ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

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AMERICAN ACADEMY OF EMERGENCY MEDICINE

ACCC
Association of Community Cancer Centers

sitc
Society for Immunotherapy of Cancer

Disclosures

- Consulting
  - AbbVie, ARIAD, AstraZeneca, Bristol-Myers Squibb, Genentech/Roche, Novartis, Pfizer
- Research Funding (to institution)
  - Celgene, Genentech/Roche, Merck, Novartis, OncoMed

- I will discussing non-FDA approved treatment/ indications during my presentation today (research findings)

Case

- 69yo female, current smoker with 60 pack year smoking history, presents with progressive cough
- CT reveals, and PET/CT confirms, 4cm LUL lesion, multifocal mediastinal LAD, and 2cm R adrenal lesion, all hypermetabolic. MRI brain negative
- Bronchoscopy with biopsy of subcarinal node reveals squamous cell carcinoma
- Primary oncologist recommends carboplatin and gemcitabine
- Saw a commercial “with a big wall” and presents for a second opinion and wants to know if she should change therapy

Immunotherapy in Lung Cancer

- PD-1/PD-L1 inhibition in the 2nd line
- PD-1 inhibition in the 1st line
- Where we're going: combinations

The New York Times

BUSINESS DAY

F.D.A. Allows First Use of a Novel Cancer Drug

By ANDREW POLLACK SEPT. 4, 2014

EMAIL

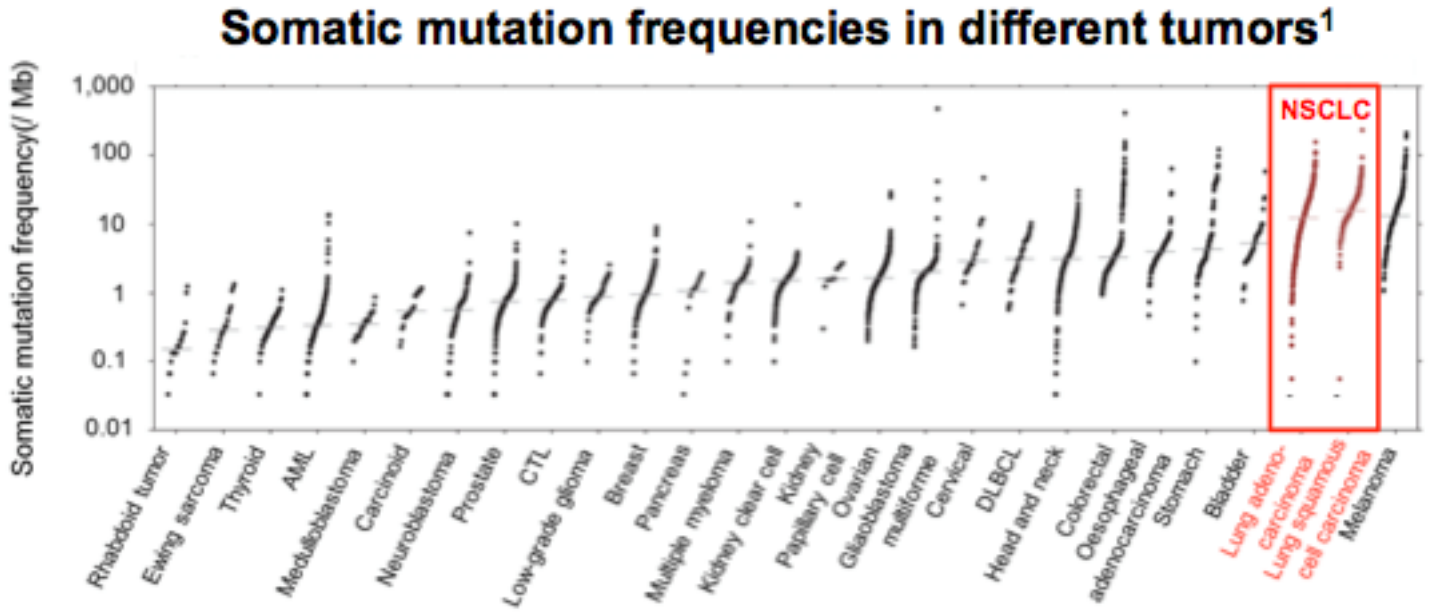
FACEBOOK

The Food and Drug Administration on Thursday approved the first of an eagerly awaited new class of cancer drugs that unleashes the body's immune system to fight tumors.

The drug, which [ ] will sell under the name [ ], was approved for patients with advanced melanoma who have exhausted other therapies.

Cancer researchers have been almost giddy in the last couple of years about the potential of drugs like [ ], which seem to solve a century-old mystery of how cancerous cells manage to evade the body's immune system.

Immunotherapy- PD1/PD-L1

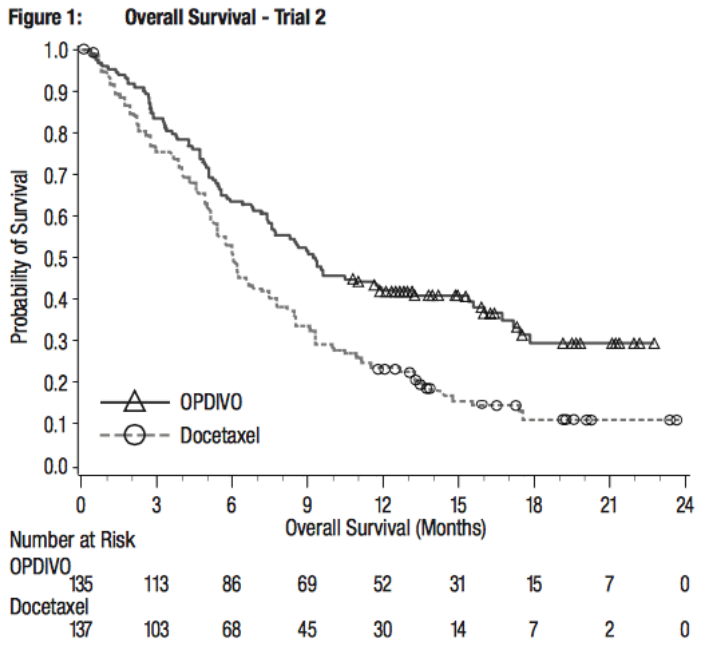


- High rates of somatic mutations in lung cancer may contribute to increased immunogenicity
- Therapies targeting the PD-L1/PD-1 pathway will alter the treatment of NSCLC

[1]Lawrence MS, et al. Nature. 2013;499(7457):214-218.
[2]Chen DS, et al. *CCR*. 2012.

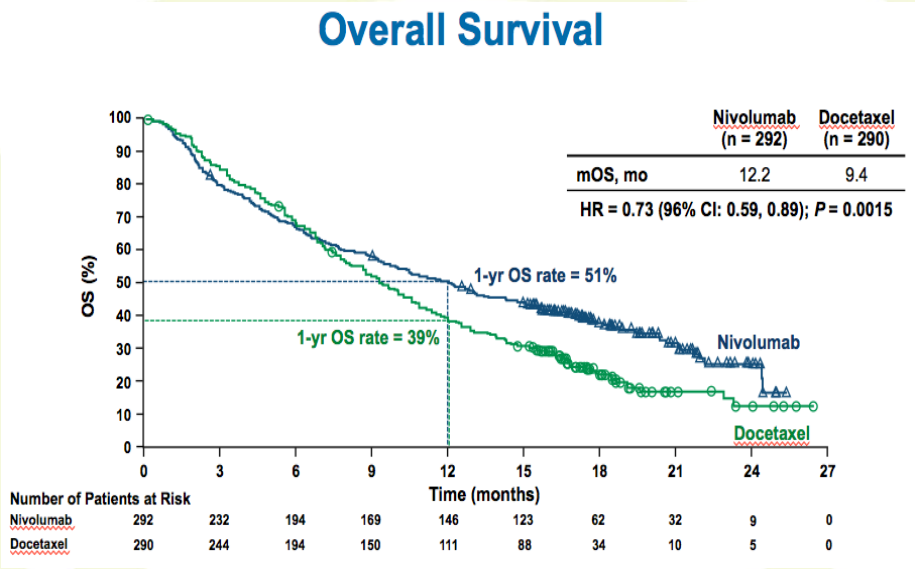
Nivolumab vs docetaxel: Checkmate 017/057

Squamous



- Response rate on 017
  - Nivo 20% vs docetaxel 9%
- Median duration of response on 017
  - Nivo NR vs docetaxel 8.4mo

