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TERAPIAS DIRIGIDAS II (Mecanismos de resistencia a Osimertinib, Inhibidores de MET)

Dra. Virginia Calvo

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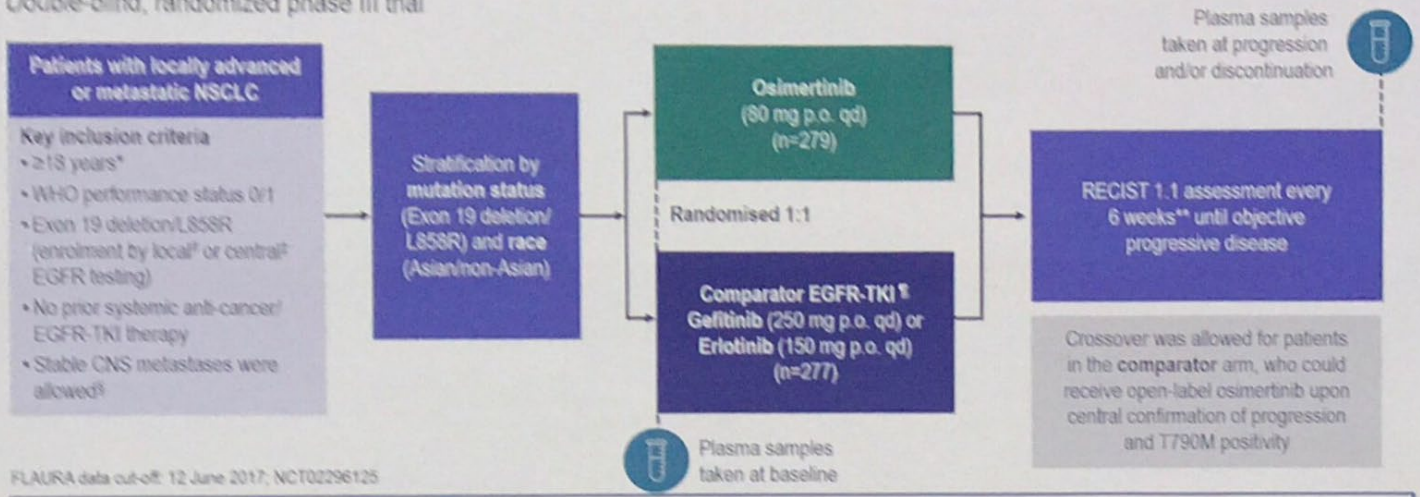
MECHANISMS OF ACQUIRED RESISTANCE TO FIRST-LINE OSIMERTINIB: PRELIMINARY DATA FROM THE PHASE III FLAURA STUDY

Suresh S Ramalingam[1], Ying Cheng[2], Caicun Zhou[3], Yuichiro Ohe[4], Fumio Imamura[5], Byoung Chul Cho[6], Meng-Chih Lin[7], Margarita Majem[8], Riyaz Shah[9], Yuri Rukazenkov[10], Alexander Todd[11], Aleksandra Markovets[12], Carl Barrett[12], Juliann Chmielecki[13],

FLAURA STUDY DESIGN

Double-blind, randomized phase III trial



FLAURA data cut-off: 12 June 2017; NCT02296125

Objective of resistance analysis

- Investigate mechanisms of acquired resistance to osimertinib and comparator from ctDNA in patients who progressed or discontinued treatment during FLAURA

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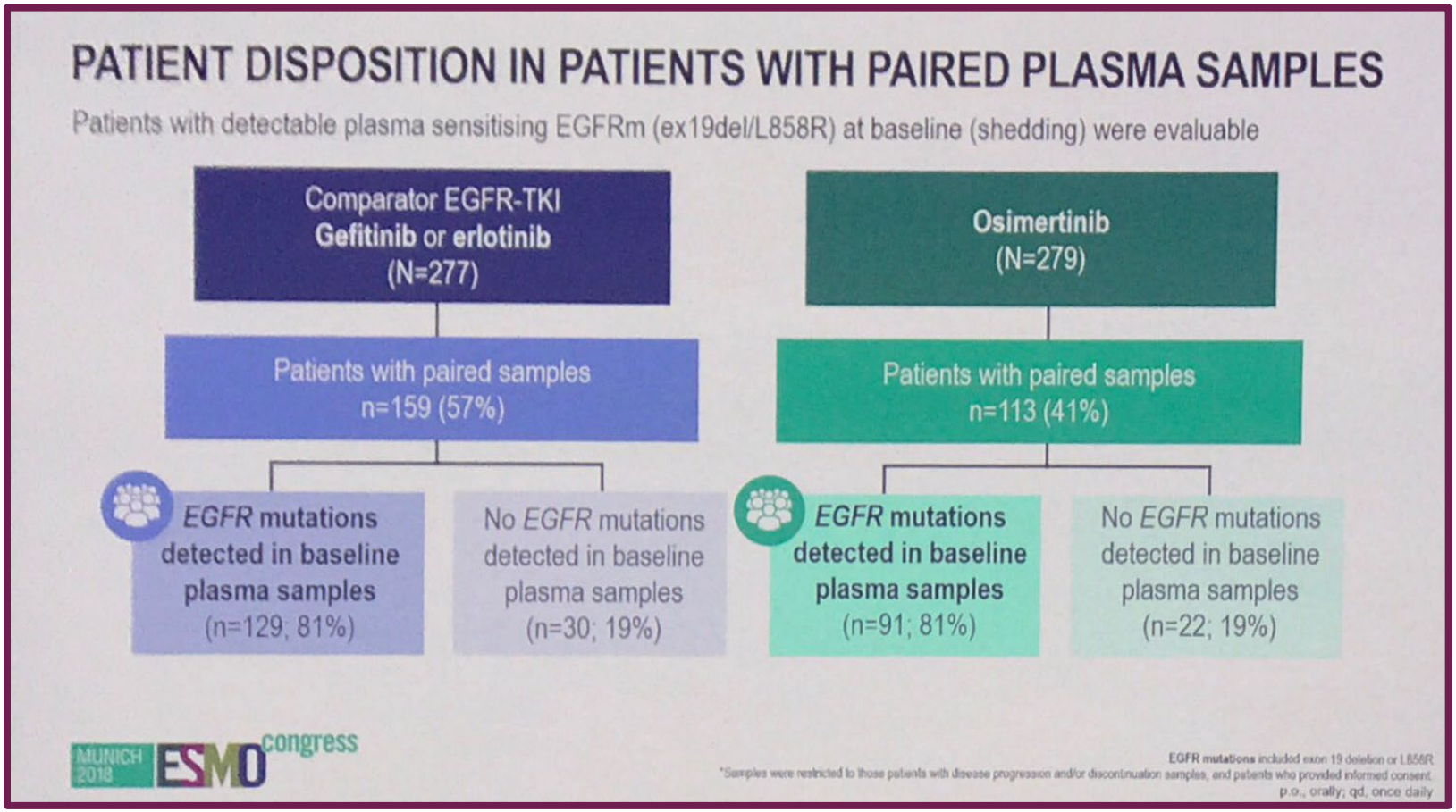

