#ESMOUPDATES

Iniciativa científica de:

GECP lung cancer research

LUNG CANCER UPDATES

ESMO HIGHLIGHTS

27 SEPTIEMBRE - 1 OCTUBRE 2019

Con la colaboración de:

Bristol-Myers Squibb

illumina

Lilly

LUNG CANCER UPDATES

ESMO HIGHLIGHTS

27 SEPTIEMBRE - 1 OCTUBRE 2019

BARCELONA

Iniciativa científica de:

GECP lung cancer research

Terapias dirigidas (II)

Dra. Noemí Reguart

Con la colaboración de:

Bristol-Myers Squibb

illumina

Lilly

Targeted Therapies (Sunday 29, Monday 30)

Poster Discussion – NSCLC, metastatic (ID 256)

Proffered Paper 2 – NSCLC, metastatic (ID 257)

- **EGFR+ Disease**
  - **LBA85-** Longitudinal **circulating tumour DNA (ctDNA)** monitoring for early detection of disease progression and resistance in advanced NSCLC in **FLAURA** (ID 2685). *Presenter Jhanelle E. Gray*
  - **1480O- CTONG 1509:** Phase 3 study of bevacizumab with or without erlotinib in untreated Chinese patients with advanced EGFR-mutated NSCLC (ID 3200). *Presenter Qing Zhou*

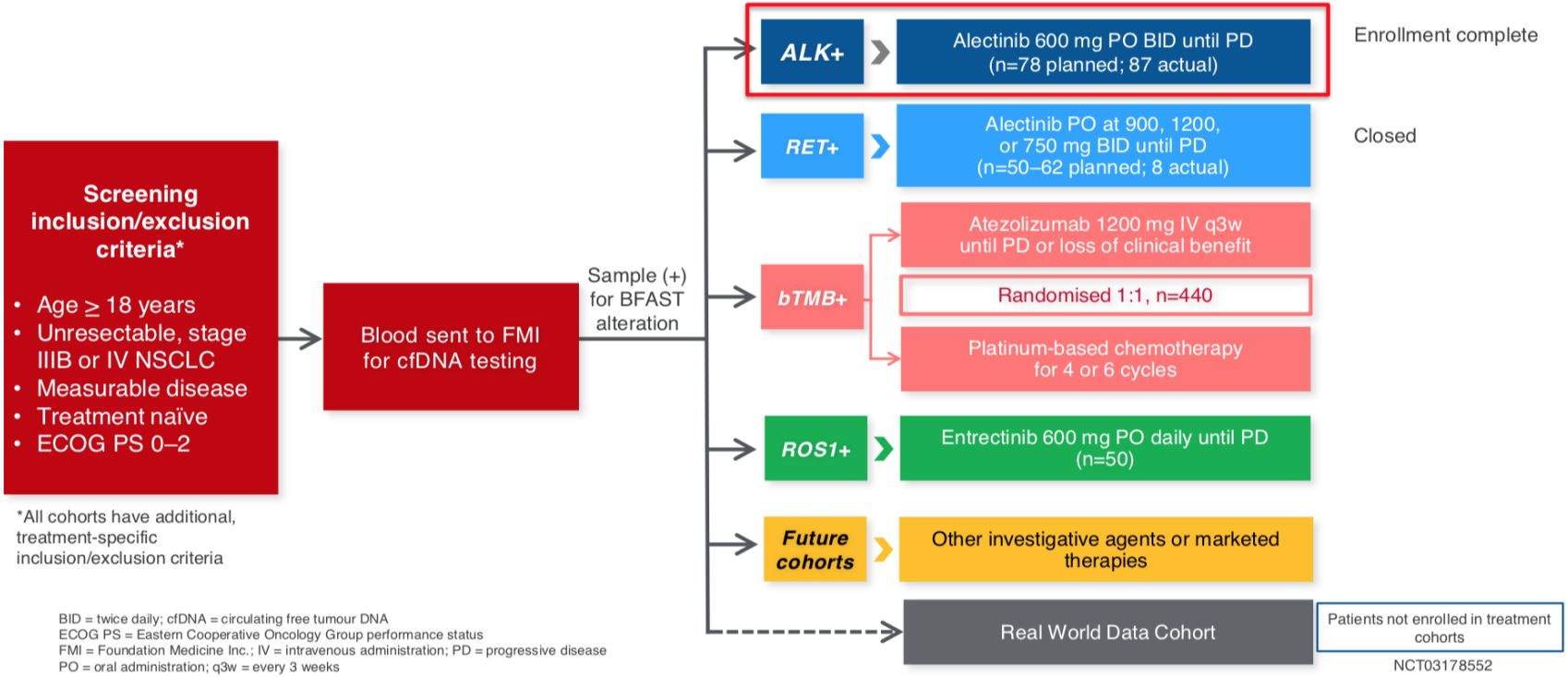
- **ROS1/NTRK+ Disease**
  - **1485PD-** Safety and efficacy of **WX-0593** in ALK-positive or ROS1-positive non-small cell lung cancer (ID 6131). *Presenter Yuan-Kai Shi*
  - **1488PD- Entrectinib** in Locally Advanced/Metastatic ROS1 and NTRK Fusion-Positive NSCLC: Updated Integrated Analysis of **STARTRK-2, STARTRK-1 and ALKA-372-001** (ID 4178). *Presenter Filippo Guglielmo M. De Braud*
  - **1489PD-** Secondary **ROS1 mutations and lorlatinib sensitivity** in crizotinib-refractory ROS1 positive NSCLC: results of the prospective **PFROST trial** (ID 4899). *Presenter Lorenza Landi*

