Expanded Application of Immunotherapy and EGFR-Tyrosine Kinase

Division of Pulmonology, Allergy and Critical Care Medicine
Department of Internal Medicine, College of Medicine
The Catholic University of Korea

Chan Kwon Park

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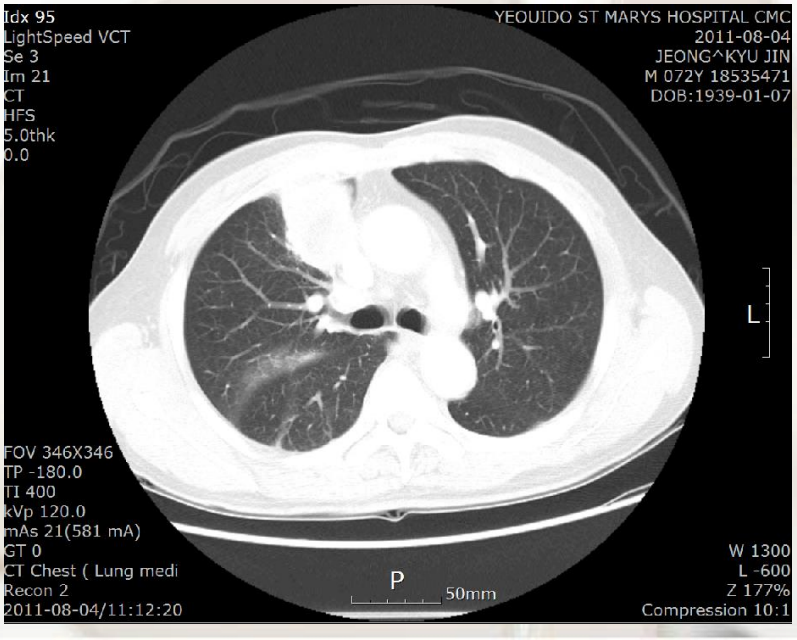
- EGFR TKI
  1) 1st – 4th Generation of TKI and LB
  2) EGFR TKI plus chemotherapy
  3) EGFR TKI plus anti-angiogenic drugs
  4) EGFR TKI plus immunotherapy
  5) Neoadjuvant and adjuvant EGFR TKI

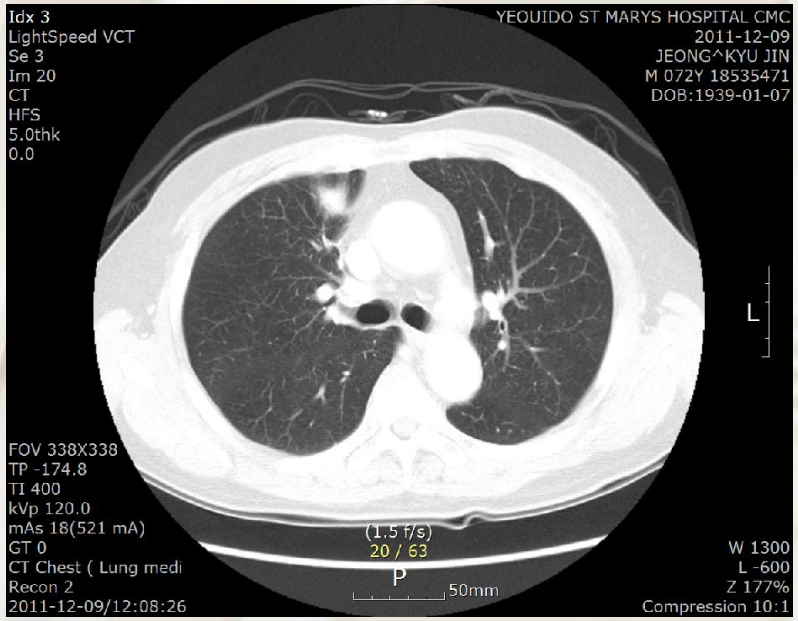
Contents

- IO
  1) ICI: CTLA4, PD-1 and PD-L1 inhibitor
  2) Combination of IO + Chemo or IO+IO
  3) Neoadjuvant, consolidative and adjuvant IO
  4) IO in SCLC

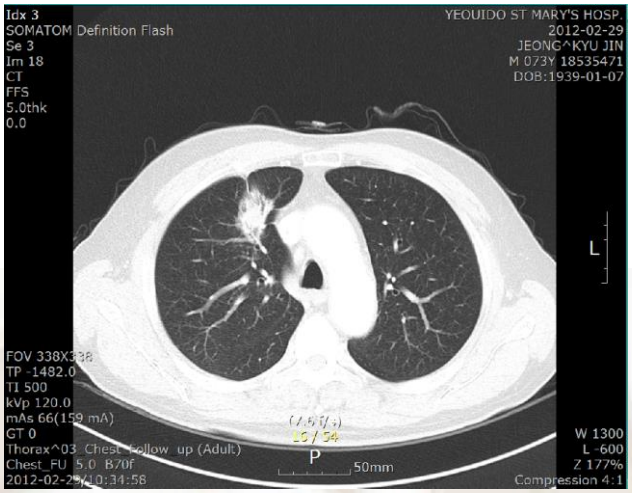
EGFR TKI

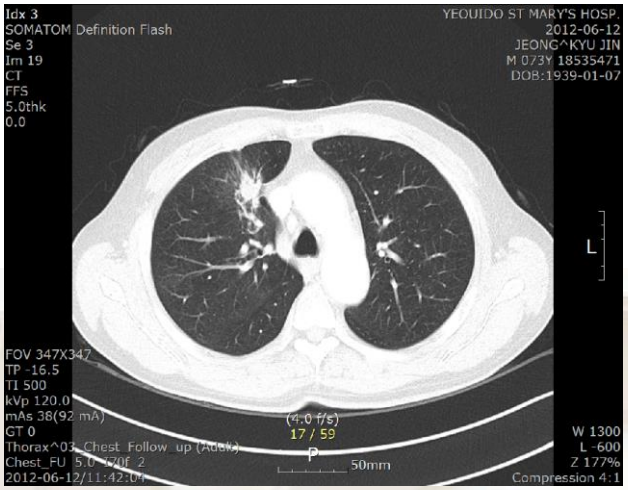
Case
: M/79 ADC, S-IV(RUL), EGFR(-) ALK(-)





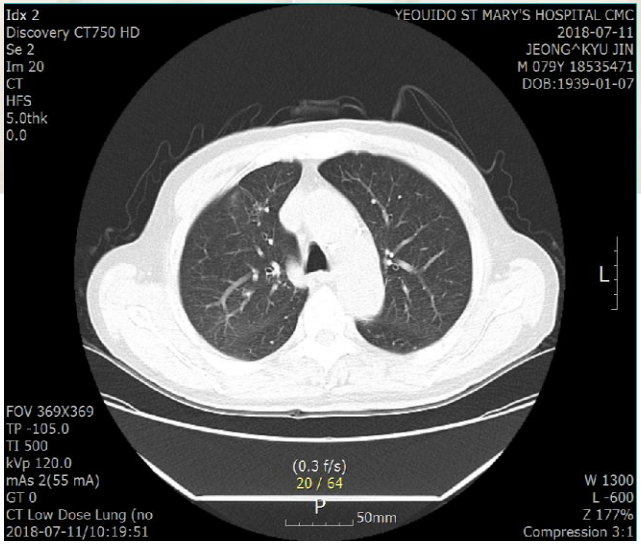
- 2011.08.04 - 2011.11.29 #1-1 ~ #1-6 Pemetrexed – Cisplatin



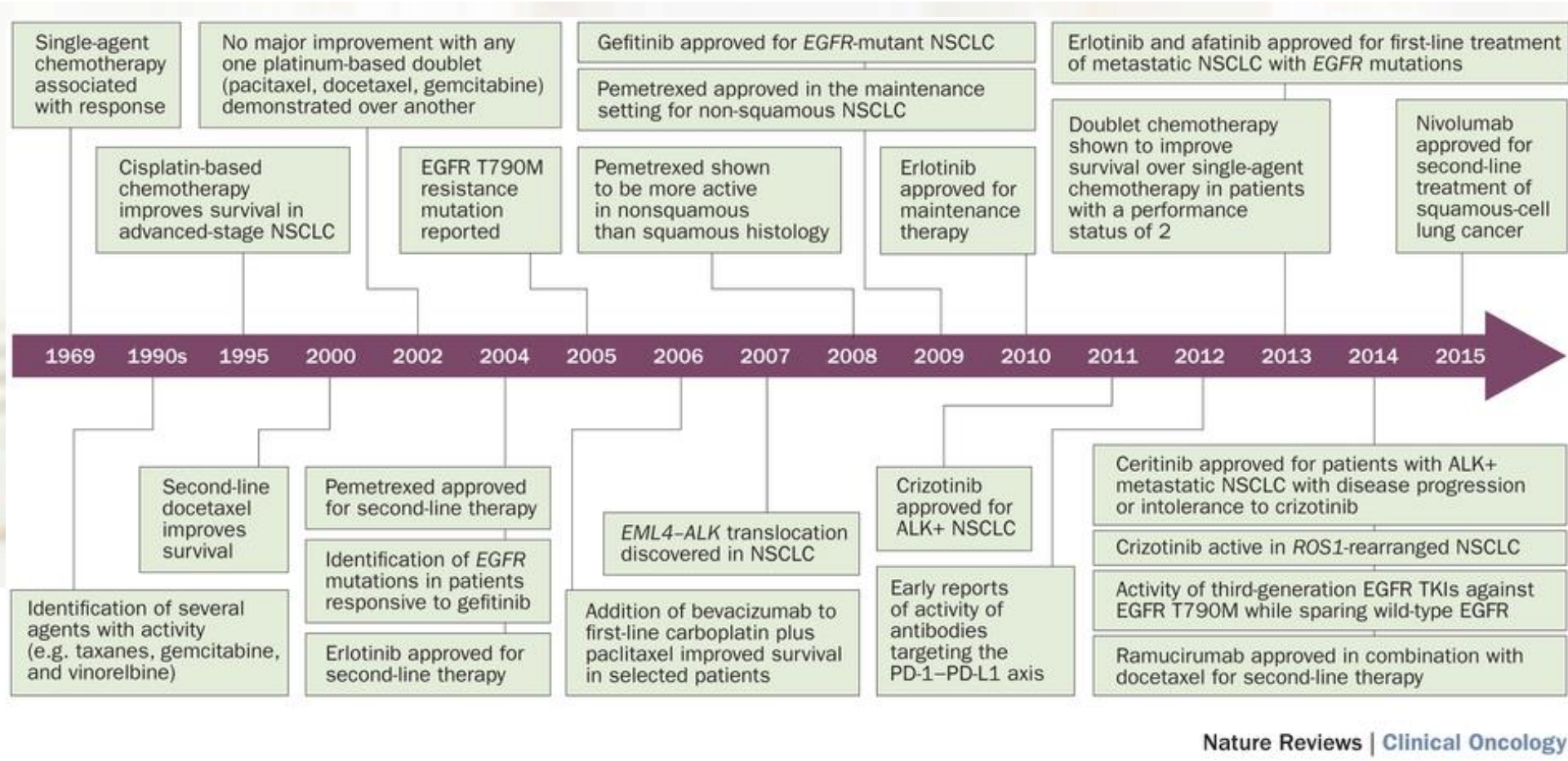


- 2012.04.13 - 2012.08.02 #2-1 ~ #2-6 Docetaxel Chemotherapy

- **2012.08.21 ~현재** : #3 Erlotinib 150mg SD



Advances in NSCLC management



Nature Reviews | Clinical Oncology

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Non-Small Cell Lung Cancer

Version 5.2018 — June 27, 2018

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National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2018
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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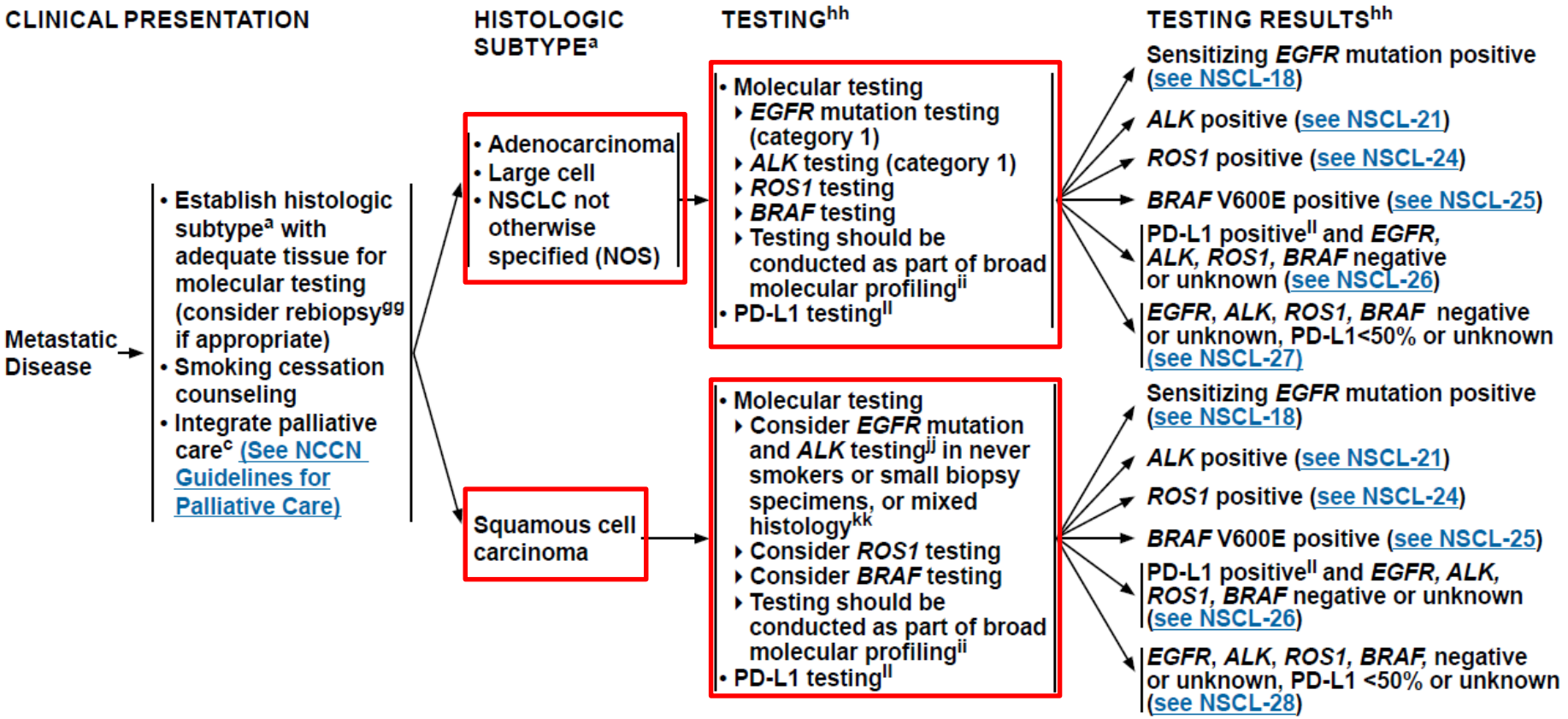
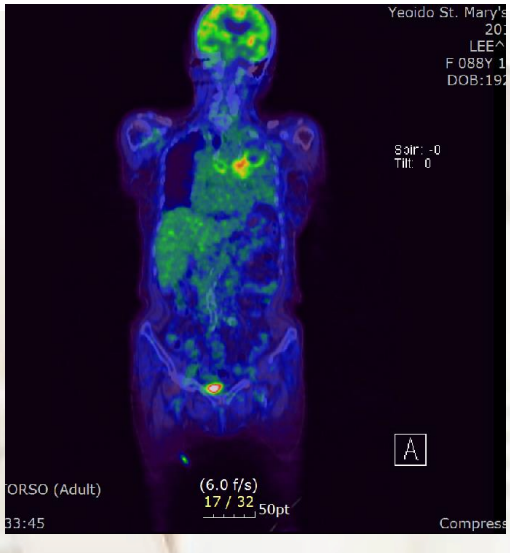
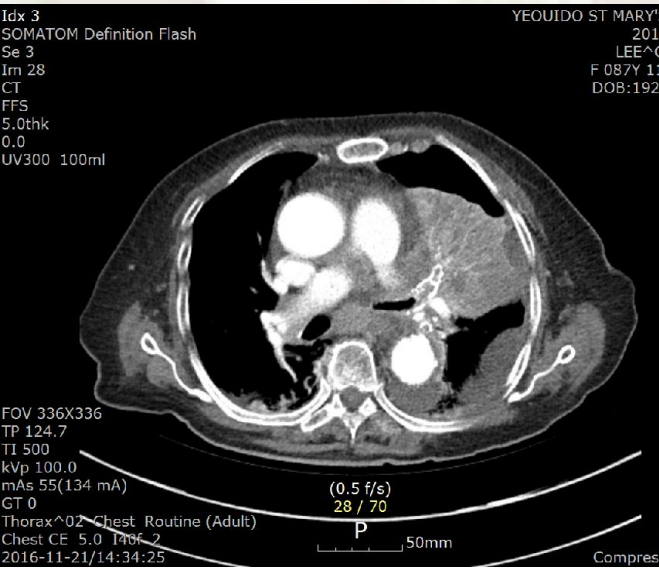


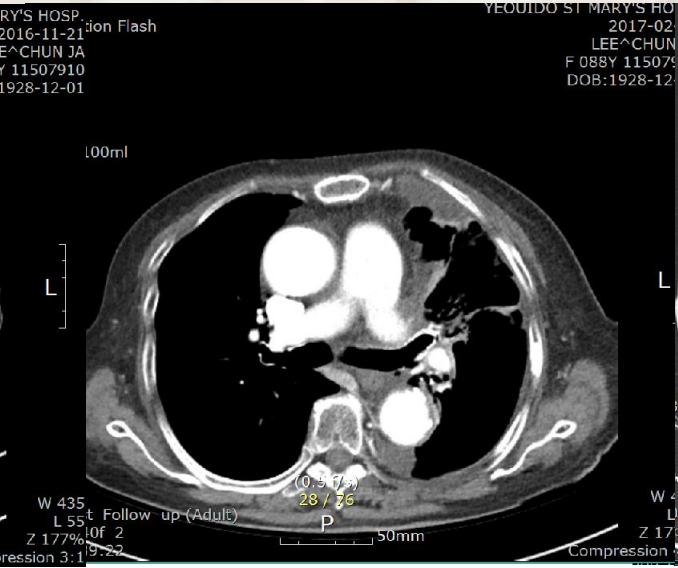
Case
:F/89, ADC ,S-IV(LUL), EGFR(+) ALK (-)

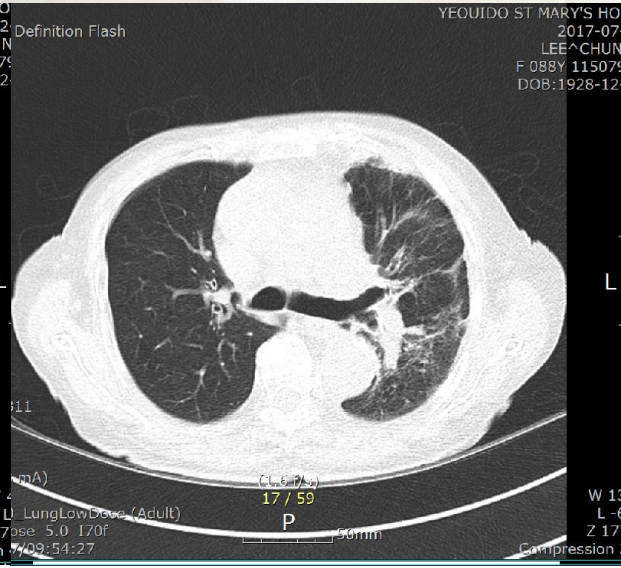
- EGFR(+) 19del
- liver, brain metastasis
- s/p #1 Afatinib 40mg start (2016.11.29~)
  -> G4 diarrhea => afatinib 30mg

- 2017.02. : 반응평가 - PR **8.3**->2.4cm
- 2017.07. : 반응평가 - PR 2.9->**1.7cm**



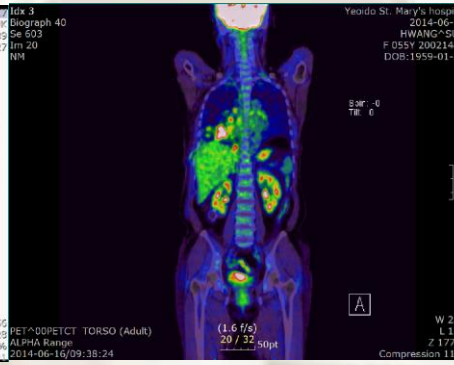


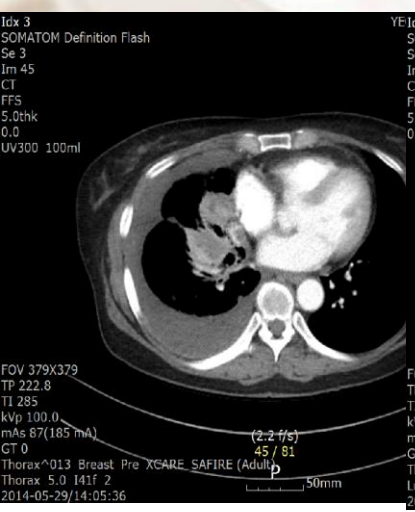


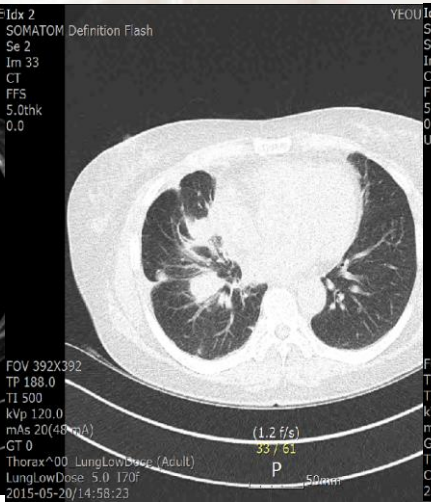


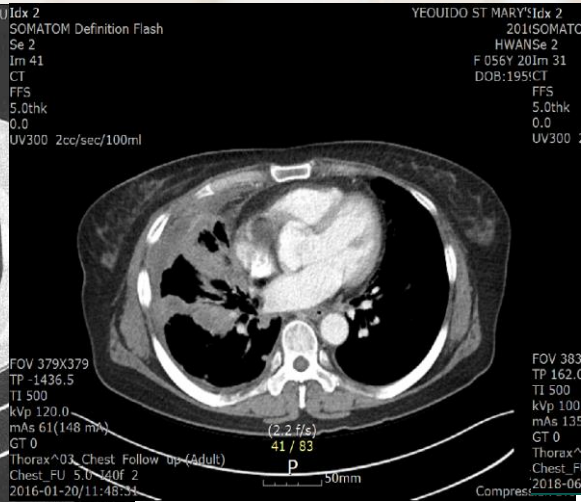
Case
:59/F, ADC, S-IV(RLL), EGFR(+) ALK(-) ROS1(-) RET(-)

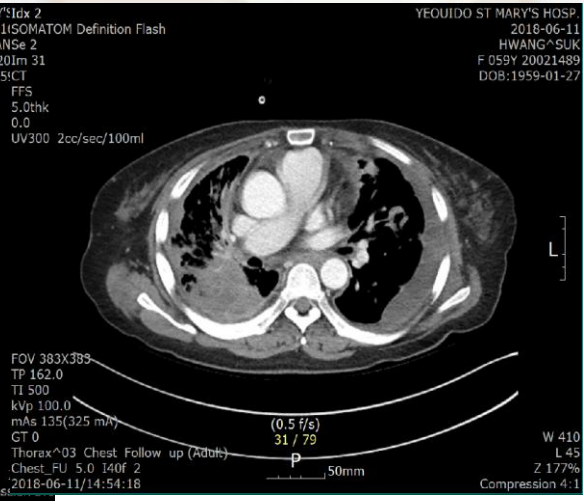
- #1- GEN250 (2014.6.) hepatitis
  - 2015.12. PD,
- #2- AFT30 (2015.12.) facial erruption
  - 2016.02. PD
- #3- Pem mono (2016.2.25~2016.4.19)
  - 2016.06. PD **, Liver meta T790M (+)**
- s/p #4 Osimertinib (2016.6.15~)





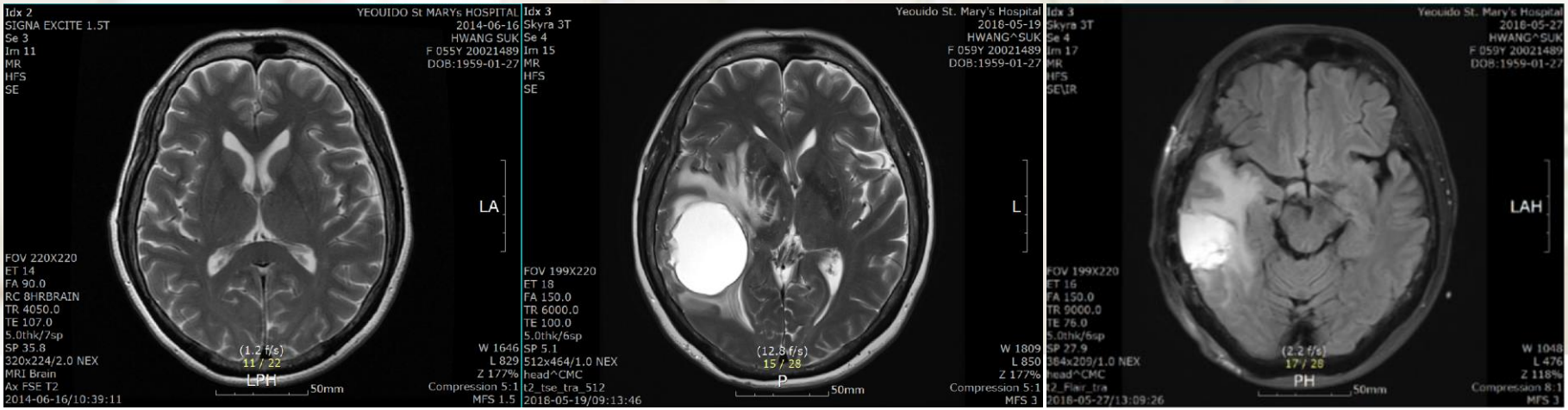






2018.05. Necrotic metastasis at the Rt temporal lobe
-> Craniotomy c tumor removal

2018.5.25~ #5-1 Gem-Carbo



Studies of **first- or second-generation EGFR TKI** in treated-naive patients with lung adenocarcinoma

Study	EGFR TKI	Chemotherapy	Mutation	Median PFS (months)	ORR (%)	Median OS (months)
IPASS	Gefitinib	Carboplatin + paclitaxel	All	9.5 vs 6.3	71.2 vs 47.3	21.6 vs 21.9
WJTOG 3405	Gefitinib	Cisplatin + docetaxel	mEtGFR	9.2 vs 6.3	62.1 vs 32.2	36 vs 39
First-SIGNA	Gefitinib	Cisplatin + gemcitabine	All	5.8 vs 6.4	55.4 vs 46.0	22.3 vs 22.9
			mEGFR subgroup	8.0 vs 6.3	84.6 vs 37.5	27.2 vs 25.6
NEJ002	Gefitinib	Carboplatin + paclitaxel	mEGFR	10.8 vs 5.4	73.7 vs 30.7	27.7 vs 26.6
EURTAC	Erlotinib	Cisplatin + docetaxel	mEGFR	9.7 vs 5.2	64 vs 18	19.3 vs 19.5
OPTIMAL	Erlotinib	Gemcitabine + carboplatin	mEGFR	13.1 vs 4.6	83 vs 36	NA
Lux-lung 3	Afatinib	Cisplatin + pemetrexed	all	11.1 vs 6.9	56.1 vs 22.6	28.2 vs 28.2
			mEGFR	13.6 vs 6.9		
Lux-lung 6	Afatinib	Gemcitabine + cisplatin	mEGFR	11.0 vs 5.6	66.9 vs 23.0	23.1 vs 23.5

Cancer Therapy: Clinical

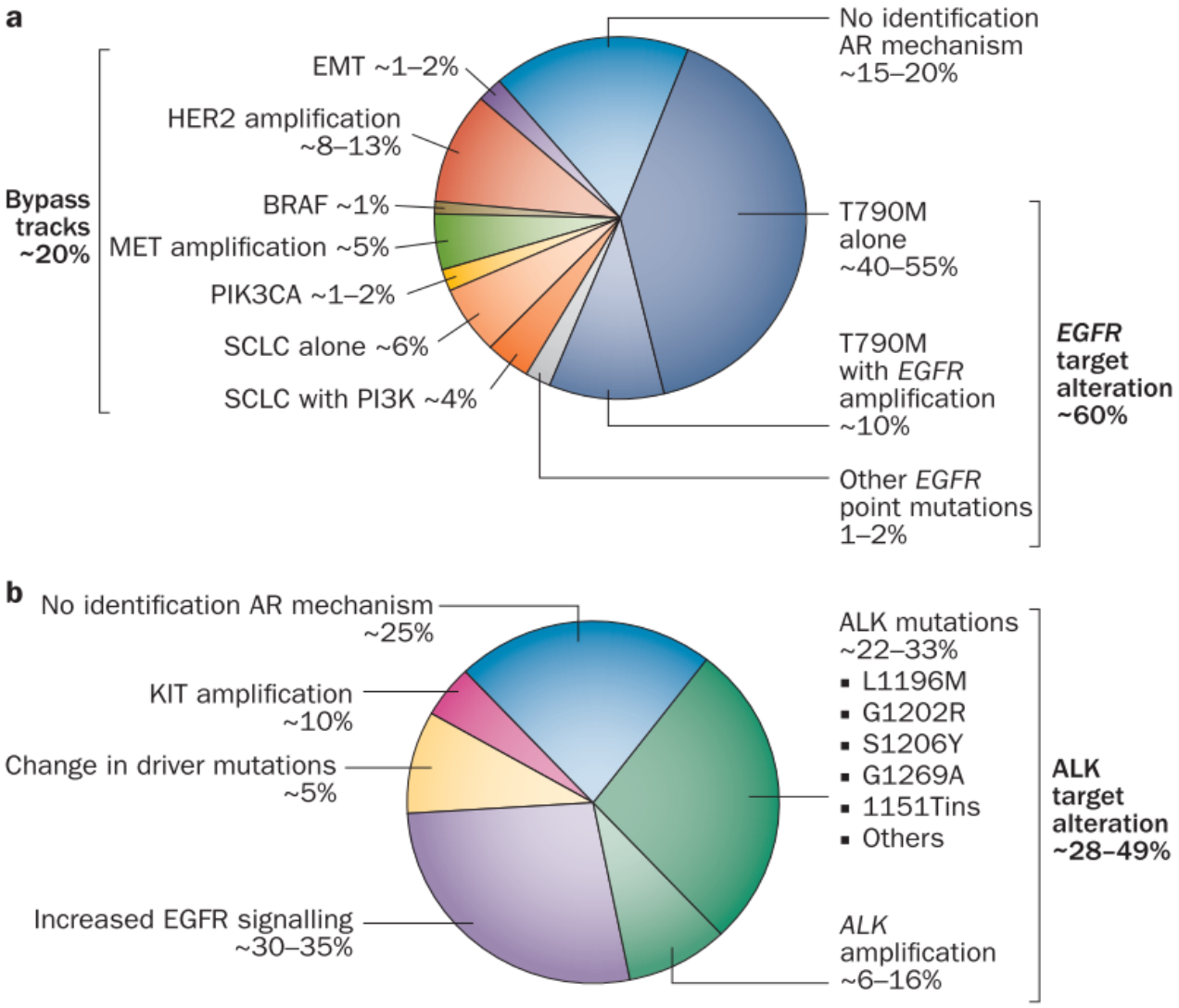
Clinical Cancer Research

Analysis of Tumor Specimens at the Time of Acquired Resistance to EGFR-TKI Therapy in 155 Patients with *EGFR*-Mutant Lung Cancers

Helena A. Yu[1], Maria E. Arcila[3], Natasha Rekhtman[3], Camelia S. Sima[2], Maureen F. Zakowski[3], William Pao[4], Mark G. Kris[1], Vincent A. Miller[1], Marc Ladanyi[3], and Gregory J. Riely[1]

- **Experimental Design:** lung adenocarcinomas and acquired resistance to erlotinib or gefitinib enrolled onto a prospective biopsy protocol and underwent a rebiopsy after the development of acquired resistance. Samples underwent genotyping for mutations in EGFR, AKT1, BRAF, ERBB2, KRAS, MEK1, NRAS and PIK3CA, and FISH for MET and HER2.
- **Results:** obtained in **155 patients**. Ninety-eight had second-site **EGFR T790M mutations [63%]** and four had small cell transformation (3%). MET amplification was seen in 4 of 75 (5%). HER2 amplification was seen in 3 of24 (13%). Overlap among mechanisms of acquired resistance was seen in 4%.
- **Conclusions: EGFR T790M as the most common mechanism** of acquired resistance, whereas MET amplification, HER2 amplification, and small cell histologic transformation occur less frequently.

