Novel Approaches in Non-Small Cell Lung Cancer - Immunotherapy and Others

Ivane Kiladze,MD

Research Institute of Clinical Medicine- F.Todua Medical Center

Department of Oncology and Hematology (Tbilisi, Georgia)

Disclosure

- No conflicts of interest

University of Zurich[UZH]

Advanced Studies in Lung Cancer Program for phD

European School of Oncology

Agenda

- Introduction
- Immunotherapy (IO) for resectable NSCLC
- Update in the treatment of locally advanced NSCLC
- First-line IO for metastatic disease
- Second-line IO
- Immunotherapy in EGFR/ALK-positive patients
- Progression after 1st line IO with or without chemo
- Conclusions

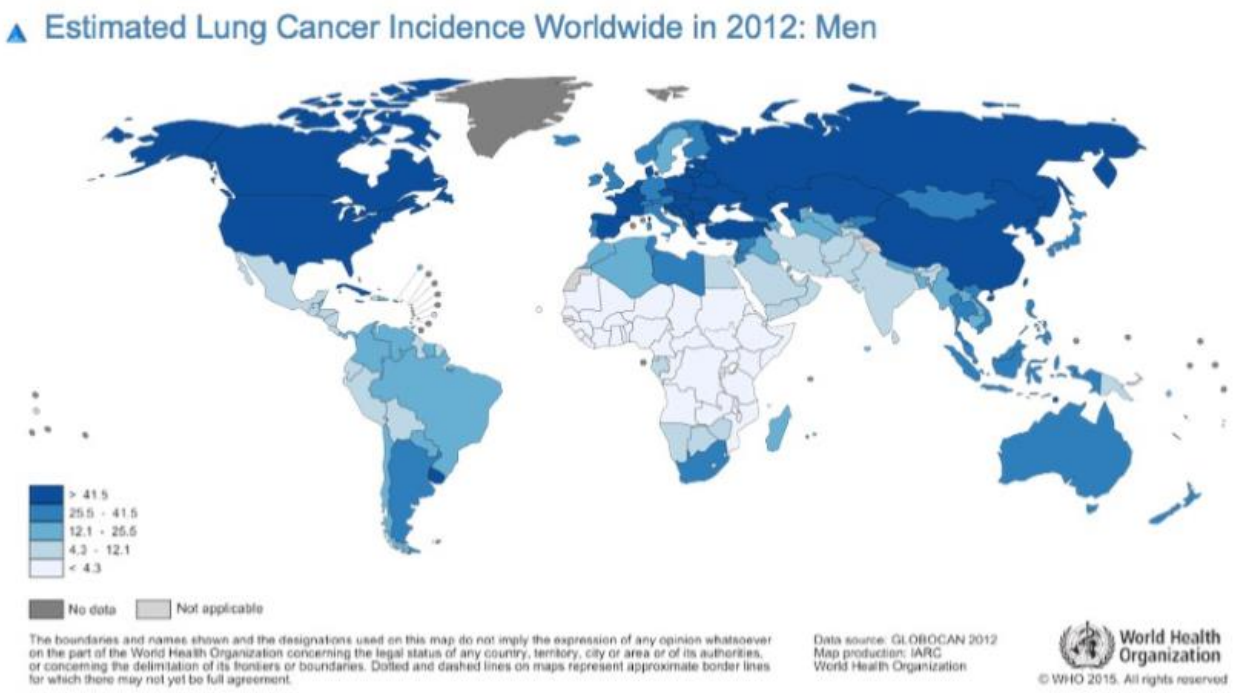
Introduction

- Statistics in 2012 identified lung cancer as the most common cancer worldwide contributing 13% of the total number of new cases
- Worldwide more than 1 in 10 of all cancers diagnosed in men are lung cancers
- Lung cancer is the leading cause of cancer-related deaths worldwide
- Properly staging the extent of disease at diagnosis influences the approach to treatment and prognosis
- Despite ostensibly curative therapy for stage I–III NSCLC, 30–60% of patients go on to develop metastatic disease
- Very heterogeneous disease

Howlader N et al, SEER Cancer Statistics Review (CSR) 2017
Jemal A et al. Global cancer statistics. CA Cancer J Clin 2011

Lung Cancer Statistics

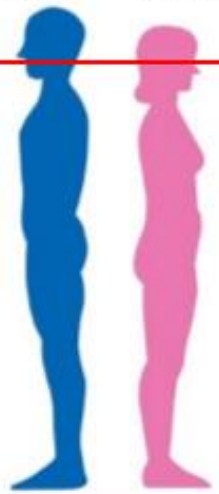
The lung cancer epidemic - men



Lung Cancer Mortality

Estimated Deaths

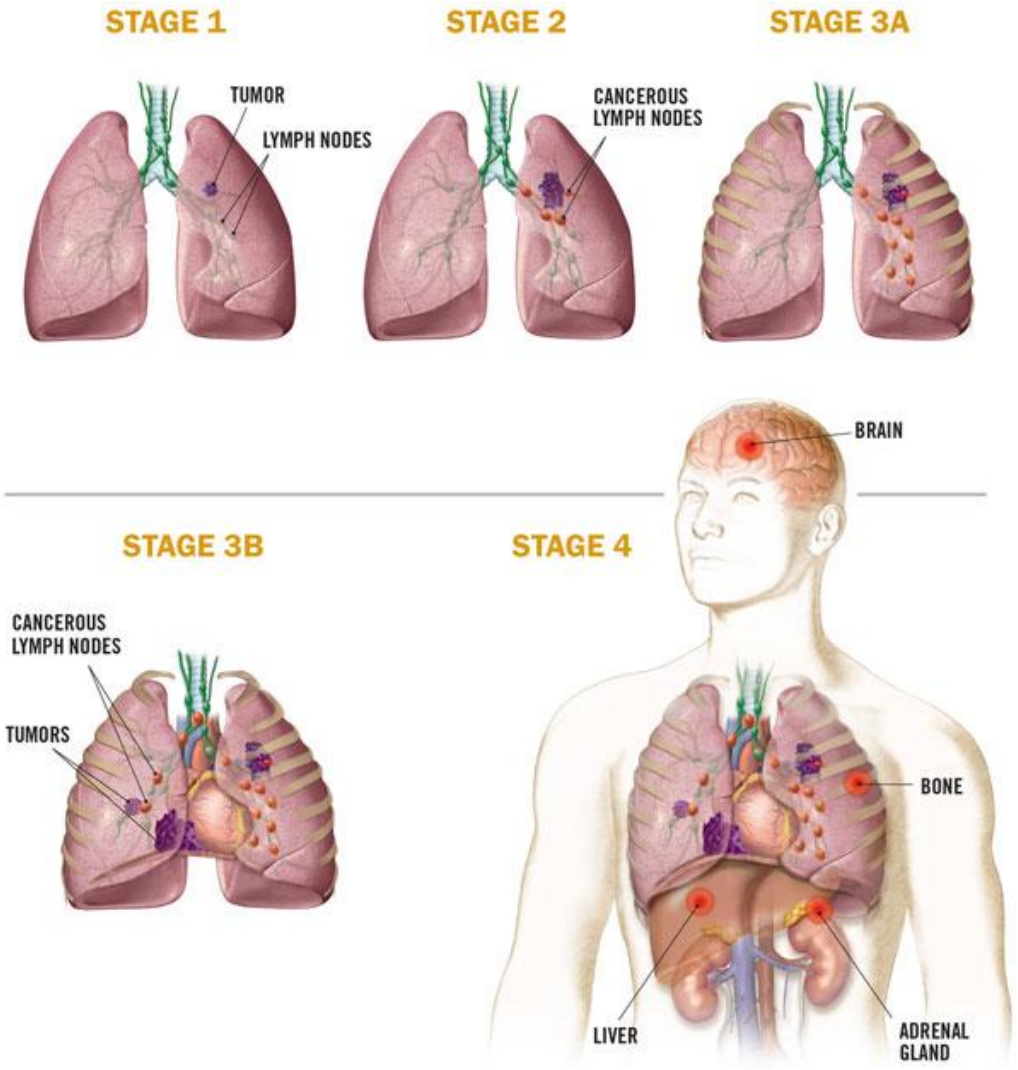
Males			Females		
Lung & bronchus	83,550	26%	Lung & bronchus	70,500	25%
Prostate	29,430	9%	Breast	40,920	14%
Colon & rectum	27,390	8%	Colon & rectum	23,240	8%
Pancreas	23,020	7%	Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%	Ovary	14,070	5%
Leukemia	14,270	4%	Uterine corpus	11,350	4%
Esophagus	12,850	4%	Leukemia	10,100	4%
Urinary bladder	12,520	4%	Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%	Brain & other nervous system	7,340	3%
All Sites	**323,630**	**100%**	**All Sites**	**286,010**	**100%**



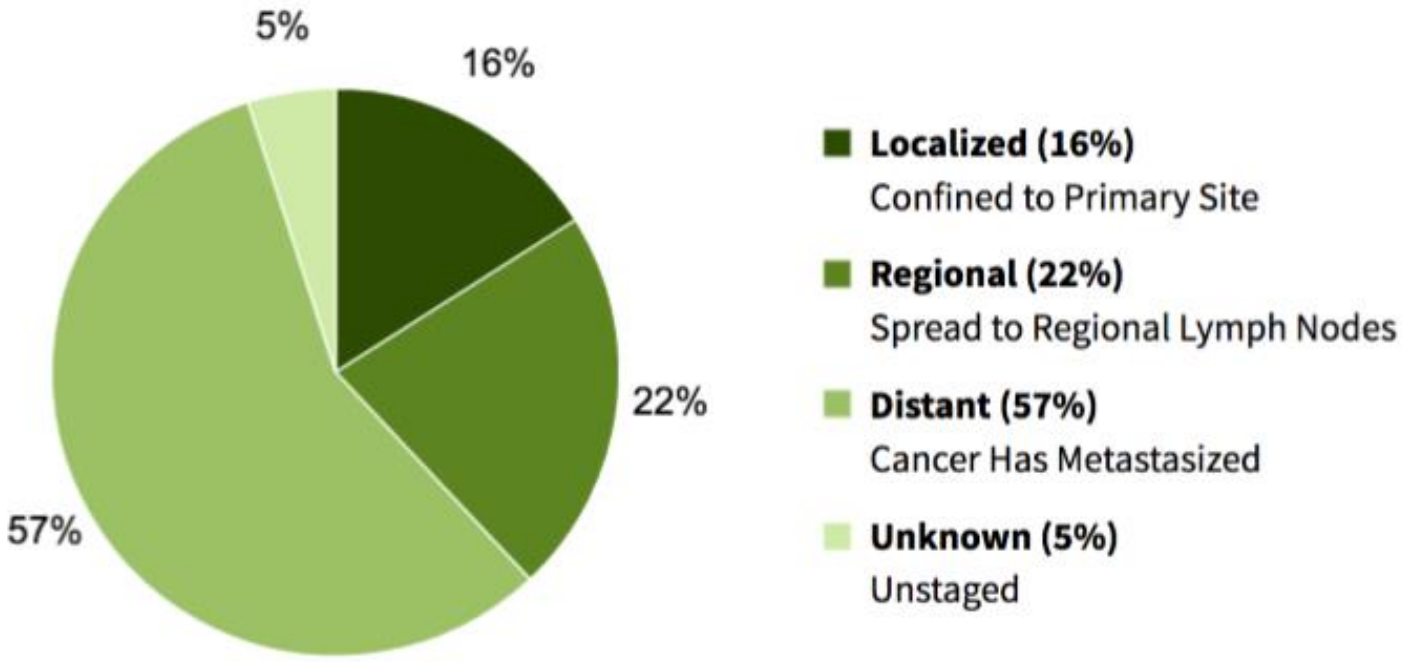
Ten Leading Cancer Types for the Estimated New Cancer Deaths by Sex, United States, 2018

Siegel et al. CA 2018

Staging


STAGE 1
TUMOR
LYMPH NODES
STAGE 2
CANCEROUS LYMPH NODES
STAGE 3A
BRAIN
STAGE 3B
CANCEROUS LYMPH NODES
TUMORS
STAGE 4
BONE
LIVER
ADRENAL GLAND

Stage at Diagnosis



Adapted from SEER 18 2007-2013

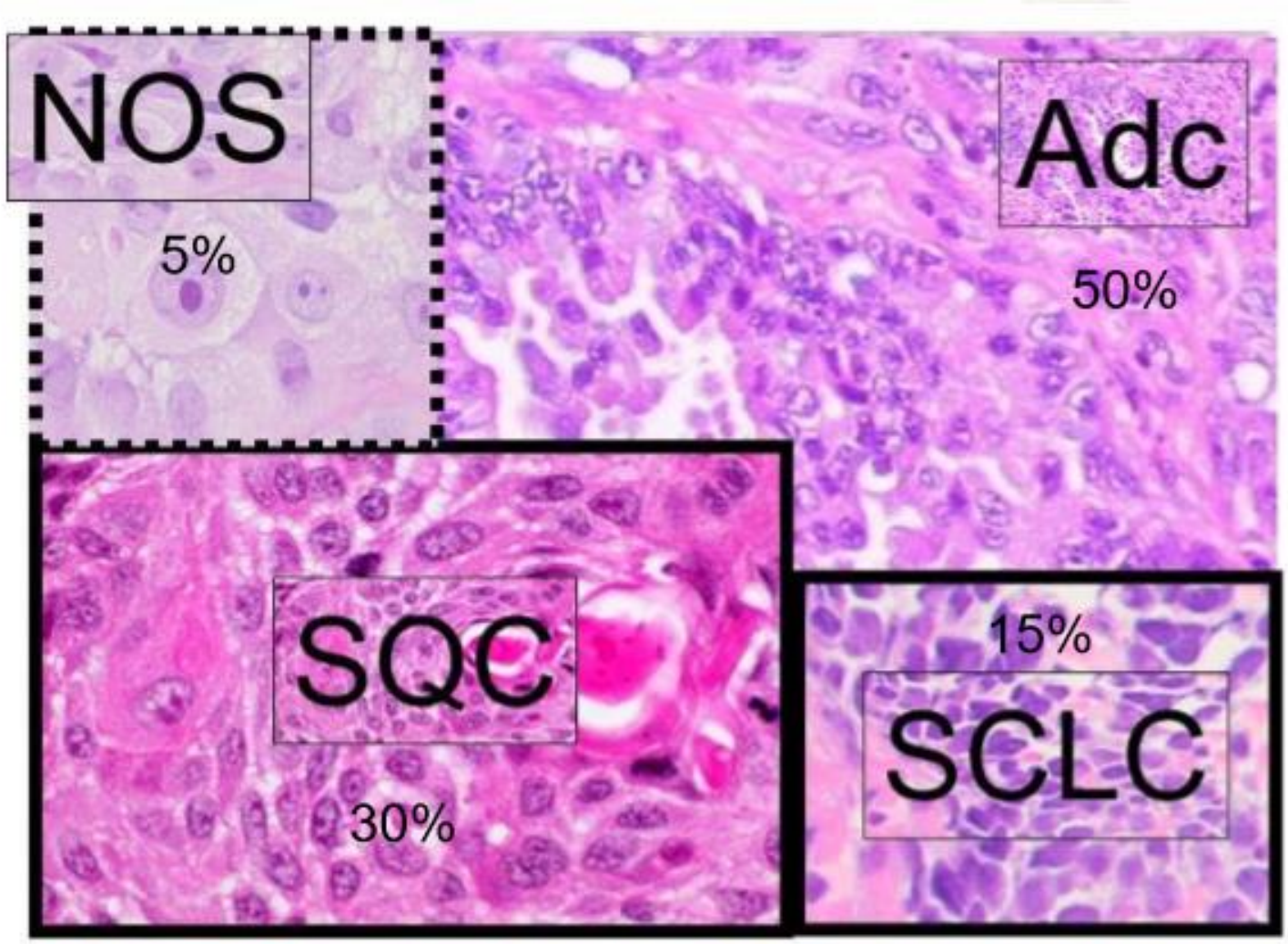
Late diagnosis

Care in the Emergency Department UK (BLF 2015)

"The fact that 34% of lung cancer patients* are diagnosed as a result of an emergency presentation may come as a surprise to many doctors working in Emergency Departments (ED)."

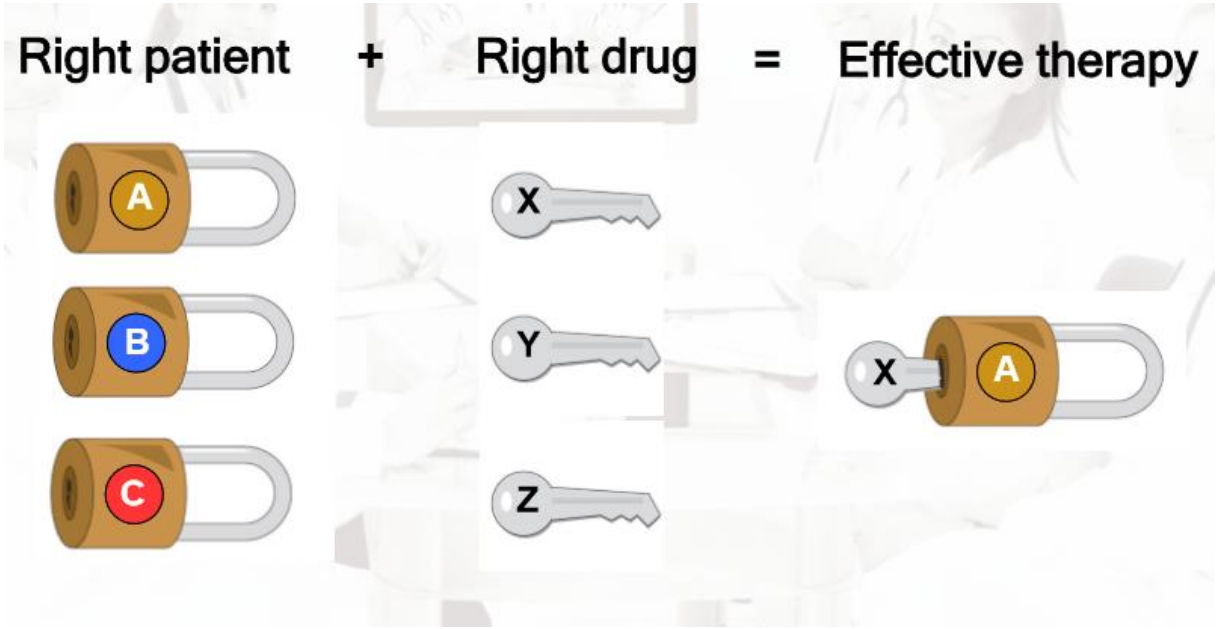
*Public Health England. (September 2015). Routes to Diagnosis 2006-2013; preliminary results. A National Cancer Intelligence Network short report. Available at: https://www.gov.uk/government/news/cancers-are Being-diagnosed-earlier-in-england.

Molecular classification starts with histology

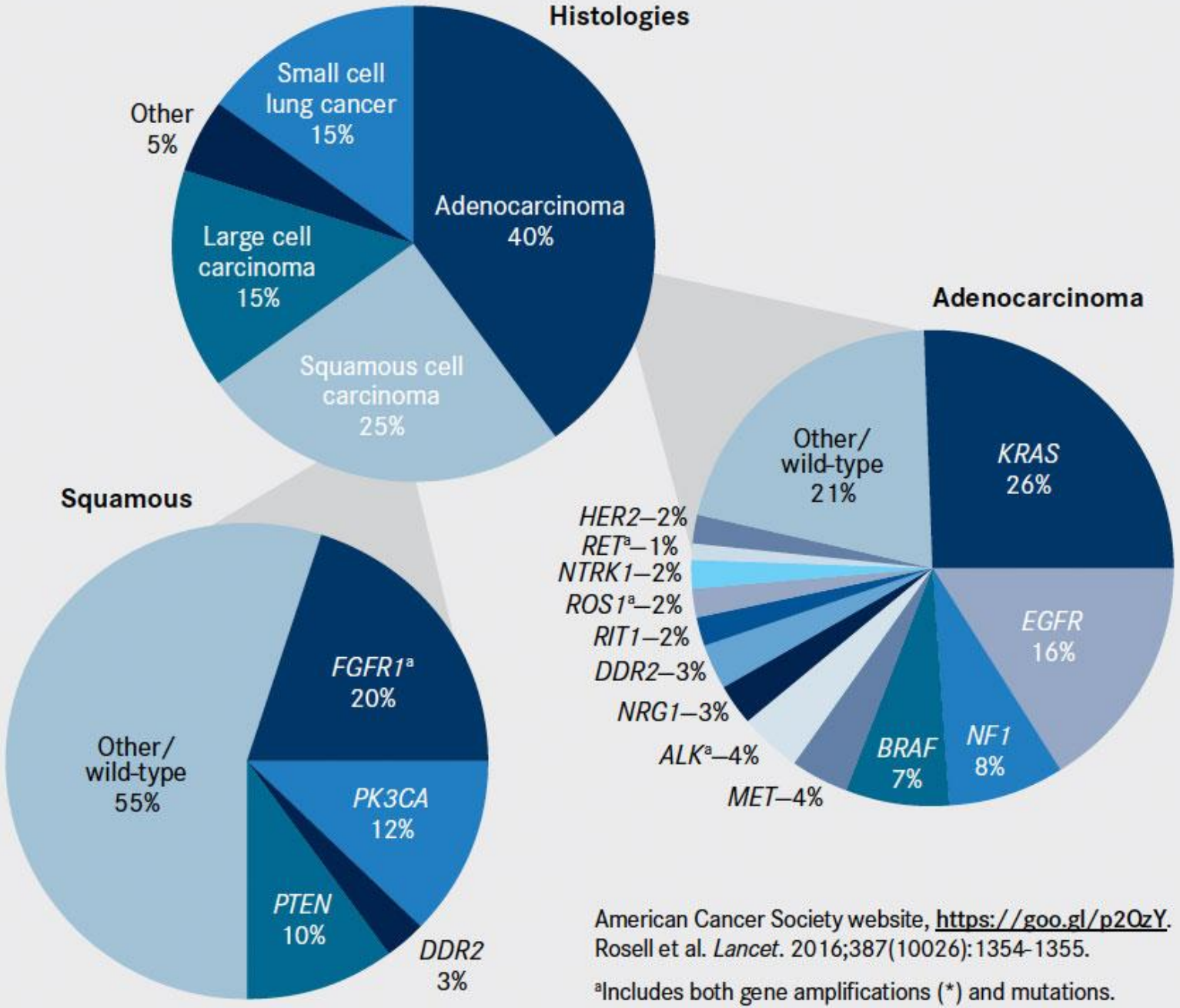


www.mh-hannover.de/35818

Why do we care about the molecular classification?