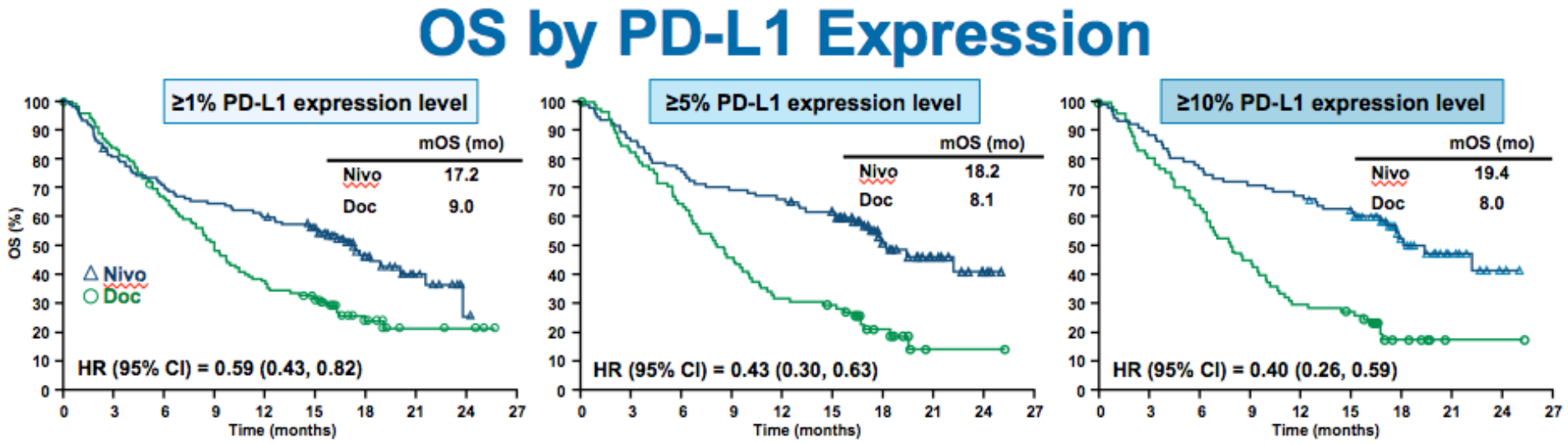
Non-squamous



- Response rate on 057
  - Nivo 19% vs docetaxel 12%
- Median duration of response on 057
  - Nivo 17.2mo vs docetaxel 5.6mo