Targeted Therapies (Sunday 29, Monday 30)

- **ALK+ Disease**
  - **1484PD-** Final PFS, updated OS and safety data from the randomised, phase III **ALEX study** of alectinib (ALC) versus crizotinib (CRZ) in untreated advanced ALK+ NSCLC (ID 3850). *Presenter Tony S.K. Mok*
  - **1486PD-** Exposure-response analyses of ALK-inhibitors **crizotinib and alectinib** in NSCLC patients (ID 1906). *Presenter Steffie L. Groenland*
  - **1487PD-** Intracranial and extracranial efficacy of **lorlatinib** in the **post second-generation ALK** tyrosine kinase inhibitor (TKI) setting (ID 2577). *Presenter Steffie L. Groenland*
  - **LBA81_PR-** Phase II/III Blood First Assay Screening Trial **(BFAST**) in patients (pts) with treatment-naïve NSCLC: initial results from the **ALK+ cohort** (ID 5026). Presenter Shingo Miyamoto. *Presenter Shirish M. Gadgeel*

Phase II/III Blood First Assay Screening Trial (BFAST) in patients (pts) with treatment-naïve NSCLC: initial results from the ALK+ cohort (ID 5026). Presenter Shingo Miyamoto. *Presenter Shirish M. Gadgeel*

Study design



Phase II/III Blood First Assay Screening Trial (BFAST) in patients (pts) with treatment-naïve NSCLC: initial results from the ALK+ cohort (ID 5026). Presenter Shingo Miyamoto. *Presenter Shirish M. Gadgeel*

Goal

Demonstrate consistency of benefit with alectinib in a population selected by blood-based NGS as opposed to tissue-based assay, using ALEX alectinib data as reference

- Unresectable, stage IIIB or IV NSCLC
- *ALK*+ by centralised blood screening only
- Treatment naïve
- ECOG PS 0–2

→ Alectinib 600mg BID → Until PD, toxicity, withdrawal or death

Primary endpoint
Confirmed ORR by investigator

Exploratory endpoint
Confirmed ORR by investigator for patients with baseline CNS metastases

Secondary endpoints

By investigator	By independent review facility
DoR	ORR
PFS	DoR
	PFS

CNS = central nervous system; DoR = duration of response
ORR = overall response rate; PD = disease progression; PFS = progression-free survival
ECOG PS = Eastern Cooperative Oncology Group performance status; NGS = next generation sequencing