Lung Cancers and Their Molecular Drivers

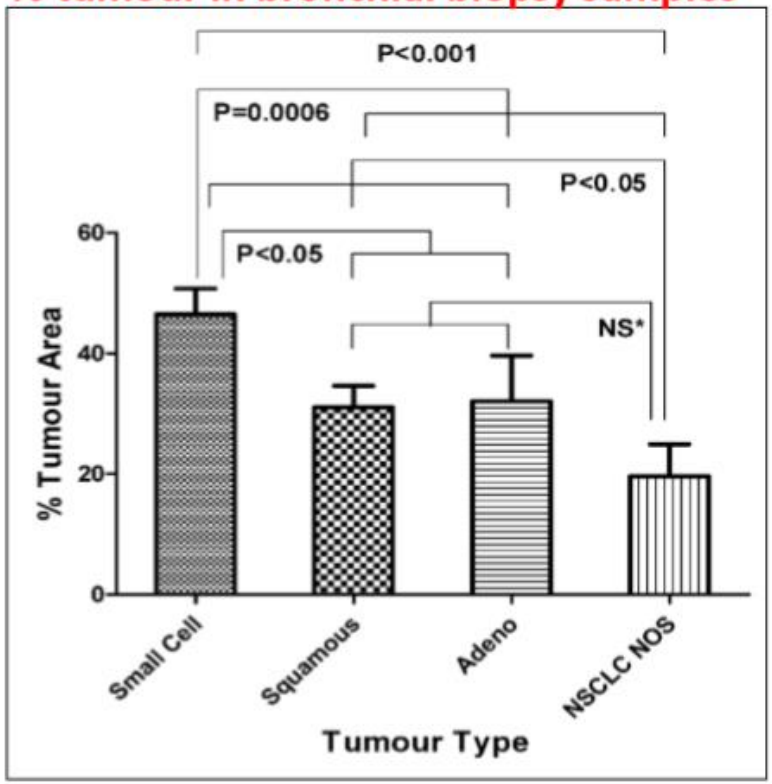


American Cancer Society website, https://goo.gl/p2QzY.
Rosell et al. *Lancet*. 2016;387(10026):1354-1355.

[a]Includes both gene amplifications (*) and mutations.

The issue is the Tissue!

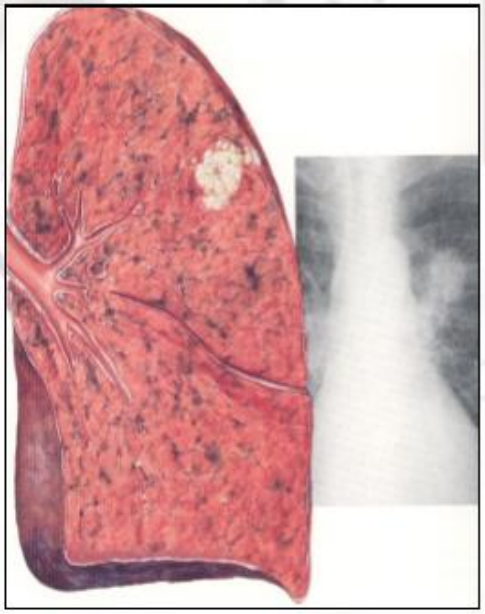
% tumour in bronchial biopsy samples

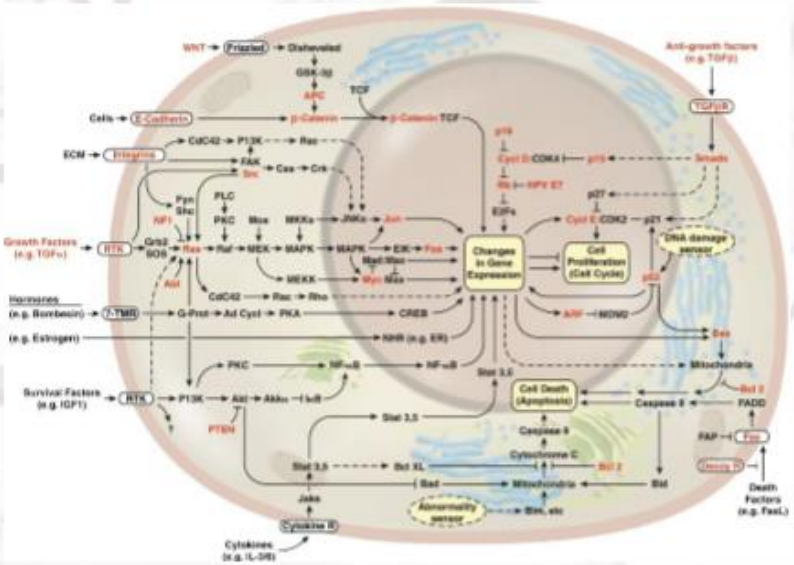


Coghlin CL et al, JTO 2010, 5:448-452

- **A surgical specimen is available in ~25% of the patients**
- **Bronchial biopsy samples are available in ~50% of the cases, and usually contain low percentage of tumor cells**
- **~25% of the patients are diagnosed on cytology samples**

From tissue to molecular signaling



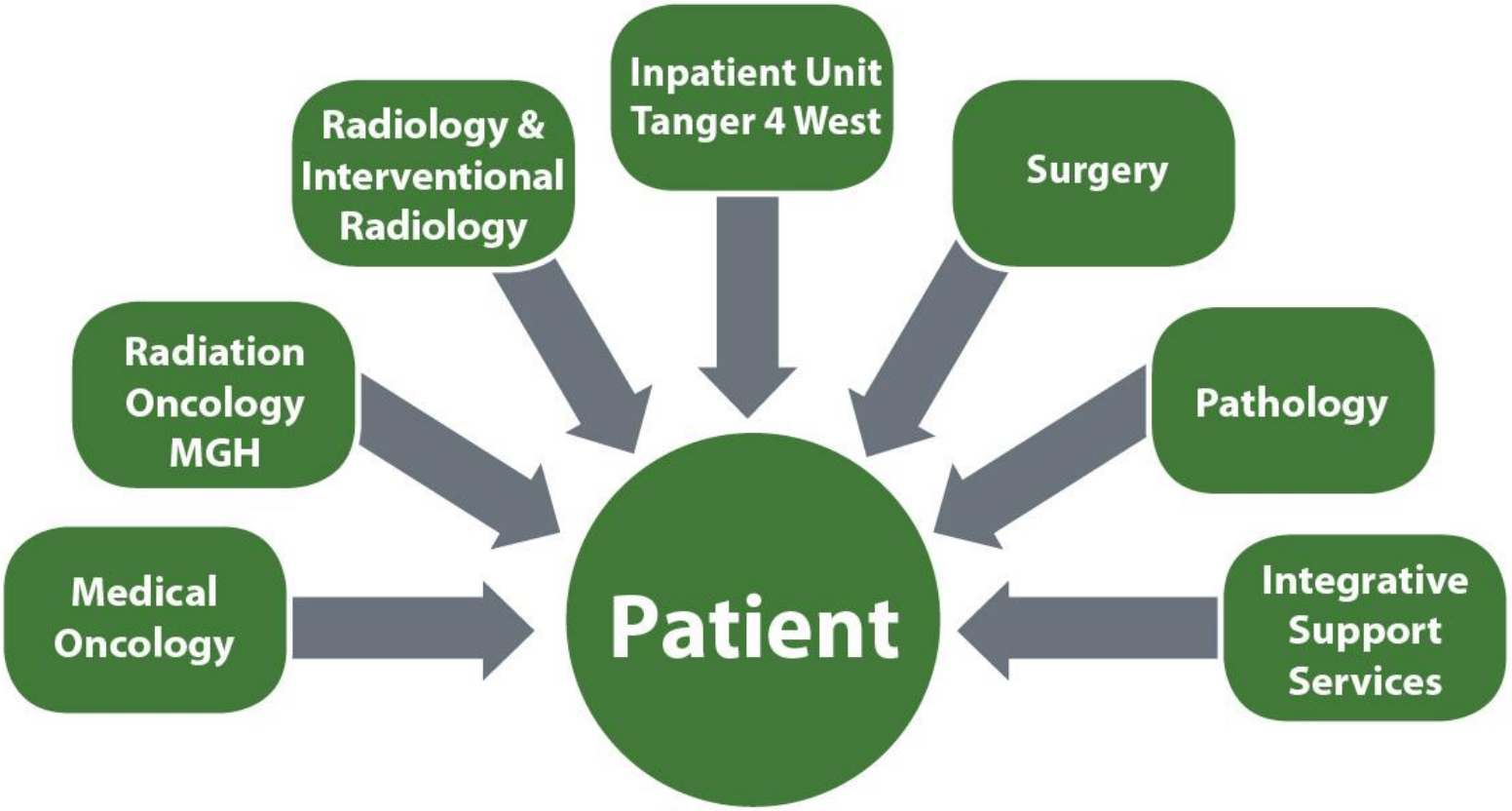


Outline

1. Lung cancer basics
2. Molecular classification
3. Precision medicine

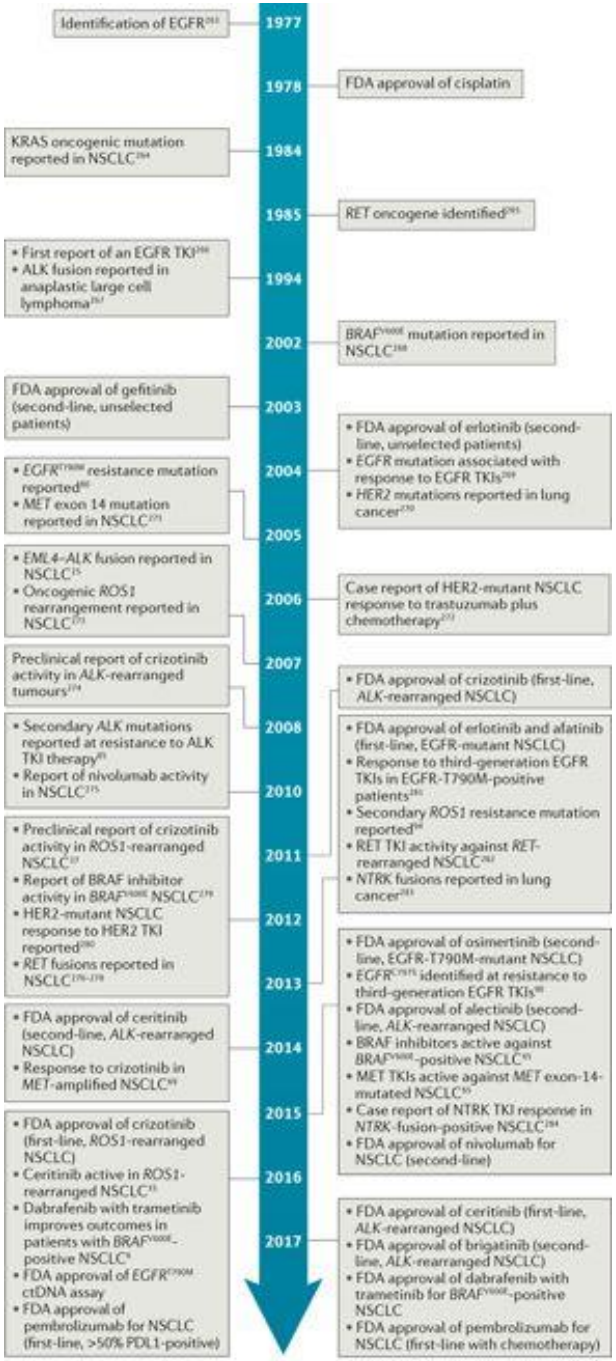
Hannavan and Weinber, Cell 2000

MDT Team



Multidisciplinary team approach to care is necessary to make the best and most informed decision for the patient

Milestones in targeted therapy for NSCLC

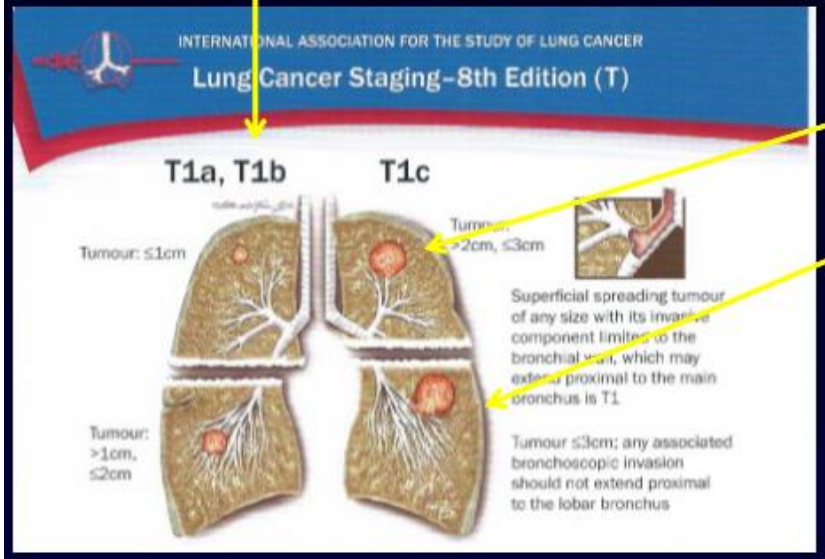


J.Rotow and T.G. Bivona, Nature Reviews Cancer.2017

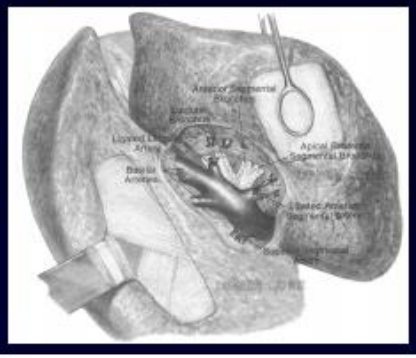
Surgery

type of resection depends on local invasion (T factor)

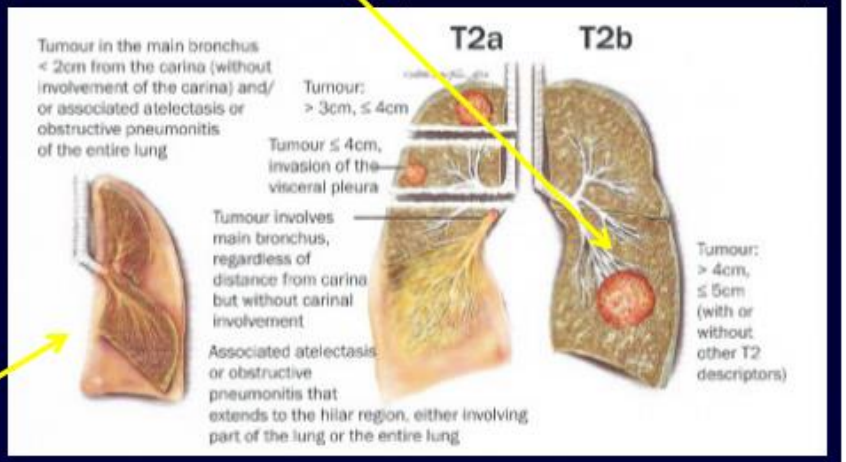
wedge resection



segmentectomy



lobectomy



pneumonectomy

along with systematic en-bloc dissection of mediastinal lymph node stations!

Neoadjuvant Immunotherapy for resectable disease

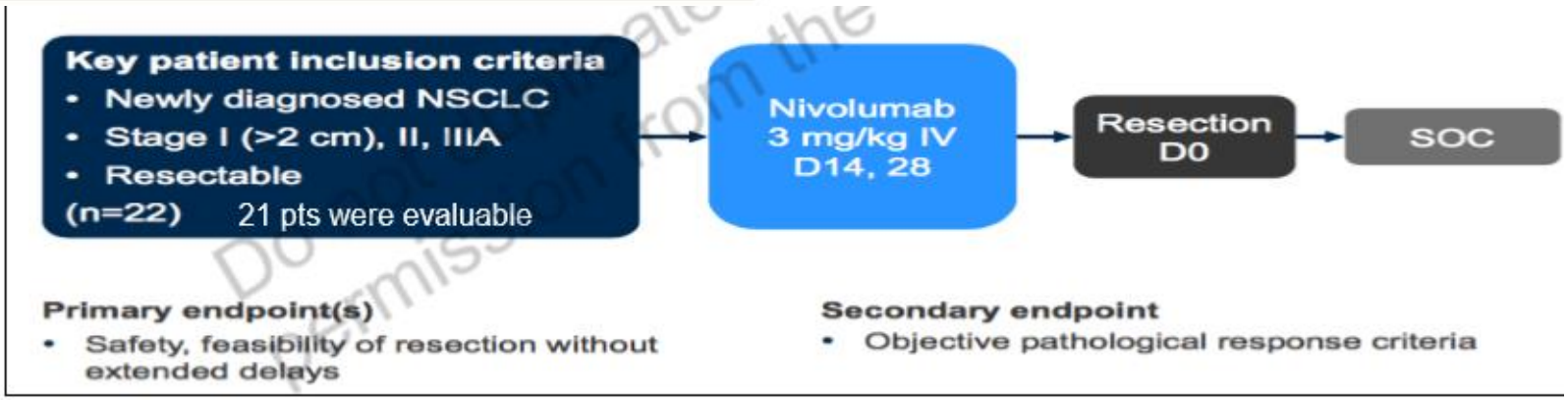
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

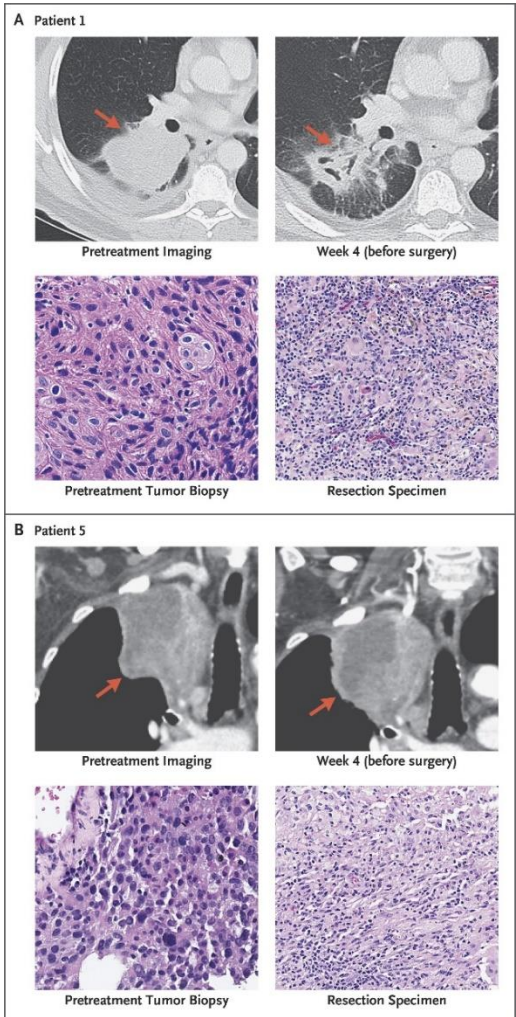
P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann, M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J.X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube, V.E. Velculescu, S.L. Topalian, J.R. Brahmer, and D.M. Pardoll

ABSTRACT



- ✓ Neoadjuvant nivolumab well tolerated and did not delay surgery.
- ✓ SD (18/21, 85%), PR- 2 (10%), PD 1 (5%)
- ✓ A major pathological response

