Lung Cancer UPDATES
ESMO HIGHLIGTHS
09-13 SEPTIEMBRE 2022
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Iniciativa científica de:
GECP lung cancer research

Biomarcadores

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KRAS y STK11 / KEAP 1 y quimio-inmunoterapia 1ª linea

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Durvalumab ± Tremelimumab + Chemotherapy in 1L Metastatic NSCLC: Overall Survival Update from POSEIDON After Median Follow-Up of Approximately 4 Years

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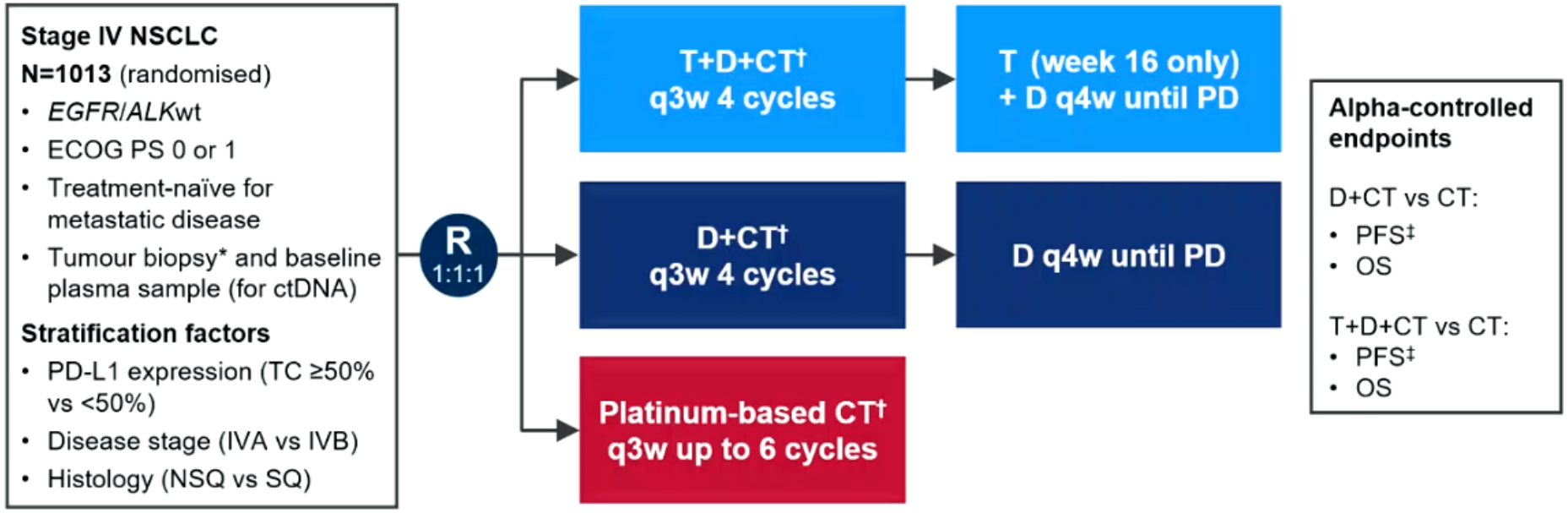
POSEIDON Study Design

Phase 3, global, randomised, open-label, multicentre study in 1L mNSCLC



- **Durvalumab** 1500mg ± **limited-course tremelimumab** 75mg + **CT** q3w for **4 cycles**
  - One additional dose of tremelimumab post-CT (week 16; 5th dose)
- Followed by **durvalumab q4w maintenance** until PD, and optional pemetrexed q4w§

ctDNA, circulating tumour DNA; D, durvalumab; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; T, tremelimumab; TC, tumour cell

*Newly acquired or archival (<3 months); †CT options: gemcitabine + carboplatin/cisplatin (SQ), pemetrexed + carboplatin/cisplatin (NSQ) or nab-paclitaxel + carboplatin (either histology);
‡By blinded independent central review (RECIST v1.1); §Patients with NSQ histology who initially received pemetrexed-platinum only (if eligible); pemetrexed q3w also permitted in the CT arm

KRAS y STK11 / KEAP 1 y quimio-inmunoterapia 1ª linea

STK11, brazo durva-tremelimumab con quimio es superior a durva-quimio o quimio

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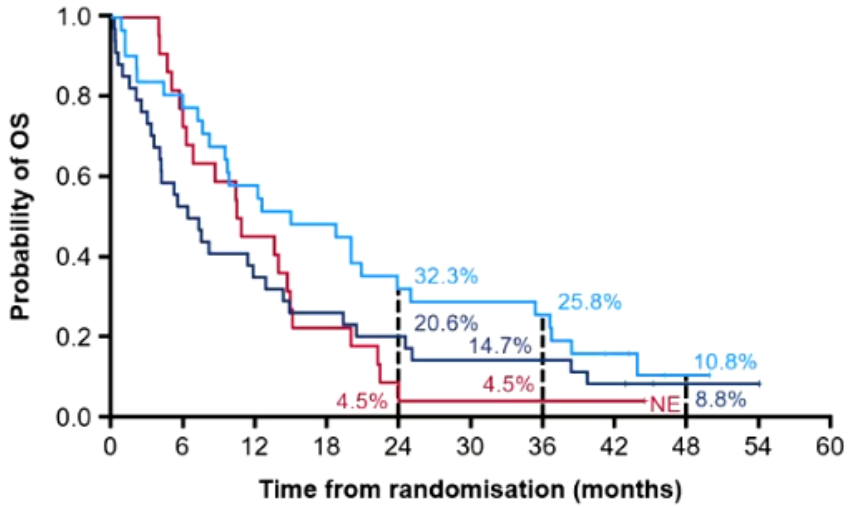
Updated OS by *STK11* Mutation Status

OS benefit observed for T+D+CT vs CT in *STK11*m with HR 0.62 and estimated 25.8% alive at 3 yrs vs 4.5%

*STK11*m

	T+D+CT	D+CT	CT
Events/patients, n/N	27/31	31/34	21/22
mOS, months (95% CI)	**15.0** (8.2–23.8)	**6.9** (3.6–12.9)	**10.7** (6.0–14.9)
HR* (95% CI)	**0.62** (0.34–1.12)	**1.06** (0.61–1.89)	–

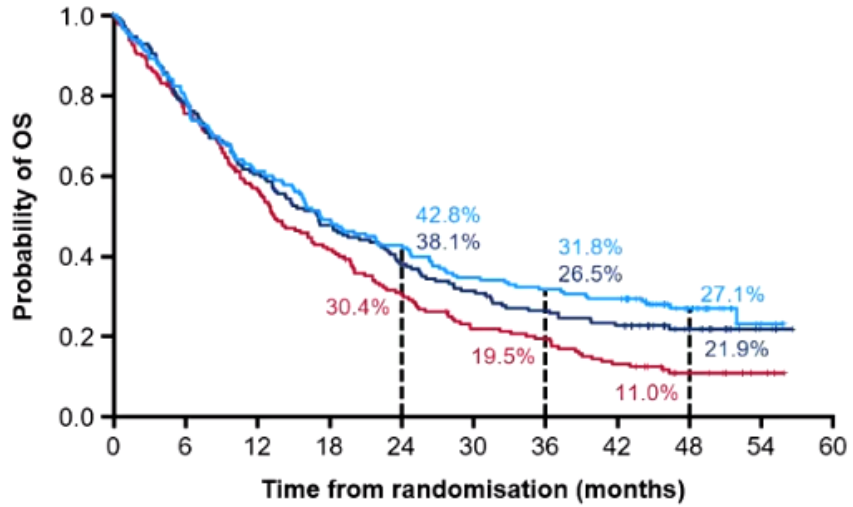


No. at risk

T+D+CT	31	24	18	15	10	9	8	4	1	0	0
D+CT	34	18	12	9	7	5	5	3	1	0	0
CT	22	16	10	5	1	1	1	1	0	0	0

*STK11*wt

	T+D+CT	D+CT	CT
Events/patients, n/N	127/177	129/169	151/179
mOS, months (95% CI)	**17.2** (14.9–22.1)	**17.1** (13.3–22.3)	**13.4** (11.5–17.5)
HR* (95% CI)	**0.70** (0.55–0.89)	**0.77** (0.61–0.98)	–



