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University of California
San Francisco

Personalized Treatment Approaches for Lung Cancer

California Thoracic Society 2018 Annual Carmel Conference
January 27, 2018

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Chair, Thoracic Oncology Site Committee
UCSF Helen Diller Family Comprehensive Cancer Center

Disclosures

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

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

Two themes

- Targeted therapies

- Immunotherapy

Two themes

- Targeted therapies
  - 2nd+ generation approaches in “old” mutations: EGFR, ALK
  - 1st generation approaches in “new” mutations
- Immunotherapy
  - Where we’re at: PD-1 inhibition in the 2nd and 1st line
  - Where we’re going: combos and early stage

Two themes

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Targets

Li TH. Genotyping and genomic profiling of NSCLC: Implications for current and future therapies. JCO 2013;31(8):1039-1049.

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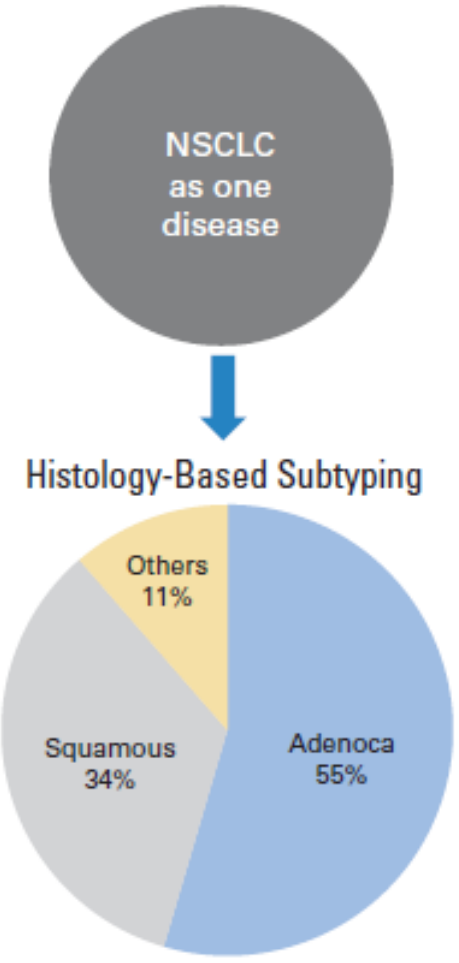
Targets



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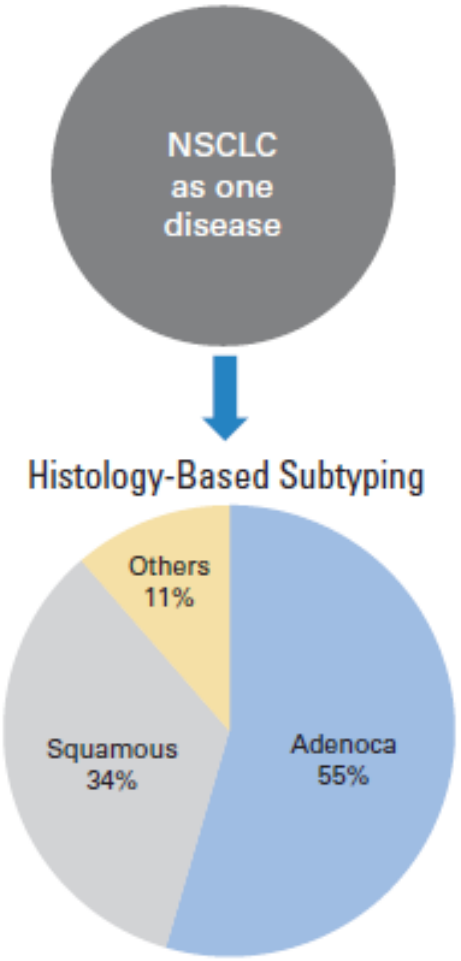
Histology??

Targets



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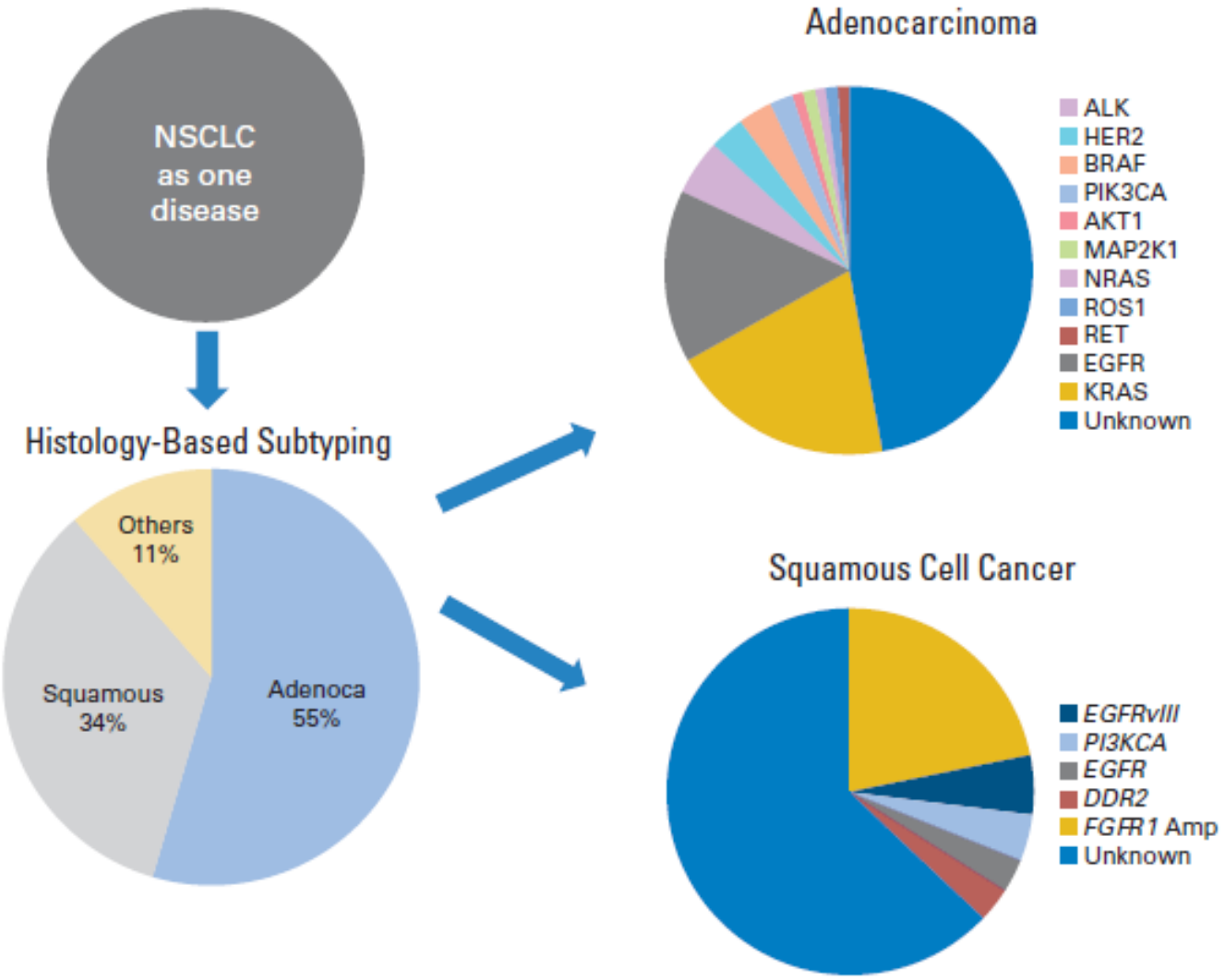

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Two themes

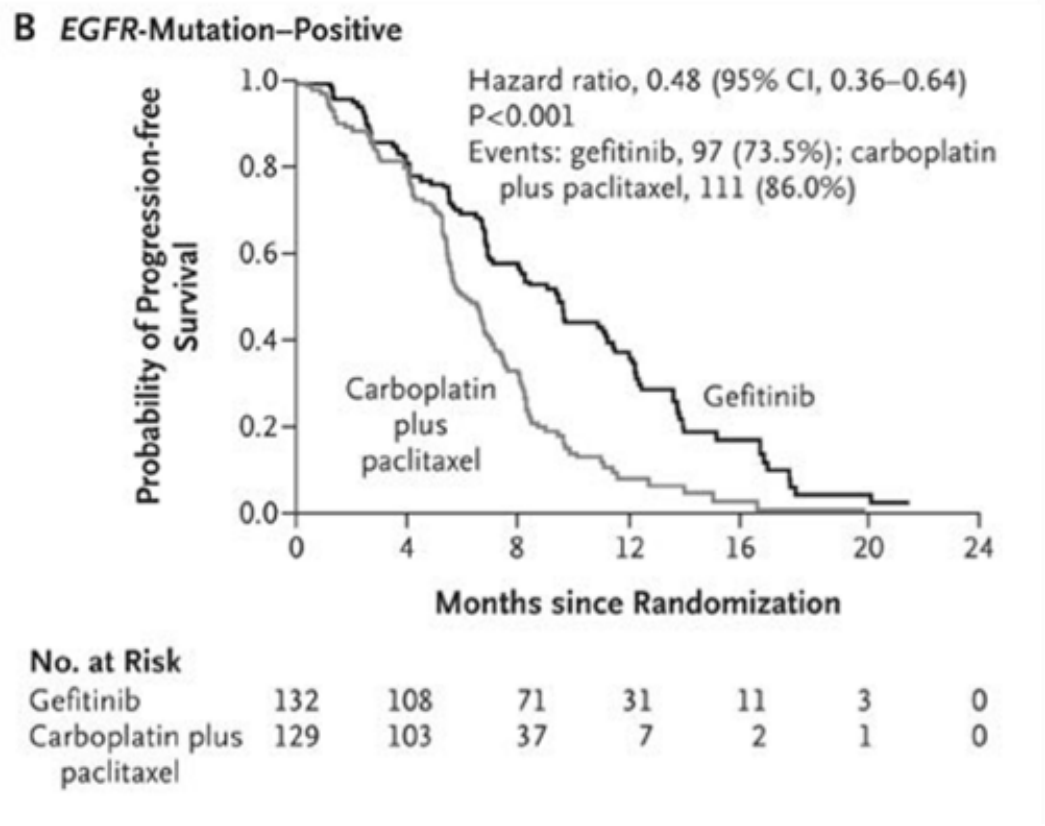
- Targeted therapies
  - 2nd+ generation approaches in “old” mutations: EGFR, ALK
  - 1st generation approaches in “new” mutations
- Immunotherapy
  - Where we’re at: PD-1 inhibition in the 1st and 2nd line
  - Where we’re going: combos and early stage

EGFR– Epidermal growth factor receptor

- 10-30% of NSCLC patients
- Higher prevalence among:
  - Asians
  - Younger patients
  - Females
  - Never-smokers
  - Adenocarcinoma

EGFR

- 3 approved first line drugs: erlotinib, gefitinib, afatinib
- 2009 IPASS study (Mok et al in NEJM)



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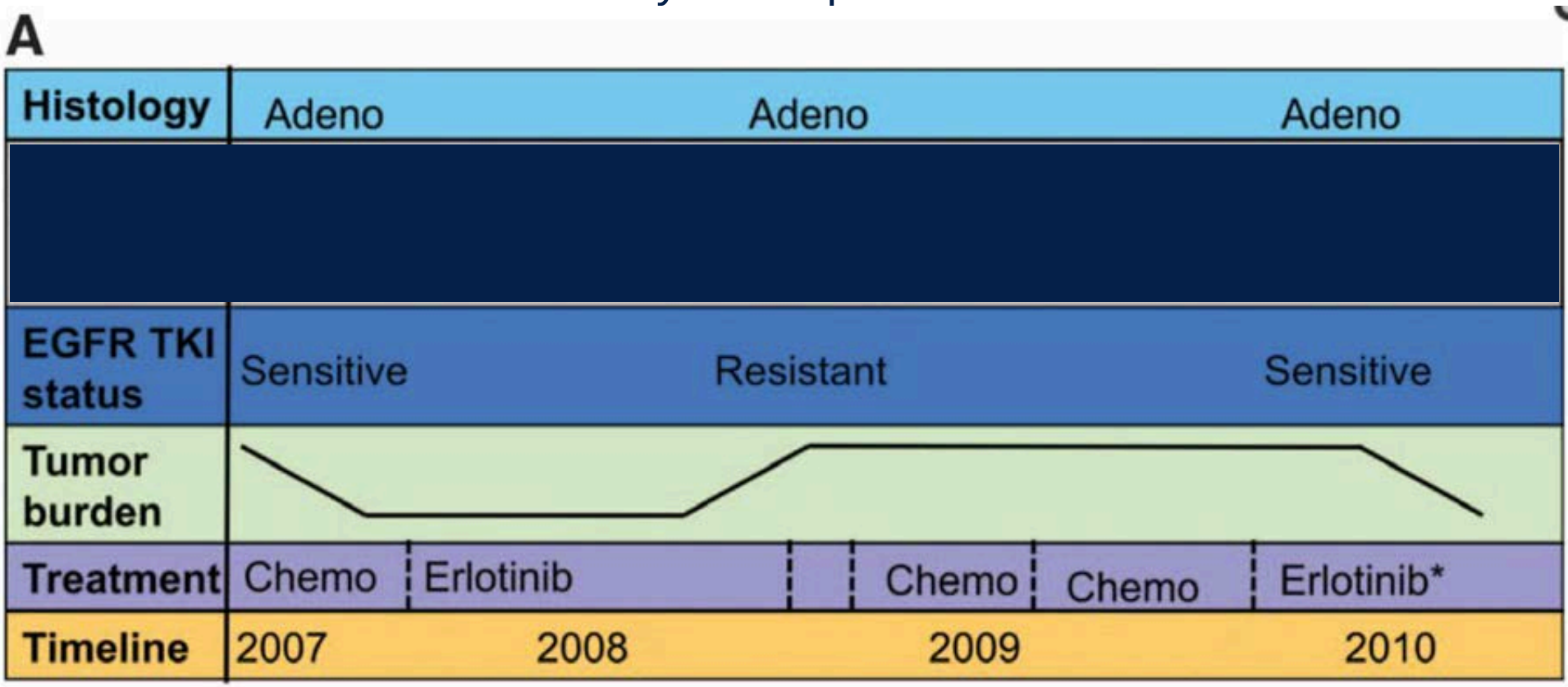
EGFR

- 1st line use established since 2009…
- ...but resistance inevitably develops.



Sequist, Sci Transl Med, 2011.