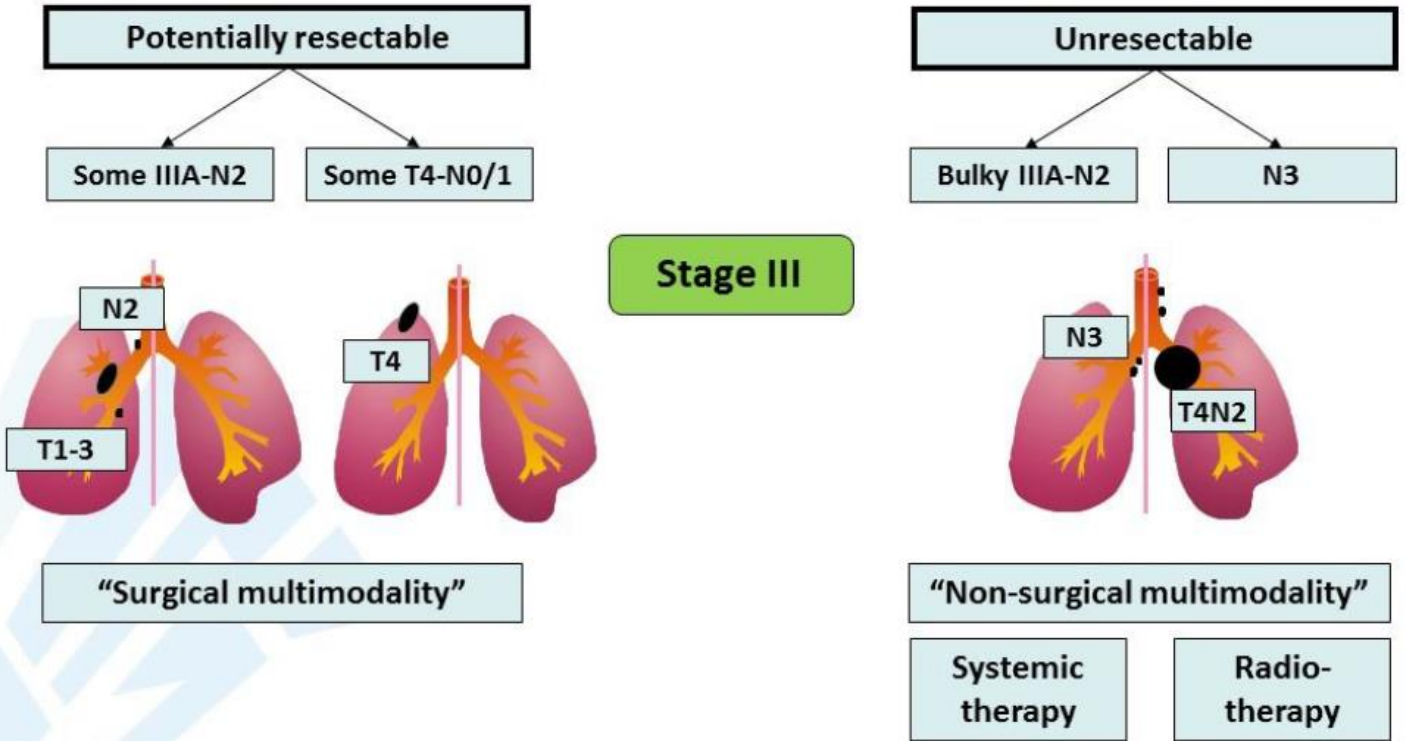
(<10% viable tumour cells in resection specimen) was achieved in 9/20 (45%) completely resected patients (independently of PD-L1 expression)



Locally advanced NSCLC

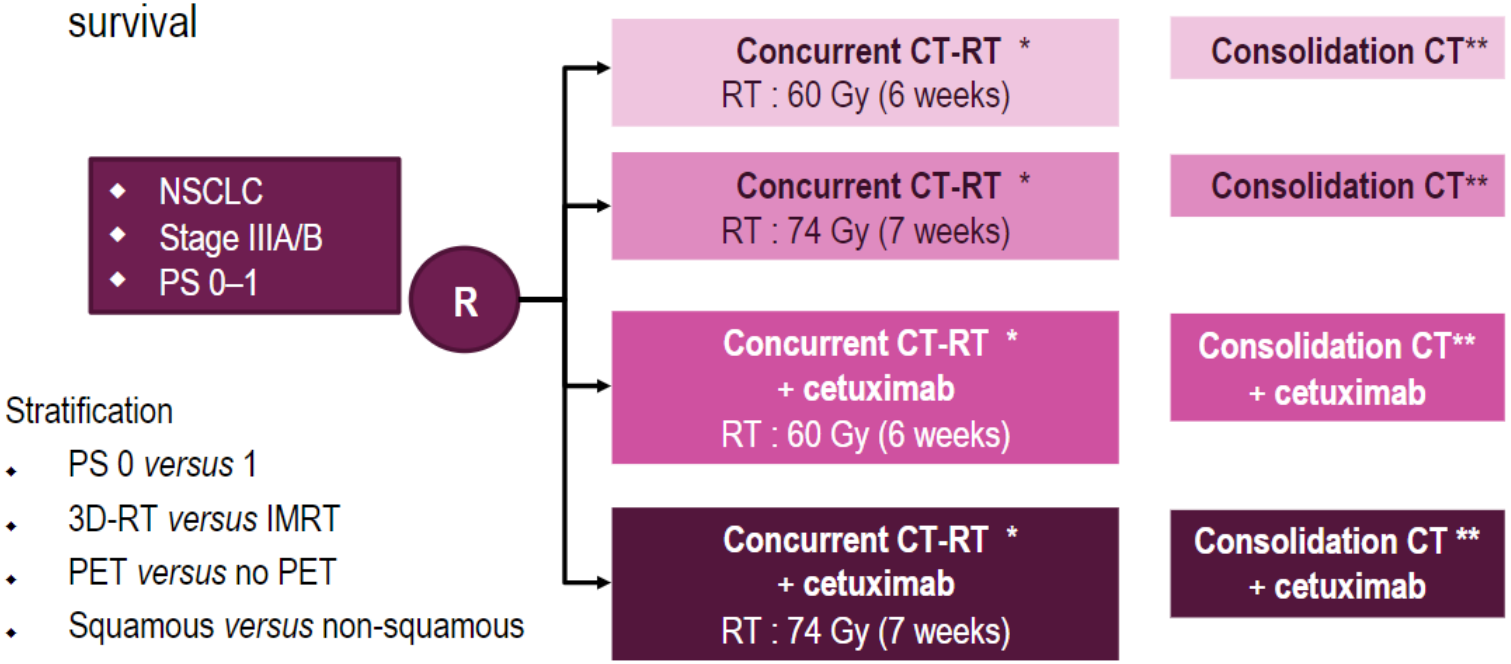
Stage III NSCLC

> heterogeneous disease in TNM and resectability



RTOG 06-17 Trial

- On the basis of encouraging phase II trials, the second aim of this phase III study was to show if addition cetuximab to concurrent standard chemo-therapy improved survival



Stratification

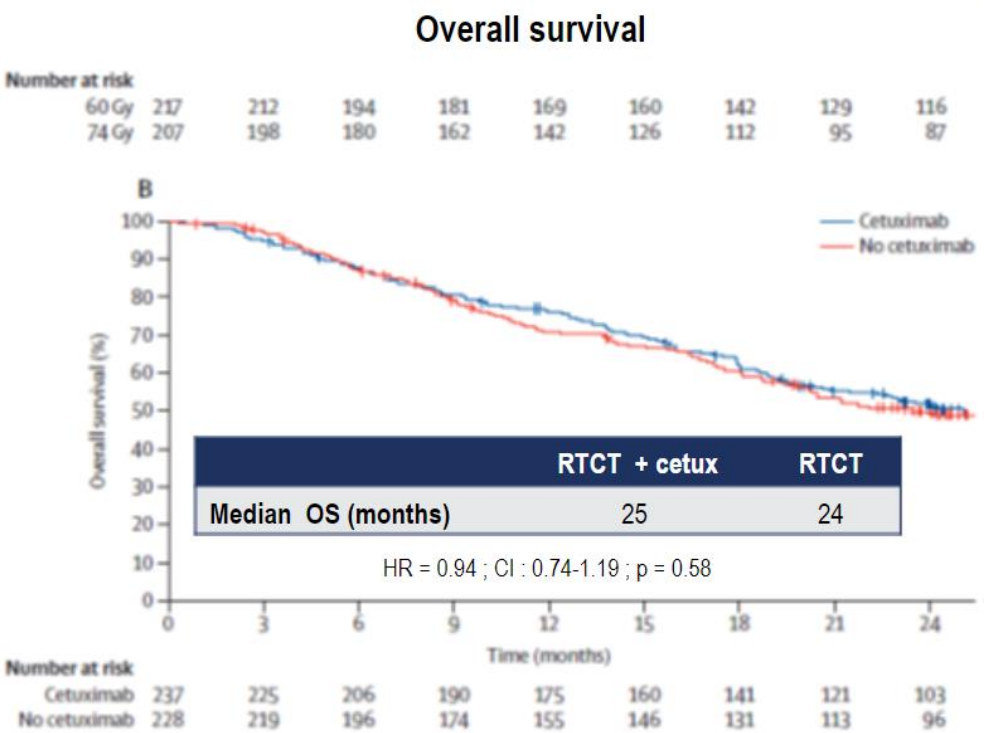
- PS 0 *versus* 1
- 3D-RT *versus* IMRT
- PET *versus* no PET
- Squamous *versus* non-squamous

***CT-RT**
Carboplatin AUC=2 + paclitaxel 45 mg/m²/week. (6 à 7 weeks)
Cetuximab 400 mg/m² initial dose then 250 mg/m²/week.

****Consolidation CT**
Carboplatin AUC=6 + paclitaxel 200 mg/m² (2 cycles)
Cetuximab 250 mg/m²/week

Bradley JD, *et al.*, Lancet Oncol 2015;16(2):187–99.

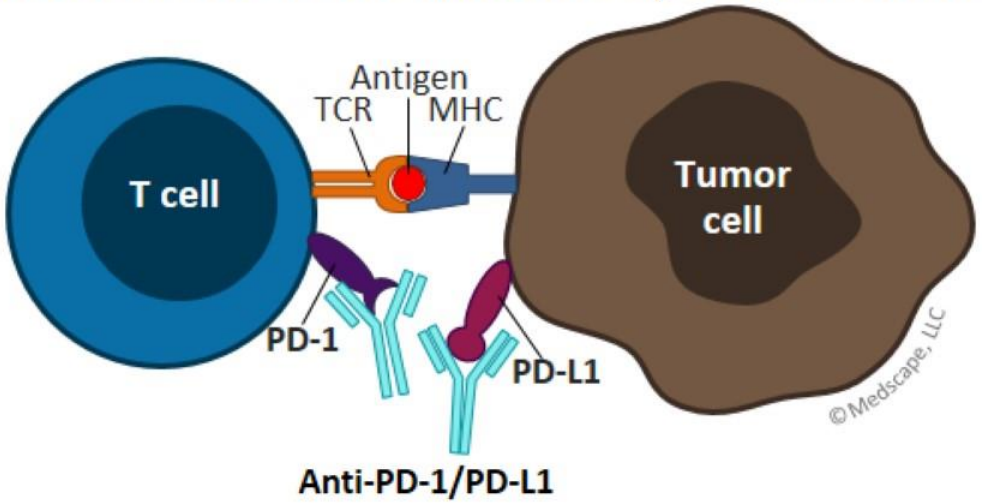
RTOG 06-17 Trial



- Addition of cetuximab to concurrent CT-RT and consolidation treatment provided no benefit survival in stage III unresectable NSCLC

Rationale for Immunotherapy After CRT

- SoC for locally advanced disease is inadequate
- Potential for neoantigen production with CRT
- Neoantigens are recognized as foreign leading to T-cell infiltration
- ... but the T cells are unable to eradicate the tumor because of checkpoint proteins that interfere with cytotoxic T-cell response (eg, PD-1/PD-L1)
- Checkpoint inhibitors allow the immune system to attack cancer cells



Chen HHW, et al. *Oncotarget.* 2017;8:62742-62758.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 16, 2017 VOL. 377 NO. 20

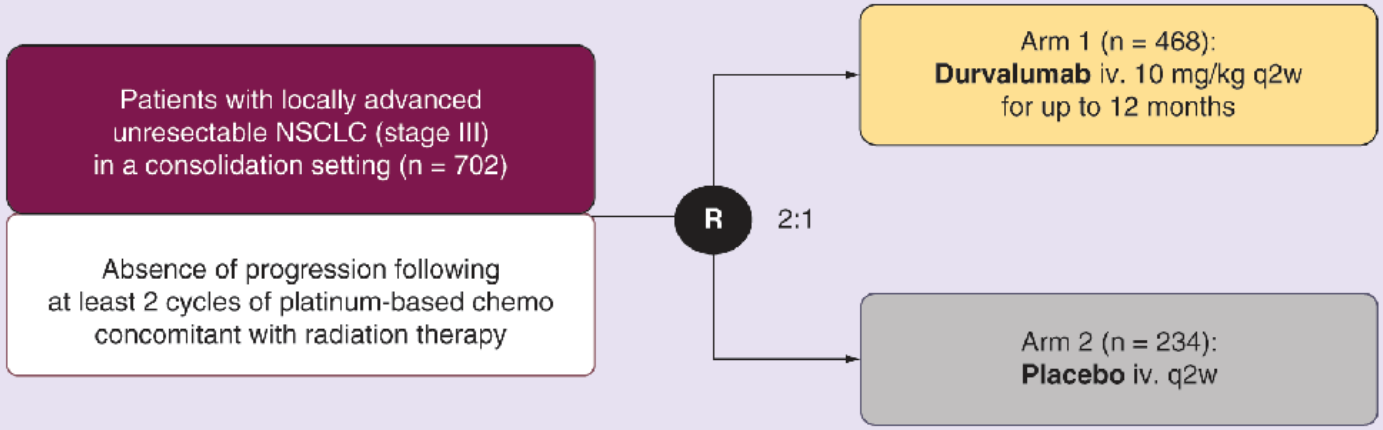
Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

PACIFIC trial: Study design

NCT02125461

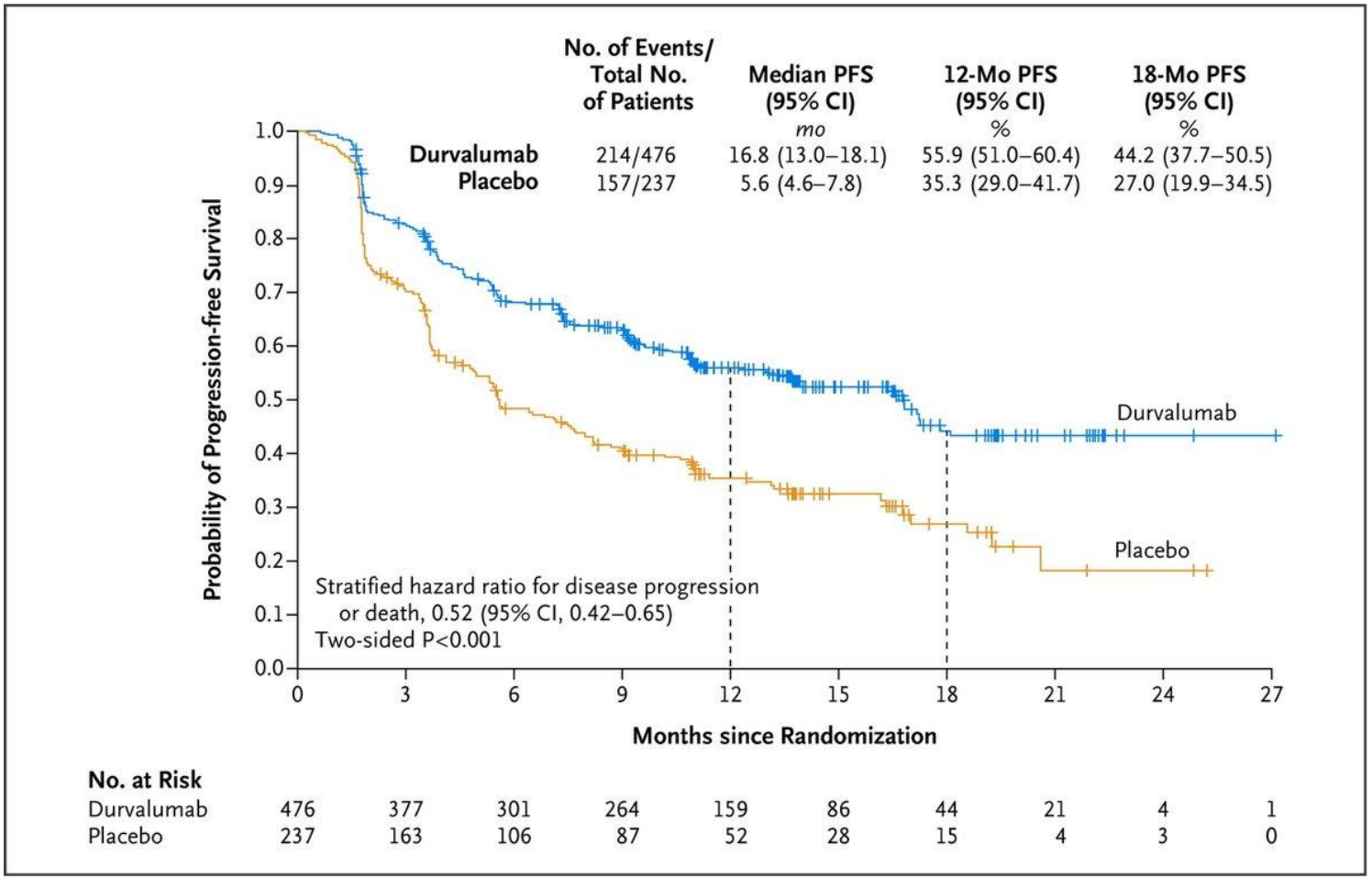
- Phase III, randomized, double-blind, placebo-controlled, multicenter, global study (26 countries)



Primary endpoints
- PFS, OS

Secondary endpoints
- ORR, DoR, DSR
- Safety/tolerability
- PK, immunogenicity, QoL

Results:PFS



PFS was significantly longer with durvalumab than with placebo
(Median PFS: 16.8 mo with durvalumab and 5.6 mo with placebo)

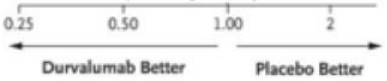
Antonia SJ, et al. *N Engl J Med*. 2017;377:1919-1929.

PACIFIC Trial

Subgroup Analysis of Prognostic Factors for PFS

PFS Subgroup Analysis in the ITT Population

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	476	237	0.55 (0.45–0.68)
Sex			
Male	334	166	0.56 (0.44–0.71)
Female	142	71	0.54 (0.37–0.79)
Age at randomization			
<65 yr	261	130	0.43 (0.32–0.57)
≥65 yr	215	107	0.74 (0.54–1.01)
Smoking status			
Smoker	433	216	0.59 (0.47–0.73)
Nonsmoker	43	21	0.29 (0.15–0.57)
NSCLC disease stage			
IIIA	252	125	0.53 (0.40–0.71)
IIIB	212	107	0.59 (0.44–0.80)
Tumor histologic type			
Squamous	224	102	0.68 (0.50–0.92)
Nonsquamous	252	135	0.45 (0.33–0.59)
Best response			
Complete response	9	7	—
Partial response	232	111	0.55 (0.41–0.75)
Stable disease	222	114	0.55 (0.41–0.74)
PD-L1 status			
≥25%	115	44	0.41 (0.26–0.65)
<25%	187	105	0.59 (0.43–0.82)
Unknown	174	88	0.59 (0.42–0.83)
EGFR mutation			
Positive	29	14	0.76 (0.35–1.64)
Negative	315	165	0.47 (0.36–0.60)
Unknown	132	58	0.79 (0.52–1.20)



From N Engl J Med., Antonia SJ, et al., Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer, 377, 1919-1929 Copyright 2017. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

PFS benefit with durvalumab was consistently observed across all subgroups, including nonsmokers, and irrespective of PD-L1 expression before CRT

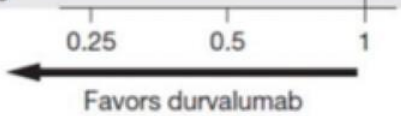
Antonia SJ, et al. *N Engl J Med*. 2017;377:1919-1929.

PACIFIC Trial

Rationale for Performing Scan Immediately After CRT

PFS* Subgroup Analysis of Additional Factors in the ITT Population

	Durvalumab No. of patients	Placebo No. of patients	Unstratified hazard ratio† (95% CI)
Type of chemotherapy gemcitabine-based	9	5	–
Type of chemotherapy non-gemcitabine-based	467	232	0.55 (0.45–0.68)
Cisplatin	266	129	0.51 (0.39–0.68)
Carboplatin	199	102	0.61 (0.44–0.83)
Cisplatin and carboplatin	8	5	–
Last radiation to randomization <14 days	120	62	0.39 (0.26–0.58)
Last radiation to randomization ≥14 days	356	175	0.63 (0.49–0.80)
Normal WHO performance status	234	114	0.56 (0.41–0.75)
Restricted WHO performance status	242	123	0.53 (0.40–0.71)
Asia	109	68	0.51 (0.34–0.77)
Europe	217	102	0.62 (0.46–0.84)
North America and South America	150	67	0.49 (0.33–0.73)
White	337	157	0.58 (0.45–0.75)
Black/African-American	12	2	–
Asian	120	72	0.48 (0.32–0.72)
Other	6	6	–



Subgroup analysis indicates that patients treated with durvalumab sooner (last radiation to randomization < 14 d) had a much better HR for improvement in PFS

*Defined by RECIST v1.1.
†Hazard ratio and 95% CI is not calculated if the subgroup level has less than 20 events.
Antonia SJ, et al. *N Engl J Med*. 2017;377:1919-1929.

PACIFIC Trial
Metastases in the ITT Population

Incidence of New Lesions in the ITT Population*

New lesion site†	Durvalumab (N=476)	Placebo (N=237)
	number of patients (percent)	
Any new lesion	97 (20.4)	76 (32.1)
Lung	56 (11.8)	41 (17.3)
Lymph nodes	27 (5.7)	27 (11.4)
Brain	26 (5.5)	26 (11.0)
Liver	9 (1.9)	8 (3.4)
Bone	8 (1.7)	6 (2.5)
Adrenal	3 (0.6)	5 (2.1)
Other	9 (1.9)	5 (2.1)

*According to RECIST v1.1.
†A patient may have had more than one new lesion site.
BICR, Blinded Independent Central Review; RECIST, Response Evaluation Criteria In Solid Tumors.

Patients treated with durvalumab had a lower rate of metastases, including to the brain

*According to RECIST v1.1.
†A patient may have had more than one new lesion site.
Antonia SJ, et al. *N Engl J Med*. 2017;377:1919-1929.