No. at risk

T+D+CT	177	140	107	85	74	60	55	51	23	3	0
D+CT	169	130	100	79	63	52	43	37	19	4	0
CT	179	131	97	71	51	36	31	21	9	4	0

*HR <1 favours D(±T)+CT vs CT (unstratified analysis); Assessed among mutation-evaluable patients with NSQ tumour histology; DCO, 11 Mar 2022

NE, not estimable

KRAS y STK11 / KEAP 1 y quimio-inmunoterapia 1ª linea

KEAP1, brazo durva-tremelimumab con quimio es superior a durva-quimio o quimio

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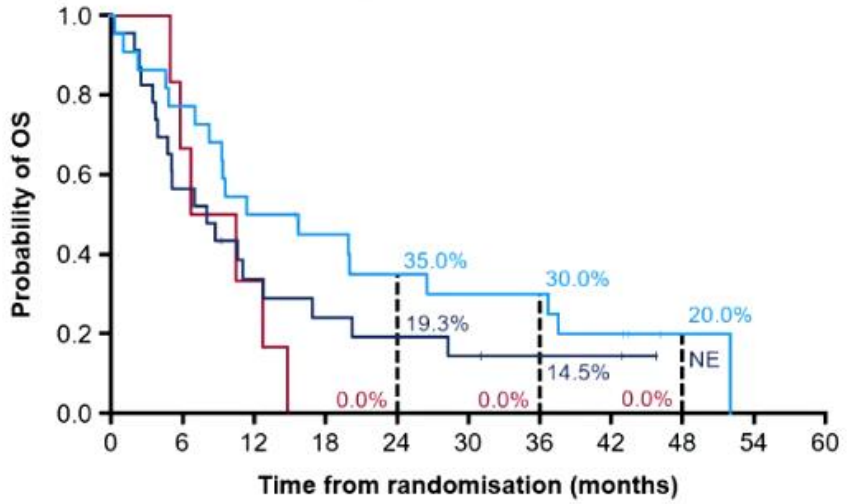
Updated OS by *KEAP1* Mutation Status

OS benefit observed for T+D+CT vs CT in *KEAP1*m with HR 0.43 (small sample size)

*KEAP1*m

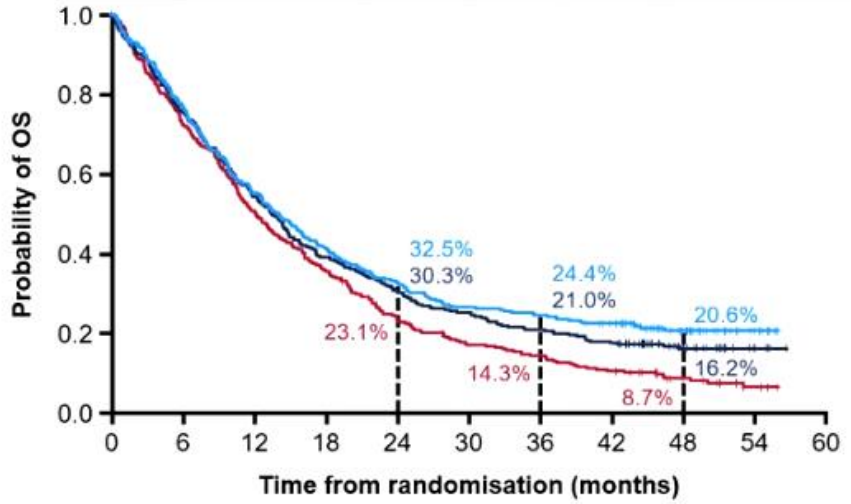
	T+D+CT	D+CT	CT
Events/patients, n/N	18/22	19/23	6/6
mOS, months (95% CI)	**13.7** (7.2–26.5)	**8.1** (4.0–12.9)	**8.7** (5.1–NE)
HR* (95% CI)	**0.43** (0.16–1.25)	**0.77** (0.31–2.15)	–



No. at risk											
T+D+CT	22	17	11	9	7	6	6	4	1	0	0
D+CT	23	13	7	5	4	3	2	2	0	0	0
CT	6	4	2	0	0	0	0	0	0	0	0

*KEAP1*wt

	T+D+CT	D+CT	CT
Events/patients, n/N	236/303	253/307	278/312
mOS, months (95% CI)	**14.0** (11.8–16.1)	**13.5** (11.7–14.9)	**12.2** (10.6–13.9)
HR* (95% CI)	**0.75** (0.63–0.89)	**0.81** (0.69–0.97)	–



No. at risk											
T+D+CT	303	230	165	123	97	79	73	63	30	6	0
D+CT	307	230	165	119	91	76	63	53	26	5	0
CT	312	221	153	108	69	50	41	30	14	5	0

In NSQ *KEAP1*m, HR (95% CI) vs CT was 0.33 (0.10–1.15) with T+D+CT and 0.67 (0.23–2.17) with D+CT

*HR <1 favours D(±T)+CT vs CT (unstratified analysis); Assessed among mutation-evaluable patients irrespective of tumour histology, due to small sample size; DCO, 11 Mar 2022

KRAS y STK11 / KEAP 1 y quimio-inmunoterapia 1ª linea

KRAS mutado, brazo durva-tremelimumab con quimio es superior a durva-quimio o quimio

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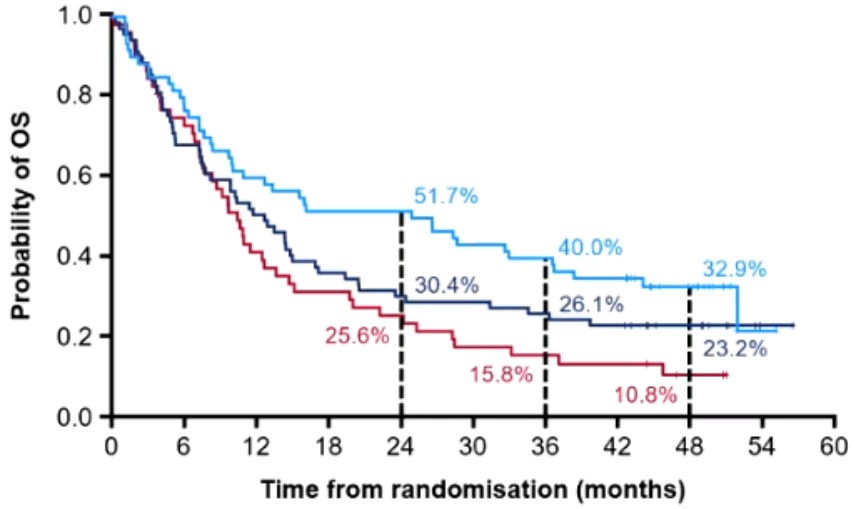
Updated OS by *KRAS* Mutation Status

OS benefit observed for T+D+CT vs CT in *KRAS*m with HR 0.55 and estimated 40.0% alive at 3 yrs vs 15.8%

*KRAS*m

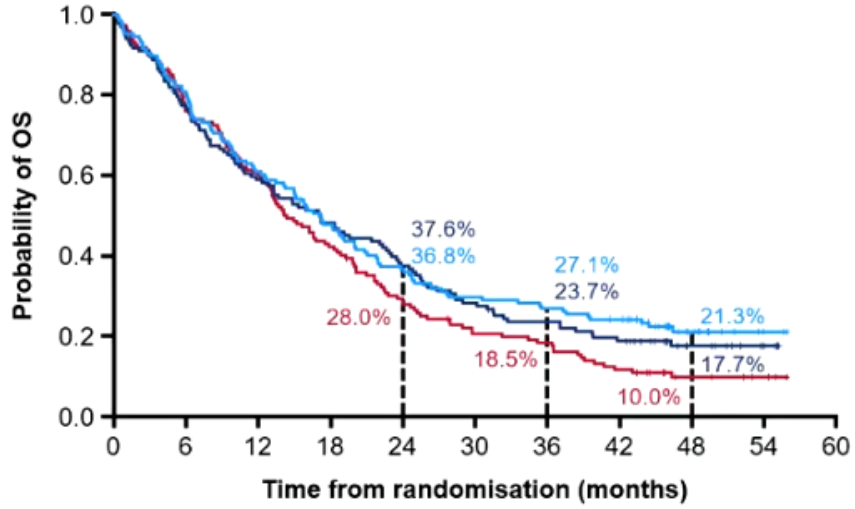
	T+D+CT	D+CT	CT
Events/patients, n/N	41/60	53/69	45/53
mOS, months (95% CI)	**25.7** (9.9–36.7)	**12.6** (7.5–16.9)	**10.4** (7.5–13.6)
HR* (95% CI)	**0.55** (0.36–0.85)	**0.78** (0.52–1.16)	–