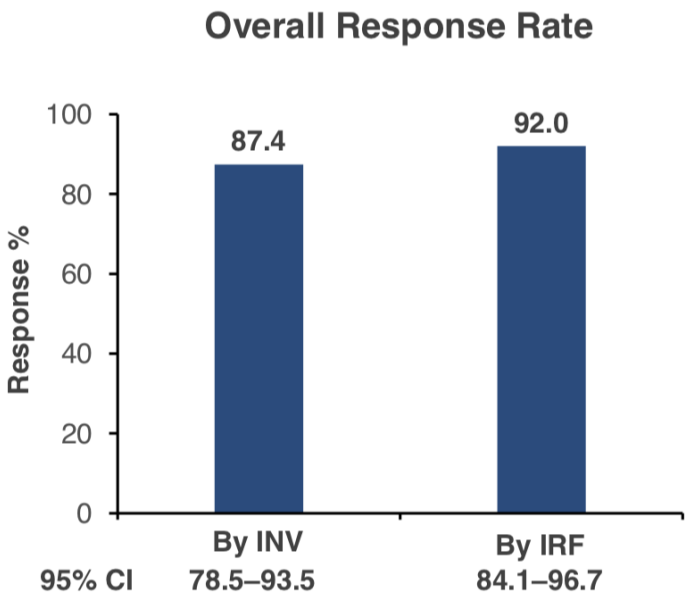
NCT03178552

Phase II/III Blood First Assay Screening Trial (BFAST) in patients (pts) with treatment-naïve NSCLC: initial results from the ALK+ cohort (ID 5026). Presenter Shingo Miyamoto. *Presenter Shirish M. Gadgeel*

Demographics and baseline characteristics

Characteristic	*ALK*+ Cohort (N=87)	ALEX alectinib arm[1] (N=152)
Median age, years (range)	**55.0 (25–82)**	**58.0 (25–88)**
Gender		
Male	35 (40)	68 (45)
Female	52 (60)	84 (55)
Race, n (%)		
Asian	29 (33)	69 (45)
Non-Asian	58 (67)	83 (55)
ECOG PS, n (%)		
0–1	82 (94)	142 (93)
2	5 (6)	10 (7)
Smoking status, n (%)		
Active smoker	5 (6)	12 (8)
Past smoker	32 (37)	48 (32)
Never smoked	50 (58)	92 (61)
Disease state, n (%)		
IIIb	5 (6)	4 (3)
IV	82 (94)	148 (97)
Histology, n (%)		
Adenocarcinoma	81 (93)	136 (90)
Other	4 (5)	16 (10)
Missing	2 (2)	0 (0)
CNS metastases by investigator, n (%)		
Yes	35 (40)	60 (40)
No	52 (60)	92 (60)

Results: Confirmed response (INV vs IRF)



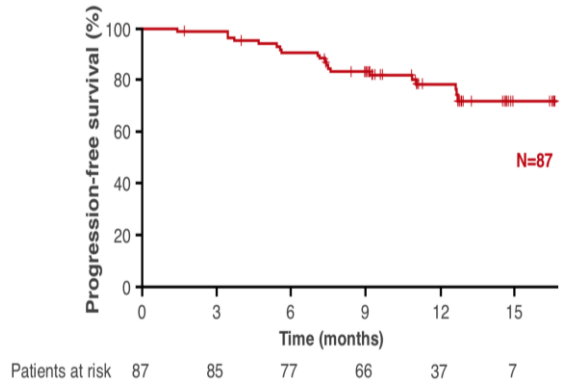
Median duration of follow-up: 12.58 months

	INV (N=87)	IRF (N=87)
Complete Response, n (%) 95% CI	**0** (0.00–4.15)	**11 (12.6)** (6.48–21.50)
Partial Response, n (%) 95% CI	**76 (87.4)** (78.50–93.52)	**69 (79.3)** (69.29–87.25)
Progressive Disease, n (%) 95% CI	**1 (1.1)** (0.03–6.24)	**1 (1.1)** (0.03–6.24)

ALEX confirmed ORR = 71.7% (95% 63.8–78.7)[1]

Phase II/III Blood First Assay Screening Trial (BFAST) in patients (pts) with treatment-naïve NSCLC: initial results from the ALK+ cohort (ID 5026). Presenter Shingo Miyamoto. *Presenter Shirish M. Gadgeel*