EGFR and ALK NSCLC resistant mechanisms

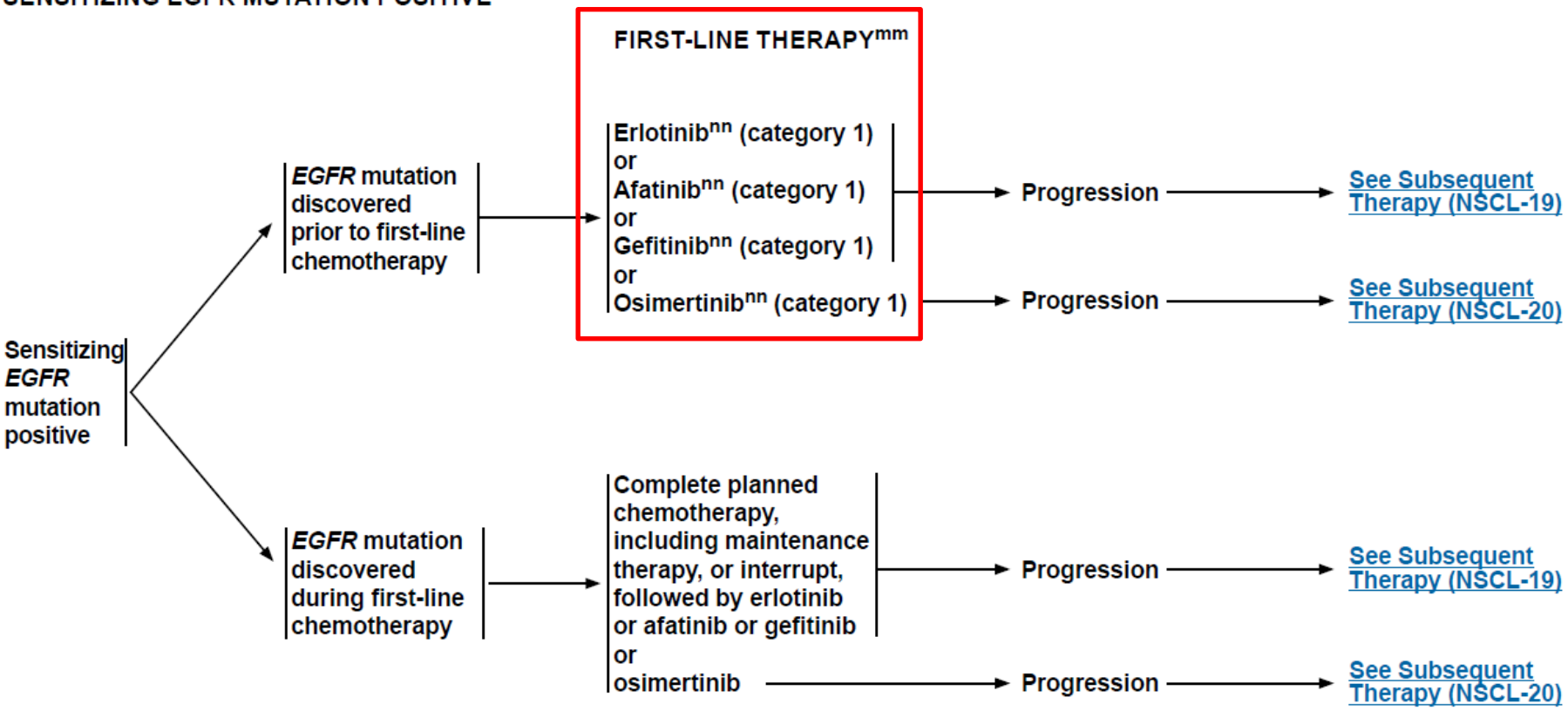


Camidge, D. R., et al. Nat Rev Clin Oncol **11**(8): 473-481.

The clinical studies for **third-generation EGFR TKI**

	Study	Number[a]	ORR	PFS (months)
AZD9291	AURA1 I	253	51% T790 m+ 60% T790 m– 28%	NA
AZD9291	AURA2 I/II	472/210	71%	8.6
AZD9291	AURA3 tIII	419/279	71%	10.1
CO1686	I/II	612/69	T790 m+ 45% T790 m– 17%	6.1 1.8
HM61713	I/II	71	56%	7.0

SENSITIZING EGFR MUTATION POSITIVE[hh]



X-ray crystal structure of gefitinib and osimertinib in EGFR

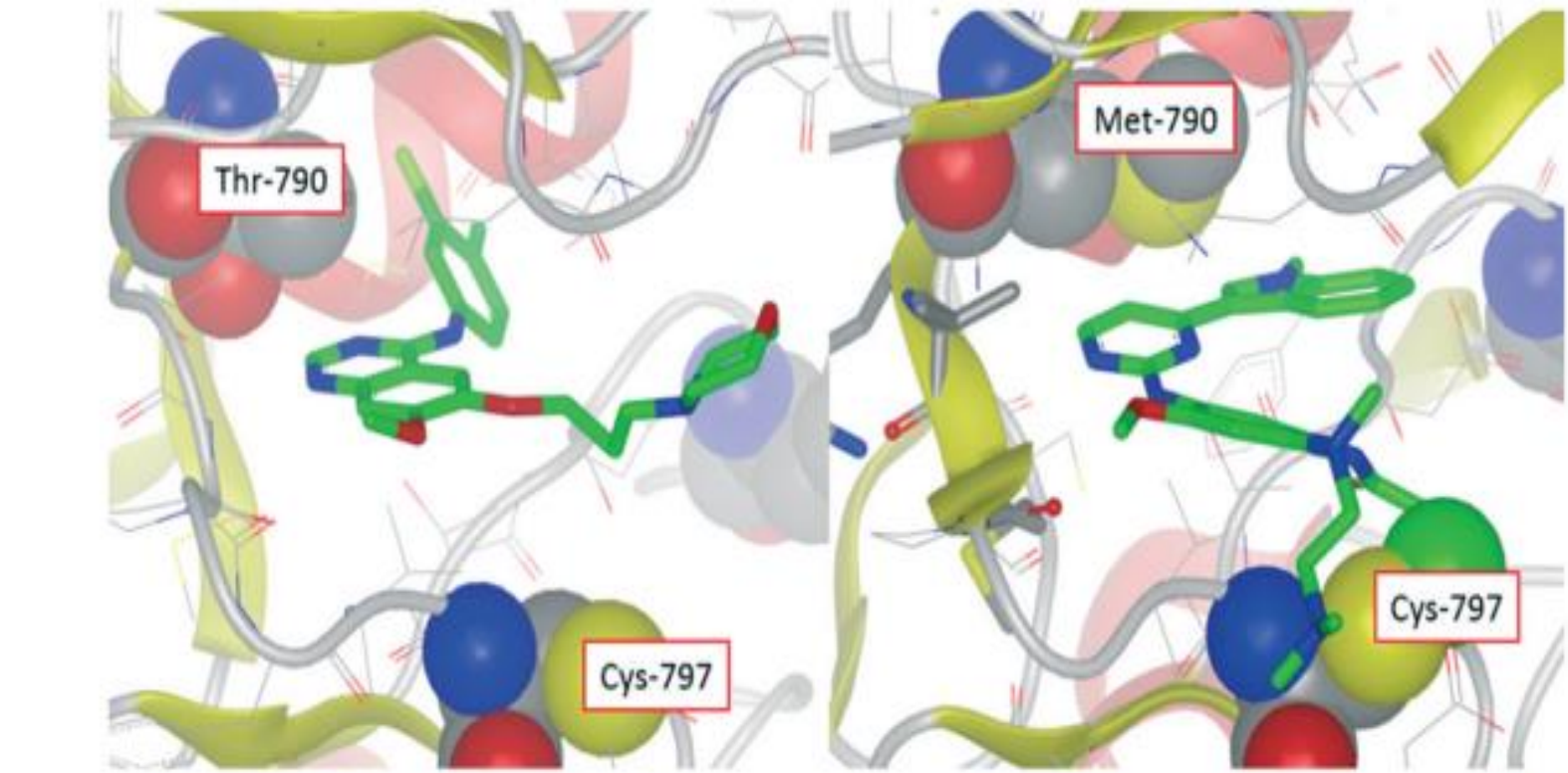


Fig. 1 X-ray crystal structure of gefitinib in wild-type EGFR showing close proximity of the compound with the threonine gatekeeper (left). Modelled structure of osimertinib in T790M mutant of EGFR showing close proximity with the methionine gatekeeper residue and also covalent bond to Cys-797 (right).

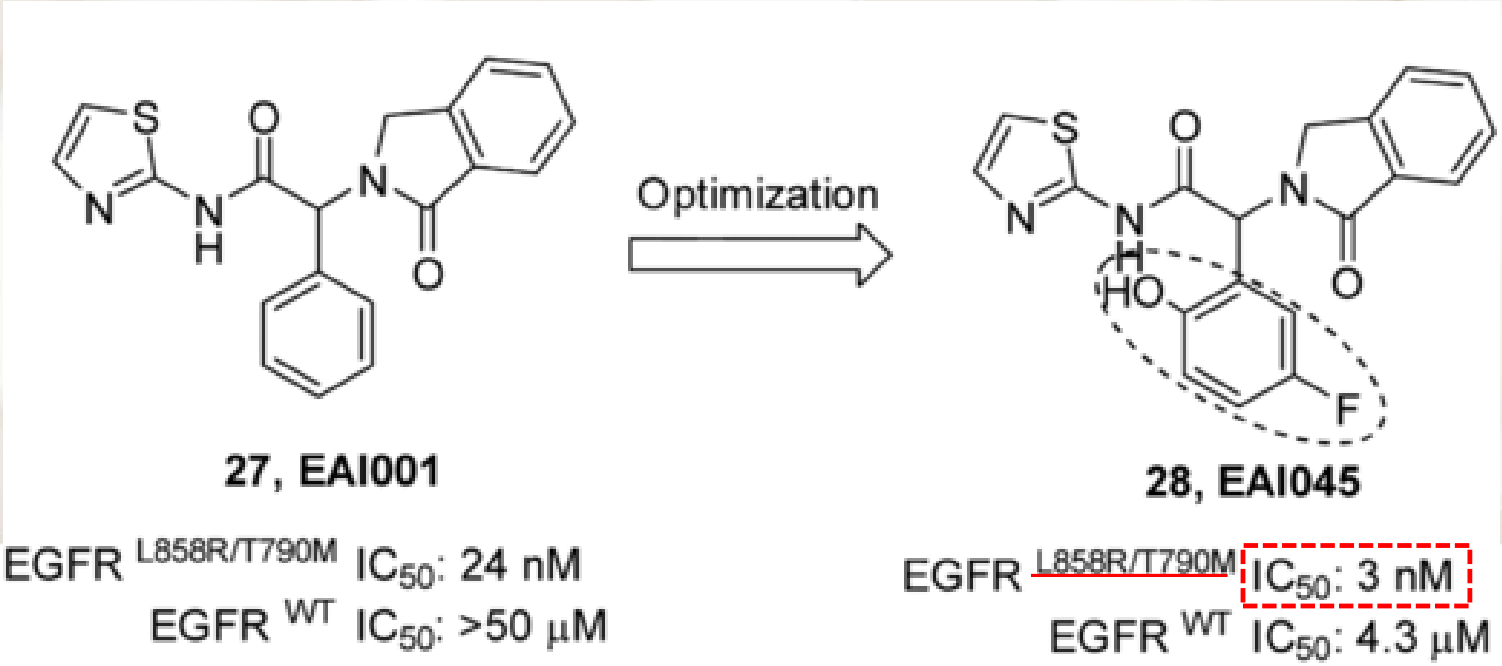
4th generation inhibitors overcoming EGFR^{C797S}

1) EAI045

2) 2-Aryl-4-aminoquinazoline compounds

3) Tri-substituted imidazole

4) 4-Amino pyrazolopyrimidine compounds

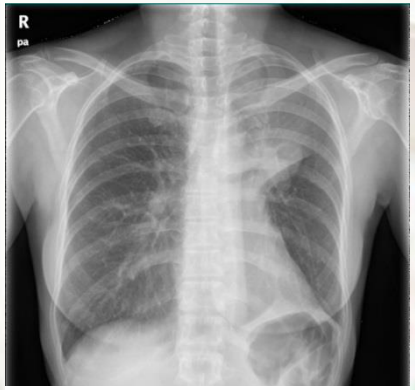


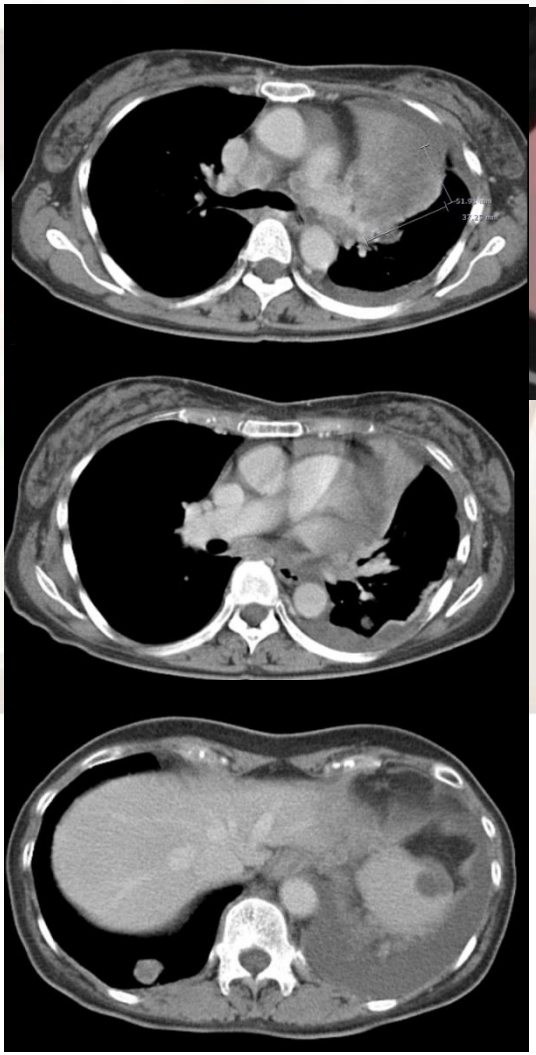
Jia Y, et al. Nature. 2016;534:129-32

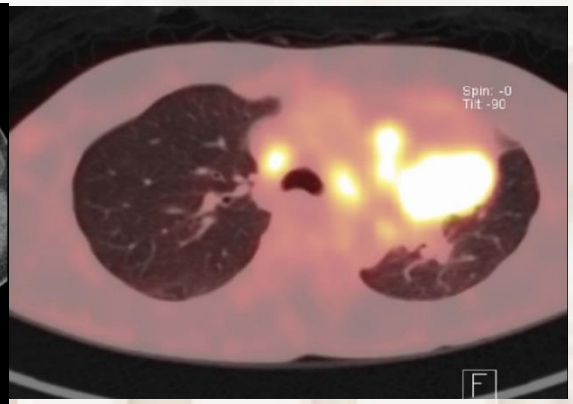
Lu X, et al. Med Res Rev. 2018. doi: 10.1002/med.21488. [Epub]

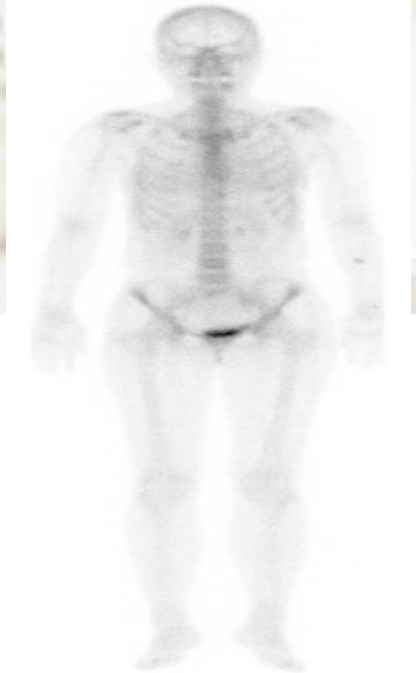
Case

: F/59, ADC, S-IV(LUL-lingula) c RLL, adrenal, Lt., bones meta (cT4N3M1b)
EGFR (+) ALK (-) ROS1 (-), GEN250 for 14month





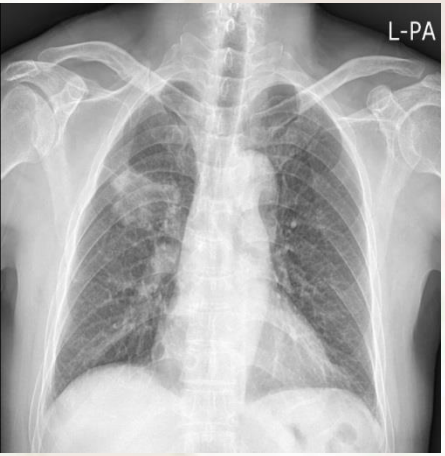


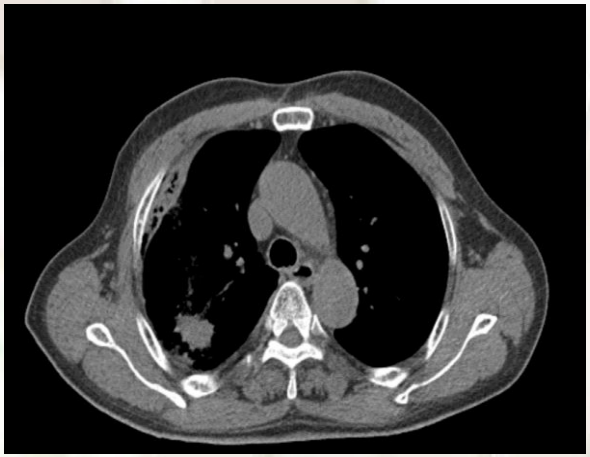


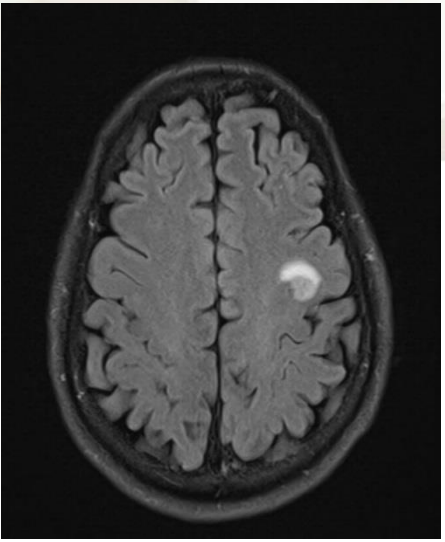
Tissue
: PD-L1(SP263: 10%) (22C3: 60%)
: T790M Cobas (-) Mutypher (-)
LB
: T790M **Cobas (+)** Muthypher (-)
=> Osimertinib start : SD

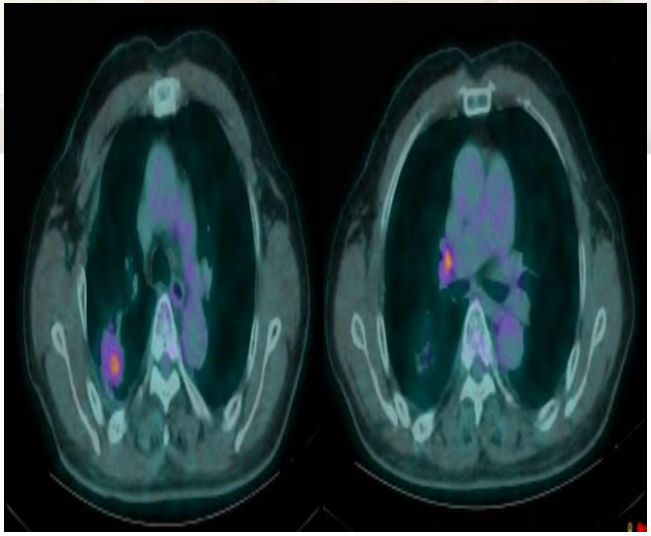
Case

:M/70, ADC (RUL) c brain meta (cT2aN0M1b stage IV)









PCNA
: 22C3 0% EGFR (-) ALK (-) ROS (-)

LB – **Cobas L858R +**

=> Afatinib 40mg start

Liquid biopsy: monitoring cancer-genetics in the blood

Emily Crowley, Federica Di Nicolantonio, Fotios Loupakis and Alberto Bardelli

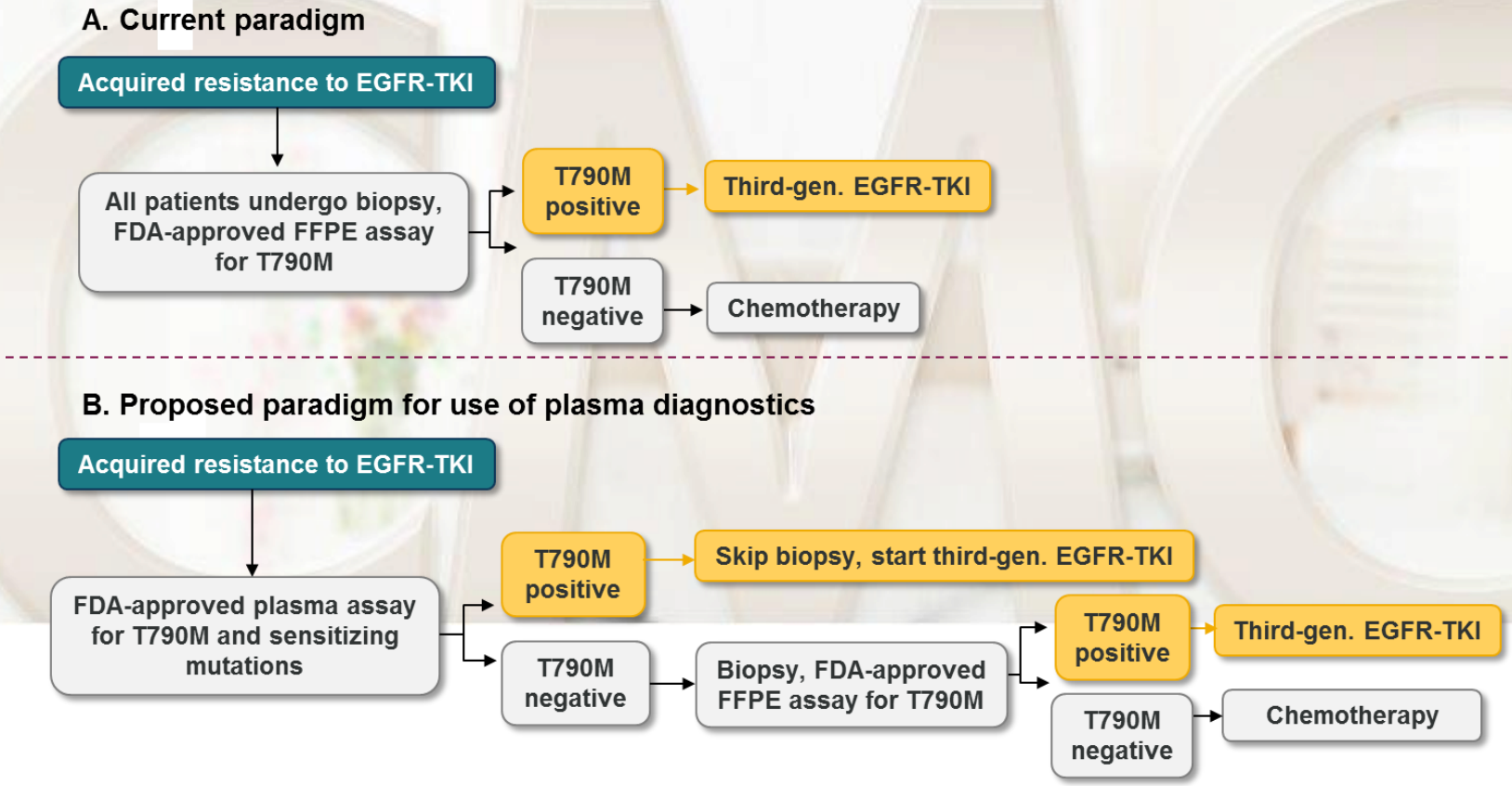
Abstract | Cancer is associated with mutated genes, and analysis of tumour-linked genetic alterations is increasingly used for diagnostic, prognostic and treatment purposes. The genetic profile of solid tumours is currently obtained from surgical or biopsy specimens; however, the latter procedure cannot always be performed routinely owing to its invasive nature. Information acquired from a single biopsy provides a spatially and temporally limited snap-shot of a tumour and might fail to reflect its heterogeneity. Tumour cells release circulating free DNA (cfDNA) into the blood, but the majority of circulating DNA is often not of cancerous origin, and detection of cancer-associated alleles in the blood has long been impossible to achieve. Technological advances have overcome these restrictions, making it possible to identify both genetic and epigenetic aberrations. A liquid biopsy, or blood sample, can provide the genetic landscape of all cancerous lesions (primary and metastases) as well as offering the opportunity to systematically track genomic evolution. This Review will explore how tumour-associated mutations detectable in the blood can be used in the clinic after diagnosis, including the assessment of prognosis, early detection of disease recurrence, and as surrogates for traditional biopsies with the purpose of predicting response to treatments and the development of acquired resistance.

Overview of plasma analyses of ctDNA in AURA trials

	Phase III: AURA3	Phase II: AURA ext and AURA2	Phase I: AURA
Treatment/dosing	Osimertinib 80 mg QD vs platinum pemetrexed	Osimertinib 80 mg QD	Osimertinib dose-escalation and dose-expansion cohorts (20–240 mg QD)
Tissue T790M status	T790M-positive	T790M-positive	T790M-positive and -negative
Analysis	Pre-planned	Pre-planned	Exploratory post hoc
Plasma assay	cobas® plasma	cobas® plasma	BEAMing
Method of comparison	cobas® FFPE tissue	NGS (MiSeq)	ddPCR or cobas® FFPE tissue

J Thorac Oncol. 2017;12(S1):S386. Abs MA08.03. 2. Jenkins S, et al. Presented at: European Lung Cancer Conference; 13-16 April 2016; Geneva, Switzerland. *J Thorac Oncol*. 2016;11(Suppl 4):S153-S154. Abs 134O_PR. 3. Oxnard GR, et al. *J Clin Oncol*. 2016;34(28):3375-3382.

Proposed paradigm for plasma genotyping



Oxnard et al. J Clin Oncol. 2016;34(28):3375-3382

Issue of LB

Primary resistance to osimertinib due to SCLC transformation: Issue of T790M determination on liquid re-biopsy

R. Minari[a], P. Bordi[a], M. Del Re[b], F. Facchinetti[a], F. Mazzoni[c], F. Barbieri[d], A. Camerini[e], C.E. Comin[f], L. Gnetti[g], C. Azzoni[g], R. Nizzoli[a], B. Bortesi[a], E. Rofi[b], P. Petreni[c], N. Campanini[g], G. Rossi[h], R. Danesi[b], M. Tiseo[a,*]

Patients

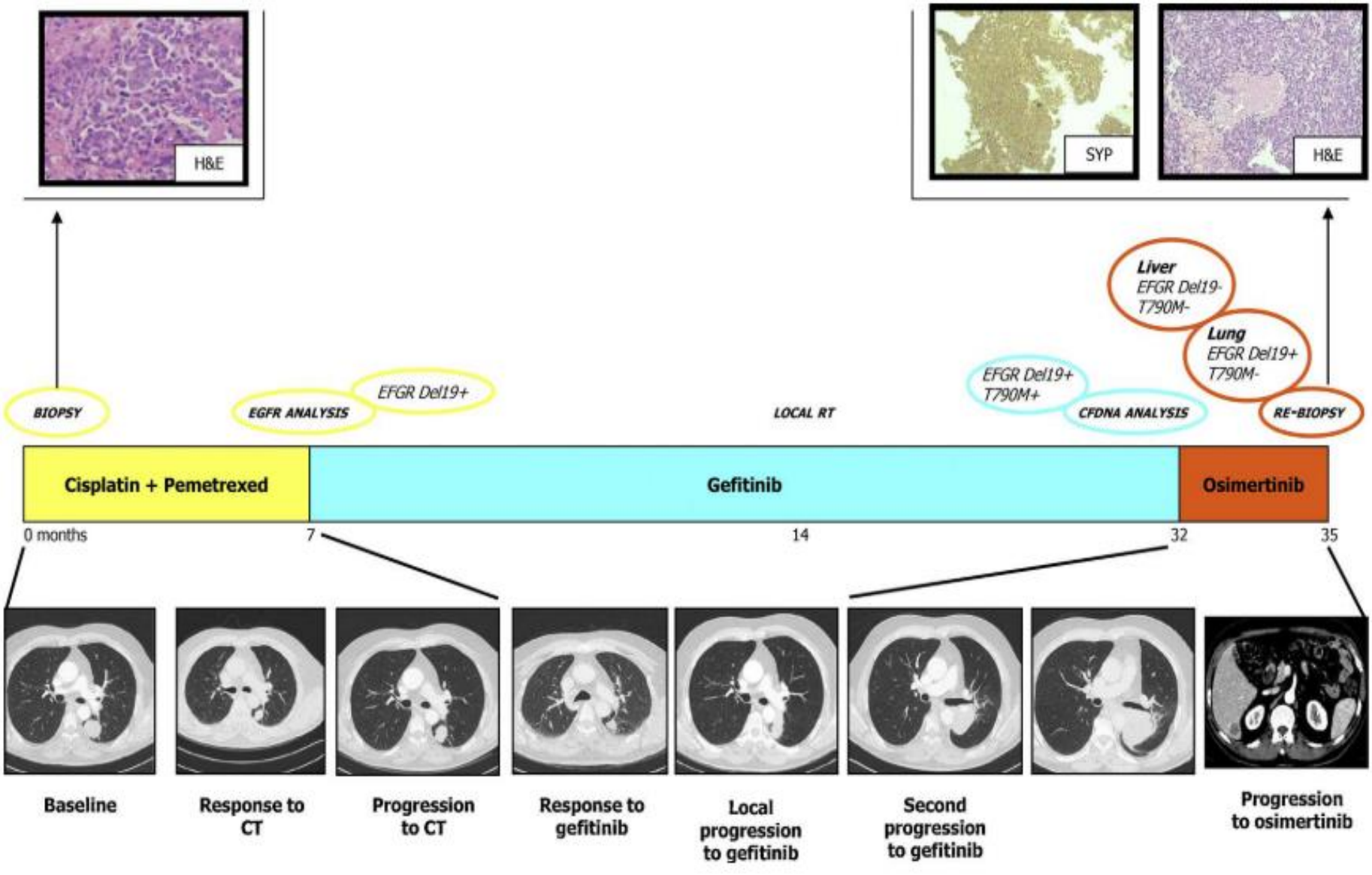
- participate in the **ASTRIS trial**

- reatment study testing the efficacy of osimertinib (80 mg os die) in advanced T790M-positive NSCLC that progressed to prior EGFR-TKI

- all the patients progressed on osimertinib at first tumor assessment after 12 weeks or less, and tissue re-biopsies revealed a switch to SCLC histology

2nd line EGFR TKI - osimertinib					
Overall 2nd line PFS (months)	Tissue re-biopsy	Re-biopsy histology	cfDNA (copies/ mL) [AF]	cfDNA thera-screen	Other anti cancer therapy
3	primary	SCLC ex19del- T790M-	–	–	–
2	liver	SCLC ex19del + T790M-	–	–	–
1	–	–	–	–	–
3	liver	SCLC ex19del- T790M-	ex19del (17000) [21.60%] T790M-	ex19del + (DCt: 3.82) T790M-	✓
	lung	SCLC ex19del + T790M-			
3	adrenal gland	SCLC L858R + T790M-	L858R + (405000) [81.40%] T790M-	L858R + (DCt: 1.46) T790M-	✓

Patient #4

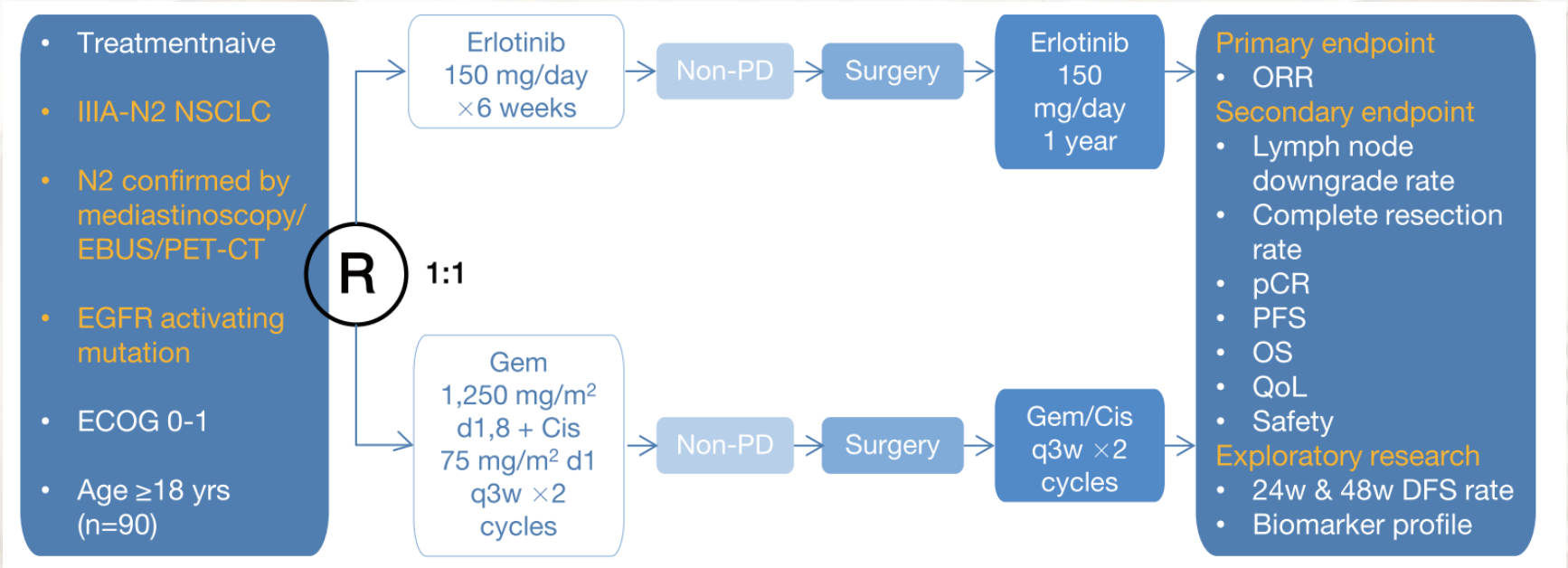

H&E
SYP
H&E
Liver
EFGR Del19-
T790M-
Lung
EFGR Del19+
T790M-
EFGR Del19+
T790M+
BIOPSY
EGFR ANALYSIS
EFGR Del19+
LOCAL RT
CFDNA ANALYSIS
RE-BIOPSY
Cisplatin + Pemetrexed
Gefitinib
Osimertinib
0 months
7
14
32
35
Baseline
Response to CT
Progression to CT
Response to gefitinib
Local progression to gefitinib
Second progression to gefitinib
Progression to osimertinib

SHORT REPORT Open Access

Phase II study of biomarker-guided neoadjuvant treatment strategy for IIIA-N2 non-small cell lung cancer based on epidermal growth factor receptor mutation status

Wenzhao Zhong†, Xuening Yang†, Honghong Yan, Xuchao Zhang, Jian Su, Zhihong Chen, Riqiang Liao, Qiang Nie, Song Dong, Qing Zhou, Jinji Yang, Haiyan Tu and Yi-Long Wu*

- Background
  : Neoadjuvant erlotinib and customized adjuvant therapy
  : to evaluate the role of biomarker-guided neoadjuvant treatment strategy in patients with IIIA-N2 NSCLC stratified by EGFR mutation status.
- Findings
  : Patients with resectable histologically documented stage IIIA-N2 NSCLC were assigned to a **neoadjuvant erlotinib** arm or **a gemcitabine/carboplatin (GC)** arm based on EGFR mutation status.
- The primary endpoint : RR.
- Secondary endpoints: PFS,OS
- Twenty-four patients with IIIA-N2 NSCLC were enrolled in the trial from January 2008 until May 2011.