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EGFR

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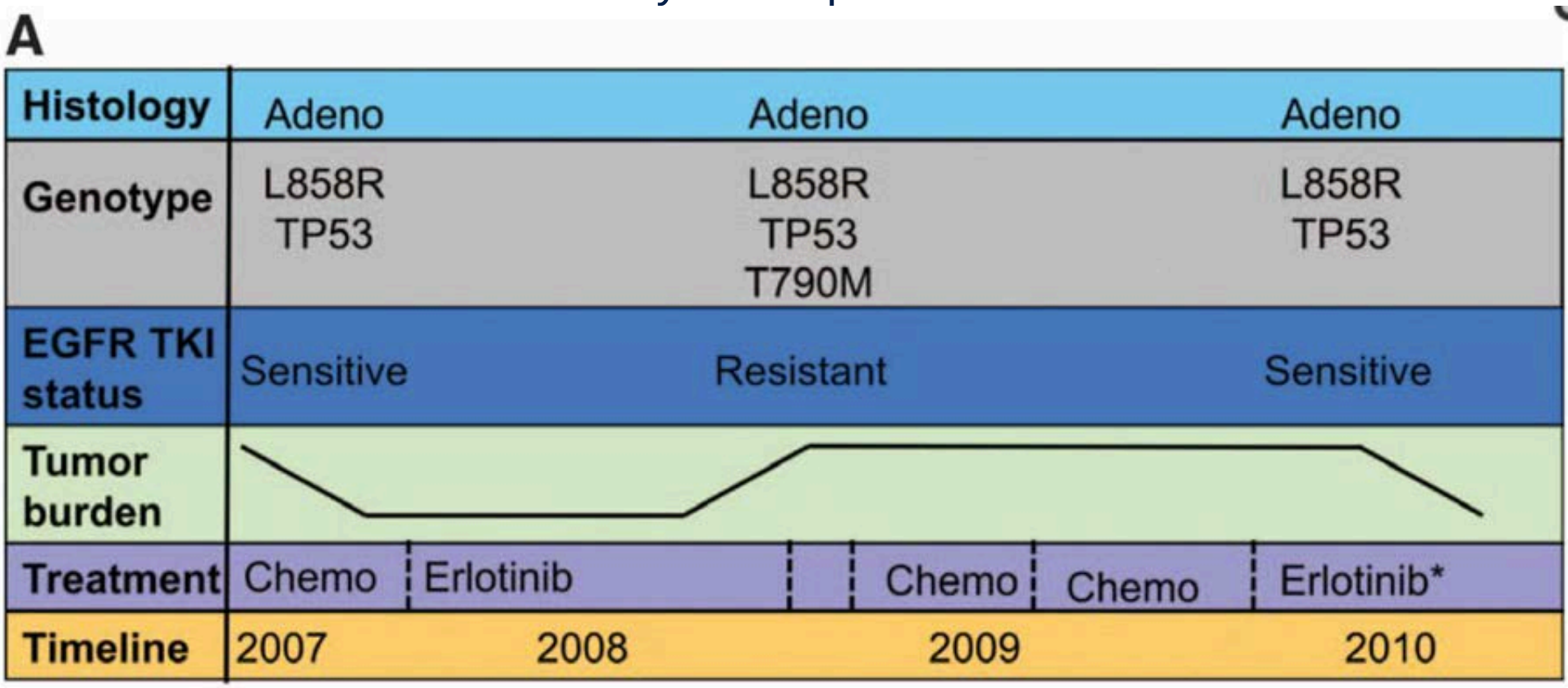

Sequist, Sci Transl Med, 2011.

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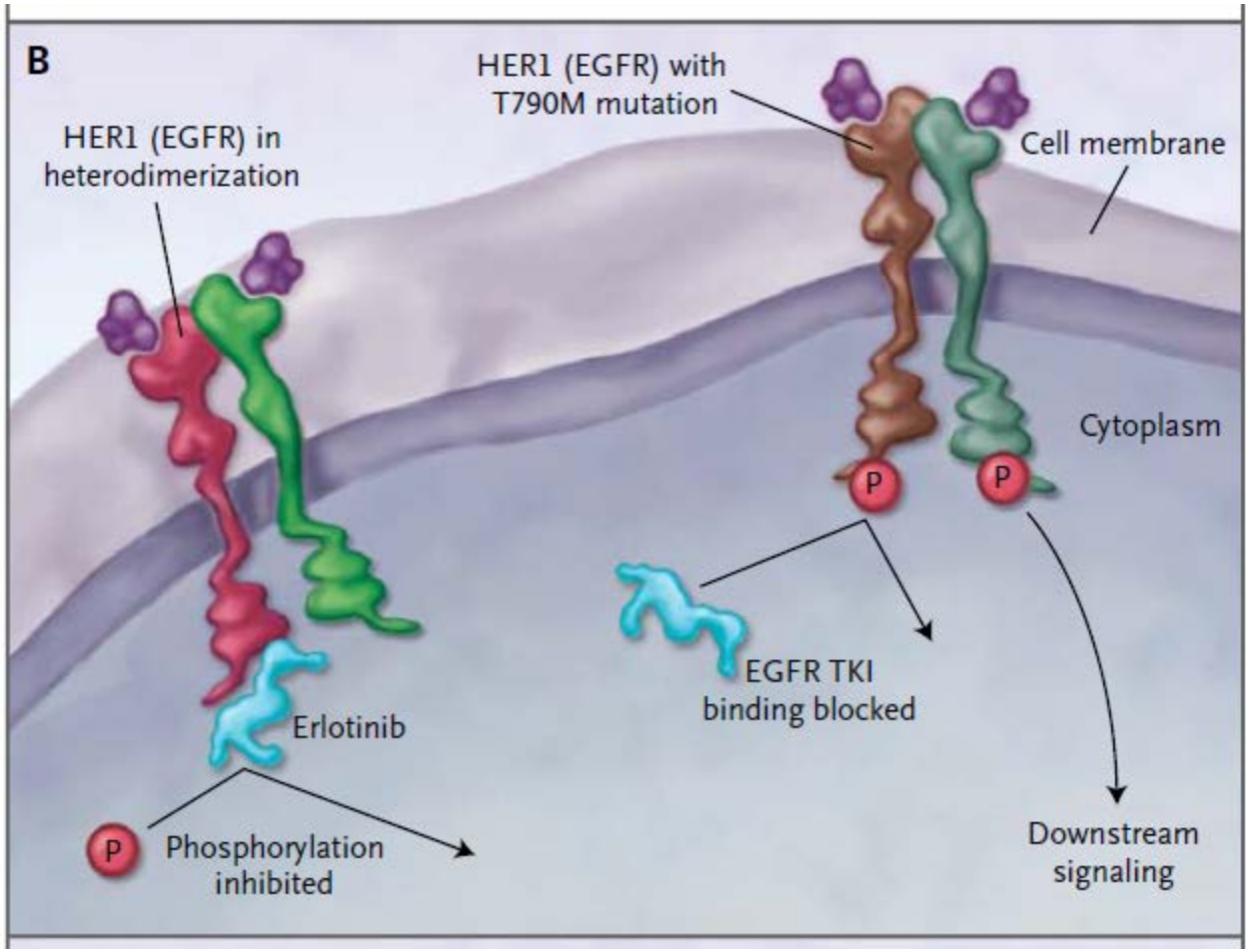
EGFR resistance: T790M, the "gatekeeper"



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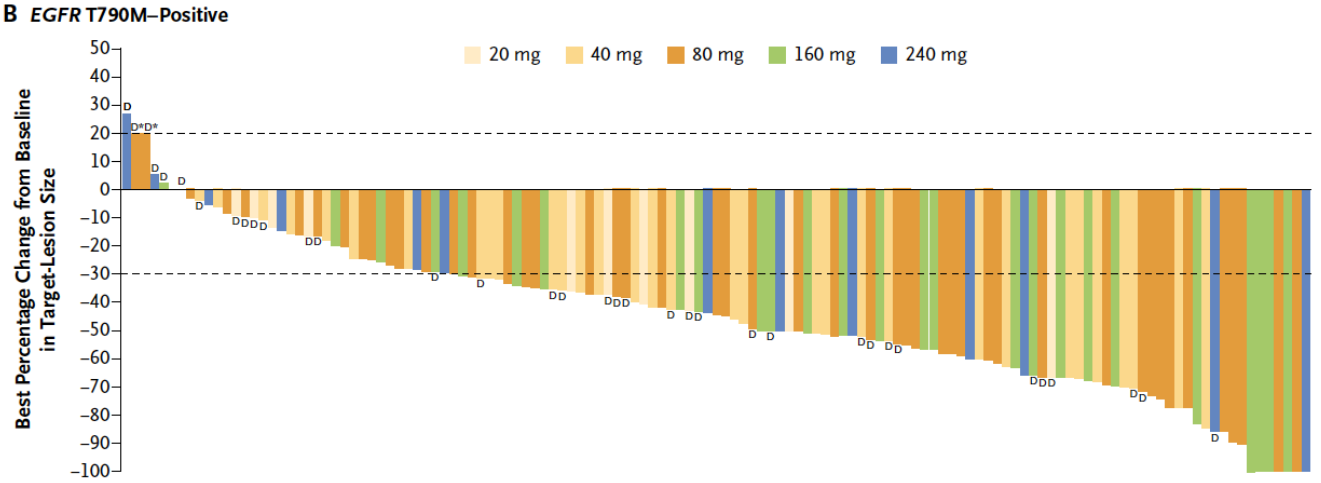
EGFR resistance: T790M, the "gatekeeper"

- Osimertinib
- Engineered to inhibit EGFR exon 19/L858R AND T790M, but less inhibitory of normal ("wild-type") EGFR
  - Effectiveness when erlotinib (or others) fail
  - Fewer toxicities



Janne, NEJM 2015.

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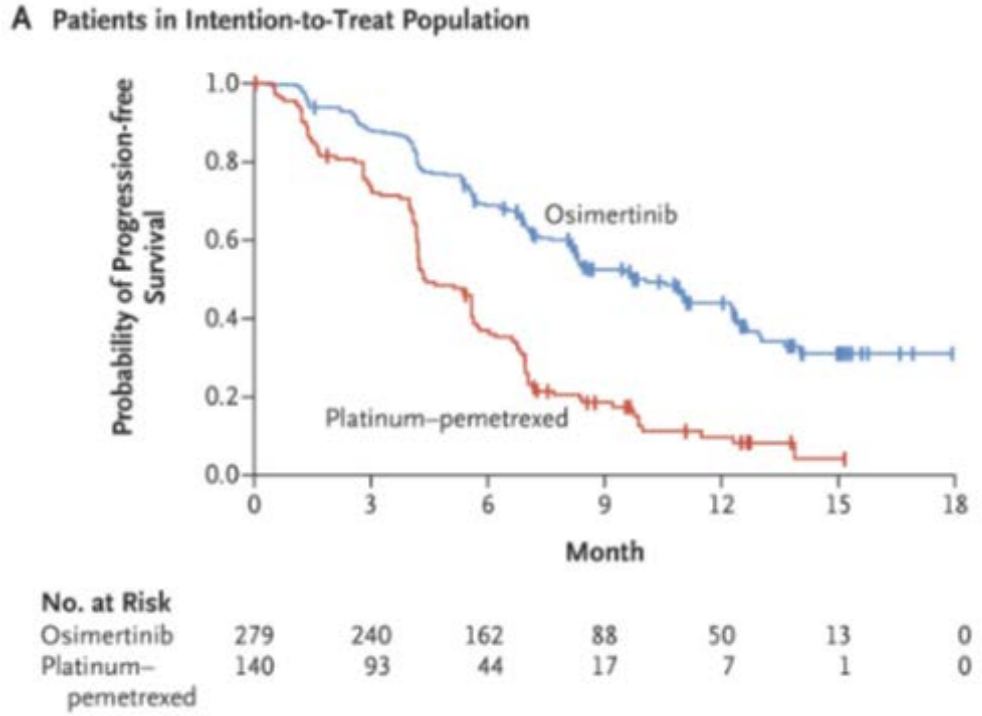
EGFR resistance: T790M, the "gatekeeper"

- AURA3: osimertinib vs platinum-pemetrexed in T790M+



- PFS 10.1 vs 4.4 mo, HR 0.3, p<0.001

Mok, NEJM 2017.

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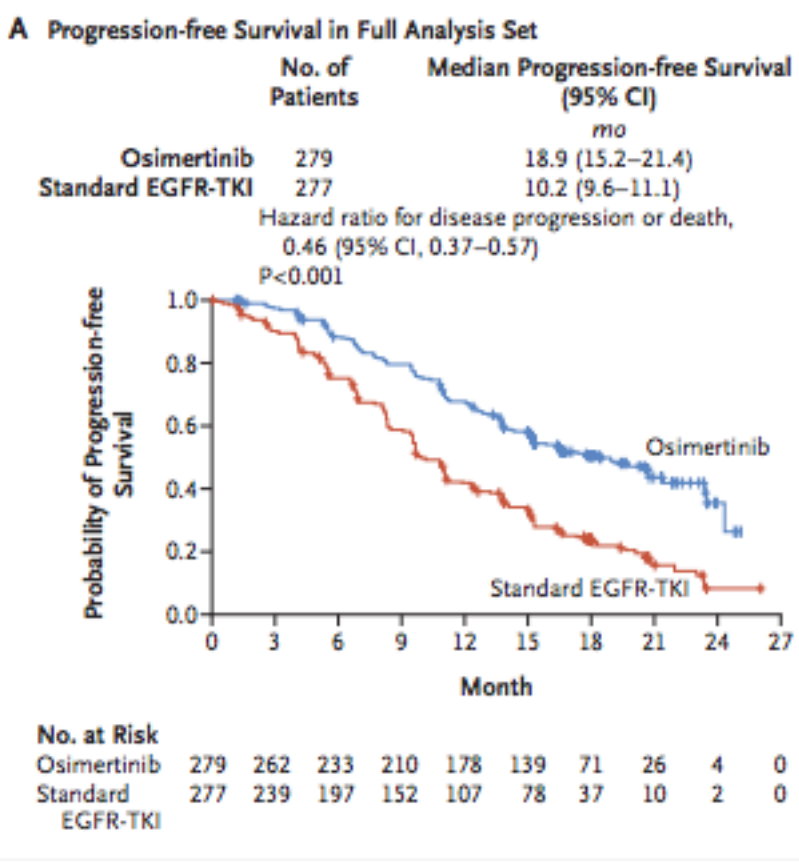
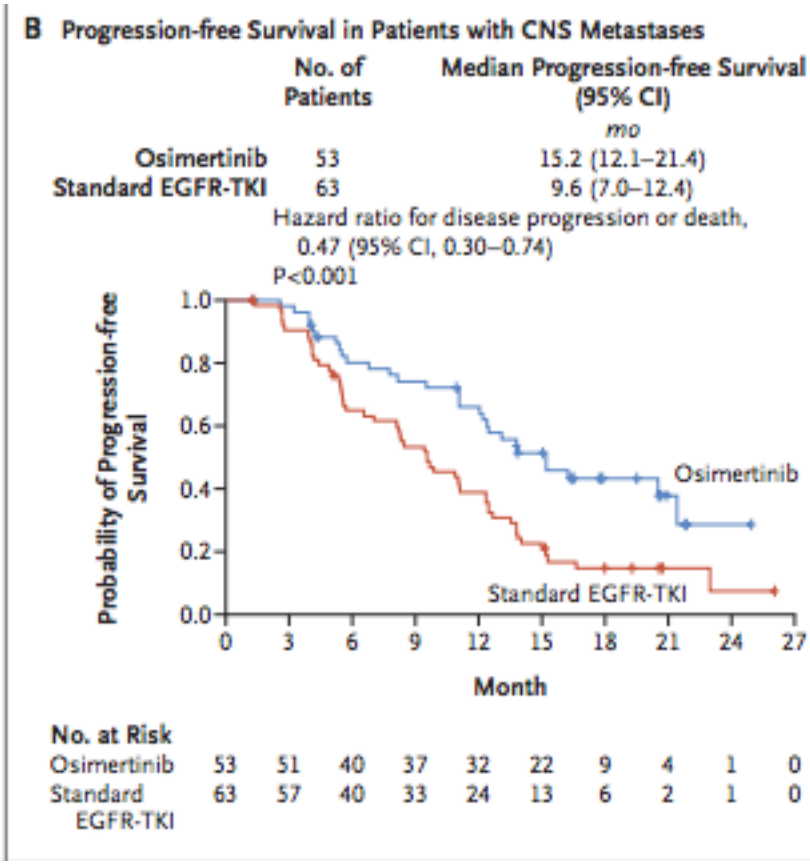
Osimertinib first line

- FLAURA: osimertinib vs erlotinib/gefitinib (not selected for T790M)





Soria, NEJM 2017.

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EGFR take-home points

- Cancers evolve
- Biopsy at the beginning to figure out the driver mutation
  - ...and consider biopsy at progression to figure out the resistance mechanism
  - Osimertinib should follow 1st line 1st/2nd gen EGFR agent if T790M found
  - ...and should now be 1st line in most patients (pending approval)
- Future directions:
  - Study resistance to osimertinib?
  - 3rd/4th generation drugs?

