Enfermedad Metastásica

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HRG

Hospital General
Requena

Organizado por:
GECP
lung cancer research

Overview of targeted therapies in 2020: the NEJM prism

EGFR


The NEW ENGLAND JOURNAL of MEDICINE

Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

KRAS


The NEW ENGLAND JOURNAL of MEDICINE

SEPTEMBER 24, 2020

$KRAS^{G12C}$ Inhibition with Sotorasib in Advanced Solid Tumors

MET


ORIGINAL ARTICLE

Capmatinib in *MET* Exon 14–Mutated or *MET*-Amplified Non–Small-Cell Lung Cancer

J. Wolf, T. Seto, J.-Y. Han, N. Reguart, E.B. Garon, H.J.M. Groen, D.S.W. Tan, T. Hida, M. de Jonge, S.V. Orlov, E.F. Smit, P.-J. Souquet, J. Vansteenkiste, M. Hochmair, E. Felip, M. Nishio, M. Thomas, K. Ohashi, R. Toyozawa, T.R. Overbeck, F. de Marinis, T.-M. Kim, E. Laack, A. Robeva, S. Le Mouhaer, M. Waldron-Lynch, B. Sankaran, O.A. Balbin, X. Cui, M. Giovannini, M. Akimov, and R.S. Heist, for the GEOMETRY mono-1 Investigators*

MET


ORIGINAL ARTICLE

Tepotinib in Non–Small-Cell Lung Cancer with *MET* Exon 14 Skipping Mutations

P.K. Paik, E. Felip, R. Veillon, H. Sakai, A.B. Cortot, M.C. Garassino, J. Mazieres, S. Viteri, H. Senellart, J. Van Meerbeeck, J. Raskin, N. Reinmuth, P. Conte, D. Kowalski, B.C. Cho, J.D. Patel, L. Horn, F. Griessinger, J.-Y. Han, Y.-C. Kim, G.-C. Chang, C.-L. Tsai, J.C.-H. Yang, Y.-M. Chen, E.F. Smit, A.J. van der Wekken, T. Kato, D. Juraeva, C. Stroh, R. Bruns, J. Straub, A. Johne, J. Scheele, J.V. Heymach, and X. Le

NTRK


ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman

EGFR


ORIGINAL ARTICLE

Overall Survival with Osimertinib in Untreated, *EGFR*-Mutated Advanced NSCLC

S.S. Ramalingam, J. Vansteenkiste, D. Planchard, B.C. Cho, J.E. Gray, Y. Ohe, C. Zhou, T. Reungwetwattana, Y. Cheng, B. Chewaskulyong, R. Shah, M. Cobo, K.H. Lee, P. Cheema, M. Tiseo, T. John, M.-C. Lin, F. Imamura, T. Kurata, A. Todd, R. Hodge, M. Saggese, Y. Rukazenkov, and J.-C. Soria, for the FLAURA Investigators*

ALK


ORIGINAL ARTICLE

First-Line Lorlatinib or Crizotinib in Advanced *ALK*-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Todd M. Bauer, M.D., Filippo de Marinis, M.D., Ph.D., Enriqueta Felip, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Geoffrey Liu, M.D., Julien Mazieres, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Tony Mok, M.D., Anna Polli, B.Sc., Holger Thurm, M.D., Anna M. Calella, Ph.D., Gerson Peltz, M.D., M.P.H., and Benjamin J. Solomon, M.B., B.S., Ph.D., for the CROWN Trial Investigators*

Inmunoterapia

Actualizaciones

- IT: KN024: datos a los 5 años
- QT-IT: KN189: análisis final

Mismas estrategias, diferentes fármacos

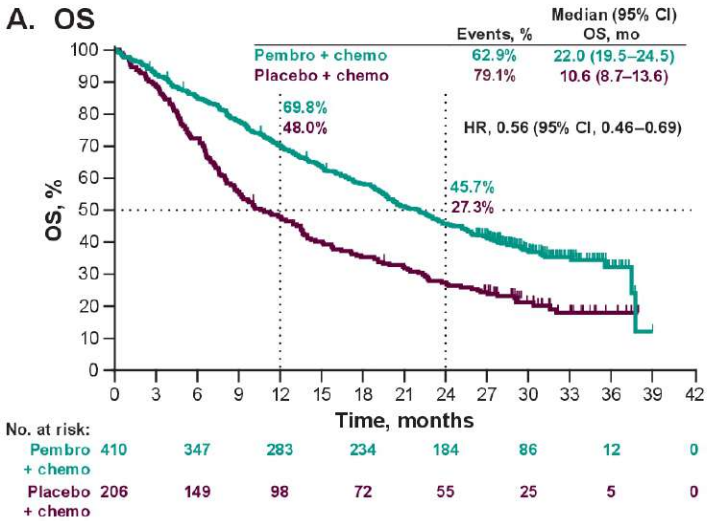
- Empower Lung 1: cemiplimab
- ORIENT 12.
- ONO 453852/TASUKI
- ORIENT 11.

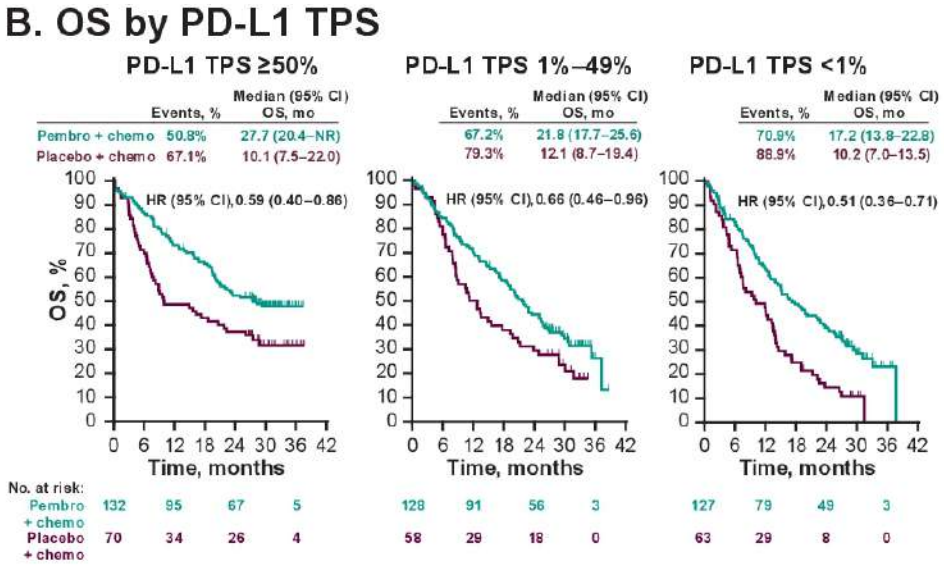
Otro tipo de nuevas estrategias

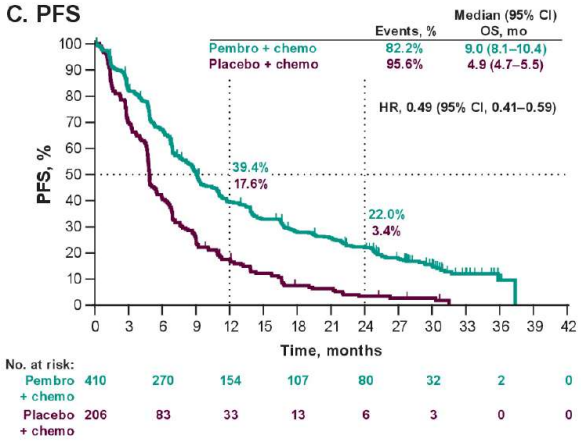
- CM227.
- CM9LA
- CCTB734: durva-treme-QT
- Cytiscape
- WJOG10718L atezo-bev.

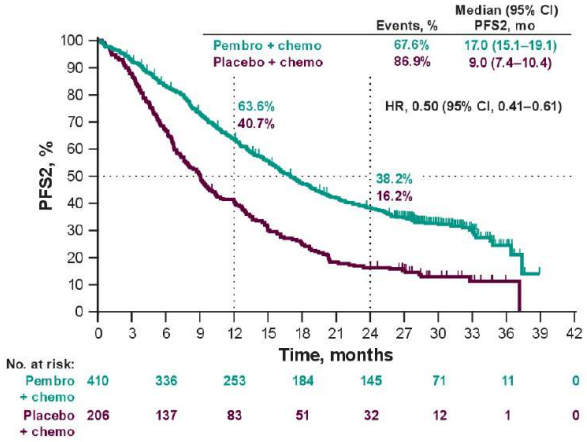
KN189

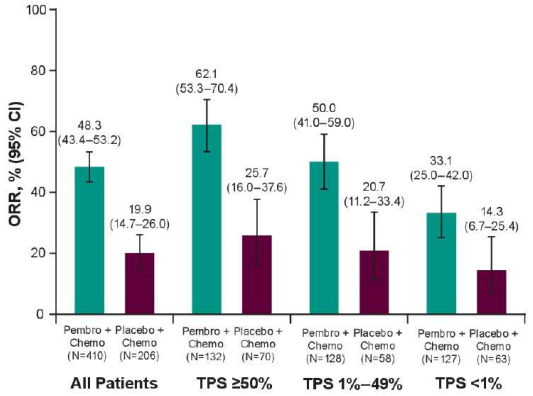
Platino-pem-pem. Analisis final











Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab

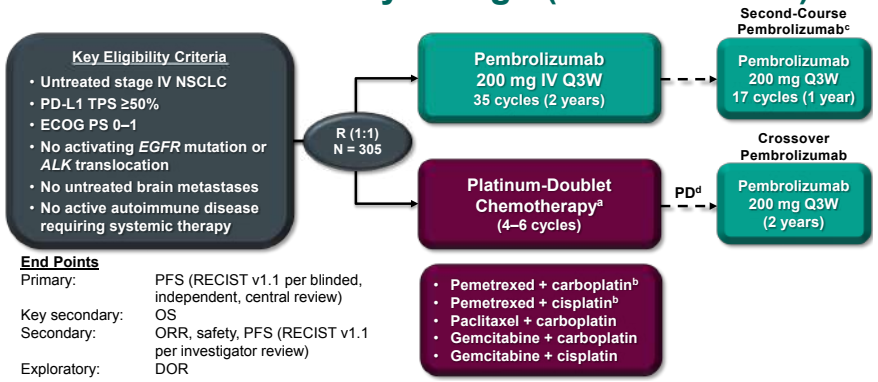
- 56 patients in the pembrolizumab plus pemetrexed-platinum arm completed 35 cycles (~2 years) of pembrolizumab treatment
  - ORR was 85.7% (4 complete response, 44 partial response, 8 stable disease)
  - Median OS was not reached (95% CI, not reached)

Rodriguez Abreu D ASCO 2020

KN024

Pembrolizumab

KEYNOTE-024 Study Design (NCT02142738)

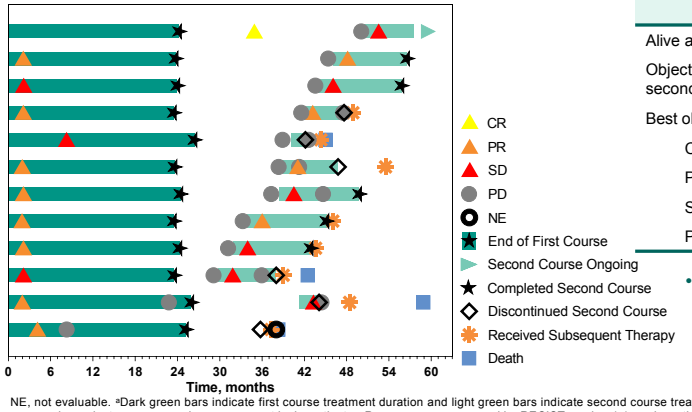


End Points

Primary:	PFS (RECIST v1.1 per blinded, independent, central review)
Key secondary:	OS
Secondary:	ORR, safety, PFS (RECIST v1.1 per investigator review)
Exploratory:	DOR

Treatment Duration and Time to Response[a]

Second Course of Pembrolizumab[b]

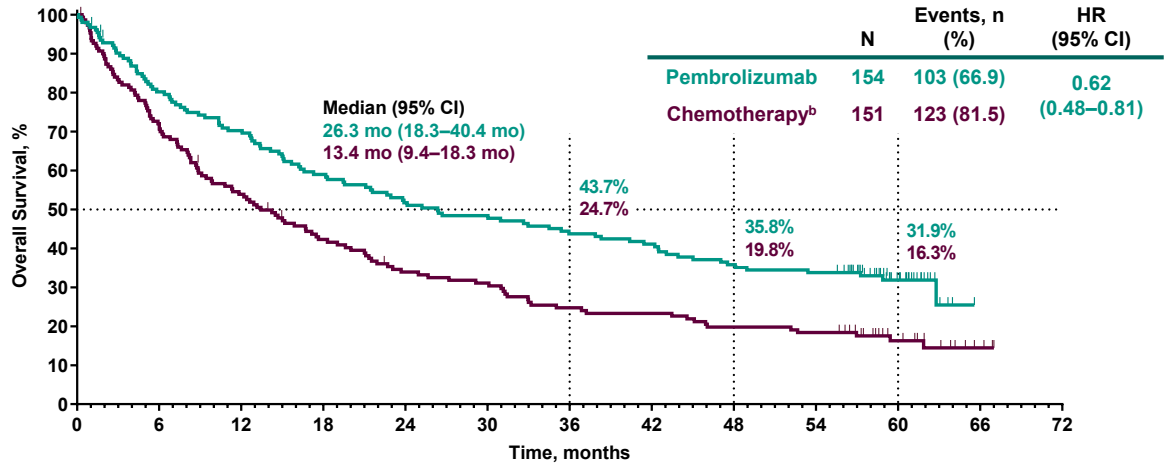


	N = 12[c]
Alive at data cutoff, n (%)	8 (67)
Objective response during second course, n (%)	4 (33)
Best objective response, n (%)	
Complete response	0
Partial response	4 (33)
Stable disease	6 (50)
Progressive disease	1 (8)

- **At data cutoff, 5/12 patients (42%) were alive without PD per investigator assessment**
  - **3 (25%) did not receive subsequent therapy**

NE, not evaluable. [a]Dark green bars indicate first course treatment duration and light green bars indicate second course treatment duration. Follow-up was defined as the time to progression or last non-progression assessment by investigator. Response was assessed by RECIST version 1.1 per investigator review. [b]For a maximum of 17 cycles. [c]5 patients (42%) experienced treatment-related AEs during second-course treatment, all grade 1–2; 1 was an immune-mediated AE (grade 1 hypothyroidism).
Data cutoff: June 1, 2020.