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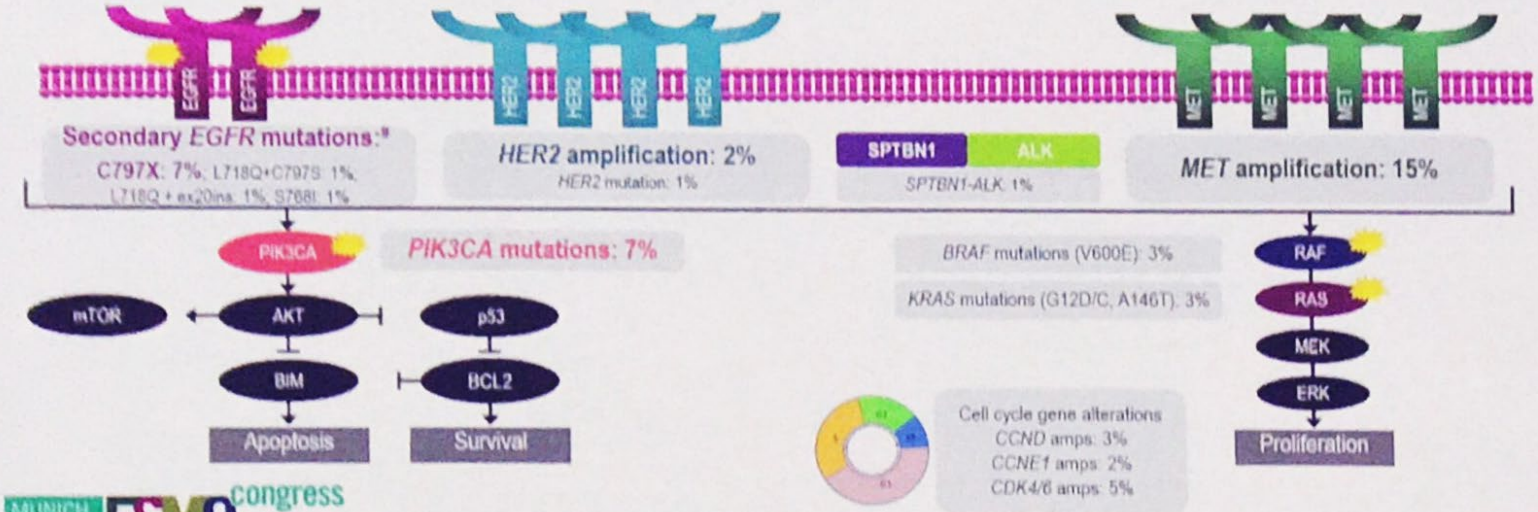
RESULTS: CANDIDATE ACQUIRED RESISTANCE MECHANISMS WITH OSIMERTINIB (n=91)*

- No evidence of acquired EGFR T790M
- The most common resistance mechanisms were *MET* amplification and EGFR C797S mutation
  - Other mechanisms included *HER2* amplification, *PIK3CA* and *RAS* mutations



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†Resistance mechanism reported may overlap with another; ‡Two patients had de novo T790M mutations at baseline of whom one acquired C797S at progression

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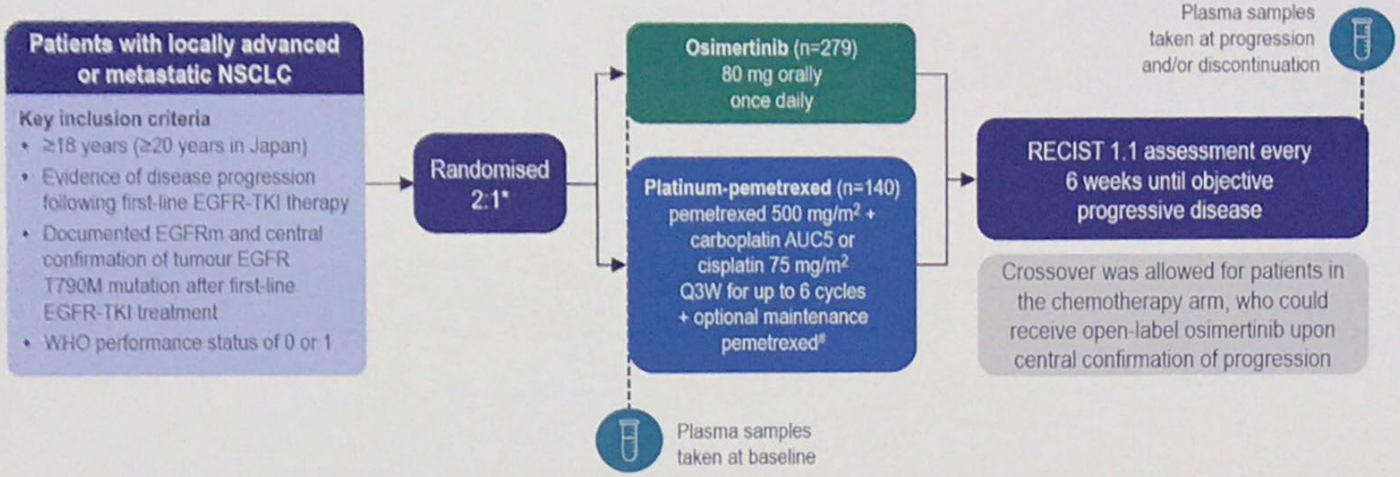
ANALYSIS OF RESISTANCE MECHANISMS TO OSIMERTINIB IN PATIENTS WITH EGFR T790M ADVANCED NSCLC FROM THE AURA3 STUDY