No. at risk											
T+D+CT	60	46	36	31	31	26	24	21	12	1	0
D+CT	69	47	35	25	21	20	18	16	9	1	0
CT	53	37	21	16	13	9	7	6	2	0	0

*KRAS*wt

	T+D+CT	D+CT	CT
Events/patients, n/N	113/148	107/134	127/148
mOS, months (95% CI)	**17.1** (13.4–20.1)	**17.1** (12.3–22.6)	**14.4** (12.6–18.3)
HR* (95% CI)	**0.78** (0.60–1.00)	**0.83** (0.64–1.08)	–



No. at risk											
T+D+CT	148	118	89	69	53	43	39	34	12	2	0
D+CT	134	101	77	63	49	37	30	24	11	3	0
CT	148	110	86	60	39	28	25	16	7	4	0

*HR <1 favours D(±T)+CT vs CT (unstratified analysis); Assessed among mutation-evaluable patients with NSQ tumour histology; DCO, 11 Mar 2022

ESTUDIO APPLE - fase 2

Biopsia líquida EGFR

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EORTC European Organisation for Research and Treatment of Cancer

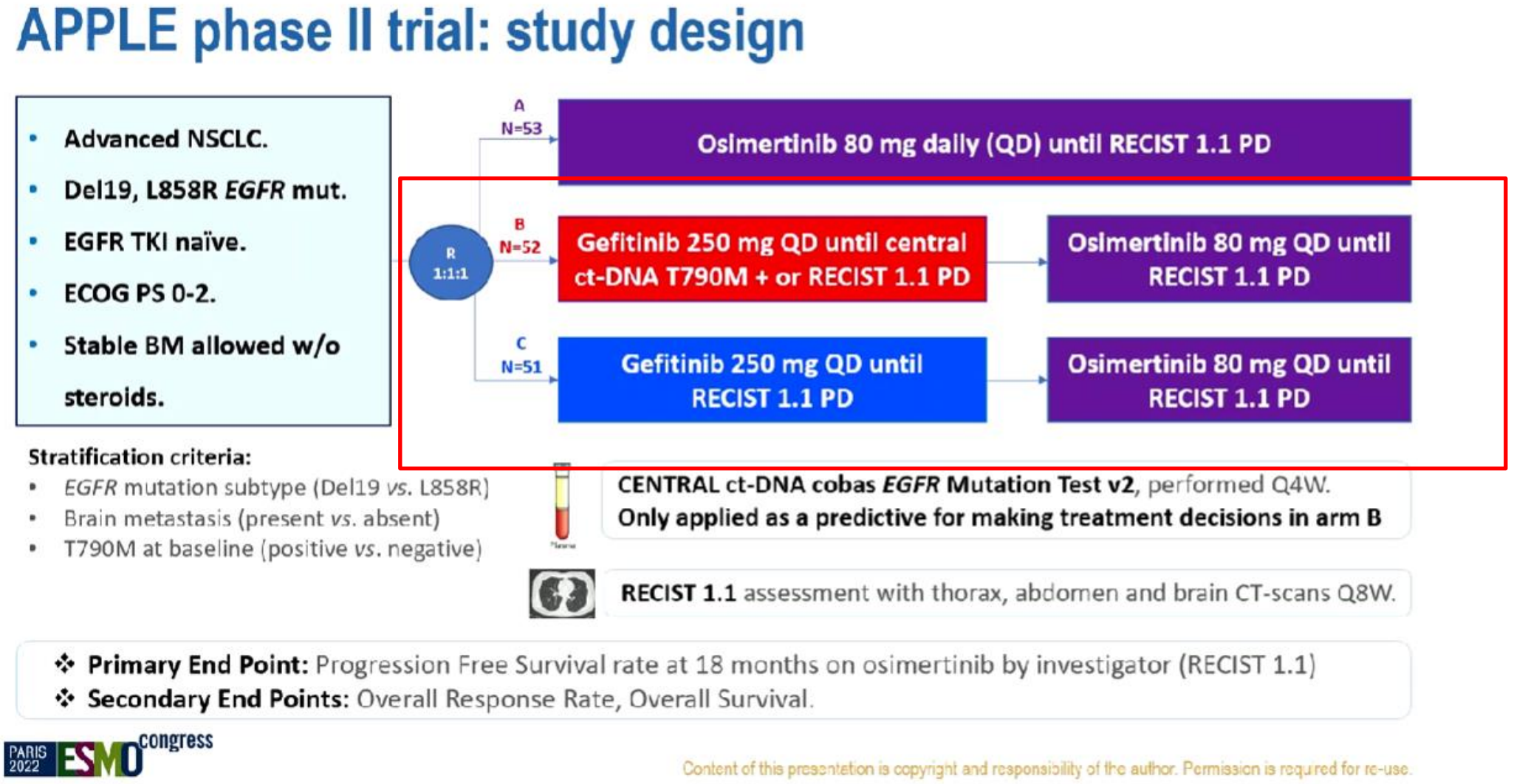
Osimertinib treatment based on plasma T790M monitoring in patients with *EGFR*-mutant advanced non-small cell lung cancer: EORTC Lung Cancer Group 1613 APPLE phase II randomized clinical trial

Jordi Remon[1], Benjamin Besse[1], Santiago Ponce[2], Ana Callejo[3], Kamal Al-Rabi[4], Reyes Bernabe[5], Laurent Greillier[6], Margarita Majem[7], Noemi Reguart[8], Isabelle Monnet[9], Sophie Cousin[10], Pilar Garrido[11], Gilles Robinet[12], Rosario Garcia-Campelo[13], Anne Madroszyk[14], Julien Mazières[15], Yassin Pretzenbacher[16], Beatrice Fournier[16], Anne-Marie C. Dingemans[17], Rafal Dziadziuszko[18]

[1]Institut Gustave Roussy (CLCC), Paris, France; [2]Hospital Universitario 12 De Octubre, Madrid, Spain; [3]Hospital Universitari Vall d'Hebron - Vall d'Hebron Institut Oncologia, Barcelona, Spain; [4]King Hussein Cancer Center, Amman, Jordan; [5]University Hospital Virgen del Rocio, Sevilla, Spain; [6]Aix Marseille University, Assitance Publique – Hôpitaux de Marseille (APHM), Marseille, France; [7]Hospital De La Santa Creu I Sant Pau, Barcelona, Spain; [8]Hospital Clinic Universitari de Barcelona, IDIBAPS, Barcelona, Spain; [9]Centre Hospitalier Intercommunal De Creteil, Creteil, France; [10]Institut Bergonie, Bordeaux, France; [11]Hospital Universitario Ramon y Cajal, Madrid, Spain; [12]CHU de Brest, Brest, France; [13]University Hospital A Coruna-Hospital Teresa Herrera, A Coruna, Spain; [14]Institut Paoli-Calmettes, Marseille, France; [15]CHU de Toulouse - Hopital Larrey, Toulouse, France; [16]EORTC Headquarters, Brussels, Belgium; [17]Erasmus Medical Center, Rotterdam, Netherlands; [18]Medical University of Gdansk, Gdansk, Poland