Treatmentnaive
IIIA-N2 NSCLC
N2 confirmed by mediastinoscopy/ EBUS/PET-CT
EGFR activating mutation
ECOG 0-1
Age ≥18 yrs (n=90)
R
1:1
Erlotinib 150 mg/day ×6 weeks
Gem 1,250 mg/m² d1,8 + Cis 75 mg/m² d1 q3w ×2 cycles
Non-PD
Surgery
Non-PD
Surgery
Erlotinib 150 mg/day 1 year
Gem/Cis q3w ×2 cycles
Primary endpoint
ORR
Secondary endpoint
Lymph node downgrade rate
Complete resection rate
pCR
PFS
OS
QoL
Safety
Exploratory research
24w & 48w DFS rate
Biomarker profile

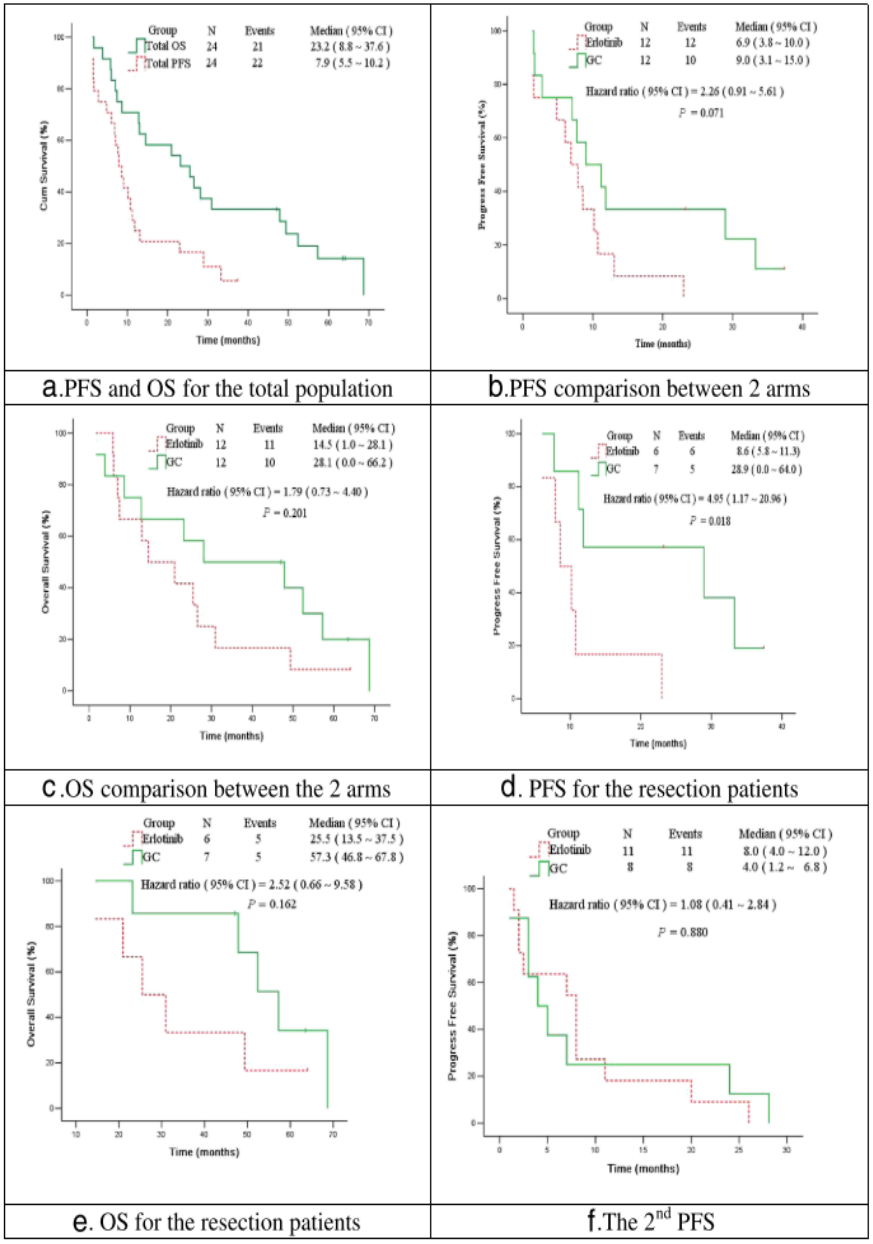


Fig. 2 PFS and OS. **a** PFS and OS for the total population; **b** PFS comparison between two arms; **c** OS comparison between two arms; **d** PFS for the resection patients; **e** OS for the resection patients; **f** The 2nd PFS. Abbreviations: GC, gemcitabine/carboplatin; PFS, progression-free survival; OS, overall survival

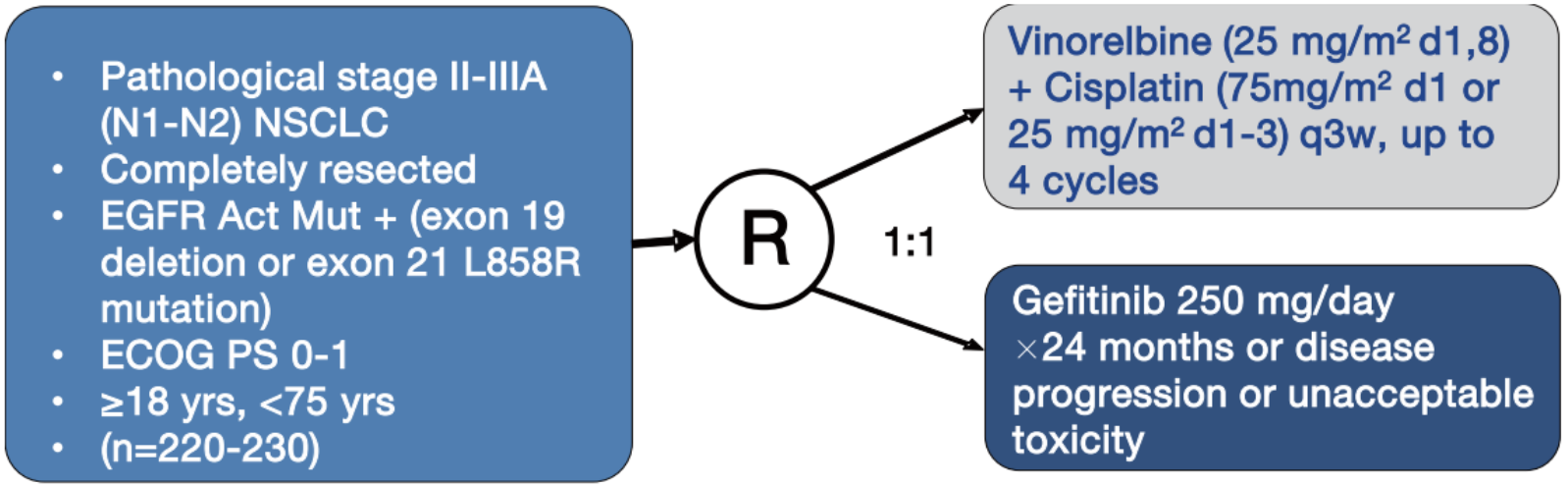
-ORR: 41.7 %
-PFS and OS: 7.9 and 23.2 months
-**RR: 58.3 % (7/12)** for the erlotinib
25.0 % (3/12) for the GC (P = 0.18)

-Median PFS
: 6.9 months vs 9.0 months (P = 0.071)
-Median OS
: 14.5 months vs 28.1 months (P = 0.201).

⇒ Improved response but
without survival benefits

Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II–IIIA (N1–N2) *EGFR*-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study

*Wen-Zhao Zhong, Qun Wang, Wei-Min Mao, Song-Tao Xu, Lin Wu, Yi Shen, Yong-Yu Liu, Chun Chen, Ying Cheng, Lin Xu, Jun Wang, Ke Fei, Xiao-Fei Li, Jian Li, Cheng Huang, Zhi-Dong Liu, Shun Xu, Ke-Neng Chen, Shi-Dong Xu, Lun-Xu Liu, Ping Yu, Bu-Hai Wang, Hai-Tao Ma, Hong-Hong Yan, Xue-Ning Yang, Qing Zhou, Yi-Long Wu, on behalf of the ADJUVANT investigators**



Primary endpoint

- Progression-free survival (PFS)

Secondary endpoints

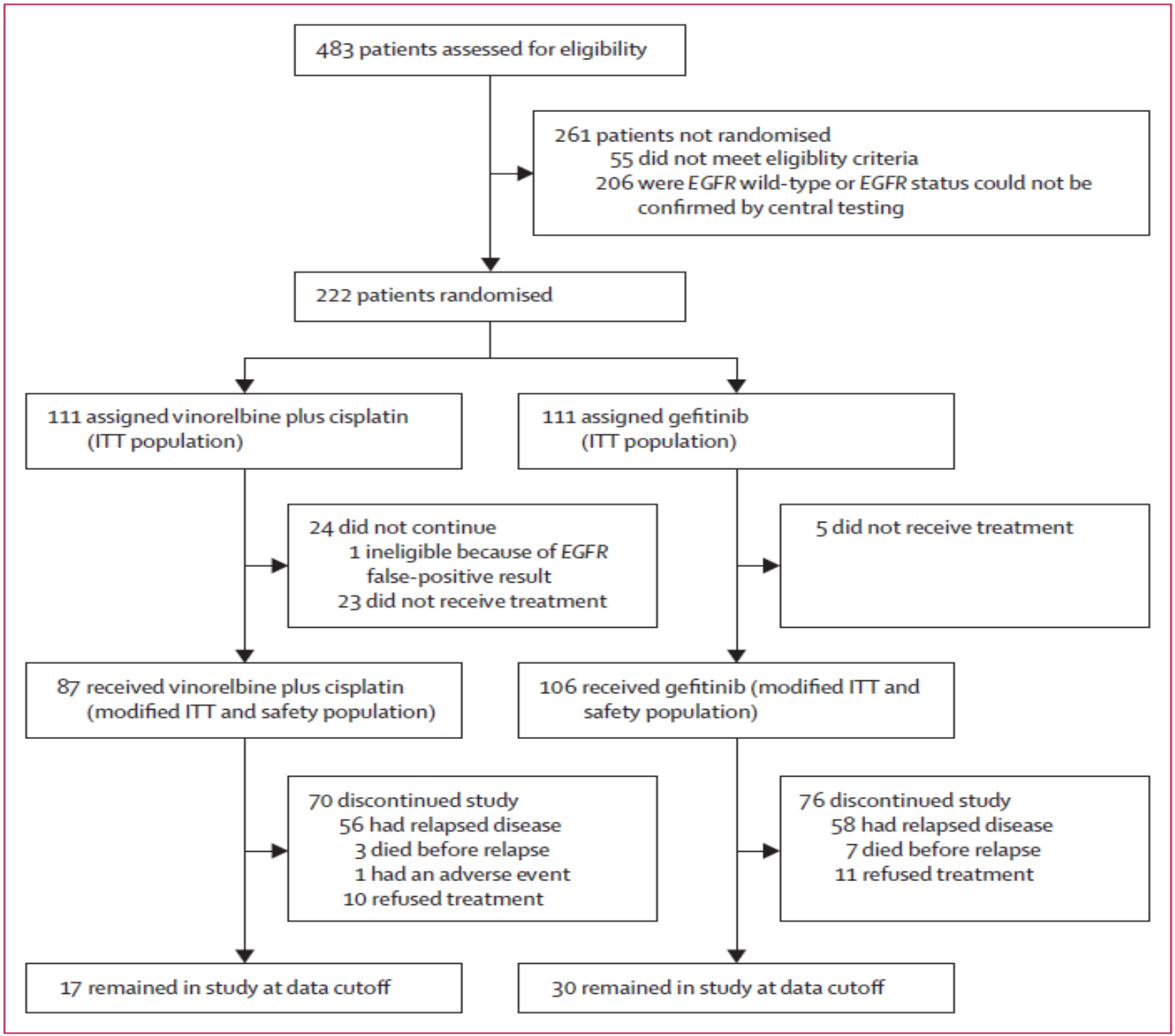
- Overall survival (OS), 3-year DFS rate, 5-year DFS rate, 5-year OS rate, safety, HR QoL (FACT-L, LCSS), exploratory biomarker analyses

Stratification factors

- **Mutation type**
- **N stage**
- **Smoking status**

Efficacy assessment

- **Every 3 months**


483 patients assessed for eligibility
261 patients not randomised
55 did not meet eligiblity criteria
206 were EGFR wild-type or EGFR status could not be confirmed by central testing
222 patients randomised
111 assigned vinorelbine plus cisplatin (ITT population)
111 assigned gefitinib (ITT population)
24 did not continue
1 ineligible because of EGFR false-positive result
23 did not receive treatment
5 did not receive treatment
87 received vinorelbine plus cisplatin (modified ITT and safety population)
106 received gefitinib (modified ITT and safety population)
70 discontinued study
56 had relapsed disease
3 died before relapse
1 had an adverse event
10 refused treatment
76 discontinued study
58 had relapsed disease
7 died before relapse
11 refused treatment
17 remained in study at data cutoff
30 remained in study at data cutoff

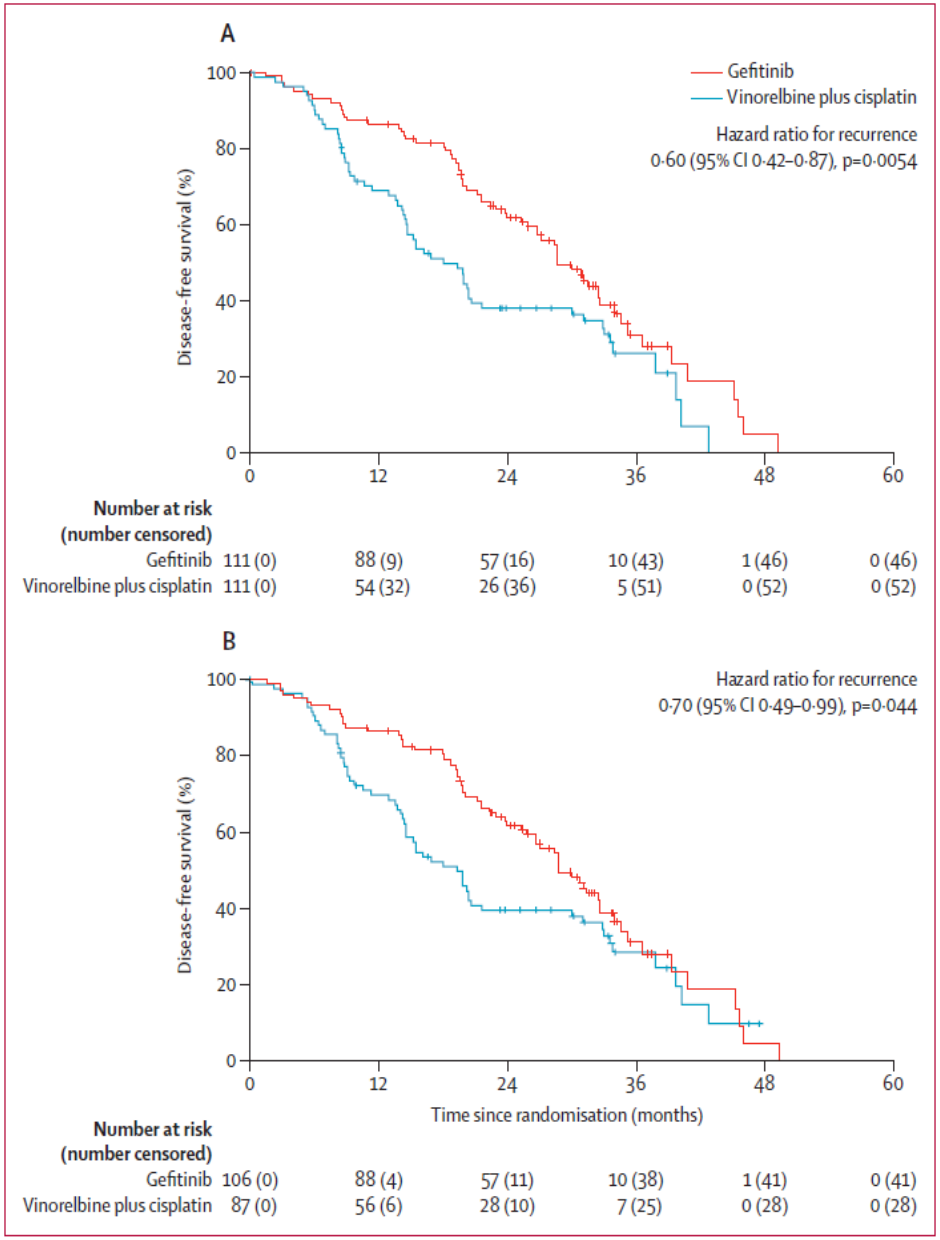


Figure 2: **Disease-free survival**
Kaplan-Meier estimates of disease-free survival as assessed by investigators in the (A) ITT and (B) modified ITT populations. Patients who had neither disease relapse or metastasis nor death were censored on their last tumour evaluable date. p values were calculated using a two-sided log-rank test. ITT=intention-to-treat.

Median disease-free survival was significantly longer with gefitinib (28·7 months)than with vinorelbine plus cisplatin (18·0 months; HR 0·60, p=0·0054).

	Total number of patients/events (n/N)	Gefitinib (n/N)	Vinorelbine plus cisplatin (n/N)	HR (95% CI)	p value	$p_{interaction}$
Sex						0·754
Male	89/46	44/23	45/23	0·60 (0·33–1·09)	0·094	
Female	130/78	65/42	65/36	0·58 (0·37–0·92)	0·020	
Smoker						0·896
No	167/95	82/49	85/46	0·61 (0·40–0·92)	0·018	
Yes	52/29	27/16	25/13	0·56 (0·27–1·19)	0·132	
EGFR mutation status						0·701
EGFR exon 19 deletion	115/63	58/33	57/30	0·55 (0·33–0·92)	0·024	
EGFR exon 21 Leu858Arg	106/61	53/32	53/29	0·62 (0·37–1·04)	0·071	
Lymph nodes						0·232
N1	77/36	40/18	37/18	0·89 (0·45–1·76)	0·743	
N2	143/87	71/47	72/40	0·52 (0·34–0·80)	0·0032	
Pathology						0·506
Adenocarcinoma	207/115	102/58	105/57	0·58 (0·40–0·84)	0·0039	
Non-adenocarcinoma	11/9	7/7	4/2	0·85 (0·16–4·46)	0·852	
Overall	**222/124**	**111/65**	**111/59**	**0·58 (0·40–0·83)**	**0·0033**	

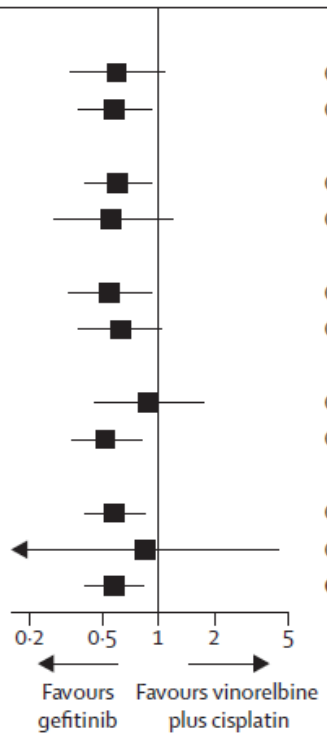


Figure 3: **Subgroup analyses of disease-free survival (ITT population)**
ITT population analyses are presented from both a Cox proportional-hazards model and the primary analysis. Disease-free survival in the overall population is presented just for the Cox proportional-hazards model. The Cox proportional-hazards model includes randomised treatment, the subgroup covariate of interest, and treatment according to subgroup interaction. HR=hazard ratio. ITT=intention-to-treat.

	Gefitinib (n=106)			Vinorelbine plus cisplatin (n=87)		
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4
Total adverse events	48 (45%)	12 (11%)	1 (1%)	28 (32%)	34 (39%)	8 (9%)
Rash	42 (40%)	1 (1%)	0	0	0	0
Diarrhoea	27 (25%)	1 (1%)	0	4 (5%)	0	0
Elevated ALT	27 (25%)	2 (2%)	0	3 (3%)	0	0
Cough	11 (10%)	0	0	15 (17%)	0	0
Elevated AST	10 (9%)	2 (2%)	0	1 (1%)	0	0
Oral ulcers	7 (7%)	1 (1%)	0	5 (6%)	0	0
Vomiting	5 (5%)	0	0	28 (32%)	8 (9%)	0
Leucopenia	4 (4%)	0	0	27 (31%)	12 (14%)	2 (2%)
Fatigue	4 (4%)	0	0	10 (11%)	0	0
Hypokalaemia	4 (4%)	0	0	5 (6%)	1 (1%)	0
Impaired hepatic function	4 (4%)	1 (1%)	0	0	0	0
Nausea	3 (3%)	0	0	32 (37%)	6 (7%)	0
Neutropenia	3 (3%)	0	0	16 (18%)	24 (28%)	6 (7%)
Insomnia	3 (3%)	1 (1%)	0	1 (1%)	0	0
Anorexia	2 (2%)	0	0	20 (23%)	0	0
Anaemia	1 (1%)	1 (1%)	0	39 (45%)	5 (6%)	0
Fever	1 (1%)	0	0	8 (9%)	1 (1%)	0
Myelosuppression	0	0	0	9 (10%)	3 (3%)	0
Hypothyroidism	0	0	0	0	1 (1%)	0
Phlebothrombosis	0	0	0	0	1 (1%)	0
Abdominal pain	0	1 (1%)	0	4 (5%)	0	0
Elevated GGT	0	1 (1%)	0	0	0	0
Epilepsy	0	1 (1%)	0	0	0	0
Intrapulmonary infection	0	1 (1%)	0	0	0	0
Brain metastases	0	1 (1%)	0	0	0	0
Urethral calculus	0	1 (1%)	0	0	0	0
Pneumothorax	0	1 (1%)	0	0	0	0
Respiratory failure	0	0	1 (1%)	0	0	0

Data are number of patients (%). Table presents grade 1–2 adverse events in 10% or more patients and all grade 3 and grade 4 adverse events. Adverse events are listed in descending order of frequency in the total patient population. There were no treatment-related deaths. ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=γ-glutamyltransferase.

Table 2: **Adverse events (safety population)**

Serious adverse events
1) 7% who received gefitinib
2) 23% who received vino+Cis

EGFR TKI plus immunotherapy

Osimertinib combined with durvalumab in EGFR-mutant non-small cell lung cancer: Results from the TATTON phase Ib trial

- ***Background***
  - : Osimertinib (AZD9291) EGFR-TKI selective for EGFRm and T790M resistance mutations
  - : durvalumab is a selective, high-affinity human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80
  - : Tolerability and safety of combining novel targeted therapies warrants investigation.
- We report updated data from the osimertinib + durvalumab (MEDI4736) arm of TATTON.

- ***Methods:***

: TATTON (NCT02143466) is a multi-arm Phase Ib trial conducted in two parts

1) dose escalation (Part A) in EGFR-TKI pretreated
2) dose expansion (Part B) in EGFR-TKI treatment naïve

: Inclusion in the osimertinib + durvalumab arm required EGFR-mutant NSCLC and no contraindication for immunotherapy, and excluded pts with a Hx of ILD

: All pts received **80mg osimertinib, orally**, qd + durvalumab at 3mg/kg or 10 mg/kg IV q2w (Part A) or 10mg/kg q2w (PartB)

: The primary objective was safety and tolerability

: Secondary objectives included clinical activity

- ***Results:*** Data are preliminary and will be updated for presentation.

- 23 and 11 pts received osimertinib + durvalumab in Part A and Part B, respectively
- AEs in Part A: nausea (39%), vomiting (39%), anaemia (35%) and diarrhoea (35%);
  Part B: ILD (64%; grouped terms), diarrhoea (55%) and nausea (45%)
- ILD was reported in 6/23 pts (26%; 2 at Gr 3/4, 0 at Gr 5) in Part A
  7/11 pts (64%; 3 at Gr 3/4, 0 at Gr 5) in Part B, with no fatalities
- Median time to ILD onset was 69 days
- **21 evaluable pts from Part A**, 12 had a partial response (PR, 9 confirmed)
  9 had stable disease (SD)
  10 evaluable pts from Part B, 8 had a PR (7 confirmed) and 2 had SD.

- ***Conclusions:*** ILD (grouped terms) have been reported in 2.9% (14 at Gr 3/4, 4 at Gr 5) of osimertinib and 2.0% (6 at Gr 3/4, 1 at Gr 5) of durvalumab monotherapy pts, compared with 38% (13/34; 5 at Gr 3/4, 0 pts at Gr 5) for the combination reported here, with no apparent increase in ILD severity.
  - Early data suggest an encouraging clinical activity profile of osimertinib + durvalumab, while the safety profile warrants further investigation.

  This arm is currently on hold.

Clinical trial identification: NCT02143466 (Release date 9 May 2014)

Nivolumab Plus Erlotinib in Patients with Epidermal Growth Factor Receptor-Mutant Advanced Non-Squamous Non-Small Cell Lung Cancer

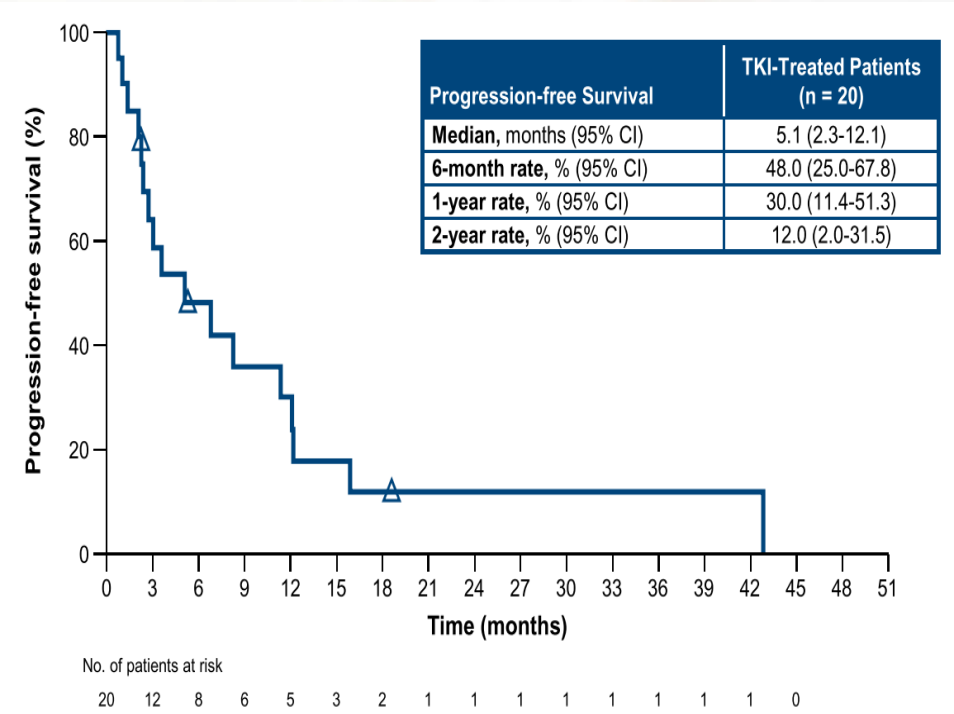
Scott Gettinger,[a1] Matthew D. Hellmann,[b1] Laura Q.M. Chow,[c] Hossein Borghaei,[d] Scott Antonia,[e] Julie R. Brahmer,[f] Jonathan W. Goldman,[g] David E. Gerber,[h] Rosalyn A. Juergens,[i] Frances A. Shepherd,[j] Scott A. Laurie,[k] Tina C. Young,[l] Xuemei Li,[l] William J. Geese,[l] Naiyer Rizvi[b2]

Methods :

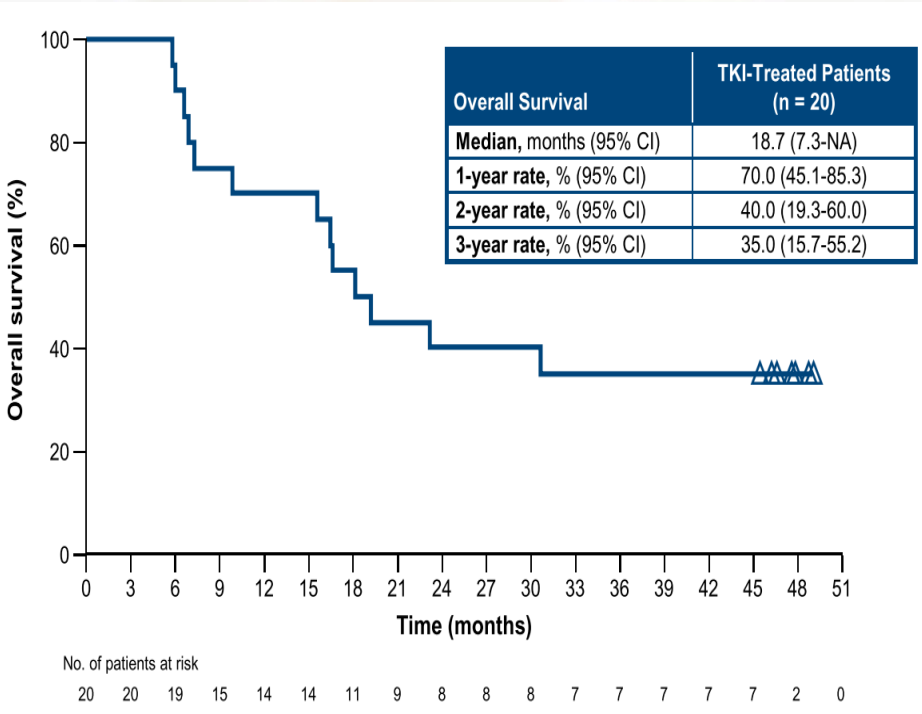
- Pt with EGFR mutant who were **TKI naïve or TKI treated but no received chemotherapy**
- cytologically **confirmed stage IIIB/IV** non-squamous NSCLC harboring an EGFR mutation
- Nivolumab 3mg /kg every 2 weeks + Erlotinib 150mg /day until disease progression or unacceoptable toxicity
- Primary objective was safety and tolerability

Results

- 20 Pts
- Tx-related G3 toxicities occurred in 5Pts with no G>4 toxicities



Progression-free Survival	TKI-Treated Patients (n = 20)
Median, months (95% CI)	5.1 (2.3-12.1)
6-month rate, % (95% CI)	48.0 (25.0-67.8)
1-year rate, % (95% CI)	30.0 (11.4-51.3)
2-year rate, % (95% CI)	12.0 (2.0-31.5)



Overall Survival	TKI-Treated Patients (n = 20)
Median, months (95% CI)	18.7 (7.3-NA)
1-year rate, % (95% CI)	70.0 (45.1-85.3)
2-year rate, % (95% CI)	40.0 (19.3-60.0)
3-year rate, % (95% CI)	35.0 (15.7-55.2)

Treatment-related grade 3 toxicities occurred in five patients (liver enzyme elevations, n = 2; diarrhea, n = 2; weight loss, n = 1), with no grade ≥4 toxicities.