PACIFIC Trial
Safety Profile

Adverse Events of any Cause[a]

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

From N Engl J Med., Antonia SJ, et al., Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer, 377, 1919-1929 Copyright 2017. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

- Pneumonitis rate was not as expected[a]
  - Not very frequent
  - No difference between durvalumab and placebo arms
- Durvalumab is very well tolerated in general[a]
- QoL was not worsened with the addition of durvalumab[b]

*Events reported in at least 10% of either group.
†Pneumonitis is a grouped term and was assessed by investigators with subsequent review and adjudication by the study sponsor.
a. Antonia SJ, et al. *N Engl J Med*. 2017;377:1919-1929; b. Hui R, et al. IASLC WCLC 2017. Abstract PL 02.02.

Metastatic Disease

Targeted agents in NSCLC

NSCLC: frequency of mutations and availability of targeted agents

Gene	Alteration	Frequency in NSCLC (%)
AKT1	Mutation	1
ALK	Rearrangement	3–7
BRAF	Mutation	1–3
DDR2	Mutation	~ 4
EGFR	Mutation	10–35
FGFR1	Amplification	20
HER2	Mutation	2–4
KRAS	Mutation	15–25
MEK1	Mutation	1
MET	Amplification	2–4
NRAS	Mutation	1
NTRK	Rearrangement	1
PIK3CA	Mutation	1–3
PTEN	Mutation	4–8
RET	Rearrangement	1
ROS1	Rearrangement	1

Key

- Drugs approved in NSCLC
- Drugs approved in NSCLC, but for other molecular subtype
- Drugs approved in other cancer
- Drugs in clinical development

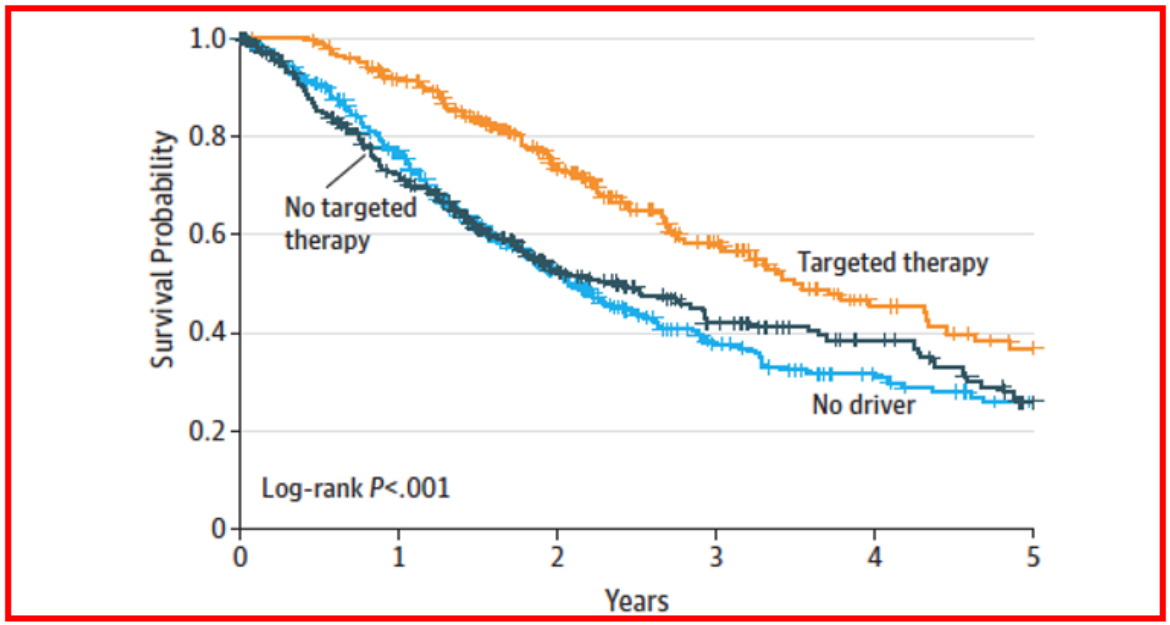
http://www.mycancergenome.org/content/disease/lung-cancer.

Targeted Therapy

Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs

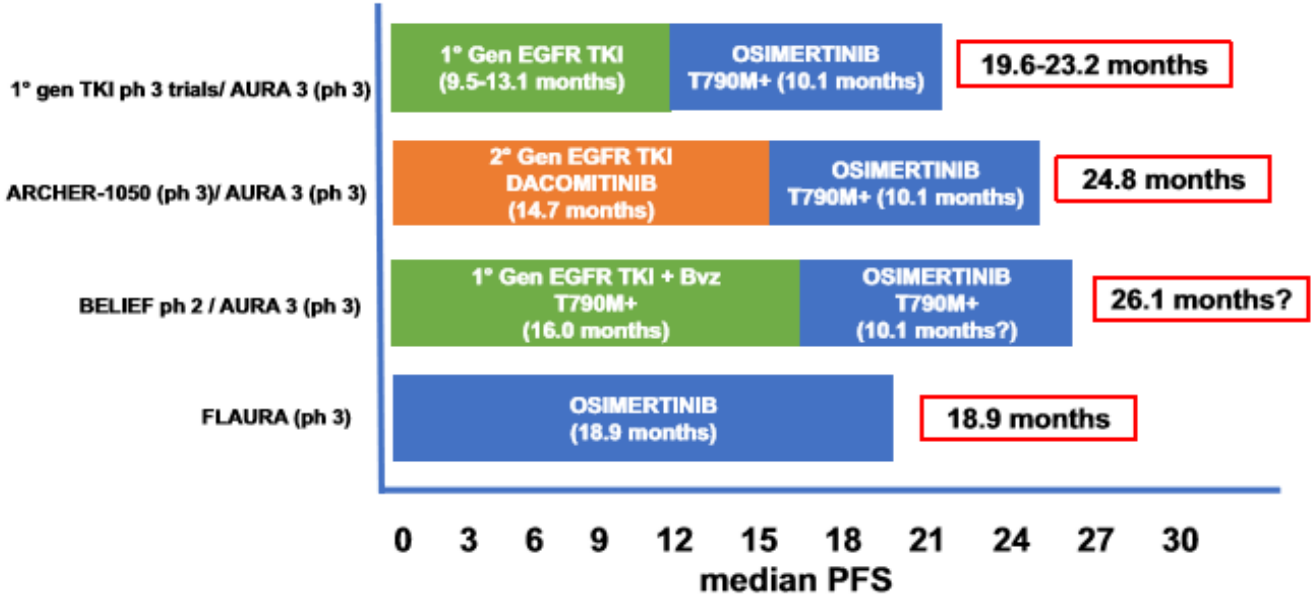
Mark G. Kris, MD; Bruce E. Johnson, MD; Lynne D. Berry, PhD; David J. Kwiatkowski, MD; A. John Iafrate, MD; Ignacio I. Wistuba, MD; Marileila Varella-Garcia, PhD; Wilbur A. Franklin, MD; Samuel L. Aronson, ALM, MA; Pei-Fang Su, PhD; Yu Shyr, PhD; D. Ross Camidge, MD, PhD; Lecia V. Sequist, MD; Bonnie S. Glisson, MD; Fadlo R. Khuri, MD; Edward B. Garon, MD; William Pao, MD, PhD; Charles Rudin, MD, PhD; Joan Schiller, MD; Eric B. Haura, MD; Mark Socinski, MD; Keisuke Shirai, MD; Heidi Chen, PhD; Giuseppe Giaccone, MD; Marc Ladanyi, MD; Kelly Kugler, BA; John D. Minna, MD; Paul A. Bunn, MD

JAMA The Journal of the American Medical Association



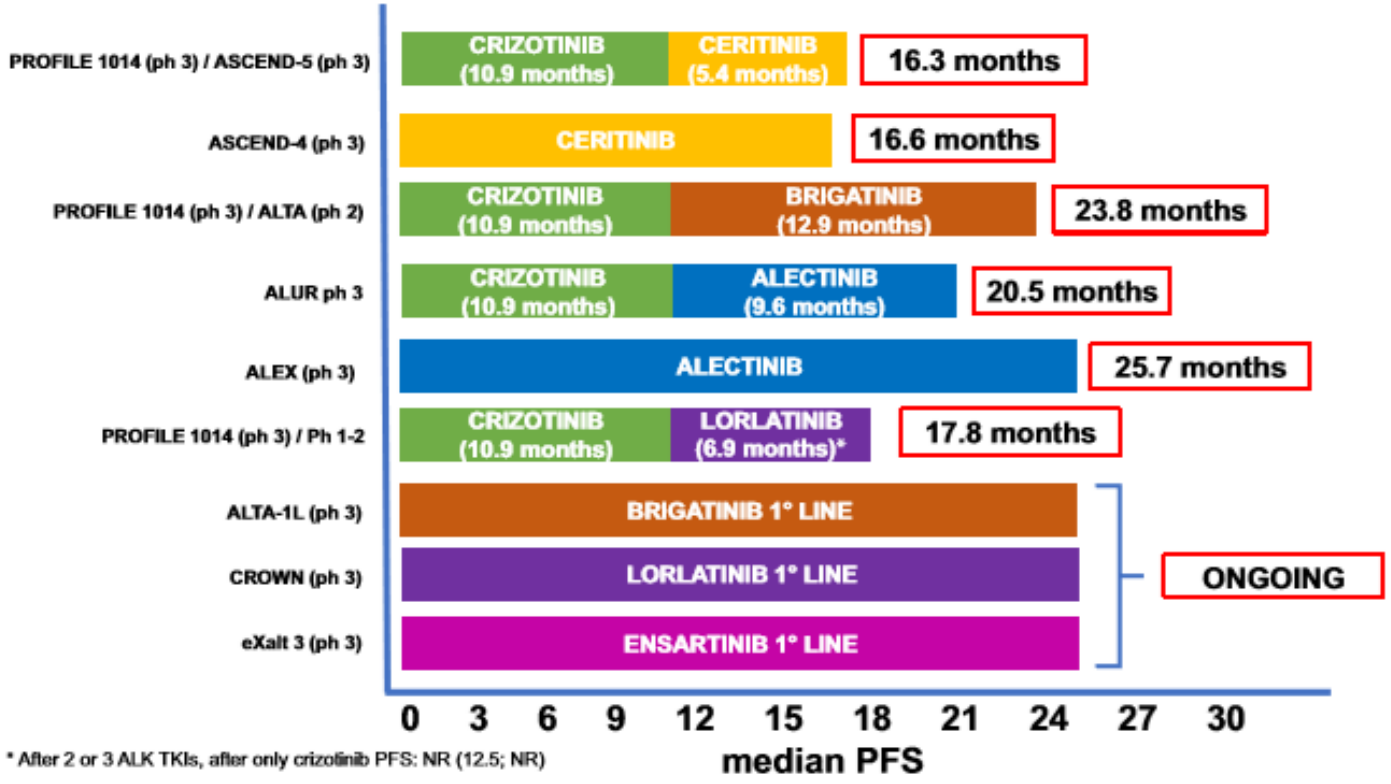
JAMA2014; 311(19)

TKIs in EGFR-mutated NSCLC



Ferrara et al, JTO, 2017

PFS with 1st and next-generation ALK-TKIs



* After 2 or 3 ALK TKIs, after only crizotinib PFS: NR (12.5; NR)

Facts: death rates falling

- Death rates due to cancer fell by only 8% between 1950 and 2012.
- By ⇩ 67% in the case of heart disease
- By ⇩ 77% for cerebrovascular diseases
- By ⇩ 66% for pneumonia and influenza.

Filipovich A. Cancer World 2017

Immunotherapy

Immunity against cancer

Theory of immune surveillance in tumor immunology

The immune system recognizes tumor Ag as "foreign" and rejects emerging cancer cells continuously

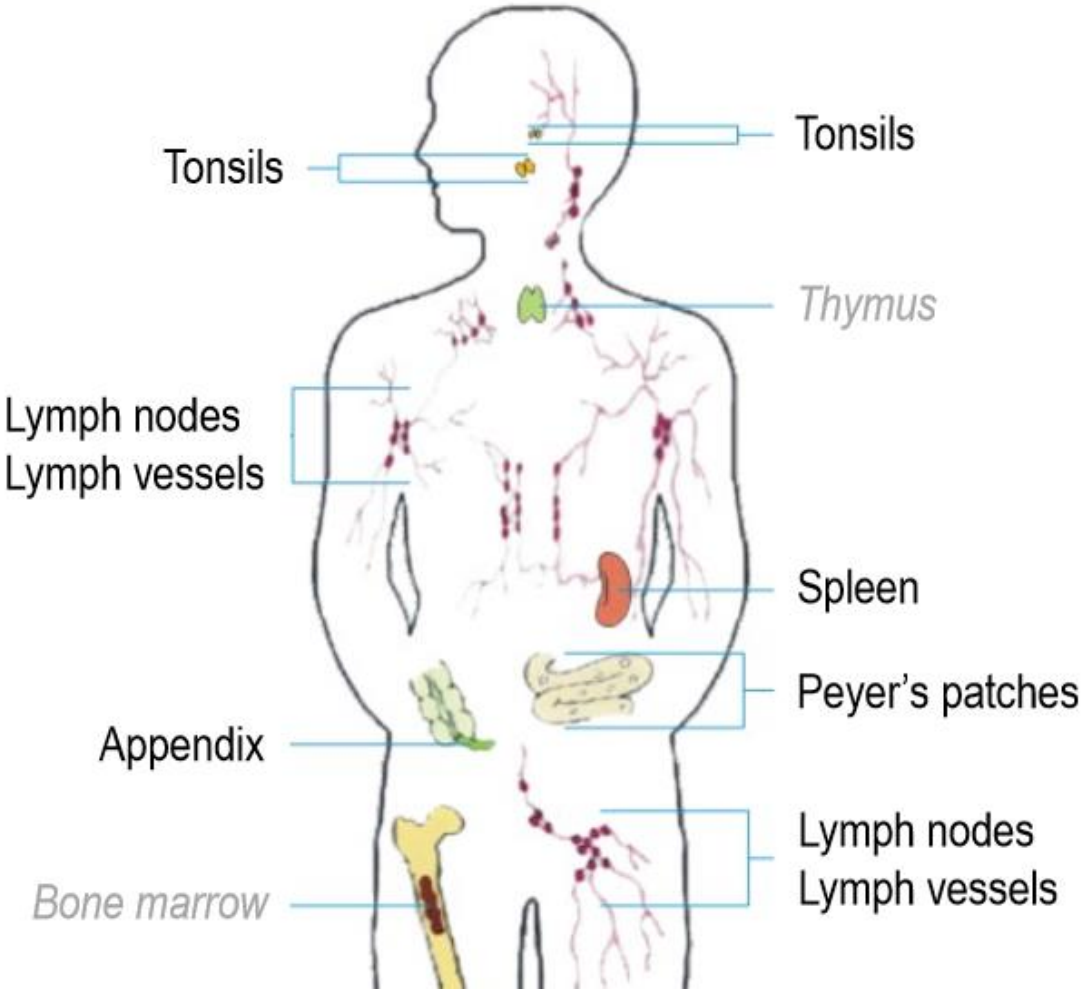
Macfarlane Burnet

"Cancer develops if an Imbalance between host immune response and the tumor environment occurs"