Vassiliki Papadimitrakopoulou[1], Yi-Long Wu[2], Ji-Youn Han[3], Myung-Ju Ahn[4],

AURA3 study design



Objective of resistance analysis
Exploratory analysis to investigate mechanisms of acquired resistance to osimertinib in patients who progressed or discontinued treatment during AURA3

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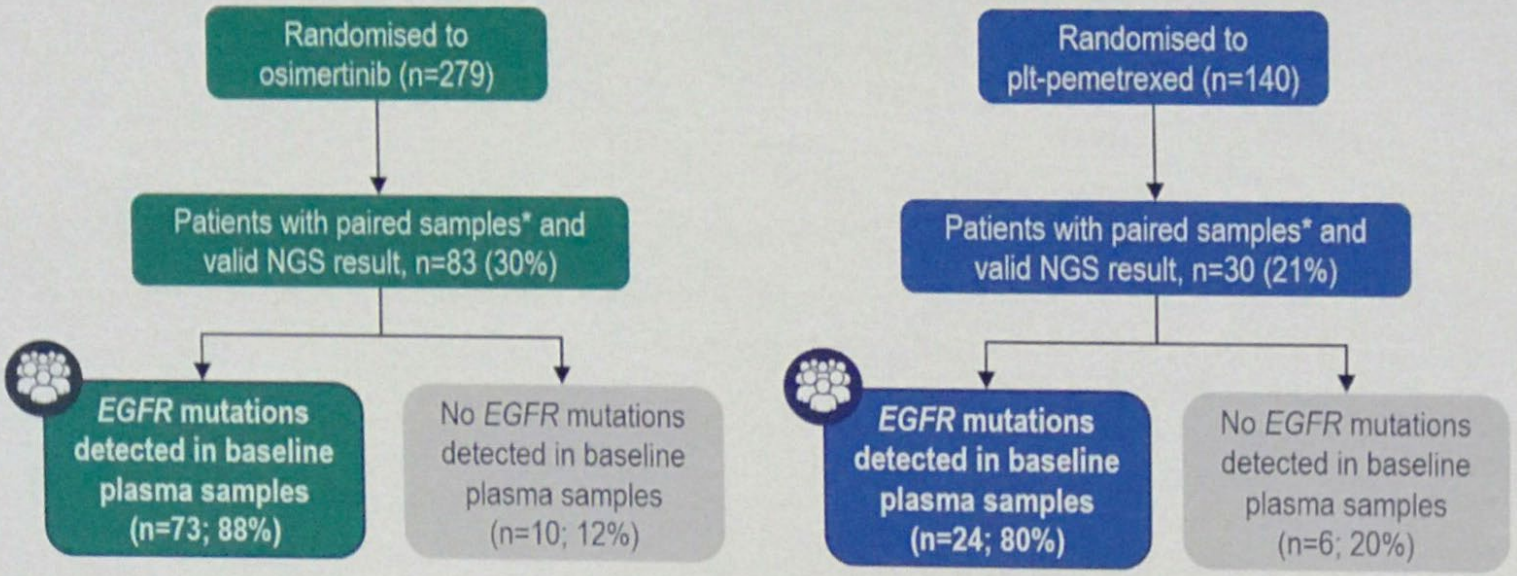
Patients with progression and/or discontinuation samples in the biobank by April 2018 were included.
*Patients were stratified at randomisation based on ethnicity (Asian/non-Asian). #For patients whose disease had not progressed after four cycles of platinum-pemetrexed.
EGFRm, EGFR mutation positive; RECIST, Response Evaluation Criteria In Solid Tumors; WHO, World Health Organization.

Patient disposition

Patients with detectable plasma sensitising EGFRm (L858R / ex19del) and/or T790M at baseline (tumour shedders) were evaluable



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EGFR mutations included ex19del, L858R or T79

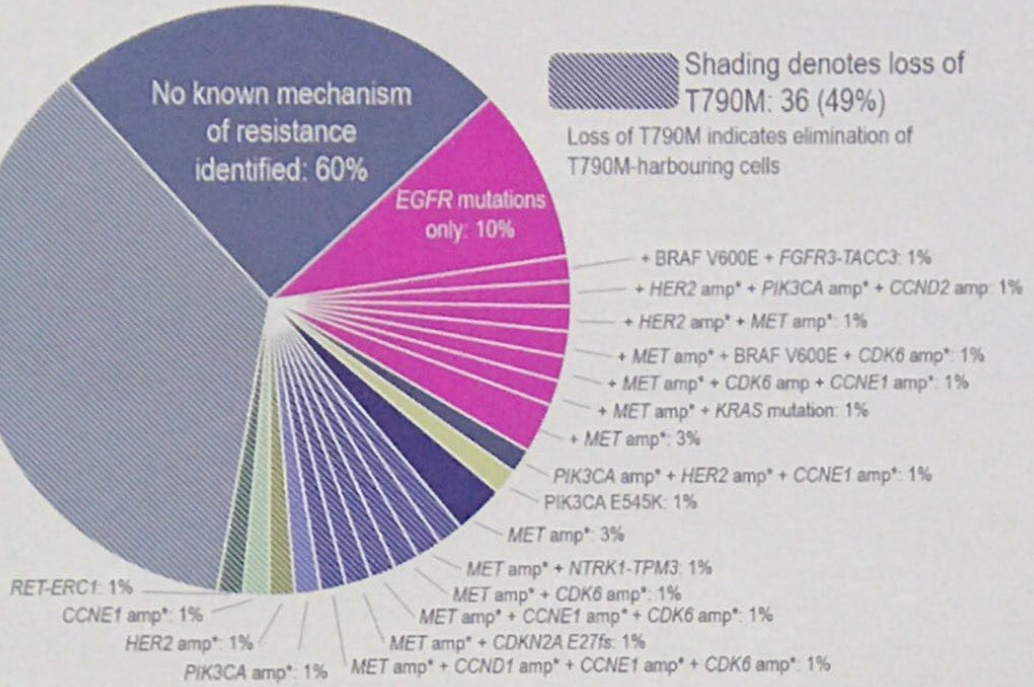
*Samples were restricted to those patients with paired baseline and disease progression and/or discontinuation samples that passed quality cont checks, and patients who provided informed consent. Samples from China were exclud

LBA51. Analysis of resistance mechanisms to osimertinib in patients with EGFR T790M advanced NSCLC from the AURA3 study