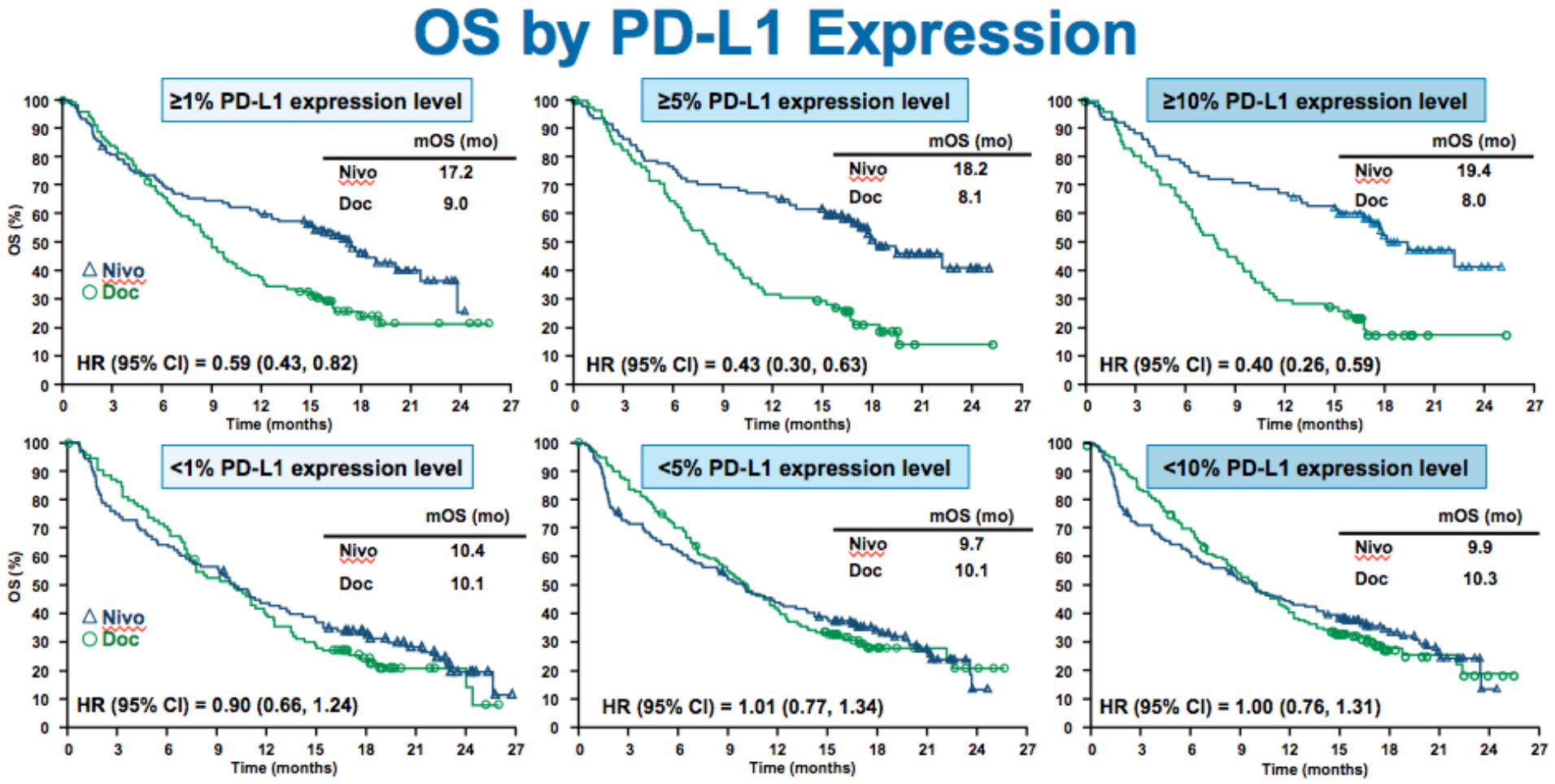
Opdivo PI, Paz-Ares, ASCO 2015

Nivo vs doce in non-squam NSCLC: Checkpoint 057



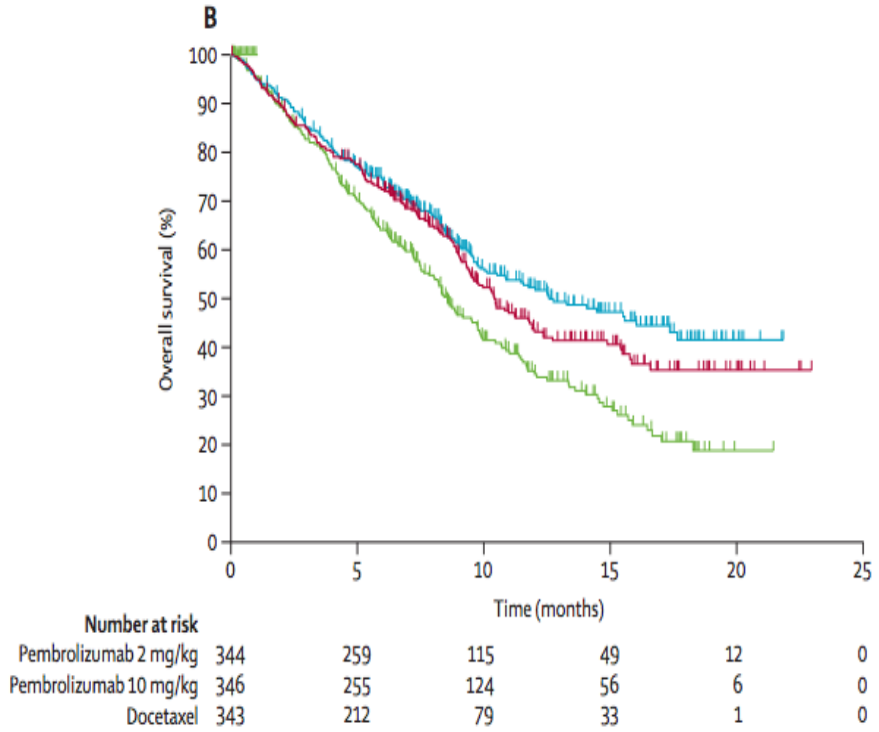
Paz-Ares, ASCO 2015

Nivo vs doce in non-squam NSCLC: Checkpoint 057



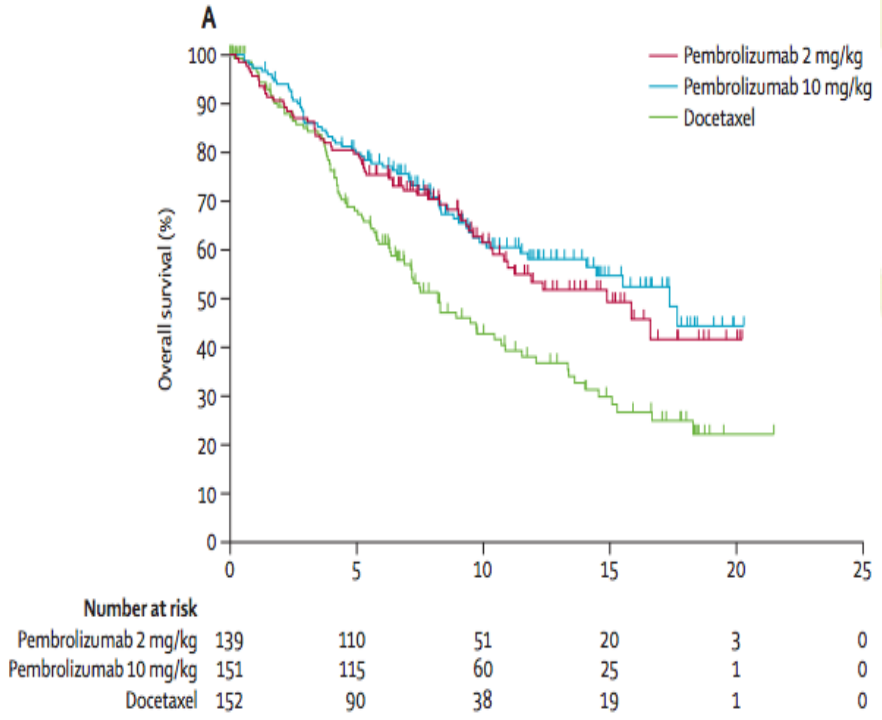
Paz-Ares, ASCO 2015

Pembrolizumab vs docetaxel: KEYNOTE-010



PD-L1>1%

- OS 10.2/12.7 vs 8.5 mos
- RR 18%/18% vs 8%

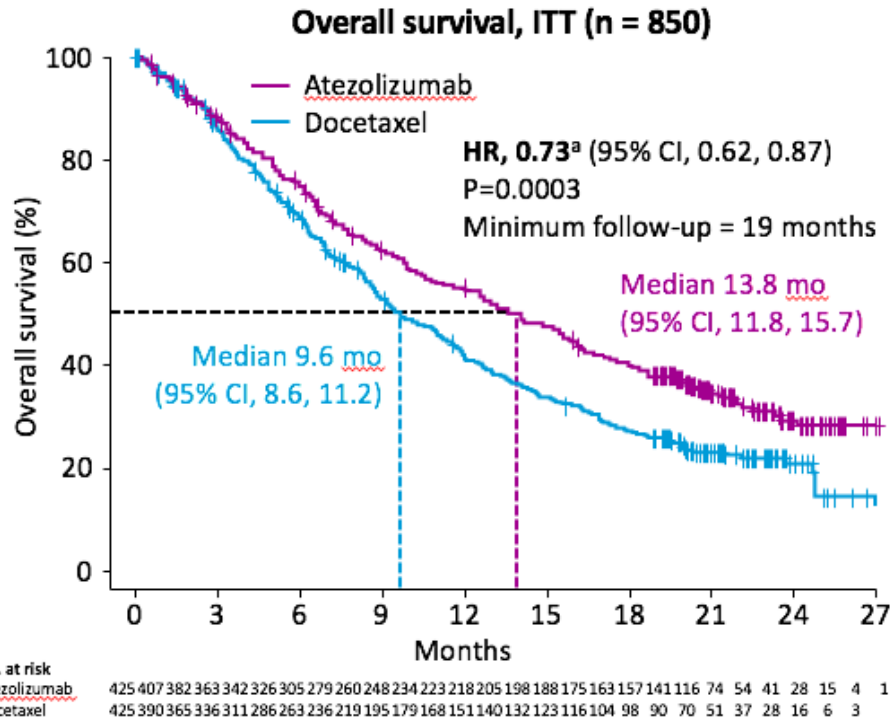


PD-L1>50%

- OS 14.9/17.3 vs 8.2mo
- RR 30/20% vs 8%

Atezolizumab vs doce, 2nd or 3rd line: OAK

Characteristics	Atezolizumab n = 425	Docetaxel n = 425
Median age, y	63	64
≥65 y	45%	49%
Male	61%	61%
Nonsquamous	74%	74%
Squamous	26%	26%
ECOG PS, 0/1	37%/64%	38%/62%
No. of prior therapies, 1/2	75%/25%	75%/25%
History of tobacco use		
Never	20%	17%
Current/previous	14% / 66%	16% / 67%
Known EGFR status, %		
Mutant/WT	10% / 75%	10% / 73%



Barlesi, ESMO 2016

Take-home points: PD-1/PD-L1 inhibitor 2nd line

- Nivolumab, pembrolizumab, and now atezolizumab with overall similar benefit and toxicity
  - Nivo and atezo approved for all comers 2nd line
  - Pembro approved for PD-L1+ >1% 2nd line
    - Nivo q2w, pembro and atezo q3w
- Toxicities DIFFERENT than chemo
  - Majority find it better tolerated…
  - ...but any organ can be inflamed
  - For new hypoxia or dyspnea, low threshold to evaluate for pneumonitis

Immunotherapy in Lung Cancer

- PD-1/PD-L1 inhibition in the 2nd line
- PD-1 inhibition in the 1st line
- Where we're going: combinations

PD-1 inhibitor 1st line?

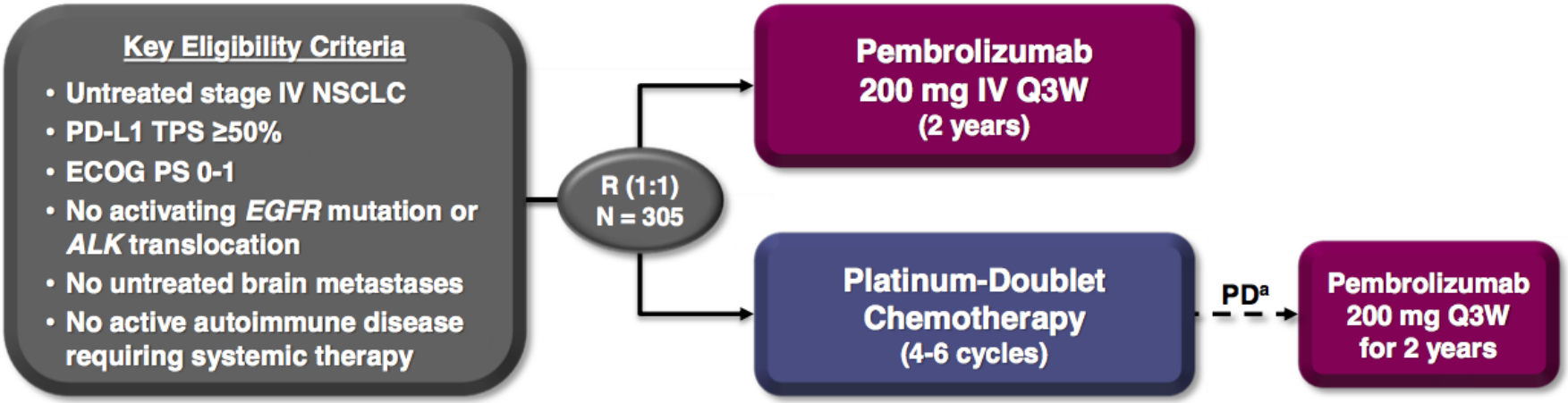
- 1st line trials presented at ESMO 2016
  - Pembro vs chemo in PD-L1≥50%
  - Nivo vs chemo in PD-L1≥5%

PD-1 inhibitor 1st line?

- 1st line trials presented at ESMO 2016
  - Pembro vs chemo in PD-L1≥50% POSITIVE
  - Nivo vs chemo in PD-L1≥5% NEGATIVE

Pembrolizumab 1st line (PD-L1≥50%)