EGFR– epidermal growth factor receptor

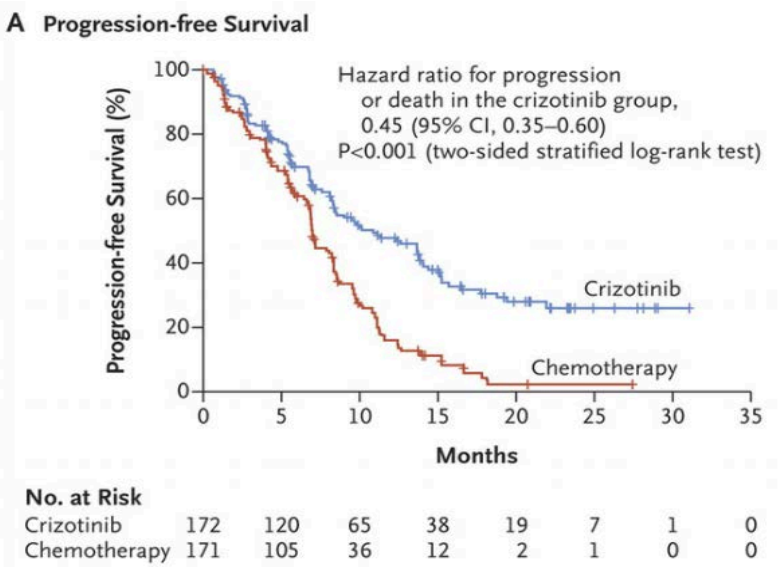
- 10-30% of NSCLC patients
- Higher prevalence among:
  - Asians
  - Younger patients
  - Females
  - Never-smokers
  - Adenocarcinoma

ALK– anaplastic lymphoma kinase

- 4-7% of NSCLC patients
- Higher prevalence among:
  - -
  - Younger patients
  - -
  - Never-smokers
  - Adenocarcinoma

ALK

- 2007 detected as an alteration in NSCLC
- 2011 crizotinib approved
  - Single-arm ORR 50, 61%
  - Vs docetaxel in the 2nd line, PFS 7.7 vs 3.0 mos
  - Vs platinum combo in the 1st line, PFS 10.9 vs 7.0 mos



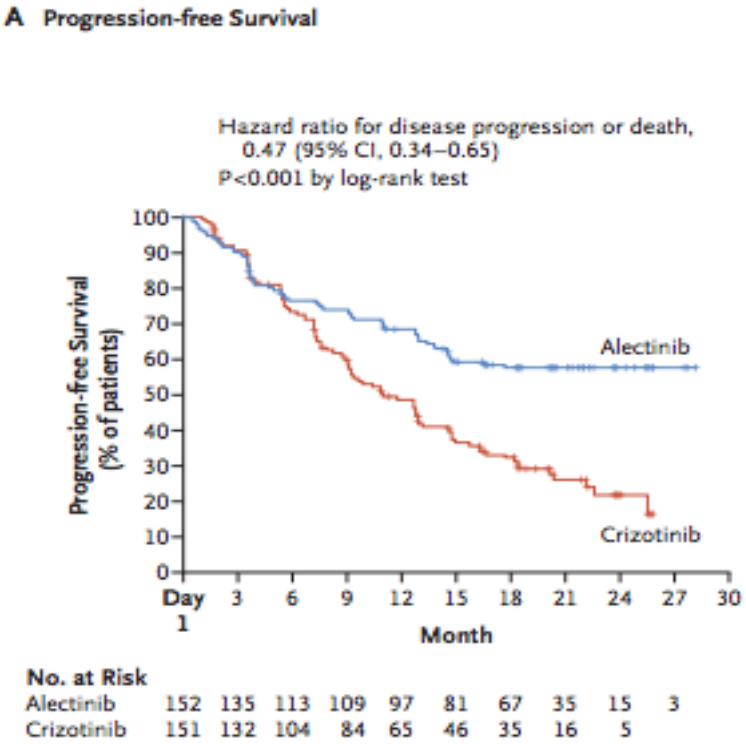
Solomon, NEJM 2014

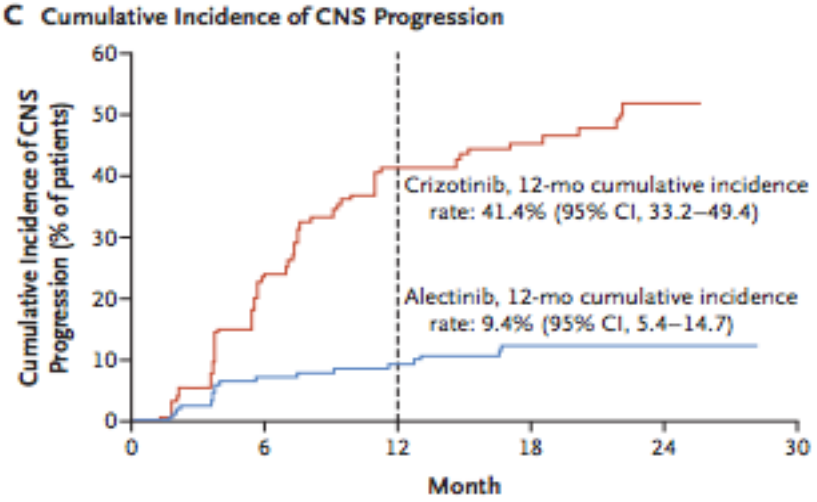
ALK

- …but resistance inevitably develops.
- Why?
  - Crizotinib good, not great as an ALK inhibitor, so cancer can overcome it
  - Poor brain penetration, so cancer can thrive there
  - Other mutations develop
- 2nd generation ALK inhibitors– better ALK activity, better CNS activity
  - Ceritinib approved 2014 (duration 7.1 mos post-crizotinib)
  - Alectinib approved 2015 (duration 7.5 mos post-crizotinib)

ALK resistance

- But what about 2nd generation first line?
- ALEX (ASCO 2017, NEJM 2017), alectinib vs crizotinib
  - RR 83 vs 76%





FDA approved 11/17

Peters, NEJM 2017

ALK take-home points

- Cancers evolve
- Biopsy at the beginning to figure out the driver mutation
  - And biopsy at progression to determine next drug?
  - Lorlatinib
    - RR 31% after 3 prior TKIs

Cellular ALK phosphorylation mean IC_{50} (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

$IC_{50} \leq 50$ nmol/L

$IC_{50} > 50 < 200$ nmol/L

$IC_{50} \geq 200$ nmol/L

Gainor, Cancer Discovery, 2016

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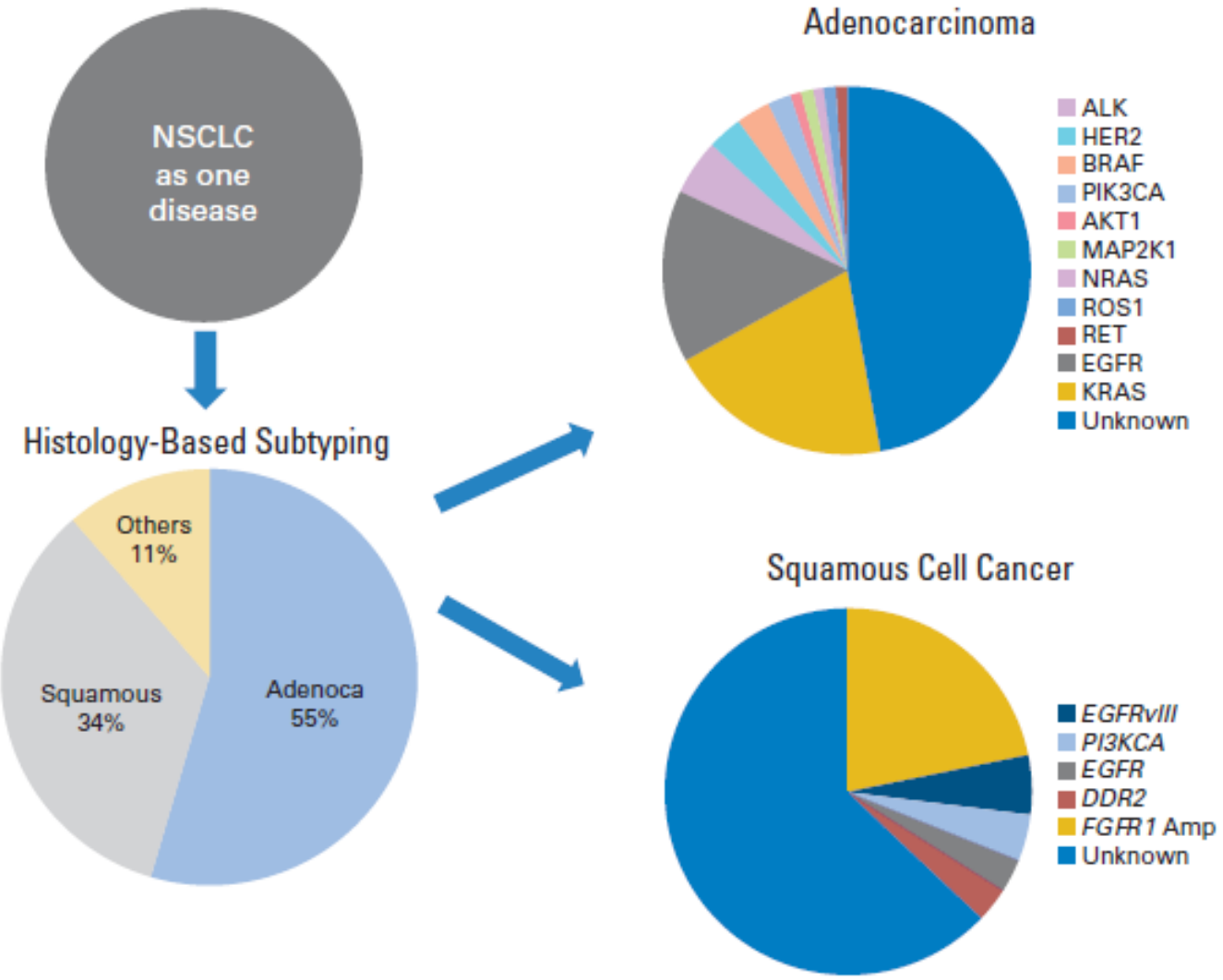
Two themes

- Targeted therapies
  - 2nd+ generation approaches in “old” mutations: EGFR, ALK
  - 1st generation approaches in “new” mutations
- Immunotherapy
  - Where we’re at: PD-1 inhibition in the 2nd and 1st line
  - Where we’re going: combos and early stage

Targets other than EGFR and ALK



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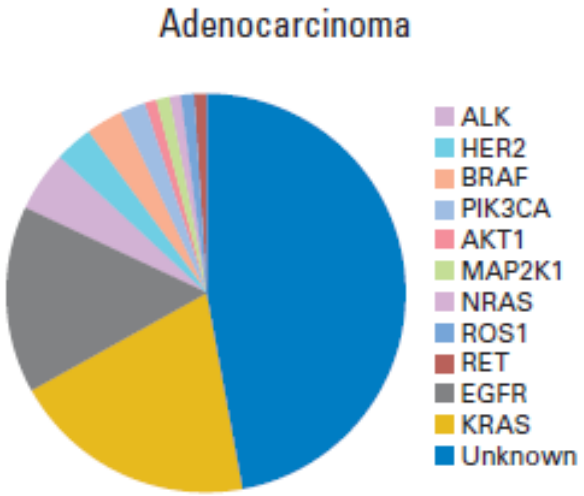

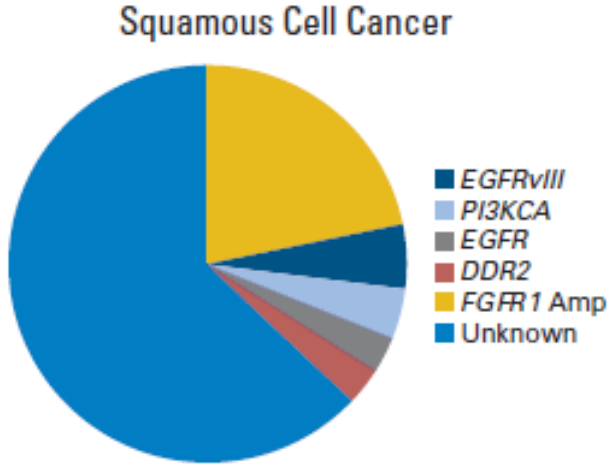

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Targets other than EGFR and ALK

- ASCO 2015
  - BRAF V600E (more often seen in melanoma), 1-2%
    - Dabrafenib + trametinib ORR 63%, PFS 9.7mo
    - Now FDA approved for NSCLC
- ASCO 2016
  - MET exon 14 skipping, 3-4%
    - (often older patients, current/former smokers, sarcomatoid)
    - Crizotinib ORR 44%, PFS not yet reached
  - RET rearrangement, 1-2%
    - Cabozantinib ORR 38%
    - Vandetinib ORR 53%

Take-home points on other targets

- You can’t treat a mutation you don’t know

NCCN Guidelines Version 9.2017
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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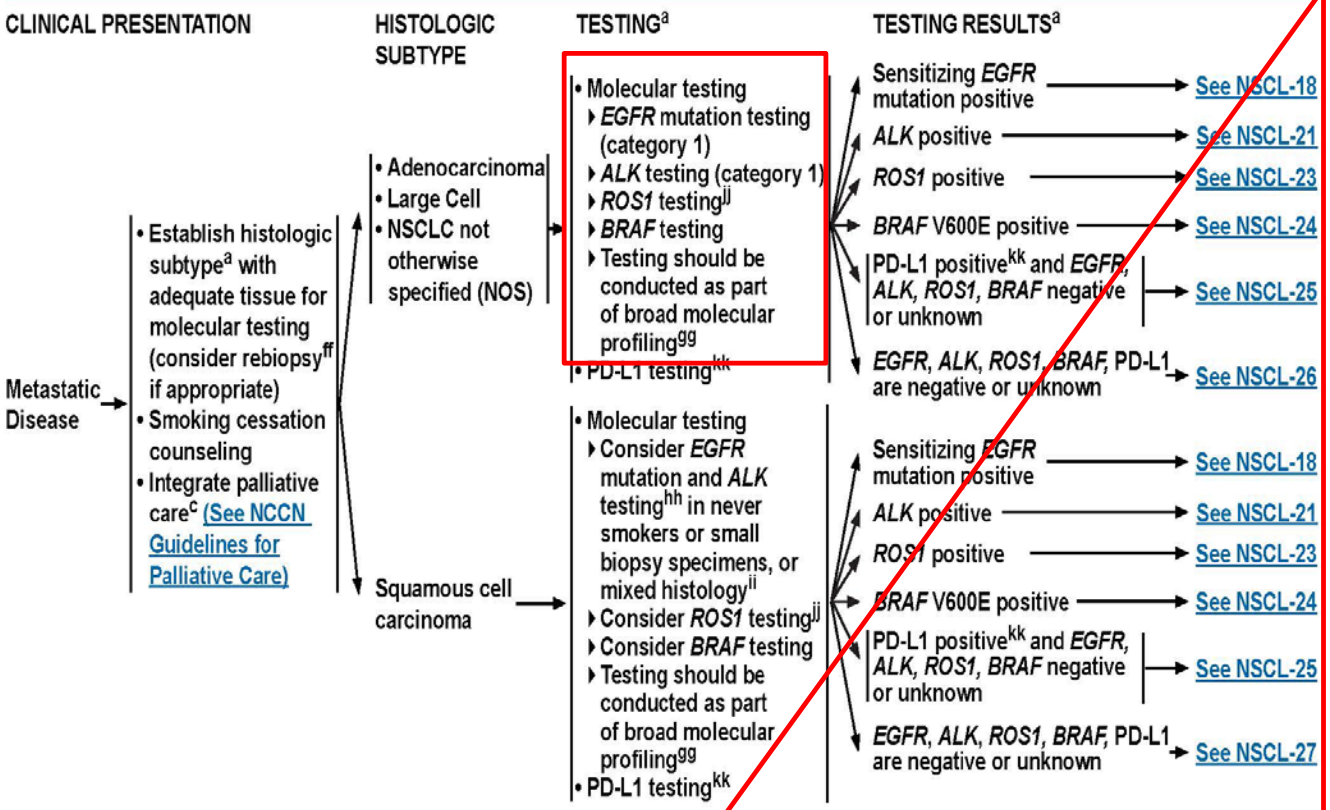

[a] See Principles of Pathologic Review (NSCL-A).