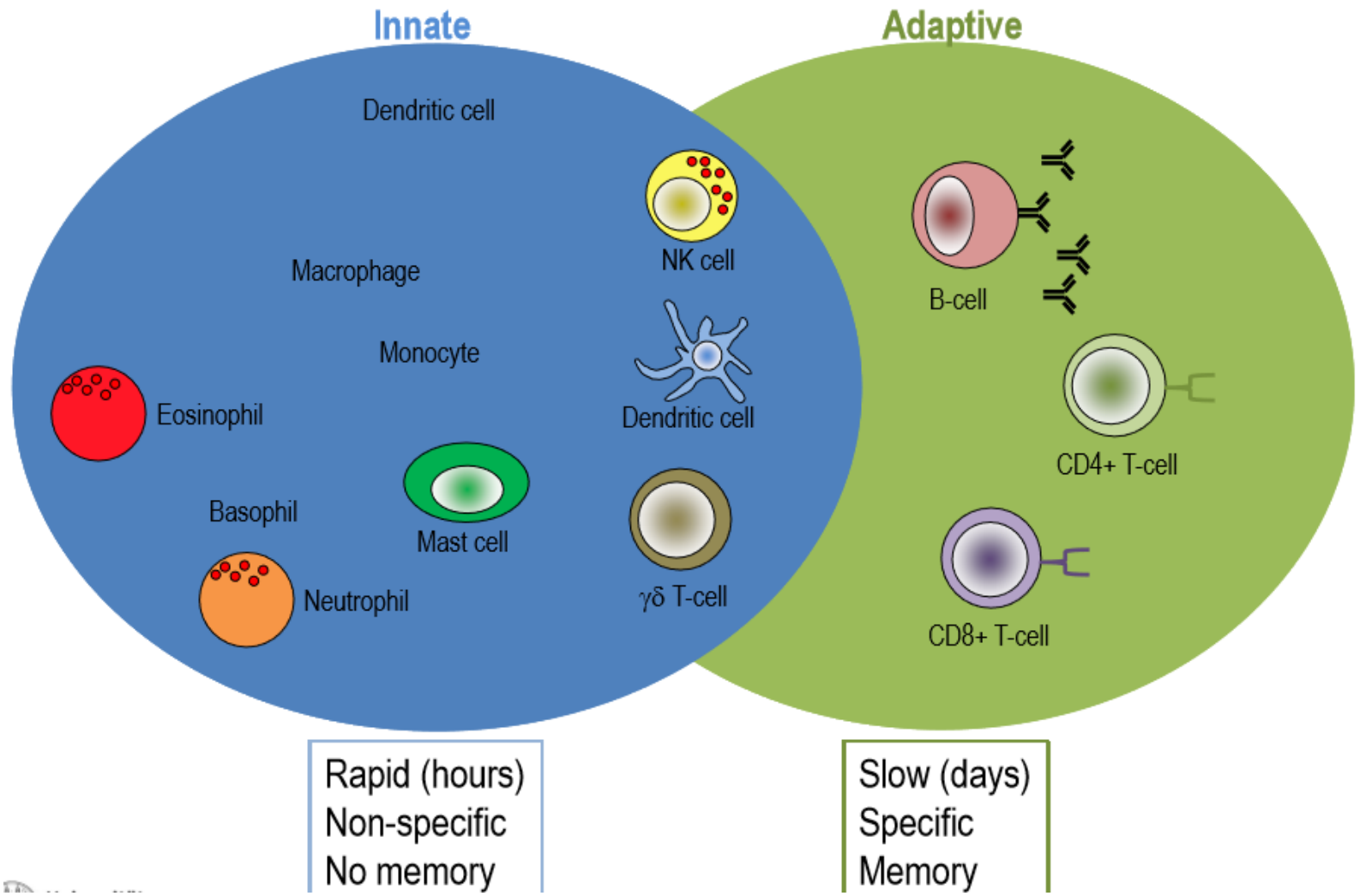
Br. Med. J. 1957

The vertebrate immune system

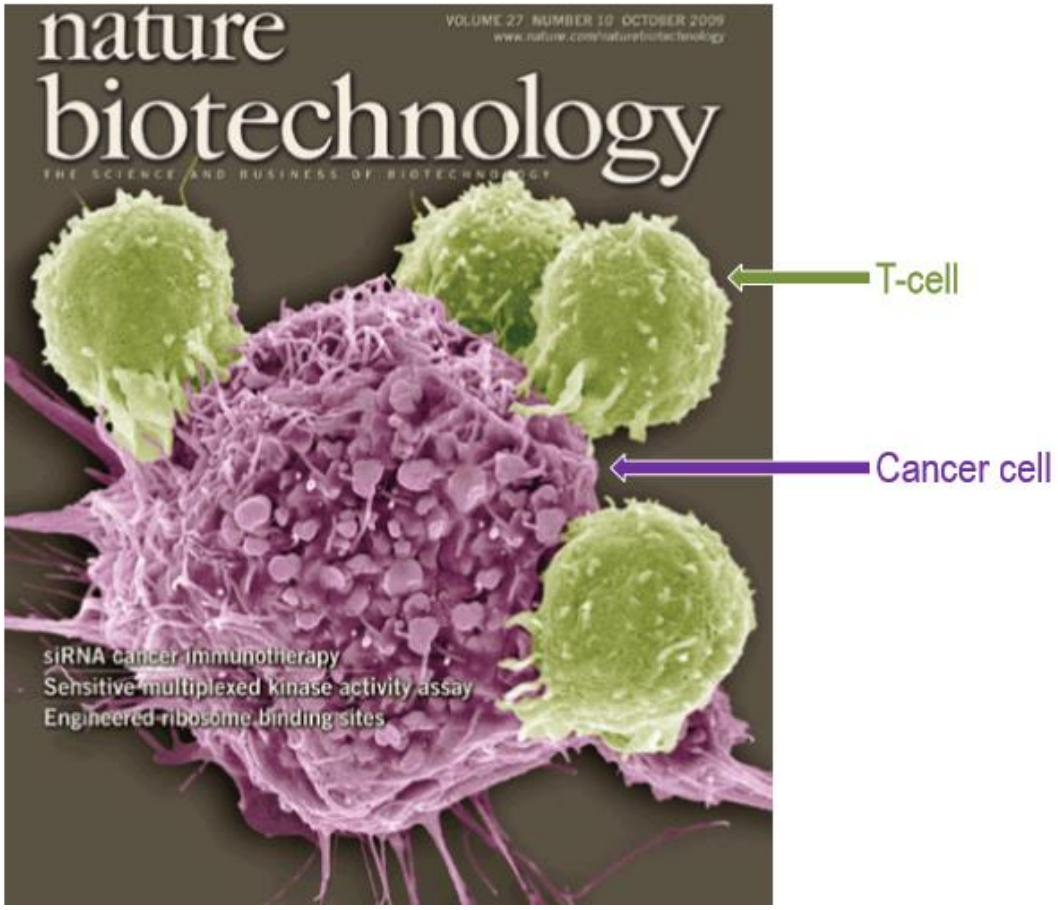
Primary LO
Secondary LO



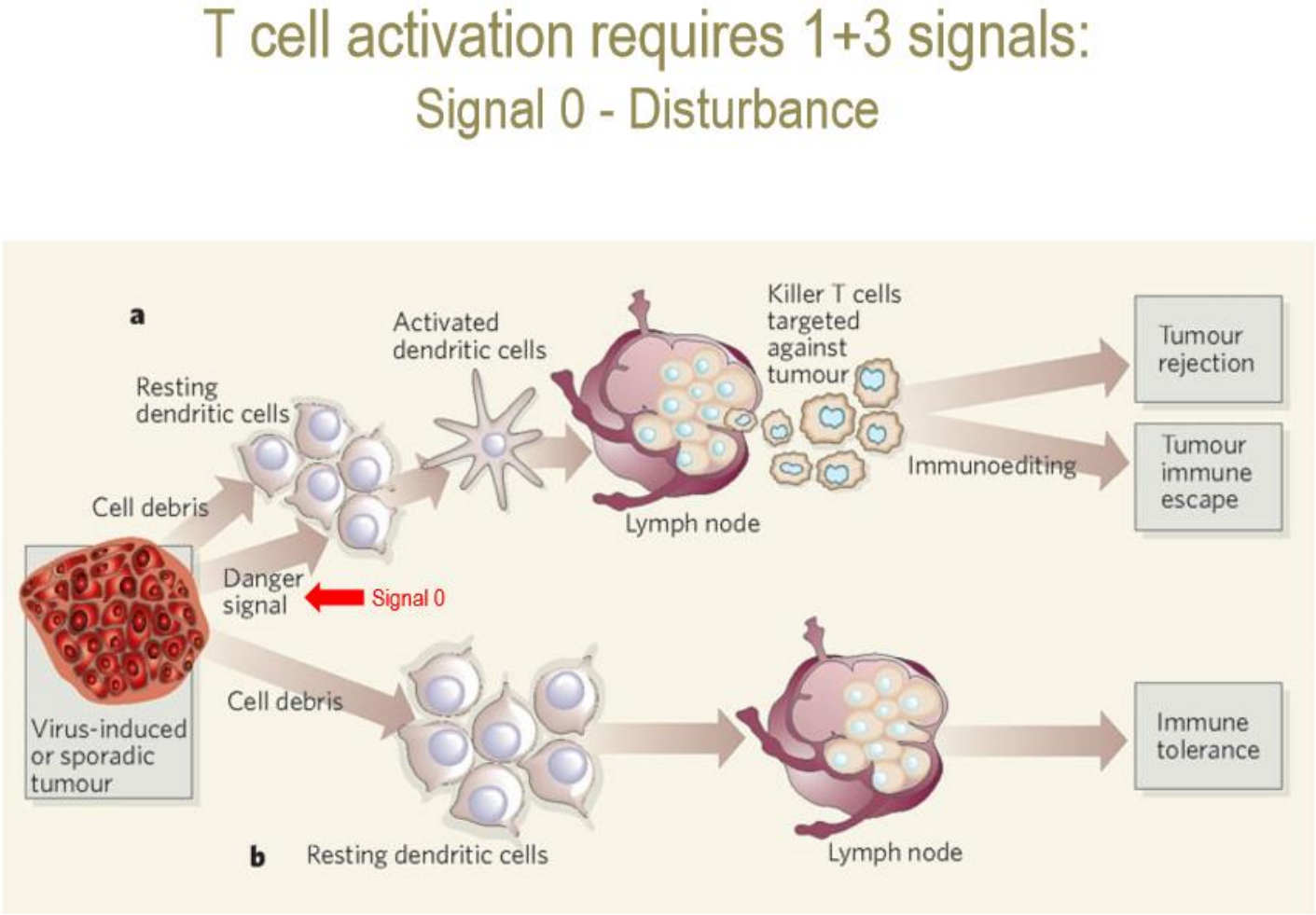
Innate and Adaptive immune systems



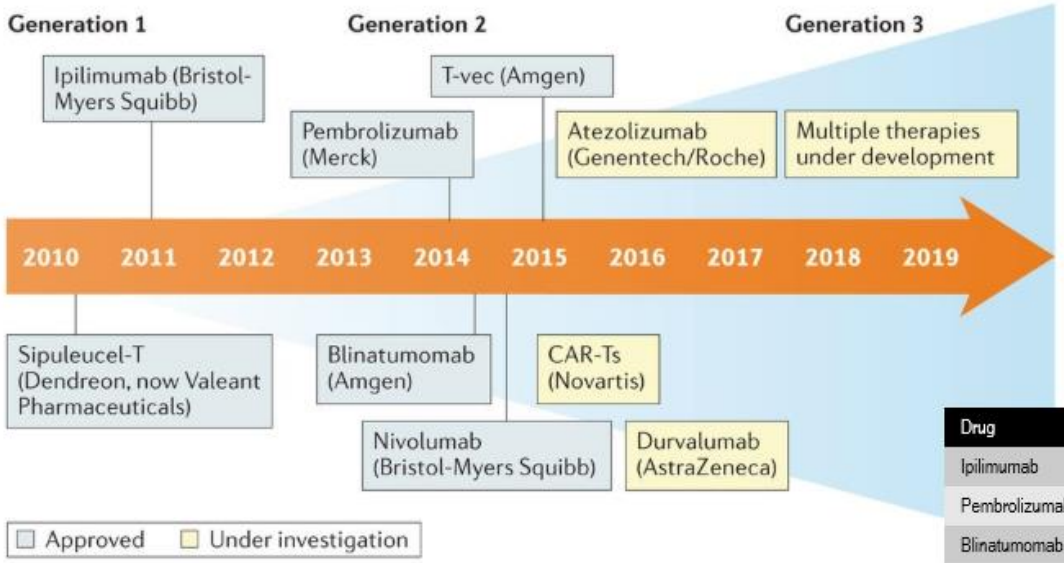
T-cells are essential to immunological control of cancer



T-cell activation requires 1+3 signals

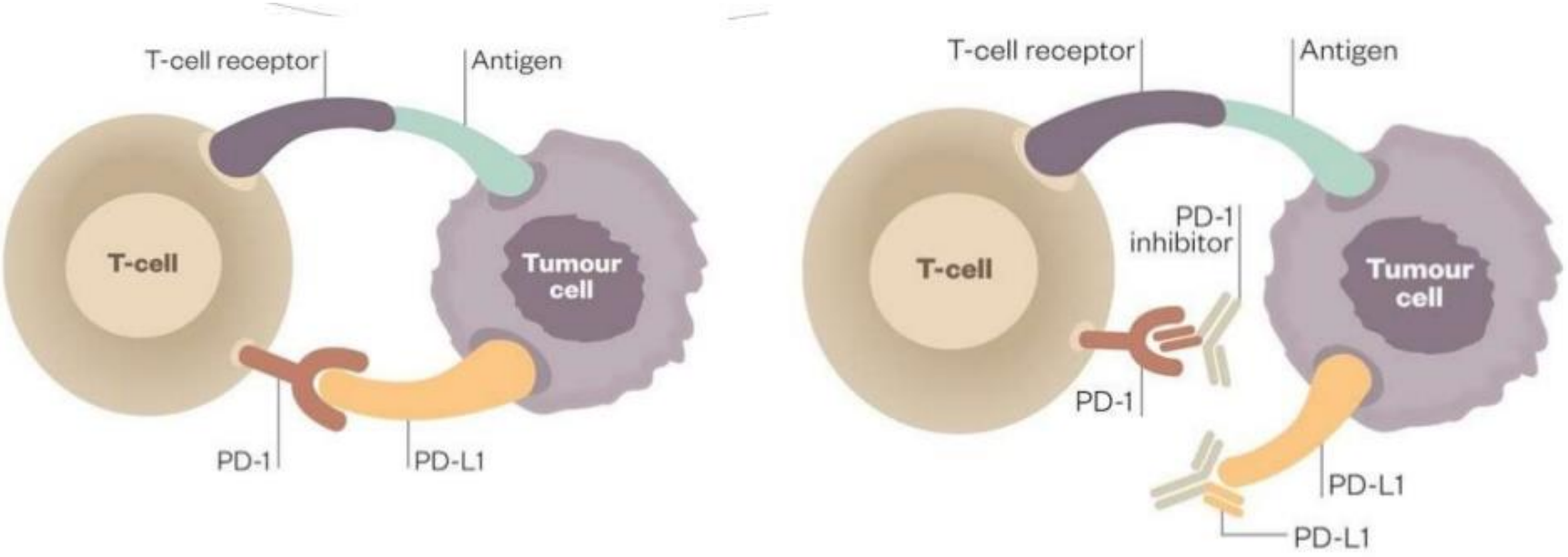


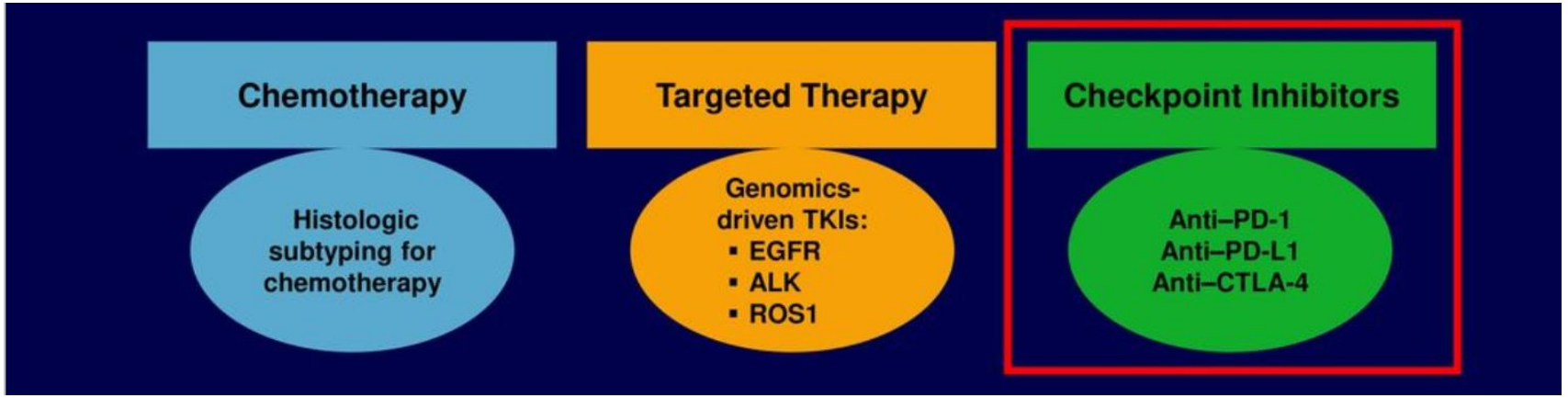
Timeline of cancer immunotherapy



Drug	Active component
Ipilimumab	Anti-CTLA-4
Pembrolizumab	Anti-PD-1
Blinatumomab	Bispecific anti-CD3/CD19
Nivolumab	Anti-PD-1
Atezolizumab	Anti-PD-L1
Durvalumab	Anti-PD-L1
Sipuleucel-T	Autologous DCs producing PAP and GM-CSF
T-vec	Talimogen laherparepvec, oncolytic attenuated and engineered HSV-1 (GM-CSF)
CAR-T	Genetically engineered autologous T cells

Checkpoint Inhibitors





IMMUNOTHERAPY

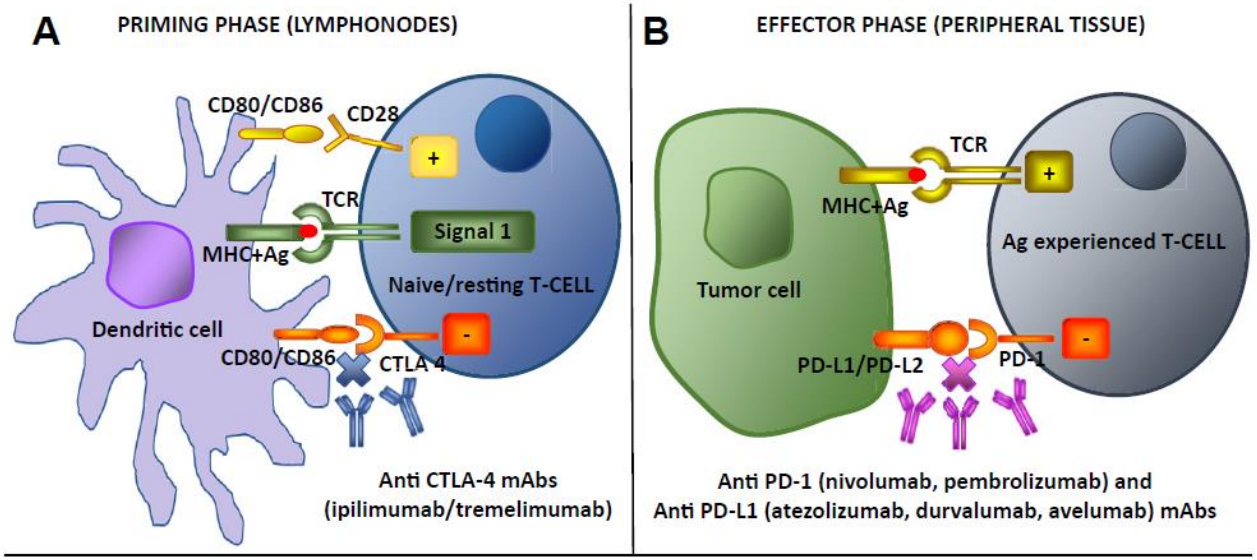


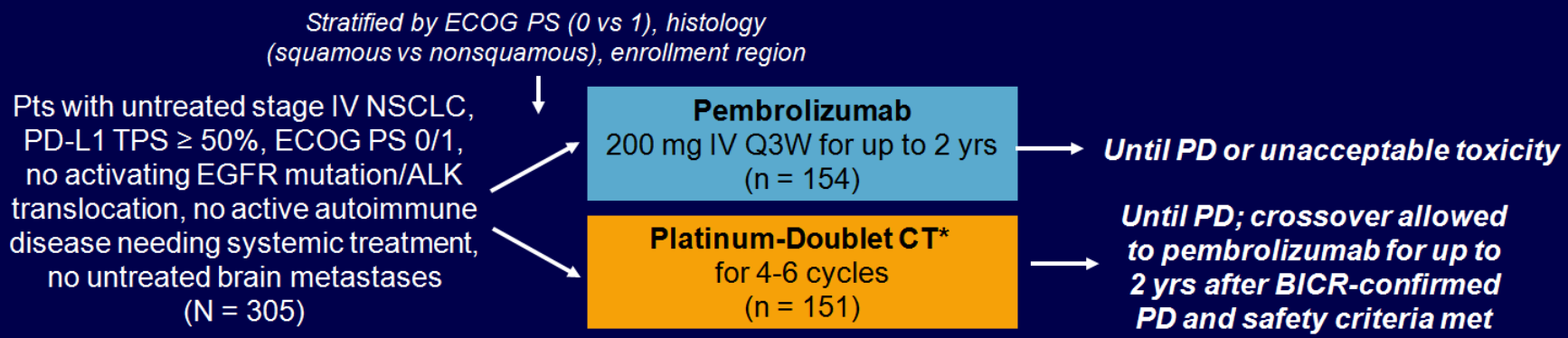
Figure 1. Mechanisms of action of cytotoxic T-lymphocyte associated protein 4 (CTLA4) (*A*) and programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) (*B*) inhibitors in different phases of the anticancer immune response. MHC, major histocompatibility complex; Ag, antigen; mAb, monoclonal antibody; TCR, T-cell receptor; PD-L2, programmed death ligand 2.

Update in the treatment of lung cancer

'End of an Era' for Chemo in Non-Small Cell Lung Cancer ?

KEYNOTE-024: Study Design

- Randomized, open-label phase III trial



*Investigator's choice of: pem + carb; pem + cis; pac + carb; gem + carb; gem + cis. Pem-containing regimens only for nonsquamous histology; these pts could receive pem maintenance treatment.

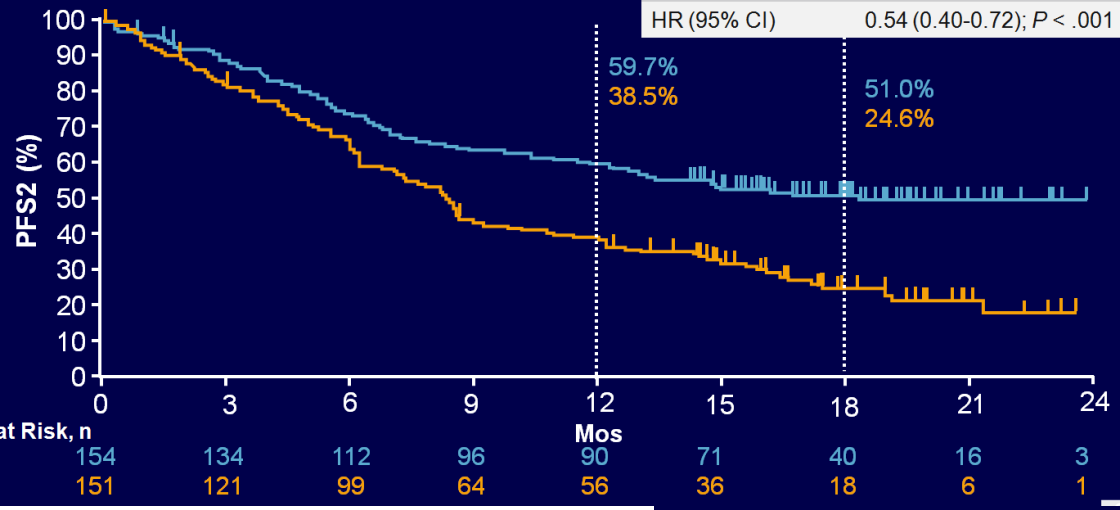
- Primary analysis endpoints (median f/u: 11.2 mos)
  - Primary: PFS per RECIST v1.1 (BICR)
  - Secondary: OS, ORR, safety

Brahmer JR, et al. ASCO2017

KEYNOTE-024: PFS and OS

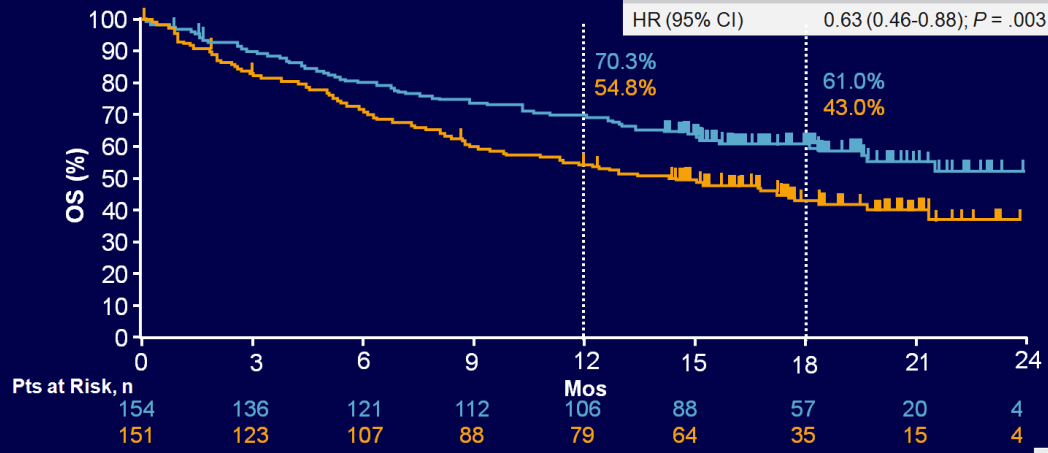
KEYNOTE-024: PFS2

	Pembrolizumab (n = 154)	Chemotherapy (n = 151)
Median PFS2 (95% CI), mos	18.3 (12.7-NE)	8.4 (6.8-9.8)
HR (95% CI)	0.54 (0.40-0.72); *P* < .001	



KEYNOTE-024: OS

	Pembrolizumab (n = 154)	Chemotherapy (n = 151)
Median OS (95% CI), mos	NR (19.4-NE)	14.5 (9.8-19.6)
HR (95% CI)	0.63 (0.46-0.88); *P* = .003	



Brahmer JR, et al. ASCO 2017. Abstract 9000. Reproduced with permission.

Slide credit: clinicaloptions.com

Conclusions

- Investigators concluded that first-line pembrolizumab should be standard of care for NSCLC pts with tumors having PD-L1 TPS ≥ 50% due to prolonged survival and improved safety profile vs platinum-doublet chemotherapy

ASCO 2018

KEYNOTE-042: First-line Pembrolizumab vs Platinum-Based Chemotherapy for Advanced or Metastatic NSCLC With PD-L1 TPS ≥ 1%

CCO Independent Conference Highlights*
of the *2018 ASCO Annual Meeting; June 1-5, 2018; Chicago, Illinois*

*CCO is an independent medical education company that provides state-of-the-art medical information to healthcare professionals through conference coverage and other educational programs.

This activity is supported by educational grants from Amgen; Astellas; AstraZeneca; Celgene Corporation; Eisai; Genentech; Janssen; Merck & Co., Inc.; and Seattle Genetics.