EGFR TKI plus anti-angiogenic drugs

Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): a double-blind, placebo-controlled, phase 3 trial

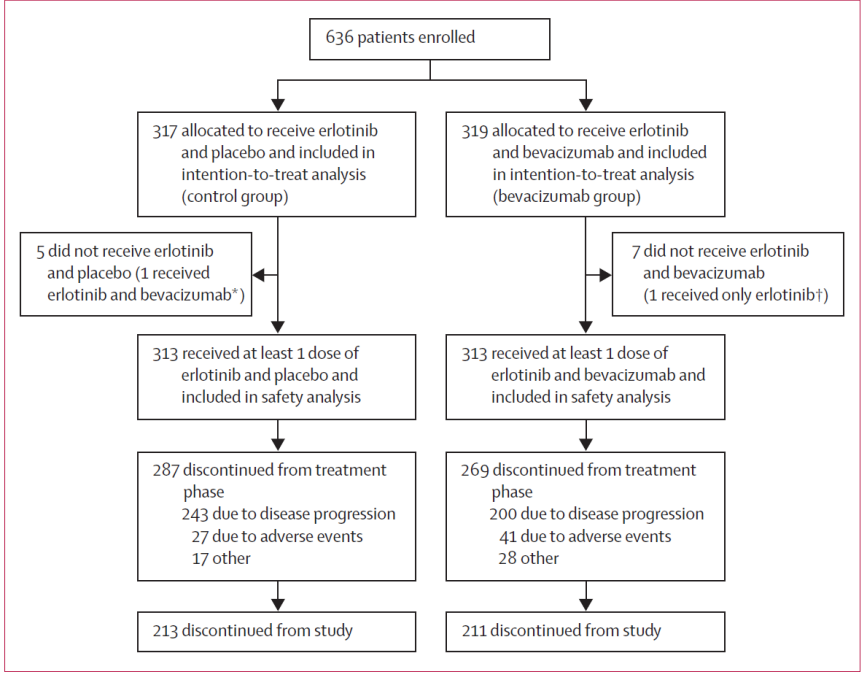
Roy S Herbst, Rafat Ansari, Frederique Bustin, Patrick Flynn, Lowell Hart, Gregory A Otterson, Gordana Vlahovic, Chang-Heok Soh, Paula O'Connor, John Hainsworth

Background

: **Bevacizumab** and erlotinib target different tumour growth pathways with little overlap in their toxic effect profiles.

: On the basis of promising results from a phase 1/2 trial assessing safety and activity of erlotinib plus bevacizumab for recurrent or refractory NSCLC, we aimed to assess efficacy and safety of this combination in a phase 3 trial.

- Methods
  : double-blind, placebo-controlled, randomised phase 3 trial (BeTa)
  : **recurrent or refractory NSCLC who presented to 177** study sites in 12 countries after failure of first-line treatment
  : randomly allocated in a one-to-one ratio to
  1) receive erlotinib plus bevacizumab (bevacizumab group)
  2) erlotinib plus placebo (control group) according to a computer-generated randomisation sequence by use of an interactive voice response system
  : primary endpoint was OS in all enrolled patients, Patients, study staff , and investigators were masked to treatment assignment
  : We assessed safety by calculation of incidence of adverse events and tissue was collected for biomarker analyses
  : ClinicalTrials.gov, number NCT00130728.



Median OS: 9.3 month vs 9.2 month

PFS: 3.4 month vs 1.7 month

Without significance

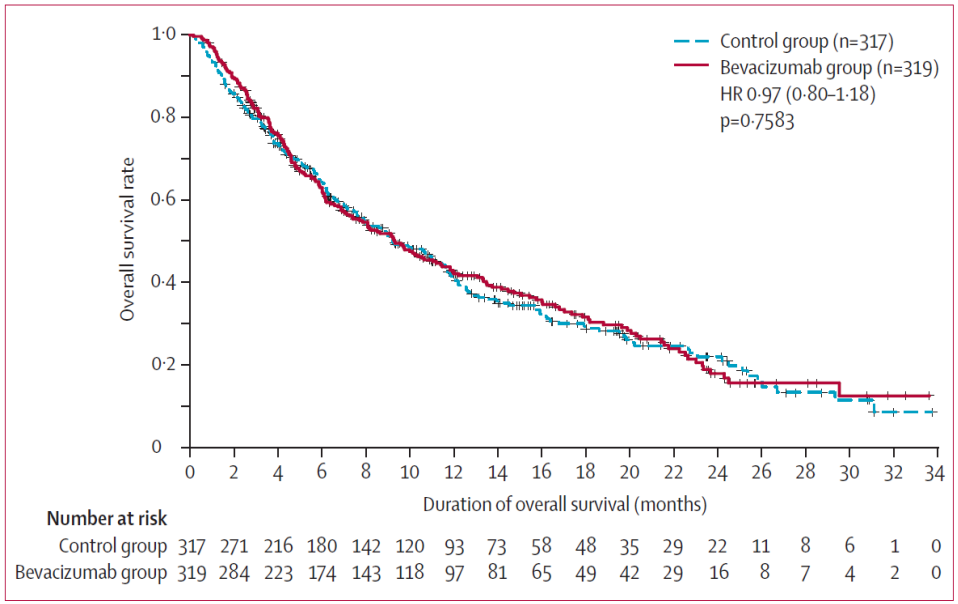


Figure 2: **Kaplan-Meier curves for overall survival**

Overall survival is shown for assessable patients randomly allocated to erlotinib plus bevacizumab (bevacizumab group) or erlotinib plus placebo (control group). The p value for overall survival is based on a stratified log-rank test; stratification factors were Eastern Cooperative Oncology Group performance status, smoking history, and sex.

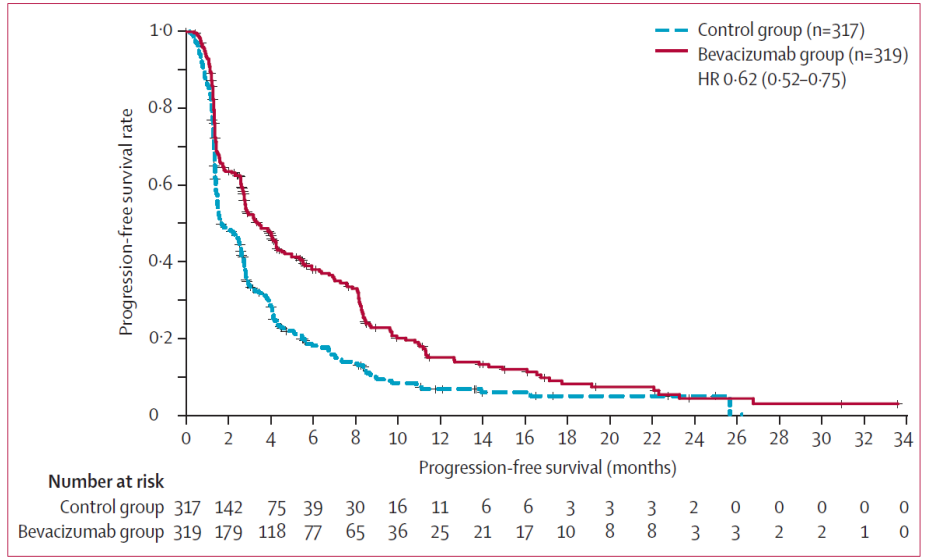
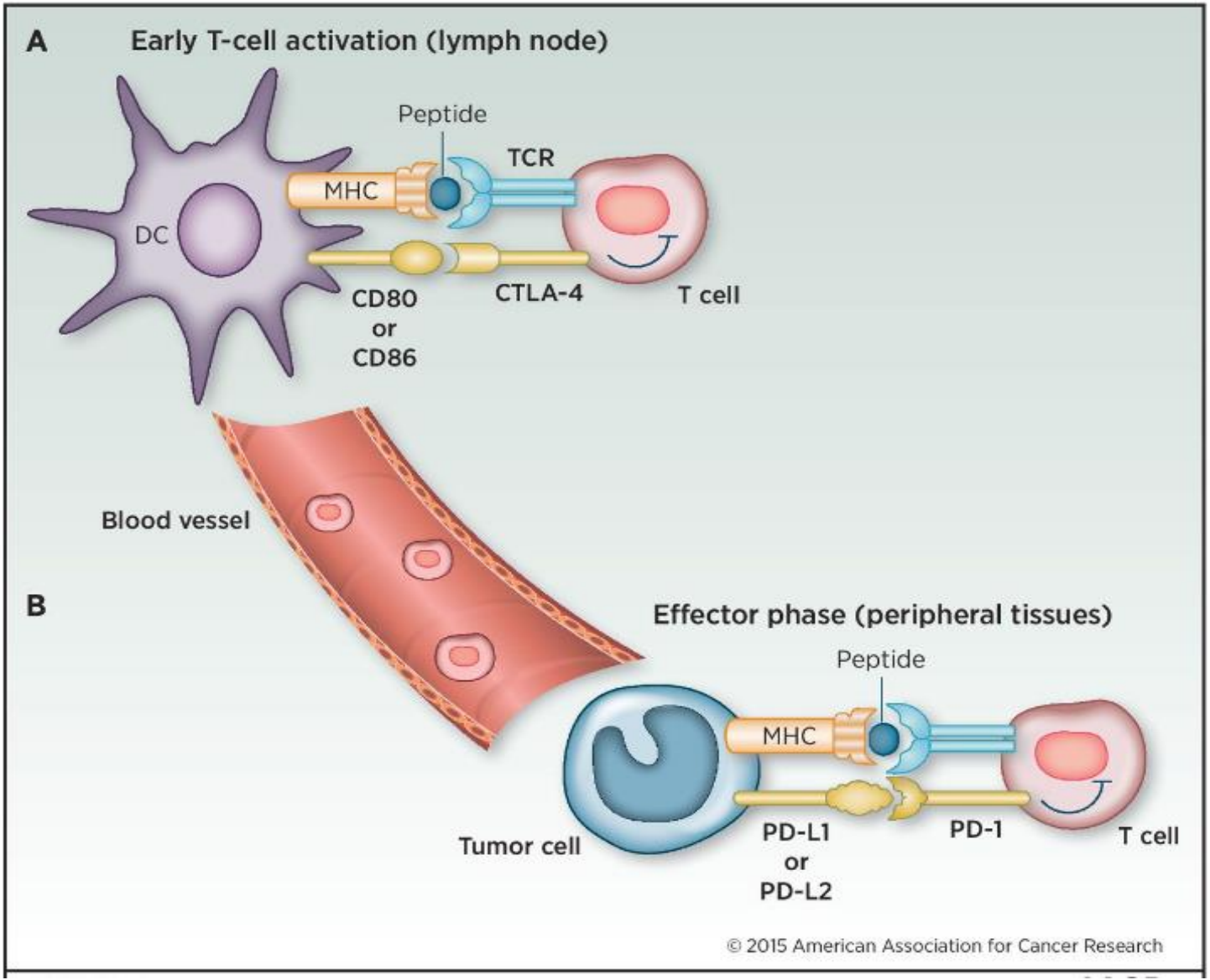


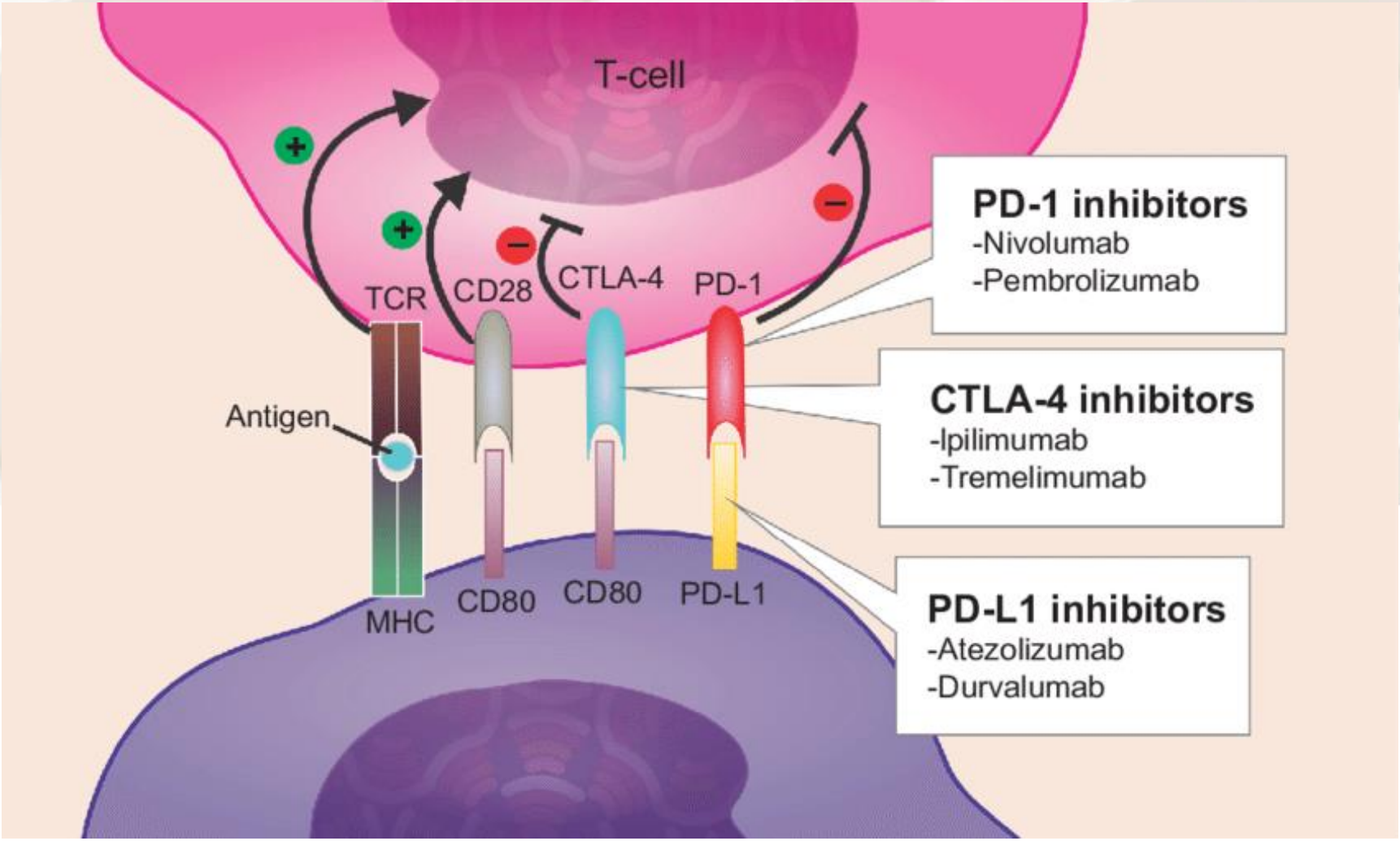
Figure 4: **Kaplan-Meier curves for progression-free survival**

Progression-free survival is shown for assessable patients in the bevacizumab group (randomly allocated to erlotinib plus bevacizumab) and control group (randomly allocated to erlotinib plus placebo). Because of the prespecified use of fixed sequence testing to control the overall type I error rate, which required that the primary endpoint (overall survival) be significant before statistical testing of key secondary endpoints, progression-free survival results could not be defined as significant.

Immune Checkpoint Inhibitor

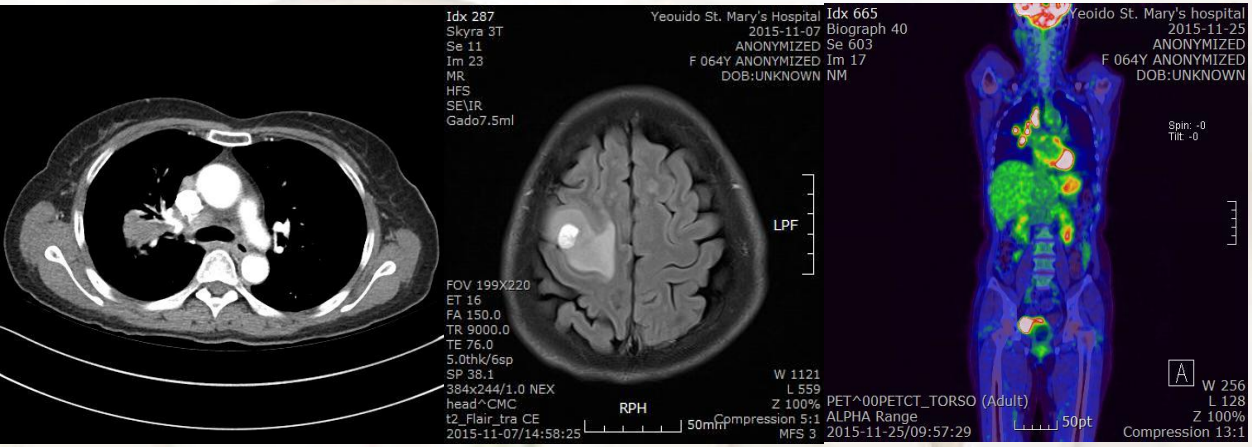


Immune Checkpoint Inhibitor

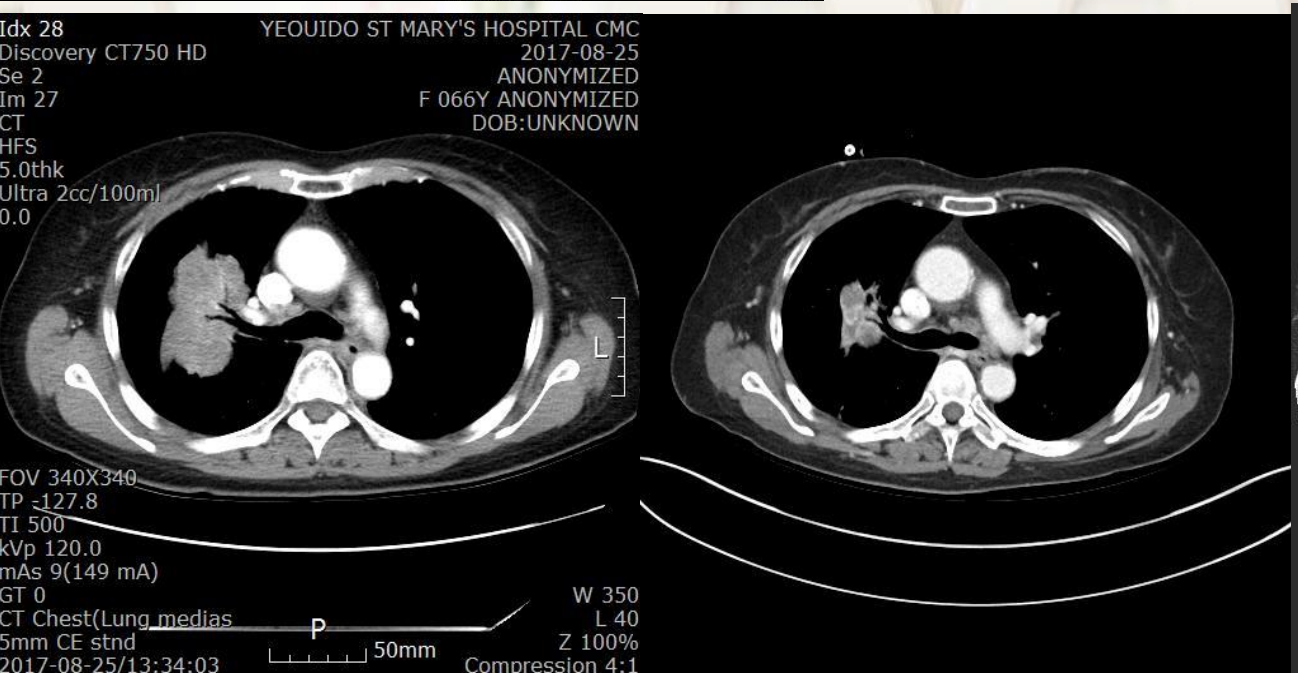


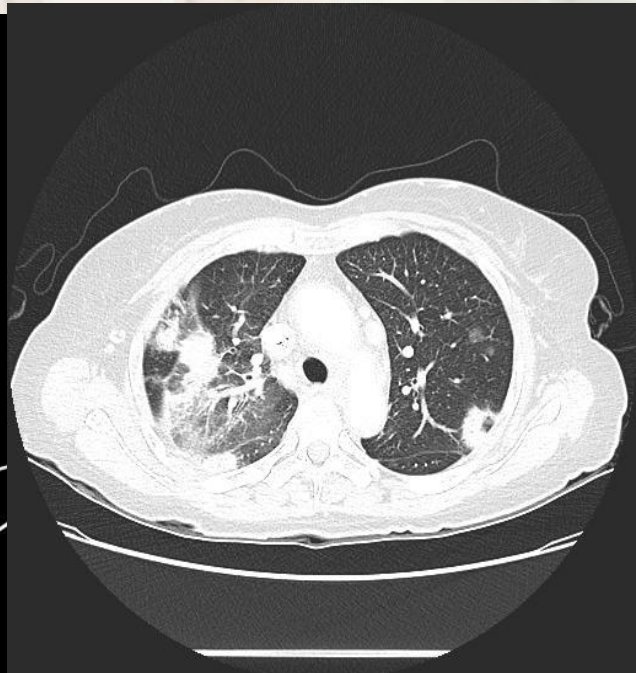
Case

: F/67, ADC, T3N3 with brain meta
EGFR(-) ALK(-) RET(-) ROS1(-) MET(-) 2016.08.
ReBx: EGFR(-) ALK(-) ROS1(-) PD-L1(22C3: positive 58 %)



- 2015.11. cyberknife on brain
  2015.12. 1-1 Pem Cis
  2016.06. Pem maintenance
  2016.08. 2-1 GEN250
  2016.11. 3-1 Gem Carbo
  2017.09. 4-1 Pembrilizumab
  2018.01. 4-6 Pembrilizumab





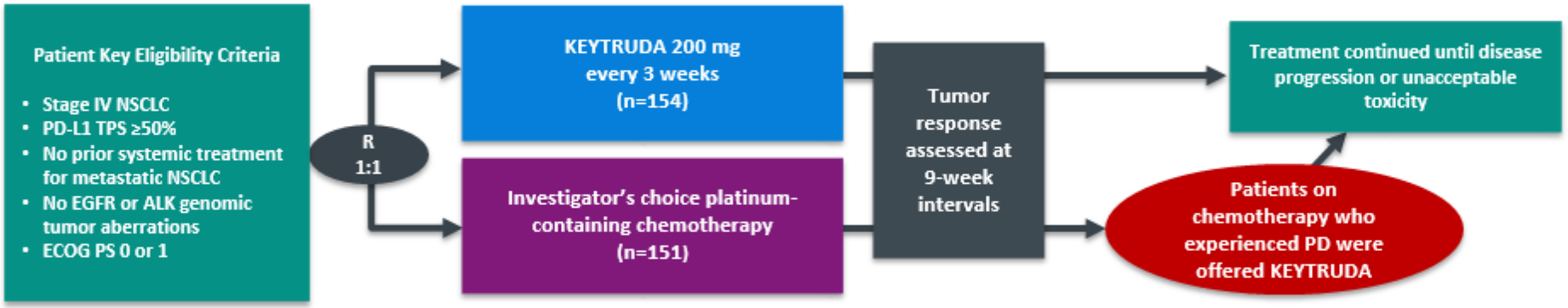
Pembrolizumab (Kytruda)

KEYNOTE-024: Study Design

KEYTRUDA® (pembrolizumab): Only* single anti–PD-1 agent to show unprecedented survival in first-line NSCLC with high PD-L1 expression [2-4]

KEYTRUDA (pembrolizumab)

- Randomized, open-label, multicenter trial of patients with previously untreated advanced NSCLC whose tumors expressed high levels of PD-L1 (TPS ≥50%)[1]



- Primary end point was progression-free survival (PFS) as assessed by blinded independent central review using RECIST v1.1.[1]
- Secondary end points were overall survival (OS) and objective response rate (ORR) as assessed by blinded independent central review using RECIST v1.1.[1]

ALK = anaplastic lymphoma kinase; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; NSCLC = non–small cell lung cancer; PD = progressive disease; PD-L1 = programmed death ligand 1; R = randomized; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1; TPS = tumor proportion score.

* As of November 13, 2017

1. Reck M *et al.* Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer *N Engl J Med.* 2016;375(14):1–11. 2. 키트루다 허가사항. 식품의약품안전처. 3. Nivolumab 허가사항. 식품의약품안전처. 4. Atezolizumab 허가사항. 식품의약품안전처

ONCO-1222402-0022 11/2019

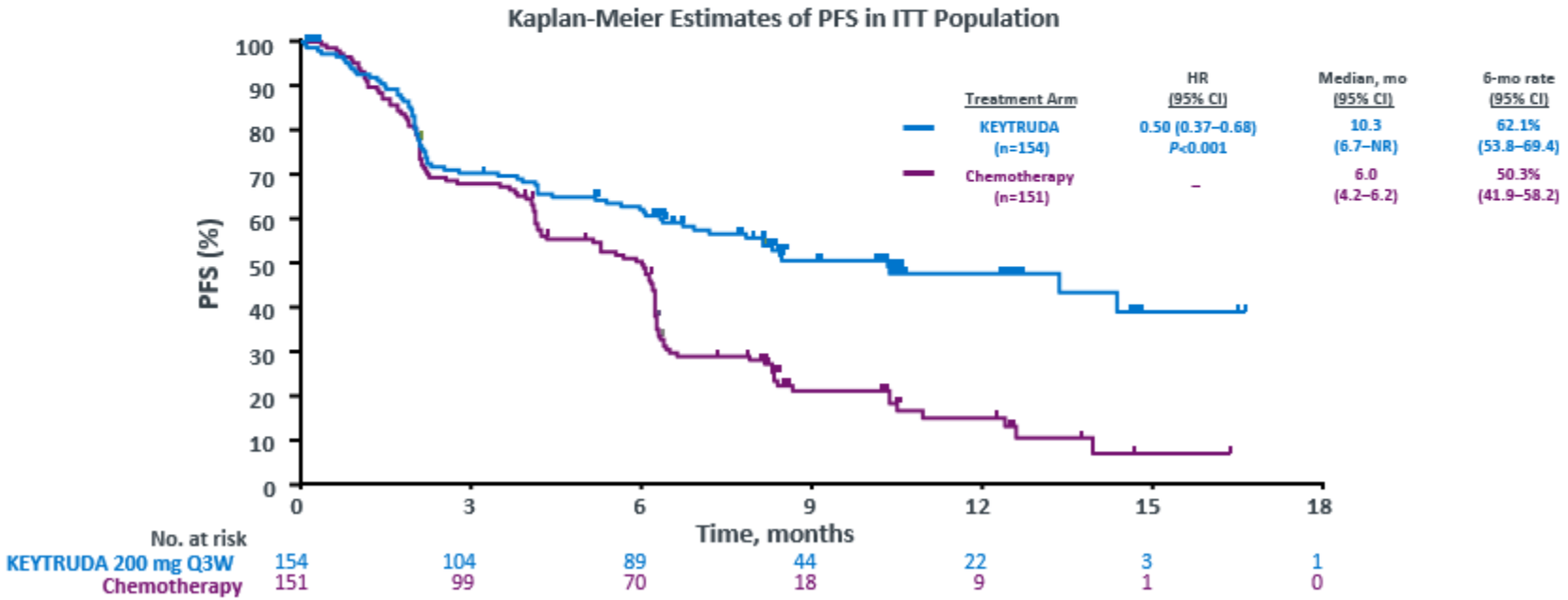
Pembrolizumab (Kytruda)

KEYNOTE-024: PFS (Primary end point)

Superior PFS with KEYTRUDA® 200mg Q3W vs. Chemotherapy in patients with PD-L1 TPS ≥50%

KEYTRUDA (pembrolizumab) Injection 100 mg

- Superior PFS with KEYTRUDA® 200 mg Q3W vs chemotherapy (HR 0.50, 95% CI, 0.37–0.68; *P*<0.001) in patients with PD-L1 TPS ≥50%
  - 50% reduction in risk of disease progression or death with KEYTRUDA® vs chemotherapy



CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; mo = month; NR = not reached; PD-L1 = programmed death ligand 1; PFS = progression-free survival; Q3W = every 3 weeks; TPS = tumor proportion score.