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

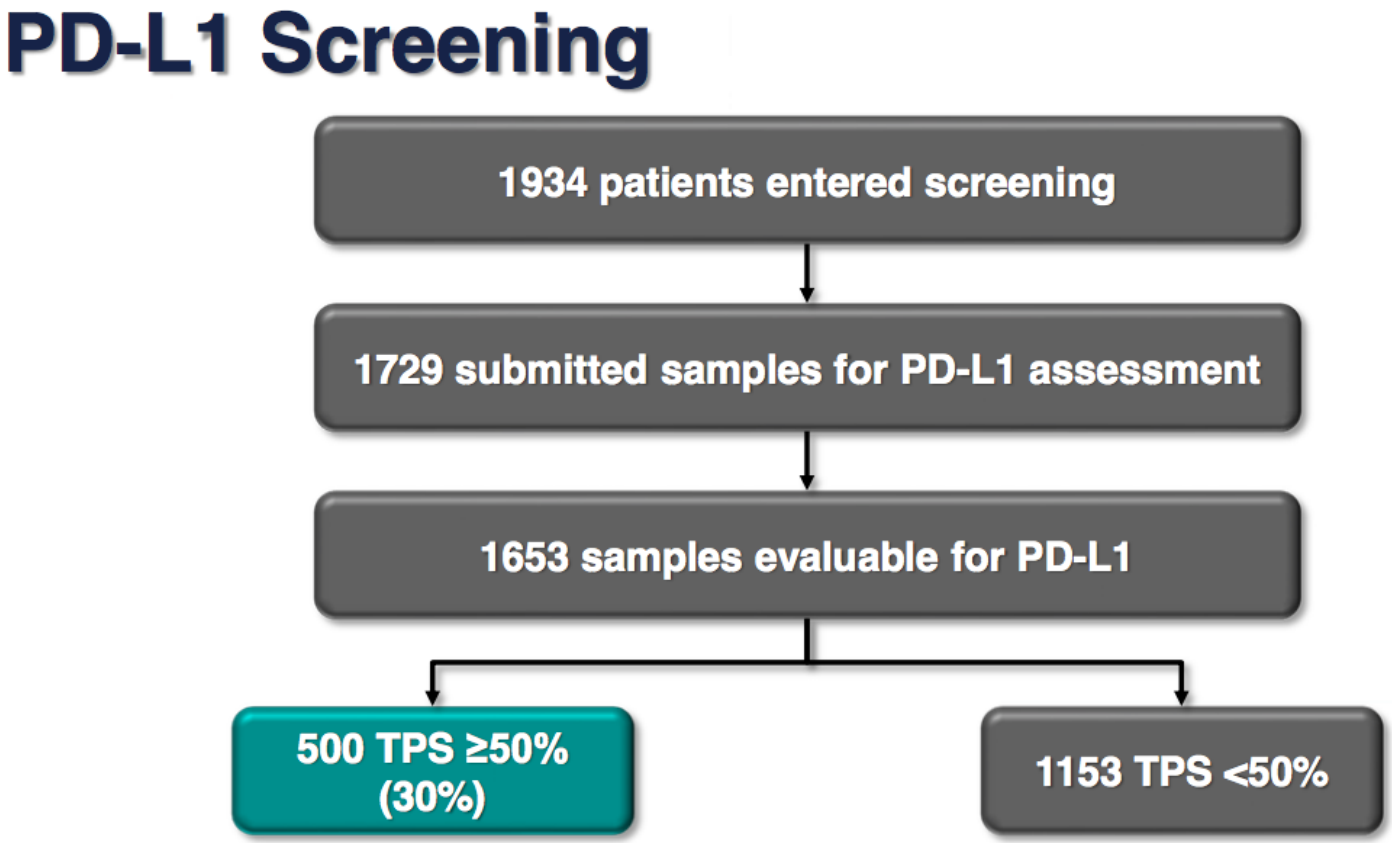
Secondary: OS, ORR, safety

Exploratory: DOR

[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

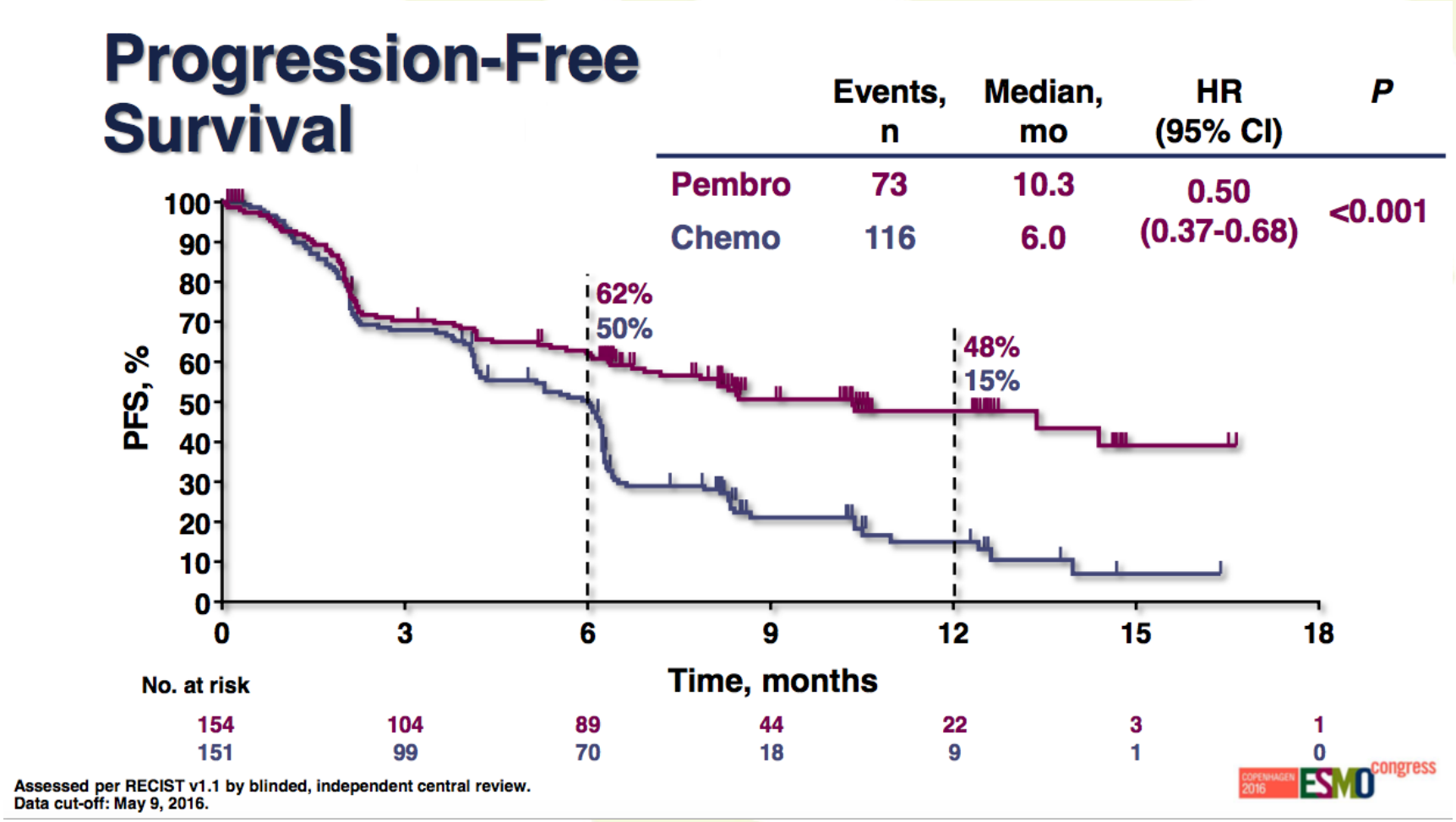
Recht, ESMO 2016

Pembrolizumab 1st line (PD-L1≥50%)



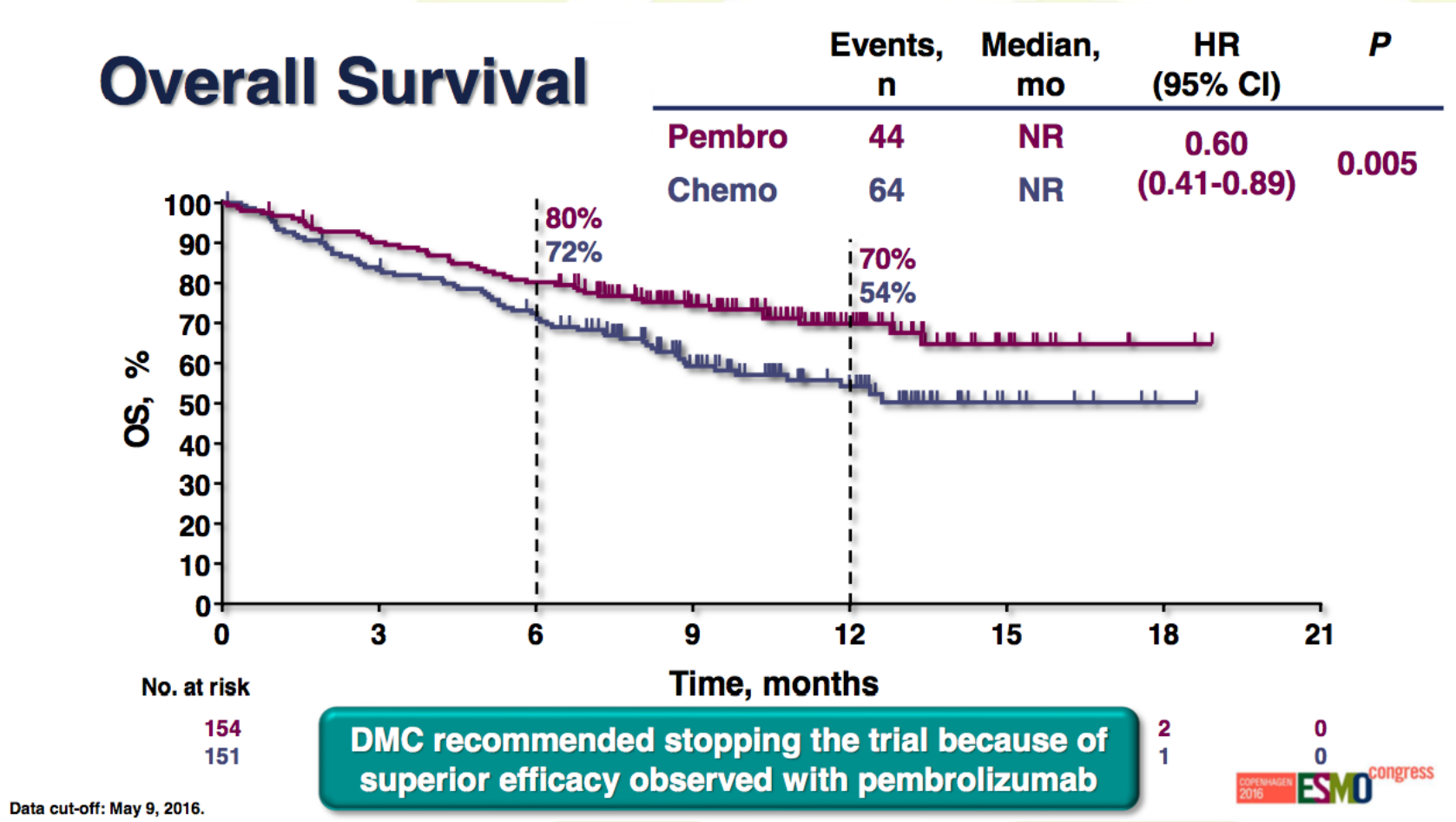
Recht, ESMO 2016

Pembrolizumab 1st line (PD-L1≥50%)