[c] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.

[ff] If repeat biopsy is not feasible, plasma biopsy should be considered.

[gg] The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).

[hh] In patients with squamous cell carcinoma, the observed incidence of *EGFR* mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of *EGFR* mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.

[ii] Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with *EGFR* mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther 2012;11:2535-2540.

[jj] Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.

[kk] PD-L1 expression levels of ≥50% are a positive test result for first-line pembrolizumab therapy.

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.

The NCCN NSCLC Guidelines panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC.

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Take-home points on other targets

- You can't treat a mutation you don't know
- Beyond EGFR and ALK, drugs may not be FDA-approved
  - Should we treat?

NCCN on "emerging targeted agents"

National Comprehensive Cancer Network®

NCCN Guidelines Version 9.2017
Non-Small Cell Lung Cancer

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EMERGING TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
High-level *MET* amplification or MET exon 14 skipping mutation	crizotinib[1-5]
RET rearrangements	cabozantinib[6,7] vandetanib[8]
HER2 mutations	trastuzumab[9] (category 2B) afatinib[10] (category 2B)

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Take-home points on other targets

- You can't treat a mutation you don't know
- Beyond EGFR and ALK, drugs may not be FDA-approved
  - Should we treat?
  - Consider clinical trials! Access to new drugs, data for everyone.

Two themes

- Targeted therapies
  - 2nd+ generation approaches in “old” mutations: EGFR, ALK
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- Immunotherapy
  - Where we’re at: PD-1 inhibition in the 2nd and 1st line
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Immunotherapy: Not a new idea

FIRST USE OF COLEY'S MIXED BACTERIAL TOXINS

Close

William B. Coley creates a filtered mixture of bacteria and bacterial lysates, composed of *Streptococcus pyogenes* and *Bacillus prodigiosus*, called "Coley's Toxins," to treat tumors. His first patient is a 21-year old man named John Ficken with a large inoperable tumor (likely a malignant sarcoma). After treatment with the toxins, Ficken had a complete remission, lasting until his death 26 years later of a heart attack.

Coley WB. May 1893. The Treatment of Malignant Tumors By Repeated Inoculations of Erysipelas: With A Report of Ten Original Cases. *The American Journal of Medical Sciences*. 1893; **10**: 487-511. *A Commotion in the Blood: Life, Death, and the Immune System*, Stephen S. Hall.

Cancer Research Institute website

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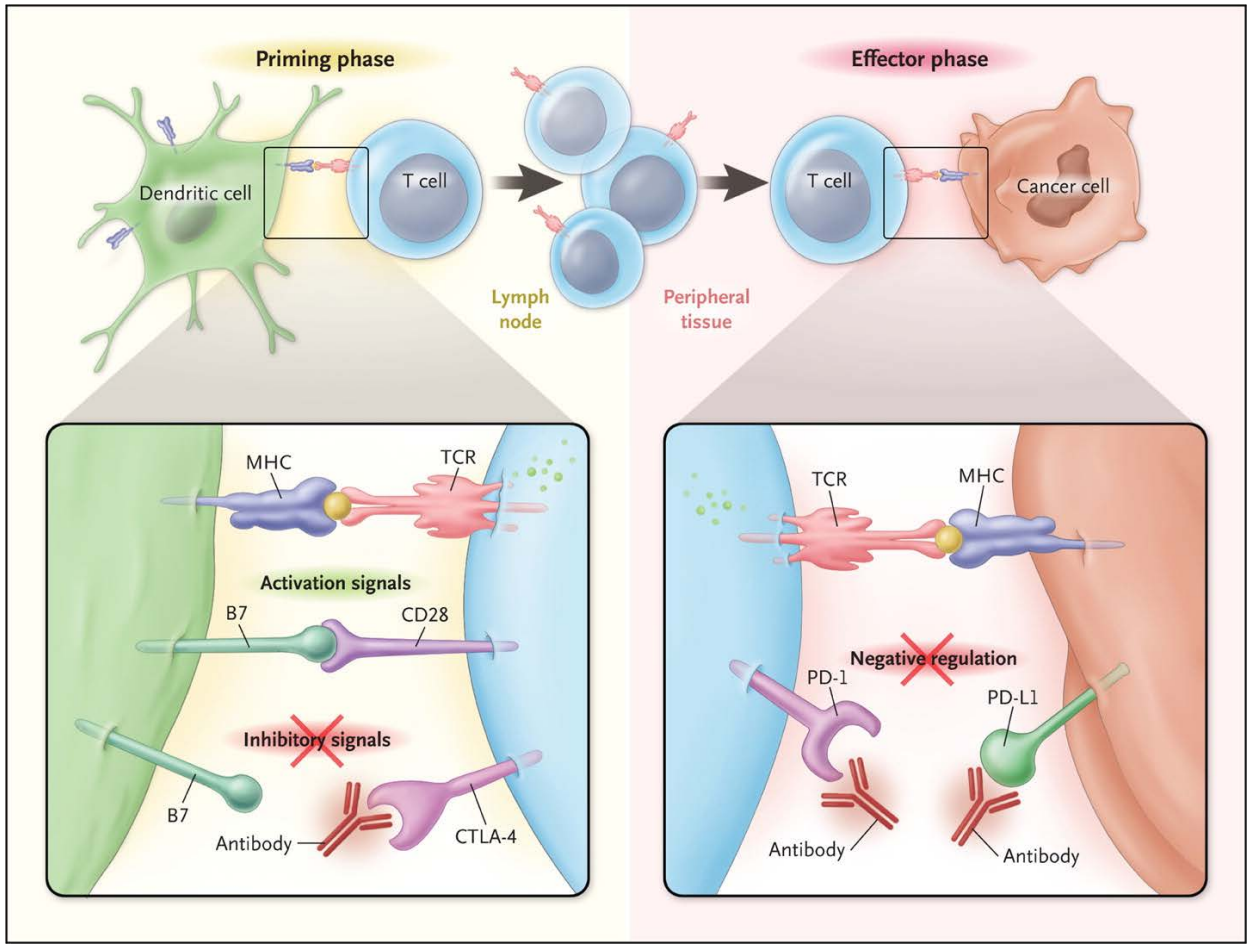
Immunotherapy: PD1/PD-L1 (and CTLA4)



Ribas A. NEJM 2012

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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.

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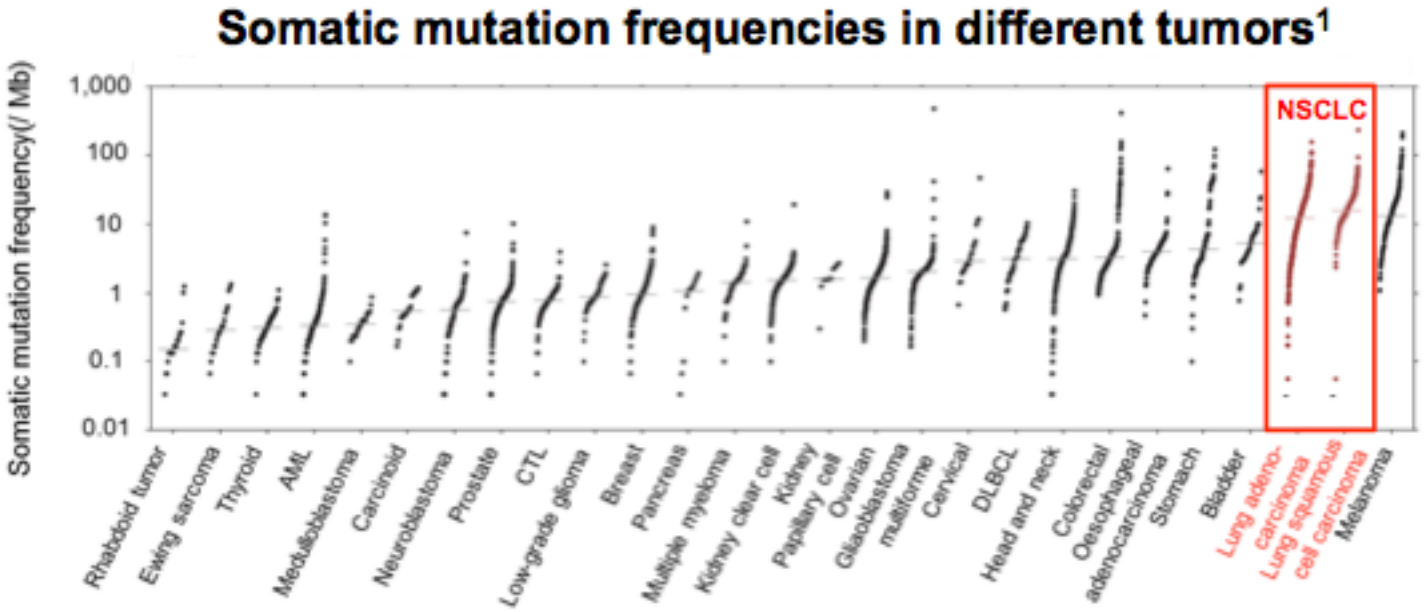
Immunotherapy- PD1/PD-L1



- 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.

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

BUSINESS DAY

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

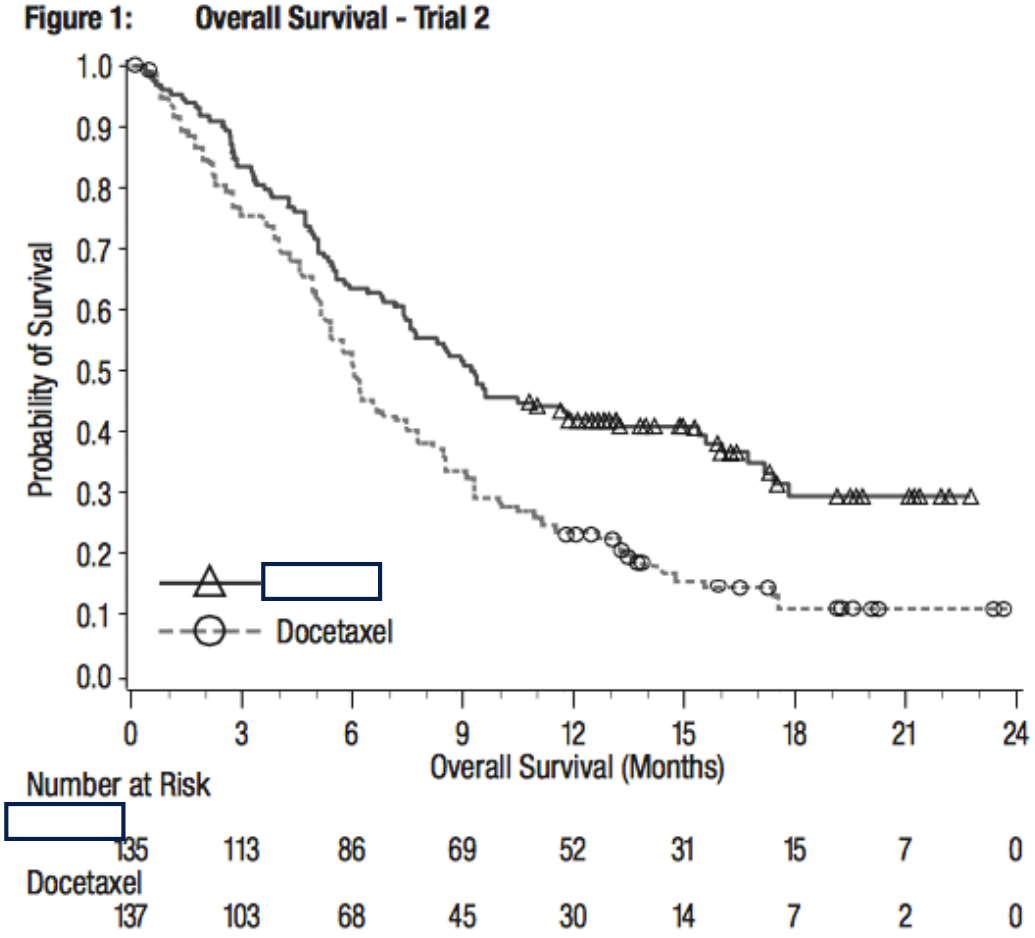
By ANDREW POLLACK MARCH 4, 2015

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.

Checkmate 017:
Nivolumab vs docetaxel in squamous cell NSCLC



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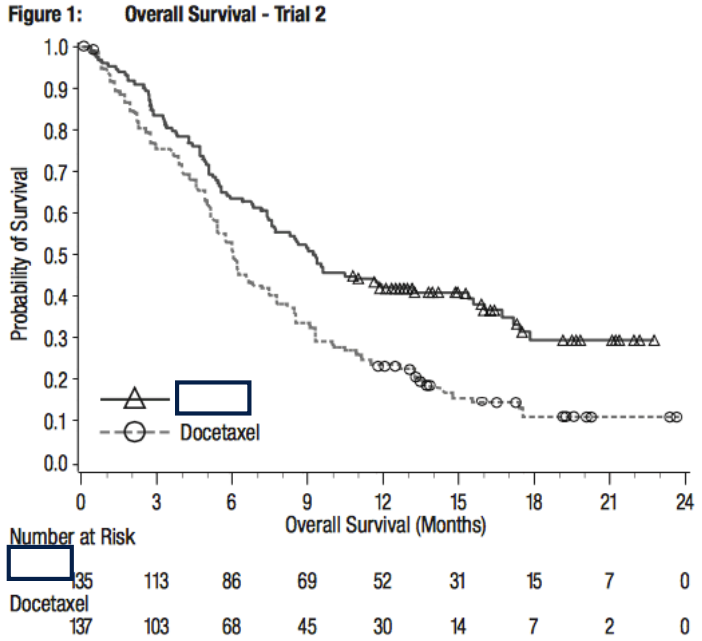
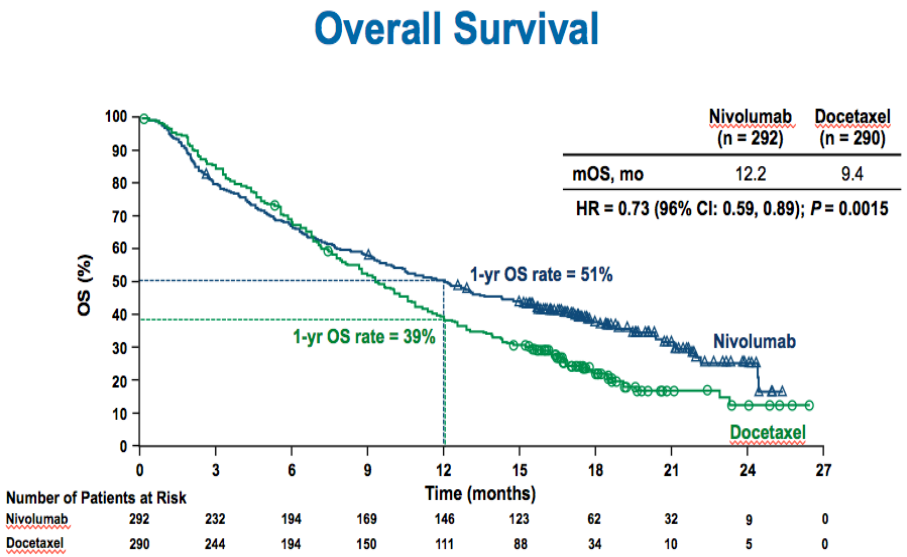
Checkmate 017/057: Nivolumab vs docetaxel