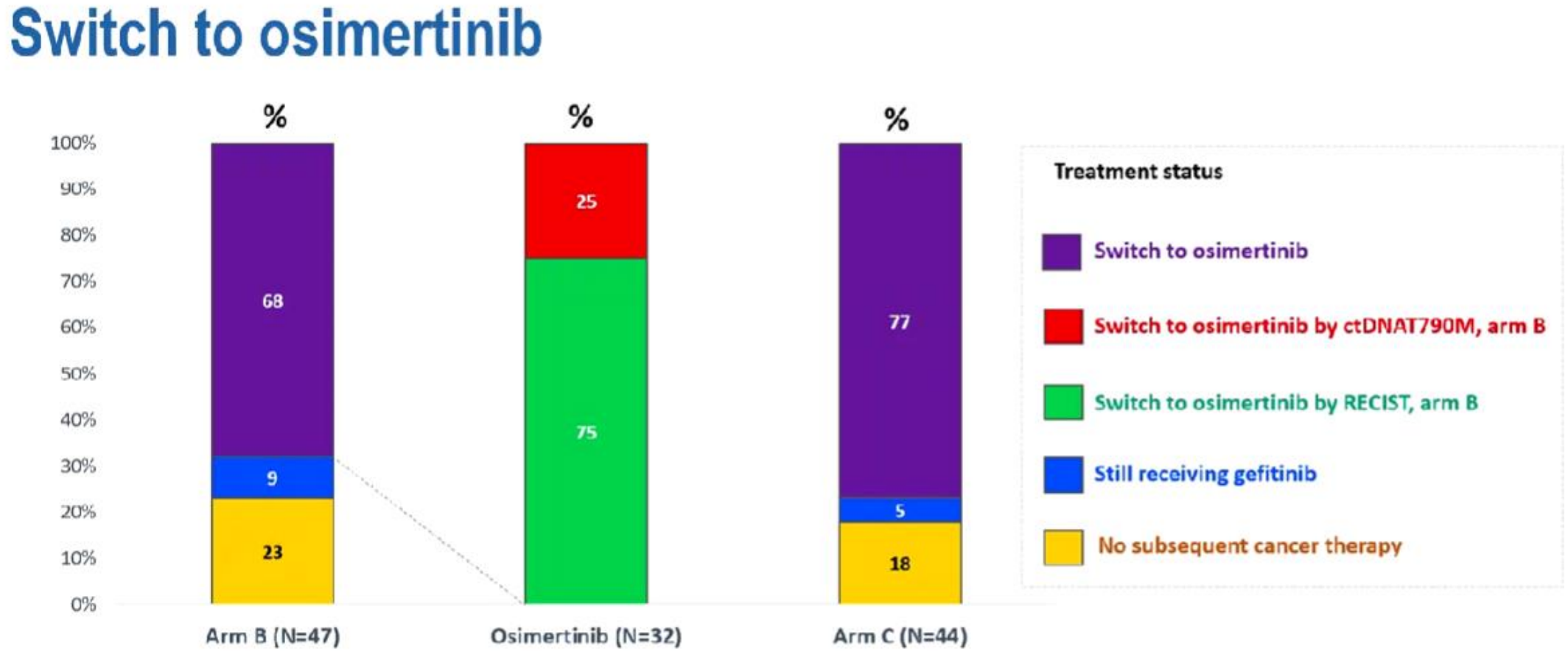
ESTUDIO APPLE - fase 2

Biopsia líquida EGFR



ESTUDIO APPLE - fase 2

Biopsia líquida EGFR

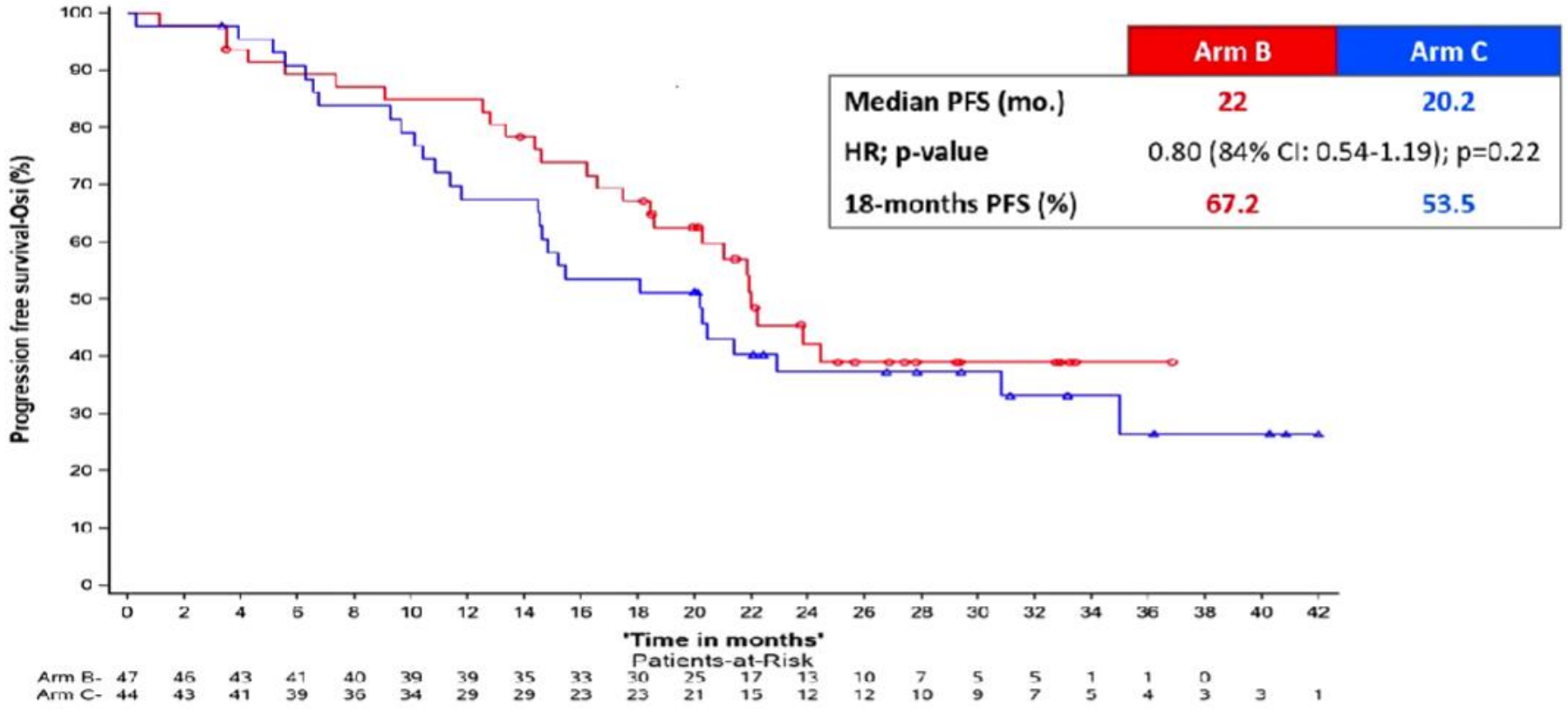


- In arm B, **17% (8/47) of PPP switched to osimertinib due to molecular progression** (ctDNA *EGFR* T790M positive)
- Median time to molecular progression was 266 days (range: 56-672 days)

ESTUDIO APPLE - fase 2

Biopsia líquida EGFR

PFS-OSI-18 rate by INV. in arm B *vs.* C, exploratory



	Arm B	Arm C
Median PFS (mo.)	22	20.2
HR; p-value	0.80 (84% CI: 0.54-1.19); p=0.22	
18-months PFS (%)	67.2	53.5

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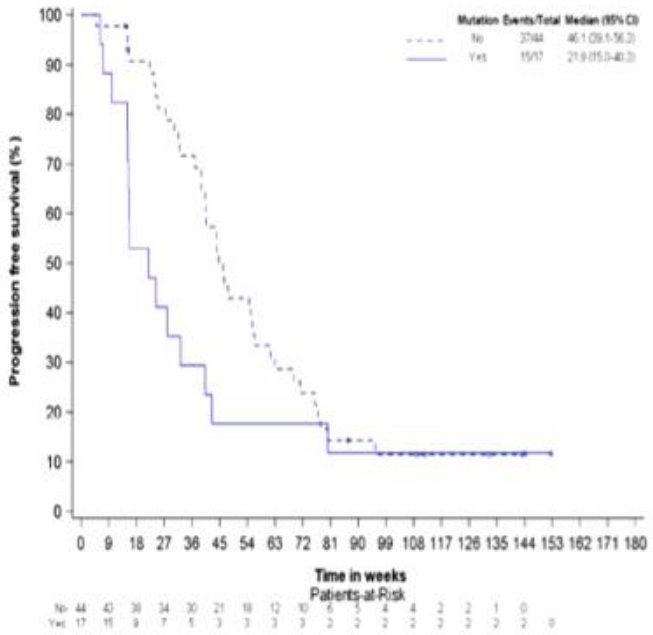
ESTUDIO APPLE - fase 2