Recht, ESMO 2016

Pembrolizumab 1st line (PD-L1≥50%)

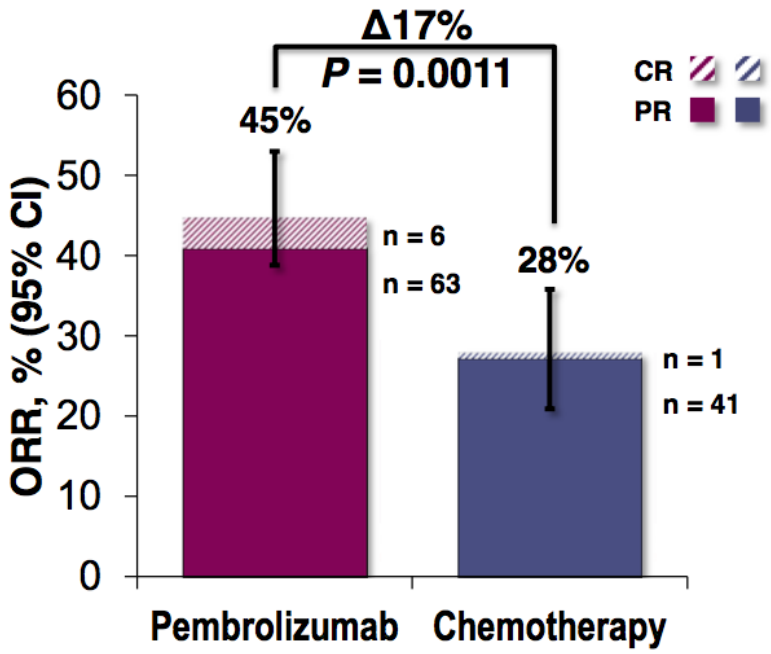


Crossover from chemo to pembro: 66/151 (44%)

Recht, ESMO 2016

Pembrolizumab 1st line (PD-L1≥50%)

Confirmed Objective Response Rate

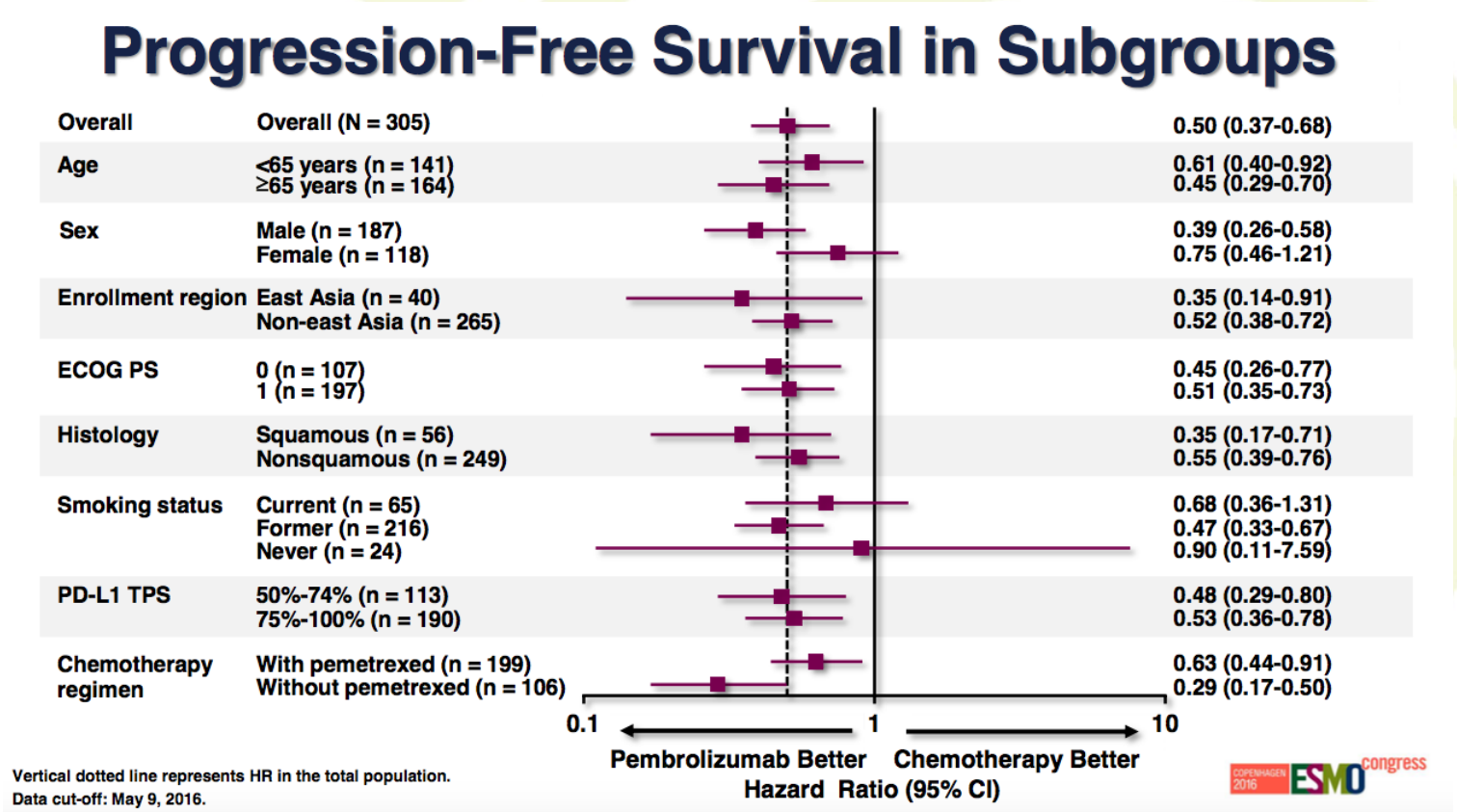


	Pembro Responders n = 69	Chemo Responders n = 42
TTR, mo median (range)	2.2 (1.4-8.2)	2.2 (1.8-12.2)
DOR, mo median (range)	NR (1.9+ to 14.5+)	6.3 (2.1+ to 12.6+)