Results: PFS by investigator



Median duration of follow-up: 12.6 months

Patients with event, n (%)	20 (23)
Median PFS, months (95% CI)	NE (NE)
12-month PFS, % (95% CI)	78.38 (69.07–87.69)
ALEX[1]	**N=152**
12-month PFS, % (95% CI)	68.4 (61.0–75.9)

Conclusions

- BFAST is the **first prospective trial to use** blood-based NGS testing **as the sole method of identifying** actionable genetic alterations and **assigning** NSCLC patients **to targeted or immunotherapy**
- The **primary endpoint** of the *ALK*+ cohort **was achieved** with an **investigator-confirmed ORR of 87.4% and an independent review facility confirmed ORR of 92.0%**
- **Key secondary endpoints: 6-month DoR 90.4%, 12-month PFS 78.38%**
- The **safety profile of alectinib was consistent** with that established in previous phase III trials and post-marketing experience
- These results demonstrate the **clinical utility of blood-based NGS** as a method to **inform clinical decision-making in *ALK*+ NSCLC**

1484PD- Final PFS, updated OS and safety data from the randomised, phase III ALEX study of alectinib (ALC) versus crizotinib (CRZ) in untreated advanced ALK+ NSCLC (ID 3850). *Presenter Tony S.K. Mok*

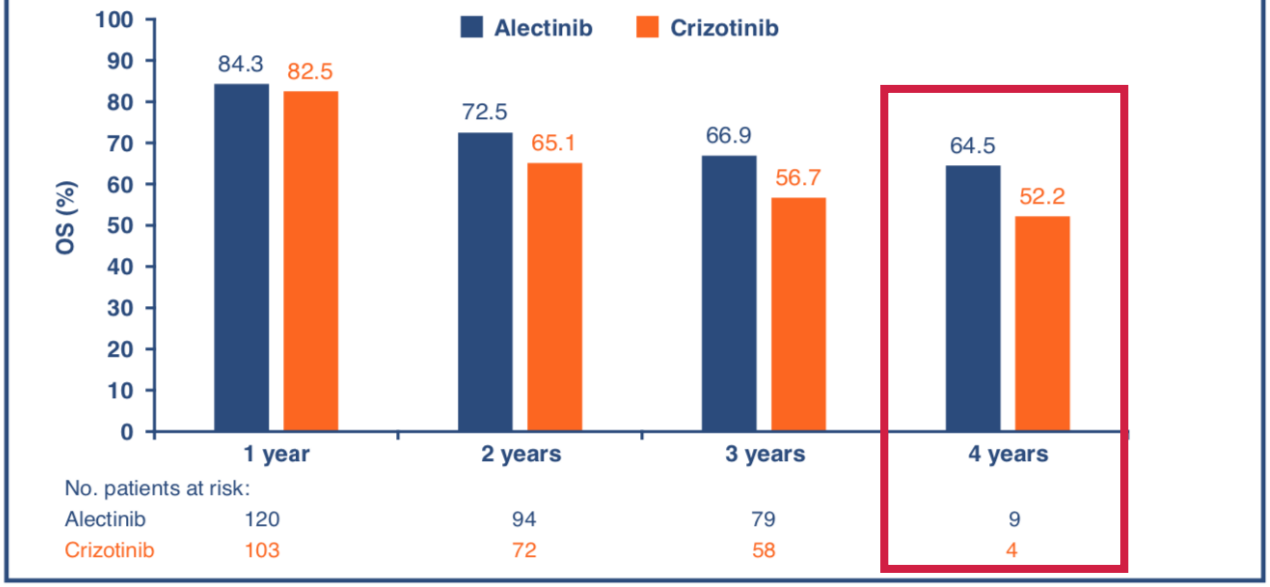
- Last update: PFS alectinib vs crizotinib HR 0.43, (95% CI: 0.32–0.58): Median 34.8 versus 10.9 months. OS immature: stratified HR 0.76, 95% CI: 0.50–1.15.2

- Present updated data median duration of follow-up 4 years (37.8 months with alectinib and 23.0 months with crizotinib)

Figure 1. Mature investigator-assessed PFS (primary endpoint).