CLINICAL CARE OPTIONS®
ONCOLOGY

First-line Pembrolizumab vs CT in Advanced NSCLC With PD-L1 ≥ 1% (KEYNOTE-042): Background

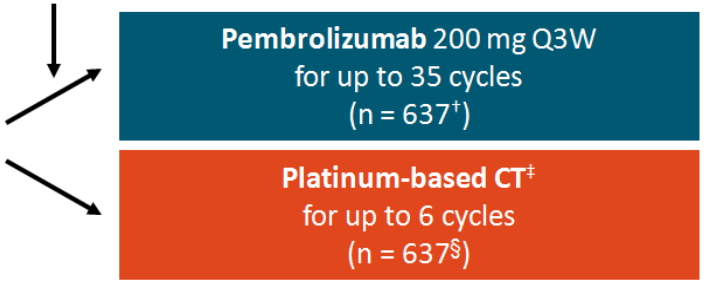
- Pembrolizumab is a SoC option for both untreated and previously untreated advanced or metastatic NSCLC[1]
  - KEYNOTE-010: pembrolizumab monotherapy significantly improved OS vs docetaxel in advanced NSCLC patients with PD-L1 TPS ≥ 1% who progressed on platinum-containing CT[2]
  - KEYNOTE-024: pembrolizumab monotherapy significantly improved PFS and OS, as well as had a better safety profile, vs platinum-based CT in previously untreated metastatic NSCLC with no sensitizing *EGFR/ALK* alterations and with PD-L1 TPS ≥ 50%[3]
  - KEYNOTE-189 and KEYNOTE-407: pembrolizumab combined with CT significantly improved survival outcomes vs CT alone in previously untreated metastatic NSCLC (nonsquamous and squamous, respectively) regardless of PD-L1 expression[4,5]
- Current planned interim analysis of KEYNOTE-042 trial evaluated efficacy, safety of first-line pembrolizumab monotherapy vs platinum-based CT in patients with NSCLC and PD-L1 TPS ≥ 1%[6]

KEYNOTE-042: Study Design

- Randomized, open-label phase III trial
  - Current second interim analysis at 38.3 mos after first patient enrolled; data cutoff: February 26, 2018

Stratified by region (East Asia vs rest of world), ECOG PS (0 vs 1), histology (squamous vs nonsquamous), PD-L1 TPS (≥ 50% vs 1% to 49%)

Patients with untreated locally advanced or metastatic NSCLC, PD-L1 TPS ≥ 1%*, no *EGFR* or *ALK* alterations, ECOG PS 0/1, no unstable or untreated CNS metastases, no prior pneumonitis requiring systemic corticosteroids (N = 1274)



*PD-L1 22C3 pharmDx IHC assay. †n = 636 treated. ‡Carboplatin AUC 5 or 6 Q3W + either paclitaxel 200 mg/m^2 Q3W or pemetrexed 500 mg/m^2 Q3W. Pemetrexed maintenance therapy permitted and highly encouraged for patients with nonsquamous histology (52.3% received). §n = 615 treated.

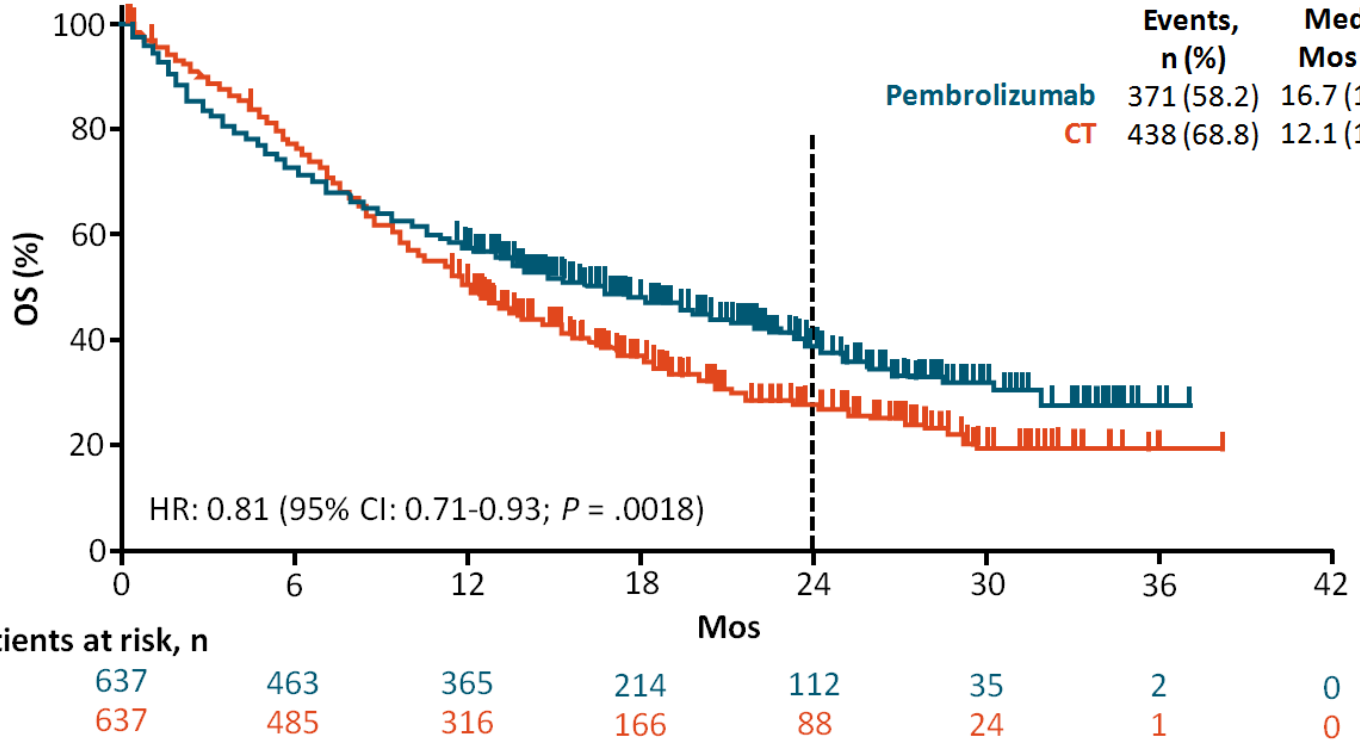
- Primary endpoints: OS in PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1% (overall) populations
  - Study has 91% power with 1-sided α = 0.025 to demonstrate piecewise HR of 0.92 (pre-Mo 6) and 0.73 (post-Mo 6) with 900 deaths/1240 patients in PD-L1 TPS ≥ 1% population
- Secondary endpoints: PFS, ORR (per RECIST v1.1) in PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1% (overall) populations; safety in PD-L1 TPS ≥ 1% (overall) population

Lopes G, et al. ASCO 2018. Abstract LBA4.

Slide credit: clinicaloptions.com

Overall Survival

KEYNOTE-042: OS in PD-L1 TPS ≥ 1% Population (Primary Endpoint)



	Events, n (%)	Median OS, Mos (95% CI)	24-Mo OS, %
Pembrolizumab	371 (58.2)	16.7 (13.9-19.7)	39.3
CT	438 (68.8)	12.1 (11.3-13.3)	28.0

Patients at risk, n

637	463	365	214	112	35	2	0
637	485	316	166	88	24	1	0

Lopes G, et al. ASCO 2018. Abstract LBA4. Reproduced with permission.

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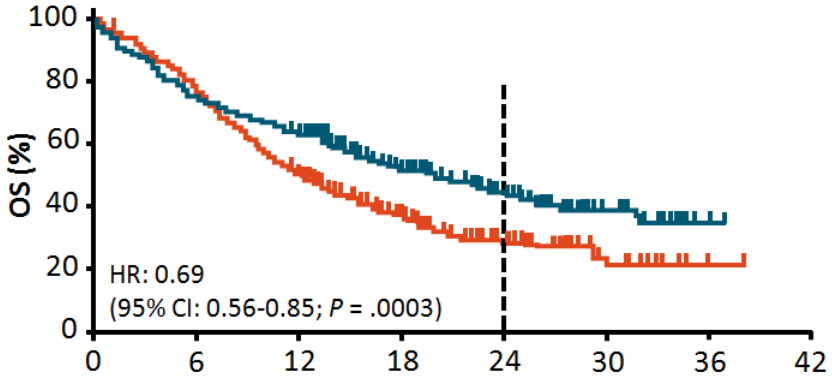
Overall Survival

KEYNOTE-042: OS in PD-L1 TPS ≥ 50% and ≥ 20% Populations (Primary Endpoint)

PD-L1 TPS ≥ 50%

	Events, n (%)	Median OS, Mos (95% CI)	24-Mo OS, %
Pembrolizumab	157 (52.5)	20.0 (15.4-24.9)	44.7
CT	199 (66.3)	12.2 (10.4-14.2)	30.1

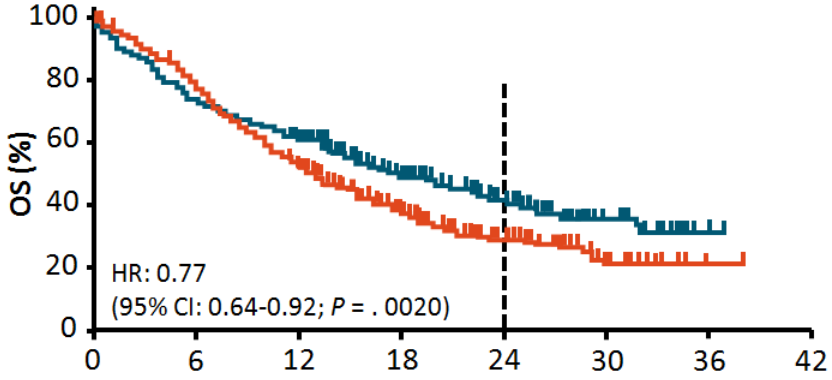


Patients at risk, n

299	224	189	107	59	22	2	0
300	231	149	75	40	11	1	0

PD-L1 TPS ≥ 20%

	Events, n (%)	Median OS, Mos (95% CI)	24-Mo OS, %
Pembrolizumab	230 (55.7)	17.7 (15.3-22.1)	40.5
CT	266 (65.7)	13.0 (11.6-15.3)	29.6



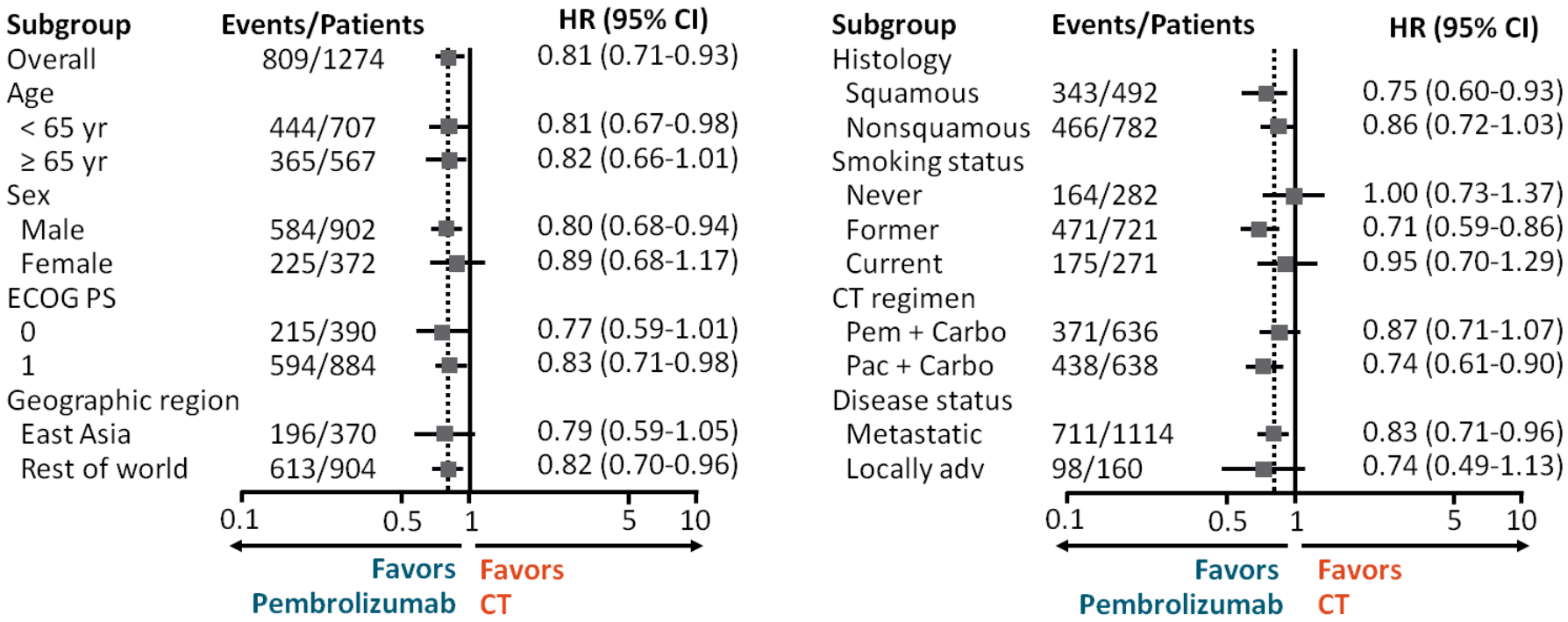
Patients at risk, n

413	305	251	144	73	24	2	0
405	313	210	106	53	14	1	0

Lopes G, et al. ASCO 2018. Abstract LBA4. Reproduced with permission.

Slide credit: clinicaloptions.com

KEYNOTE-042: OS in Subgroups of PD-L1 TPS >1% Population



Dotted vertical line represents the HR in the total population.

Lopes G, et al. ASCO 2018. Abstract LBA4. Reproduced with permission.

Slide credit: clinicaloptions.com

KEYNOTE-042: Safety in All Treated Patients

Safety Parameter	Pembrolizumab (n = 636)	CT (n = 615)
Median no. doses (range)	9 (1-36)	6 (1-42)
Treatment-related AEs, n (%)	399 (62.7)	553 (89.9)
▪ Grade 3-5	113 (17.8)	252 (41.0)
▪ Leading to death	13 (2.0)	14 (2.3)
▪ Leading to discontinuation	57 (9.0)	58 (9.4)
Immune-mediated AEs and infusion reactions, n (%)	177 (27.8)	44 (7.2)
▪ Grade 3-5	51 (8.0)	9 (1.5)
▪ Leading to death	1 (0.2)*	0

*Pneumonitis.

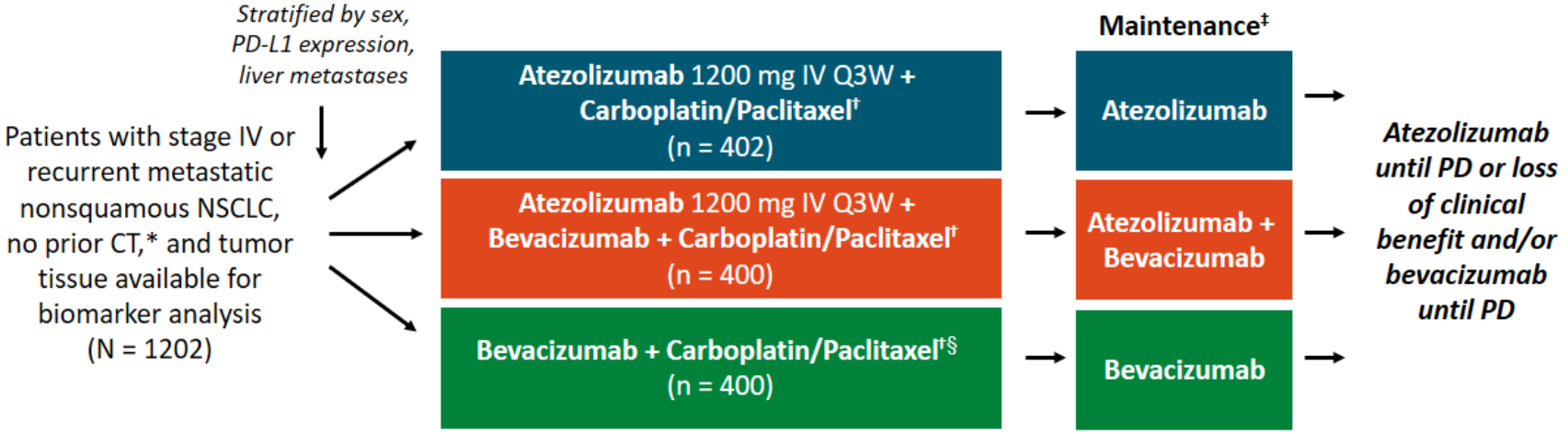
KEYNOTE-042: Conclusions

- In patients with advanced or metastatic NSCLC without *EGFR/ALK* alterations and with PD-L1 TPS ≥ 1%, first-line pembrolizumab significantly improved OS vs platinum-based CT
  - HR: 0.81 (95% CI: 0.71-0.93; *P* = .0018)
- Greater benefit of pembrolizumab monotherapy with higher levels of PD-L1 expression consistent with prior reports in this setting
  - TPS ≥ 50%, HR: 0.69 (95% CI: 0.56-0.85; *P* = .0003)
  - TPS ≥ 20%, HR: 0.77 (95% CI: 0.64-0.92; *P* = .0020)
- Analysis found no significant improvement in PFS with pembrolizumab, with study continuing to evaluate
- Responses more durable with pembrolizumab vs CT at all levels of PD-L1 expression
- TRAEs consistent with known safety profiles, less frequent with pembrolizumab despite longer exposure
- Investigators concluded that data support expanded use of pembrolizumab monotherapy as a standard first-line treatment option for all PD-L1–positive cancers

Immunotherapy+anti-VEGFR+ChT

IMpower150: Study Design

- Multicenter, open-label, randomized phase III trial (data cutoff: January 22, 2018)

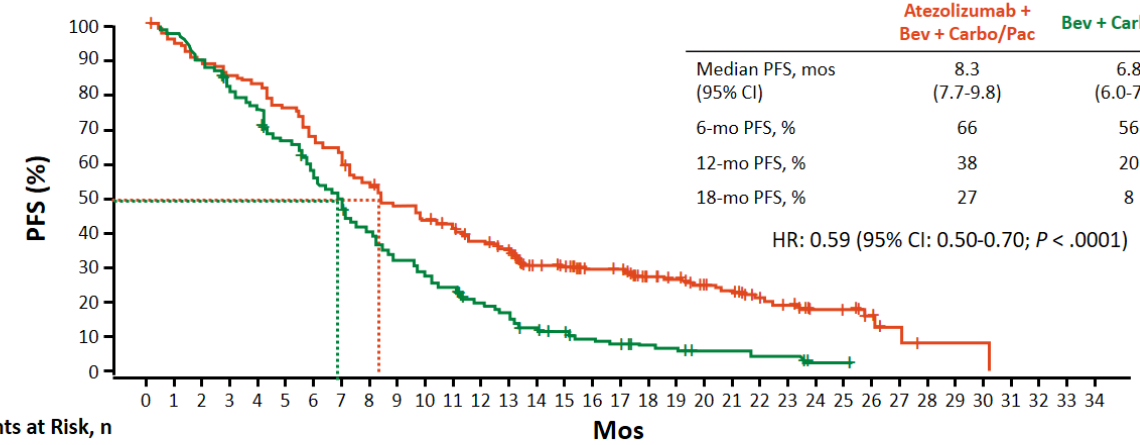


*If sensitizing *EGFR* mutation or *ALK* translocation present, must have PD on or intolerance to ≥ 1 approved targeted therapy. †Bevacizumab 15 mg/kg; carboplatin AUC 6; paclitaxel 200 mg/m²; all given IV Q3W for 4 or 6 cycles. ‡No crossover permitted. §Control arm.

- Coprimary endpoints: investigator-assessed PFS in ITT WT, Teff-high WT; OS in ITT WT
- Secondary endpoints: investigator-assessed PFS, OS in ITT; investigator-assessed PFS in PD-L1 subgroups; IRF-assessed PFS; ORR, DoR per RECIST v1.1; safety in ITT

Socinski MA, et al ASCO 2018

IMpower150: Updated PFS in ITT WT Population* (Coprimary Endpoint)



	Atezolizumab + Bev + Carbo/Pac	Bev + Carbo/Pac
Median PFS, mos (95% CI)	8.3 (7.7-9.8)	6.8 (6.0-7.1)
6-mo PFS, %	66	56
12-mo PFS, %	38	20
18-mo PFS, %	27	8

HR: 0.59 (95% CI: 0.50-0.70; *P* < .0001)

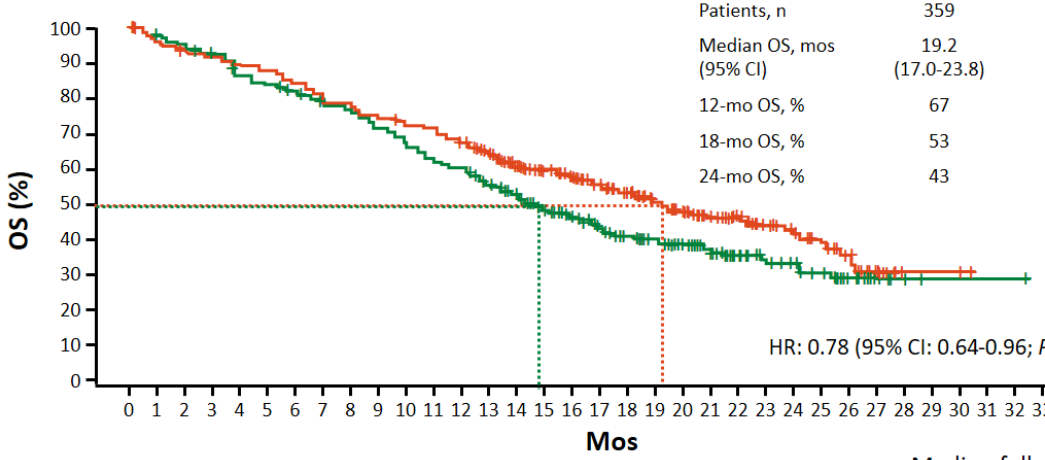
Patients at Risk, n

Atezolizumab + Bev + Carbo/Pac	359	336	315	301	293	267	234	213	190	168	154	146	125	112	85	80	69	68	53	50	37	33	24	20	12	11	6	3	1	1	1
Bev + Carbo/Pac	337	323	294	263	244	215	180	148	127	103	89	78	61	50	35	29	21	18	14	13	6	6	5	5	1	1					

*ITT WT: patients without *EGFR* or *ALK* genetic alterations; 87% of randomized patients.