1. Reck M *et al.* Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer *N Engl J Med.* 2016;375(14):1–11.

Pembrolizumab (Kytruda)

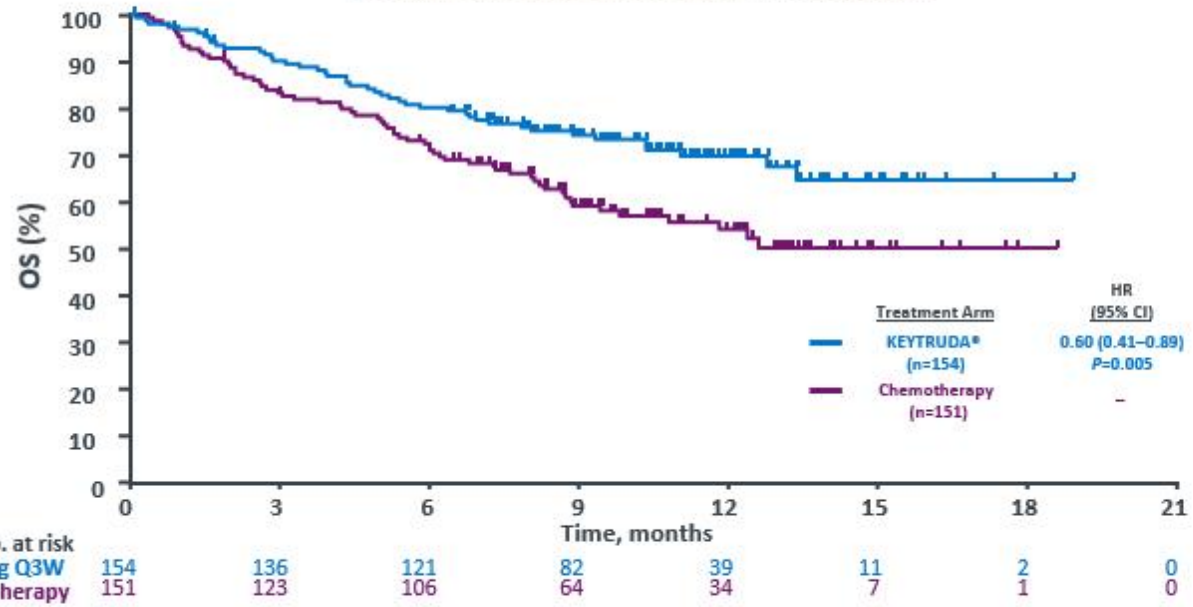
KEYNOTE-024: OS (Secondary end point)

Superior OS with KEYTRUDA® 200mg Q3W vs. chemotherapy in patients with PD-L1 TPS ≥50%*

KEYTRUDA (pembrolizumab)

- Superior OS with KEYTRUDA® 200 mg Q3W vs chemotherapy (HR 0.60, 95% CI, 0.41–0.89; *P*=0.005) in patients with PD-L1 TPS ≥50%
  - 40% reduction in risk of death with KEYTRUDA® vs chemotherapy

Kaplan-Meier Estimates of OS in ITT Population[1]



Treatment Arm	HR (95% CI)	Median, mo (95% CI)	6-mo rate (95% CI)
KEYTRUDA® (n=154)	0.60 (0.41–0.89) *P*=0.005	Not reached	80.2% (72.9–85.7)
Chemotherapy (n=151)	–	Not reached	72.4% (64.5–78.9)

No. at risk								
KEYTRUDA® 200 mg Q3W	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; mo = month; OS = overall survival; PD-L1 = programmed death ligand 1; Q3W = every 3 weeks; TPS = tumor proportion score.

* The external data and safety monitoring committee recommended that the trial be stopped early to give the patients who were receiving chemotherapy the opportunity to receive pembrolizumab based on the second interim analysis.

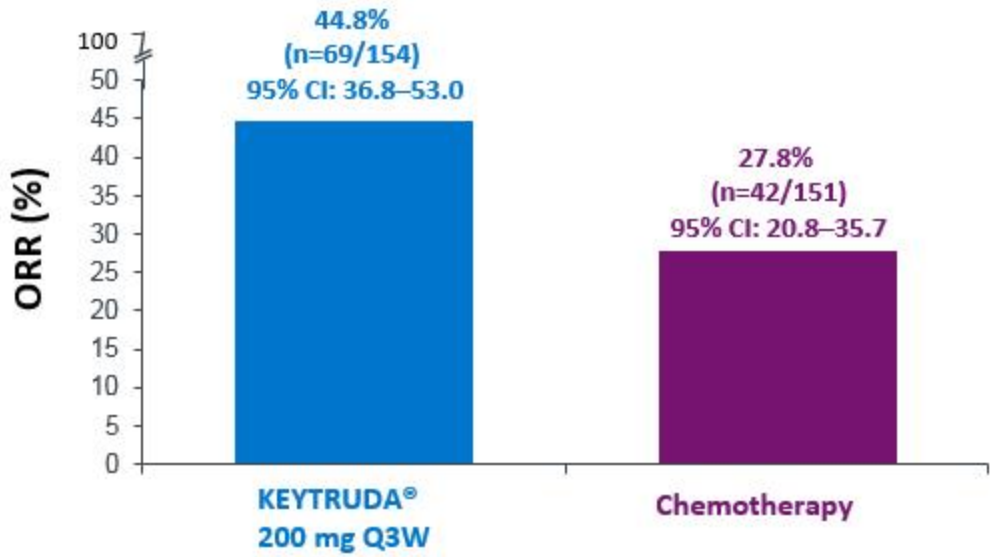
1. Reck M *et al*. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer *N Engl J Med*. 2016;375(14):1–11.

Pembrolizumab (Kytruda)

KEYNOTE-024: ORR(Secondary end point)

ORR was greater with KEYTRUDA® 200mg Q3W vs. Chemotherapy in patients with PD-L1 ≥50%

KEYTRUDA (pembrolizumab)



- Median duration of response was not reached (range, 1.9+ to 14.5+ months) in the KEYTRUDA group vs 6.3 months (range, 2.1+ to 12.6+ months) in the chemotherapy group.[1]

CI = confidence interval; ORR = objective response rate; PD-L1 = programmed death ligand 1; Q3W = every 3 weeks; TPS = tumor proportion score..

1. Reck M *et al.* Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer *N Engl J Med.* 2016;375(14):1–11.

Pembrolizumab (Kytruda)

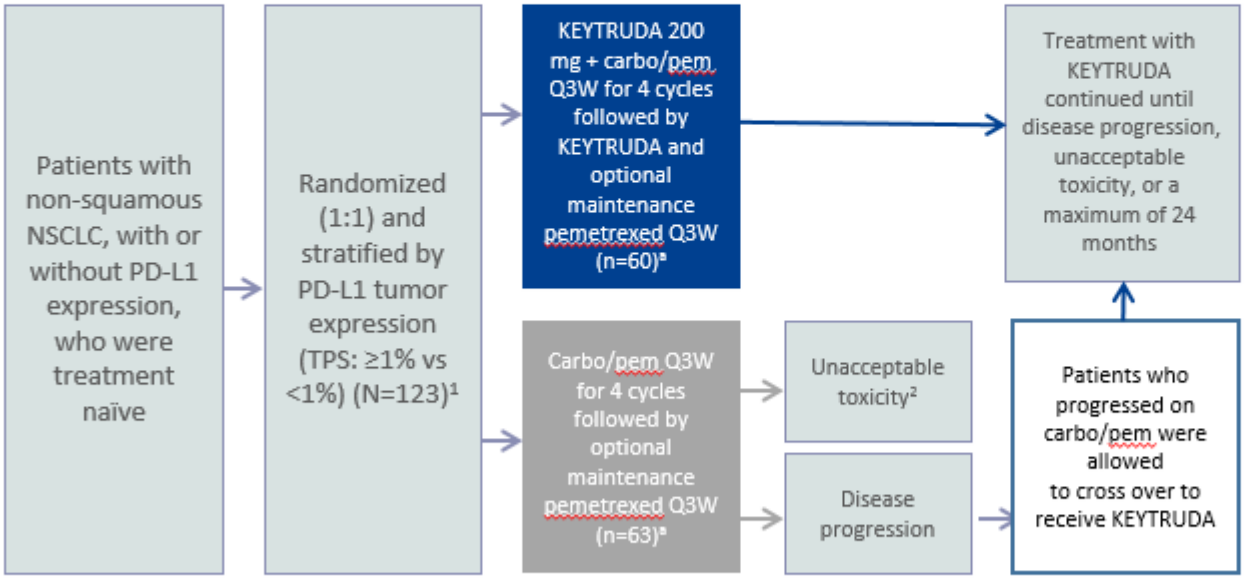
KEYNOTE-021 cohort G: Study Design

FIRST-LINE COMBINATION TRIAL in non-squamous NSCLC WITH OR WITHOUT PD-L1 EXPRESSION[1]

KEYTRUDA (pembrolizumab) Injection 100 mg

KEYNOTE-021: A phase 2, randomized, multicohort, open-label, multicenter trial-cohort G was controlled and included non-squamous mNSCLC.

The primary endpoint was objective response rate(ORR).
Secondary endpoints were progression-free survival(PFS), duration of response and overall survival(OR).



- Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator.[1]
- Patients with an autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or patients who had received more than 30 Gy of thoracic radiation within 6 months were ineligible.[1]

carbo = carboplatin; **pem** = pemetrexed; **NSCLC** = non–small cell lung carcinoma; **mNSCLC** = metastatic NSCLC ; **PD-L1** = programmed death ligand 1 ; **Q3W** = every 3 weeks

[a] 60 were randomly assigned to the pembrolizumab plus chemotherapy group and 63 to the chemotherapy alone group. Patients received either KEYTRUDA 200 mg with pemetrexed 500 mg/m² and carboplatin AUC 5 mg/mL/min intravenously Q3W for 4 cycles followed by KEYTRUDA 200 mg intravenously Q3W and optional pemetrexed 500 mg/m2 Q3W or pemetrexed 500 mg/m² and carboplatin AUC 5 mg/mL/min intravenously Q3W for 4 cycles followed by optional pemetrexed 500 mg/m² Q3W.

Reference 1. Langer CJ, *et al*, for the KEYNOTE-021 investigators. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol.* 2016;17(11):1497–1508.

ONCO-1222402-0022 11/2019

Pembrolizumab (Kytruda)

KEYNOTE-021 cohort G: FIRST-LINE COMBINATION TRIAL in non-squamous NSCLC WITH OR WITHOUT PD-L1 EXPRESSION[1]

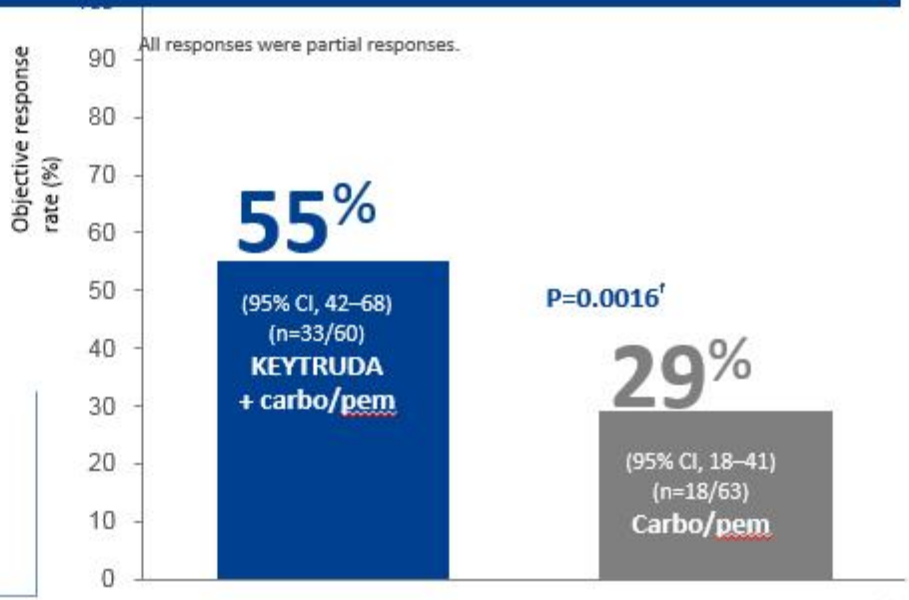
Superior ORR: 55% vs. 29%

KEYTRUDA (pembrolizumab) Injection 100 mg

ORR(objective responsive rate)[1] : Primary endpoint

Superior ORR with KEYTRUDA + carbo/pem vs carbo/pem alone[1]

ORR in KEYNOTE-021G[e]



ORR NEARLY DOUBLED with KEYTRUDA + carbo/pem with or without PD-L1 expression

Adapted from Langer, *et al*[1]

- **92% of responders had ongoing responses** with KEYTRUDA + carbo/pem vs 81% with carbo/pem alone (response duration ≥6 months) based on Kaplan-Meier estimation.[1]
- **Median duration of response was not reached** with KEYTRUDA + carbo/pem (range: 4.2-9.0 months) or carbo/pem alone (range: 3.5–10.4 months) at the time of analysis.[1]

Earlier time to response

- 1.5-month median time to response (IQR 1.4–2.8) with KEYTRUDA + carbo/pem vs 2.7 months (1.4–2.8) with carbo/pem alone.[1]

carbo = carboplatin; pem = pemetrexed; PD-L1 = programmed death ligand 1; CI = confidence interval; IQR = interquartile range

[e] ORR was assessed by BICR using RECIST 1.1. [f] Based on Miettinen-Nurminen method.

Reference 1. Langer CJ, *et al*, for the KEYNOTE-021 investigators. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol.* 2016;17(11):1497–1508.

Pembrolizumab (Kytruda)

KEYNOTE-021 cohort G: FIRST-LINE COMBINATION TRIAL in non-squamous NSCLC WITH OR WITHOUT PD-L1 EXPRESSION[1]

Superior PFS : 13 months vs. 8.9months (HR 0.53)

KEYTRUDA (pembrolizumab) Injection 100 mg

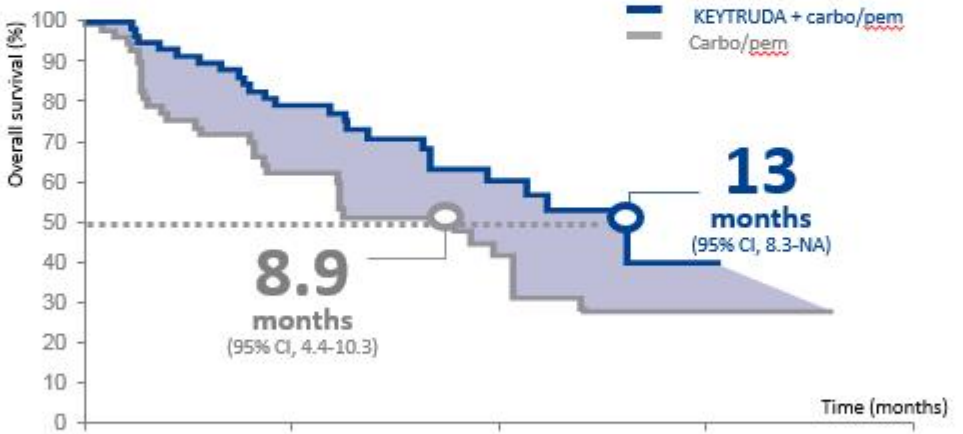
PFS(progression-free survival)[1] : Secondary endpoint

Superior PFS with KEYTRUDA + carbo/pem vs carbo/pem alone

Kaplan-Meier Estimates of PFS in KEYNOTE-021G[1,b,c]

HR=0.53; 95% CI, 0.31–0.91; P=0.010[d]

13.0-
MONTH MEDIAN PFS with KEYTRUDA + carbo/pem with or without PD-L1 expression



Number at risk					
KEYTRUDA + carbo/pem	60 (0)	43 (5)	20 (20)	1 (36)	0 (37)
Carbo/pem	63 (0)	32 (10)	13 (21)	1 (29)	0 (30)

Adapted from Langer, *et al*[1]

- Number of events (death and disease progression) observed in each treatment arm: 23 (38%) with KEYTRUDA + carbo/pem and 33 (52%) with carbo/pem alone.[1]

carbo = carboplatin; pem = pemetrexed; PD-L1 = programmed death ligand 1; CI = confidence interval; HR = hazard ratio; ; NA = not reached

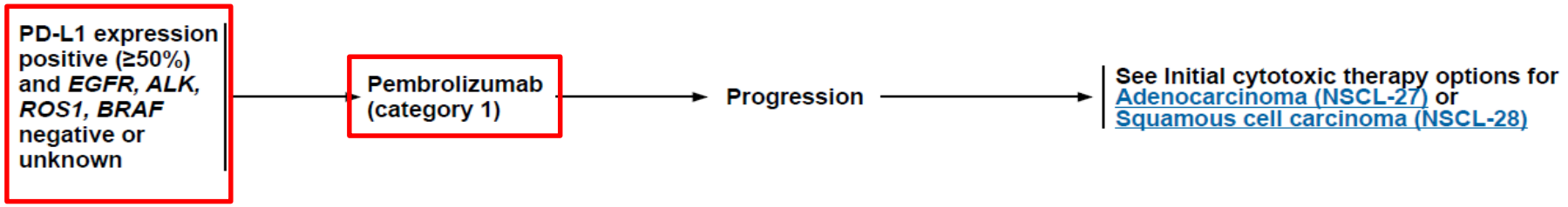
[b] At data cutoff, median follow-up was 10.6 months.[1] [c] PFS was assessed by BICR using RECIST 1.1.[d] HR based on the Cox proportional hazard model and P-value based on the log-rank test, both stratified by PD-L1 status (TPS <1% vs TPS ≥1%).

Reference 1. Langer CJ, *et al*, for the KEYNOTE-021 investigators. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol.* 2016;17(11):1497–1508.

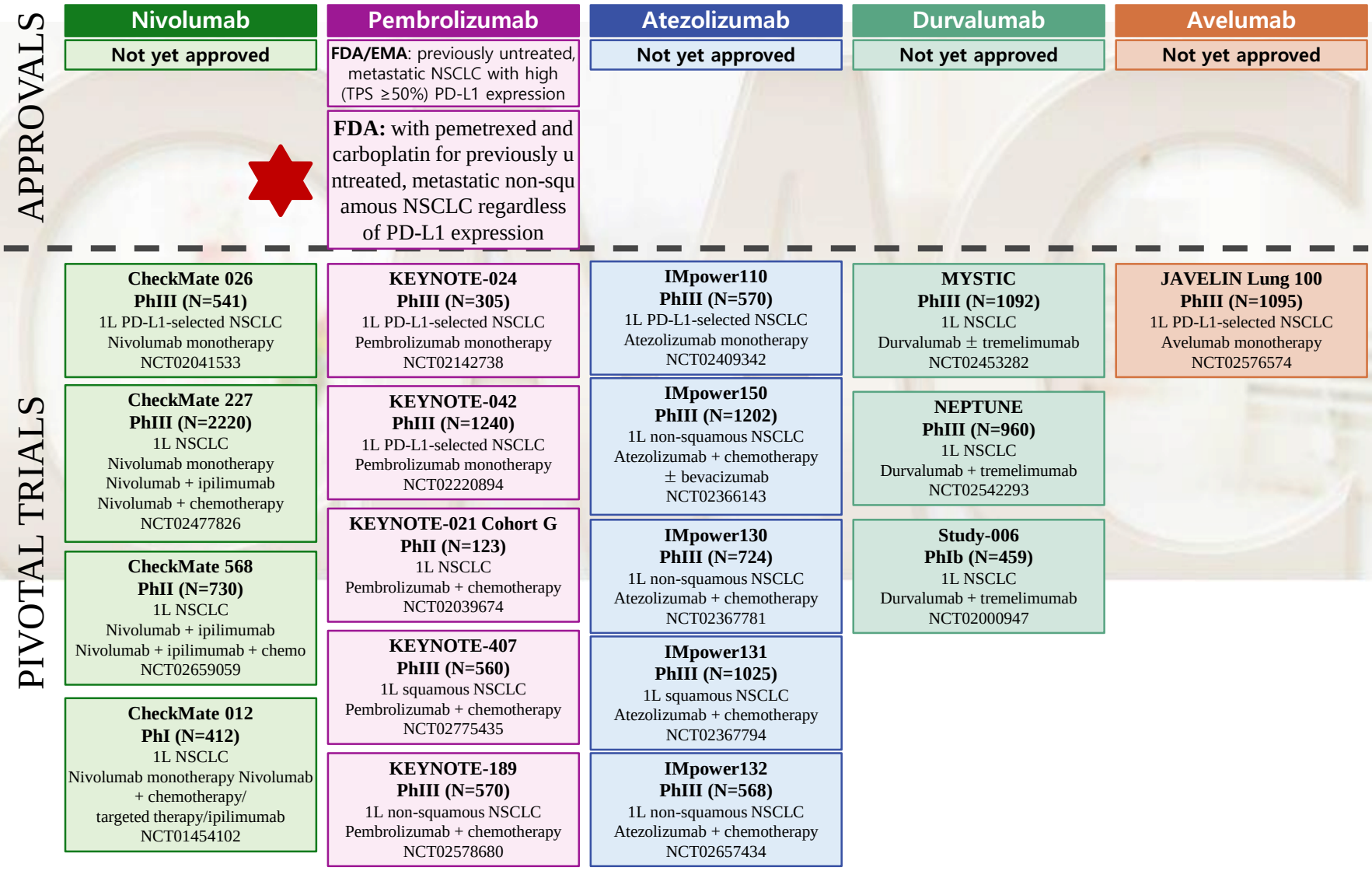
ONCO-1222403-0022 11/2015

PD-L1 EXPRESSION POSITIVE[hh]

FIRST-LINE THERAPY[mm] | **SUBSEQUENT THERAPY[mm]**

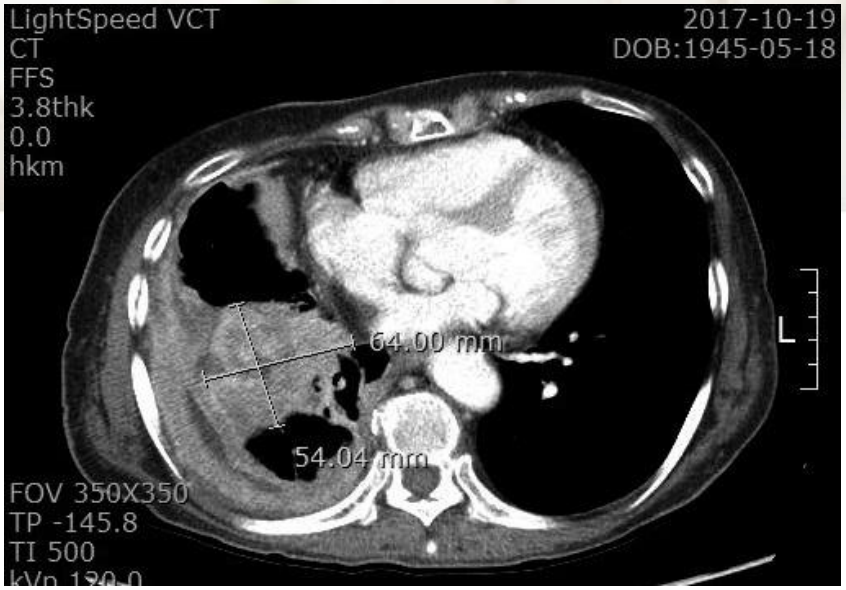


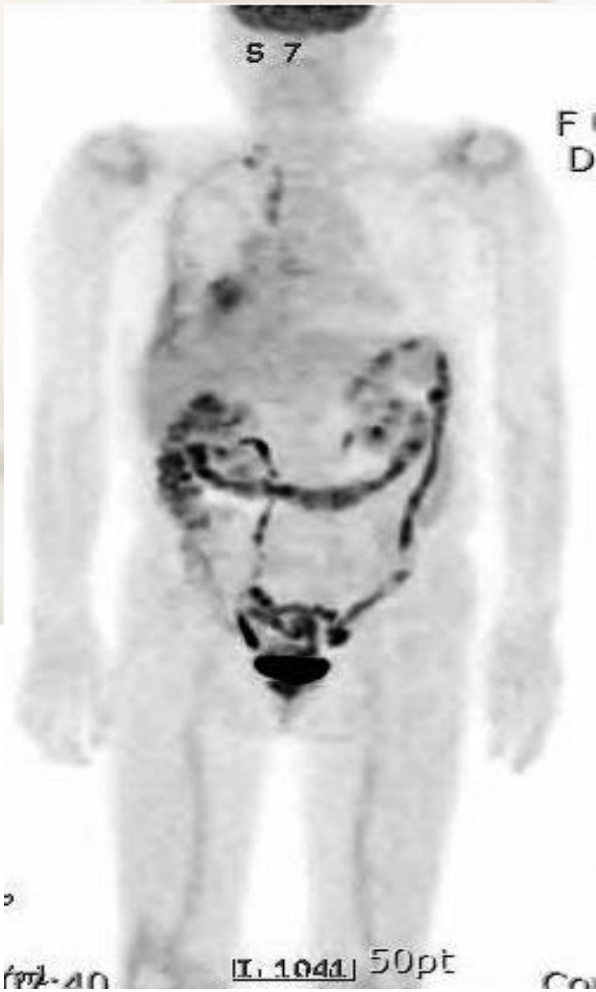
PD-1/PD-L1 inhibitor approved for Tx-naïve NSCLC



72/F, ADC, S-IV, EGFR/ALK (-)

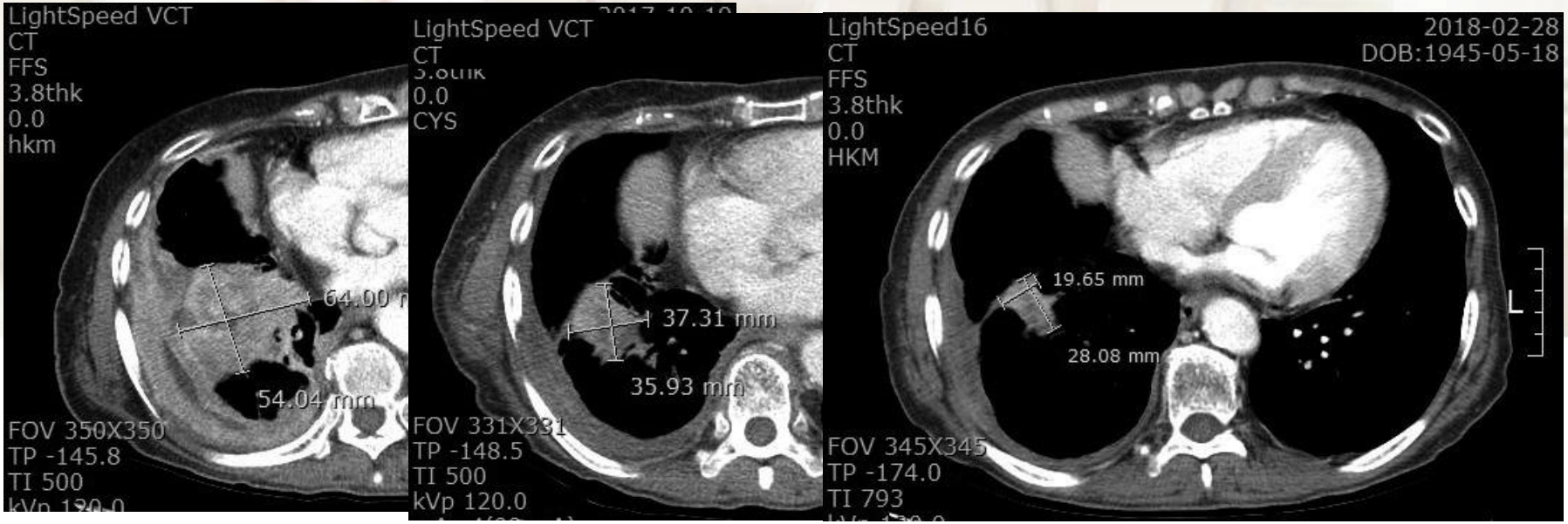
- 1-Pemetrexed Cisplatin 2017 Sep 2x PD.
- PDL1 SP263 70%
- 2-Nivolumab 2017 Oct 26 ~





72/F, ADC, IV, EGFR/ALK (-)

- 1-Pemetrexed Cisplatin 2017 Sep 2x PD.
- PDL1 SP263 70%
- 2-Nivolumab 2017 Oct 26 ~



2017 Oct 19 2017 Dec 16 2018 Feb 28

Nivolumab (Opdivo)

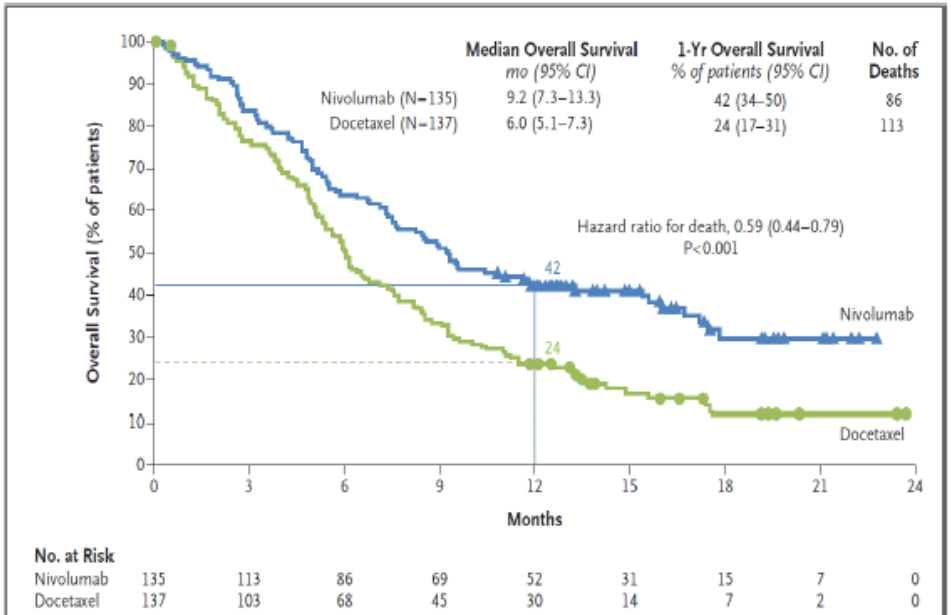
ORIGINAL ARTICLE

Phase III study (CheckMate 017)

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

NEJM 2015 JUL



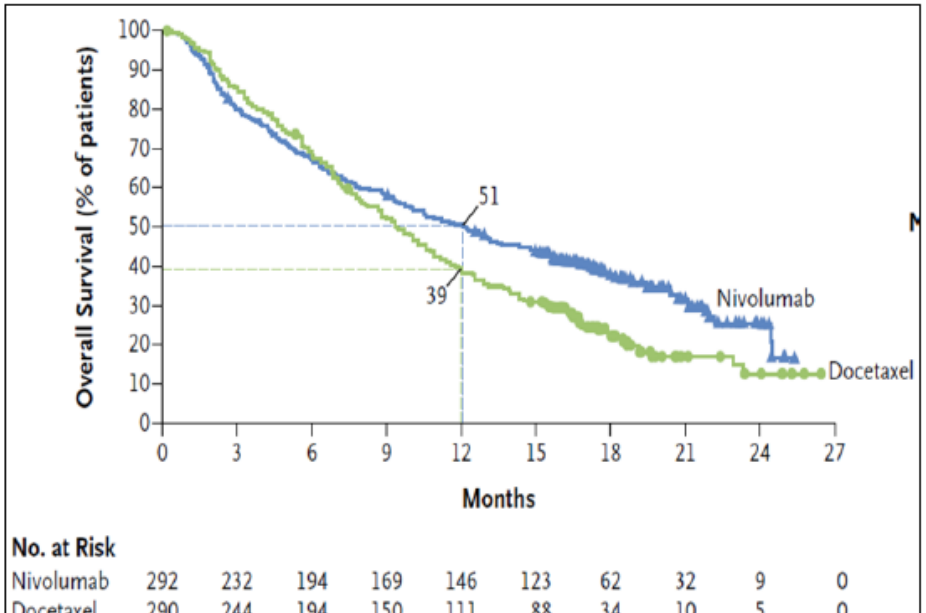
ORIGINAL ARTICLE

Phase III study(CheckMate 057)

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, and J.R. Brahmer

NEJM 2015 OCT



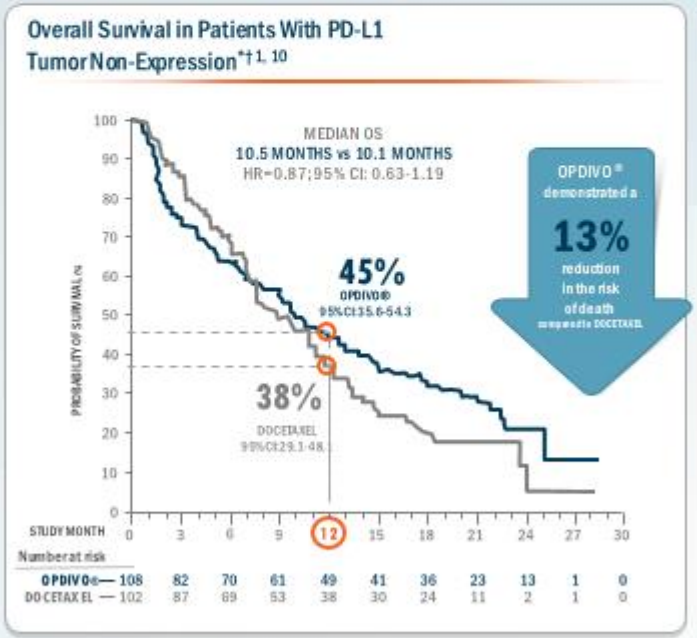
Nivolumab (Opdivo)