Acquired resistance mechanisms post-osimertinib (n=73)

Summary

- Acquired *EGFR* mutations: 21%
- *MET* amp*: 19%
- Cell cycle gene alterations: 12%
- *HER2* amp*: 5%
- *PIK3CA* amp* / mutation: 5%
- Oncogenic fusion: 4%
- BRAF V600E: 3%



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*Amplification events may be underrepresented in plasma analyses
amp, amplification

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RESULTS OF THE GEOMETRY MONO-1 PHASE II STUDY FOR EVALUATION OF THE MET INHIBITOR CAPMATINIB (INC280) IN PATIENTS WITH *METΔEX14* MUTATED ADVANCED NON-SMALL CELL LUNG CANCER

Juergen Wolf,[1] Takashi Seto,[2] Ji-Youn Han,[3] Noemi Reguart,[4] Edward B. Garon,[5] Harry J. M. Groen,[6] Daniel S. W. Tan,[7] Toyoaki Hida,[8] Maja de Jonge,[9] Sergey V. Orlov,[10] Egbert F. Smit,[11] Pierre-Jean Souquet,[12] Johan Vansteenkiste,[13] Monica Giovannini,[14] Sylvie Le Mouhaer,[15] Anna Robeva,[14] Maeve Waldron-Lynch,[16] Rebecca S. Heist[17]

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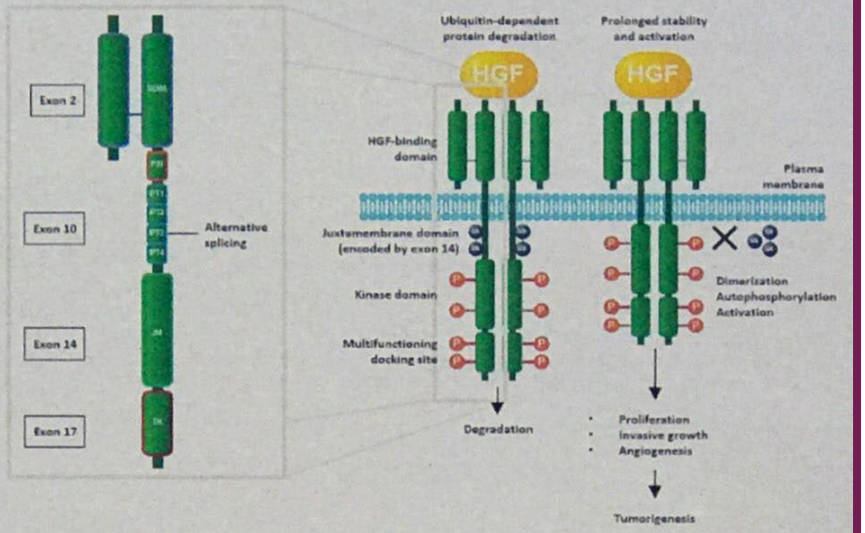
*MET*exon-14 SKIPPING MUTATIONS IN NSCLC

- Occurs in 3-4% of NSCLC[1-3]
  - Encodes the juxtamembrane region of the receptor responsible for MET degradation
  - Results in an overabundance of MET receptors
- Considered to be an oncogenic driver[4,5]
- Poor prognostic factor in advanced NSCLC[6]
  - Preliminary data shows that these patients show poor responses to standard therapies including immunotherapy, even when PD-L1 expression and mutation load are high[7,8]

Effect of Exon 14 Deletions on MET[2,3]



1. Reungwetwattana T, et al. *Lung Cancer*. 2017;103:27-37. 2. Gelsomino F, et al. *Cancers (Basel)*. 2014;6(4):2100-2115. 3. Ma PC. *Cancer Discov*. 2015;5:802-805. 4. Paik PK, et al. *Cancer Discov*. 2015;5:842-849. 5. Frampton GM, et al. *Cancer Discov*. 2015;5:850-859. 6.Awad MM, et al. ASCO 2017, Abstract 8511. 7. Sabari JK, et al. ASCO 2017, Abstract 8512. 8. Sabari JK, et al. *Ann Oncol*. 2018; Epub.

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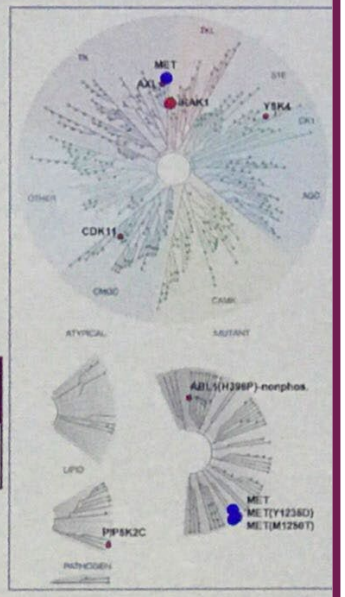
CAPMATINIB (INC280)

- Oral ATP competitive, reversible inhibitor of the MET receptor tyrosine kinase
  - High selectivity for MET
    - Capmatinib inhibited no other kinase than MET when tested across 442 kinases[1]
    - Other kinase screen hits show at least 1000-fold higher dissociation constant than MET
  - High potency against *METΔex14* compared to other MET inhibitors[2,3,4]
    - Capmatinib is the most potent inhibitor against *METΔex14*[5]

	Capmatinib	Savolitinib	Tepotinib	Cabozantinib	Merestinib	Glesatinib	Crizotinib
IC_{50} (nM)	0.6	2.1	3.0	7.8	8.1	21.1	22.5



- Manageable safety profile and promising efficacy both as single agent and in combination with EGFR TKI in MET aberrant NSCLC[6,7,8,9,10]
- Crosses the blood brain barrier - preliminary brain activity reported[8,11]

1. DiscoveRx KINOMEscan, kinase panel screened at 10 mM capmatinib, data on file .2. Reungwetwattana T, et al. *Lung Cancer*. 2017;103:27-37. 3. Lara MS, et al. *Clin Lung Cancer*. 2017;18(3):281-285. 4. Liu X, et al. *Clin Cancer Res*. 2011;17(22):7127-38. 5. Fujino T, et al. WCLC 2018, Poster P1.13-41. 6. Schuler M, et al. ASCO 2016, Abstract 9067. 7. Wu YL, et al. WCLC 2018, Poster P1.01-97. 8. Wolf J, et al. WCLC 2017, Poster P2.04-005. 9. Wu YL, et al. *J Clin Oncol*. 2018: Epub. 10. Schuler M, et al. ASCO 2016, Abstract #9067; 11. Shih K, et al. SNO 2016, Poster ACTR-45