Median follow-up: ~ 20 mos.

IMpower150: Interim OS in ITT WT Population* (Coprimary Endpoint)



	Atezolizumab + Bev + Carbo/Pac	Bev + Carbo/Pac
Patients, n	359	337
Median OS, mos (95% CI)	19.2 (17.0-23.8)	14.7 (13.3-16.9)
12-mo OS, %	67	61
18-mo OS, %	53	41
24-mo OS, %	43	34

HR: 0.78 (95% CI: 0.64-0.96; *P* = .0164)

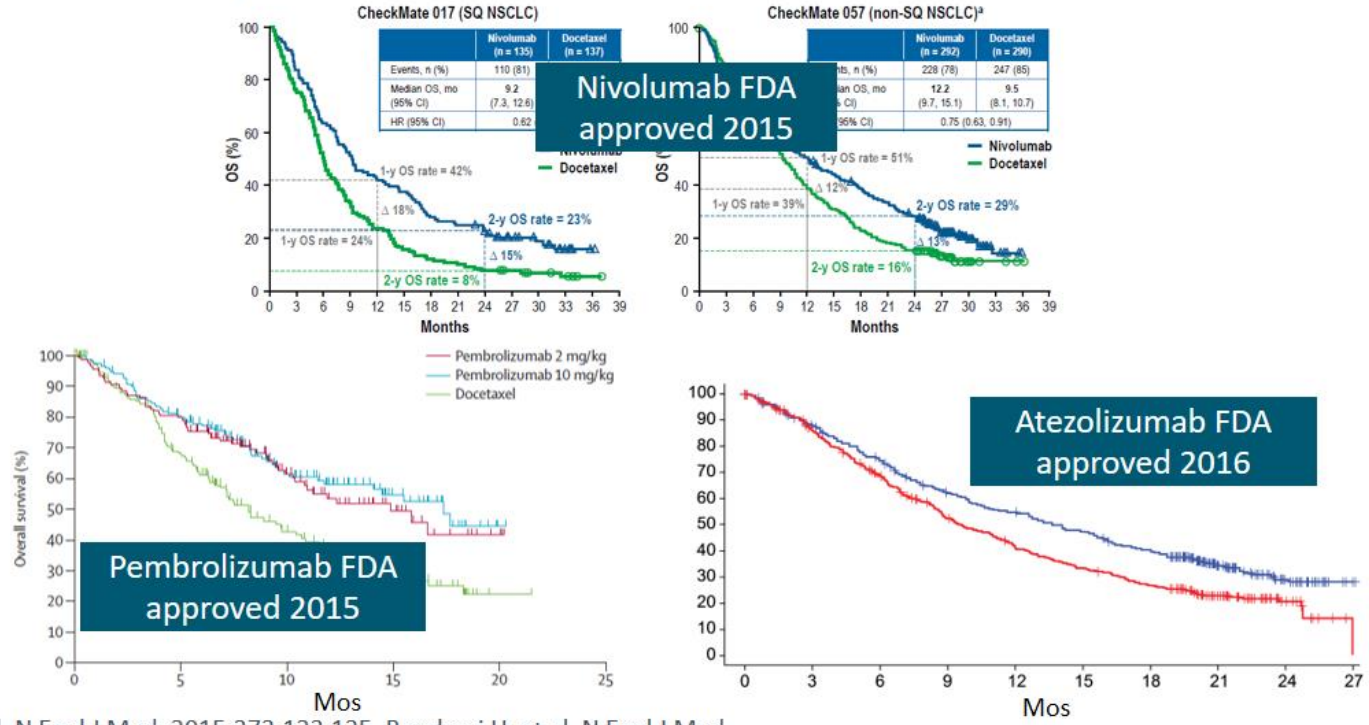
*ITT WT: patients without *EGFR* or *ALK* genetic alterations; 87% of randomized patients.

Median follow-up: ~ 20 mos.

- Median OS for atezolizumab + carbo/pac vs bev + carbo/pac: 19.4 vs 14.7 mos (HR: 0.88; *P* = .2041)

Second line immunotherapy

Approval of 3 PD-1/PD-L1 Inhibitors in Rapid Succession for Previously Treated Advanced NSCLC

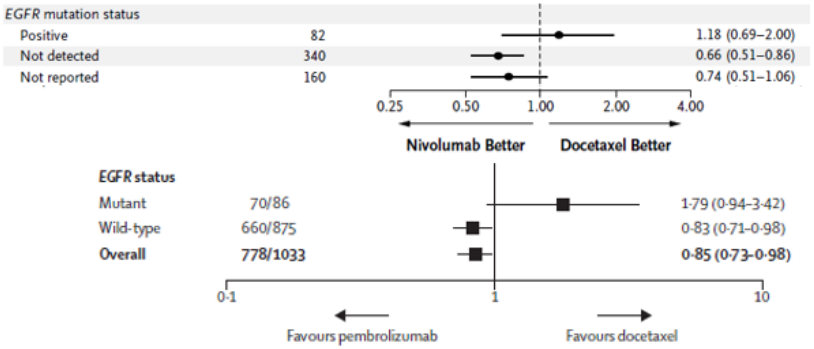


Brahmer J, et al. N Engl J Med. 2015;373:123-135. Borghaei H, et al. N Engl J Med. 2015;373:1627-1639. Horn L, et al. J Clin Oncol. 2017;35:3924-3933. Herbst RS, et al. Lancet. 2016;387:1540-1550. Rittmeyer A, et al. Lancet. 2017;389:255-265.

Slide credit: clinicaloptions.com

EGFR-positive NSCLC

Immunotherapy in *EGFR* Mutation–Positive Adv NSCLC



CHECKMATE 057
Nivolumab vs Docetaxel

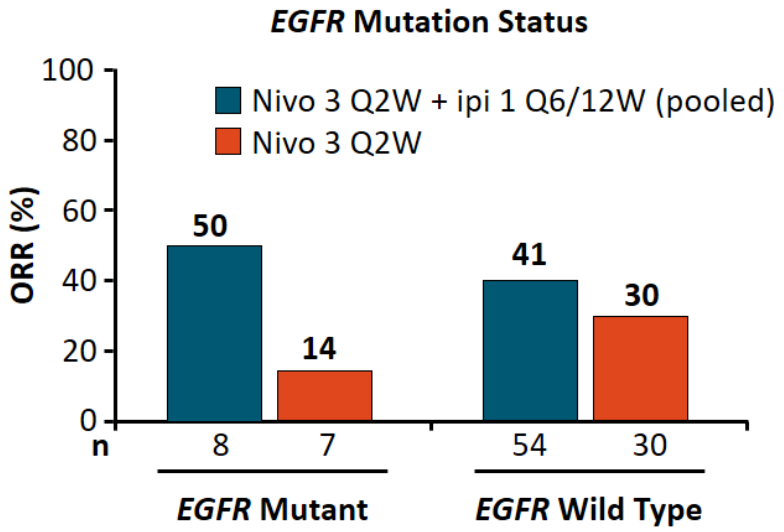
KEYNOTE-010
Pembrolizumab vs Docetaxel

- Chemotherapy favored over IO for patients with *EGFR* mutations in second-line setting[1-4]
- In retrospective analysis, 3.6% response to PD-L1 pathway inhibitors (n = 28) compared with 23.3% (n = 30) in similar *EGFR* WT cohorts[5]
  - Few patients with both PD-L1 ≥ 5% and high CD8+ TILs (2%, n = 48)
- Retrospective analysis of PD-L1 expression in EGFR-mutant NSCLC found 49% of patients PD-L1 negative and only 8% with PD-L1 ≥ 50%, and TMB largely low[6]
  - Comparison for all NSCLC: PDL1 0% (34%), PDL1 1-49% (38%), PDL1≥50% (28%)

Lee CK, et al. J Thoracic Oncol.2017; Lee CK, et al. JAMA Oncol. 2018; Borgaei H, et al N England J Med, 2015; Herbst RS, et al Lancet 2016; Gainor JF, et al Clin Cancer Res. 2016; Cho JH, et al. Cancer Res Treat 2018

EGFR-positive NSCLC

CheckMate 012: Nivolumab + Ipilimumab in *EGFR* Mutation–Positive Advanced NSCLC



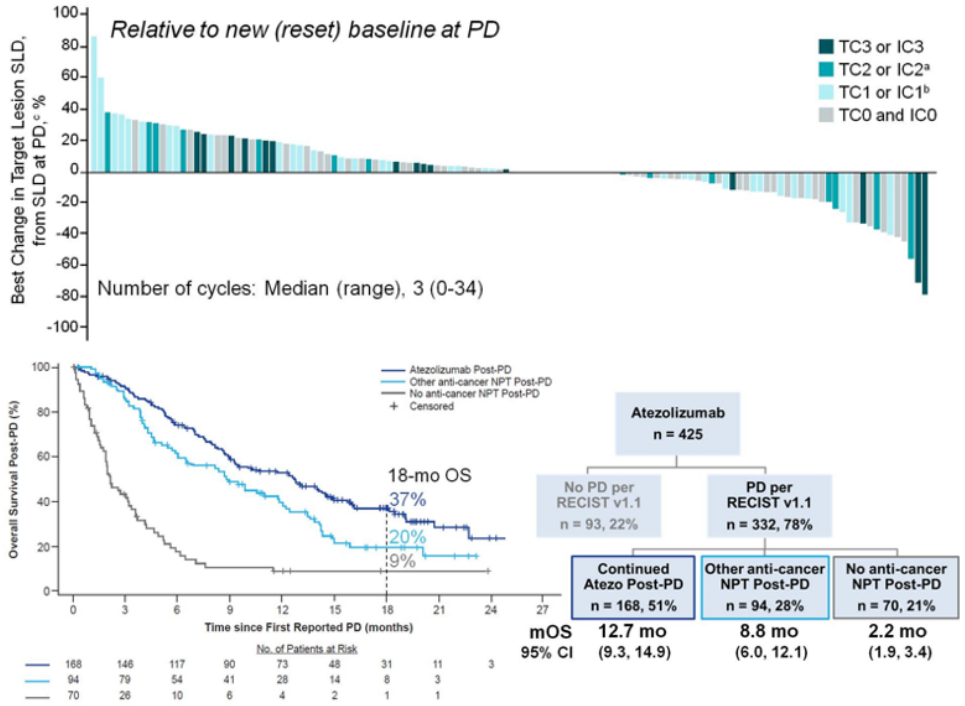
- Among *EGFR* mutation–positive patients receiving nivolumab + ipilimumab (n = 8): ORR 50%
  - PD-L1 ≥ 1%: 88%
  - PD-L1 ≥ 50%: 38%
- Tumor mutation burden unknown

Gettinger S, et al. J Clin Oncol. 2016;34:2980-2987. Hellmann MD, et al. Lancet Oncol. 2017;18:31-41.

Slide credit: clinicaloptions.com

Progression after Immunotherapy

Treatment Beyond Disease Progression: OAK



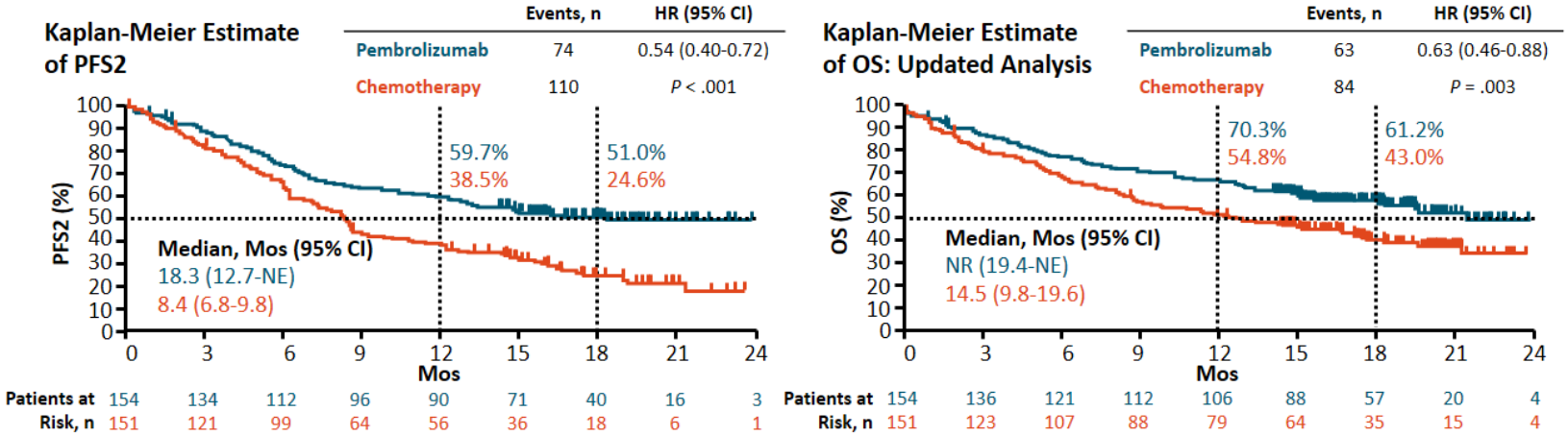
- 51% of patients who progressed on atezolizumab continued beyond progression
  - 7% (12/168) had subsequent PR; 49% (83/168) had stable disease
- Clinical characteristics similar at baseline and upon progression between those who continued atezolizumab or who switched to new treatments
- No increased safety risk in those treated beyond progression

Gandara DR, et al. ASCO 2017. Abstract 9001.

Slide credit: clinicaloptions.com

Progression after Immunotherapy

Response to Subsequent Treatment After Immunotherapy in Advanced NSCLC: KEYNOTE-024

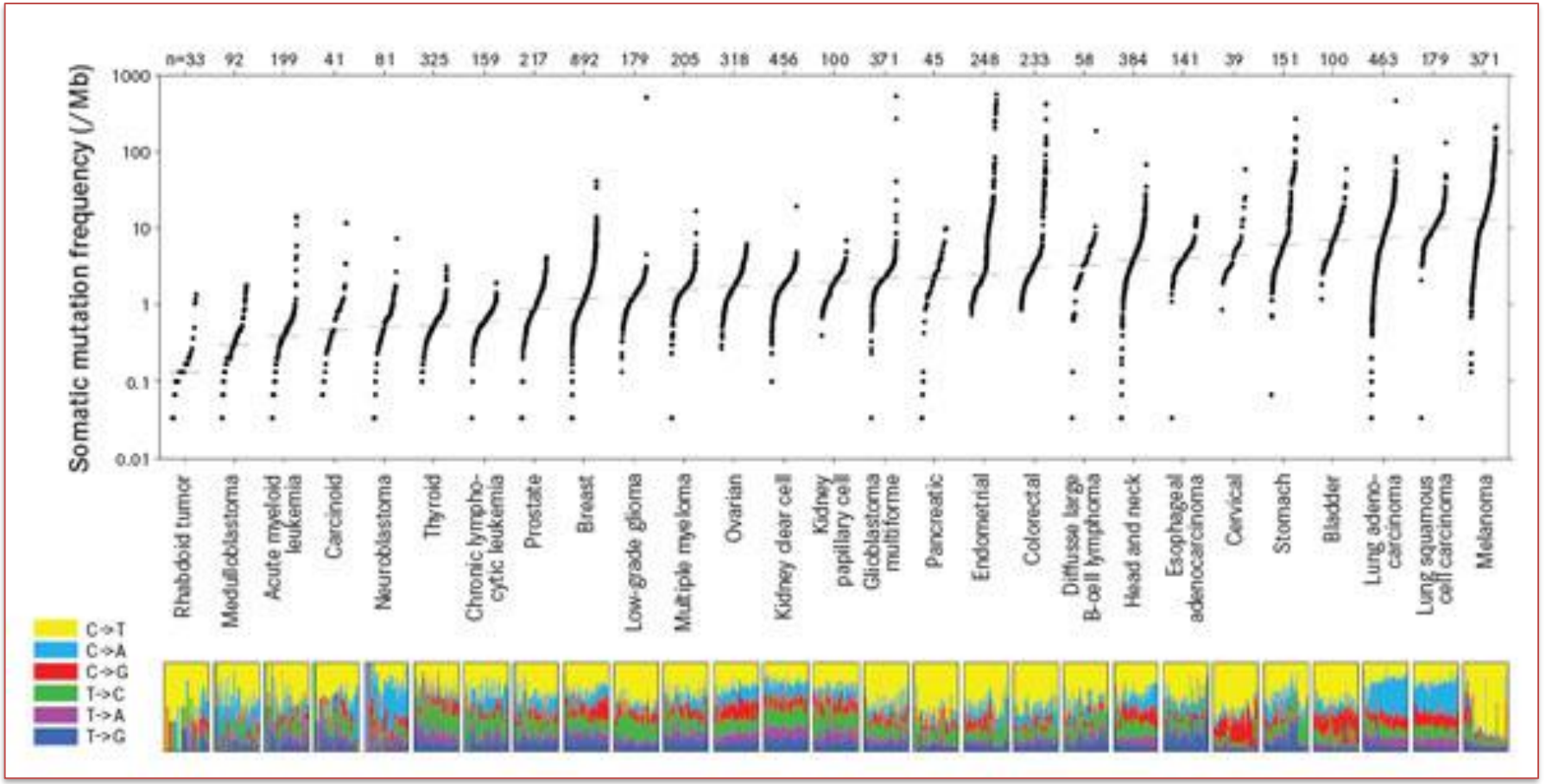


- KEYNOTE-024: patients with metastatic NSCLC PD-L1 ≥ 50% were randomized to received pembrolizumab or platinum-doublet chemotherapy
- After discontinuation, 45% of pembrolizumab patients (48/107) and 81% (97/120) of chemo patients went on to subsequent therapy; 66% (79/120) of patients who discontinued chemo crossed over to pembrolizumab
- Pembrolizumab showed continued OS benefit and improved PFS2 (time from randomization to progression on next-line treatment or death) with further follow-up

Brahmer JR, et al. ASCO 2017. Abstract 9000.

Slide credit: clinicaloptions.com

TMB in Lung Cancer

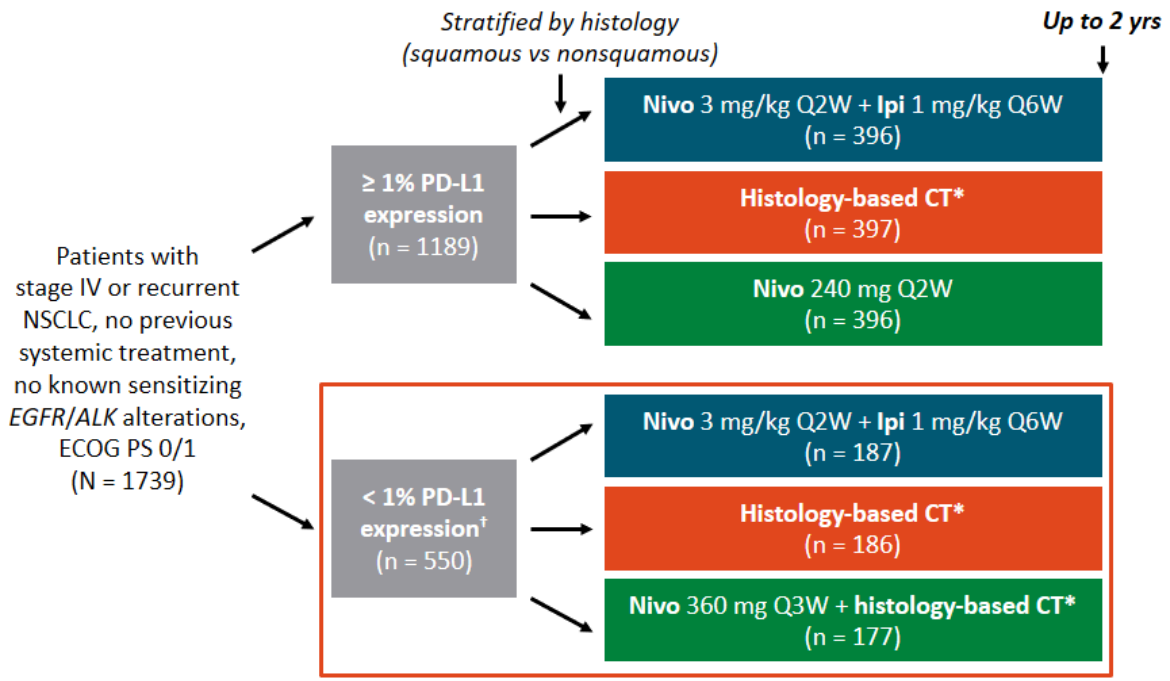


Schumacher and Schreiber, Science 2015

Is PDL>1% a selection criterion in II line treatment?

