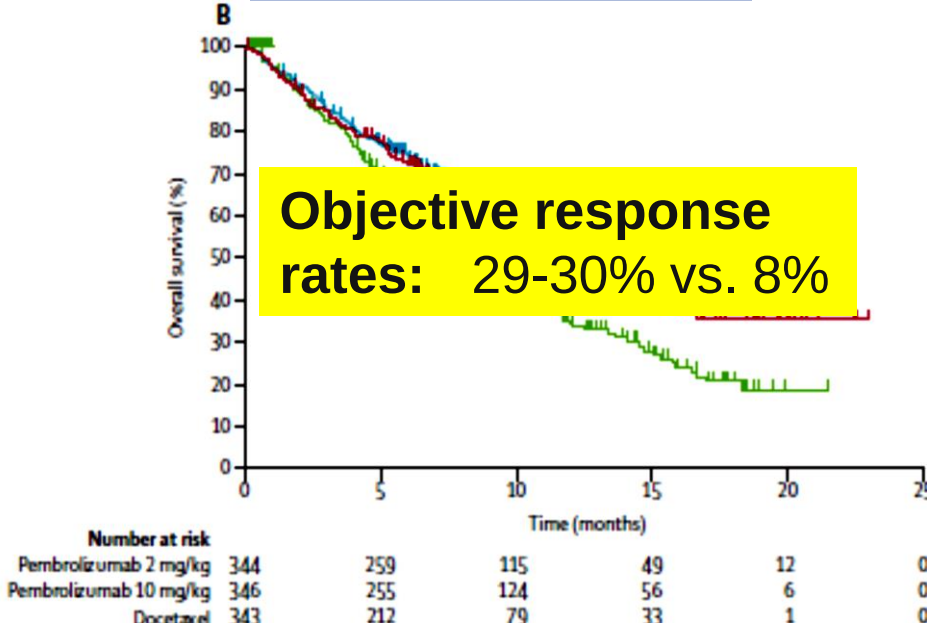


Objective response rates: 18% vs. 9%

Median overall survival:

10.4-12.7 mos vs 8.5 mos

PD-L1 ≥ 50%



Objective response rates: 29-30% vs. 8%

Median overall survival:

14.9-17.3 vs 8.2 mos

Median duration of response:
10-12+ vs 6-8 mos

Herbst R et al, Lancet, Dec 2016

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KEYNOTE-010: Adverse events fewer and less severe with Pembrolizumab

- Pembrolizumab:
  - -13-16% moderate/severe toxicities
  - -fatigue, anorexia (11-14%)
  - -immune-related toxicities:
    - hypothyroidism (8%),
    - hyperthyroidism (4-6%),
    - pneumonitis (4-5%)-- 3 deaths due to pneumonitis
- Docetaxel:
  - -35% moderate/severe toxicities
  - -alopecia, fatigue, diarrhea (18-33%)

Herbst R et al, Lancet, Dec 2016

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BACK TO OUR PATIENT…

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A 65 y/o fit gentleman with an 80 pack/year tobacco hx presents with stage IV adenocarcinoma of the lung (KRAS-mutated).

- Following 4 cycles of 1st line palliative Carboplatin/Pemetrexed, he receives maintenance Pemetrexed
- 8 months after initial diagnosis, he experiences disease progression in the lungs

- PS is 0, end organ function is normal, and no concurrent autoimmune disease
- Tumor tests positive for PDL1 by IHC
- He proceeds to receive 2nd line Pembrolizumab IV every 3 weeks

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Nivolumab vs. Pembrolizumab for previously treated advanced NSCLC