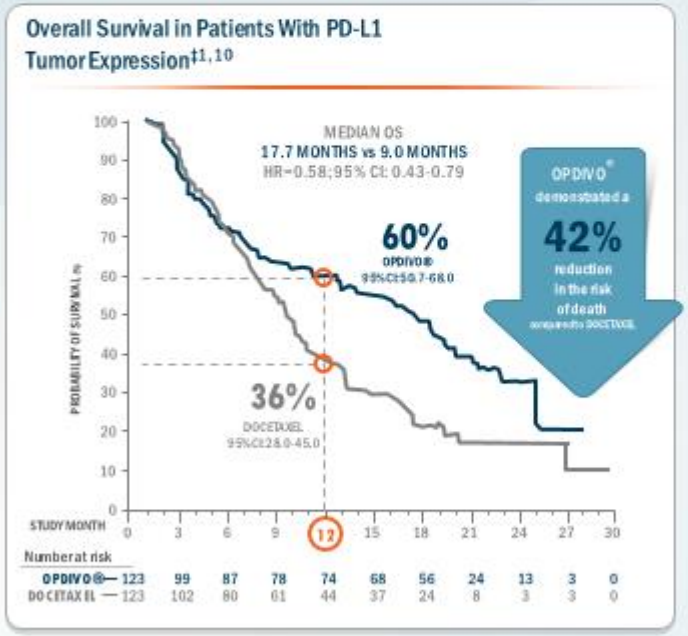
OPDIVO™ (nivolumab)

CheckMate 057 (Non-Squamous NSCLC)

모든 환자에서 PD-L1 발현 여부와 관계없이 OS benefit을 나타냄[1,6,8]

- PD-L1 expression is defined as ≥1% of tumor cells expressing PD-L1, and non-expression at <1%

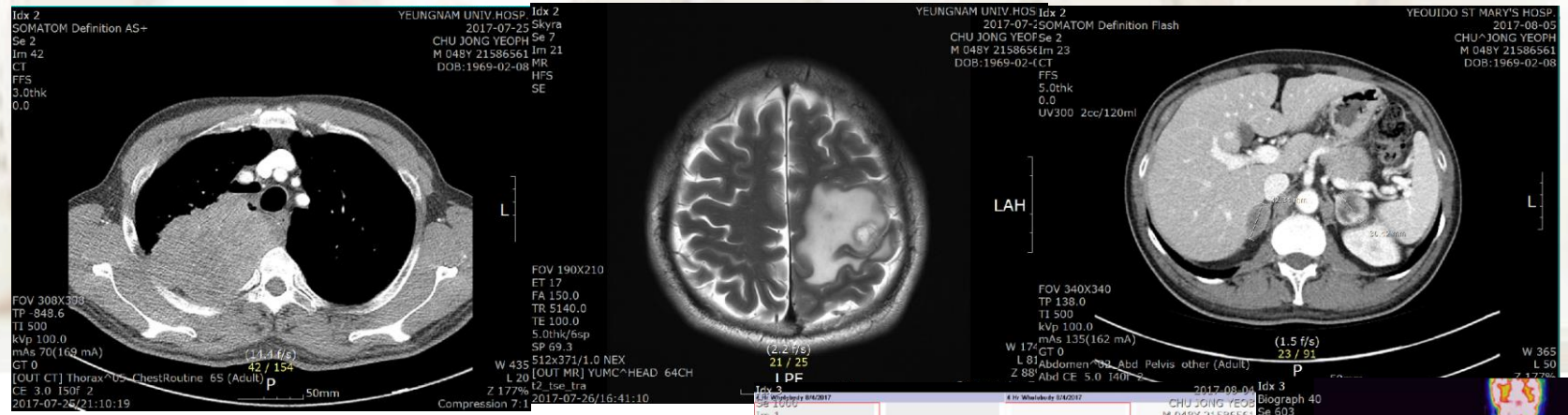


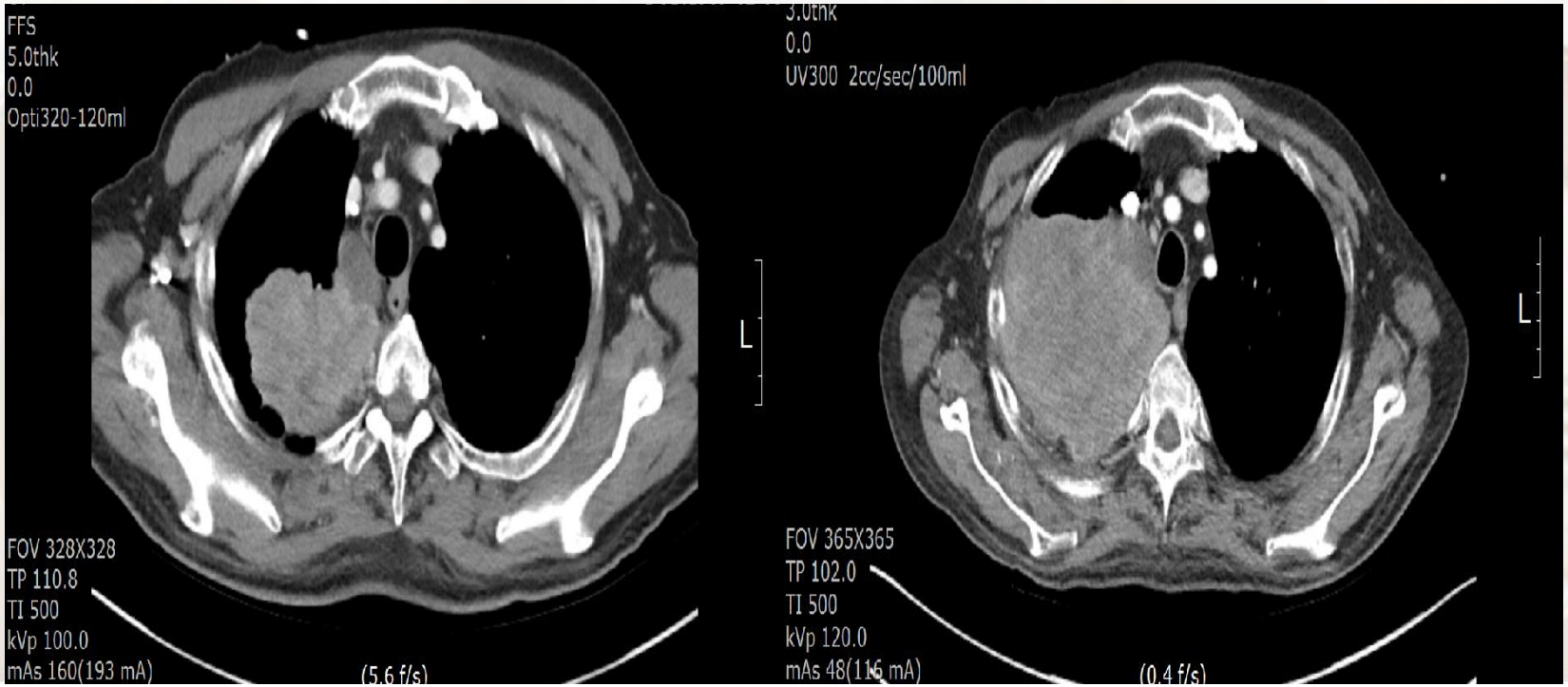


OPDIVO® is the Only MFDS & FDA Approved PD-1 Inhibitor That Does Not Require PD-L1 Testing

Case
: M/49, ADC,IV , EGFR/ALK/ROS1 (-)

- Current smoker (30*2 PYS)
- RUL c brain, both adrenal gl.metastasis
- s/p Craniotomy c tumor removal (2017.08.01)
- s/p Lap aderenalectomy, Rt (2017.09.08)
- s/p #1-1~1-4 Pem Cis (2017.08.18 ~ 2017.11.02)

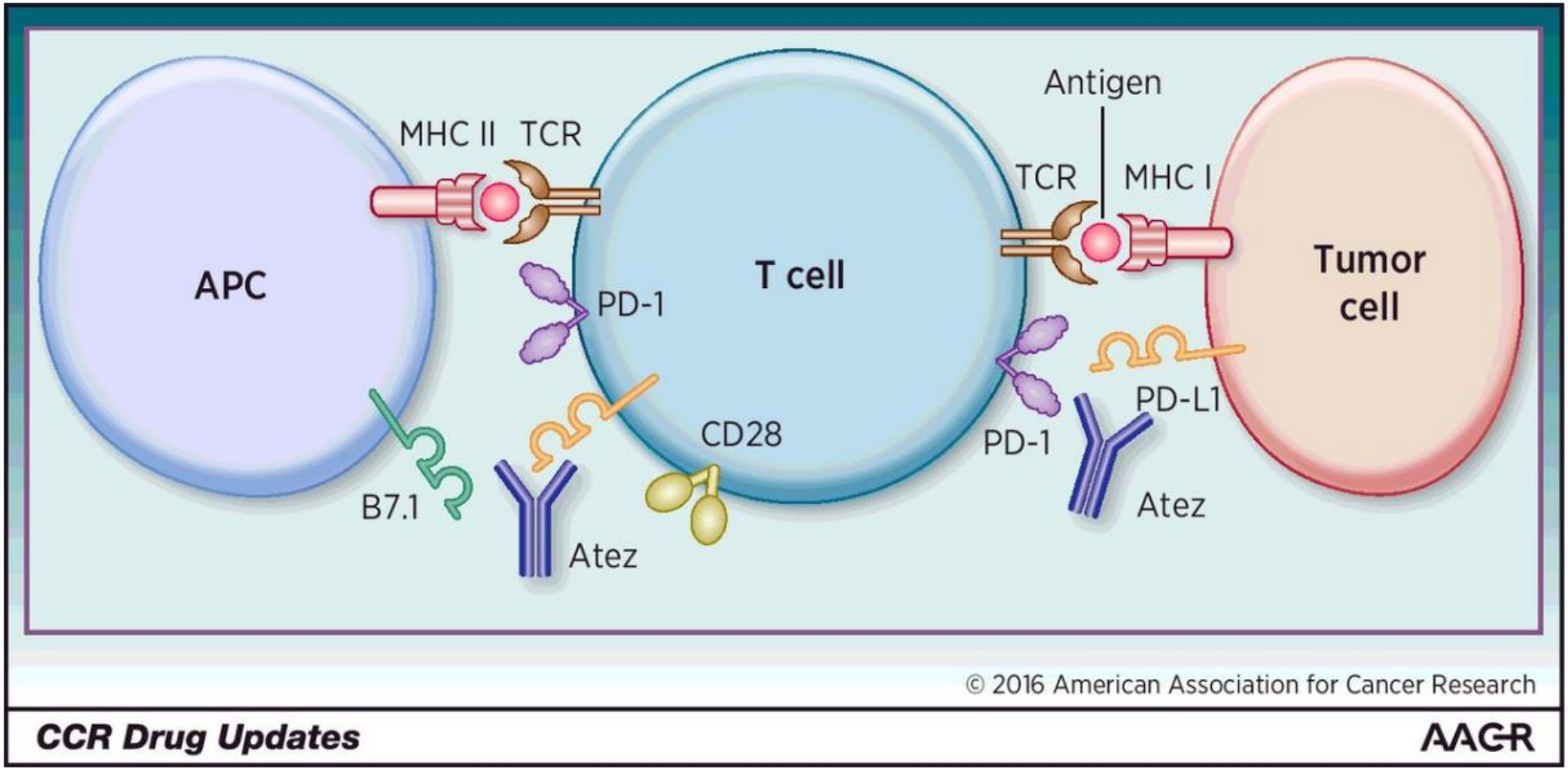




PD-L1(SP142)TC 10%[TC1], IC 30%[IC2/3]
2017.12.05 ~ 2018.03.15 s/p #2-1~2-4 **Atezolizumab**

2018.04.02 ~ 2018.6.15 s/p #3-1~3-4 Gem-Carbo ()

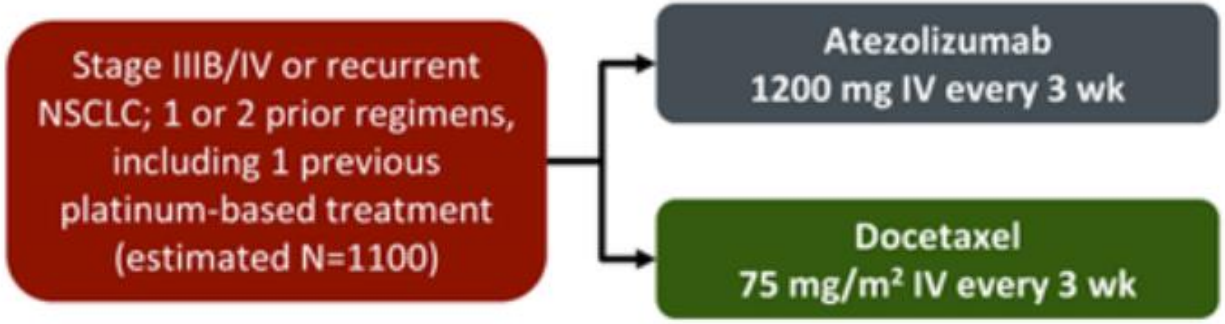
Atezolizumab (Tecentriq)



Atezolizumab (Tecentriq)

Phase 3 OAK Trial: Atezolizumab vs Docetaxel in Previously Treated NSCLC

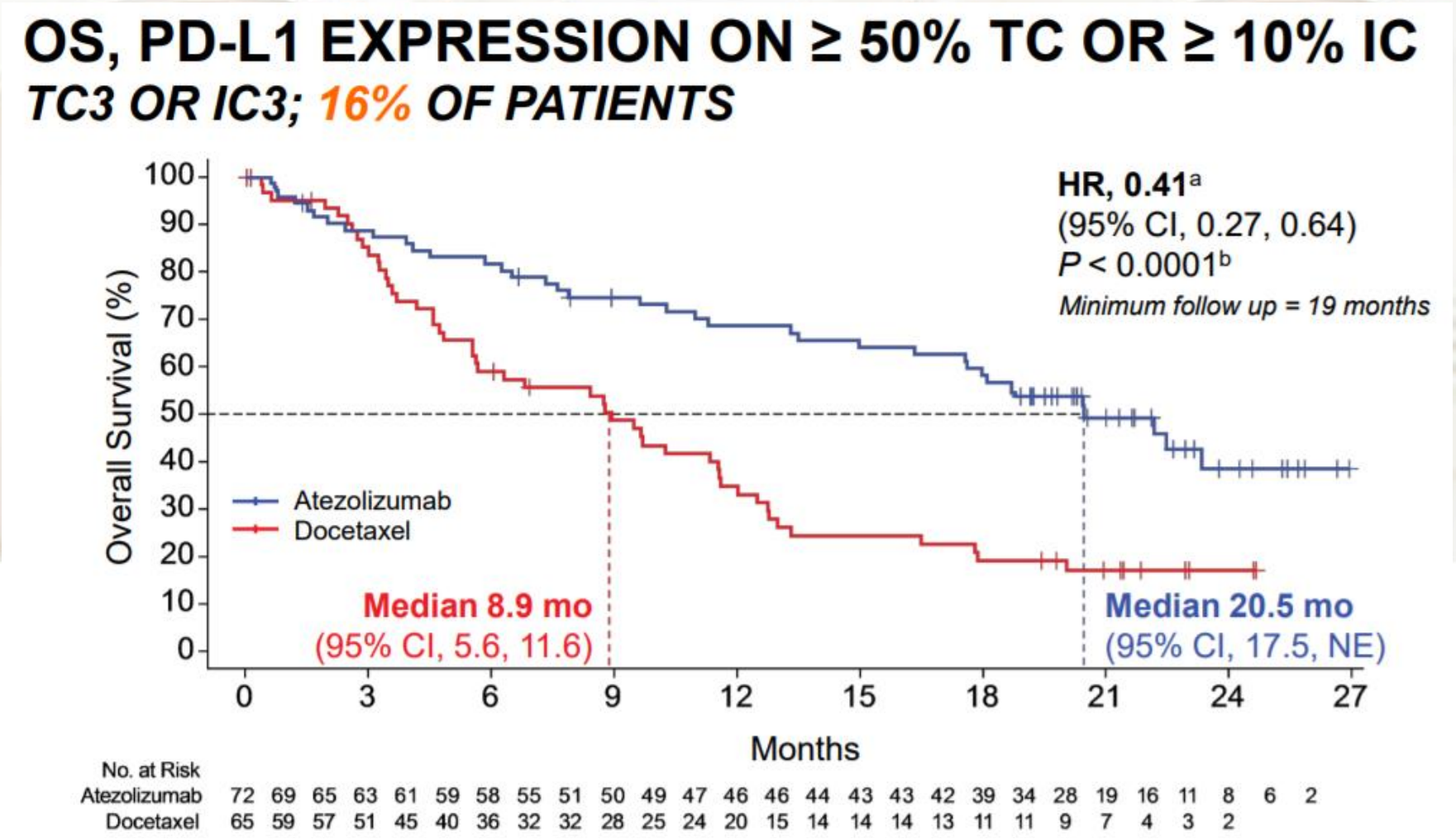
Stratified by tumor PD-L1 status (IHC), prior chemotherapy regimens (1 vs 2), and histology (nonsquamous vs squamous)



- Primary endpoint: OS
- Secondary endpoints: ORR, PFS, duration of response, safety

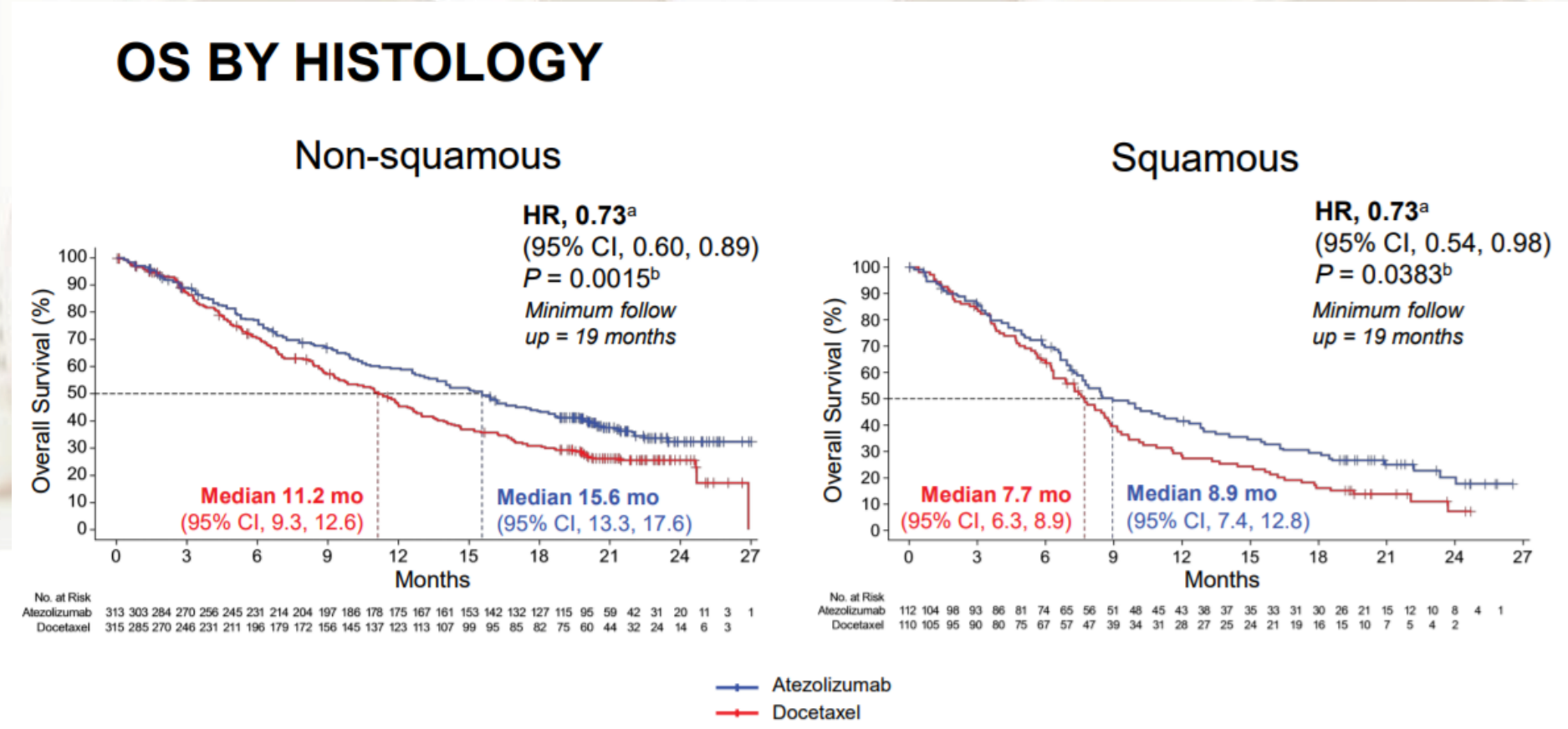
Atezolizumab (Tecentriq)

OAK trial

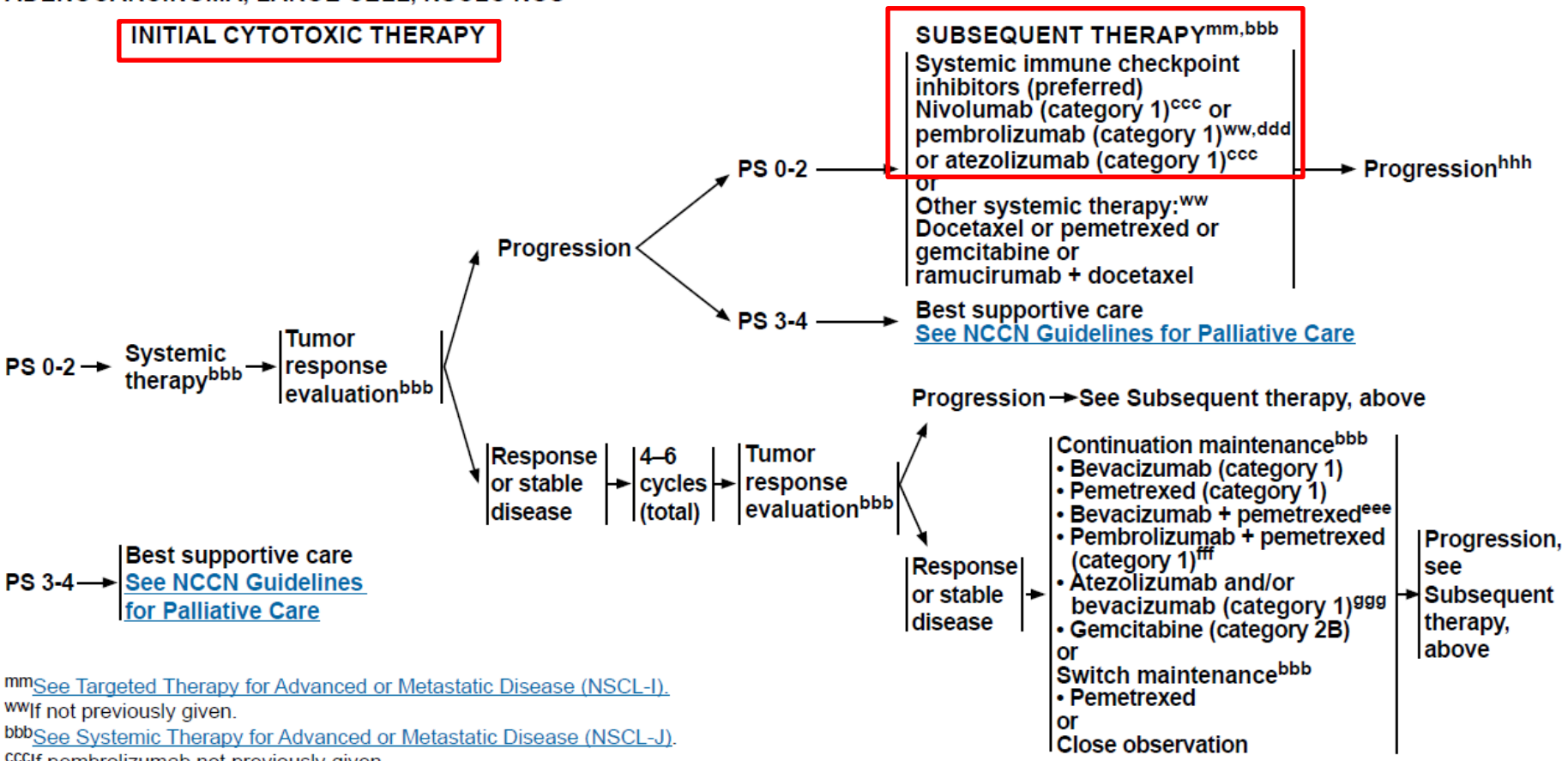


Atezolizumab (Tecentriq)

OAK trial



ADENOCARCINOMA, LARGE CELL, NSCLC NOS

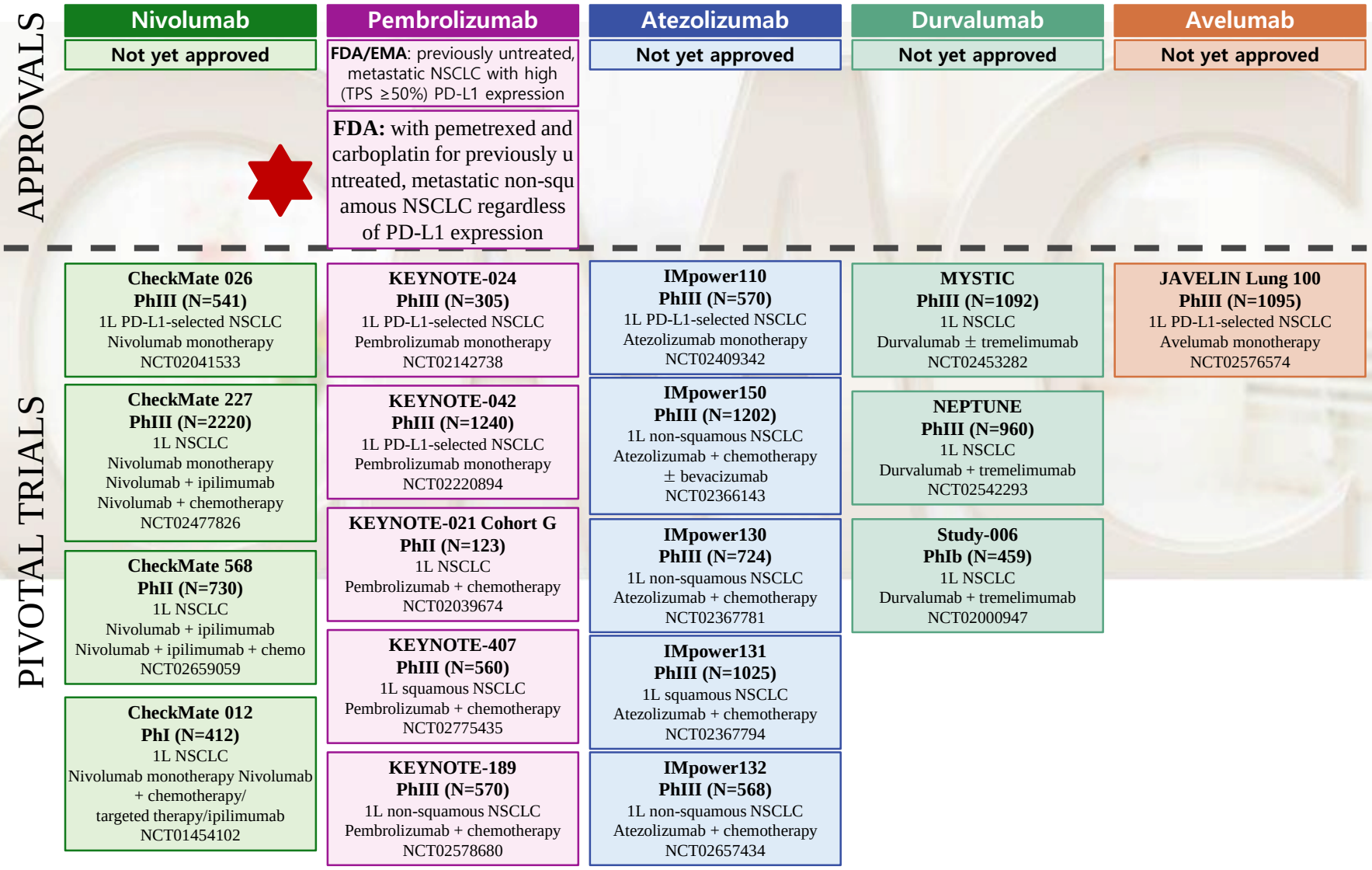


[mm] See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[ww] If not previously given.
[bbb] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-J).
[ccc] If pembrolizumab not previously given.

PD-1/PD-L1 inhibitor approved for **previous treatment NSCLC**

	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab	Avelumab
APPROVALS	**FDA/EMA**: metastatic NSCLC after prior CT*	**FDA/EMA**: metastatic PD-L1+‡ NSCLC after prior CT*	**FDA/EMA**: metastatic NSCLC after prior CT*	**Not yet approved**	**Not yet approved**
PIVOTAL TRIALS	**CheckMate 017** **PhIII (N=272)** 2L squamous NSCLC Nivolumab monotherapy NCT01642004	**KEYNOTE-010** **PhII/III (N=1033)** ≥2L PD-L1-selected NSCLC Pembro monotherapy NCT01905657	**POPLAR** **PhII (N=287)** ≥2L NSCLC Atezolizumab monotherapy NCT01903993	**ATLANTIC** **PhII (N=1980)** ≥3L NSCLC Durvalumab monotherapy NCT02087423	**JAVELIN Lung 200** **PhIII (N=792)** 2L NSCLC Avelumab monotherapy NCT02395172
	CheckMate 057 **PhIII (N=582)** 2/3L non-squamous NSCLC Nivolumab monotherapy NCT01673867		**OAK** **PhIII (N=850)** ≥2L NSCLC Atezolizumab monotherapy NCT02008227	**ARCTIC** **PhIII (N=730)** ≥3L NSCLC Durvalumab ± tremelimumab NCT02352948	
	CheckMate 078 **PhIII (N=500)** 2L NSCLC Nivolumab monotherapy NCT02613507				

PD-1/PD-L1 inhibitor approved for **treatment-naïve NSCLC**



채 O O (67 YO Male)

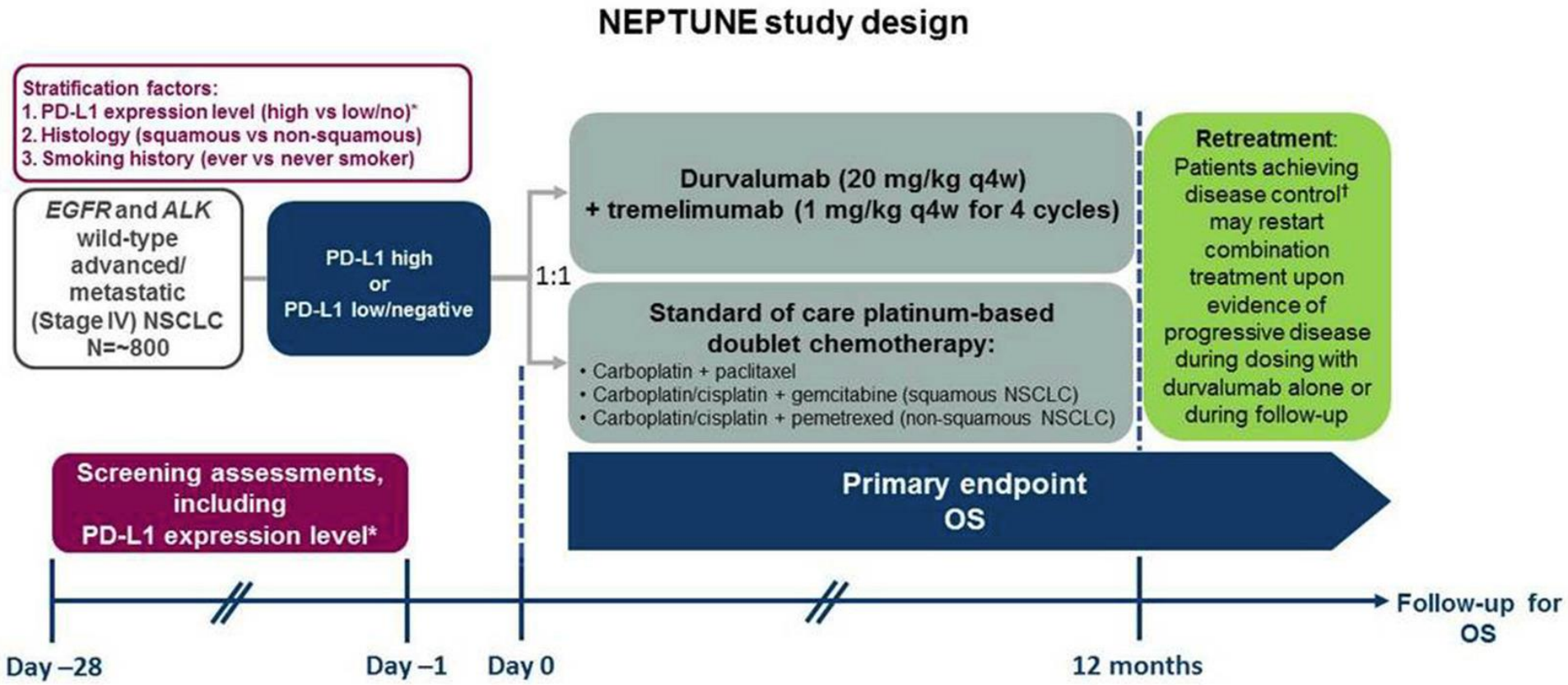
30 PYS Ex-smoker

SQC,RUL(2015.1.20) IIIA(T2aN2M0) -> IV(T2aN2M1a)

- 1CCRT(TP)6 : 2015.2.9 ~ 3.25, 30 fx

→NEPTUNE Study

Combo: Anti-CTLA-4 Plus Anti-PD-L1



*Tumour PD-L1 expression level will be assessed via the VENTANA PD-L1 (SP263) CDx Assay, where PD-L1 high is defined as ≥25% of tumour cells with membrane staining and PD-L1 low/negative is defined as <25% of tumour cells with membrane staining. Disease assessment (Response Evaluation Criteria In Solid Tumors [RECIST] v1.1) will be performed every 6 weeks for the first 48 weeks and then every 8 weeks, thereafter. Patients will be assigned to durvalumab + tremelimumab for 12 months (no maximum treatment duration for standard of care). †Disease control defined as complete response, partial response or stable disease. Patients discontinuing study treatment enter follow-up.