CheckMate 227: Study Design

- Randomized, open-label, multipart phase III trial

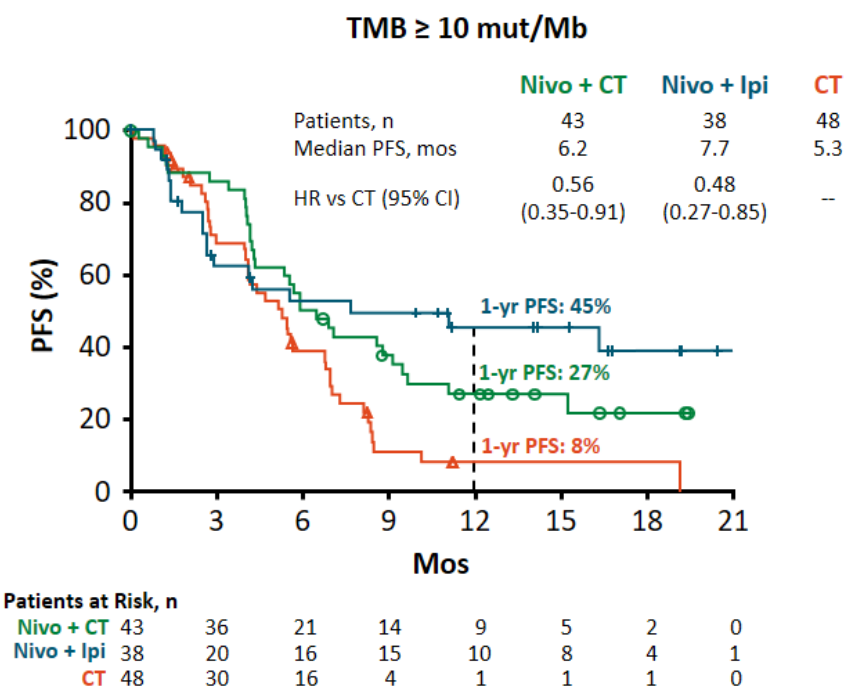


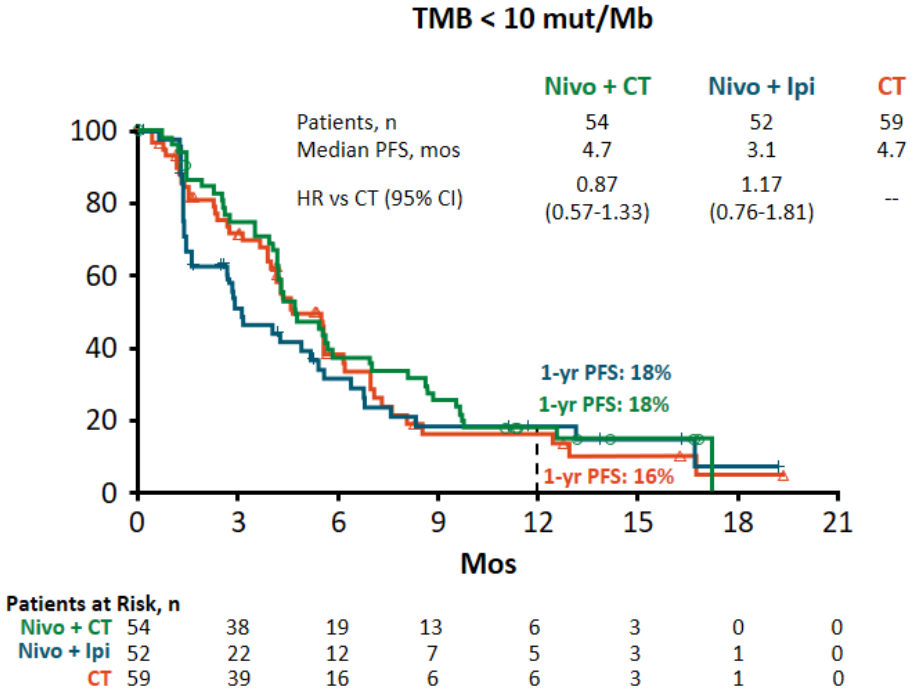
- Coprimary endpoints: OS in PD-L1–selected populations, PFS in TMB-selected populations receiving nivolumab + ipilimumab vs CT
- **Secondary endpoint (current analysis):** PFS in patients with < 1% PD-L1 expression receiving nivolumab + CT vs CT

*Nonsquamous: pem + cis or carbo Q3W f ≤ 4 cycles with optional maintenance (CT: nivolumab + CT: nivolumab + pem); squan gem + cis or carbo Q3W for ≤ 4 cycles.
†1 patient randomized as < 1% PD-L1 and subsequently determined to have ≥ 1% PD expression.

Borghaei H, et al. ASCO 2018

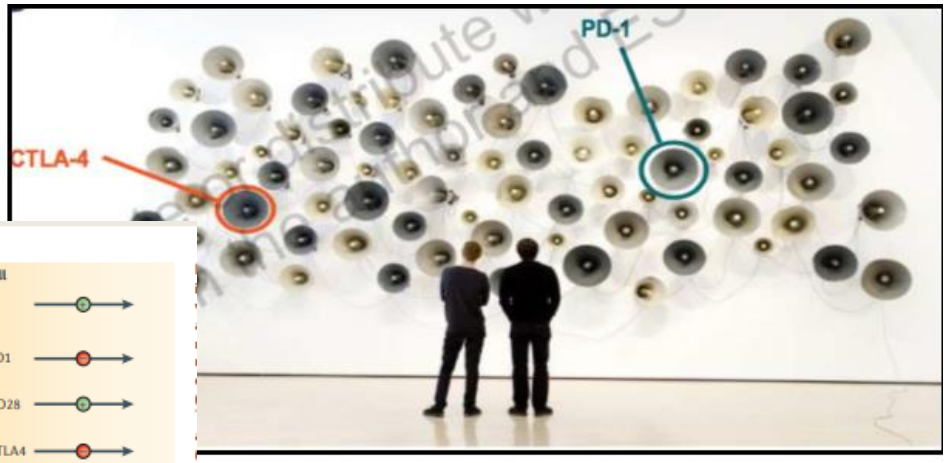
CheckMate 227: Exploratory Analysis of PFS by TMB in Patients With < 1% PD-L1 Expression



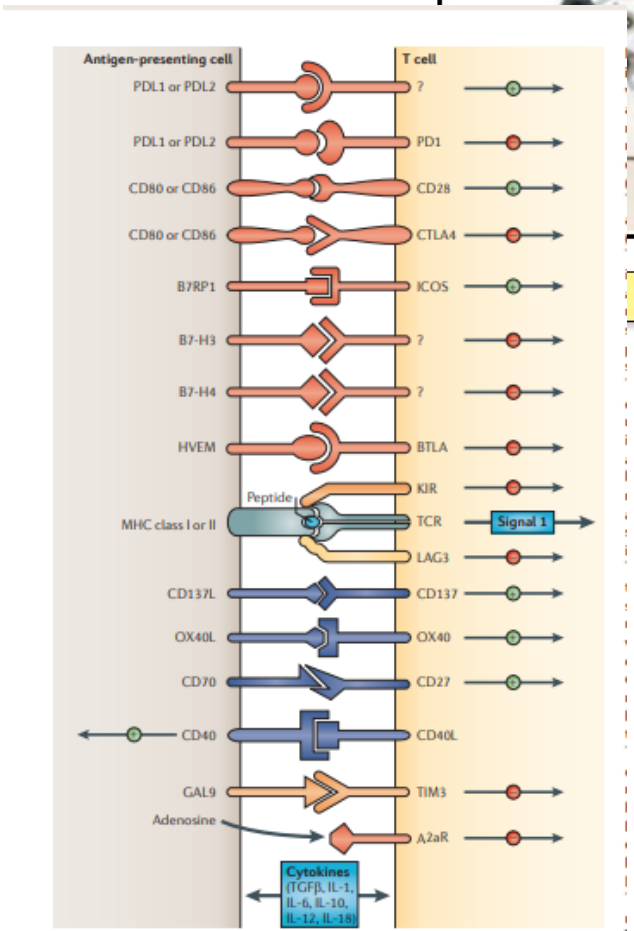


Borghaei H, et al. ASCO 2018

Not only CTLA-4 and PD-1/PD-L1



Pardoll et al., Nat Rev Cancer 2012



Need of patient selection

- Selection by PD-L1 expression
- Selection by Tumor Mutation Burden (TMB)
- Clinical Criteria

Unanswered Questions

- Are there some patients for whom immunotherapy with chemotherapy is superior to immunotherapy alone?
- Are combinations of immunotherapy going to be superior to a single agent?
- How do we integrate targeted agents?
- How do we deal with tumors once they've progressed after PD-1 monotherapy?

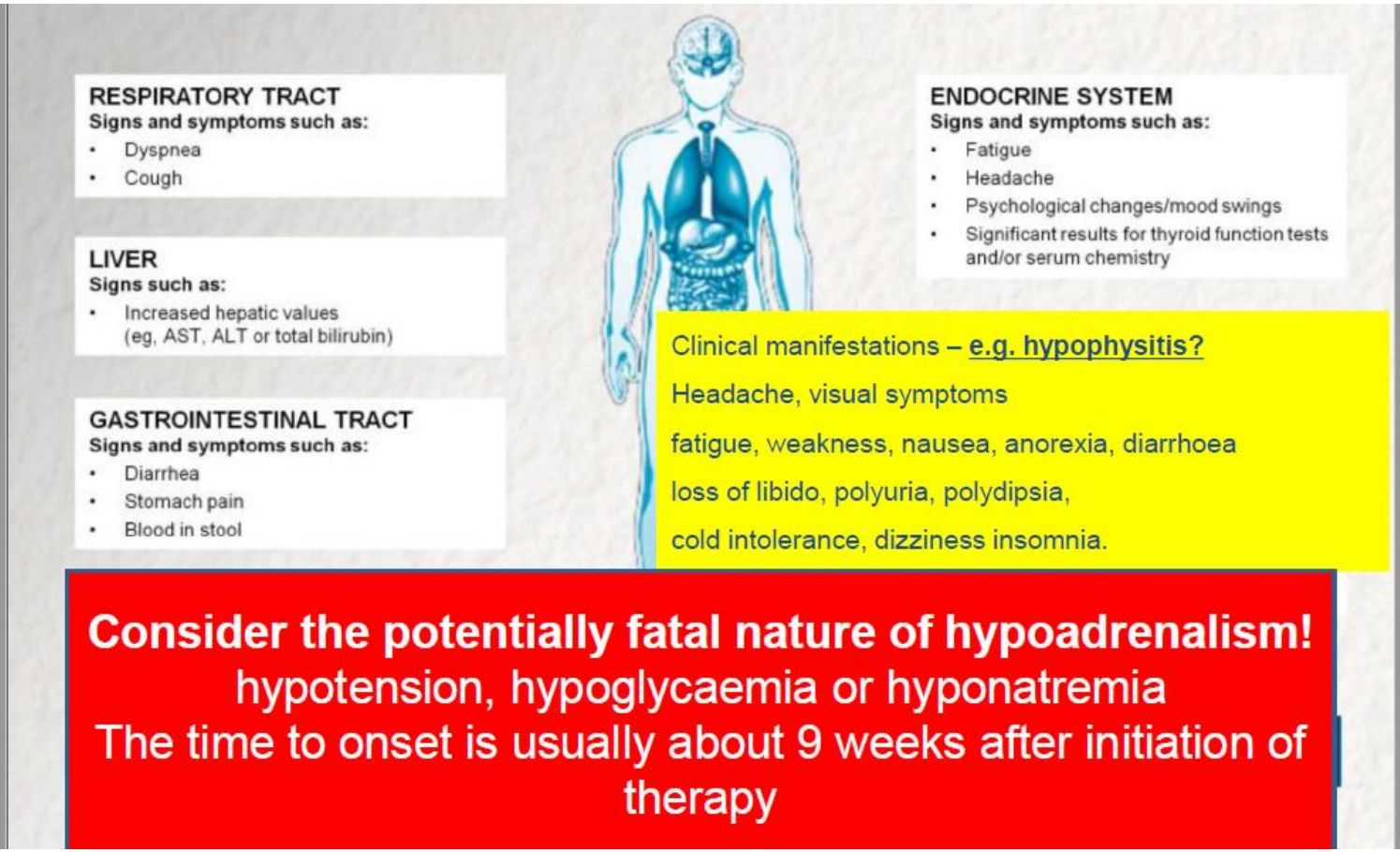
New Trials in NSCLC

Sub group	ONCOGENE ADDICTED	OTHERS		HIGHLY SENSITIVE TO IMMUNO
		NON SQUAMOUS	SQUAMOUS	
First Line	EGFR: gefitinib, erlotinib, afatinib, icotinib, dacomitinib, osimertinib, poziotinib (if EGFR exon 20 mut) ALK: crizotinib, ceritinib 750 mg, ceritinib 450 mg (low fat meal), alectinib, lorlatinib, ensartinib BRAF: dabrafenib + trametinib ROS1: crizotinib, ceritinib, entrectinib MET: crizotinib NTRK: larotrectinib, entrectinib	Platinum-CT Pemetrexed is an option Bevacizumab can be added Pembrolizumab + platinum/pemetrexed (US) Nivolumab + Ipilimumab Nivolumab + platinum CT	Platinum-CT Necitumumab can be added Nivolumab + ipilimumab Nivolumab + platinum CT	Pembrolizumab if PDL1 ≥ 50% tumor cells Atezolizumab in TC 2/3 - IC 2/3 tumors Avelumab in PD-L1 ≥ 1% Durvalumab in PD-L1 ≥25% Nivolumab + Ipilimumab Nivolumab + platinum CT Pembrolizumab + platinum/pemetrexed (in non-squamous histology)
Second And Further Line	EGFR: osimertinib if T790M+ EGFR+/ MET+: savolitinib + osimertinib ALK: ceritinib 750 mg, ceritinib 450 mg (low fat meal), alectinib, brigatinib, lorlatinib, ensartinib BRAF: dabrafenib + trametinib RET: vandetanib, LOXO-292 HER2 : TDM-1 ROS1: lorlatinib	Docetaxel +/- nintedanib Docetaxel +/- ramucirumab Bevacizumab + Paclitaxel is an option in non-squamous (if Beva not administered in 1st line). Nivolumab Atezolizumab Avelumab		Platinum CT based on histology (if Pembro in first line). Pembrolizumab in PD-L1 ≥ 1% (if not administered in 1st line). Nivolumab Atezolizumab Durvalumab in PD-L1 ≥25% Avelumab

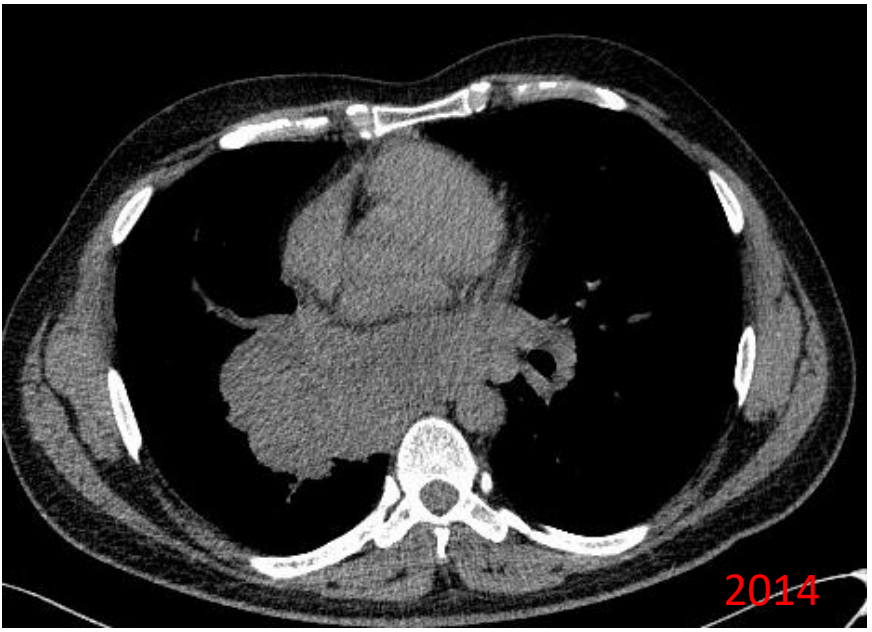
Phase I-II studies Phase III studies

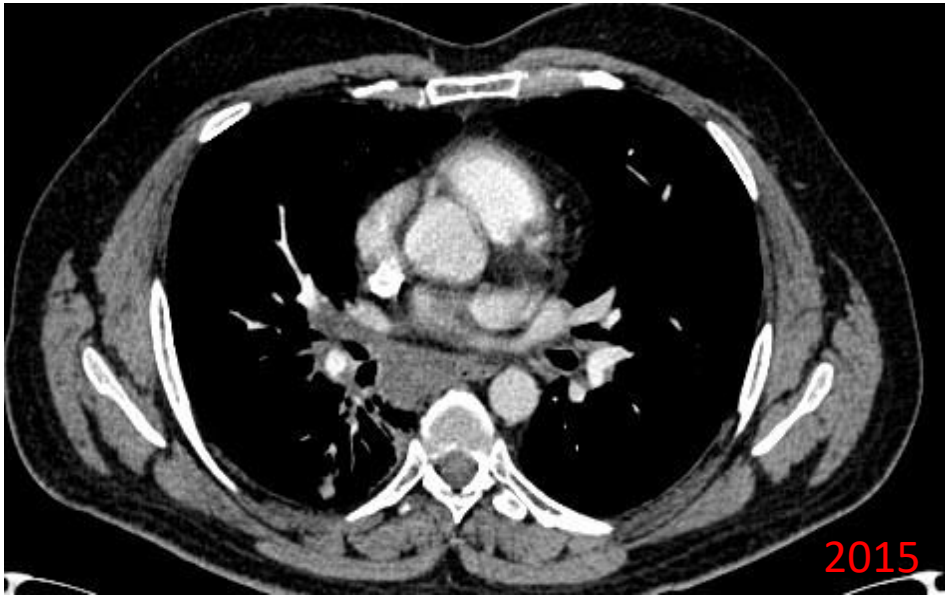
Roberto Ferrara et al. 2017 Scientific Advances in Thoracic Oncology

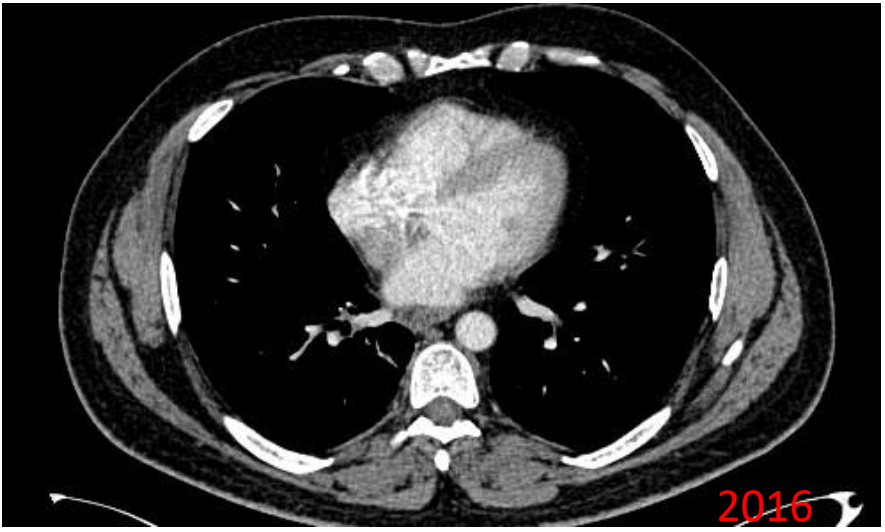
IMMUNE-Mediated Adverse Events

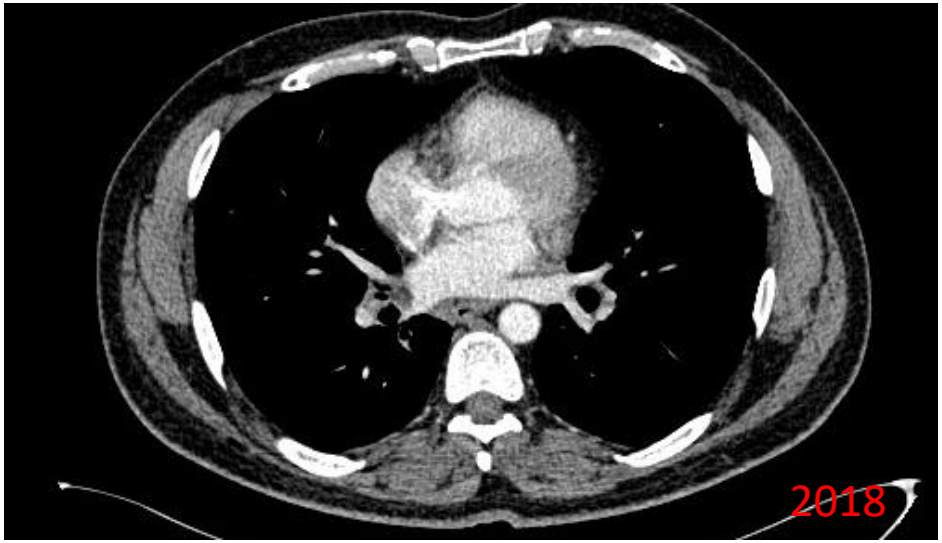


Epilogue: How Immunotherapy has changed a patient's life









Conclusions:

- Immunotherapy with immune checkpoints inhibitors has changed the way we treat and will treat many cancers, including NSCLC and (hopefully) SCLC.
- Response to ICI is related to the balance between innate (myeloid cells) and adaptive (T lymphocytes) immunity
- More research is needed on predictive factors (PDL1, TMB) in order to extend the benefit of ICI.
- Combinations of ICIs, combinations of PD-1/PD-L1 inhibitors with chemo and radiotherapy, and dual blockade of IC and VEGF pathways are promising strategies
- Beware of toxicities, mainly with combo regimens
- Many trials ongoing and in preparation

Acknowledgments