Nivolumab

- Previously treated NSCLC
- 3mg/kg IV

every 2 weeks

Pembrolizumab

- Previously treated PDL1+ NSCLC
- 2mg/kg IV

every 3 weeks

There are many ongoing phase III trials of checkpoint inhibitors in NSCLC…

2nd line/refractory

1st line metastatic

Adjuvant

Table 5. Ongoing Phase III Clinical Trials of Checkpoint Inhibitors in NSCLC

Immune Checkpoint Target	Trial ID	Study Phase and Setting	Regimen	Accrual Status and Estimated Enrollment (No. of patients)	Primary End Point and Estimated PCD
Second line and beyond					
PD-1 inhibitors					
PD-1	CheckMate 153, NCT02066636	aNSCLC, second line	Nivolumab 1 year *v* nivolumab until progression	Recruiting, N = 780	Safety, March 2019
PD-1	KEYNOTE-010, NCT01905657	Phase II/III aNSCLC, PD-L1 positive, second line	Pembrolizumab *v* docetaxel	Active, not recruiting, N = 920	OS, November 2015
PD-L1 inhibitors					
PD-L1	OAK, NCT02008227	aNSCLC, second line*	Atezolizumab *v* docetaxel	Active, not recruiting, N = 1,225	OS, June 2017
PD-L1	JAVELIN Lung 200, NCT02395172	aNSCLC, PD-L1 positive, second line	Avelumab *v* docetaxel	Recruiting, N = 650	OS, October 2021
PD-L1 and/or CTLA-4	ARCTIC, NCT02352948	aNSCLC, *EGFR* and *ALK* negative or unknown, third line	PD-L1 positive: durvalumab *v* standard care; PD-L1 negative: durvalumab and/or tremelimumab *v* standard care	Recruiting, N = 900	OS, February 2017
[illegible]	[illegible]04933	aNSCLC *EGFR* T790M positive, EGFR inhibitor pretreated, second line	Durvalumab plus AZD9291 *v* AZD9291	Not yet recruiting, N = 350	PFS, August 2017
First line					
[illegible]tors					
	CA184-104, NCT01285609	Squamous aNSCLC, first line	Ipilimumab plus PacCarbo *v* PacCarbo	Completed accrual, N = 920	OS, June 2015
CTLA-4	CA184-153, NCT02279732	Squamous aNSCLC, first line	Ipilimumab plus PacCarbo *v* PacCarbo	Recruiting, N = 867	OS, September 2019
PD-1 inhibitors					
PD-1	CheckMate 026, NCT02041533	aNSCLC, PD-L1 positive, first line	Nivolumab *v* PlatD	Recruiting, N = 535	PFS, August 2016
PD-1	KEYNOTE-024, NCT02142738	aNSCLC, PD-L1 positive, *EGFR* and *ALK* negative, first line	Pembrolizumab *v* PlatD	Recruiting, N = 300	PFS, June 2016
PD-1	KEYNOTE-042, NCT02220894	aNSCLC, PD-L1 positive, *EGFR* and *ALK* negative or unknown, first line	Pembrolizumab *v* PlatD	Recruiting, N = 1,240	OS, June 2018
PD-L1 inhibitors					
PD-L1 and/or CTLA-4	MYSTIC, NCT02453282	aNSCLC, *EGFR* and *ALK* negative or unknown, first line	Durvalumab *v* durvalumab plus tremelimumab *v* PlatD	Not yet recruiting, N = 675	PFS, April 2018
PD-L1	IMpower 110, NCT02409342	aNSCLC nonsquamous, PD-L1 positive, first line	Atezolizumab *v* PemPlat	Recruiting, N = 400	PFS, April 2018
PD-L1	IMpower 111, NCT02409355	aNSCLC squamous, PD-L1 positive, first line	Atezolizumab *v* GemPlat	Recruiting, N = 400	PFS, July 2019
PD-L1	IMpower 130, NCT02367781	aNSCLC nonsquamous, first line	Atezolizumab plus nabpacCarbo *v* nabpacCarbo	Recruiting, N = 550	PFS, July 2018
PD-L1	IMpower 131, NCT02367794	aNSCLC squamous, first line	Atezolizumab plus nabpacCarbo *v* atezolizumab plus PacCarbo *v* nabpacCarbo	Recruiting, N = 1,200	PFS, February 2023
PD-L1	IMpower 150, NCT02366143	aNSCLC nonsquamous, first line	Atezolizumab plus PacCarbo *v* atezolizumab plus PacCarboBev *v* PacCarboBev	Recruiting, N = 1,200	PFS, January 2017
Early disease					
PD-L1	PACIFIC, NCT02125461	Stage III unresectable NSCLC	Durvalumab *v* placebo after chemoradiation	Recruiting, N = 702	OS, May 2017
PD-L1	BR31, IFCT1401, NCT02273375	Completely resected NSCLC, adjuvant	Durvalumab *v* placebo	Recruiting, N = 1,100	DFS, January 2025

NOTE. Clinical trial data as listed on ClinicalTrials.gov as of June 19, 2015.

Abbreviations: ALK, anaplastic lymphoma kinase; aNSCLC, advanced non–small-cell lung cancer; Bev, bevacizumab; Carbo, carboplatin; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DFS, disease-free survival; EGFR, epidermal growth factor receptor; Gem, gemcitabine; NABpac, nanoparticle albumin-bound paclitaxel; NSCLC, non–small-cell lung cancer; OS, overall survival; Pac, paclitaxel; PCD, primary completion date; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; Pem, pemetrexed; PFS, progression-free survival; Plat, platinum; PlatD, platinum doublet.

*First-line patients were allowed if they had disease recurrence within 6 months of treatment with a platinum-based adjuvant/neoadjuvant regimen or combined-modality (eg, chemoradiation) regimen with curative intent.

Melosky et al, J Clin Oncol, May 2016

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Conclusions

- Outcomes for advanced NSCLC are poor

- Available 2nd line therapies are toxic and with modest efficacy

- Immune checkpoint inhibitors have improved survival in the 2nd line

  …Survival benefit = 2-6 months

  (And may be true for 1st line/initial treatment, too)

- PDL1 remains a challenging marker to predict who will best respond to immune checkpoint inhibitors

  …Patients with PDL1- tumors may still benefit from drug

- IF response, then typically durable (>6 mos)

- Immune toxicities are real, but can be managed

  …And are typically less severe than with chemotherapy

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Conclusions & Future Directions

- Combination vs. sequential chemotherapy/immunotherapy is being explored
- Oral targeted therapies (TKIs) remain the standard initial treatment for mutated advanced tumors (i.e. *EGFR, ALK*)
- Immunotherapy for small cell lung cancer is up and coming