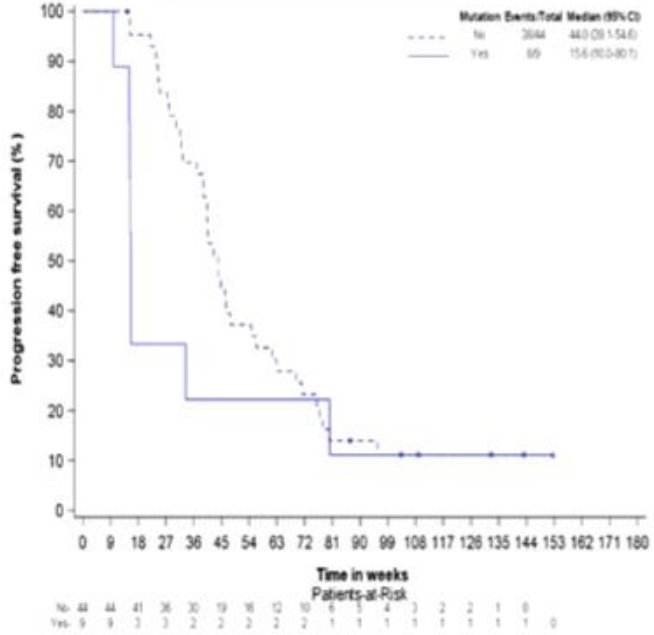
Biopsia líquida EGFR

ctDNA clearance of *EGFR*m and PFS: exploratory analysis

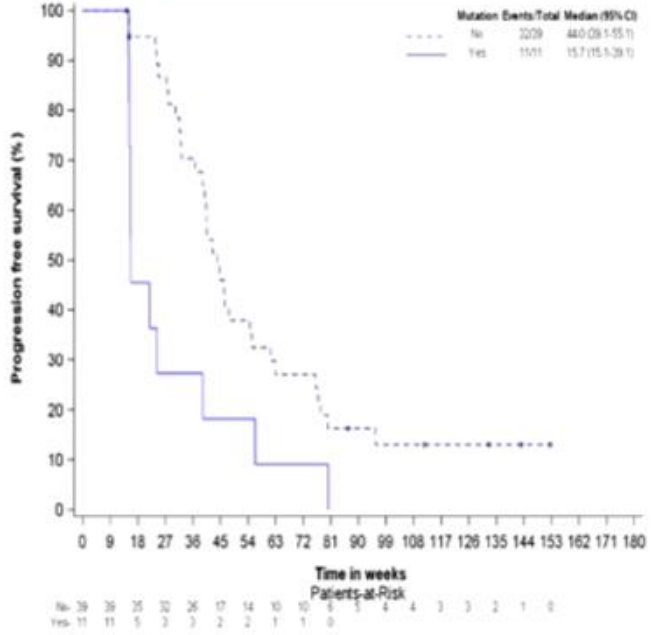
Clearance at week 4



Clearance at week 8



Clearance at week 12



- The incidence of *EGFR* mutant positive by ctDNA test at baseline was 65% (67/103).
- Clearance of ct-DNA is an early predictor of favorable outcomes on treatment with gefitinib.

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ctDNA en estadios precoces

Biopsia líquida en EGFR mutados

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Longitudinal Monitoring of Circulating Tumor DNA from Plasma in Patients with Curative Resected Stage IA-IIIA *EGFR* mutant Non-small Cell Lung Cancer

Myung-Ju Ahn, Hyun-Ae Jung, Bo Mi Ku, Yeon Jeong Kim, Sehhoon Park, Jong-Mu Sun, Se-Hoon Lee, Jin Seok Ahn, Jong Ho Cho, Hong Kwan Kim, Yong Soo Choi, Jhingook Kim

Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

ctDNA en estadios precoces

Biopsia líquida en EGFR mutados

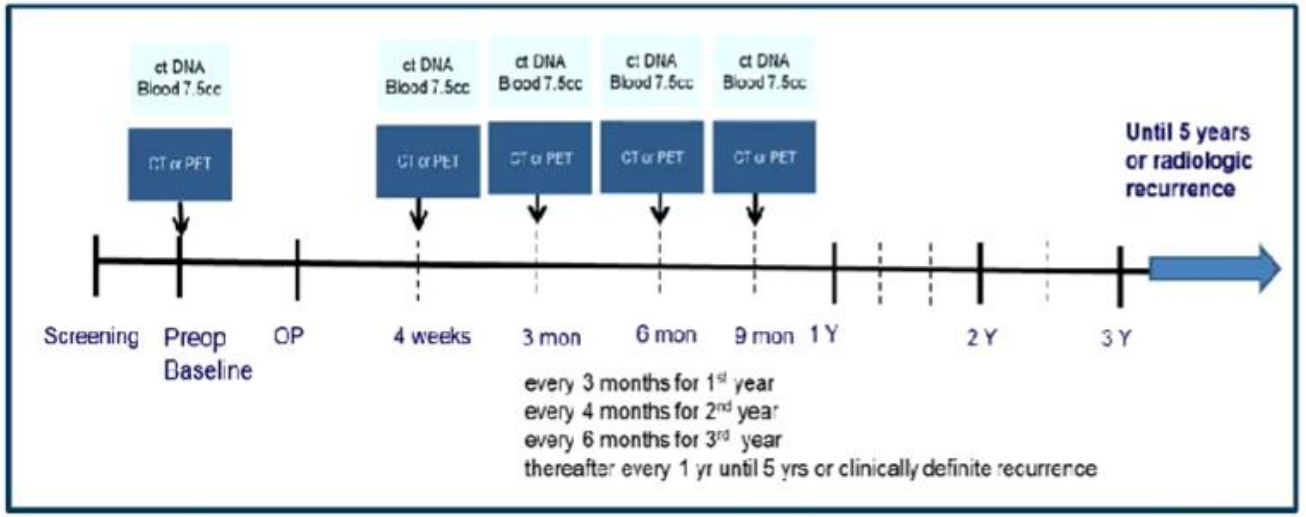
Methods

Purpose

- To investigate the role of longitudinal monitoring of ctDNA test in curative resected early-stage (stage IA-IIIA) *EGFR*-M+ NSCLC

Study population

- Between August 2015 and October 2017
- Patients with curative resected stage IA-IIIA (AJCC 7th edition) *EGFR*-M+ (Del 19 or L858R) NSCLC
- Radiological follow-up including chest CT or PET-CT was accompanied with serial longitudinal monitoring of ctDNA using a droplet digital PCR(BioRad)



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Myung-Ju Ahn, M.D.

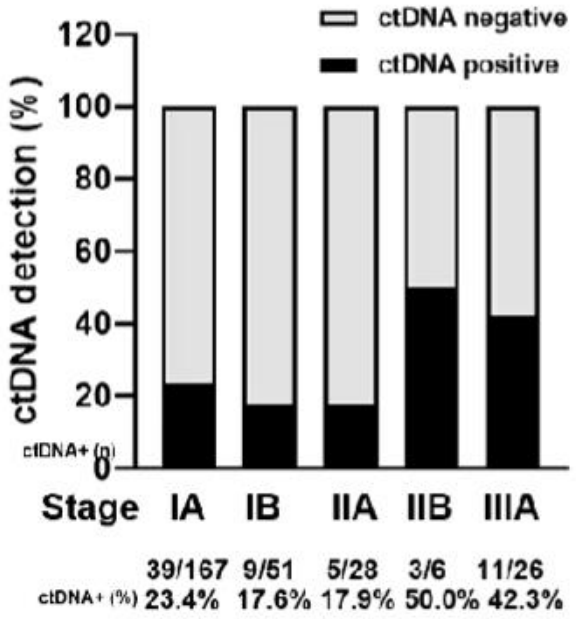
ctDNA en estadios precoces

Biopsia líquida en EGFR mutados

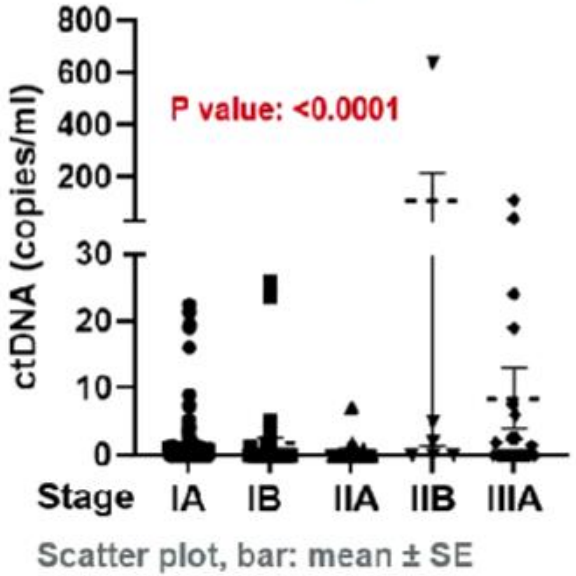
Results

- Among 278 patients, baseline ctDNA was detected in 67 (24.1%) patients: 23.4% (stage IA), 17.6% (IB), 17.9% (IIA), 50.0% (IIB), and 42.3% (IIIA) (P=0.06). Baseline ctDNA copy numbers are increasing according to stage
- Among 67 patients with baseline ctDNA+, 76.1% (51/67) showed ctDNA clearance 4 weeks after surgery
- No difference in ctDNA detection rate (24% vs 24.3%) or clearance rate (75% vs 77.8%) between exon 19 del and L858R