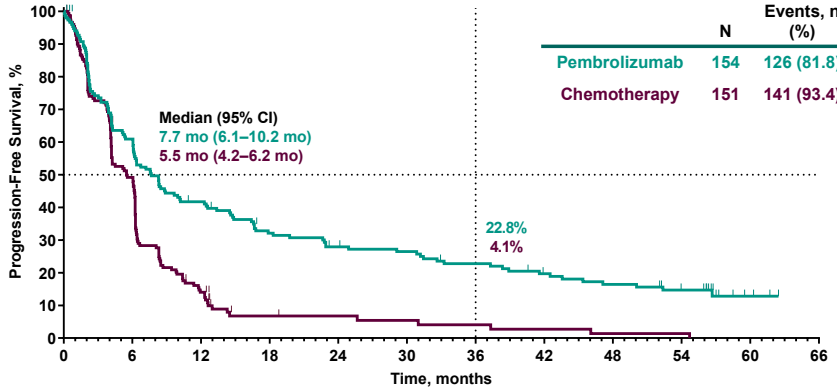
Overall Survival[a]



	N	Events, n (%)	HR (95% CI)
Pembrolizumab	154	103 (66.9)	0.62 (0.48–0.81)
Chemotherapy[b]	151	123 (81.5)	

No. at risk													
Pembrolizumab	154	121	106	89	78	73	66	62	54	51	20	0	0
Chemotherapy	151	108	80	61	48	44	35	33	28	26	13	3	0

[a]ITT population.

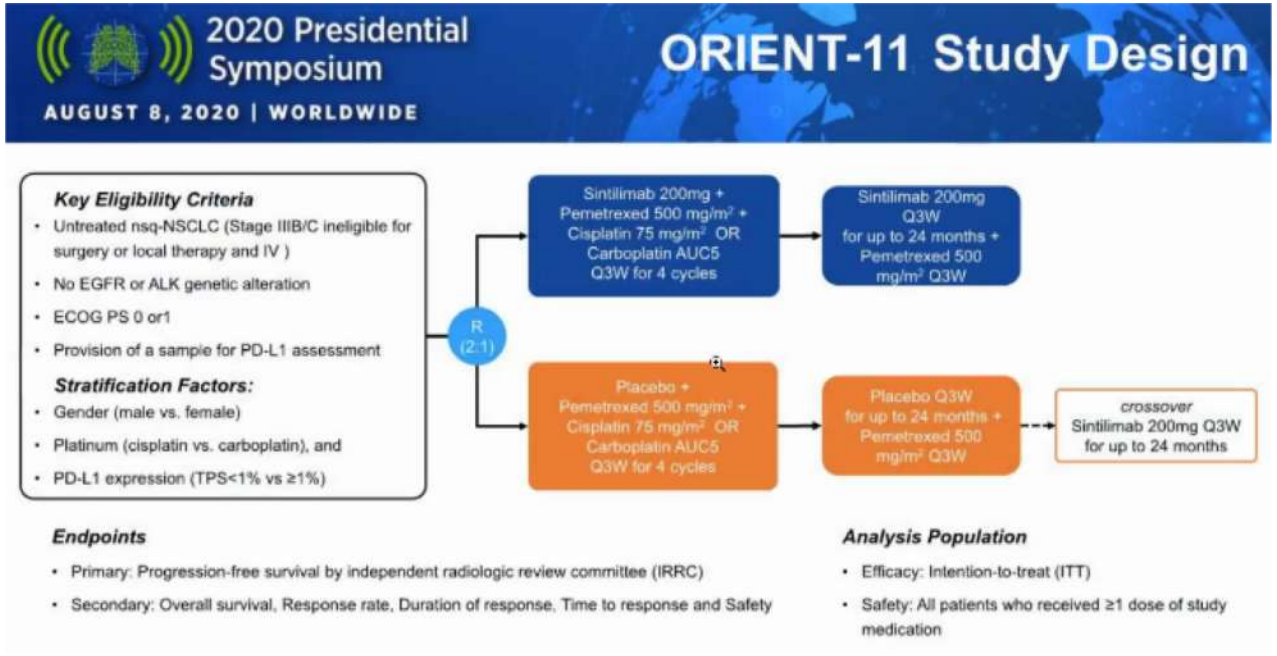


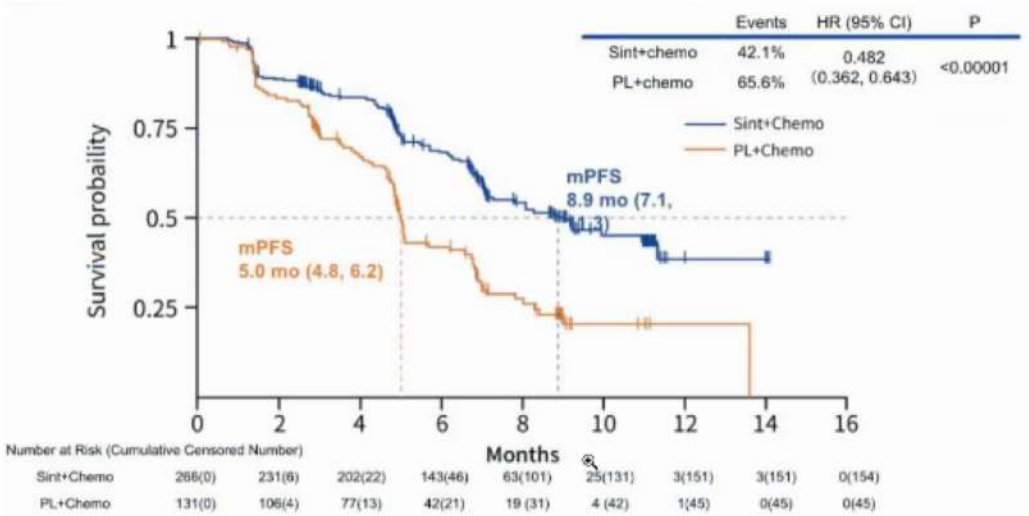
	N	Events, n (%)	HR (95% CI)
Pembrolizumab	154	126 (81.8)	0.50 (0.39–0.65)
Chemotherapy	151	141 (93.4)	

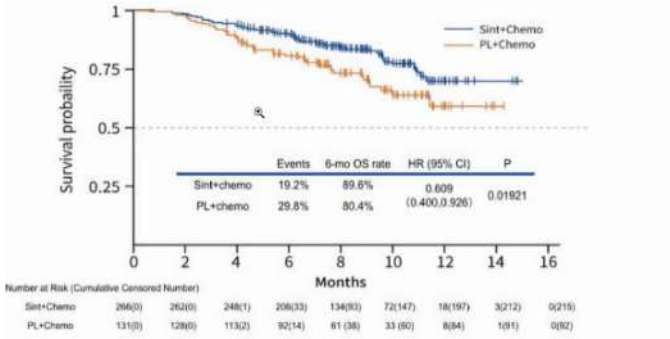
Brahmer JR ESM0 2020

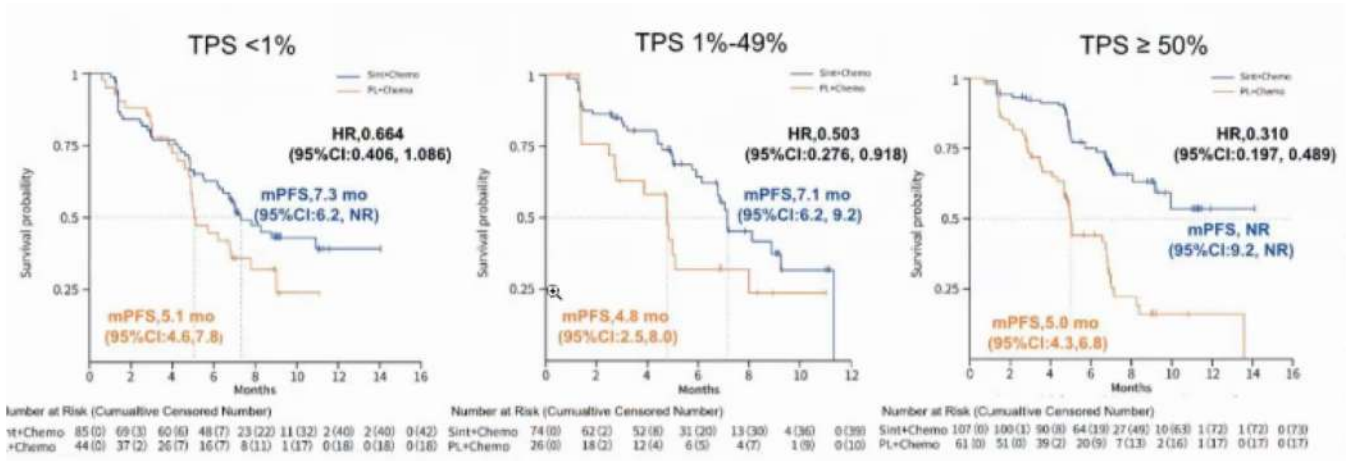
Orient 11:

Sintilimab









Zhang Li WCLC symposium 2020

Orient 12

Sintilimab+ platino/GMZ.

Randomized, double-blind, Phase 3

Key Eligibility Criteria

- Chemo-naïve sqNSCLC (Stage IIIB/C ineligible for surgery or local therapy or Stage IV)
- 18-75 years old
- ECOG PS 0 or 1
- At least 1 measurable lesion per RECIST v1.1
- Tissue sample available for PD-L1 assessment

Stratification factors:

- Disease stage (IIIB / IIIC vs IV)
- Platinum (cisplatin vs carboplatin)
- PD-L1 expression (TPS<1% vs ≥1%)

R 1:1

Sintilimab 200mg D1+ Gemcitabine 1.0 g/m² D1,8+ Cisplatin 75 mg/m² or Carboplatin AUC 5 D1
Q3W for 4 or 6 cycles → Sintilimab 200mg Q3W → Until PD, intolerability or for up to 2 years

Placebo D1+ Gemcitabine 1.0 g/m² D1,8+ Cisplatin 75 mg/m² or Carboplatin AUC 5 D1
Q3W for 4 or 6 cycles → Placebo Q3W → Until PD, intolerability or for up to 2 years

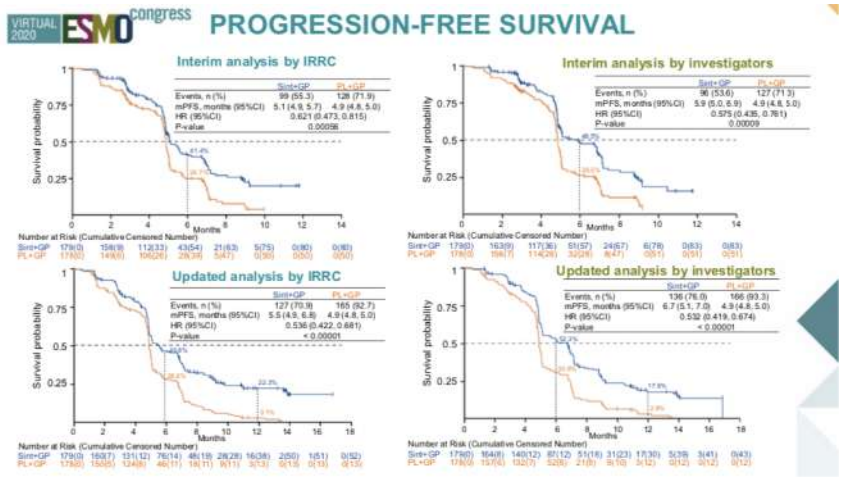
PD by IRRC → Sintilimab 200mg Q3W Until PD, intolerability, or up to 2 years

Endpoints

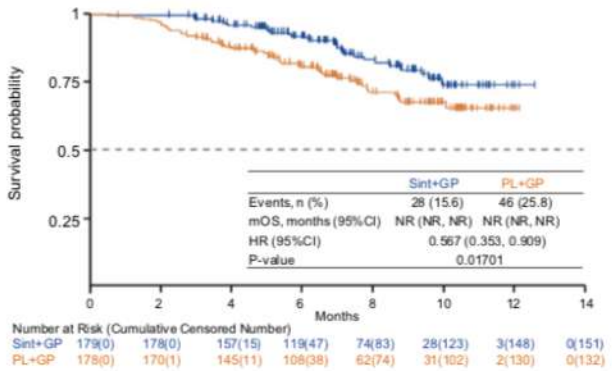
- Primary: Progression-free survival by independent radiologic review committee (IRRC)
- Secondary: overall survival (OS), objective response rate (ORR), duration of response (DOR) and Safety

Analysis Population

- Efficacy: Intention-to-treat (ITT)
- Safety: All patients who received at least 1 dose of study treatment



Overall survival (Interim analysis)



Objective response by IRRC

	Sint + GP (N=179)	PL + GP (N=178)
Best of response – no. (%)		
CR	1 (0.6)	0
PR	79 (44.1)	63 (35.4)
SD	74 (41.3)	80 (44.9)
PD	18 (10.1)	25 (14.0)
ORR, % (95%CI)	44.7 (37.3, 52.3)	35.4 (28.4, 42.9)
DCR, % (95%CI)	86.0 (80.1, 90.8)	80.3 (73.7, 85.9)

Zhou C ESMO 2020

ONO-4538-52/TASUKI-52

Nivolumab+ Carbo-taxol-bevacizumab

Key Eligibility Criteria

- Treatment-naïve stage IIIB / IV non-squamous NSCLC patients
- No sensitizing *EGFR* or *ALK* alterations
- PD-L1 all comer
- ECOG PS 0–1

N = 550

R 1:1

Nivolumab / Carboplatin / Paclitaxel / Bevacizumab[a)] NIVO : 360 mg IV q3w → SD, PR, CR → **Nivolumab / Bevacizumab**