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

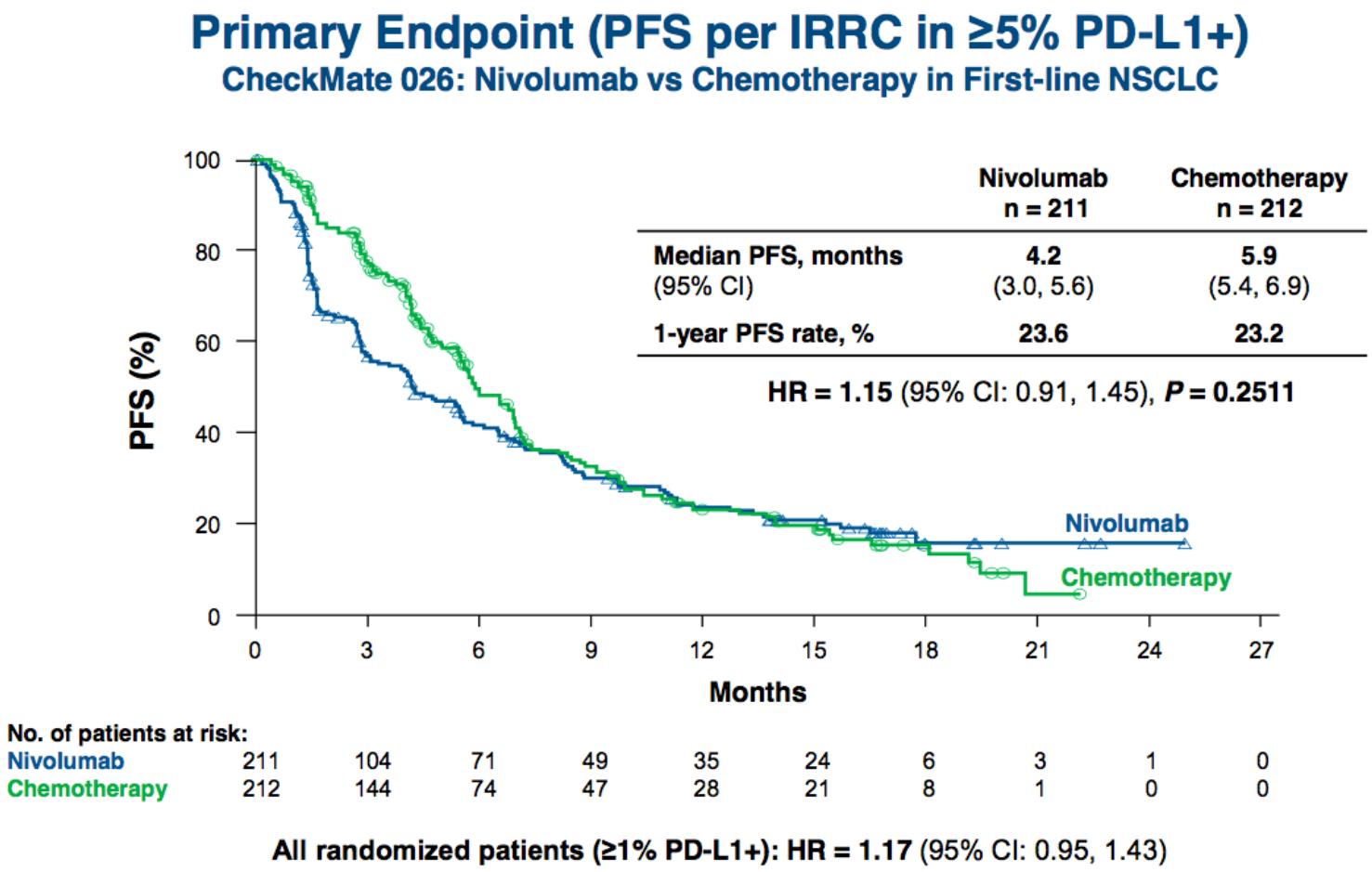
Recht, ESMO 2016

Pembrolizumab 1st line (PD-L1≥50%)



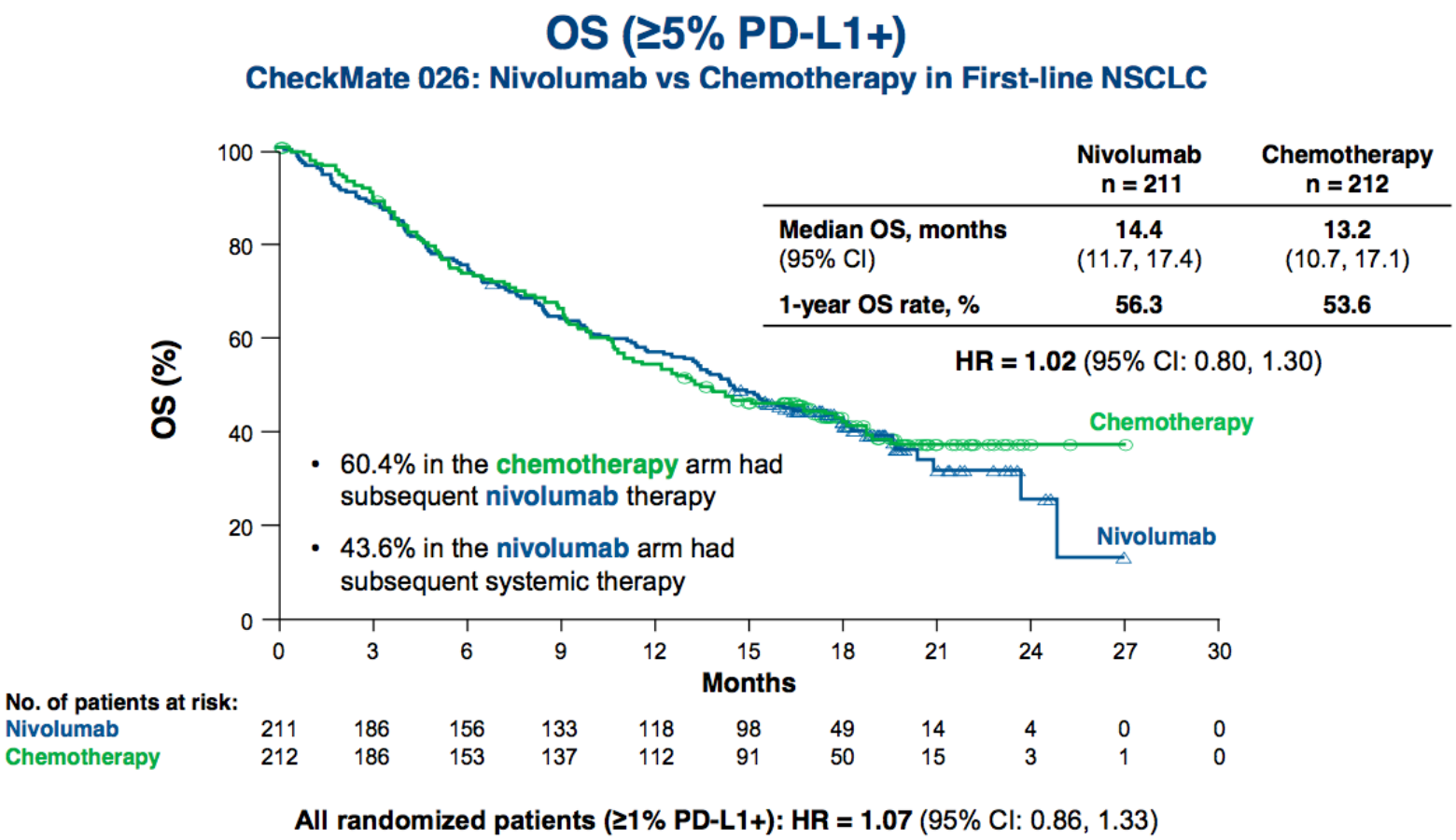
Recht, ESMO 2016

Nivolumab 1st line (PD-L1≥5%)



Socinski, ESMO 2016

Nivolumab 1st line (PD-L1≥5%)



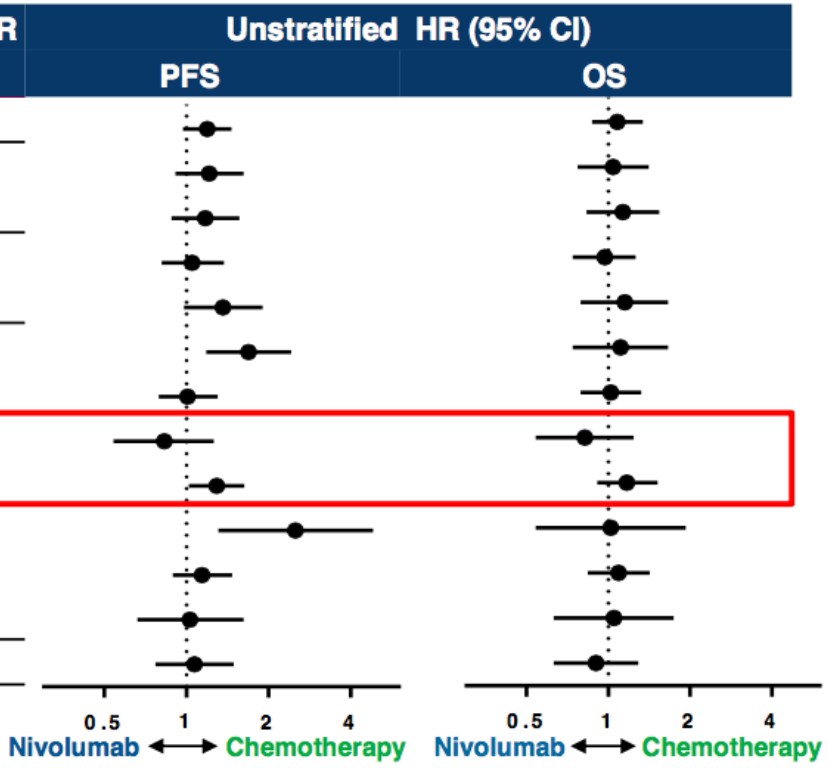
Socinski, ESMO 2016

Nivolumab 1st line (PD-L1≥5%)

PFS and OS Subgroup Analyses (All Randomized Patients)