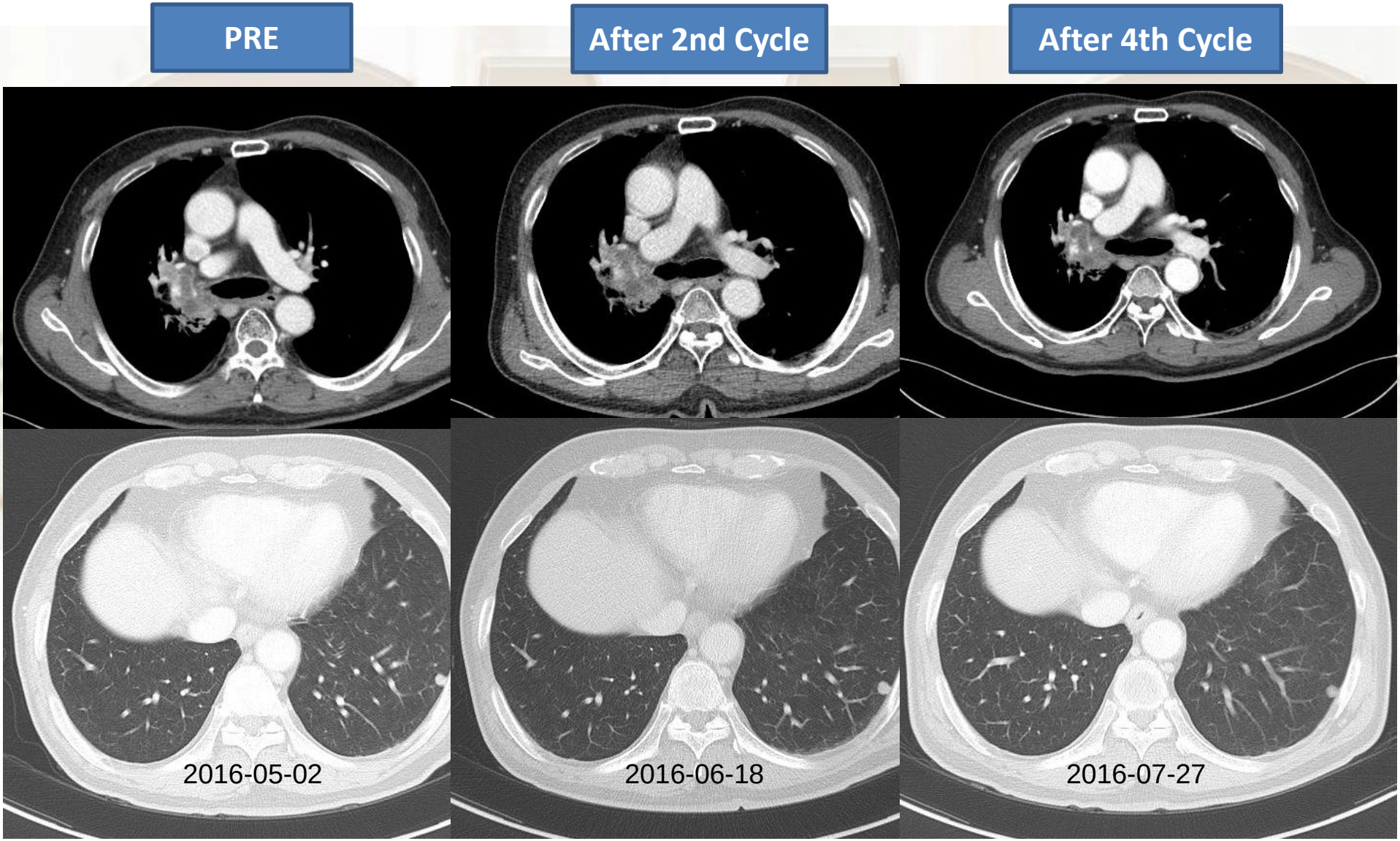
ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; OS, overall survival; PD-L1, programmed cell death ligand-1; q4w, every 4 weeks.

2016.5.2 ~ NEPTUNE Study

PDL1[SP263](1+,15%)

채 O O (67 YO Male)

NEPTUNE Study

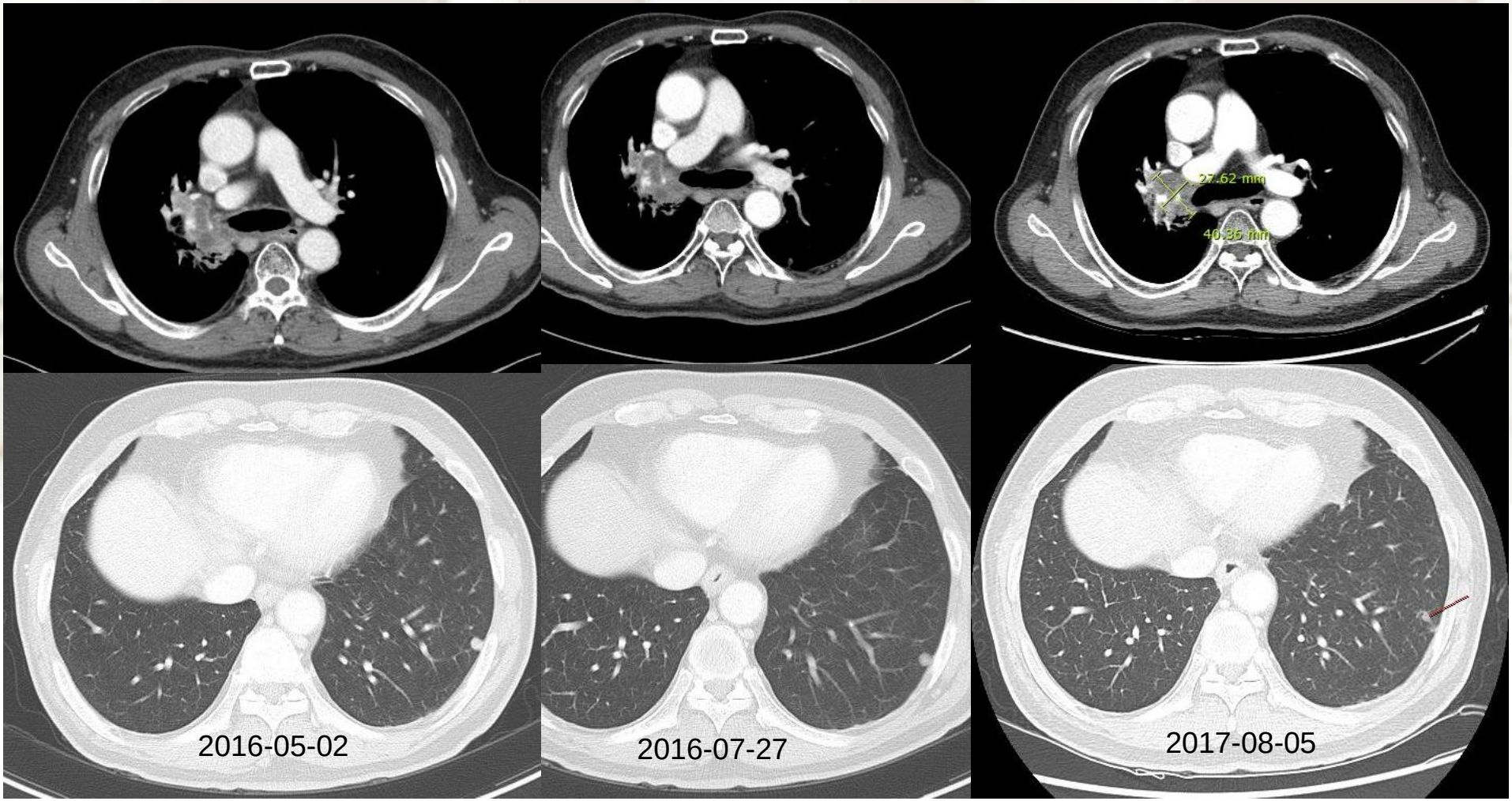


채 O O (67 YO Male)

NEPTUNE Study

***Thyroiditis**: synthroid 2016.8.8 -*

PRE | **After 4th Cycle** | **After 17th Cycle**



The New England Journal of Medicine, April 16 2018, 377;20

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

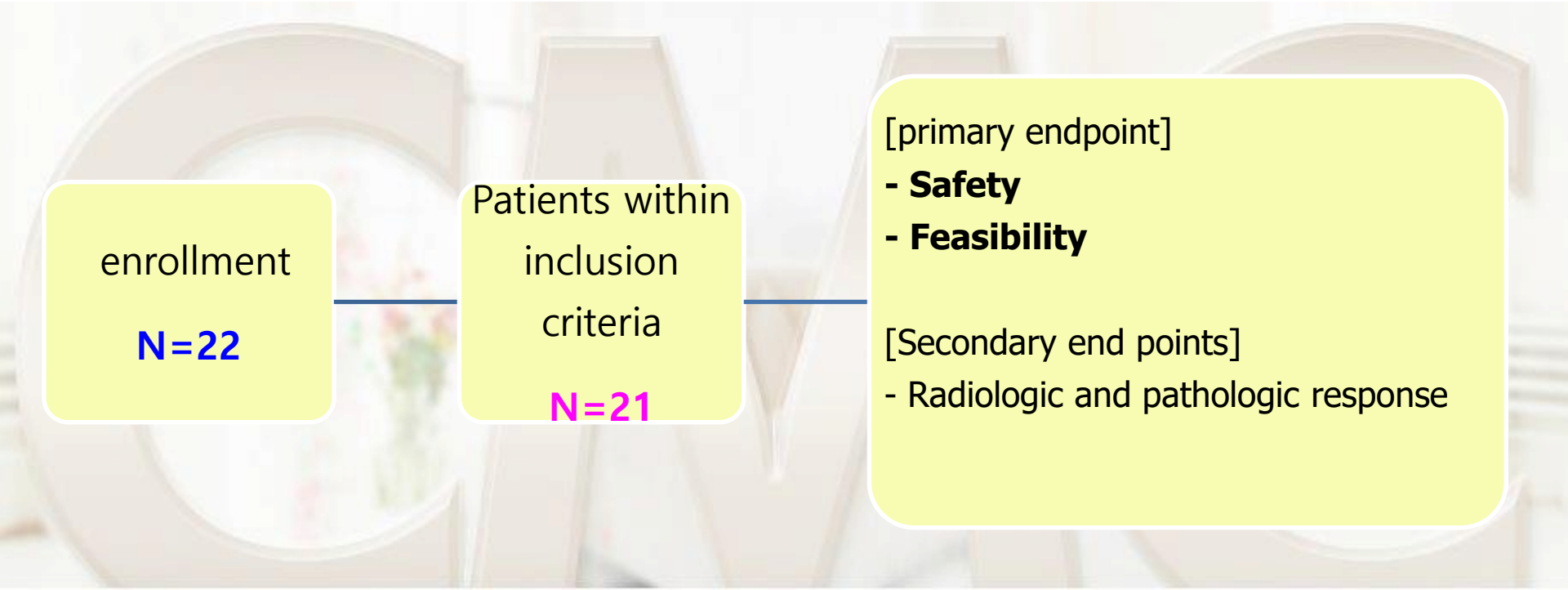
Patrick M. Forde, M.B., B.Ch., , Jamie E. Chaft, M.D., Kellie N. Smith, Ph.D., Valsamo Anagnostou, M.D., Ph.D., Tricia R. Cottrell, M.D., Ph.D., Matthew D. Hellmann, M.D., Marianna Zahurak, M.S., Stephen C. Yang, M.D., David R. Jones, M.D., Stephen Broderick, M.D., Richard J. Battafarano, M.D., Ph.D., Moises J. Velez, M.D., et al.

Research Design and Methods

Patients

Inclusion Criteria	Exclusion criteria
- Patients 18 years of age or older with stage **1, 2, 3A** NSCLC that was seemed to be **surgically resectable** - Eastern cooperative oncology Group **performance-status score of 0 or 1**	- Immunodeficiency, ongoning systemic immunosuppressive therapy - active autoimmune or infectious disease and clinically significant concurrent cancer.

Research Design and Methods



one patient was found to have small cell lung cancer and was excluded.
2 doses of intravenous nivolumab were given every 2 weeks.
Surgery performed approximately 4 weeks after the first dose.
20 of 21 eligible patients underwent complete resection.

Results

Baseline Characteristics

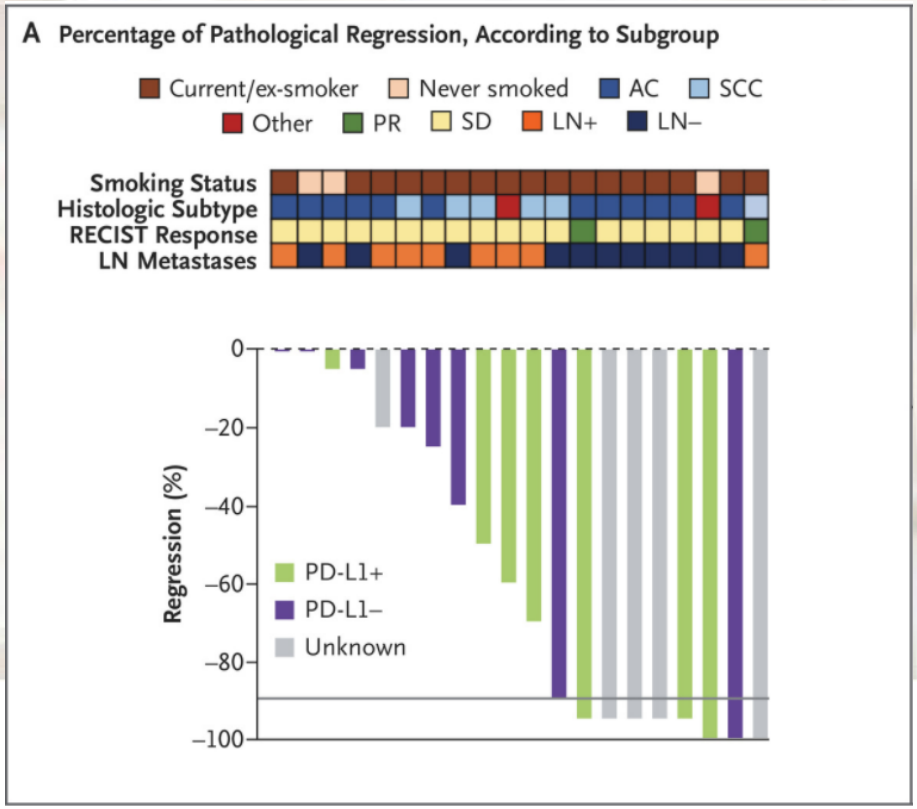
: Major pathological response indicates more than 90 % regression of tumor cell.

Table 1. Characteristics of the Patients at Baseline, According to Pathological Response.*

Characteristic	All Patients (N=21)	Patients with Major Pathological Response (N=9)	Patients without Major Pathological Response (N=11)†
Age at enrollment — yr			
Mean ±SD	66.9±8.3	67.7±8.3	65.8±8.5
Median (range)	67 (55–84)	66 (57–79)	67 (55–84)
Sex — no. (%)			
Female	11 (52)	6 (67)	4 (36)
Male	10 (48)	3 (33)	7 (64)
Histologic diagnosis — no. (%)			
Adenocarcinoma	13 (62)	6 (67)	6 (55)
Squamous-cell carcinoma	6 (29)	2 (22)	4 (36)
Other‡	2 (10)	1 (11)	1 (9)
Clinical disease stage — no. (%)§			
I	4 (19)	2 (22)	2 (18)
II	10 (48)	5 (56)	5 (45)
IIIA	7 (33)	2 (22)	4 (36)
Smoking status — no. (%)			
Never	3 (14)	1 (11)	2 (18)
Former or current	18 (86)	8 (89)	9 (82)

Results

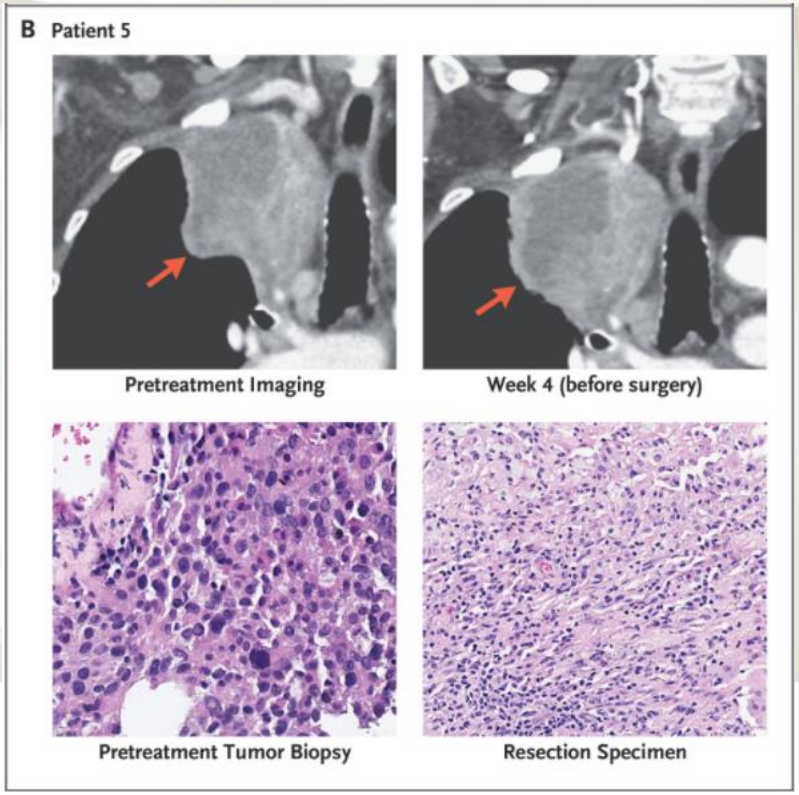
Pathologic assessment of response to neoadjuvant blockade of PD-1



- **9 out of 20 showed major pathologic response**, **with 3 patients showing CR (no viable tumor cell)**
- pathologic down-staging occurred in 8 patients
- median degree of pathological regression in the primary tumor : –65%

Results

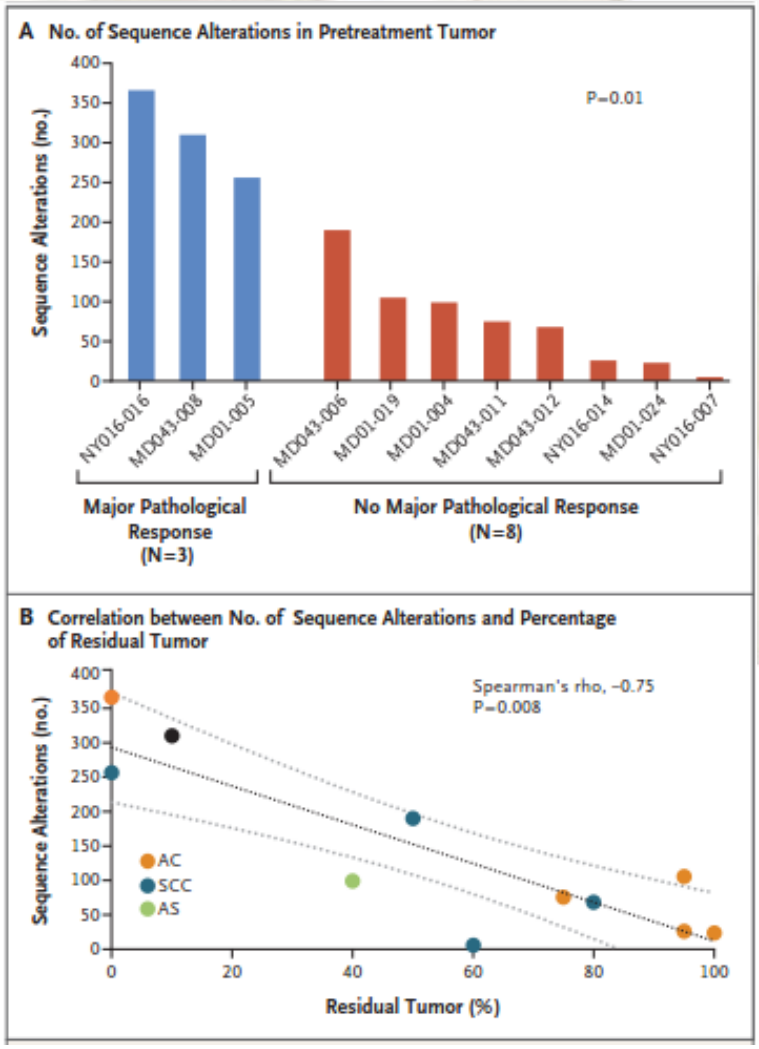
Radiologic assessment of response to neoadjuvant blockade of PD-1



- 2 partial response, 18 stable disease, 1 progression
- For patient 5, radiologic finding indicates tumor progression but pathologic finding indicate major response to neoadjuvant treatment.

Results

Correlation between No. of Sequence Alteration and Percentage of Residual tumo

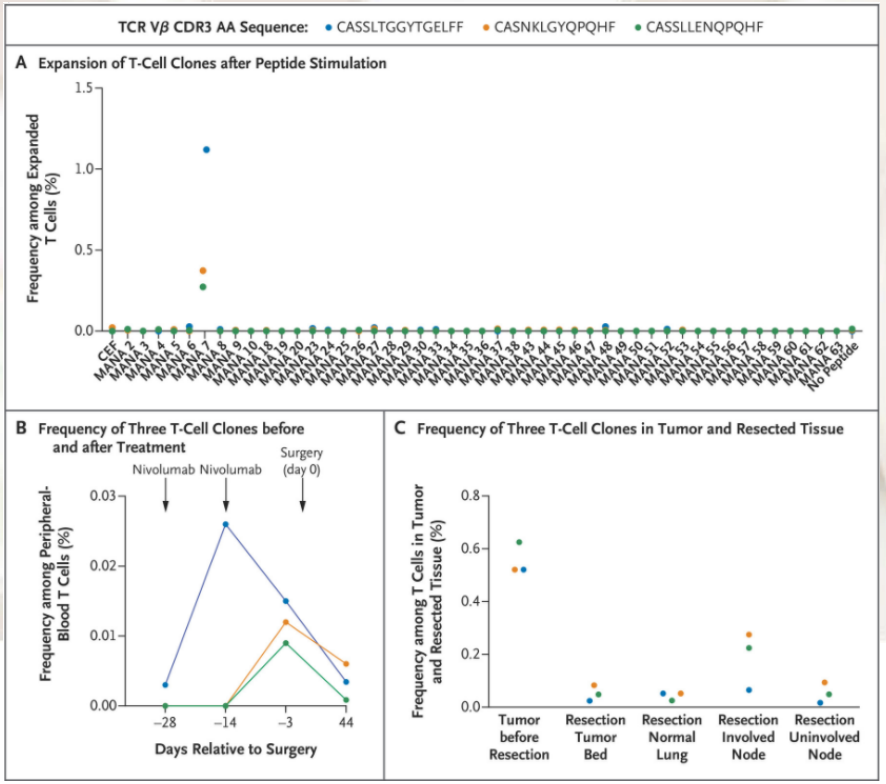


- significantly higher mean of mutational burden observed in tumors with a major pathological response than in tumors without a major response

- number of sequence alterations was inversely associated with the percentage of residual tumor

Results

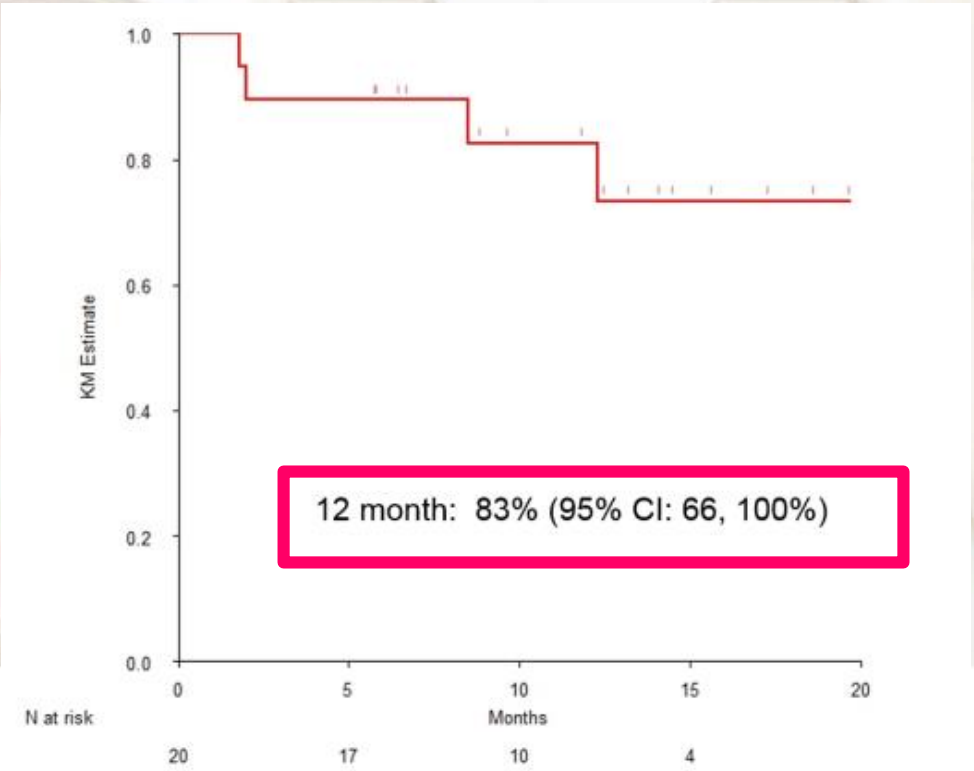
Identification of Mutation-Associated, Neoantigen-Specific T Cells after Neoadjuvant Treatment with Nivolumab



- After nivolumab treatment, specific T cell clones associated with neo-antigens are found more frequently in tumor sites.
- They are also found in peripheral blood which acts as surveillance for micrometastasis.

Results

Recurrence Free survival



- RFS is calculated from the time of surgery to recurrence or death.
- With an overall median follow-up for the study of 12 months, the 12-month RFS is 83% (95% CI: 66, 100%).

Results

Safety and Feasibility

Table S1. Treatment-related adverse events

N=22 (All patients who received at least 1 dose of nivolumab)	Grade 1-2 n (%)	Grade 3-4 n (%)
Fever	1 (5)	0
GI:		
Abdominal pain	1 (5)	0
Anorexia/dysgeusia	3 (14)	0
Vomiting/diarrhea	2 (10)	0
LFT abnormality	1 (5)	0
Infusion reaction	1 (5)	0
Dry Skin	1 (5)	0
CNS (delirium)	1 (5)	0
Pneumonia	0	1 (5)

- adverse events occurred in 5 of 22 patients, and only one event was of grade 3 or higher.
- No treatment related surgical delay

The New England Journal of Medicine, November 16, 2017, 377;20

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

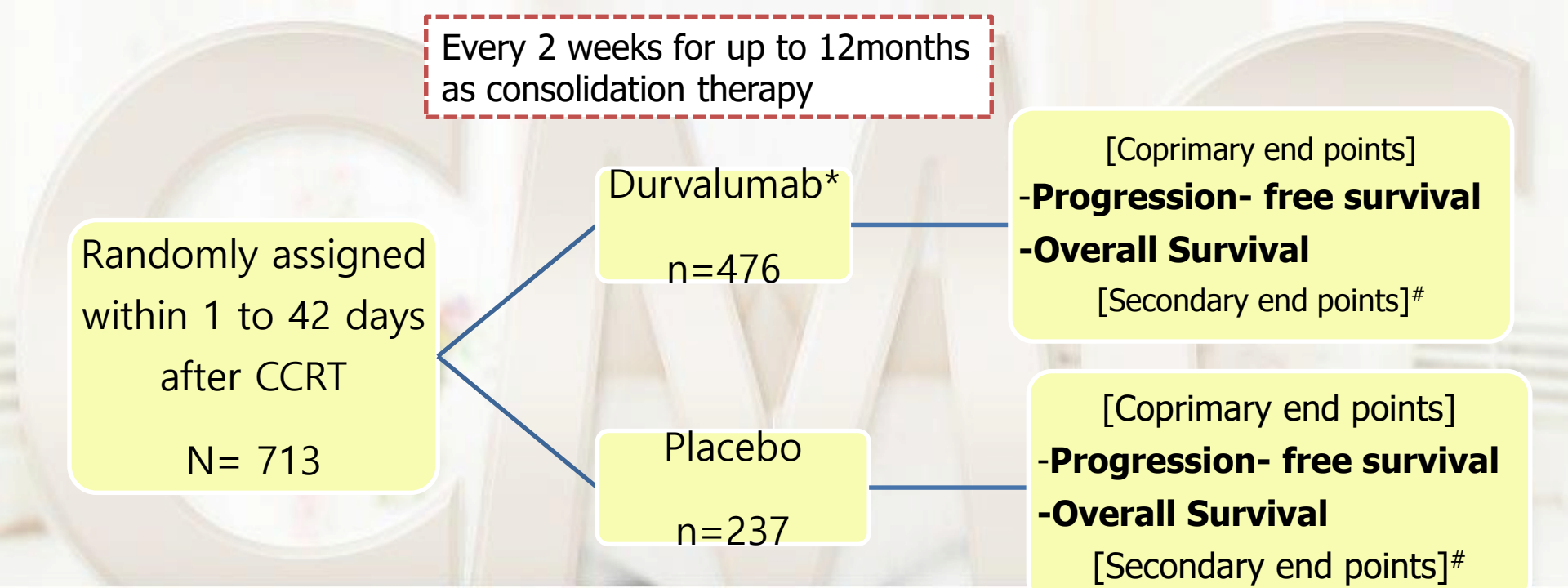
S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth,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

Research Design and Methods

Patients

Inclusion Criteria	Exclusion criteria
- Histologically or cytologically documented **stage III, locally advanced, unresectable NSCLC** - **No disease progression after two or more cycles of platinum-based chemotherapy**(containing etoposide, vinblastine, vinorelbine, taxane, or pemetrexed)**+concurrent radiation therapy** - An age of 18 years or older - WHO performance Status of 0 or 1 - An estimated life expectancy of 12 weeks or longer - Completion of the last radiation dose within 1 to 42 days before randomization	- Previous exposure to anti PD-1 or PD-L1 antibodies - Receipt of immunotherapy or an investigational drug within 4 weeks before the first dose. - Active or previous autoimmune disease or a history of primary immunodeficiency - Evidence of uncontrolled, concurrent illness or ongoing or active infections - Unresolved toxic effects of grade 2 or higher(CTCAE) - Grade 2 or higher pneumonitis from previous chemo- radiotherapy.

Research Design and Methods



* Durvalumab at a dose of 10 mg per kilogram of body weight intravenously.
# Secondary end points : 12-month and 18-month PFS rates, ORR, the DOR the time to death or distant metastasis, and safety.