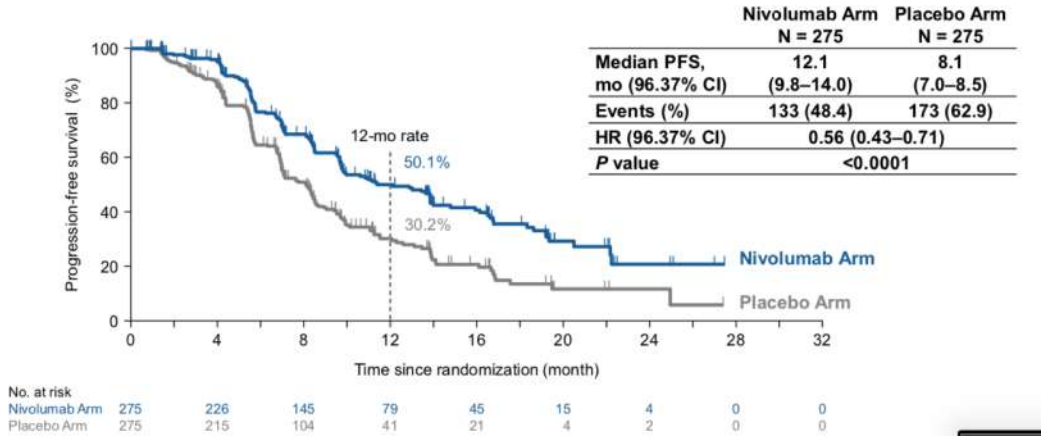
Placebo / Carboplatin / Paclitaxel / Bevacizumab[a)] → SD, PR, CR → **Placebo / Bevacizumab**

Treatment was continued until PD, unacceptable toxicity

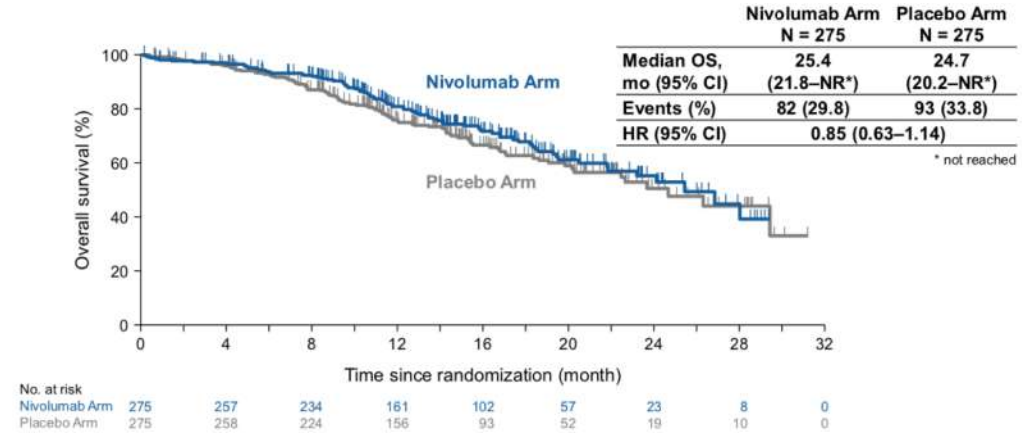
- **Primary Endpoint:**
  - PFS assessed by IRRC[b)]
- **Secondary Endpoint:**
  - OS, ORR, Safety

Stratification Factors

- **PD-L1 (IHC 28-8) : ≥ 50%, 1%–49%, < 1% or indeterminate**
- **ECOG PS : 0, 1**
- **Sex : Male, Female**



	Nivolumab Arm N = 275	Placebo Arm N = 275
Median PFS, mo (96.37% CI)	12.1 (9.8–14.0)	8.1 (7.0–8.5)
Events (%)	133 (48.4)	173 (62.9)
HR (96.37% CI)	0.56 (0.43–0.71)	
P value	<0.0001	



	Nivolumab Arm N = 275	Placebo Arm N = 275
Median OS, mo (95% CI)	25.4 (21.8–NR*)	24.7 (20.2–NR*)
Events (%)	82 (29.8)	93 (33.8)
HR (95% CI)	0.85 (0.63–1.14)	

* not reached

Lee JS ESMO 2020

Empower-Lung 1

Cemiplimab

Key Eligibility Criteria
- Treatment-naïve advanced NSCLC
- PD-L1 ≥50%
- No *EGFR*, *ALK* or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases and controlled hepatitis B or C or HIV were allowed

Stratification Factors:
- Histology (squamous vs non-squamous)
- Region (Europe, Asia or ROW)

R 1:1

Arm A
Cemiplimab monotherapy IV
350 mg Q3W
Treat until PD or 108 weeks

PD → Optional continuation of cemiplimab + 4 cycles of chemotherapy

Arm B
4–6 cycles of investigator's choice chemotherapy

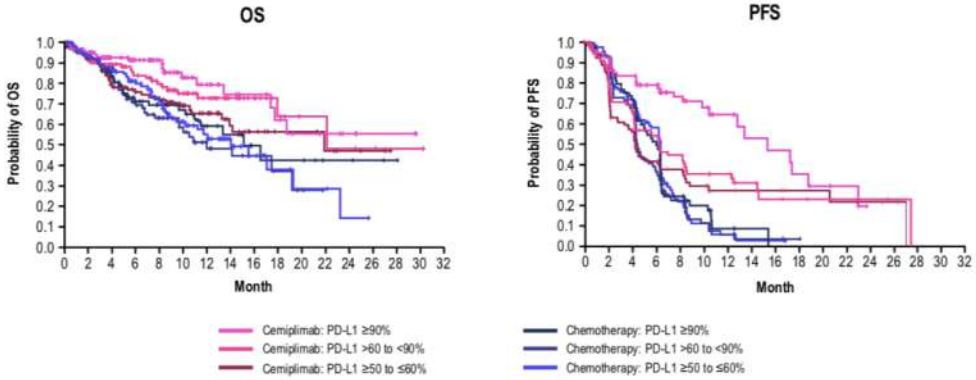
PD → Optional crossover to cemiplimab monotherapy

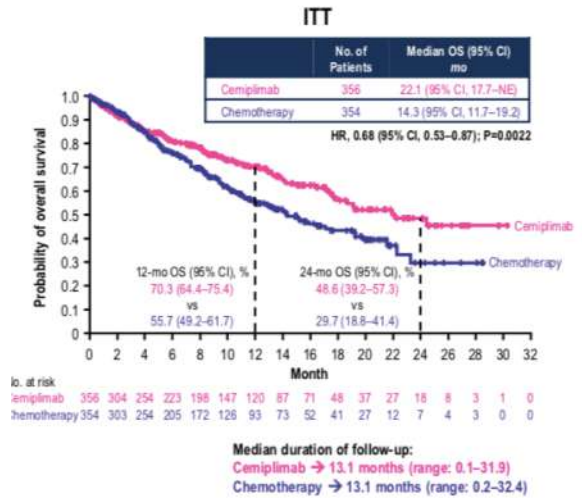
Follow-up

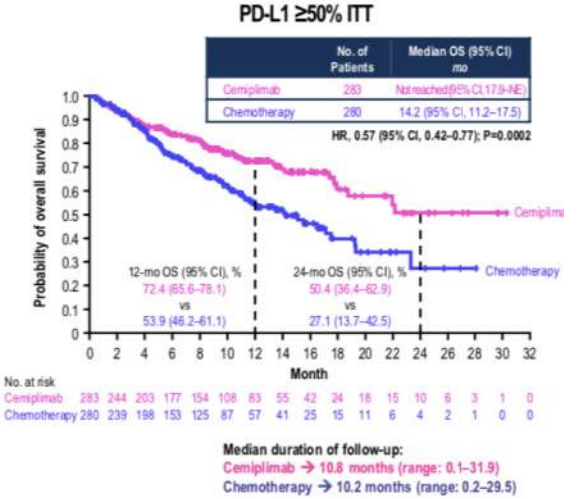
Endpoints:
- Primary: OS and PFS
- Secondary: ORR (key), DOR, HRQoL and safety

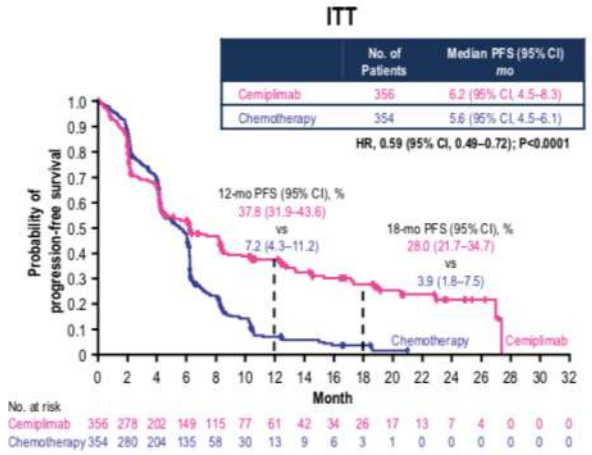
N=710

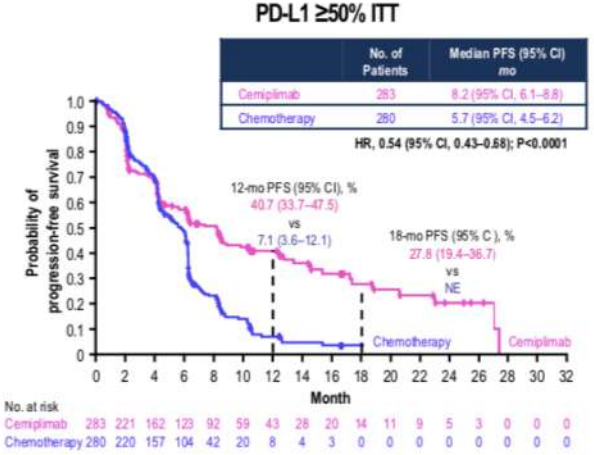
Five interim analyses were prespecified per protocol
Second interim analysis (1 March 2020) presented here







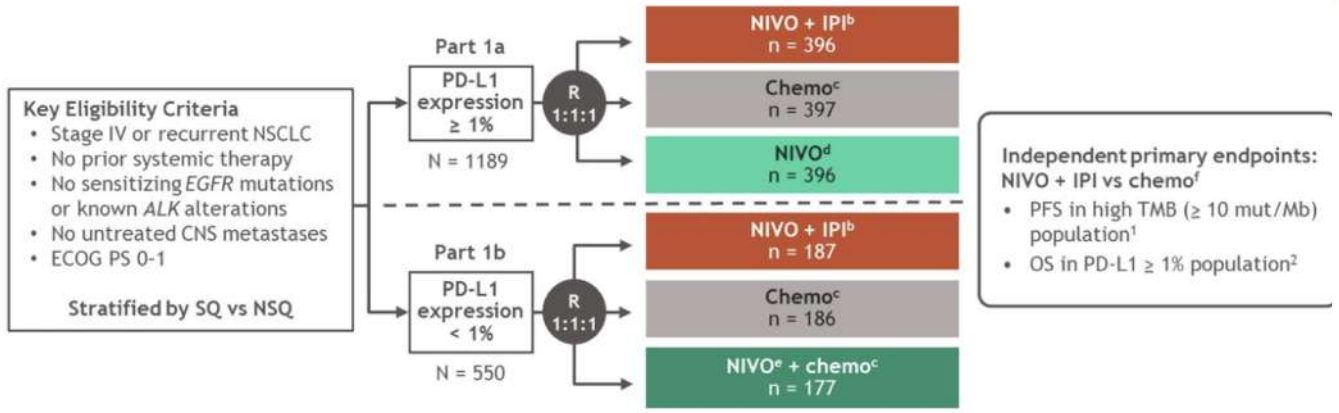


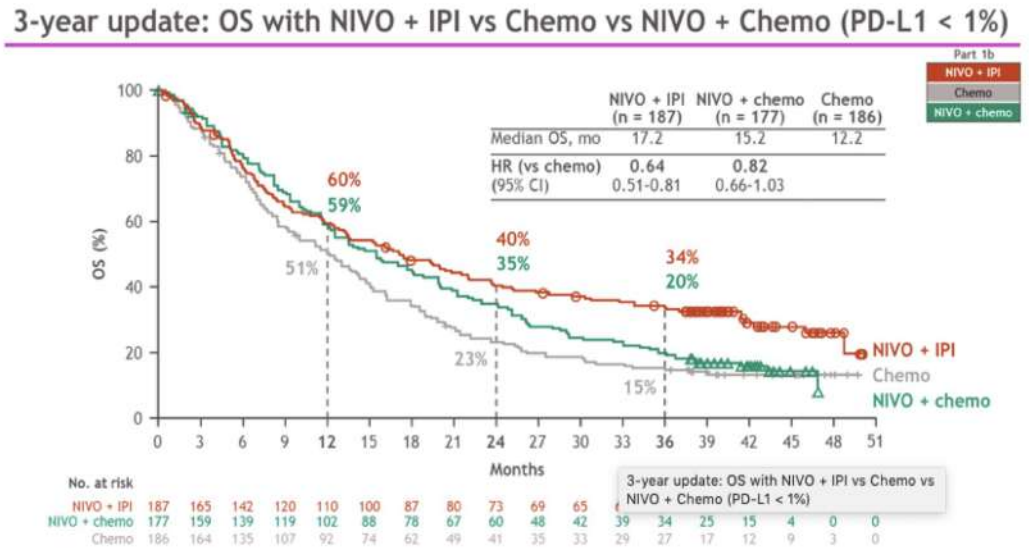


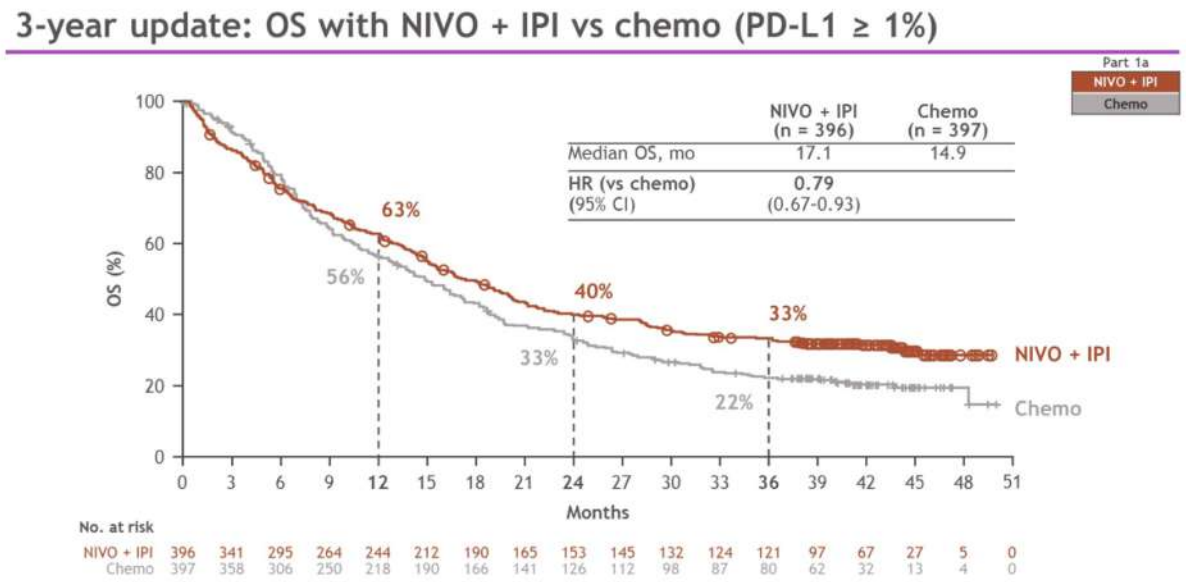
Sezer A ESMO 2020

CheckMate 227 parte 1

Nivolumab + ilipilumab: datos a 3 años







Suresh Ramalingam ASCO 2020

CheckMate 227 parte 1

Nivolumab + ilipilumab: datos a 3 años

FDA approves nivolumab plus ipilimumab for first-line mNSCLC (PD-L1 tumor expression ≥1%)