1484PD- Final PFS, updated OS and safety data from the randomised, phase III ALEX study of alectinib (ALC) versus crizotinib (CRZ) in untreated advanced ALK+ NSCLC (ID 3850). *Presenter Tony S.K. Mok*

Figure 3. OS event-free rate in the ITT population.



OS data remain immature, with a 4-year OS rate of 64.5% (95% CI: 55.6–73.4) with alectinib versus 52.2% (95% CI: 42.6–61.8) with crizotinib

CTONG 1509: Phase 3 study of bevacizumab with or without erlotinib in untreated Chinese patients with advanced EGFR-mutated NSCLC (ID 3200). *Presenter Qing Zhou*

STUDY DESIGN

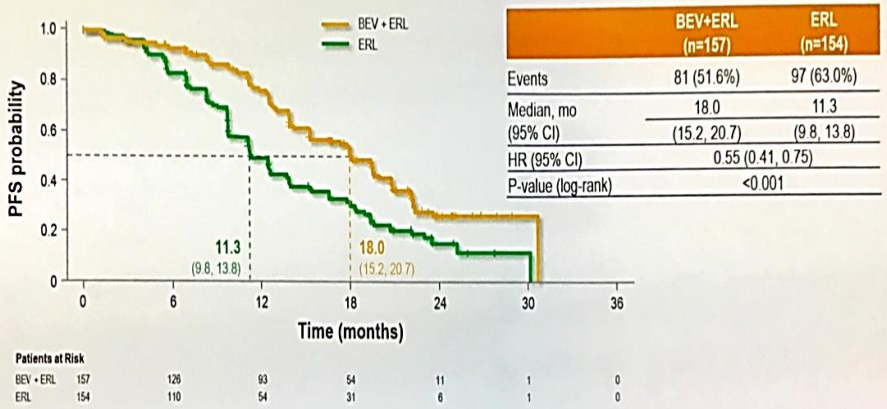
- Primary endpoint: PFS (Independent Review Committee,IRC)
- Secondary endpoints:
  - ✓ PFS(Investigator, INV), ORR, DCR, DOR, OS, TTF, safety
- Exploratory endpoints:
  - ✓ To identify biomarkers in tissue and plasma that are associated with acquired resistance to bevacizumab combined with erlotinib or erlotinib alone in NSCLC
- Stratified by
  - ✓ Sex (female vs. male)
  - ✓ Disease stage(stage IIIb vs. stage IV vs. recurrence)
  - ✓ EGFR gene mutation (exon 19 del vs. exon 21 L858R)

BARCELONA 2019 ESMO congress

PFS: Progression-free Survival; ORR: Objective Response Rate; DCR: Disease Control Rate; DOR: Duration of Response; OS: Overall Survival; TTF: Time to Treatment Failure

CTONG 1509: Phase 3 study of bevacizumab with or without erlotinib in untreated Chinese patients with advanced EGFR-mutated NSCLC (ID 3200). *Presenter Qing Zhou*

PRIMARY ENDPOINT: PFS BY IRC (ITT POPULATION)



	BEV+ERL (n=157)	ERL (n=154)
Events	81 (51.6%)	97 (63.0%)
Median, mo (95% CI)	18.0 (15.2, 20.7)	11.3 (9.8, 13.8)
HR (95% CI)	0.55 (0.41, 0.75)	
P-value (log-rank)	<0.001	

BARCELONA 2019 ESMO congress

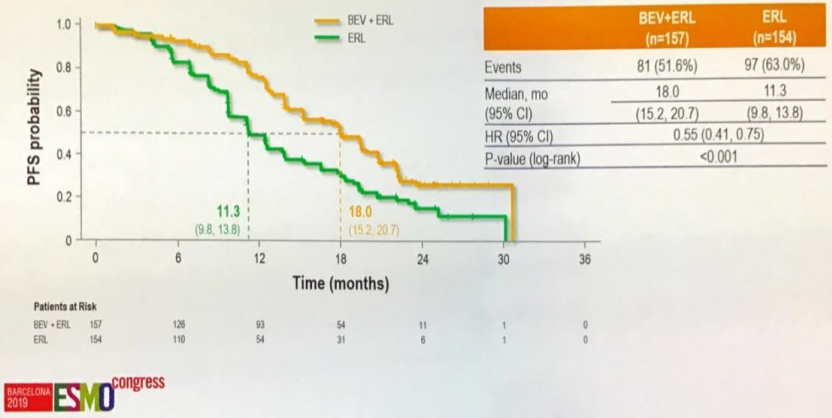
SUBGROUP ANALYSIS OF PFS BY INV (ITT POPULATION)