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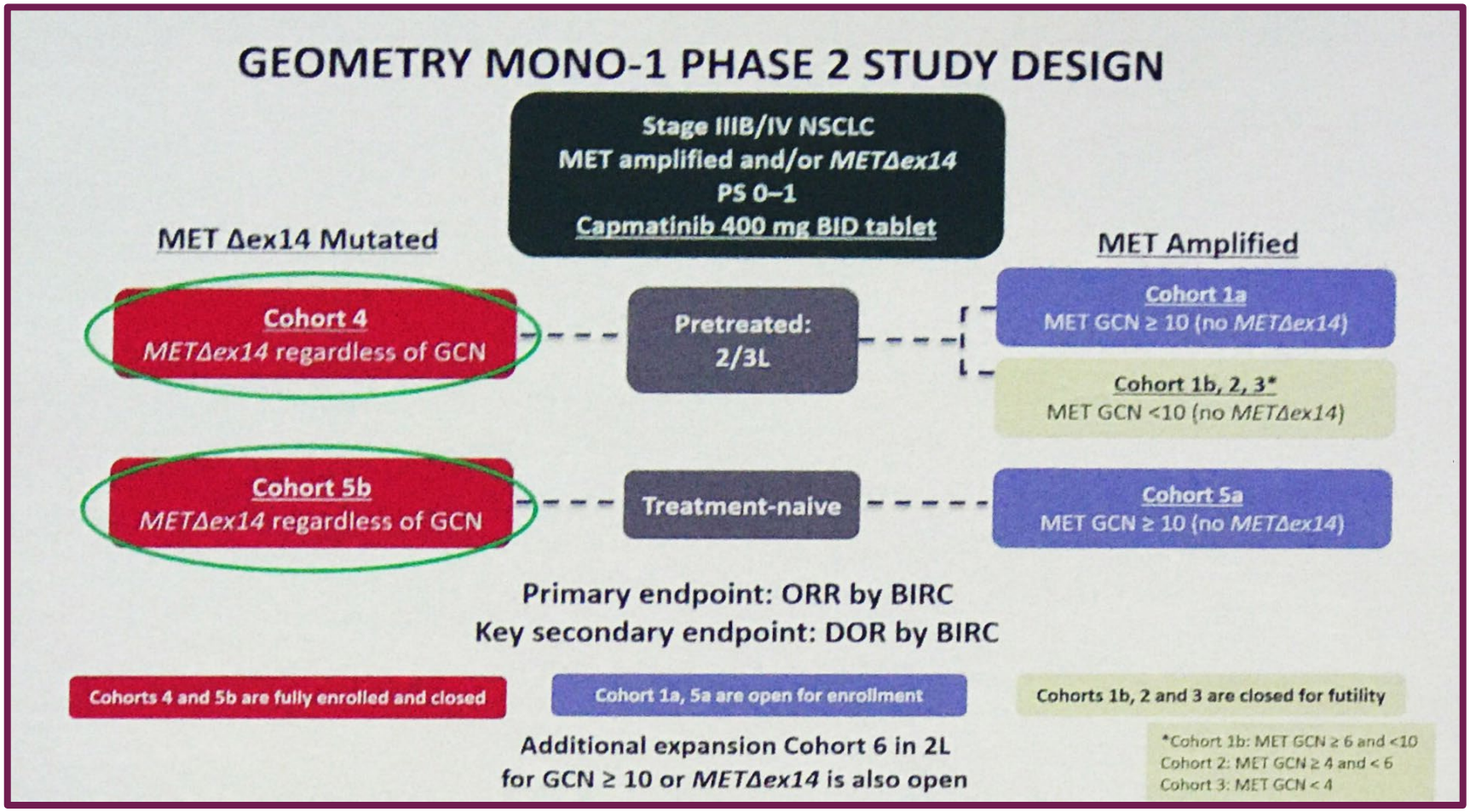

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LBA52. Results of the GEOMETRY MONO-1 phase II study for evaluation of the MET inhibitor Capmatinib (INC280) in patients with METΔEX14 mutated advanced non-small cell lung cancer

BASELINE CHARACTERISTICS (COHORTS 4 AND 5B)

Demographics		Cohort 4 (*METΔex14*; 2/3L) n = 69	Cohort 5b (*METΔex14*; 1L) n = 28
Age (years)	Median (range)	71 (49-90)	71 (57-86)
	< 65	14 (20.3)	3 (10.7)
	≥ 65-< 75	31 (44.9)	14 (50.0)
	≥ 75	24 (34.8)	11 (39.3)
Race, n (%)	Caucasian	48 (69.6)	23 (82.1)
	Asian	19 (27.5)	4 (14.3)
	Other	2 (2.9)	1 (3.6)
Sex, n (%)	Female	40 (58.0)	18 (64.3)
	Male	29 (42.0)	10 (35.7)
Smoking history, n (%)	Never smoked	40 (58.0)	18 (64.3)
	Ex-smoker	27 (39.1)	9 (32.1)
	Current smoker	2 (2.9)	1 (3.6)
ECOG status, n (%)	0	16 (23.2)	7 (25.0)
	1	52 (75.4)	21 (75.0)
	≥ 2	1 (1.4)	0

DISEASE CHARACTERISTICS AND PRIOR THERAPIES (COHORTS 4 AND 5B)

		Cohort 4 (*METΔex14*; 2/3L) n = 69	Cohort 5b (*METΔex14*; 1L) n = 28
Histology, n (%)	Adenocarcinoma	53 (76.8)	25 (89.3)
	Squamous / Others[a]	6 (8.7) / 10 (14.5)	2 (7.1) / 1 (3.6)
Key metastatic site of cancer, n (%)	Brain	11 (15.9)	3 (10.7)
	Liver	16 (23.2)	5 (17.9)
	Bone	41 (59.4)	15 (53.6)
Concurrent MET amplification, n (%)	<4 GCN	18 (26.1)	4 (14.3)
	≥4-6 GCN	15 (21.7)	10 (35.7)
	≥6-10	17 (24.6)	3 (10.7)
	≥10 GCN	11 (15.9)	4 (14.3)
	Missing or not available	8 (11.6)	7 (25.0)
Prior therapies in advanced stage		**n = 69**	
Number of prior antineoplastic regimens, n (%)	1	51 (73.9)	NA
	2	15 (21.7)	
	3	3 (4.4)	
Prior antineoplastic therapies, n (%)	1L platinum based chemo	61 (88.4)	NA
	2L platinum based chemo	7 (10.1)	
	1L immunotherapy	8 (11.6)	
	2/3L immunotherapy	10 (14.5)	
	Any line single agent chemo	8 (11.6)	