Squamous



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

Non-squamous



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

Nivolumab PI, Paz-Ares, ASCO 2015

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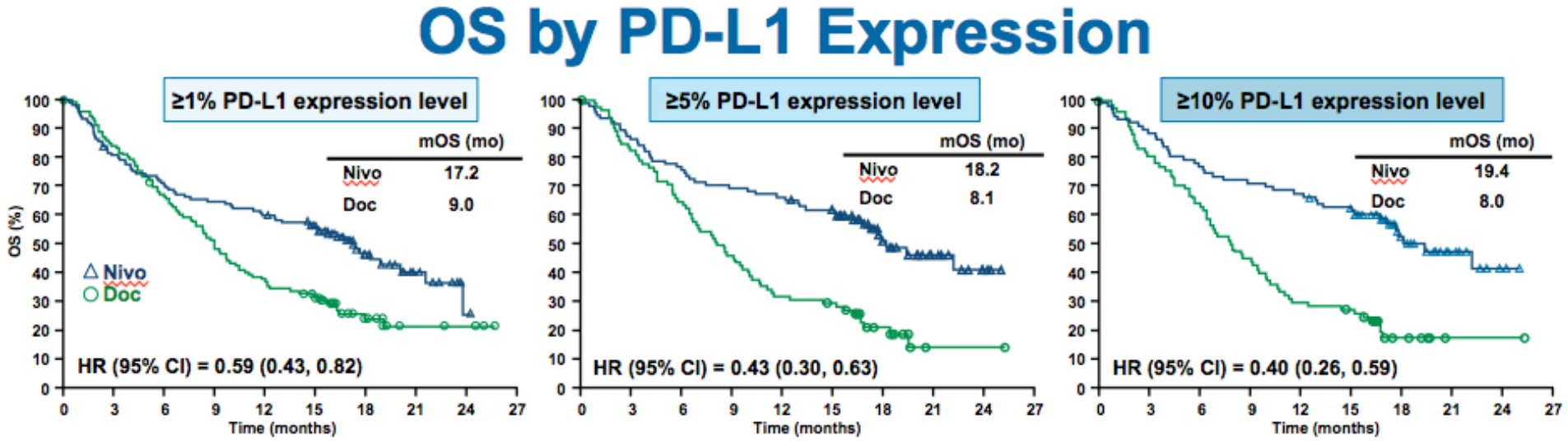
Checkmate 057: Nivo vs doce in non-squam NSCLC



Paz-Ares, ASCO 2015

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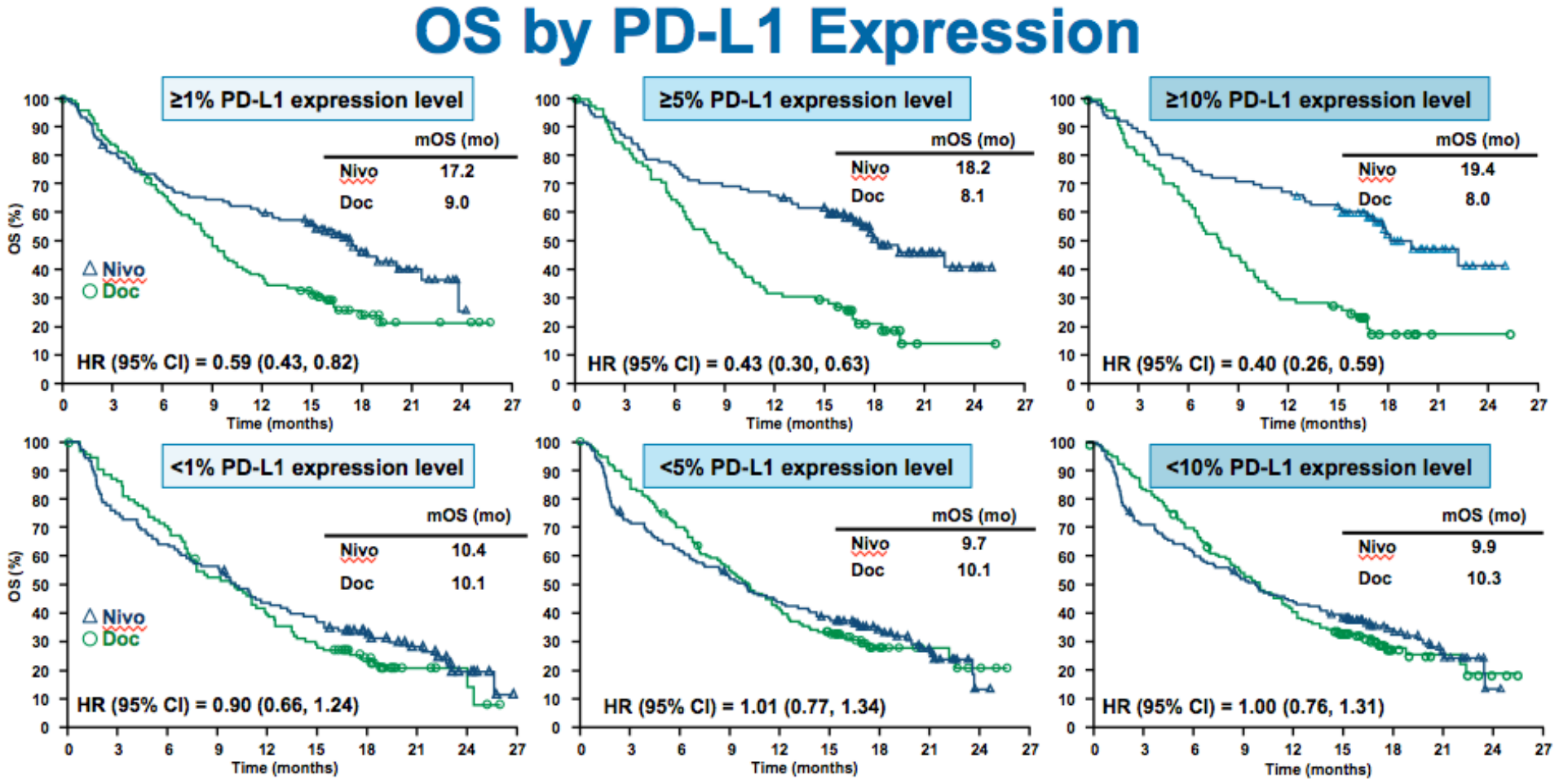
Checkmate 057: Nivo vs doce in non-squam NSCLC



Paz-Ares, ASCO 2015

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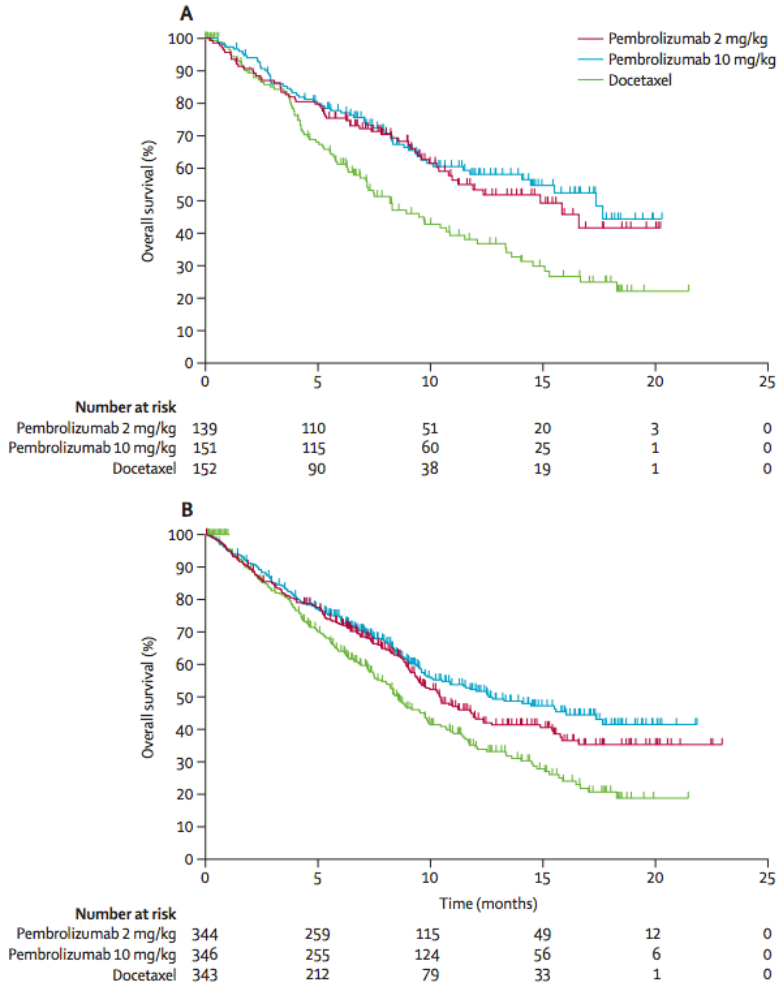
KEYNOTE-010: Pembrolizumab vs docetaxel in PD-L1+ NSCLC



- Overall survival
- PD-L1>50% pts
  - Pembro 14.9 vs 17.3 vs docetaxel 8.2 mo
- All pts PD-L1>1%
  - Pembro 10.2 vs 12.7 vs docetaxel 8.5 mo

Herbst, Lancet 2016

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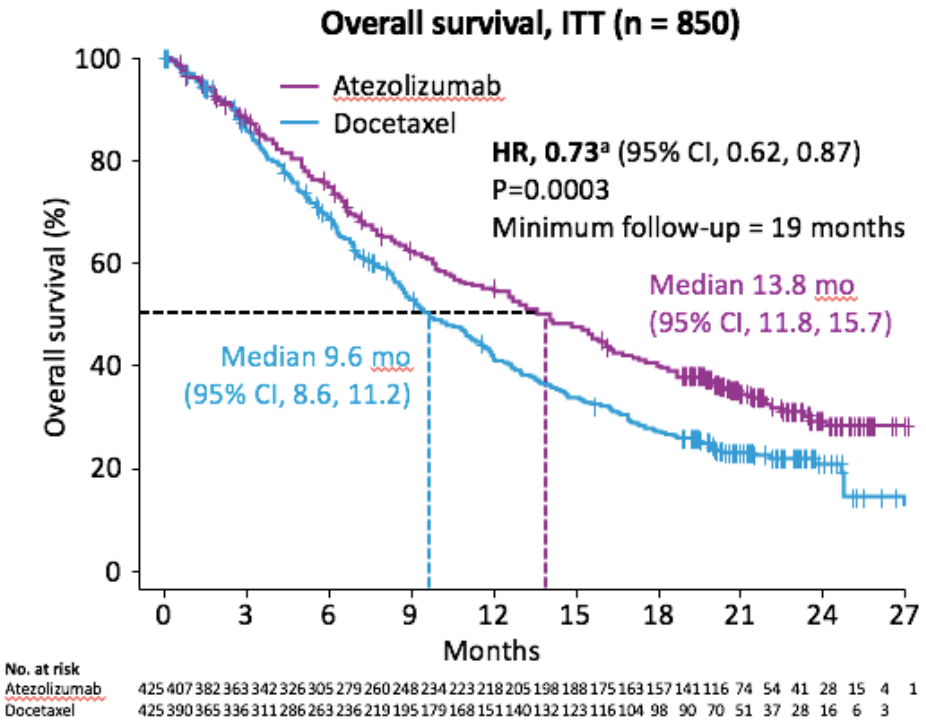
OAK: Atezolizumab vs docetaxel, 2nd or 3rd line (PD-L1 inhibitor)

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

UCSF

Safety of PD-1 inhibitors

	Pembrolizumab 2 mg/kg (n=339)		Pembrolizumab 10 mg/kg (n=343)		Docetaxel (n=309)	
	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5
Related to treatment*						
Any	215 (63%)	43 (13%)	226 (66%)	55 (16%)	251 (81%)	109 (35%)
Occurring in ≥10% of patients in any group						
Decreased appetite	46 (14%)	3 (1%)	33 (10%)	1 (<1%)	49 (16%)	3 (1%)
Fatigue	46 (14%)	4 (1%)	49 (14%)	6 (2%)	76 (25%)	11 (4%)
Nausea	37 (11%)	1 (<1%)	31 (9%)	2 (1%)	45 (15%)	1 (<1%)
Rash	29 (9%)	1 (<1%)	44 (13%)	1 (<1%)	14 (5%)	0 (0%)
Diarrhoea	24 (7%)	2 (1%)	22 (6%)	0 (0%)	56 (18%)	7 (2%)
Asthenia	20 (6%)	1 (<1%)	19 (6%)	2 (1%)	35 (11%)	6 (2%)
Stomatitis	13 (4%)	0 (0%)	7 (2%)	1 (<1%)	43 (14%)	3 (1%)
Anaemia	10 (3%)	3 (1%)	14 (4%)	1 (<1%)	40 (13%)	5 (2%)
Alopecia	3 (1%)	0 (0%)	2 (1%)	0 (0%)	101 (33%)	2 (1%)
Neutropenia	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	44 (14%)	38 (12%)
Of special interest occurring in ≥2 patients in the pembrolizumab groups†						
Hypothyroidism	28 (8%)	0 (0%)	28 (8%)	0 (0%)	1 (<1%)	0 (0%)
Pneumonitis‡	16 (5%)	7 (2%)	15 (4%)	7 (2%)	6 (2%)	2 (1%)
Hyperthyroidism	12 (4%)	0 (0%)	20 (6%)	1 (<1%)	3 (1%)	0 (0%)
Colitis	4 (1%)	3 (1%)	2 (1%)	1 (<1%)	0 (0%)	0 (0%)
Severe skin reactions	4 (1%)	3 (1%)	7 (2%)	6 (2%)	2 (1%)	2 (1%)
Pancreatitis§	3 (1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Adrenal insufficiency	2 (1%)	0 (0%)	3 (1%)	1 (<1%)	0 (0%)	0 (0%)
Myositis	2 (1%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
Thyroiditis	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Autoimmune hepatitis	1 (<1%)	1 (<1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Hypophysitis	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
Type 1 diabetes	1 (<1%)	1 (<1%)	2 (1%)	1 (<1%)	0 (0%)	0 (0%)

Superior tolerability compared to chemo

Immune-related toxicity is unique: anything "-itis"

*Decided by the investigator. Events are listed in descending frequency in the pembrolizumab 2 mg/kg group. †Irrespective of attribution to study drug. Events are listed in descending order of frequency in the pembrolizumab 2 mg/kg group. ‡Includes patients with interstitial lung disease (one in the pembrolizumab 2 mg/kg group, two in the pembrolizumab 10 mg/kg group, and two in the docetaxel group). §Includes one patient with acute pancreatitis.

Table 2: **Adverse events in the safety population**

PD-1 inhibitor 2nd line take-home messages

- Nivolumab, pembrolizumab and atezolizumab with similar benefit and toxicity, ~20% in all comers
  - Nivo and atezo approved for all comers 2nd line
  - Pembro approved for PD-L1+ >1% 2nd line
    - Nivo q2w, atezo and pembro q3w
- Toxicities DIFFERENT than chemo
  - Majority find it better tolerated…
  - ...but any organ can be inflamed
  - Low threshold to evaluate CT chest (pneumonitis), thyroid function tests (hypo or hyperthyroiditis), etc
  - Consider use of steroid, other immune modulators

PD-1 inhibitor 1st line?