Baseline ctDNA detection rate

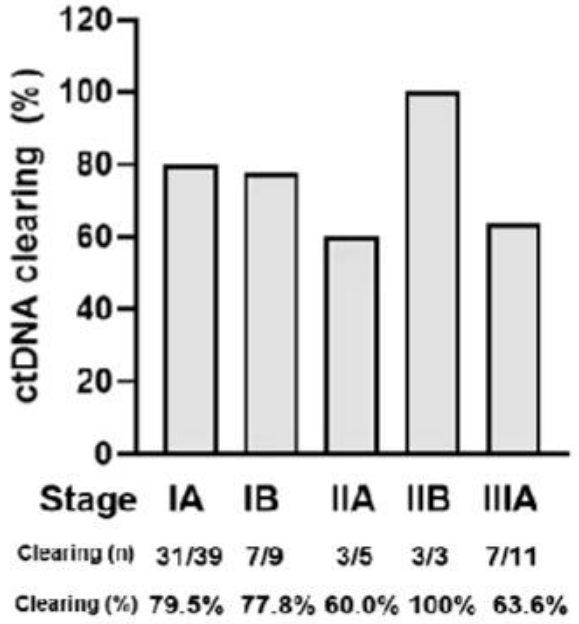


Baseline ctDNA copy numbers



Scatter plot, bar: mean ± SE

ctDNA clearance after surgery



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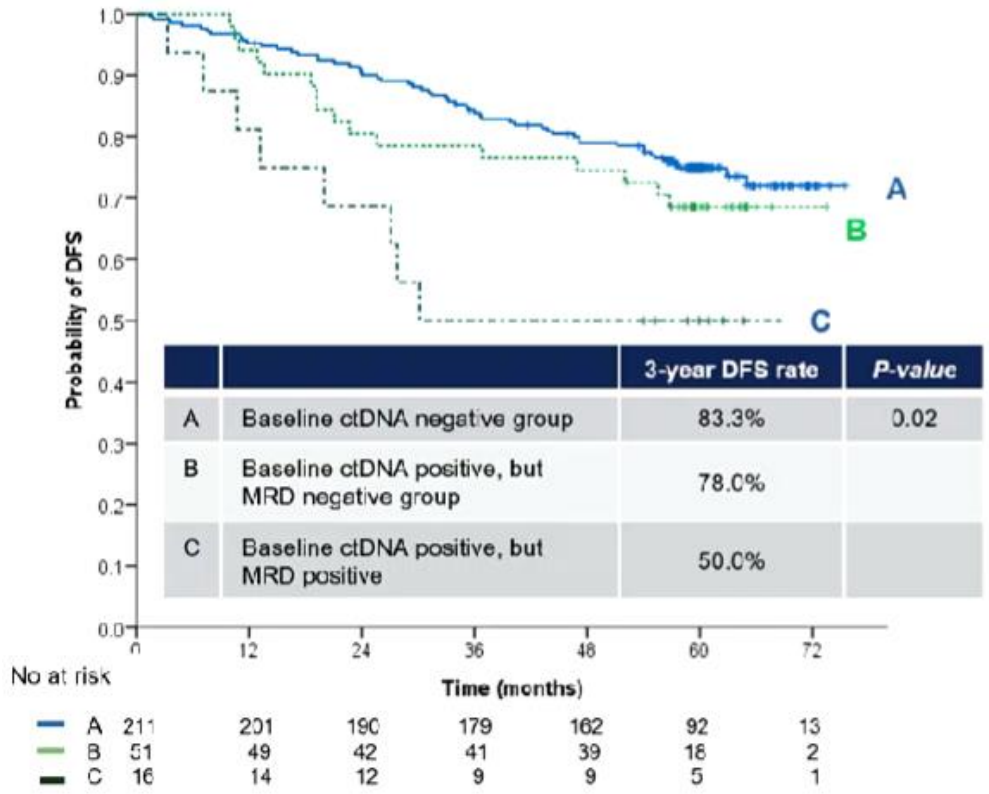
Myung-Ju Ahn, M.D.

ctDNA en estadios precoces

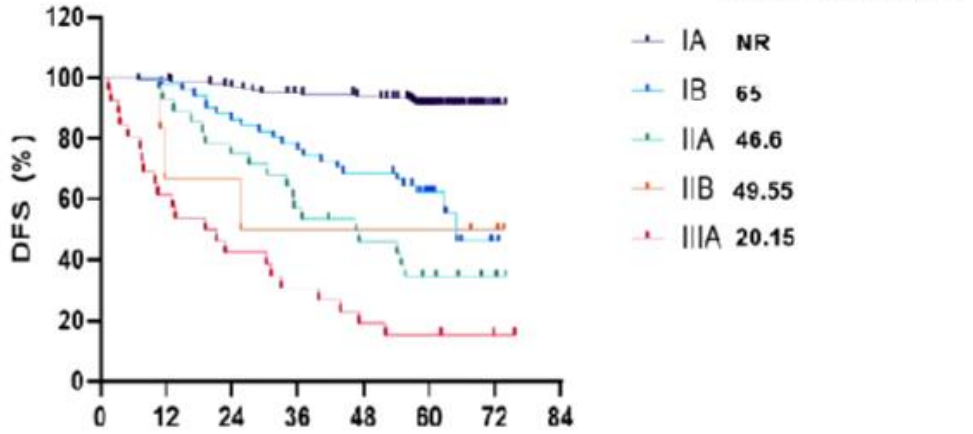
Biopsia líquida en EGFR mutados

DFS by ctDNA status



		3-year DFS rate	*P-value*
A	Baseline ctDNA negative group	83.3%	0.02
B	Baseline ctDNA positive, but MRD negative group	78.0%	
C	Baseline ctDNA positive, but MRD positive	50.0%	

DFS by Stage



Multivariate Analysis for DFS

Variable	HR (95% CI)	P-value
Sex (Female vs. Male)	0.70 (0.31-1.58)	0.39
Smoking status (Never vs. Ever)	1.55 (0.67-3.55)	0.31
EGFR mutation (Del19 vs. L858R)	0.68 (0.42-1.11)	0.12
ECOG PS (0 vs.1)	0.91 (0.21-4.01)	0.91
Stage (I vs II-III)	3.84 (2.91-5.06)	<0.001
ctDNA group	1.27 (1.03-1.57)	0.03

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Myung-Ju Ahn, M.D.

MRD: minimal residual disease

Mecanismos resistencia Osimertinib

Estudio ELIOS

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ELIOS: a multicentre, molecular profiling study of patients with EGFRm advanced NSCLC treated with first-line osimertinib

Zofia Piotrowska[1], Myung-Ju Ahn[2], Yong Kek Pang[3], Soon Hin How[4], Sang-We Kim[5], Pei Jye Voon[3], Diego Cortinovis[7], Javier de Castro Carpeno[8], Marcello Tiseo[9], Delvys Rodriguez Abreu[10], Suresh S. Ramalingam[11], Jingyi Li[12], Leslie Servidio[12], Samuel Sadow[13], Ryan Hartmaier[14], Byoung Chul Cho[15]