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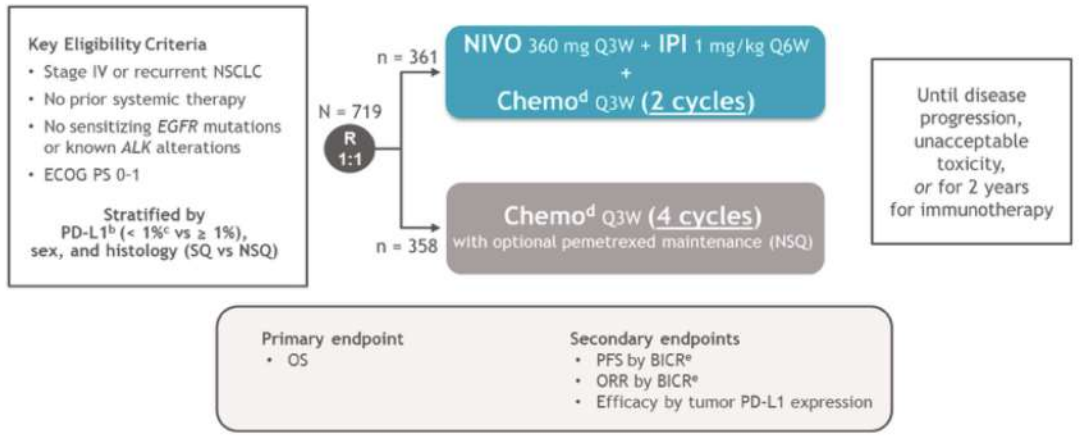
On May 15, 2020, the Food and Drug Administration approved the combination of nivolumab (OPDIVO, Bristol-Myers Squibb Co.) plus ipilimumab (YERVOY, Bristol-Myers Squibb Co.) as first-line treatment for patients with metastatic non-small cell lung cancer whose tumors express PD-L1(≥1%), as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

Today, the FDA also approved the PD-L1 IHC 28-8 pharmDx (Agilent Technologies, Inc.) as a companion diagnostic device for selecting patients with NSCLC for treatment with nivolumab plus ipilimumab.

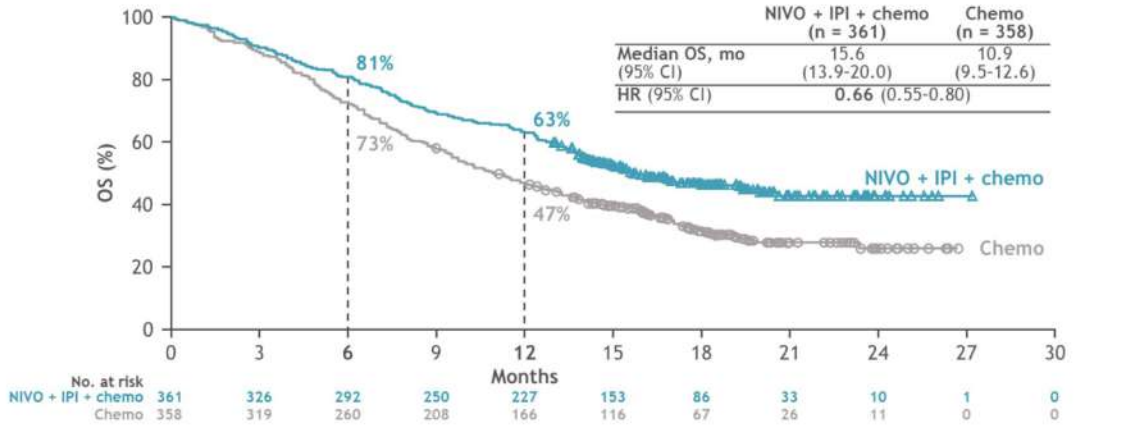
Efficacy was investigated in CHECKMATE-227 (NCT02477826), a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC and no prior anticancer therapy. In Part 1a of the trial, 793 patients with PD-L1 tumor expression ≥1% were randomized to receive either the combination of nivolumab plus with ipilimumab (n=396) or platinum-doublet chemotherapy (n=397).

CheckMate 9LA

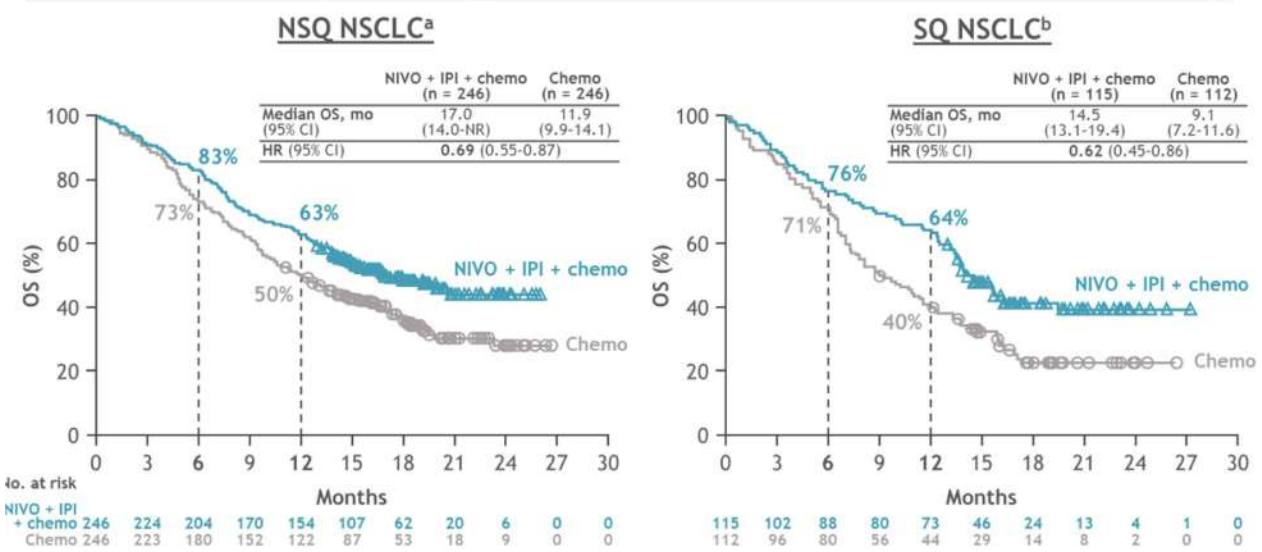
Nivolumab + ipilimumab + 2 ciclos de doblete de platino



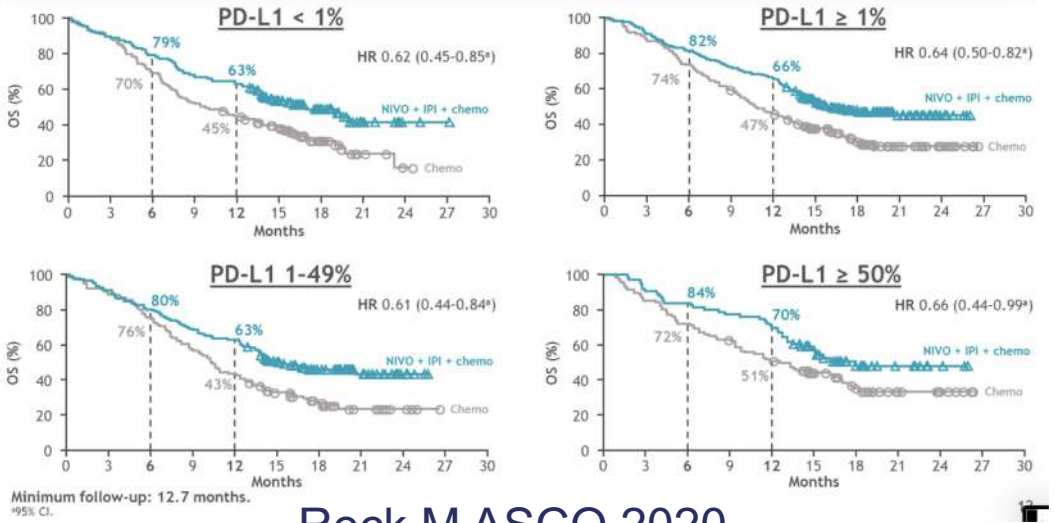
Primary endpoint (updated): Overall survival[a]



Overall survival by histology



Overall survival by PD-L1 expression level



Reck M ASCO 2020

CheckMate 9LA

Nivolumab + ipililulamb + 2 ciclos de doblete de platino

FDA approves nivolumab plus ipilimumab and chemotherapy for first-line treatment of metastatic NSCLC

On May 26, 2020, the Food and Drug Administration approved the combination of nivolumab (OPDIVO, Bristol-Myers Squibb Co.) plus ipilimumab (YERVOY, Bristol-Myers Squibb Co.) and 2 cycles of platinum-doublet chemotherapy as first-line treatment for patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

Efficacy was investigated in CHECKMATE-9LA (NCT03215706), a randomized, open-label trial in patients with metastatic or recurrent NSCLC. Patients were randomized to receive either the combination of nivolumab plus ipilimumab and 2 cycles of platinum-doublet chemotherapy (n=361) or platinum-doublet chemotherapy for 4 cycles (n=358). The trial demonstrated a statistically significant benefit in overall survival (OS) for patients treated with nivolumab plus ipilimumab plus chemotherapy compared to those who received chemotherapy. Median OS was 14.1 months (95% CI: 13.2, 16.2) versus 10.7 months (95% CI: 9.5, 12.5), HR 0.69; 96.71% CI: 0.55, 0.87).

CCTG BR.34

Durvalumab+ tremelitumab +/- QT basada en platino

Metastatic squamous or non-squamous NSCLC:
- Stage IVA (high risk) or IVB*
- No prior chemotherapy for Stage IV
- EGFR wild type, ALK fusion negative**
- ECOG PS 0 or 1
- Adequate organ function
- No prior autoimmune disease
- No untreated CNS metastases
- Measurable disease (RECIST 1.1)

Stratification factors:
- Squamous versus non-squamous
- Stage IVA vs B
- Never vs current vs former smoker

RANDOMIZED

1:1

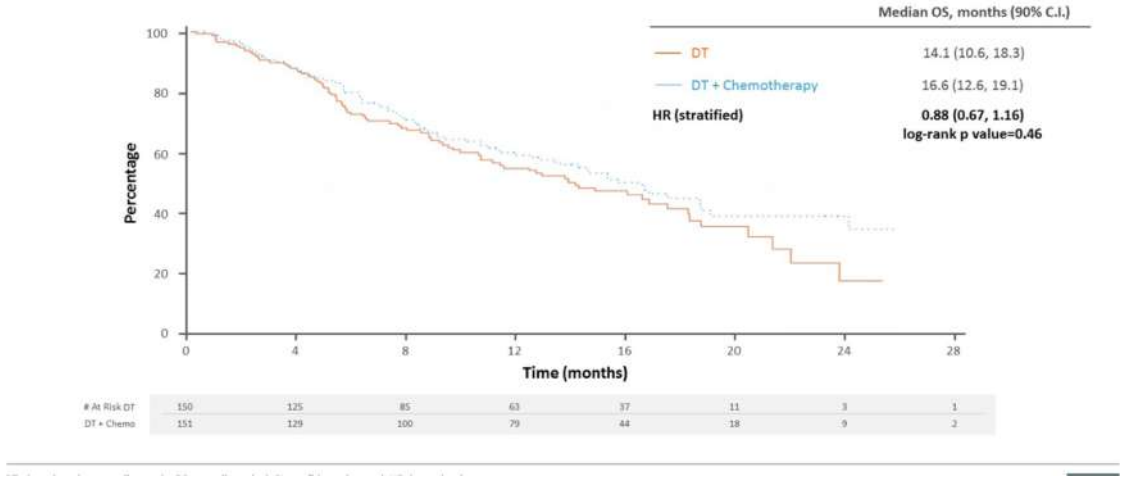
ARM 1 Durvalumab + Tremelimumab

Durvalumab 1500 mg IV + Tremelimumab 75 mg IV q28 days x 4 then Durvalumab 1500 mg IV until Disease Progression

Crossover between treatment arms not permitted

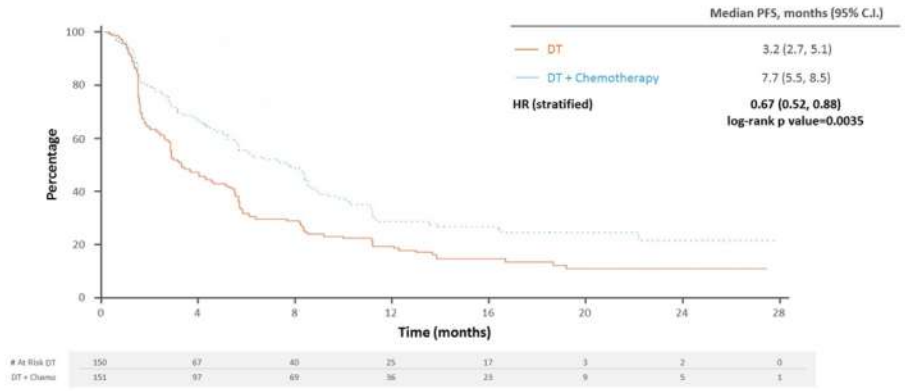
ARM 2 Durvalumab + Tremelimumab + Chemotherapy

Durvalumab 1500 mg IV + Tremelimumab 75 mg IV + Platinum Doublet Chemotherapy# IV q21 days x 4, then Durvalumab 1500 mg alone (squamous) or plus Pemetrexed 500 mg/m^2 IV (non-squamous) q28 days until Disease Progression



Primary Objective:

- To compare overall survival (OS) between patients receiving durvalumab plus tremelimumab and durvalumab, tremelimumab plus platinum chemotherapy in patients with advanced NSCLC



Natasha Leighl ASCO 2020

WJOG10718L.