Subgroup	Total number of patients/events (n/N)	BEV + ERL (n/N)	ERL (n/N)	Hazard Ratio and 95% CI	HR with its 95%CI
All	311/221	157/100	154/121		0.57 (0.44, 0.75)
Gender: Male	118/81	60/37	58/44		0.54 (0.35, 0.85)
Gender: Female	193/140	97/63	96/77		0.59 (0.42, 0.82)
Stage: IIIb	10/6	4/4	6/2		2.09 (0.36, 12.1)
Stage: IV	275/199	141/89	134/110		0.52 (0.39, 0.69)
Stage: recurrence	26/16	12/7	14/9		0.77 (0.28, 2.12)
EGFR mutation type: Exon 19 Del	161/115	82/56	79/59		0.63 (0.44, 0.92)
EGFR mutation type: Exon 21 L858R	150/106	75/44	75/62		0.50 (0.34, 0.74)
Age: ≥75yr	6/2	3/0	3/2		NA
Age: <75yr	305/219	154/100	151/119		0.59 (0.45, 0.77)
Pathological type: adenocarcinoma	311/221	157/100	154/121		0.57 (0.44, 0.75)
Baseline ECOG score: 0	42/31	25/16	17/15		0.41 (0.20, 0.85)
Baseline ECOG score: 1	269/190	132/84	137/106		0.60 (0.45, 0.80)
Baseline brain metastasis: Yes	91/75	44/32	47/43		0.42 (0.26, 0.67)
Baseline brain metastasis: No	220/146	113/68	107/78		0.63 (0.45, 0.87)

BARCELONA 2019 ESMO congress

CTONG 1509: Phase 3 study of bevacizumab with or without erlotinib in untreated Chinese patients with advanced EGFR-mutated NSCLC (ID 3200). *Presenter Qing Zhou*

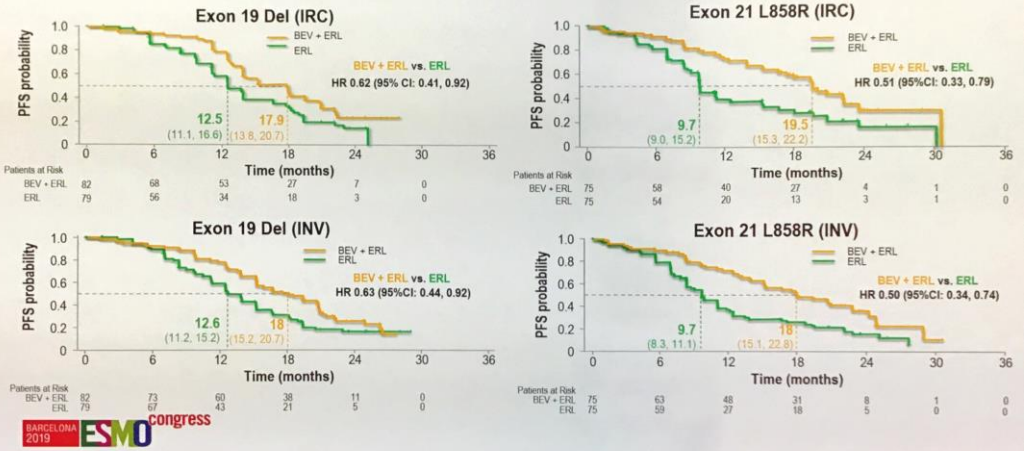
PRIMARY ENDPOINT: PFS BY IRC (ITT POPULATION)



	BEV+ERL (n=157)	ERL (n=154)
Events	81 (51.6%)	97 (63.0%)
Median, mo (95% CI)	18.0 (15.2, 20.7)	11.3 (9.8, 13.8)
HR (95% CI)	0.55 (0.41, 0.75)	
P-value (log-rank)	<0.001	