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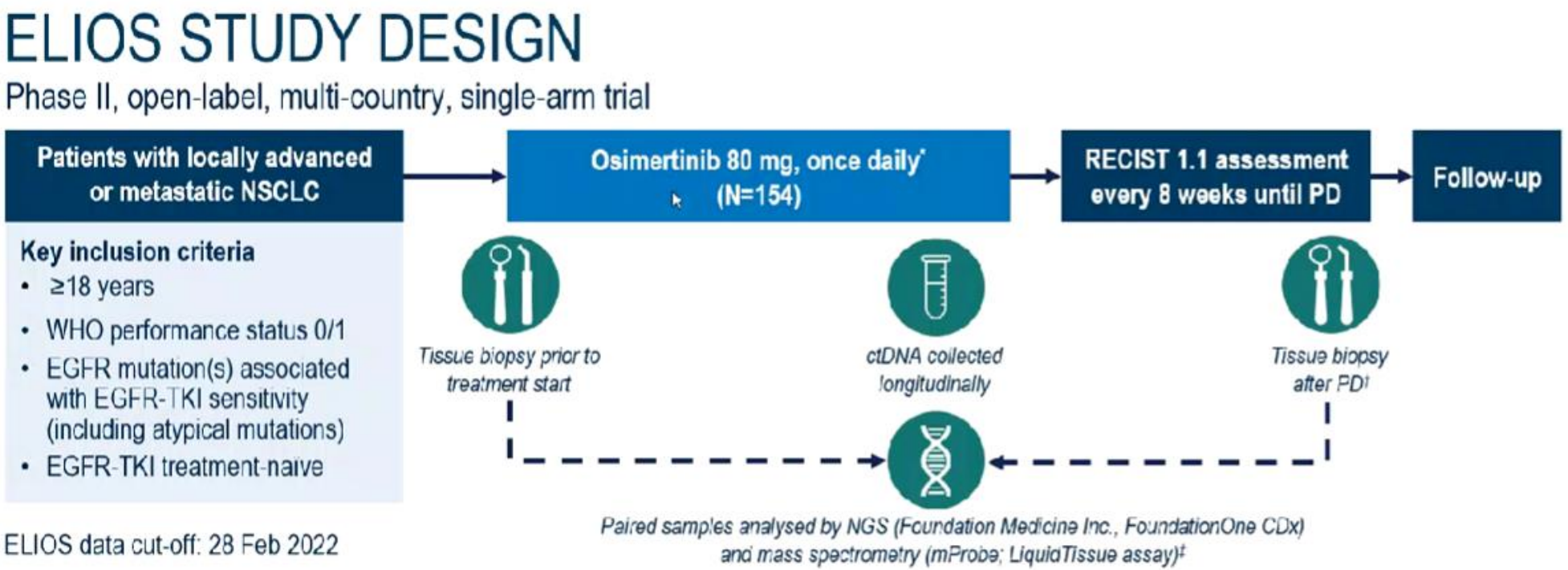
Mecanismos resistencia Osimertinib

Estudio ELIOS



- **Primary endpoint**: proportion of patients with a given tumour genetic and proteomic marker (including, but not limited to, EGFR mutations, HER2 and MET expression and / or amplification) at PD
- Secondary endpoints: PFS (investigator-assessed), ORR, DoR, DCR, TTD, TFST, and safety

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* Treatment beyond PD was permitted in patients who continued to show clinical benefit as judged by the investigator; †Performed between investigator-assessed RECIST 1.1-defined PD and the start of any new anticancer therapy; ‡NGS performed first and, in case of sufficient tissue, mass spectrometry was subsequently performed.

Zofia Piotrowska, MD

ctDNA, circulating tumour DNA; DCR, disease control rate; DoR, duration of response; EGFR, epidermal growth factor receptor; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TFST, time to first subsequent therapy or death; TKI, tyrosine kinase inhibitor; TTD, time to treatment discontinuation or death; WHO, World Health Organization

Mecanismos resistencia Osimertinib

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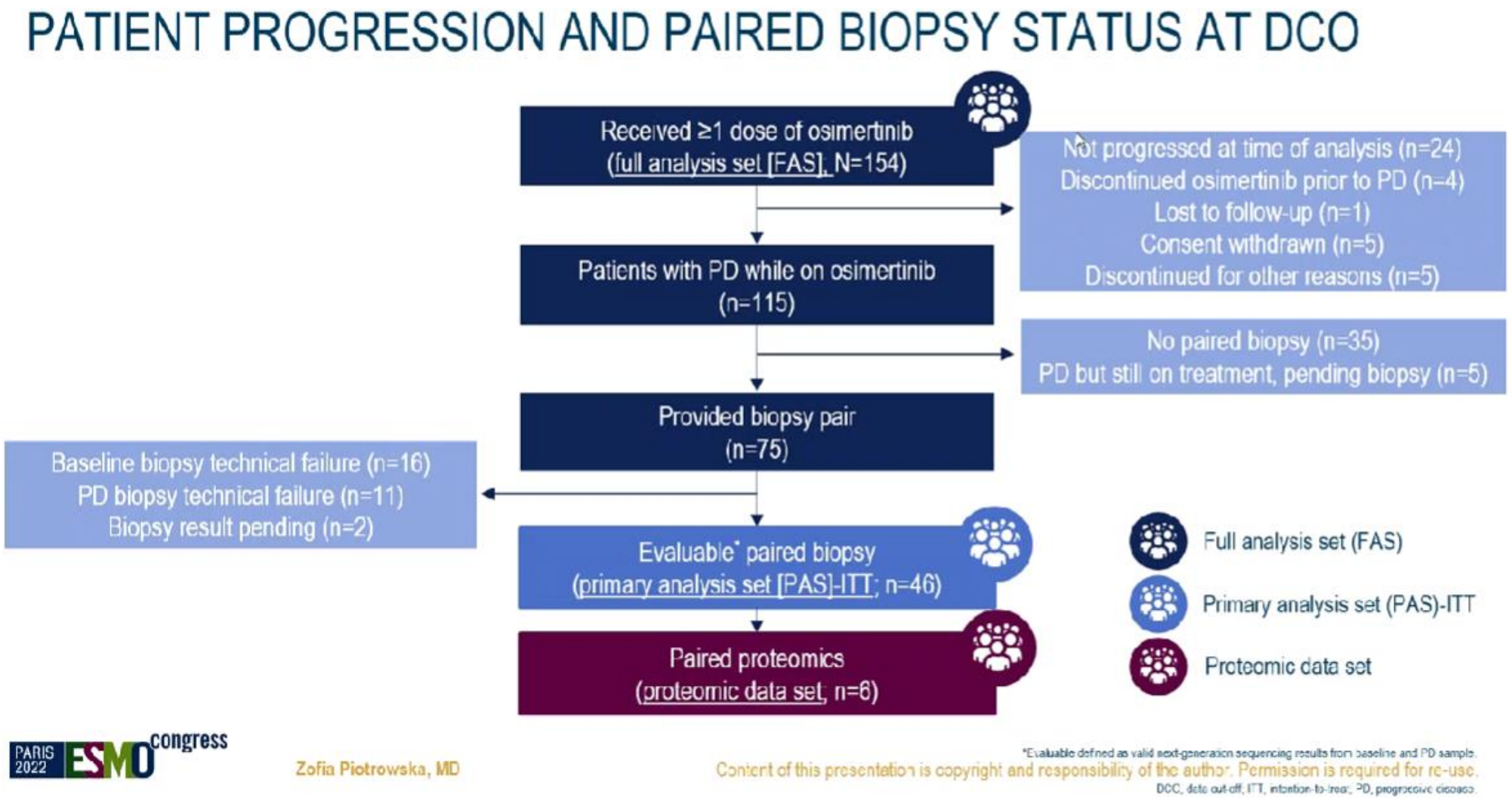

Mecanismos resistencia Osimertinib

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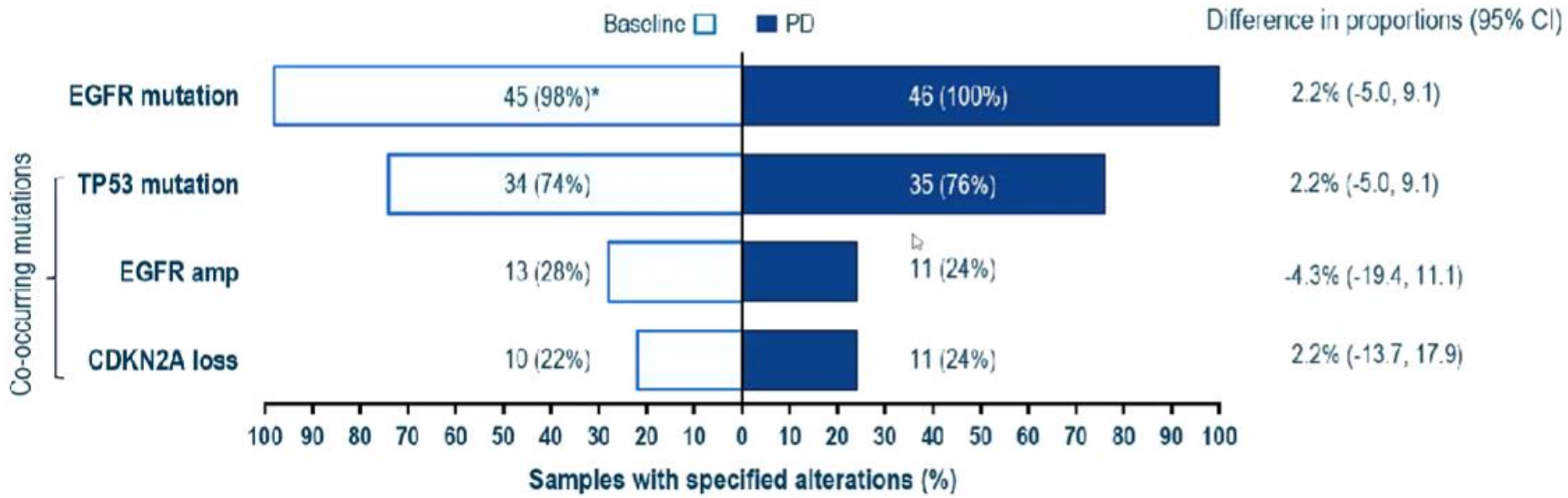
PRIMARY ENDPOINT: HIGH-FREQUENCY MUTATIONS FROM BASELINE TO PD (PAS-ITT)