Atezolizumab bevacizumab PDL1>50%.

WJOG10718L; A single arm, open label, multi-institutional study

Advanced Non-Sq NSCLC

- PD-L1 TPS ≥ 50% (Dako 22C3)
- w/o EGFR/ALK/ROS1 alterations
- ECOG PS=0-1
- No prior therapy
- Fit to anti-angiogenesis therapy

→ Atezolizumab 1200mg + Bevacizumab 15mg/kg, Every 3 weeks, Up to 2years → Until PD or intolerable toxicity

JapicCTI-184038

Sample size: 38
Threshold-Expected ORR: 40-62%.
One side α = 0.05 1-β = 0.8

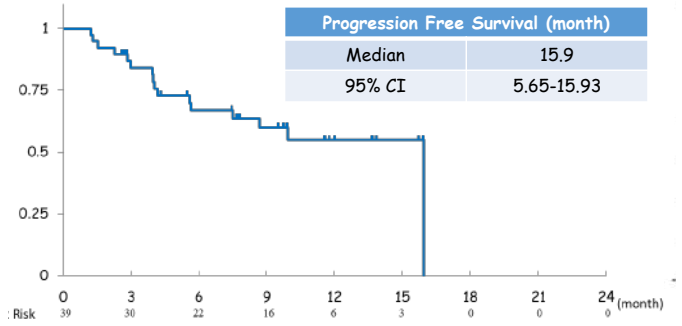
Primary endpoint: ORR (IRC)
Secondary endpoints: PFS (IRC), DoR (IRC), OS, Safety

Best Response	N	%
CR	0	0
PR	25	64.1
SD	11	28.2
PD	3	7.7
NE	0	0
CR+PR	25	64.1
90% CI	49.69-76.83	
95% CI	47.18-78.80	

n=39

Sample size: 38
Threshold-Expected: ORR: 40-62%.
One side α = 0.05 1-β = 0.8

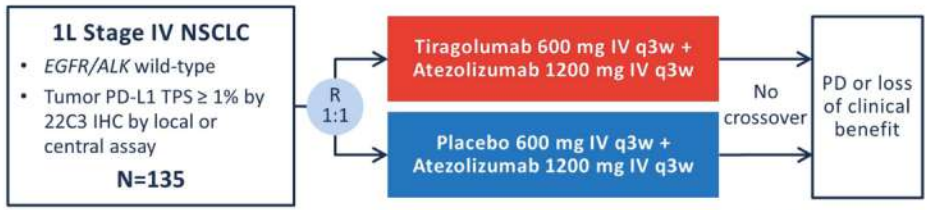
Progression Free Survival



Seto T ESMO 2020

CITYSCAPE

Tiragolumab plus atezolizumab

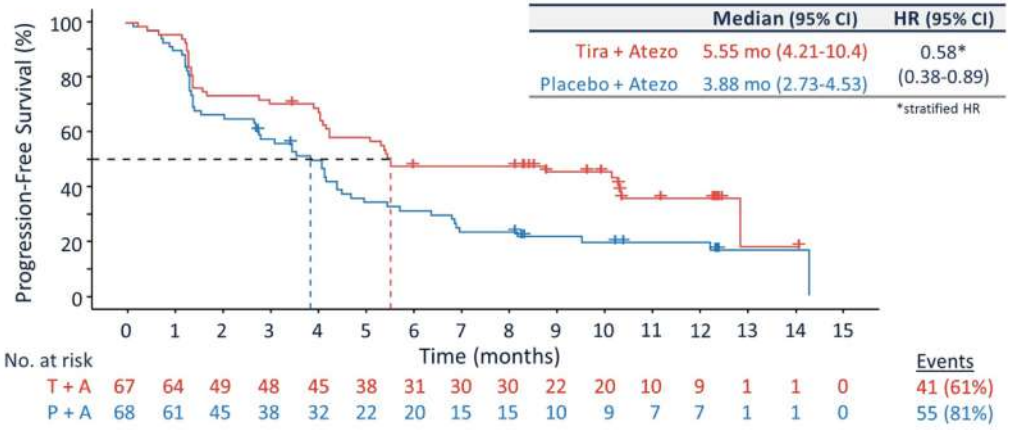


Stratification Factors:
- PD-L1 TPS (1-49% vs ≥ 50%)
- Histology (Non-Squamous vs Squamous)
- Tobacco use (yes vs no)

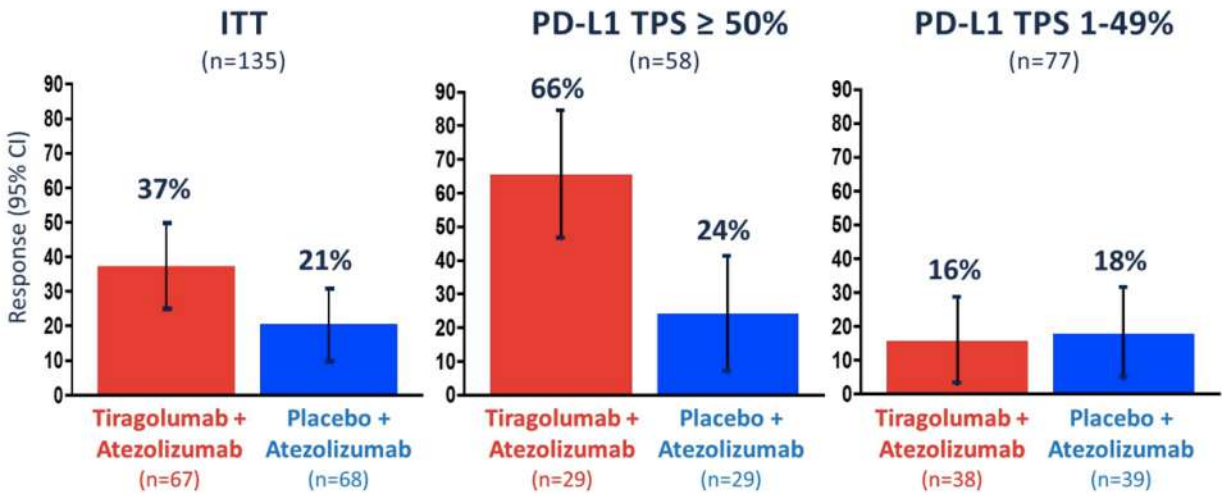
- **Co-Primary Endpoints: ORR** and **PFS**
- **Key Secondary Endpoints: Safety,** DOR, OS, Patient-reported outcomes (PROs)
- **Exploratory Endpoints:** Efficacy analysis by PD-L1 status

- **Updated Analysis**
  - Follow-up performed to assess safety and efficacy
  - Cutoff date of *02 December 2019*
  - Median follow-up of 10.9 months

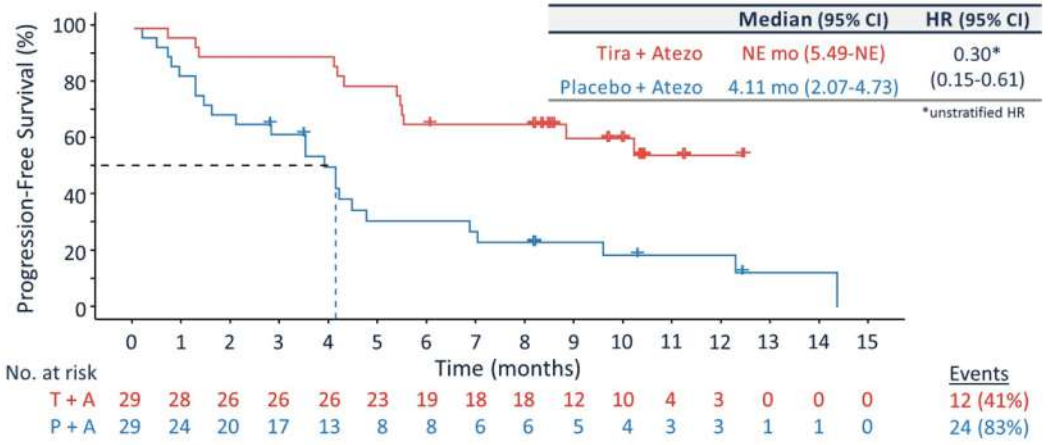
Updated Investigator-Assessed PFS: ITT



Updated Confirmed Overall Response Rate (ORR)



Updated Investigator-Assessed PFS: PD-L1 TPS ≥ 50%



Melissa Johnson ASCO 2020

EGFR

Referente: Flaura: SLP 18.9 m y SG 38.6 meses

Tkis 3º gen ⇨
- Alflutinib:

RT ⇨
- SINDAS:

Tki+ Antiangiogenicos
- NEJ026: bev + Erlotinib
- Active: Apatinib + Gefitinib
- WJOG9715L Fase II: osi+ bev

Nuevos fármacos o combinaciones
- CHRYSALIS: amivantomab + lazertinib
- Patritumab deruxtecan:
- Osimertinib-gefitinib

Alflutinib

Abstract ID: 9602

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Efficacy and safety of Alflutinib (AST2818) in patients with T790M mutation positive NSCLC: A phase IIb multicenter single arm study

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The affiliations of authors are listed below.

Abstract

Background:
Alflutinib (AST2818) is a third generation EGFR-TKI targeting both sensitizing EGFR and EGFR T790M mutations. This phase IIb, multicenter, single arm study (ALSC003, NCT03452592) aimed to assess the efficacy and safety of Alflutinib in patients with EGFR T790M mutated non-small cell lung cancer (NSCLC).

Methods:
Patients with centrally confirmed EGFR T790M mutation in tumor tissue, locally advanced or metastatic NSCLC who progressed after first/second-generation EGFR-TKIs or primary EGFR T790M mutation positive received 80 mg Alflutinib orally once daily. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety. Efficacy was assessed by independent radiological review committee (IRRC) per RECIST 1.1. Safety was assessed by NCI CTCAE version 4.03.

Results:
From Jun 4, 2018 to Dec 8, 2018, 220 patients were enrolled. Patients were representative: median age 61, stage IV 96.4%, ECOG PS 1/2 77.3%/4.1%, CNS metastatic 39.5% (by IRRC). By Jan 29, 2020, the median follow-up time was 9.6 months. The ORR was 74.1% (163/220 [95% CI 67.8–79.7]). The DCR was 93.6% (206/220). The median PFS was 9.6 months (95% CI 8.2–9.7). Median OS was not yet reached. By Nov 6, 2019, 19 (65.5%) of 29 patients with measurable CNS metastases had an intracranial objective response, and the median PFS was 11.0 months (95% CI 8.3, NA). By Nov 6, 2019, 214 (97.3%) patients had at least one adverse events (AEs), which were mostly grade 1 or 2. The most common AEs were cough (49 [22.3%]), increased aspartate aminotransferase (37 [16.8%]), and upper respiratory tract infection (37 [16.8%]). Grade ≥ 3 AEs occurred in 53 (24.1%) patients. Drug related ≥ Grade 3 AEs assessed by investigator occurred in 22 (10.0%) patients.

Conclusions:
Alflutinib has promising efficacy and acceptable safety profile for the treatment of EGFR T790M mutated NSCLC patients.

Background

- Alflutinib (AST2818) is a newly developed, oral, irreversible third generation Epidermal growth factor receptor (EGFR) Tyrosine kinase inhibitor (TKI) targeting both sensitizing EGFR and EGFR T790M mutations.
- Preclinical studies revealed alflutinib had potent antitumor activity comparable to that of osimertinib (data on file).
- The phase I/II study (NCT02973763, NCT03127449) of aluflutinib has shown alflutinib is clinically effective with an acceptable safety profile in patients with EGFR T790M mutated advanced non-small cell lung cancer (NSCLC) , even in those with central nervous system (CNS) metastases.
- This phase IIb, multicenter, single arm study (ALSC003, NCT03452592) aimed to further assess the efficacy and safety of Alflutinib in patients with EGFR T790M mutated NSCLC.

Methods

- This is a phase IIb, multicenter, single arm study conducted at 46 centers in China.
- Eligible patients were aged 18 years or older, had histologically or cytologically confirmed locally advanced or metastatic NSCLC, not suitable for surgery or radiotherapy, radiologically progressed after first or second generation EGFR TKI with centrally confirmed EGFR T790M mutation, or with primary EGFR T790M mutation, had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients with asymptomatic, stable CNS metastases not requiring steroids for at least 4 weeks before the first dose of alflutinib were allowed to be included.
- Eligible patients received alflutinib 80mg orally per day until disease progression or intolerable toxicity. Efficacy was evaluated every 6 weeks in the first 48 weeks, then every 12 weeks in the following weeks by independent radiological review committee (IRRC) using RECIST 1.1. Safety was assessed by NCI CTCAE version 4.03.
- The primary endpoint was objective response rate (ORR) by IRRC. Secondary endpoints included progression free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), clinical benefit rate (CBR) and safety.

Results

- From Jun 4, 2018 to Dec 8, 2018, 220 patients were enrolled in total.
- Baseline characteristics of patients were representative: median age 61, stage IV 96.4%, ECOG PS 1/2 77.3%/4.1%, CNS metastatic 39.5% (Table 1).