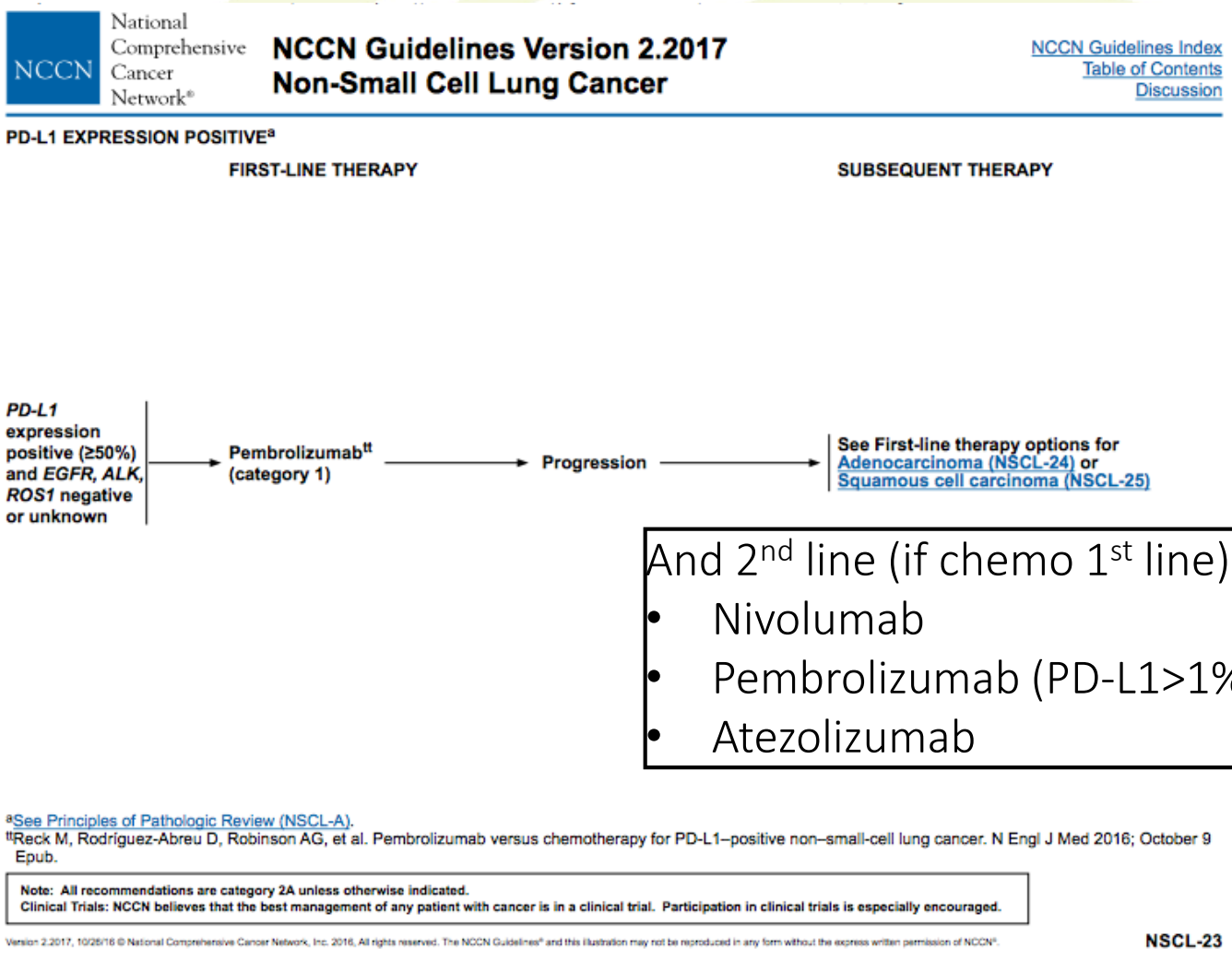
CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

Subgroup	Patients, n		Unstratified HR	
	Nivolumab	Chemotherapy	PFS	OS
Overall	271	270	1.19	1.08
≥65 years	123	137	1.21	1.04
<65 years	148	133	1.17	1.13
Male	184	148	1.05	0.97
Female	87	122	1.36	1.15
ECOG PS = 0	85	93	1.69	1.11
ECOG PS ≥1	185	177	1.01	1.02
Squamous	65	64	0.83	0.82
Non-squamous	206	206	1.29	1.17
Never smoker	30	29	2.51	1.02
Former smoker	186	182	1.14	1.09
Current smoker	52	55	1.03	1.05
≥50% PD-L1+	88	126	1.07	0.90



Socinski, ESMO 2016

Take-home points: 1st line



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PD-L1 EXPRESSION POSITIVE[a]

FIRST-LINE THERAPY | **SUBSEQUENT THERAPY**

PD-L1 **expression positive (≥50%) and *EGFR, ALK, ROS1* negative or unknown** → **Pembrolizumab[tt] (category 1)** → **Progression** → **See First-line therapy options for Adenocarcinoma (NSCL-24) or Squamous cell carcinoma (NSCL-25)**

And 2nd line (if chemo 1st line):

- Nivolumab
- Pembrolizumab (PD-L1>1%)
- Atezolizumab

[a]See Principles of Pathologic Review (NSCL-A).
[tt]Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med 2016; October 9 Epub.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NSCL-23

Case

- 69yo female, current smoker with 60 pack year smoking history, presents with progressive cough
- CT reveals, and PET/CT confirms, 4cm LUL lesion, multifocal mediastinal LAD, and 2cm R adrenal lesion, all hypermetabolic. MRI brain negative
- Bronchoscopy with biopsy of subcarinal node reveals squamous cell carcinoma
- What to do?
  - PD-L1 by 22C3
    - If PD-L1≥50%, pembrolizumab
    - Otherwise, platinum-based chemo, then 2nd line nivolumab, pembrolizumab (if PD-L1≥1%) or atezolizumab

Immunotherapy in Lung Cancer

- PD-1/PD-L1 inhibition in the 2nd line
- PD-1 inhibition in the 1st line
- Where we're going: combinations

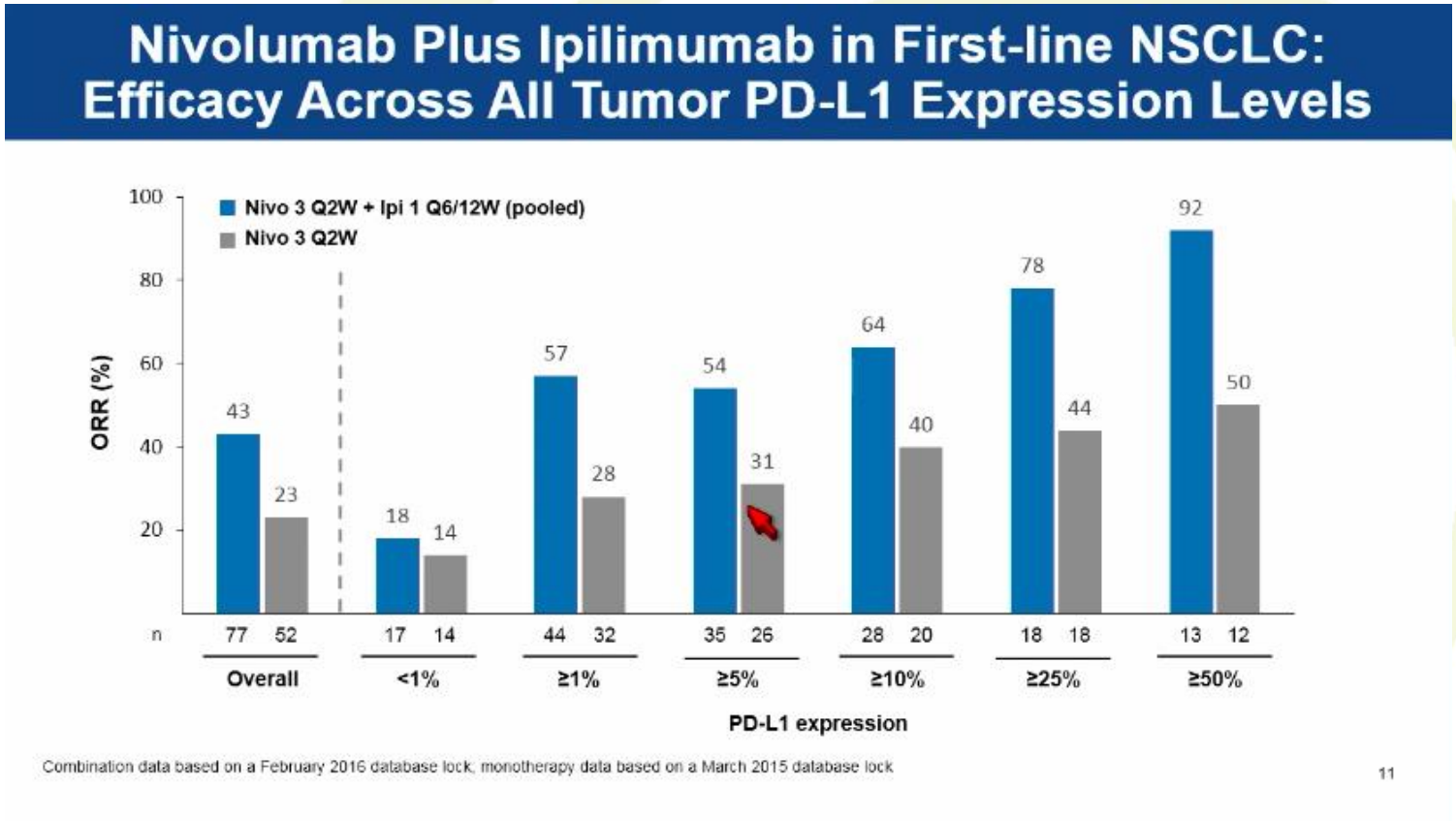
Future of immunotherapy in NSCLC

- Use PD1 inhibitors with chemo?
  - Motivation: Cancer cell death → release of cancer cell antigens → improved priming and activation might let PD1 inhibitors work better
  - Caveats:
    - Steroids with some chemos
    - General immunosuppressive state post-chemo
    - Compound toxicity
- Awaiting phase 3 studies of chemo +/- PD1 inhibitors
  - Early data: Langer et al (Lancet Oncol and ESMO), n=123 carbo/pem +/- pembro
    - RR 55 vs 29%, PFS 13.0 vs 8.9 mo