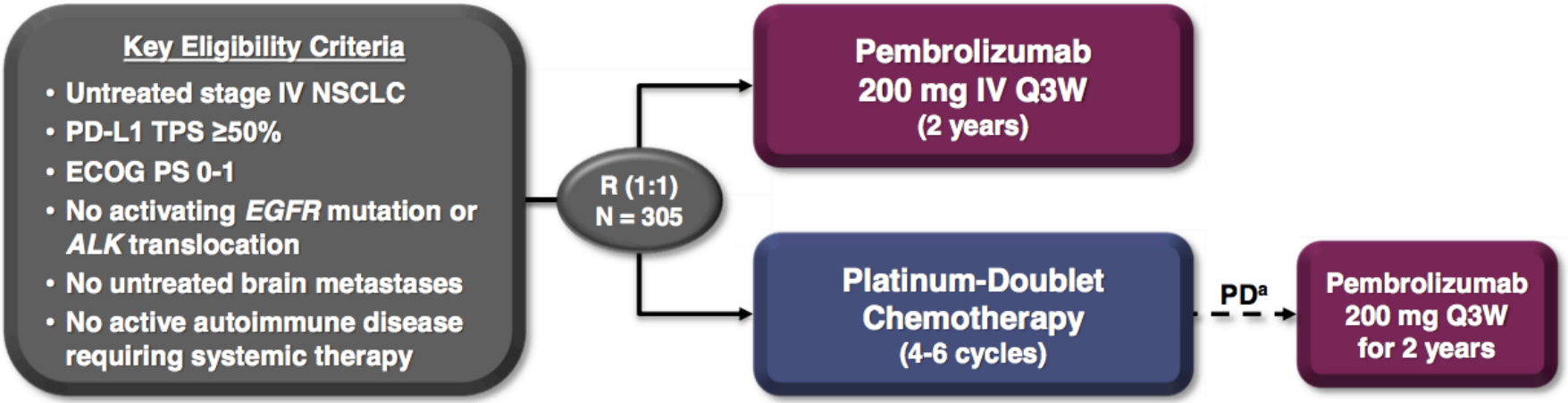
- 1st line trials presented at ESMO 2016
  - Pembro vs chemo in PD-L1≥50%
  - Nivo vs chemo in PD-L1≥5%

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

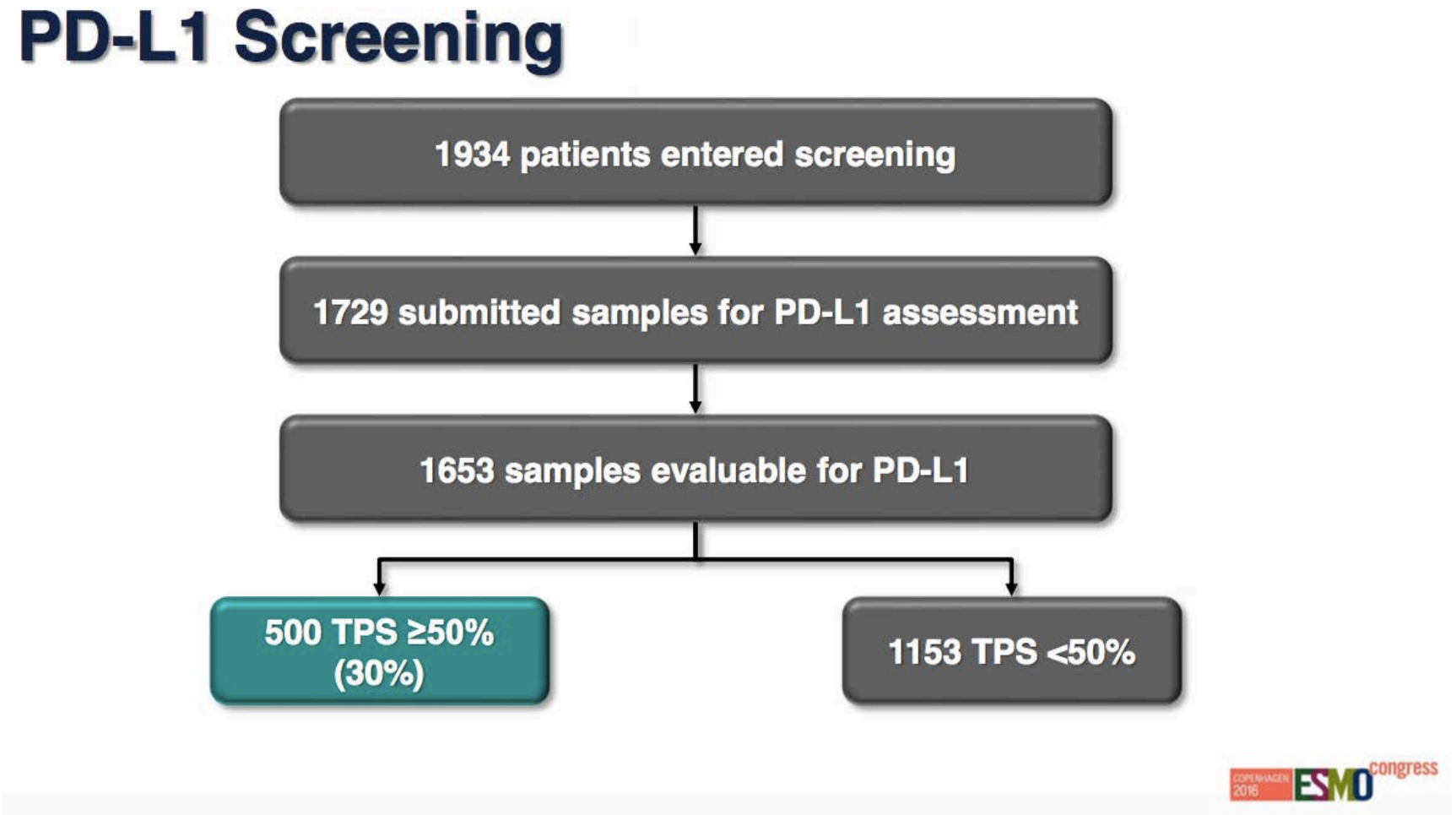
[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

COPENHAGEN 2016 ESMO congress

Recht, ESMO 2016

UCSF

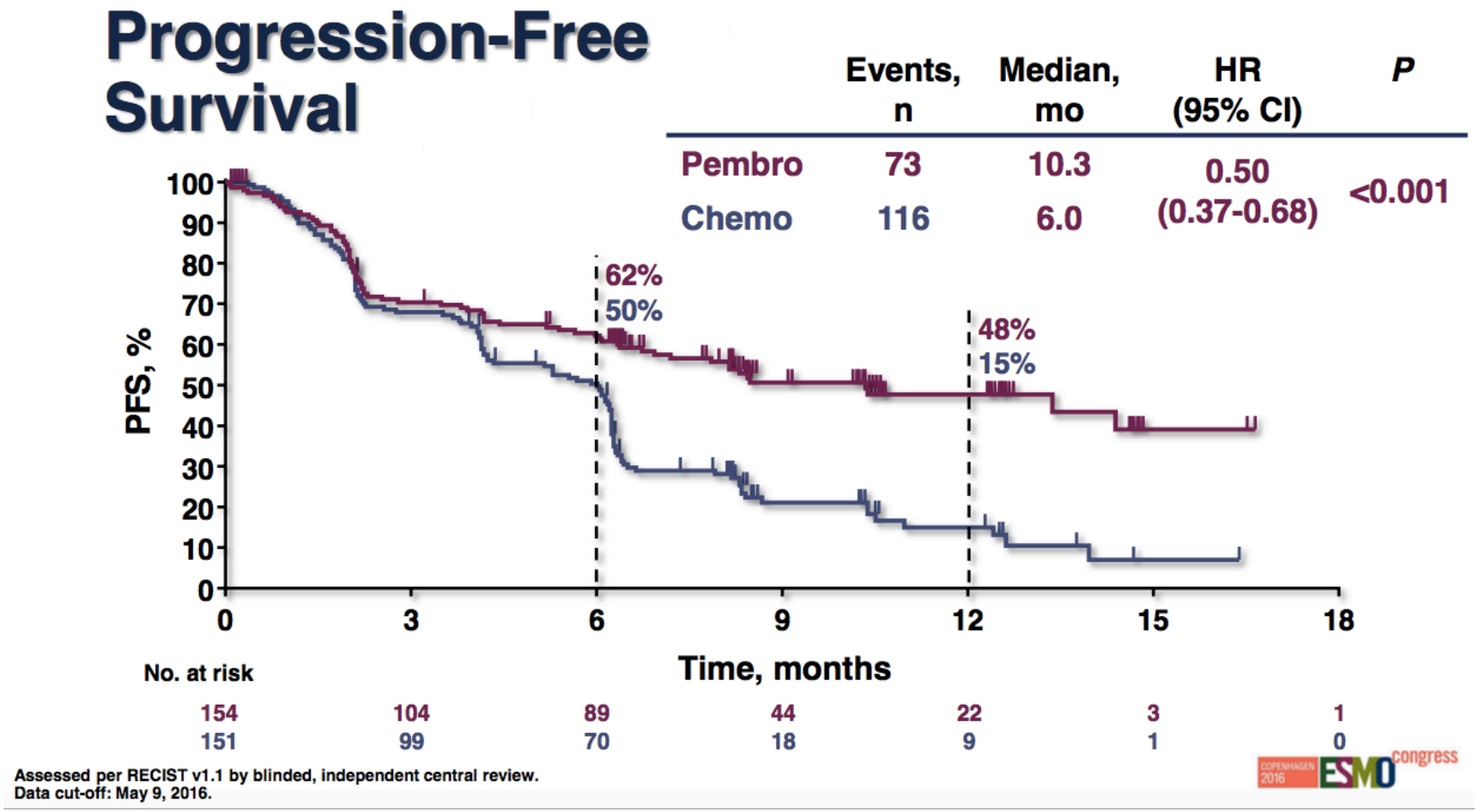
Pembrolizumab 1st line (PD-L1≥50%)



Recht, ESMO 2016

UCSF

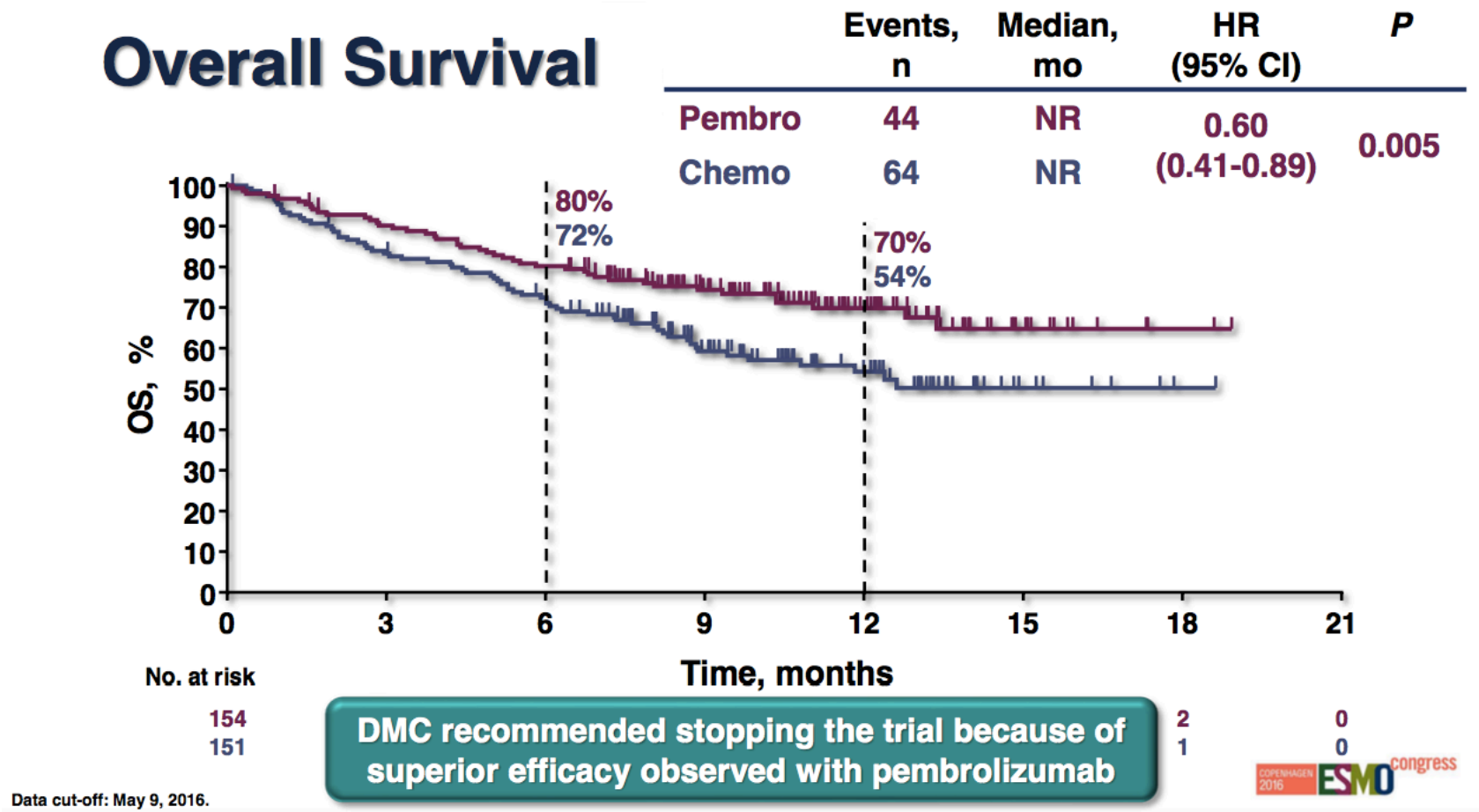
Pembrolizumab 1st line (PD-L1≥50%)



Recht, ESMO 2016

UCSF

Pembrolizumab 1st line (PD-L1≥50%)



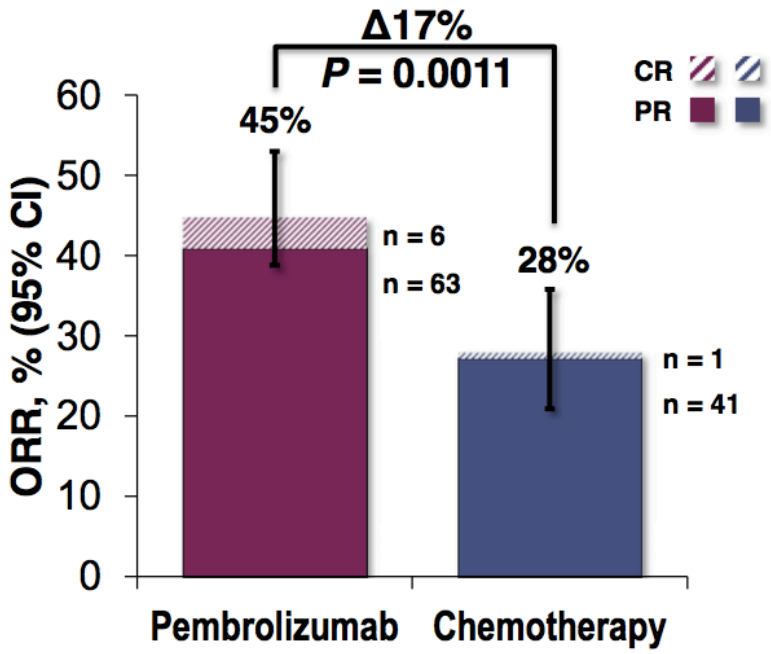
Crossover from chemo to pembro: 66/151 (44%)

Recht, ESMO 2016

UCSF

Pembrolizumab 1st line (PD-L1≥50%)