Results

Baseline Characteristics

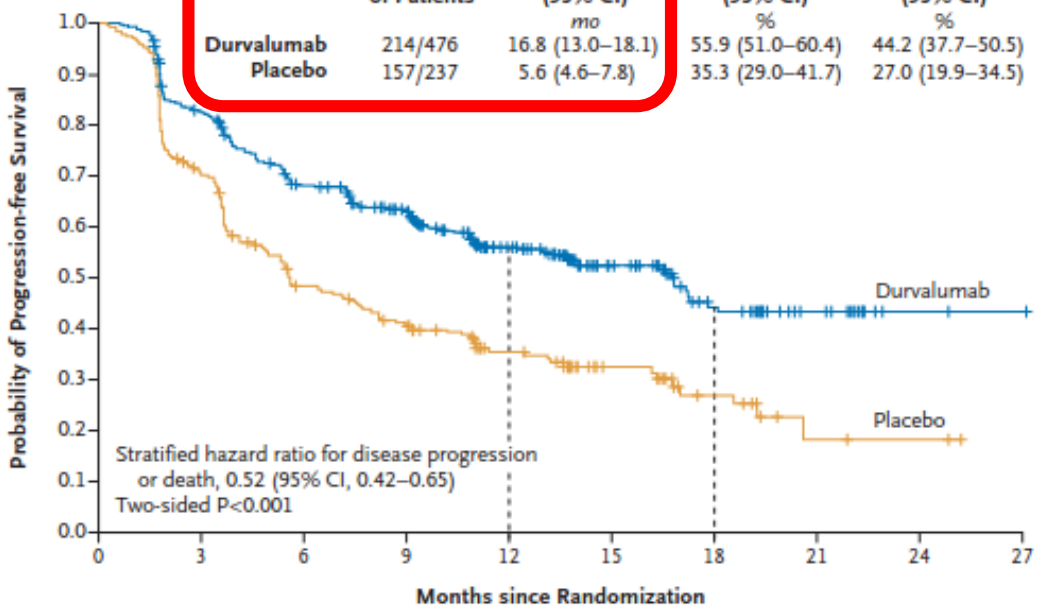
	Durvalumab (N=476)	Placebo (N=237)
PD-L1 status – no. (%)		
TC <25%	187 (39.3)	105 (44.3)
TC ≥25%	115 (24.2)	44 (18.6)
Unknown†	174 (36.6)	88 (37.1)
EGFR mutation status – no. (%)		
Positive	29 (6.1)	14 (5.9)
Negative	315 (66.2)	165 (69.6)
Unknown†	132 (27.7)	58 (24.5)

No significant (P<0.05) between-group differences were noted in either PD-L1 expression or EGFR mutation status.

Results

Efficacy - Progression-free Survival

	No. of Events/ Total No. of Patients	Median PFS (95% CI)	12-Mo PFS (95% CI)	18-Mo PFS (95% CI)
		mo	%	%
Durvalumab	214/476	16.8 (13.0–18.1)	55.9 (51.0–60.4)	44.2 (37.7–50.5)
Placebo	157/237	5.6 (4.6–7.8)	35.3 (29.0–41.7)	27.0 (19.9–34.5)



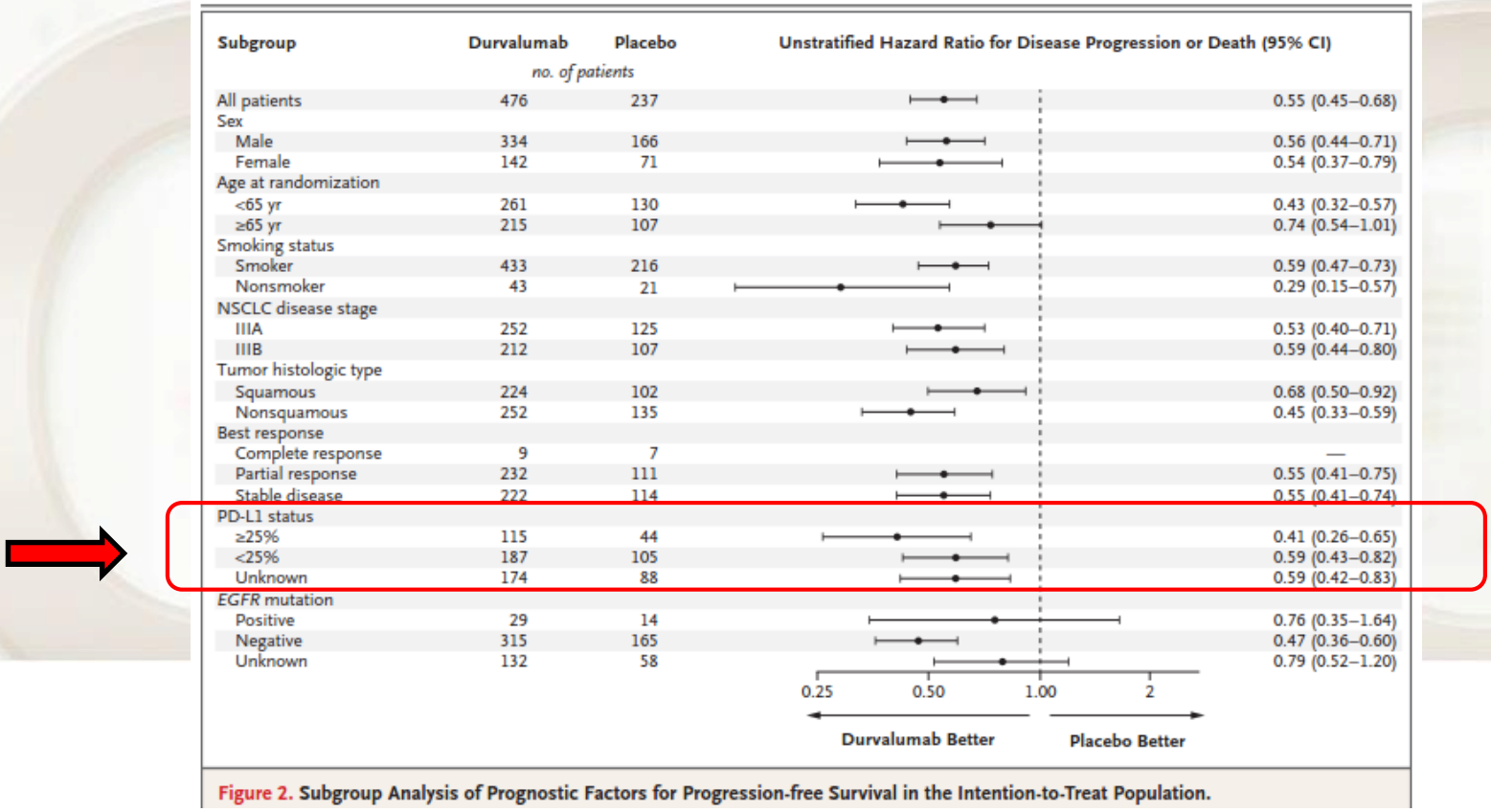
No. at Risk										
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

Figure 1. Progression-free Survival in the Intention-to-Treat Population.

The median PFS from randomization was 16.8 months (95% confidence interval [CI], 13.0 to 18.1) with durvalumab versus 5.6 months (95% CI, 4.6 to 7.8) with placebo.

Results

Efficacy - Progression-free Survival



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)

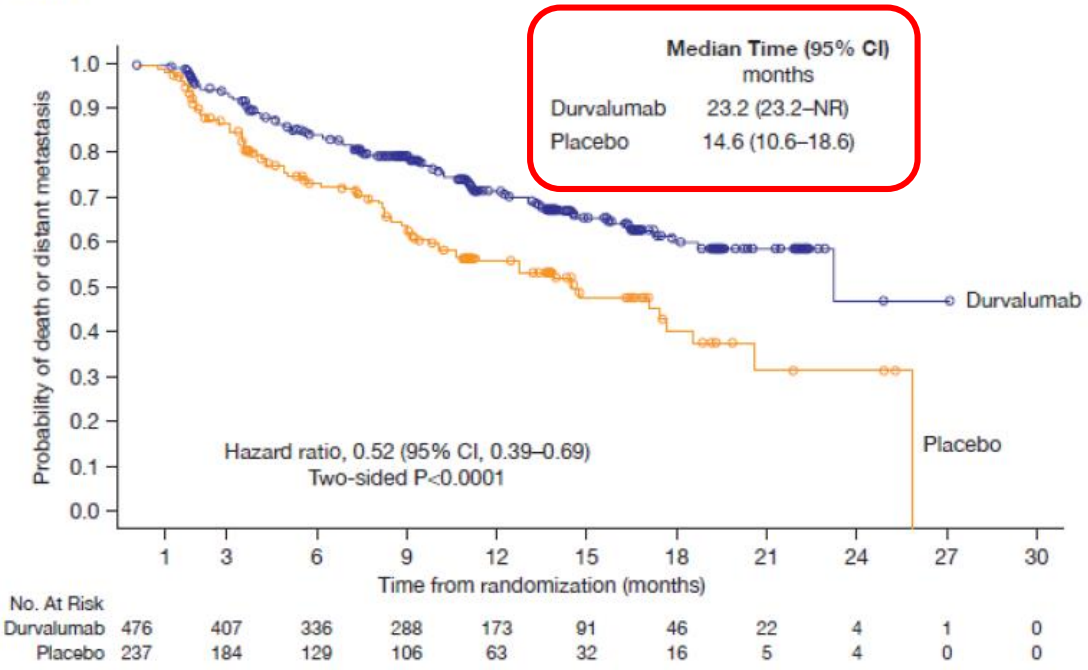
Figure 2. Subgroup Analysis of Prognostic Factors for Progression-free Survival in the Intention-to-Treat Population.

A progression-free survival benefit with durvalumab was consistently observed across all prespecified subgroups, as defined according to patient demographic characteristics, baseline clinicopathologic features, and response to previous treatment.

Results

Efficacy - The time to death or distant metastasis

Figure S3. Time to Death or Distant Metastasis in the Intention-to-Treat Population (BICR).



The median time to death or distant metastasis was **23.2 months** (95% CI, 23.2 to not reached) with durvalumab versus **14.6 months** (95% CI, 10.6 to 18.6) with placebo (hazard ratio, 0.52; 95% CI, 0.39 to 0.69; two-sided P<0.001).

Results

Efficacy – Tumor response

Table 2. Antitumor Activity in the Intention-to-Treat Population.*

Variable	Durvalumab (N=443)†	Placebo (N=213)†	Treatment Effect‡	P Value
Objective response				
No. of patients with response	126	34		
% of patients (95% CI)	28.4 (24.3–32.9)	16.0 (11.3–21.6)	1.78 (1.27–2.51)	<0.001
Best overall response — no. (%)§				
Complete response	6 (1.4)	1 (0.5)		
Partial response	120 (27.1)	33 (15.5)		
Stable disease	233 (52.6)	119 (55.9)		
Progressive disease	73 (16.5)	59 (27.7)		
Could not be evaluated	10 (2.3)	1 (0.5)		
Duration of response — mo				
Median	NR	13.8	0.43	
95% CI		6.0–NR	0.22–0.84	
Ongoing response at data cutoff point — %¶				
At 12 mo	72.8	56.1		
At 18 mo	72.8	46.8		

The ORR, as assessed by means of blinded independent central review, was significantly higher with durvalumab than with placebo (28.4% vs. 16.0%; P<0.001).

The **median DOR was longer with durvalumab than with placebo**.

Results

Safety – Adverse Events

Table 3. Adverse Events of Any Cause.

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)

Results

Safety – Adverse Events

- **Discontinuation due to adverse events** occurred in **15.4%** of patients in the durvalumab group and **9.8%** of patients in the placebo group, and **serious adverse events** occurred in **28.6% and 22.6%**, respectively.

- The most frequent adverse events leading to discontinuation of durvalumab and placebo were **pneumonitis or radiation pneumonitis** (in **6.3%** and **4.3%**, respectively) and **pneumonia** (in **1.1%** and **1.3%**).

- **Immune-mediated adverse events** of any grade, regardless of cause, were reported in **24.2%** of patients in the durvalumab group and **8.1%** of patients in the placebo group; **grade 3 or 4 immune-mediated adverse events** were reported in **3.4%** and **2.6%** of patients, respectively

Adjuvant IO in NSCLC

Adjuvant NSCLC				
	Population	**Arms**	**Results**	**Reference**
PACIFIC NCT02125461	Stage III unresectable NSCLC Post chemoradiation All PD-L1	• Durvalumab 10 mg/kg q2w for up to 12 m • Placebo	12 m PFS: 55.9 v 35.3% 18 m PFS: 44.2 v 27.0%	Antonia et al, New Engl J Med 2017; 377: 1919–1929
START NCT00409188	Unresectable stage III NSCLC Post chemoradiation	• Tecomotide (T) q1w for 8 w, then q6w until PD • Placebo (P), as above	**mOS 25.6 v 22.3 m**	Butts et al., Lancet Oncology 2014; 15(1): 59–68
MAGRIT NCT00480025	Completely resected stage I-IIIA NSCLC	• IM recMAGE-A3 with AS15 immunostimulant • placebo	**Median DFS 60.5 v 57.9 m**	Vansteenkiste et al, Lancet Oncology 2016; 17(6): 822–835

Immunotherapy in SCLC

Immunotherapy			
Ipilimumab	Phase III	Awaiting the results	NCT01450761
Nivolumab	Phase III	Awaiting the results	NCT02481830
Pembrolizumab	Phase III	Awaiting the results	NCT03066778
Combination of novel agents			
Nivolumab & ipilimumab	Phase III	Awaiting the results	NCT02538666
Rova-T & nivolumab +/– ipilimumab	Phase I	Awaiting the results	NCT03026166

SCLC, small cell lung cancer.

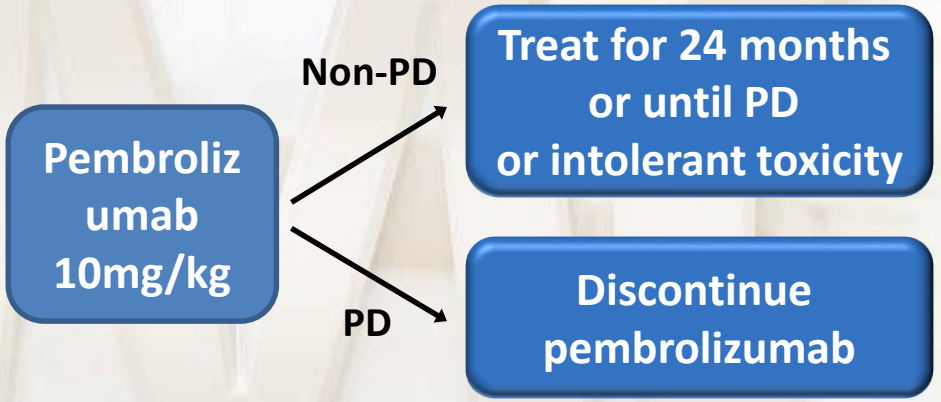
Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study

Patrick A. Ott, Elena Elez, Sandrine Hiret, Dong-Wan Kim, Anne Morosky, Sanatan Saraf, Bilal Piperdi, and Janice M. Mehnert

- Purpose
  : The safety and efficacy of pembrolizumab, assessed in patients with PD-L1 – expressing ES-SCLC in the multicohort, phase Ib open-label KEYNOTE-028 study (ClinicalTrials.gov identifier: NCT02054806)
- Methods
  : SCLC received pembrolizumab 10 mg/kg every 2 weeks for 24 months or until disease progression or intolerable toxicity occurred.
  : PD-L1 expression was assessed by IHC. PD-L1–positive patients had membranous PD-L1 expression in $ 1% of tumor and associated inflammatory cells or positive staining in stroma.
  : Response was assessed by investigator per RECIS version 1.1 every 8 weeks for the first 6 months and every 12 weeks thereafter.
  : Primary end points were safety, tolerability, and ORR.
  Secondary end points included PFS, OS, and DOR.

KEYNOTE-028; Pembrolizumab in PD-L1 (+) advanced solid cancer (phase Ib multicohort)

- SCLC
- Failure or inability to receive standard Tx
- ECOG PS 0-1
- PD-L1 (+)*
- No systemic immunosuppression



- Primary endpoint: ORR
- Secondary endpoint: PFS, OS, DoR
- *PD-L1 expression ≥ 1%

2016 17th WCLC abstract #OA05.01

Table 2. Treatment-Related Adverse Events

Adverse Event and Grade	No. (%)
Any	16 (66.7)
Arthralgia	
1	3 (12.5)
2	1 (4.2)
Asthenia	
1	2 (8.3)
2	1 (4.2)
3	1 (4.2)
Rash*	4 (16.7)
Diarrhea*	3 (12.5)
Fatigue*	3 (12.5)
Dry skin*	2 (8.3)
Insomnia*	2 (8.3)
Excessive tearing*	2 (8.3)
Myalgia	
1	1 (4.2)
2	1 (4.2)
Nausea*	2 (8.3)

NOTE. Experienced by ≥ 5% of patients regardless of grade.
*Grade 1 only.

Table 3. Confirmed Efficacy Results (investigator-assessed) in the Total Population

Efficacy	Value of Patient Population (n = 24)
ORR*, No. (% [95% CI])	8 (33.3 [15.6-55.3])
CR, No. (%)	1 (4.2)
PR, No. (%)	7 (29.2)
SD, No. (%)	1 (4.2)
Median DOR, months† (range)	19.4 (≥ 3.6 to ≥ 20.0)
Median TTR, months (95% CI)	2.0 (1.7–3.7)
DCR‡, No. (% [95% CI])	8 (33.3 [15.6-55.3])
Progressive disease, No. (%)	13 (54.2)
Not evaluable, No. (%)	2 (8.3)
PFS	
Events, No. (%)	20 (83.3)
Median, months (95% CI)	1.9 (1.7-5.9)
Six-month rate, % (95% CI)	28.6 (12.4-47.2)
Twelve-month rate, % (95% CI)	23.8 (9.1-42.3)
OS	
Events, No. (%)	15 (62.5)
Median, months (95% CI)	9.7 (4.1-NR)
Six-month rate, % (95% CI)	66.0 (43.3-81.3)
Twelve-month rate, % (95% CI)	37.7 (18.4-57.0)

Abbreviations: CR, complete response; DCR, disease control rate; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TTR, time to response.
*ORR is CR + PR.
†Calculated with the Kaplan-Meier method for censored data.
‡DCR is CR + PR + SD ≥ 6 months.

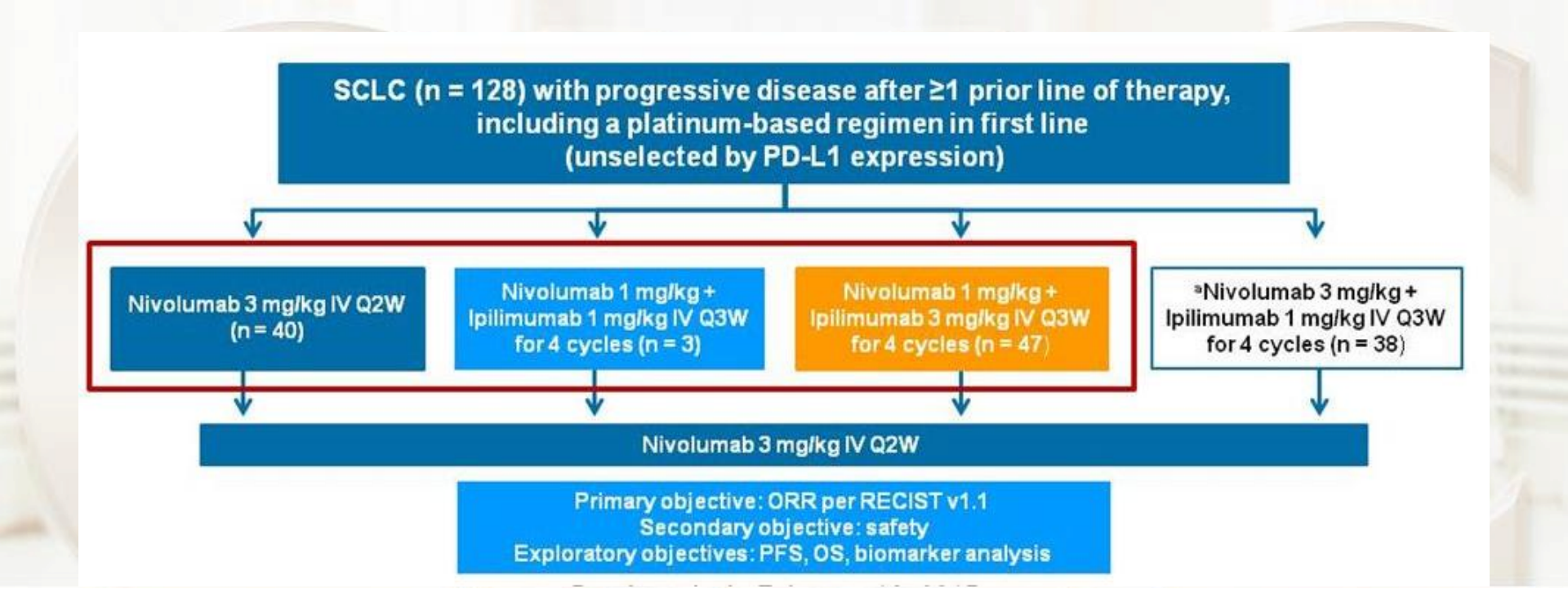
Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial

Scott J Antonia, José A López-Martin, Johanna Bendell, Patrick A Ott, Matthew Taylor, Joseph Paul Eder, Dirk Jäger, M Catherine Pietanza, Dung T Le, Filippo de Braud, Michael A Morse, Paolo A Ascierto, Leora Horn, Asim Amin, Rathi N Pillai, Jeffry Evans, Ian Chau, Petri Bono, Akin Atmaca, Padmanee Sharma, Christopher T Harbison, Chen-Sheng Lin, Olaf Christensen, Emiliano Calvo

- Background
  : Treatments for small-cell lung cancer (SCLC) after failure of platinum-based chemotherapy are limited
  : safety and activity of nivolumab and nivolumab plus ipilimumab in patients with SCLC who progressed after one or more previous regimens

- Methods

  : The SCLC cohort of this phase 1/2 multicentre, multi-arm, open-label trial, 23 sites in six countries



: The primary endpoint - objective response by investigator assessment

: All analyses included patients who were enrolled at least 90 days before database lock.

CheckMate 032

	Nivolumab 3 mg/kg (n=98)	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (n=61)	Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n=54)
1 YR PFS Median PFS	11% 1.4 mon	19% 2.6 mon	NR 1.4 mon
1 YR OS Median OS	33% 4.4 mon	43% 7.7 mon	35% 6.0 mon

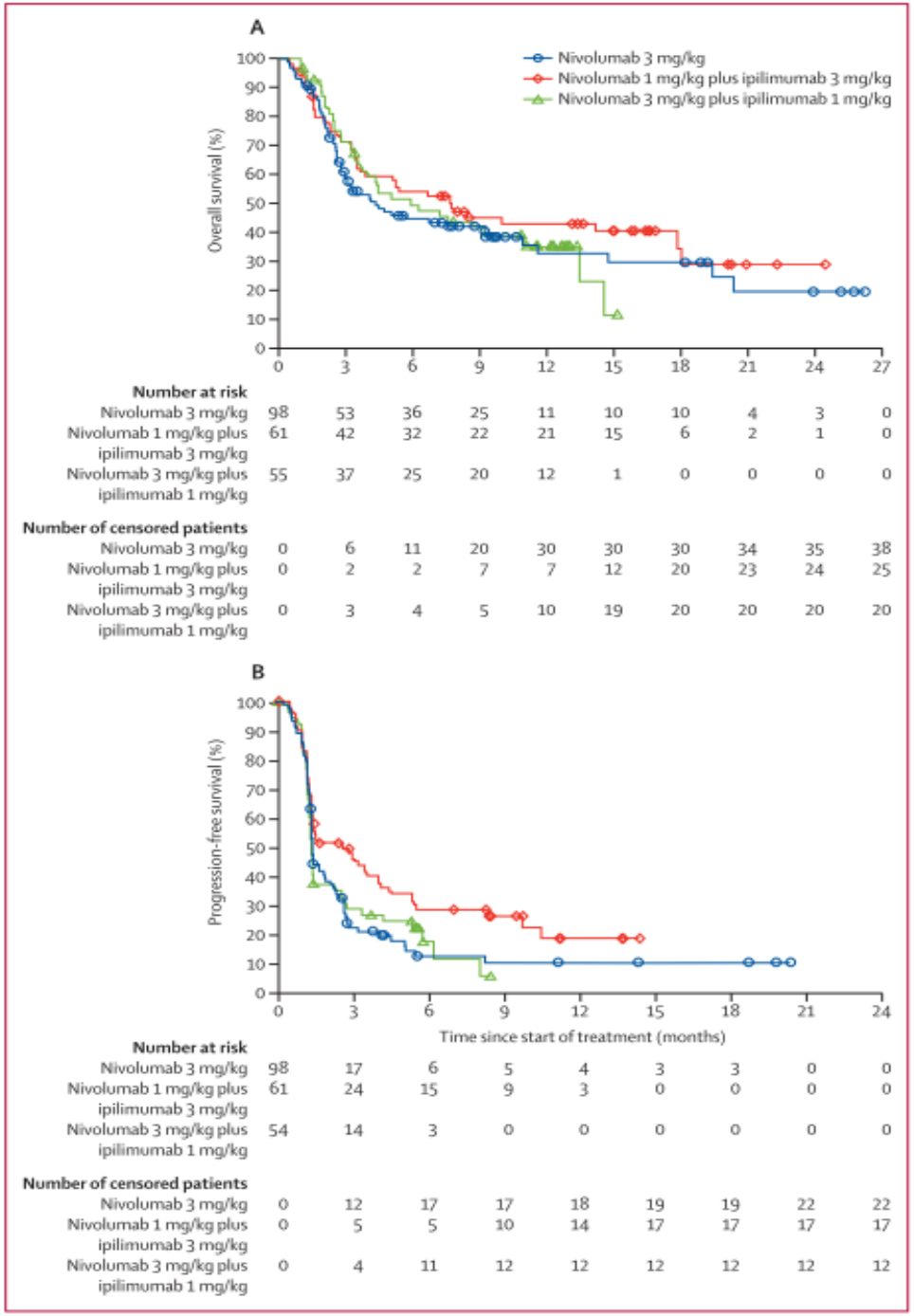


Figure 3: Kaplan-Meier curves of overall survival (A) and progression-free survival (B)

Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial†

M. Reck[1*], I. Bondarenko[2], A. Luft[3], P. Serwatowski[4], F. Barlesi[5], R. Chacko[6], M. Sebastian[7], H. Lu[8], J. -M. Cuillerot[8] & T. J. Lynch[9]

Background

: Ipilimumab, an anti-CTLA4 monoclonal antibody, demonstrated survival benefit in melanoma

: phase 2 study evaluated ipilimumab+paclitaxel(Taxol)/carboplatin in ED-SCLC

- Design

  : **Patients(n = 130)** with chemo-naïve ED-SCLC were randomized 1: 1: 1

  =>paclitaxel (175 mg/ m2)/carboplatin

  with either placebo (control) or ipilimumab 10 mg/kg in two alternative concurrent ipilimumab

  (ipilimumab + paclitaxel/carboplatin followed by placebo + paclitaxel/carboplatin)

  or phased ipilimumab

  (placebo + paclitaxel/carboplatin followed by ipilimumab + paclitaxel/carboplatin)

  : administered every 3 weeks for a maximum of 18 weeks (induction), followed by maintenance ipilimumab or placebo every 12 weeks

- End points : PFS, irPFS, best overall response rate (BORR); irBORR, overall survival (OS), and safety.

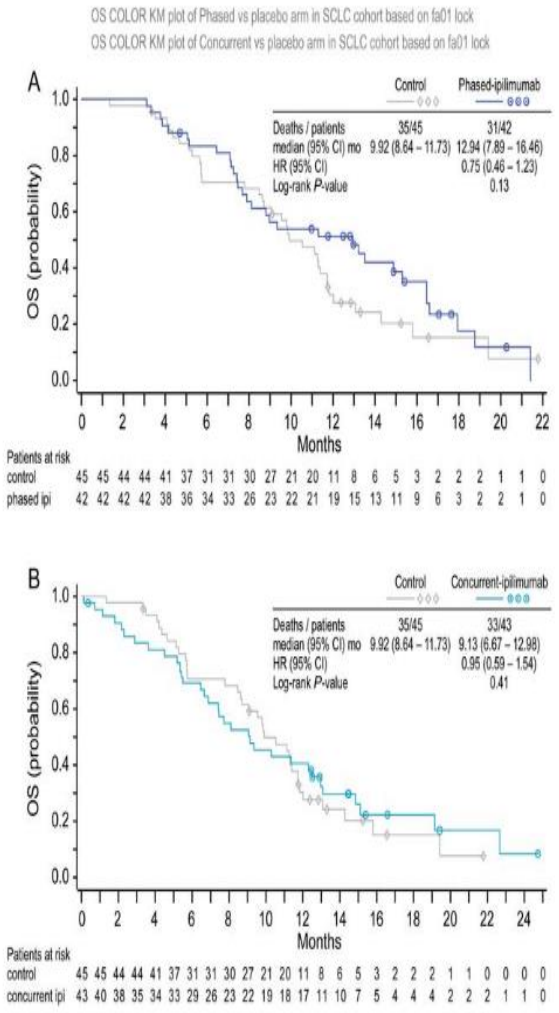


Figure 4. Kaplan–Meier plots for overall survival (OS). OS was defined as the time from randomization until death from any cause. As indicated by symbols, patients who had not died or who were lost to the follow-up were censored on the last date on which they were known to have been alive. Data cut-off for this analysis was 27 August 2010. *P*-values are based on an unstratified log-rank test with a one-sided α of 0.1.

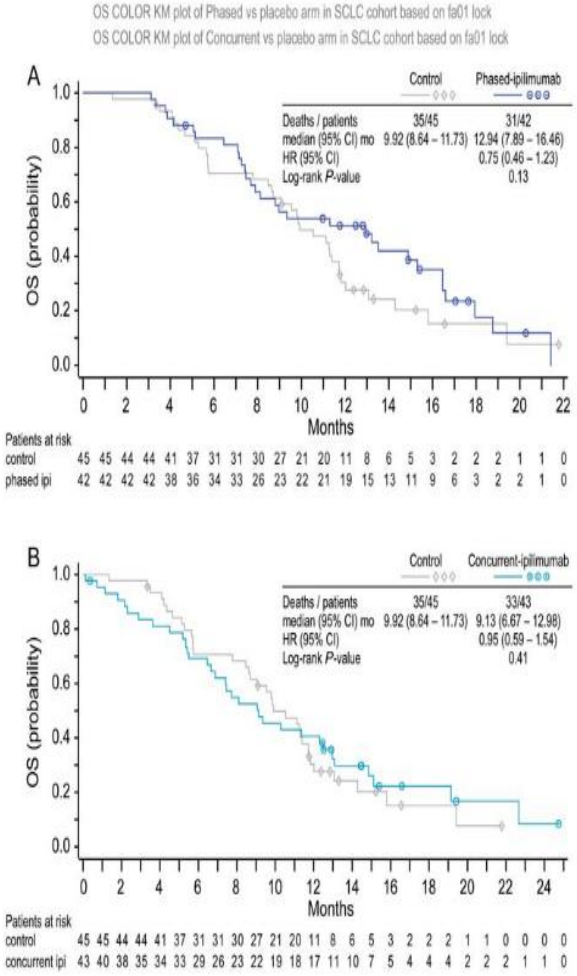


Figure 4. Kaplan–Meier plots for overall survival (OS). OS was defined as the time from randomization until death from any cause. As indicated by symbols, patients who had not died or who were lost to the follow-up were censored on the last date on which they were known to have been alive. Data cut-off for this analysis was 27 August 2010. *P*-values are based on an unstratified log-rank test with a one-sided α of 0.1.

No improvement in PFS (HR = 0.93; P= 0.37) or OS (HR = 0.75; P= 0.13)

Take Home Message

- EGFR TKI
  1) 1st – 4th Generation of TKI : following 5th TKI or TKI+TKI
  2) EGFR TKI plus chemotherapy, anti-angiogenic drugs immunotherapy
  3) Neoadjuvant and adjuvant EGFR TKI

- IO
  1) PD-1 inhibitor, PD-L1 inhibitor : biomarker
  2) Combination of IO + Chemo or IO+IO
  3) Neoadjuvant and Consolidation IO
  4) IO in SCLC

감사합니다.