[a] Other: all other histologies (adenosquamous, large cell, carcinosarcoma, and undifferentiated etc)

Clinicopathologic features:

- Older patients
- Less proportion of never smokers
- Mutually exclusive with other drivers
- 15-20% with concurrent MET amplification

LBA52. Results of the GEOMETRY MONO-1 phase II study for evaluation of the MET inhibitor Capmatinib (INC280) in patients with METΔEX14 mutated advanced non-small cell lung cancer

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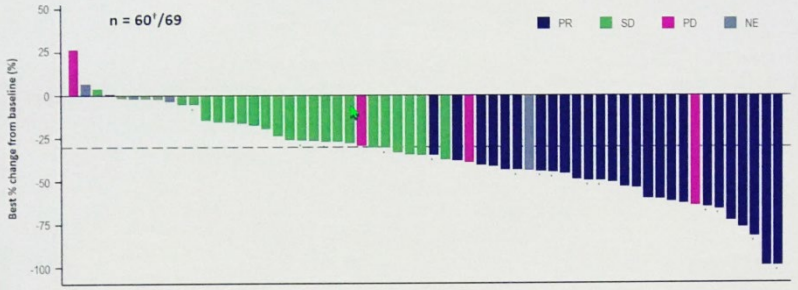
TUMOR RESPONSE BY BIRC (PRETREATED COHORT 4)

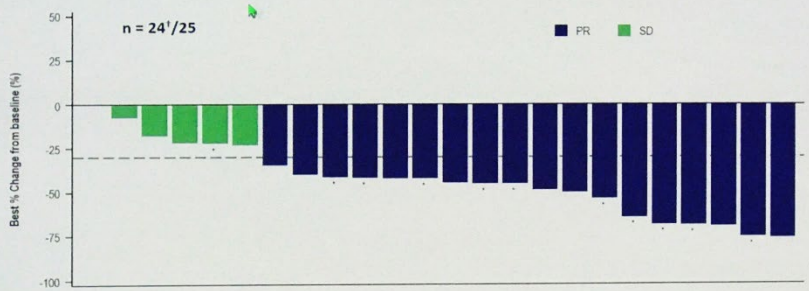
Confirmed ORR by BIRC is 39.1%; most patients show deep responses



*Patients still on treatment
†number of patients with measurable disease at baseline and ≥1 post-baseline assessment

TUMOR RESPONSE BY BIRC (TREATMENT NAIVE COHORT 5B)

Confirmed ORR by BIRC is 72%; deep responses were observed in almost all patients



*Patients still on treatment
†number of patients with measurable disease at baseline and ≥1 post-baseline assessment

MOST COMMON ADVERSE EVENTS (≥ 10% ALL GRADES, ALL PTS)

Suspected to be Drug-Related

AE, n (%)	Cohort 4 (*METΔex14*; 2/3L) n = 69		Cohort 5b (*METΔex14*; 1L) n = 28		All Patients N = 302	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Any	60 (87.0)	33 (47.8)	27 (96.4)	14 (50.0)	253 (83.8)	100 (33.1)
Peripheral edema	31 (44.9)	10 (14.5)	18 (64.3)	1 (3.6)	122 (40.4)	19 (6.3)
Nausea	24 (34.8)	0	11 (39.3)	0	99 (32.8)	5 (1.7)
Vomiting	13 (18.8)	0	4 (14.3)	0	58 (19.2)	6 (2.0)
Blood creatinine increased	15 (21.7)	0	7 (25.0)	0	58 (19.2)	0
Fatigue	9 (13.0)	4 (5.8)	2 (7.1)	1 (3.6)	40 (13.2)	10 (3.3)
Decreased appetite	10 (14.5)	1 (1.4)	5 (17.9)	0	40 (13.2)	3 (1.0)
Diarrhea	8 (11.6)	0	3 (10.7)	0	35 (11.6)	0

Overall, 31/302 (10.3%) patients discontinued for AEs suspected to be related to the study treatment

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CONCLUSIONS

- *METΔex14* oncogenic mutations represent a novel driver mutation in advanced NSCLC and are recognized as a poor prognostic factor
- Capmatinib is a selective MET inhibitor and highly potent against *METΔex14*
- Capmatinib has demonstrated a clinically meaningful response rate and manageable toxicity profile in patients with *METΔex14* advanced NSCLC regardless of the line of therapy
  - Efficacy in treatment naive patients with ORR by BIRC of 72%
  - Durability data are not mature at the time of this analysis
- The differential benefit observed between patients treated in 1L and 2L/3L highlights the need of early diagnosis and prompt targeted treatment of this challenging patient population with *METΔex14* advanced NSCLC
- Capmatinib showed preliminary activity in brain metastases
- Overall, these encouraging data characterize Capmatinib as a very promising MET inhibitor for patients with *METΔex14* advanced NSCLC