Confirmed Objective Response Rate

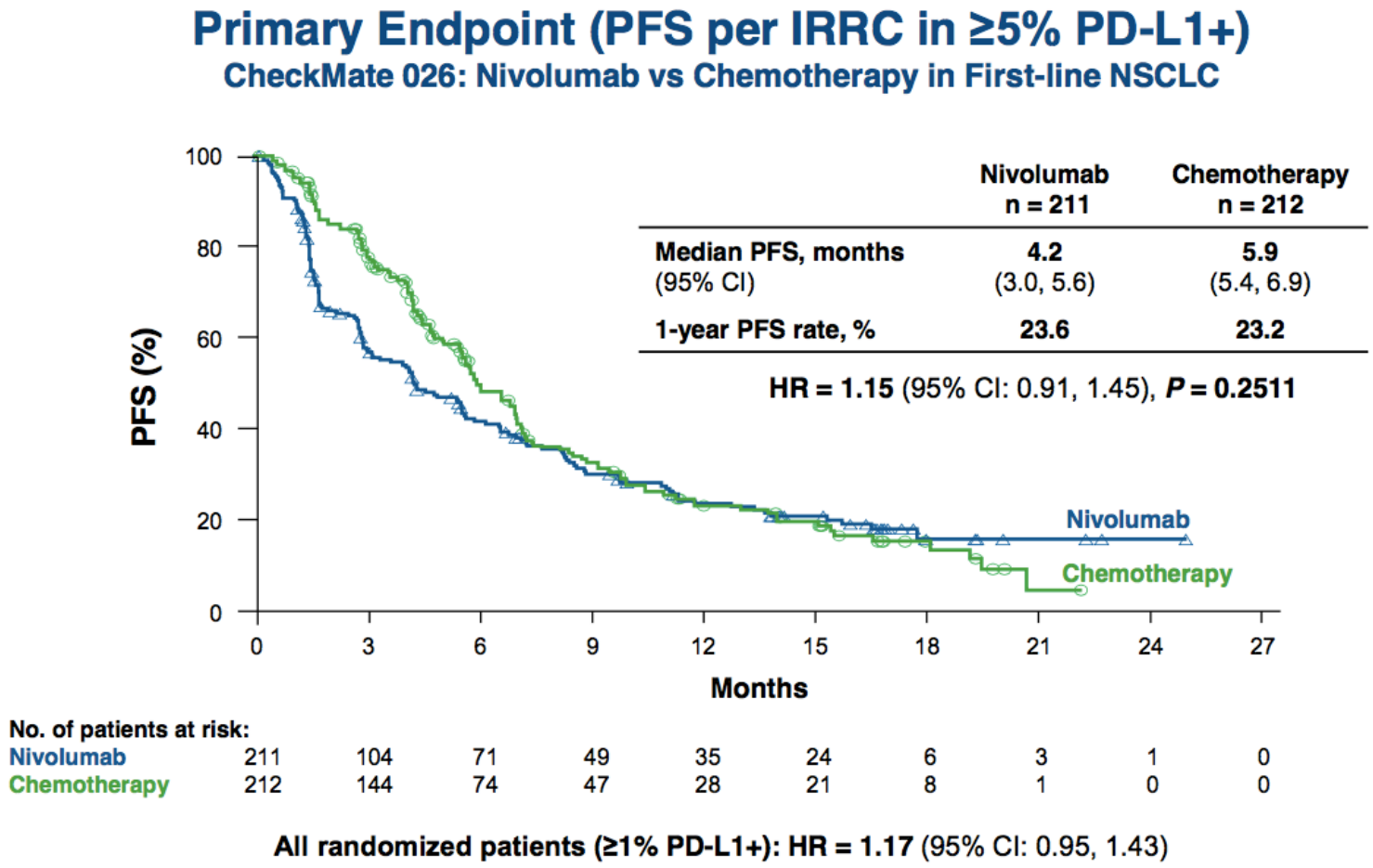


	Pembro Responders n = 69	Chemo Responders n = 42
TTR, mo median (range)	2.2 (1.4-8.2)	2.2 (1.8-12.2)
DOR, mo median (range)	NR (1.9+ to 14.5+)	6.3 (2.1+ to 12.6+)

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

COPENHAGEN 2016 ESMO congress

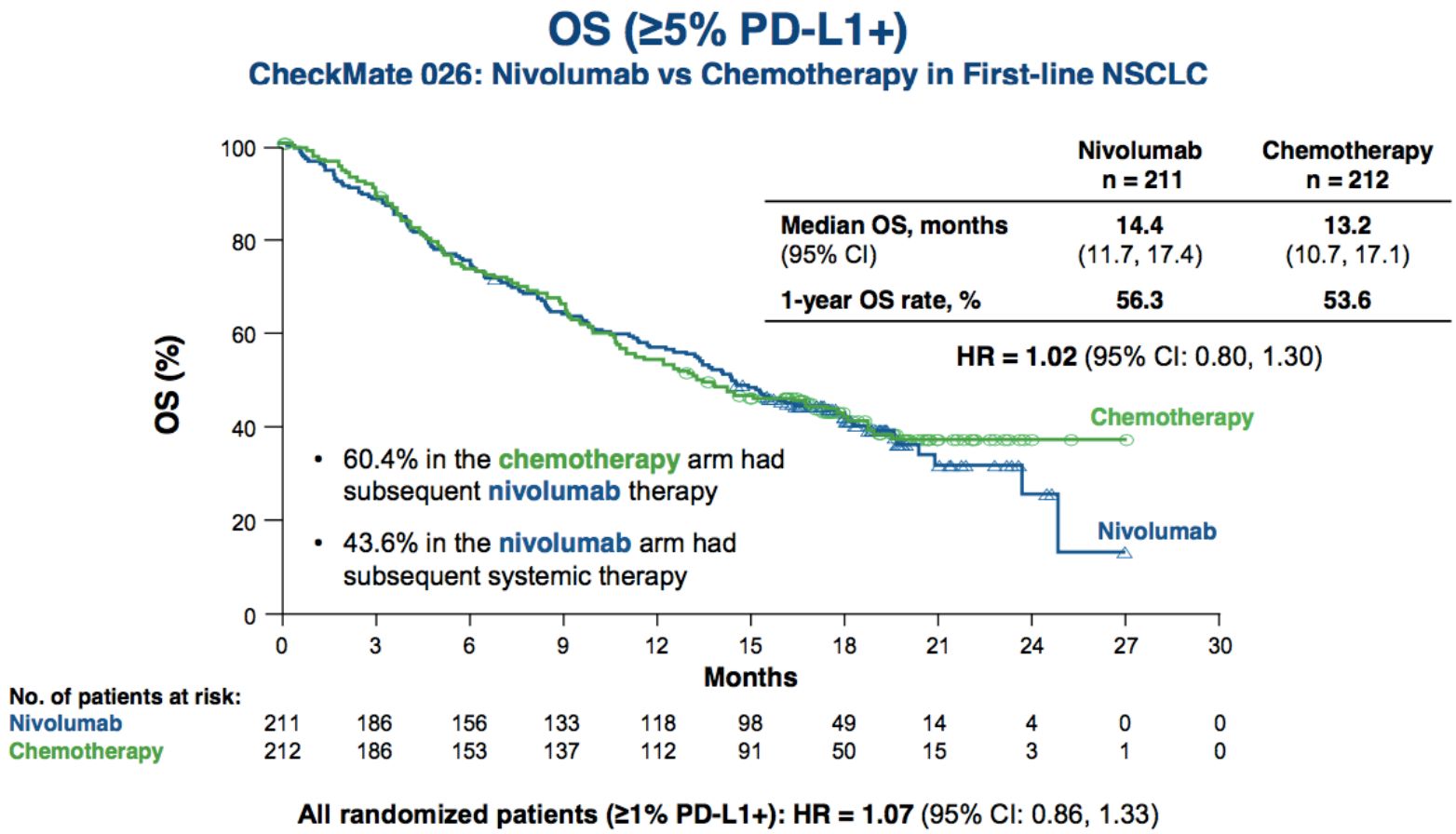
Nivolumab 1st line (PD-L1≥5%)



Socinski, ESMO 2016

UCSF

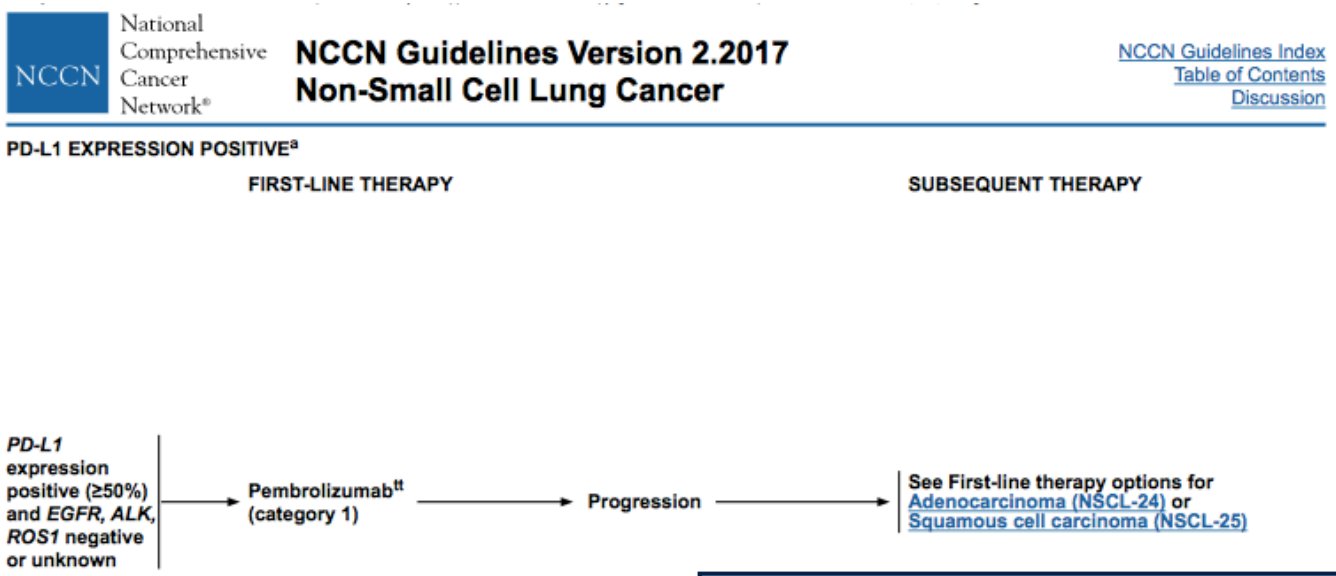
Nivolumab 1st line (PD-L1≥5%)



Socinski, ESMO 2016

UCSF

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

UCSF

Two themes

- Targeted therapies
  - 2nd+ generation approaches in “old” mutations: EGFR, ALK
  - 1st generation approaches in “new” mutations
- Immunotherapy
  - Where we’re at: PD-1 inhibition in the 2nd and 1st line
  - Where we’re going: combos and early stage

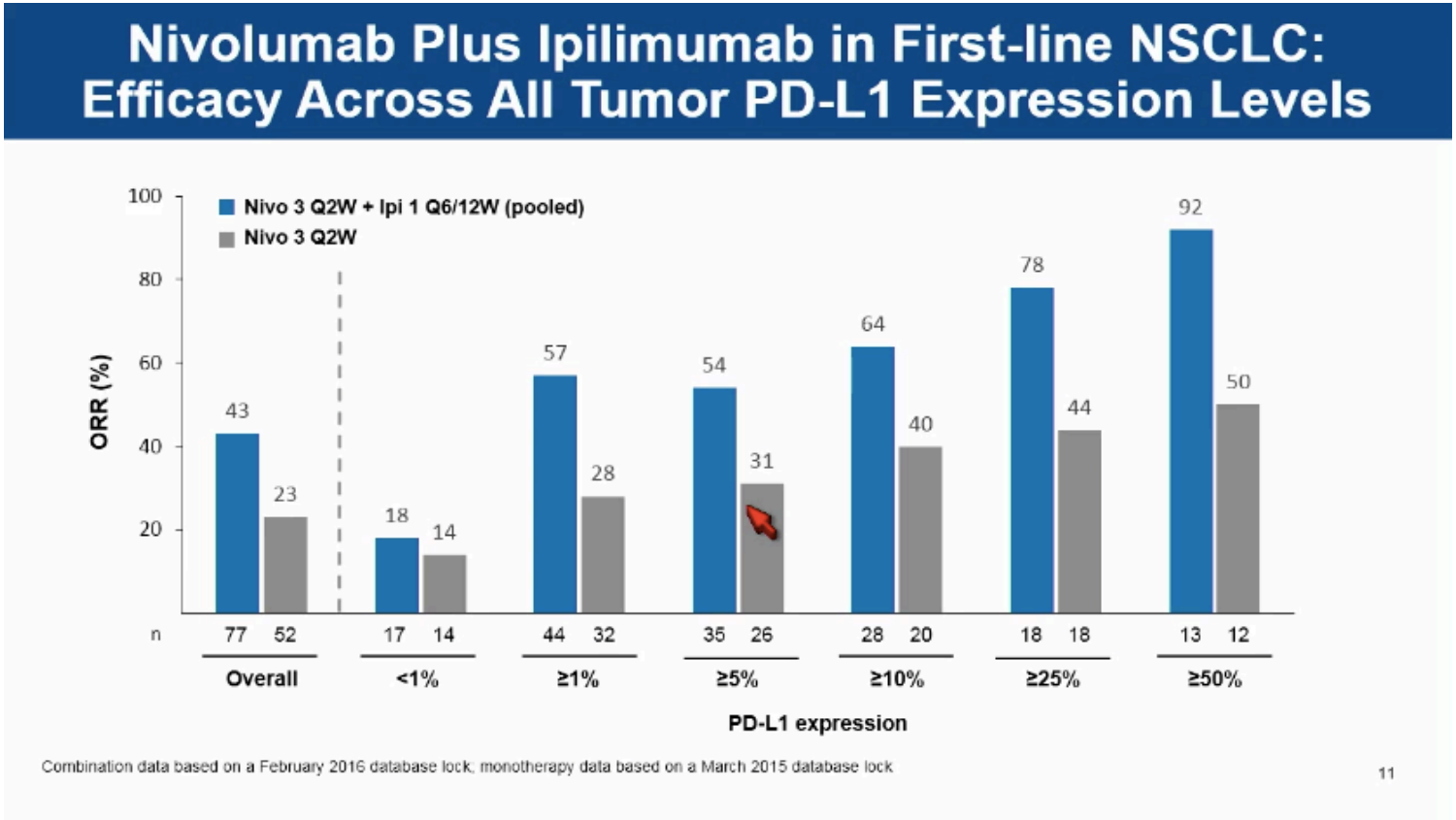
Future of immunotherapy in NSCLC

- Use PD1 inhibitors with chemo?
  - Motivation: Cancer cell death → release 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 2016), n=123 carboplatin/pemetrexed +/- pembrolizumab
    - RR 55 vs 29%, PFS 13.0 vs 8.9 mo
- APPROVED by FDA 5/10/17, before phase 3 data released

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? Can we prime for response to PD1 inhibition?
  - 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) nivolumab vs nivolumab/ipilimumab

Early data: 1st line nivo/ipi



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

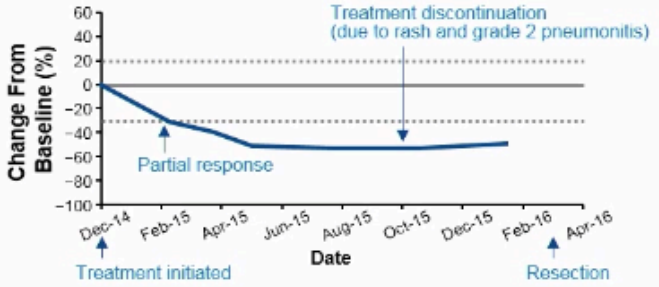
Hellman, ASCO 2016

UCSF

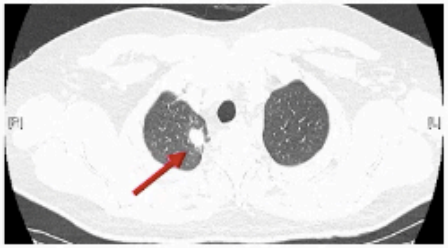
Early data: 1st line nivo/ipi

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

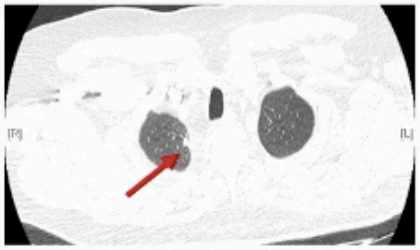
- 54-yr-old male (former smoker, 52 pack-yr) with metastatic large-cell lung cancer (PD-L1 <1%[a])
  - 53% total tumor size reduction by RECIST
  - Radiographic residual lesions in the lung and mediastinal lymph nodes, without distant disease