- High frequency mutations at baseline (EGFR, TP53 mutations, EGFR amplification and CDKN2A loss) did not differ significantly at PD



*Baseline EGFR mutation not detected in one sample likely due to low tissue content.
Figure compares proportions of patients with a given marker at baseline to that at PD for markers where it was present in >20% of patients at baseline.
Differences in proportions calculated as PD – baseline.
CI calculated using the adjusted Wald method. EGFR mutation and TP53 mutation are any short variant.

amp, amplification; CI, confidence interval; EGFR, epidermal growth factor receptor; PAS-ITT, primary analysis set intention-to-treat; PD, progressive disease.

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PRIMARY ENDPOINT: SUMMARY OF MAJOR ALTERATIONS AT BASELINE AND PD (PAS-ITT)

- Selected genetic alterations based on high frequency of detection and / or prior knowledge of involvement in osimertinib resistance are shown below

Gene alteration, N (%)	Baseline (n=46)	PD (n=46)	Acquired* (n=46)	Evidence of sensitivity
MET amp	2 (4)	9 (20)	**8 (17)**	✓[1,2]
CDKN2A del	10 (22)	11 (24)	**7 (15)**	
CDKN2B del	9 (20)	11 (24)	**7 (15)**	
MTAP del	7 (15)	10 (22)	**7 (15)**	
EGFR C797S	0 (0)	7 (15)	**7 (15)**	✓[3]
NKX2-1 amp	4 (9)	9 (20)	**5 (11)**	
EGFR amp	13 (28)	11 (24)	**5 (11)**	
CCNE1 amp	3 (7)	6 (13)	**3 (7)**	
ARAF amp	0 (0)	2 (4)	**2 (4)**	
ALK fusion	0 (0)	1 (2)	**1 (2)**	✓[4]

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*Defined as mutations detectable at PD that were not detectable at baseline (for an individual patient).

1. Yu et al. Ann Oncol. 2021;32(Suppl 5):S649–S1039; 2. Aha et al. WCLC 2022. EP08.02-140; 3. Yu et al. Clin Lung Cancer 2021;22:001–006; 4. von Buttlar et al. JTO Clin Res Rep 2021;2:100179.

amp, amplification; del, deletion; EGFR, epidermal growth factor receptor; PAS-ITT, primary analysis set intention-to-treat; PD, progressive disease.

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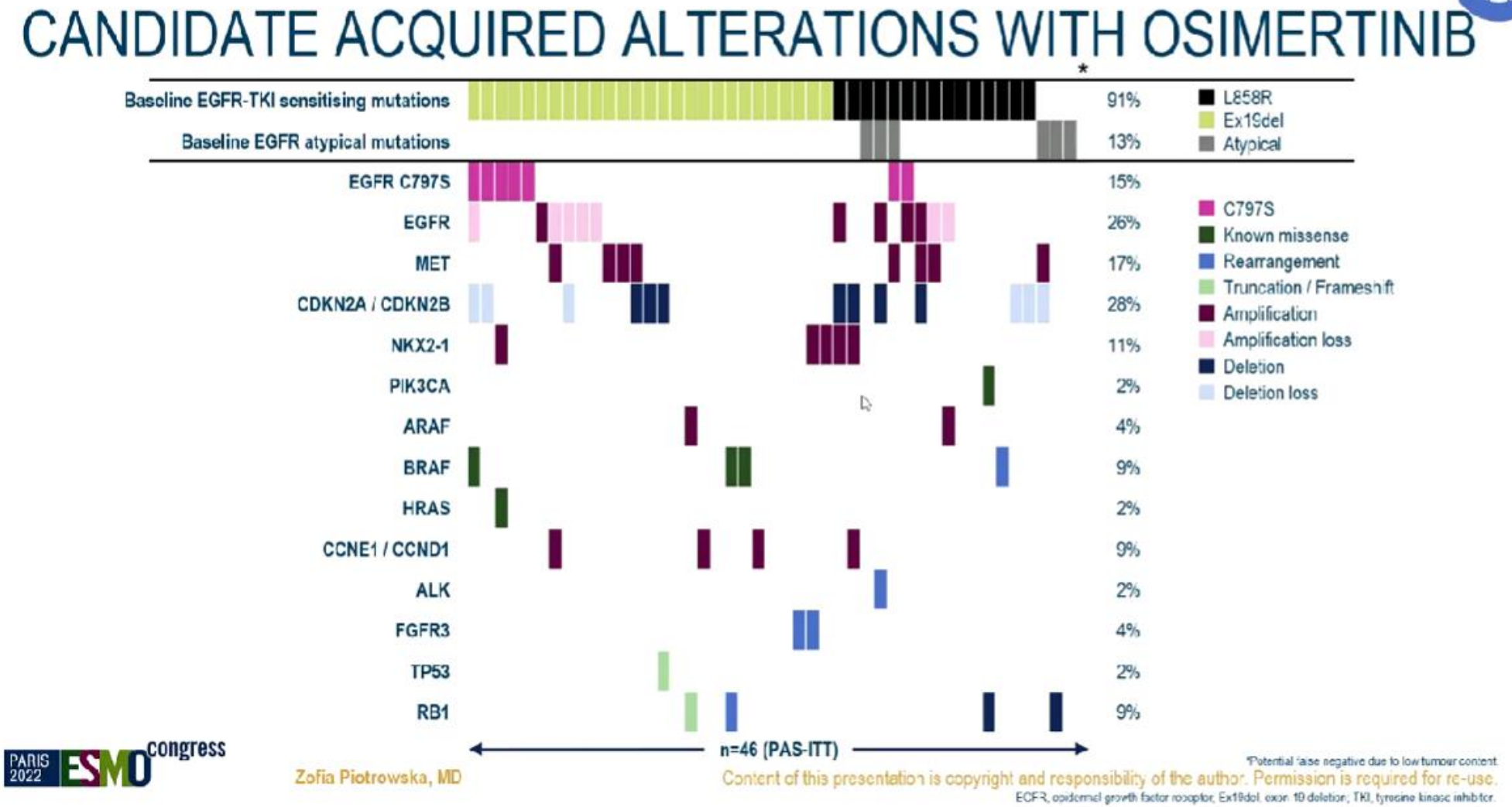

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PRIMARY ENDPOINT: PROTEOMIC EXPRESSION OF 15 SELECTED MARKERS FROM 6 PAIRED TISSUE SAMPLES

Protein	Increased relative to baseline, n (%)	Decreased relative to baseline, n (%)
AXL	4 (67)	0
MET	3 (50)	1 (17)
E-cadherin	2 (33)	2 (33)
EGFR	2 (33)	2 (33)
SLFN11	2 (33)	3 (50)
TOP1	2 (33)	0
TROP2	2 (33)	1 (17)
CD56	1 (17)	0
Chromogranin A	1 (17)	0
HER2	1 (17)	2 (33)
SYP	1 (17)	0
VIM	1 (17)	0
HER3	0	0
FRα	0	3 (50)
PD-L1	0	0

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Displayed markers selected based on those deemed most relevant for resistance to osimertinib, including markers of signalling bypass, SCLC transformation and biomarkers relevant to second-line treatment options under investigation.

EGFR, epidermal growth factor receptor; SCLC, small-cell lung cancer.