Table 1. Baseline patient characteristics (n=220)

Characteristics		No. of patient (%)
Age	Median (range)	61 (29-80)
Sex	Male	99 (45.0%)
	Female	121 (55.0%)
Stage	III	8 (3.6%)
	IV	212 (96.4%)
Smoking history	Smoker	60 (27.3%)
	Non-smoker	160 (62.7%)
Prior lines of therapy	0*	6 (2.7%)
	1	162 (73.6%)
	2	38 (17.3%)
	3	9 (4.1%)
	4	4 (1.8%)
	>5	1 (0.5%)
EGFR mutations in tumor	T790M	220 (100%)
	19del	133 (60.5%)
	L858R	81 (36.8%)
	19del + L858R	3 (1.4%)
	others	3 (1.4%)
ECOG PS	0	41 (18.6%)
	1	170 (77.3%)
	2	9 (4.1%)
CNS metastases by IRRC	Yes	87 (39.5%)
	No	133(60.5%)

* de novo T790M mutation

Efficacy
- At the data cut-off (DCO, Jan 29, 2020), the ORR and DCR by IRRC was 74.1% (163/220) and 93.6% (206/220) respectively (Table 2). At the DCO, the median follow-up of PFS was 9.6 months, the median PFS was 9.6 months (95% CI 8.2, 9.7) (Figure 1).
- Of the 220 enrolled patients, 87 had measurable and/or non-measurable CNS metastases, and 29 had one or more measurable CNS metastases assessed by IRRC. At DCO of Nov 6, 2019, the CNS ORR and DCR in patients with one or more measurable CNS lesions was 65.5% and 100% respectively. Median CNS PFS was 11.0 months (95% CI 8.3, NA) in patients with measurable and/or non-measurable CNS lesions.

Table 2. Summary of response to alflutinib assessed by IRRC

	N=220
Complete response (CR)	0
Partial response (PR)	163 (74.1%)
Stable disease (SD)	43 (19.5%)
Progressed disease (PD)	12 (5.5%)
Unevaluable (UE)	1 (0.5%)
Not evaluated	1 (0.5%)
ORR	74.10%
95% CI	67.8%-79.7%

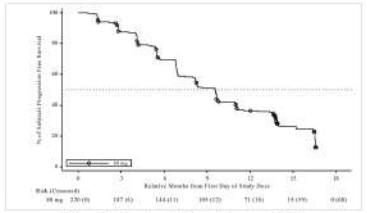


Figure 1. Kaplan-Meier estimates of PFS

Safety
- At the DCO of Nov 6, 2019, the median time of exposure to alflutinib was 9.7 months.
- 24.1%(53/220) of patients had grade ≥ 3 adverse events (AEs), and 10.0% (22/220) had drug-related grade ≥ 3 AEs. The most common drug related grade ≥ 3 AEs were increased aspartate aminotransferase (three [1.4%]), increased alanine aminotransferase (three [1.4%]) and increased γ-glutamyltransferase (three [1.4%]).
- 21.4%(47/220) of patients had serious AEs (SAEs) and 5.5% (12/220) had drug related SAEs.
- Only 8.6% (19/220) and 8.2% (18/220) of patients had diarrhea and rash of all grade respectively. No grade ≥ 3 diarrhea or rash were observed. Interstitial lung disease was observed in 1 patient (0.5%).
- Dose interruption and reduction were reported in 11.4% (25/220) and 2.3% (5/220) patients. Permanent discontinuation of alflutinib occurred in 3.6% (8/220) patients.
- 4 patients experienced AEs with death outcome, including CNS metastases (n=2), respiratory failure (n=1) and unknown death (n=1). The causality between study drug and first 3 events were assessed as probably not related by investigators, whereas the last one could not be determined due to the unknown cause of death.
- The detailed adverse events were listed in table 3.

Table 3. Treatment emerged adverse events (TEAEs, n=220)

TEAEs (overall rate ≥ 10%)	Any Grade TEAEs	Grade ≥ 3 TEAEs	Grade ≥ 3drug related TEAEs by investigator
At least one TEAE	214(97.3%)	53(24.1%)	22(10.0%)
Cough	49(22.3%)	0	0
Upper respiratory tract infection	37(16.8%)	1(0.5%)	0
Increased aspartate aminotransferase	37(16.8%)	3(1.4%)	3(1.4%)
Increased alanine aminotransferase	35(15.9%)	3(1.4%)	3(1.4%)
Prolonged electrocardiogram QT	33(15.0%)	0	0
Urinary tract infection	30(13.6%)	1(0.5%)	1(0.5%)
Decreased white blood cell count	28(12.7%)	0	0
Anemia	27(12.3%)	2(0.9%)	0
Increased weight	24(10.9%)	0	0
Increased serum creatinine	22(10.0%)	0	0

Conclusions

- Aflutinib showed promising clinical antitumor activity in patients with EGFR T790M mutation NSCLC, including those with CNS metastases.
- Alflutinib also showed an acceptable and manageable safety profile.
- Therefore, alflutinib should be considered as a treatment option for NSCLC patients with EGFR T790M mutation.
- The randomized, double-blind phase III trial (NCT03787992, FLAG study) comparing alflutinib versus gefitinib as first line therapy in EGFR mutation positive, locally advanced or metastatic NSCLC patients is ongoing and the enrollment has been completed.

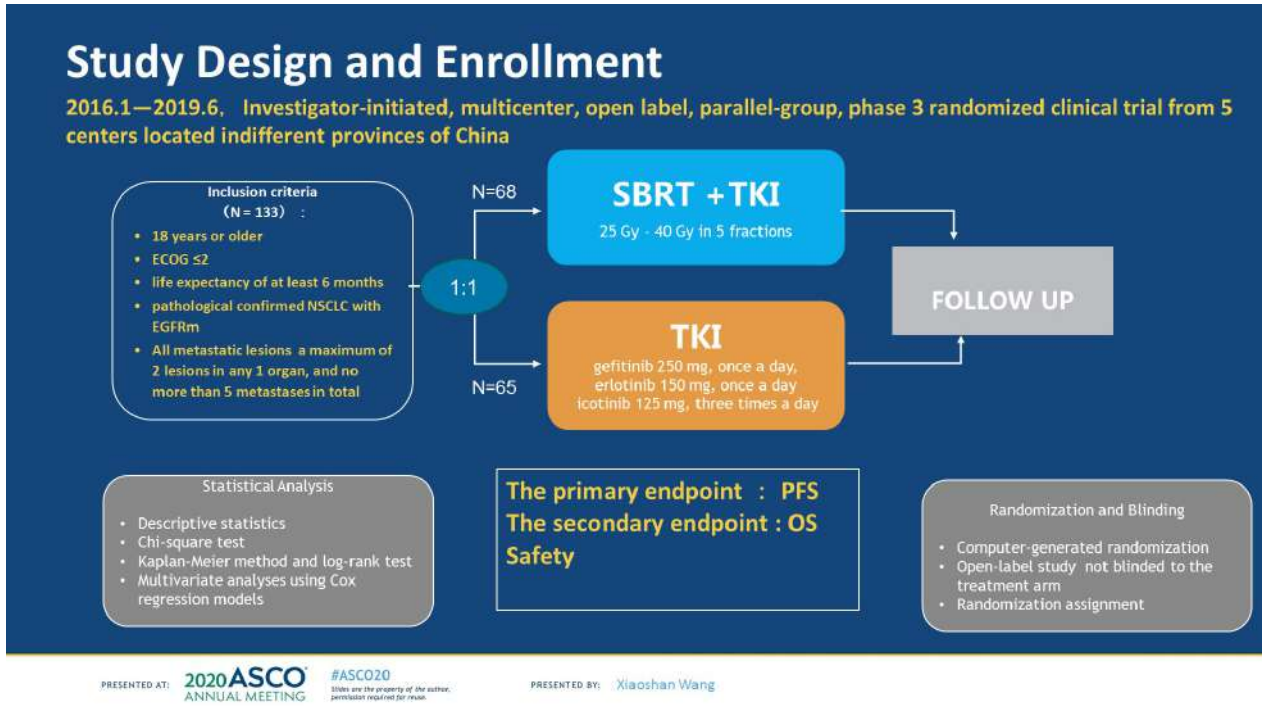
Acknowledgement

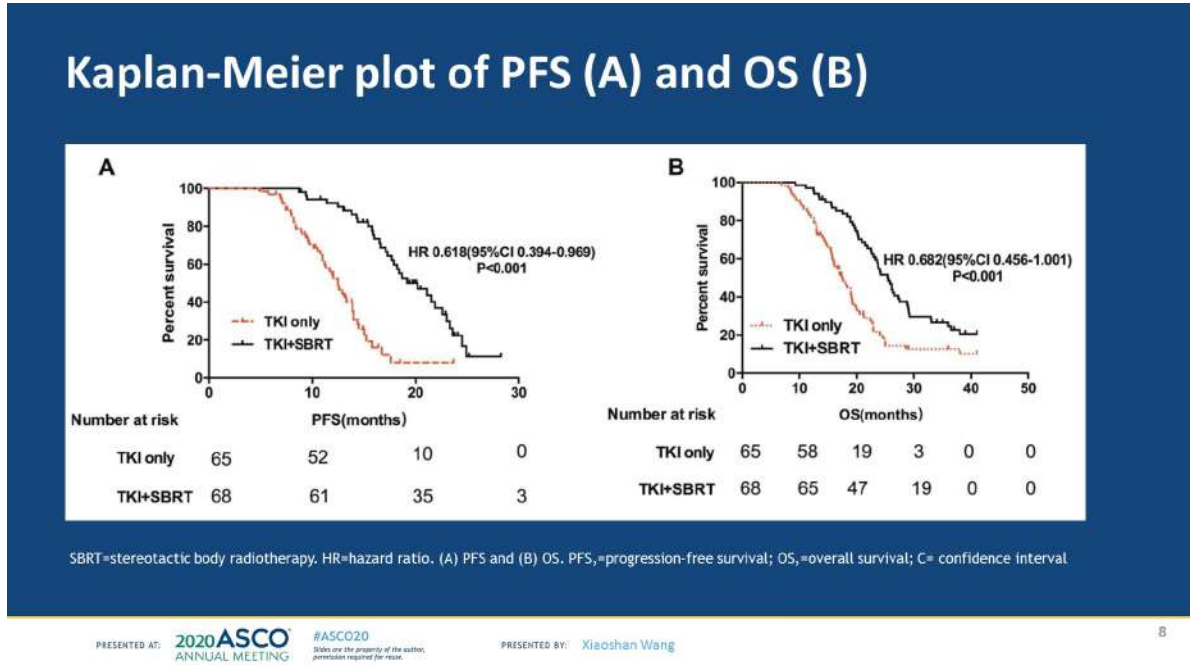
- This study was sponsored by Shanghai Allist Pharmaceutical Inc,. China. This study was also supported by China National Major Project for New Drug Innovation (2017ZX09304015, 2018ZX09301014009 and 2019ZX-09201-002) and CAMS Innovation Fund for Medical Sciences (CIFMS) (2016-I2M-1-001).
- We thank all the sites that contributed to recruitment, the investigators, patients and their families who participated in the study.