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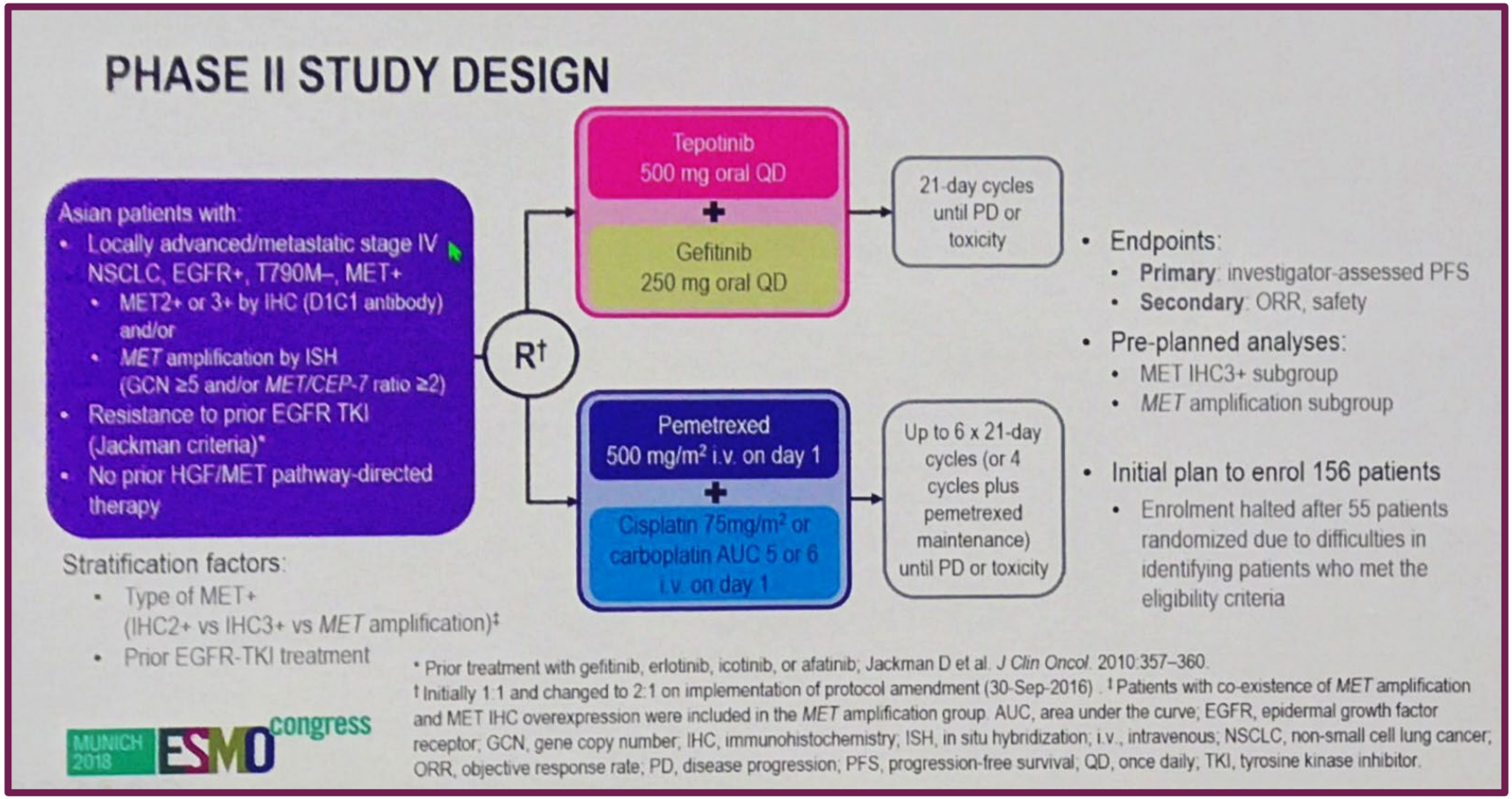
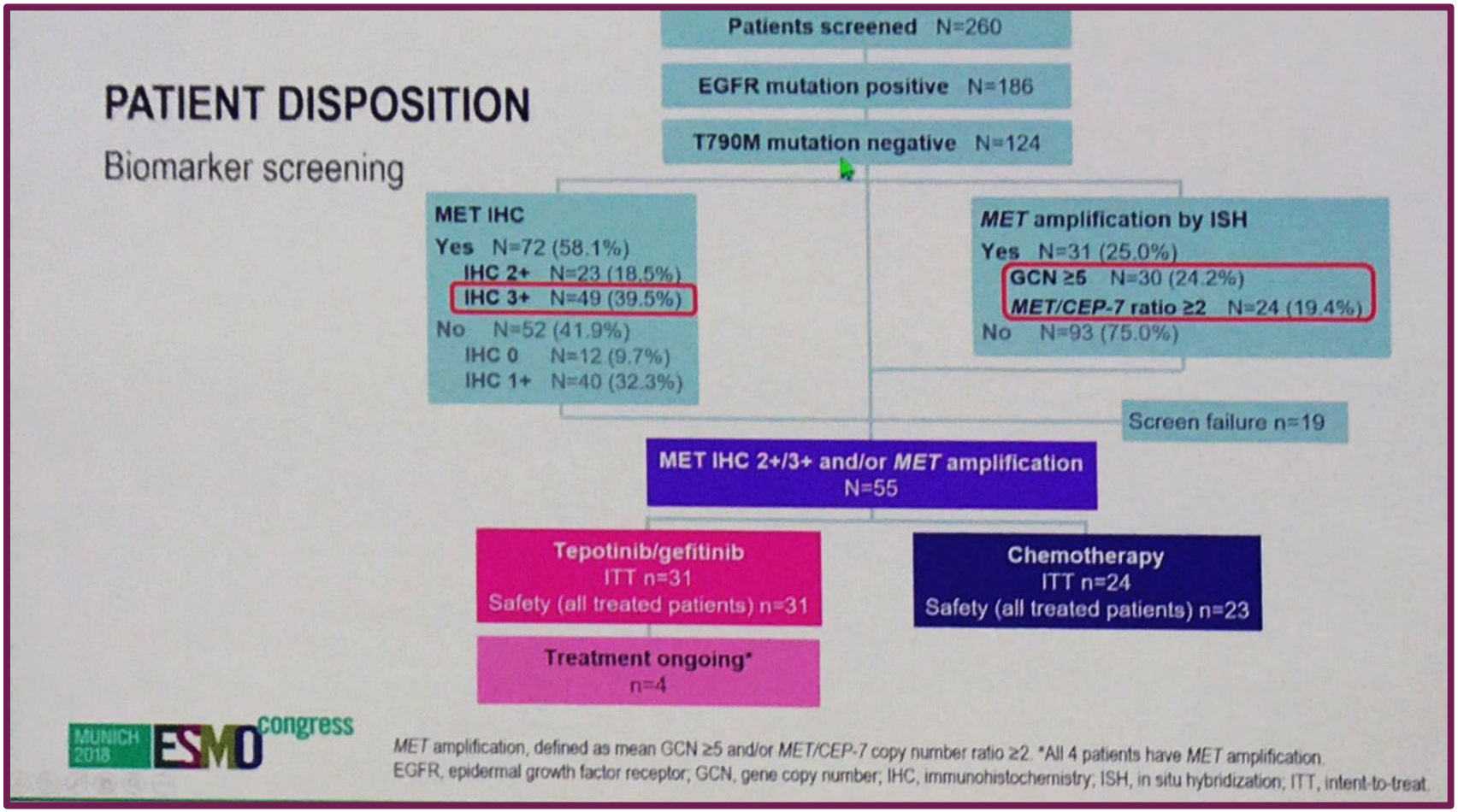
13770. Phase 2 study of tepotinib + gefitinib (TEP+GEF) in MET-positive (MET+)/epidermal growth factor receptor (EGFR) - mutant (MT) non-small cell lung cancer (NSCLC)