BARCELONA 2019 ESMO congress

PFS BY EGFR MUTATUION TYPE (ITT POPULATION)

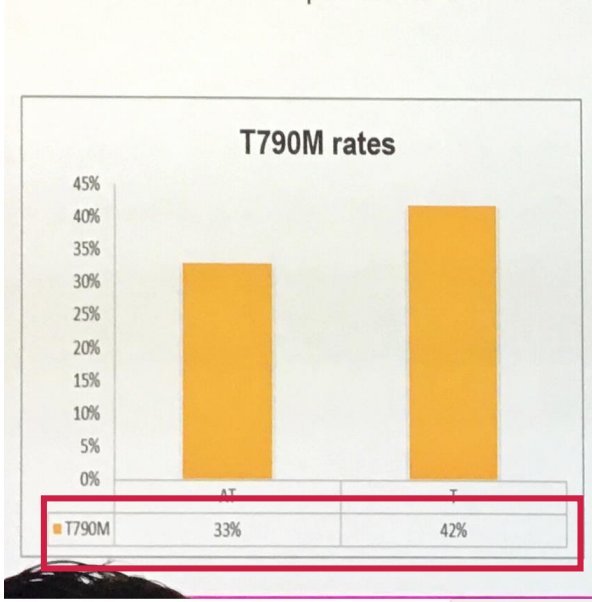


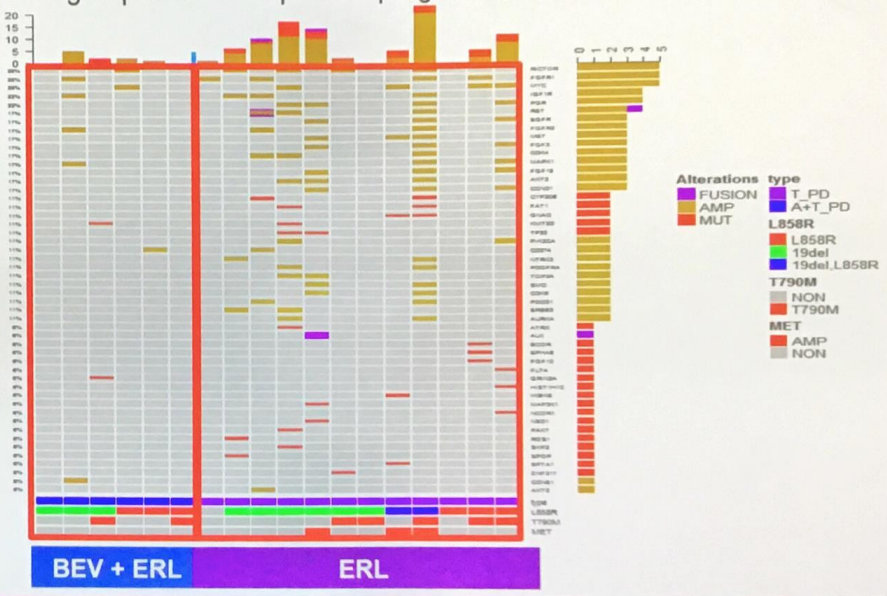
BARCELONA 2019 ESMO congress

CTONG 1509: Phase 3 study of bevacizumab with or without erlotinib in untreated Chinese patients with advanced EGFR-mutated NSCLC (ID 3200). *Presenter Qing Zhou*

RESISTANCE BIOMARKER ANALYSIS

- 22 baseline-PD paired frozen tissue samples in ERL group and 10 paired tissue samples in BEV + ERL group underwent Next-generation sequencing (NGS) of a 448-gene panel and transcriptome sequencing (RNA-Seq) was used for resistance biomarker analysis. Relatively less T790M was found in BEV + ERL group and more mutations and amplifications were found in ERL group at the time point of progression disease.





CTONG 1509: Phase 3 study of bevacizumab with or without erlotinib in untreated Chinese patients with advanced EGFR-mutated NSCLC (ID 3200). *Presenter Qing Zhou*