Shi Y. ASCO 2020

SINDAS

EGFR oligometastasico: Tki+/- SBRT

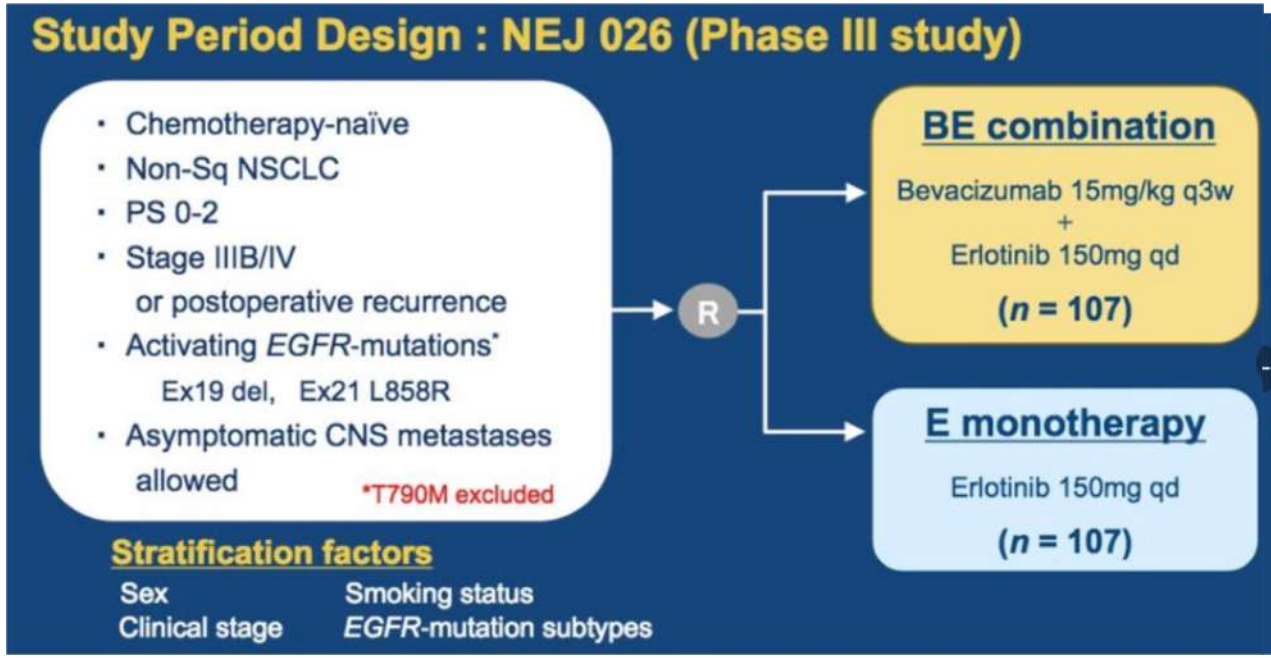


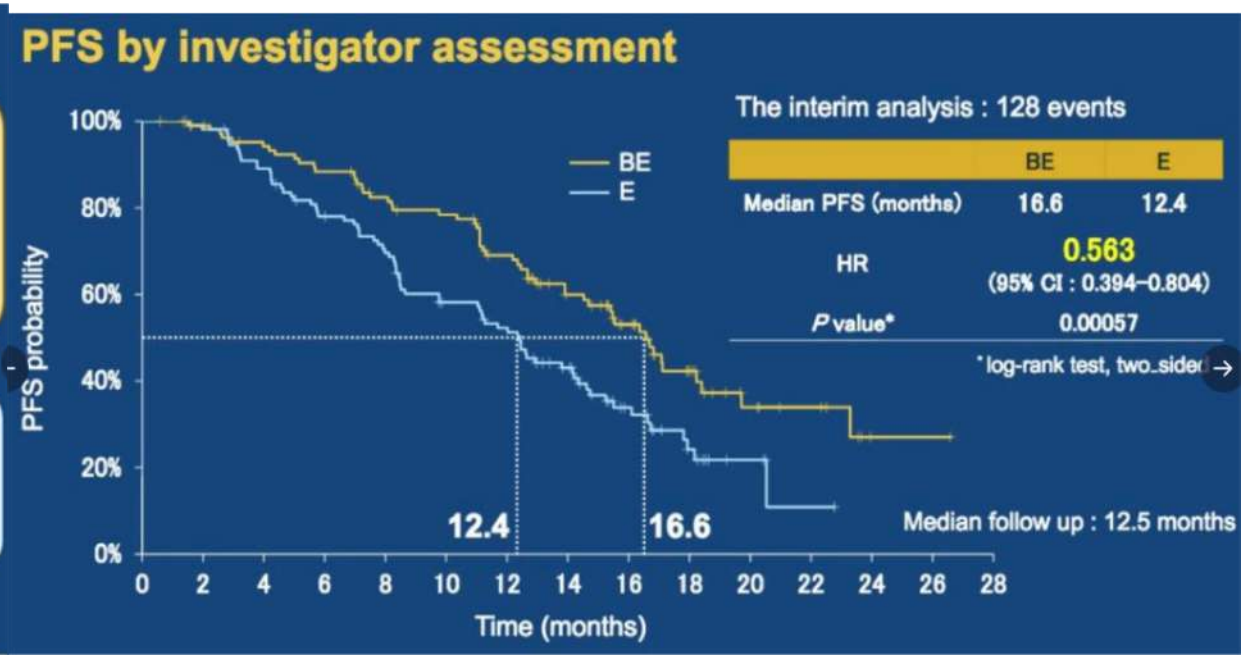


Xiaoshan Wang ASCO 2020

NEJ026

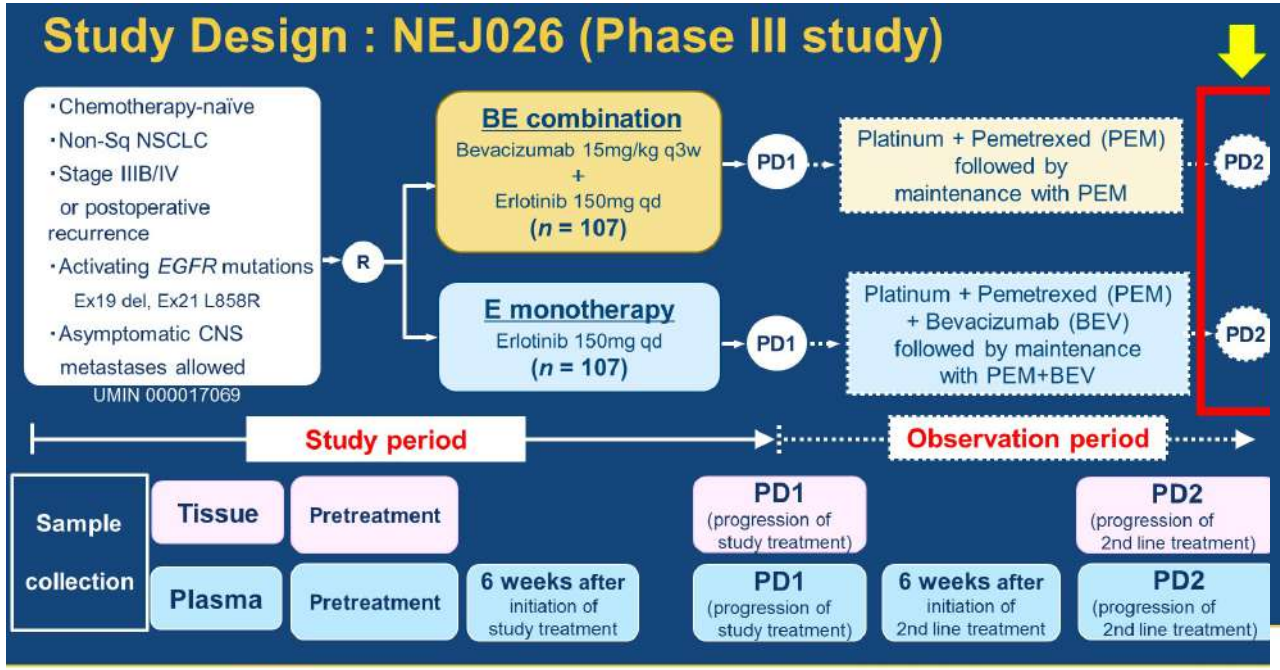
Erlotinib + Bevacizumab

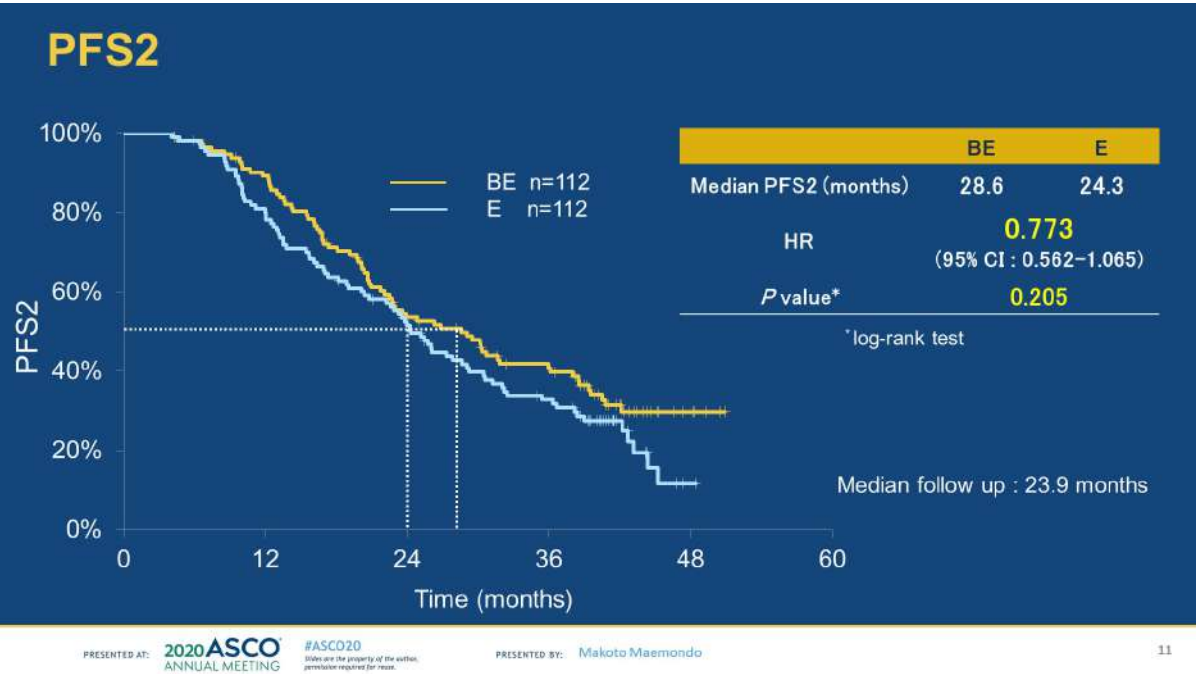


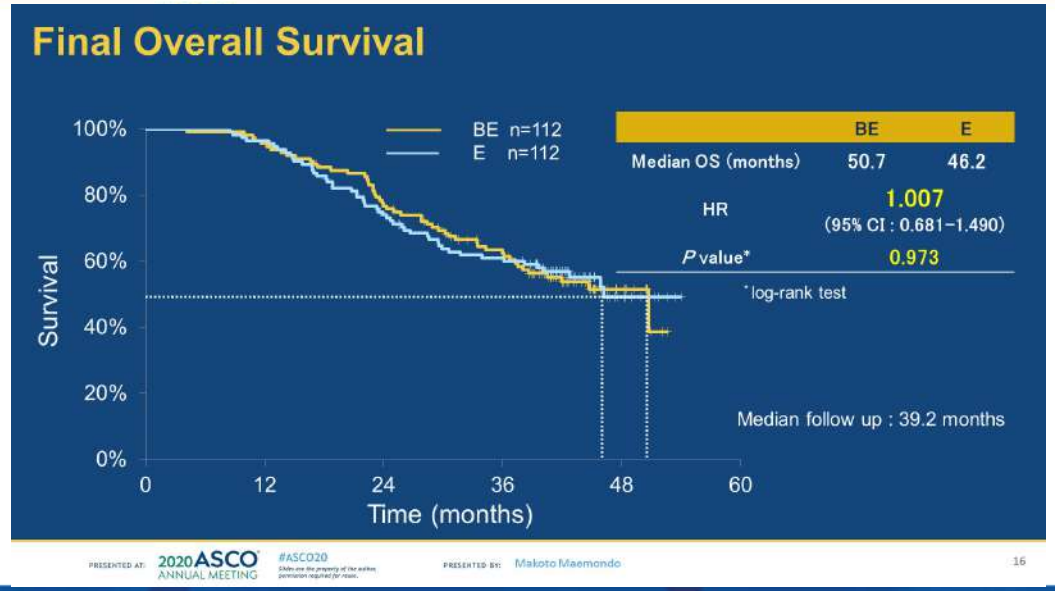


Furuya N ASCO 2018
Makoto Maemondo ASCO 2020

NEJ026







Makoto Maemondo ASCO 2020

WJOG9715L

Osimertinib + bevacizumab

Key Inclusion Criteria
- Advanced lung adeno carcinoma
- EGFR-TKI resistant
- Acquired EGFR T790M
- ECOG PS 0-1

Stratification factors
- Sex
- No. of prior chemotherapy
- Institution

Lead-in part (N = 6) → Osi 80 mg/day + Bv 15 mg/kg, q3w until PD

Phase II part (N = 81) → R 1 : 1
- Osi 80 mg/day + Bv 15 mg/kg, q3w until PD
- Osi 80 mg/day alone until PD

- Primary endpoint: PFS by investigator
- Secondary endpoints: overall response rate (ORR), time to treatment failure (TTF), overall survival (OS) and adverse events (Aes)

Characteristic		Osimertinib (n = 41)	Osimertinib + bevacizumab (n = 40)	*P* value
Age	Median (range)	70 (41-82)	68 (43-82)	0.57
Sex-no. (%)	Male	17 (41)	16 (40)	0.58
	Female	24 (59)	24 (60)	
Smoking status-no. (%)	Never	20 (49)	21 (53)	0.91
	Smoker or ex-smoker	21 (51)	19 (48)	
ECOG performance status-no. (%)	0	17 (42)	20 (50)	0.58
	1	24 (58)	20 (50)	
Clinical stage-no. (%)	IIIb	2 (5)	2 (5)	0.11
	IV	26 (63)	33 (83)	
	Recurrence	13 (32)	5 (12)	
Number of pior cytotoxic chemotherapy-no. (%)	0	34 (83)	30 (75)	0.54
	≥ 1	7 (17)	10 (25)	
Types of EGFR mutation-no. (%)	Exon 20 T790M	41 (100)	40 (100)	
	Exon 19del	28 (68)	22 (55)	(19 del vs. L858R) 0.32
	Exon 21 L858R	13 (32)	18 (45)	
Prior anti-VEGF inhibitor	Yes	4 (10)	8 (20)	0.22
	No	36 (88)	31 (78)	
	Unknown	1 (2)	1 (2)	
Brain metastasis	Yes	9 (22)	12 (30)	0.46
	No	32 (78)	28 (70)	
Sites of detecting EGFR exon 20 T790M no. (%)				1.00
	Peripheral blood	19 (46)	18 (45)	
	Others	22 (54)	22 (55)	

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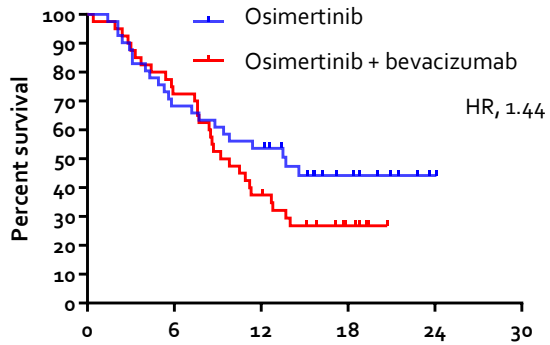
Kaplan-Meier curves of progression-free survival

Treatment arm	Event (no)	Median PFS (months)
Osimertinib	22 of 41	13.5
Osimertinib + bevacizumab	29 of 40	9.4

HR, 1.44 (95%CI, 1.00-2.08, p = 0.20)



No. at risk					
Osimertinib	41	29	23	9	2
Osimertinib+Bv	40	30	16	6	1

Toi Y ESMO 2020

Active

Apatinib + Gefitinib

- Locally advanced, metastatic or recurrent non-squamous NSCLC
- Chemo-naive
- EGFR mutation positive (exon 19 deletion or exon 21 L858R)
- ECOG PS 0-1

R 1:1

AG group (N=157): Apatinib 500mg q.d. + Gefitinib 250mg q.d.

G group (N=156): Placebo q.d. + Gefitinib 250mg q.d.