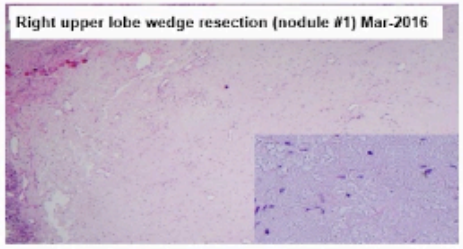
Before nivo + ipi therapy



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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Future of immunotherapy in NSCLC

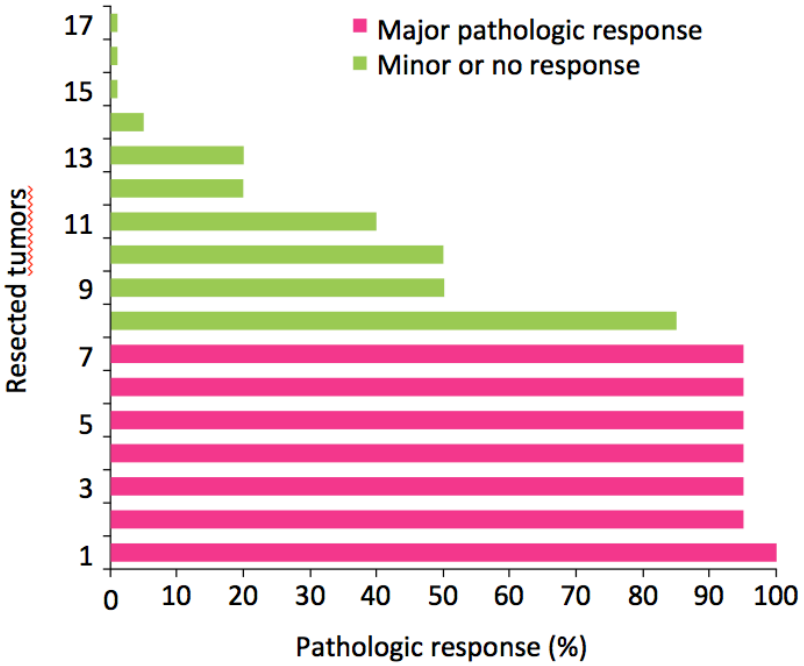
- Use PD1 inhibitors in early stage disease?
  - Motivation: Potential downstaging, research platform for evaluating treatment effect *in vivo*
  - Caveats:
    - Toxicity
    - Upstaging if not effective, esp in aggressive tumors
- Awaiting early studies

Early data: Neoadjuvant nivo

Neoadjuvant anti-PD1, nivolumab, in early stage, resectable NSCLC

- **Day -28 and -14 nivolumab followed by surgery at Day 0**
  - **Primary: safety**
  - **Exploratory endpoints: correlatives in blood and tumor, % pathologic response, RFS, OS**
- **18 pts enrolled: ~1/3 at stage IIIA**
- **Only one grade 3/4 toxicity, no delay in surgery**
- **Radiographic response: 4 pts (3 were PD-L1+)**
- **Pathologic response (<10% residual viable tumor at resection[1]): 7/18 pts (39%)**
- **Pathologic downstaging: 7/18**

Tumor pathologic response after neoadjuvant anti-PD-1 (n=17)



1. Pataer et al. JTO 2012
P. Forde, et al. ESMO 2016. Abstract LBA41_PR

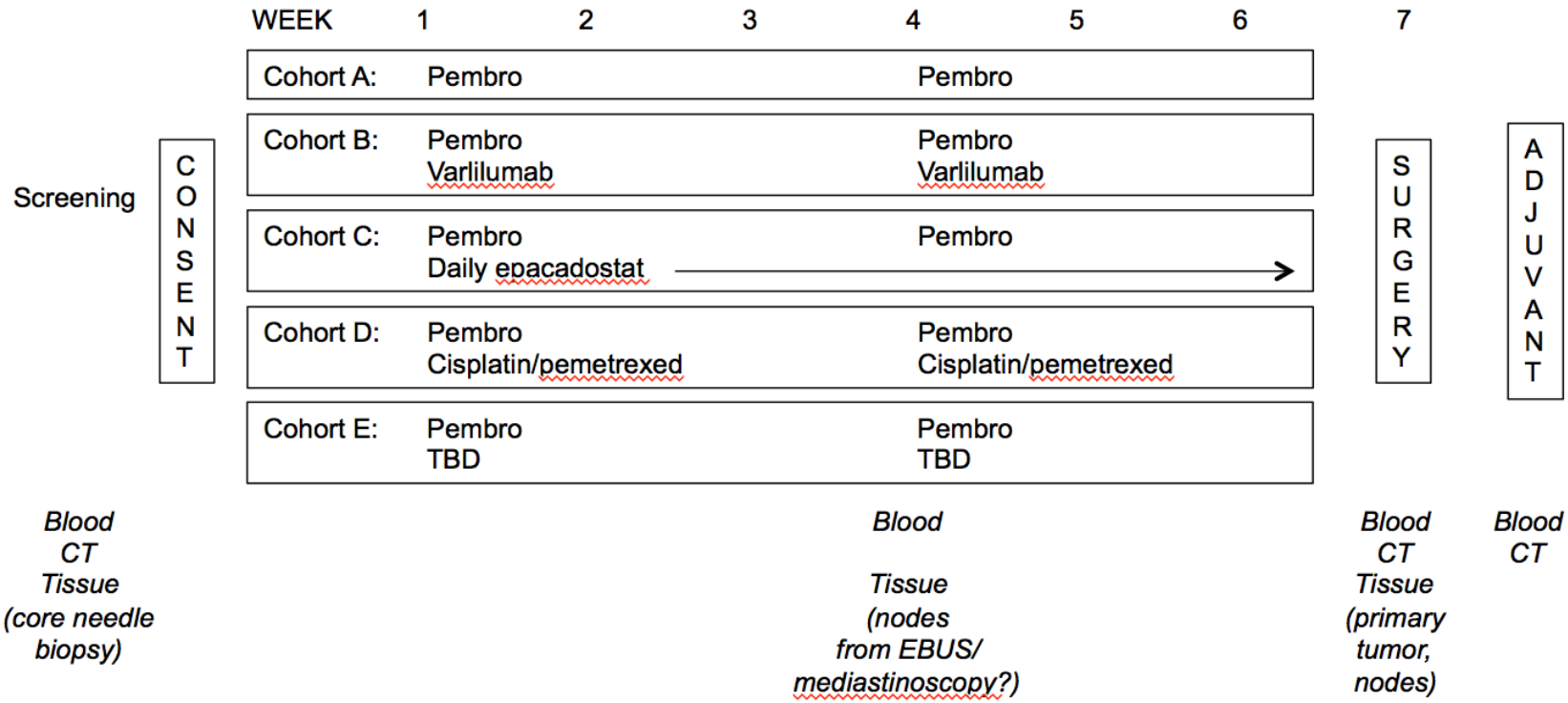
UCSF

UCSF efforts: Neoadjuvant pembrolizumab

- 2 approved investigator-initiated studies
  - PembroX (Yom, Fong, Gubens, Jablons)
    - Neoadjuvant pembro +/- XRT
  - “IO-SPY Lung” (Gubens, Fong, Jablons)
    - Neoadjuvant pembro combinations

UCSF efforts: Neoadjuvant pembrolizumab

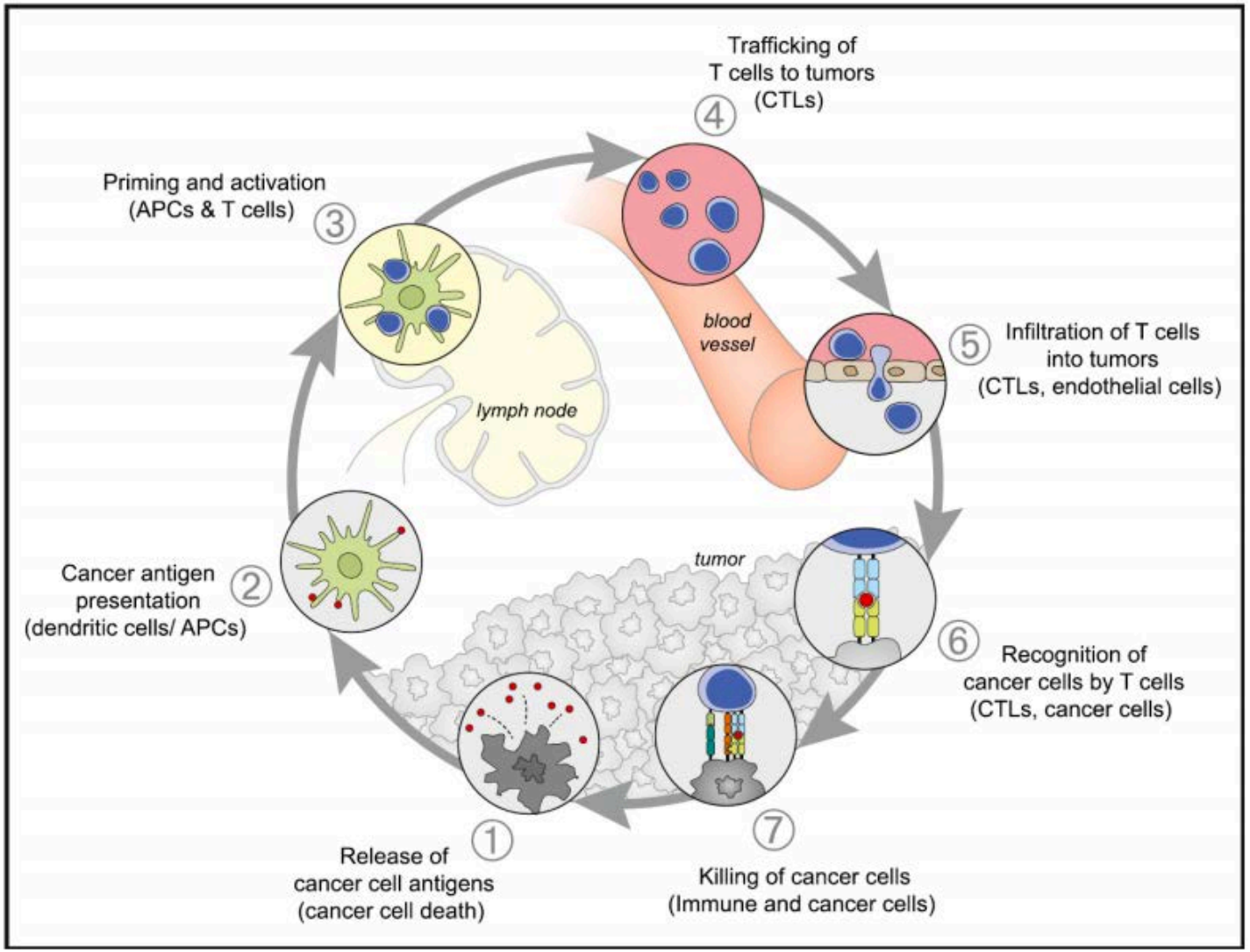
- "IO-SPY Lung" (Gubens, Fong, Jablons)



varlilumab = CD27 agonist, epacadostat = IDO inhibitor

UCSF

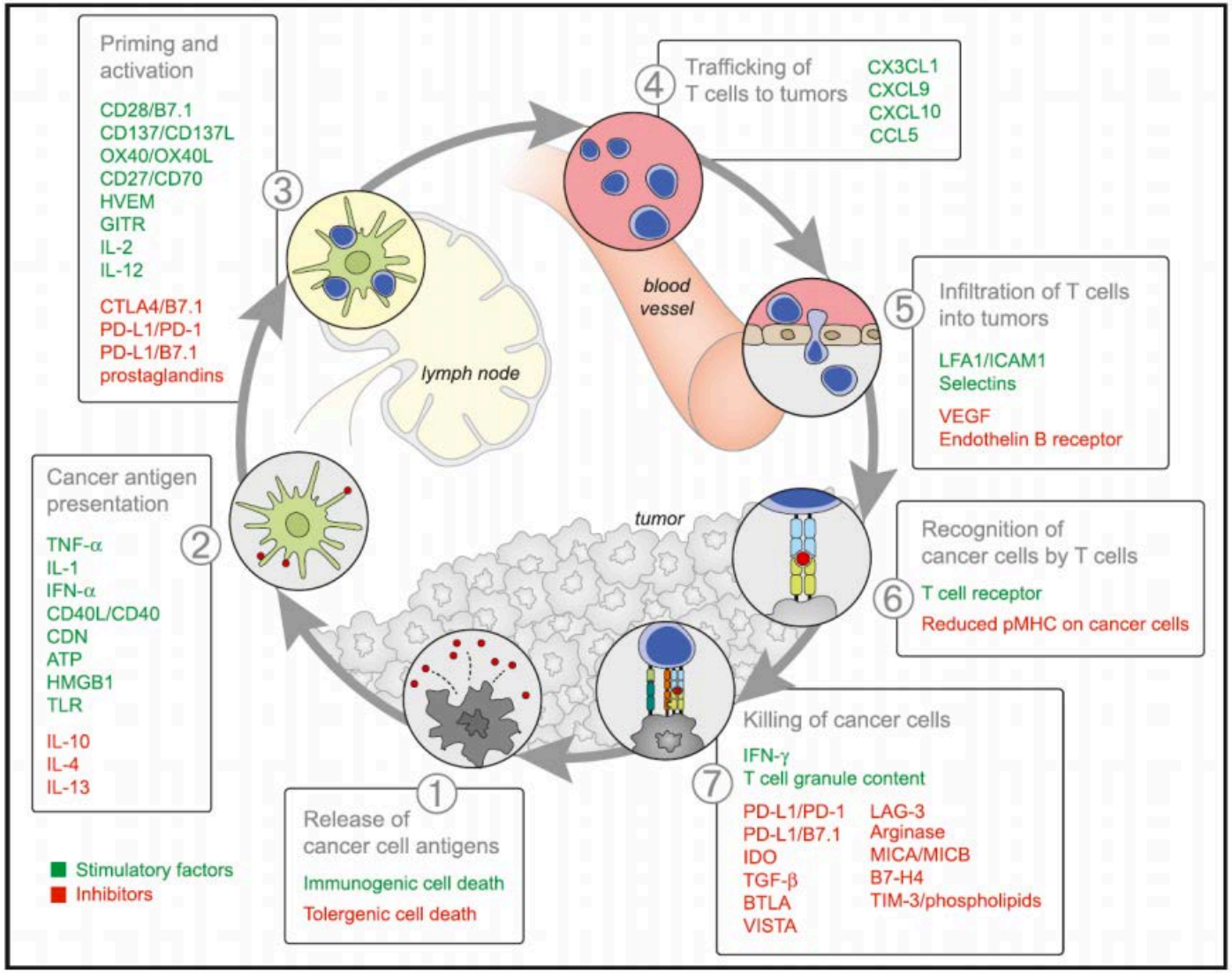
Future of immunotherapy in NSCLC



Chen and Mellman, Immunity 2013

UCSF

Future of immunotherapy in NSCLC



Chen and Mellman, Immunity 2013

UCSF

Future of immunotherapy key points

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

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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.

Future of immunotherapy key points

- Stay tuned…
  - for data on chemo combos
  - for data on immunotherapy combos
  - 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!