Future of immunotherapy in NSCLC

- Use PD1 inhibitors with other immunotherapy?
  - Motivation: PD1 inhibition alone only works in 20% of tumors– what about the rest?
  - Caveats:
    - Hard to anticipate results based on pre-clinical models
    - Additive (even synergistic) efficacy possible, but so is additional toxicity
- Awaiting studies of chemo vs PD1 vs PD1/CTLA4
  - CTLA4 inhibitor already approved in melanoma (ipilimumab)
  - Early data: Hellman et al (ASCO 2016) nivo vs nivo/ipi

Early data: 1st line nivo/ipi



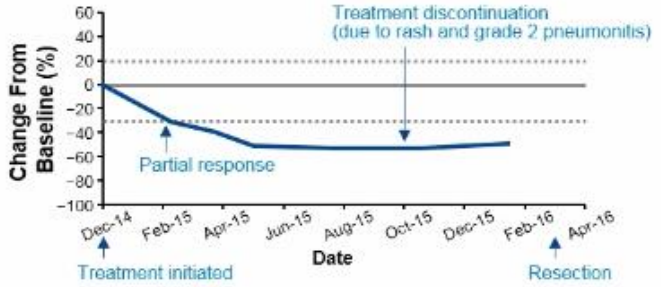
Await data from adequately powered phase 3 trials… next year?

Hellman, ASCO 2016

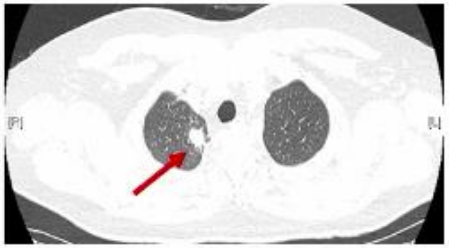
Early data: 1st line nivo/ipi

Case of Pathological CR in One Patient Treated With Nivo 3 Q2W + Ipi 1 Q6W

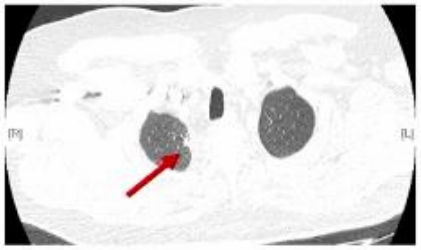
- 54-yr-old male (former smoker, 52 pack-yr) with metastatic large-cell lung cancer (PD-L1 <1%[a])
  - 53% total tumor size reduction by RECIST
  - Radiographic residual lesions in the lung and mediastinal lymph nodes, without distant disease



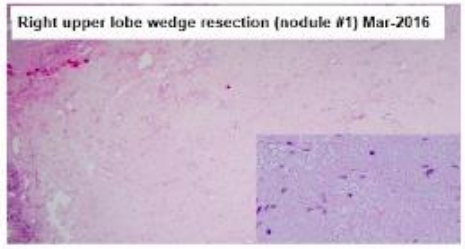
Before nivo + ipi therapy



Following nivo + ipi therapy



No viable tumor in resected residual lesion



Courtesy of Dr. William Travis, MSKCC

[a]Patient was included as having partial response and PD-L1 expression unknown in analysis at time of database lock

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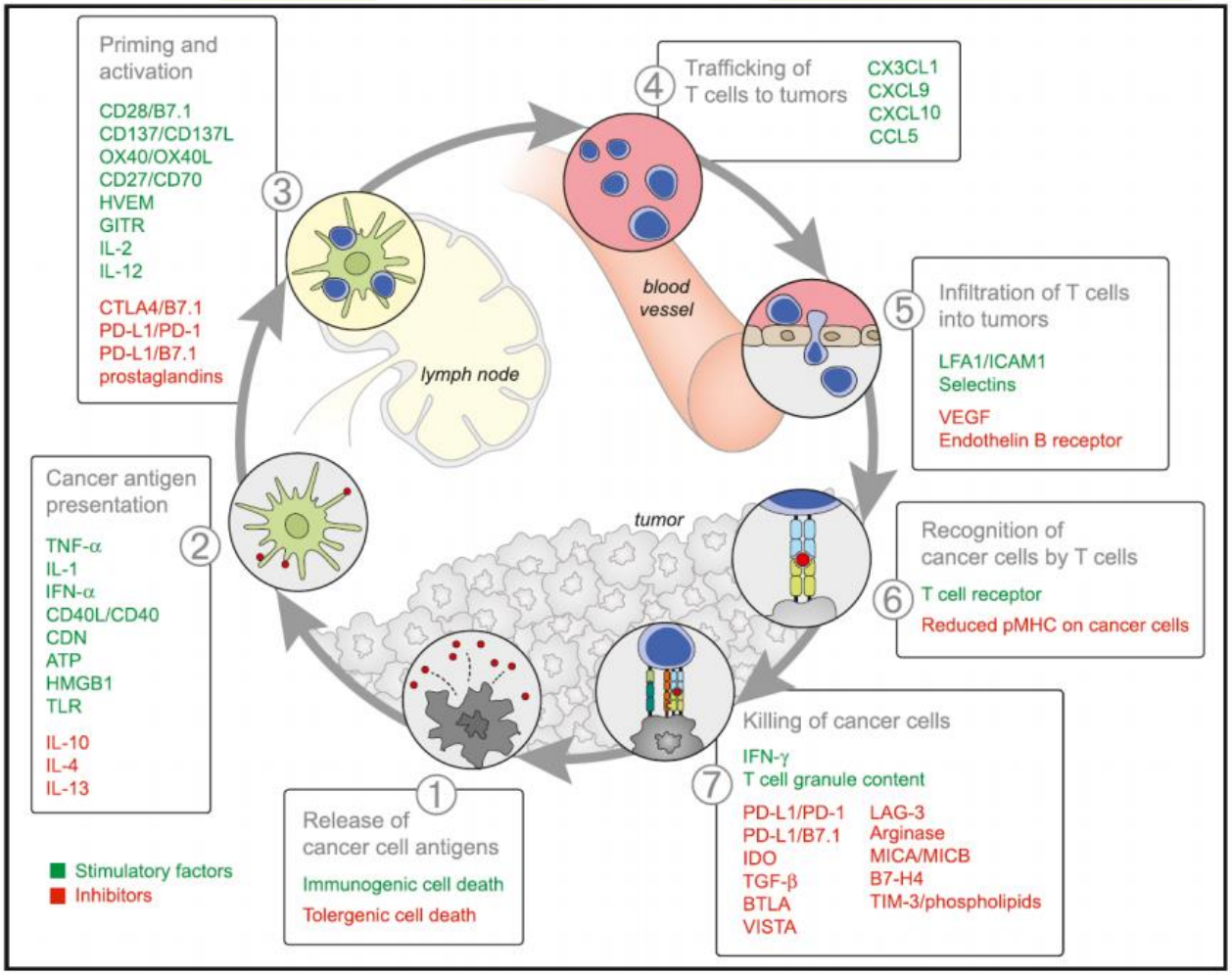
Hellman, ASCO 2016

Future of immunotherapy in NSCLC



Chen and Mellman, Immunity 2013

Take-home points: Future of immunotherapy

- Stay tuned for data on chemo combos
- Stay tuned for data on immunotherapy combos
- Stay tuned for data on immunotherapy in earlier stage disease
- Stay tuned for data on better biomarkers than PD-L1

- Clinical trials are the way forward
    - Special role for immunoREFRACTORY patients

- Value in medicine

The New York Times | http://nyti.ms/1DWovl7

BUSINESS DAY

Lung Cancer Treatment Using Immune System Wins F.D.A. Approval

By ANDREW POLLACK MARCH 4, 2015

The first immune-based treatment for lung cancer won approval from the Food and Drug Administration on Wednesday, and it could displace more conventional chemotherapy for certain patients, at least.

The drug, [ ], from [ ] is one of a class of medicines that have electrified oncologists in recent years because they free the body's own immune system to attack tumors.

[ ], also known as nivolumab, was approved last year to treat advanced cases of the skin cancer melanoma, but the approval for lung cancer is in some ways more significant.

The New York Times | http://nyti.ms/1DWovl7

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, also known as nivolumab, was approved last year to treat advanced cases of the skin cancer melanoma, but the approval for lung cancer is in some ways more significant.

Lung cancer is the leading cause of cancer deaths by far, with 224,000 new diagnoses and nearly 160,000 deaths last year. That means approval to treat lung cancer could help more patients and also result in much larger sales for Bristol-Myers. The drug sells for about $12,500 a month.

Take-home points: Future of immunotherapy

- Stay tuned for data on chemo combos
- Stay tuned for data on immunotherapy combos
- Stay tuned for data on immunotherapy in earlier stage disease

- Clinical trials are the way forward
    - Special role for immunoREFRACTORY patients

- Value in medicine
    - These are expensive drugs…
    - ...but optimizing them (better combos, better patient selection) may yield superior value by meaningfully improving survival in our patients

Thank you!