13770. Phase 2 study of tepotinib + gefitinib (TEP+GEF) in MET-positive (MET+)/epidermal growth factor receptor (EGFR) - mutant (MT) non-small cell lung cancer (NSCLC)



13770. Phase 2 study of tepotinib + gefitinib (TEP+GEF) in MET-positive (MET+)/epidermal growth factor receptor (EGFR) - mutant (MT) non-small cell lung cancer (NSCLC)

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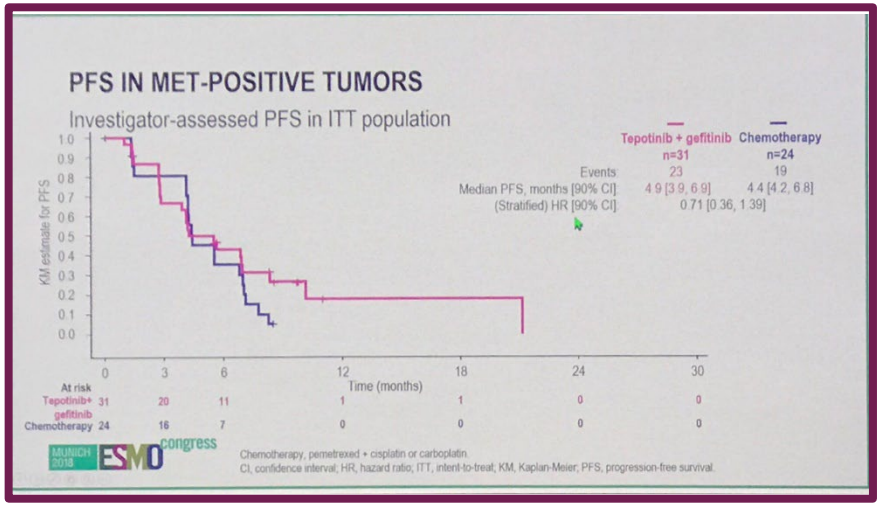

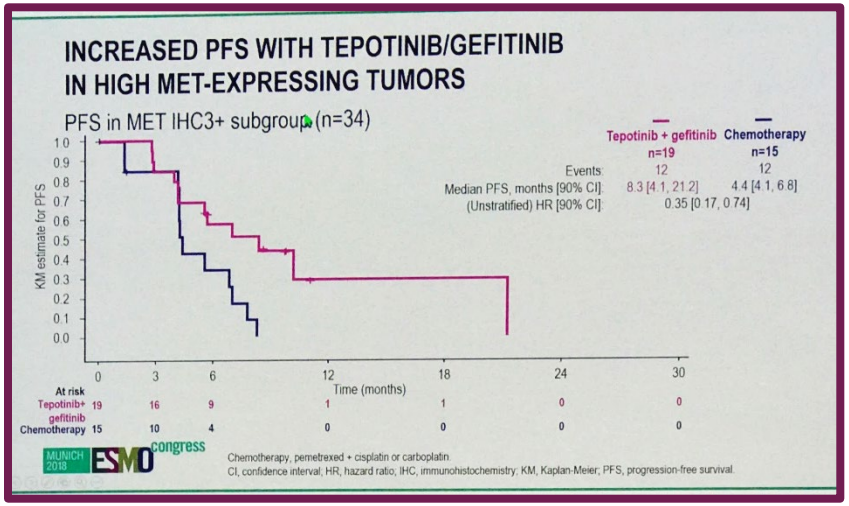

Median PFS:

- In MET-positive tumors: 4.9 m (TEP+GEF) vs 4.4 m (CT); HR 0.71 (n.s.)
- In MET IHC 3+: 8.3 m (TEP+GEF) vs 4.4 m (CT); HR 0.35 (significant)
- In MET amplified: 21.1 m (TEP+GEF) vs 4.2 m (CT); HR 0.17 (significant)

HIGH ORR WITH TEPOTINIB/GEFITINIB IN PATIENTS WITH HIGH MET-EXPRESSING TUMORS OR WITH *MET* AMPLIFICATION

Investigator-assessed responses (RECIST 1.1)

Analysis Set	Tepotinib + gefitinib		Pemetrexed + cisplatin/carboplatin		Odds Ratio (90% CI)
	Responders* n/n	ORR, % (90% CI)	Responders* n/n	ORR, % (90% CI)	
Overall (N=55)	14/31	**45.2** (29.7, 61.3)	8/24	**33.3** (17.8, 52.1)	1.99† (0.56, 6.87)
MET IHC3+ (n=34)	13/19	**68.4** (47.0, 85.3)	5/15	**33.3** (14.2, 57.7)	4.33 (1.03, 18.33)
MET amplification (n=19)	8/12	**66.7** (39.1, 87.7)	3/7	**42.9** (12.9, 77.5)	2.67 (0.37, 19.56)

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CONCLUSIONS

- This is the first randomized study to compare tepotinib plus gefitinib with chemotherapy in relapsed EGFR-mutant NSCLC with MET overexpression (IHC3+) and/or *MET* amplification
  - Enrolment was halted early due to low recruitment
- Patients whose tumors harbor *MET* amplifications experienced improved PFS with the tepotinib/gefitinib combination compared with chemotherapy (HR 0.17 [90% CI 0.05, 0.57])
  - *MET* can be considered a suitable biomarker for treatment with tepotinib
- Higher ORR with the tepotinib/gefitinib combination (45.2%) than chemotherapy (33.3%)
  - ORR was highest in patients with MET IHC3+ and *MET*-amplified tumors in the tepotinib/gefitinib combination arm (68.4% and 66.7%, respectively)
- Treatment with tepotinib and gefitinib was generally well-tolerated and most AEs were mild to moderate in severity

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MET-amplified, defined as mean gene copy number ≥5 and/or *MET/CEP-7* copy number ratio ≥2.
AE, adverse event; CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival.

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