Until PD, unacceptable toxicity, study ends or withdrawal of patient's consent, whichever occurs first

Survival follow-up

- Stratified by
  - ✓ EGFR gene mutation (exon 19 del vs. exon 21 L858R)
  - ✓ Gender (female vs. male)
  - ✓ ECOG PS (0 vs. 1)
- Primary endpoint: PFS (Independent Radiology Review Committee, IRRC)
- Secondary endpoints:
  - ✓ PFS (investigator, INV), OS, ORR, DCR, DOR, TTPD, QoL and safety
- Exploratory endpoints:
  - ✓ to analyze baseline and post-progression samples for exploring efficacy predictors and acquired resistance

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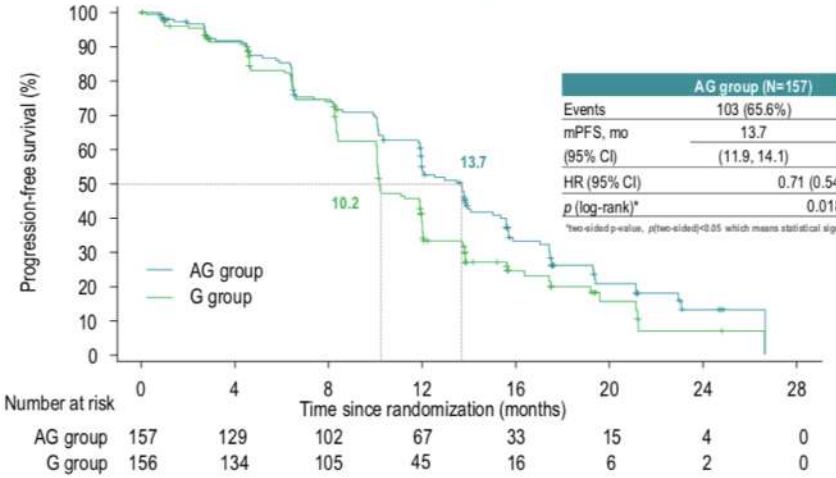
PRIMARY ENDPOINT: PFS BY IRRC (ITT POPULATION)



	AG group (N=157)	G group (N=156)
Events	103 (65.6%)	111 (71.2%)
mPFS, mo	13.7	10.2
(95% CI)	(11.9, 14.1)	(10.1, 11.9)
HR (95% CI)	0.71 (0.54, 0.95)	
p (log-rank)*	0.0189	

*two-sided p-value, p(two-sided)<0.05 which means statistical significance.

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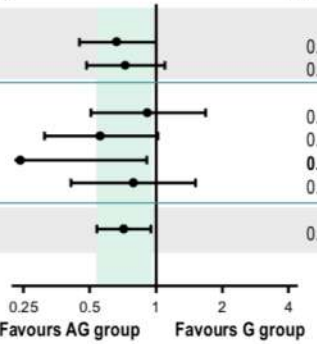
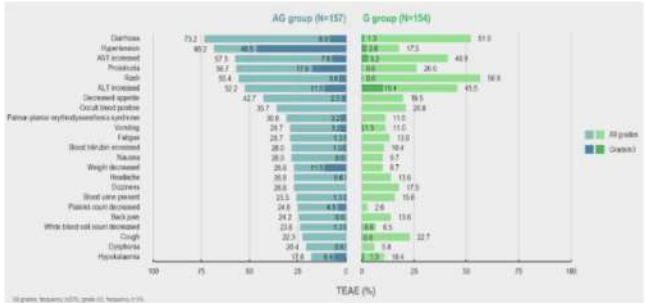
Subgroup analysis by baseline mutation status

	AG group Events/patients	G group Events/patients	Hazard ratio (95%CI)
EGFR mutation type			
Exon 19 deletion	52/81	57/83	0.67 (0.45, 0.99)
Exon 21 L858R	49/74	54/73	0.72 (0.48, 1.09)
TP53 mutation			
No	25/43	20/32	0.92 (0.50, 1.67)
Yes	23/30	31/40	0.56 (0.31, 1.01)
Exon 8	5/7	9/11	**0.24 (0.06, 0.91)**
Non-exon 8	18/23	22/29	0.79 (0.41, 1.52)
Overall	103/157	111/156	0.71 (0.54, 0.95)





Zhang L ESMO 2020

CHRYSALIS

Amivantamab + lazertinib

Key Objectives
- Establish RP2CD
- Safety and efficacy at RP2CD

Key Eligibility Criteria
- Metastatic/unresectable NSCLC
- Measurable disease (expansion cohort)
- EGFR Exon19del or L858R mutation

Dose Escalation (n=26)

1050/1400 mg amivantamab + 240 mg lazertinib

700/1050 mg amivantamab + 240 mg lazertinib

RP2CD

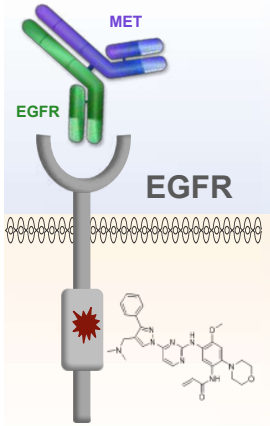
Amivantamab
1050 mg (<80 kg)
1400 mg (≥80 kg)
Intravenous dosing
C1 QW, C2+ Q2W
+
240 mg lazertinib
Oral daily dosing

Expansion Cohorts

Osimertinib-resistant, Chemo-naïve
EGFR Exon19del or L858R (n=45)

Treatment-naïve[a]
EGFR Exon19del or L858R (n=20)

- Combination dose is at the recommended monotherapy doses of each molecule
- Proactive rash management included topical antibiotics to sun-exposed skin



Amivantamab
(am-e-van-tuh-mab)

- Fully human bispecific (Duobody®) antibody that targets EGFR and MET
- Has immune cell-directing activity[1]
- Demonstrated clinical activity across diverse EGFRm NSCLC[2]
- Granted FDA Breakthrough Therapy Designation for EGFRm Exon20ins NSCLC post-chemotherapy

Lazertinib

- Potent 3rd-gen TKI with efficacy seen in activating EGFR mutations, T790M, and CNS disease[3-4]
- Low rates of EGFR-related toxicity such as rash and diarrhea[3]
- Safety profile that supports combination with other anti-EGFR molecules

Post osimertinib

- **ORR: 36% (95% CI, 22 – 51)**
  - 1 CR
  - 15 PR (1 pending confirmation)
- **CBR: 60% (95% CI, 44 – 74)**

1º línea

- **ORR: 100% (95% CI, 83 – 100)**
  - 20 PR
- **CBR: 100% (95% CI, 83 – 100)**
- **mDOR: not estimable**

Phase 3 MARIPOSA Study (NCT04487080)

28-day Cycles

Key Eligibility Criteria
- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- EGFR Exon19del or L858R mutation

Stratification
- EGFR mutation (Exon19del/L858R)
- Asian race (yes/no)
- Brain metastases (yes/no)

Randomization (2:2:1; N~1000)

Arm A (n~400)	**Amivantamab** 1050/1400 mg **Lazertinib** 240 mg QD
Arm B (n~400)	**Osimertinib** 80 mg QD
Arm C (n~200)	**Lazertinib** 240 mg QD

Primary Endpoint: (Arm A vs Arm B)
- PFS by BICR

Secondary Endpoint: (Arm A vs Arm B)
- Overall survival
- Objective response rate
- Duration of response
- PFS2
- Time to symptomatic progression
- Intracranial PFS
- Safety

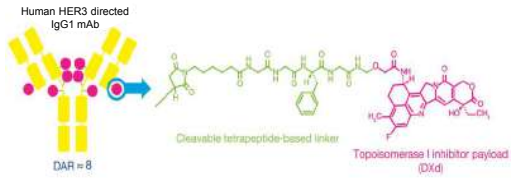
Cho BC ESMO 2020

Patritumab deruxtecan

HER3 is expressed in most lung cancers, (~80% of *EGFR*-mutated NSCLC), overexpression is associated with worsened clinical outcomes[1]

Patritumab Deruxtecan (U3-1402)

A novel HER3 directed antibody drug conjugate composed of the monoclonal antibody patritumab, a tetrapeptide-based linker, and a topoisomerase I inhibitor payload



Dose Escalation[a]

*Metastatic/unresectable **EGFR-mutated NSCLC** either after progression on osimertinib or T790M-negative after progression on erlotinib, gefitinib, or afatinib*

Patritumab deruxtecan 5.6 mg/kg Q3W
n = 12

Dose Expansion Cohort 1[b]

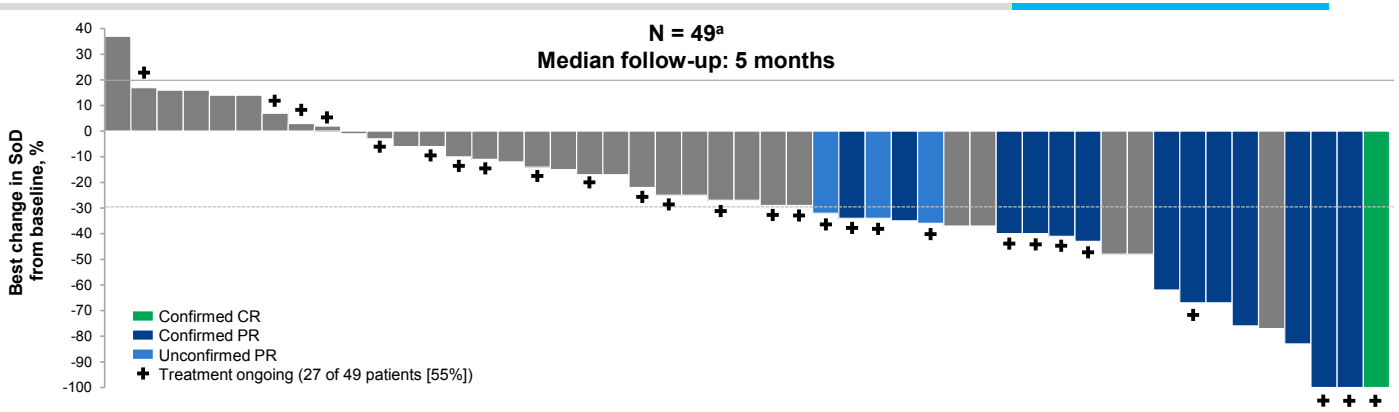
Metastatic/unresectable ***EGFR*-mutated NSCLC** and treatment with ≥ 1 EGFR TKI and ≥ 1 prior platinum-based chemotherapy regimen

Patritumab deruxtecan 5.6 mg/kg Q3W
n = 45

Primary Objective: Antitumor activity of patritumab deruxtecan

Secondary Objectives: Safety and tolerability of patritumab deruxtecan

Activity according to BICR evaluation (efficacy-evaluable population) N = 56[a]	
Confirmed BOR, n/N (%)	
CR	1/56 (2%)
PR	13/56 (23%)
SD	25/56 (45%)
PD	9/56 (16%)
NE	8/56 (14%)
Confirmed ORR, % (n/N; 95% CI)	25% (14/56; 14.4-38.4)
DCR, % (n/N; 95% CI)	70% (39/56; 55.9-81.2)
Median TTR, months (range)	2.0 (1.2-2.8)
Median DoR, months (range)	6.9 (3.0-7.0)



Yu HA ESMO 2020

Osimertinib + gefitinib

Study Schema

Phase I/II study, EGFR-mutated stage IV NSCLC without prior treatment

	DOSE ESCALATION	DOSE EXPANSION
Cohort A Concurrent Dosing	**DL1** Gefitinib 250 mg + Osimertinib 40 mg PO daily* (n = 3) **DL2** Gefitinib 250 mg + Osimertinib 80 mg PO daily (n = 3)	Gefitinib 250 mg + Osimertinib 80 mg PO daily (n = 24)
Cohort B Alternating Dosing	Gefitinib 250 mg, Osimertinib 80 mg PO daily Alternating monthly (n = 3)	Gefitinib 250 mg, Osimertinib 80 mg PO daily Alternating monthly (n = 3)

Cohort B enrollment terminated July 2018 following FDA approval of first-line osimertinib, excluded from present analysis

*Intrapatient dose escalation to osimertinib 80 mg po daily following study amendment

Primary Endpoints
- Dose Escalation: MTD
- Dose Expansion: Feasibility, defined as receipt of combination therapy for ≥ 6 28-day cycles

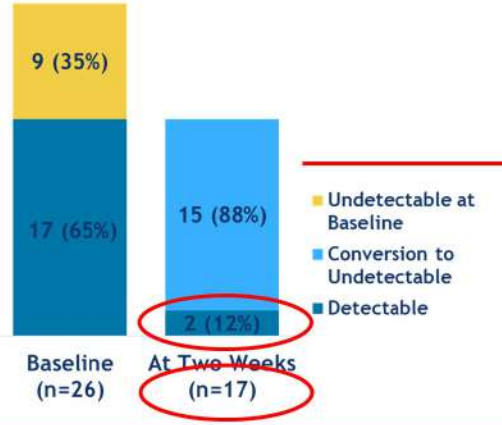
Secondary Endpoints
- Rate of G3-5 TRAEs
- ORR per RECIST 1.1
- Progression free survival
- Overall survival
- cfDNA clearance
- Genomic alterations at progression

NCT03122717

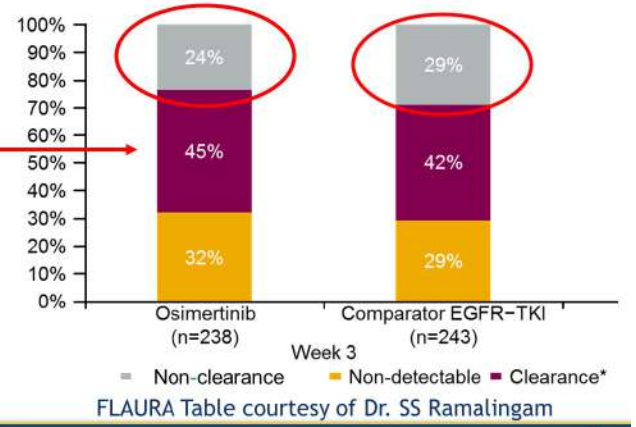
PRESENTED AT: 2020ASCO ANNUAL MEETING #ASCO20 PRESENTED BY: Julia Rotow, MD 4

Rapid plasma clearance of EGFR mutations

Osimertinib + Gefitinib
Rotow, ASCO 2020 #9507



FLAURA*
Zhou, ASCO 2019 #9020



FLAURA Table courtesy of Dr. SS Ramalingam

PRESENTED AT: 2020ASCO ANNUAL MEETING #ASCO20 PRESENTED BY: Rachel E. Sanborn, M.D. 14

Julia Rotow ASCO 2020
Sanbom RE ASCO2020

ALK

ASCO

- Alex
- ALTA 1: correlación molecular

IASLC Symposium

- eXalt3

ESMO

- Crown

Alectinib: Alex

Figure 1. OS in the ITT population

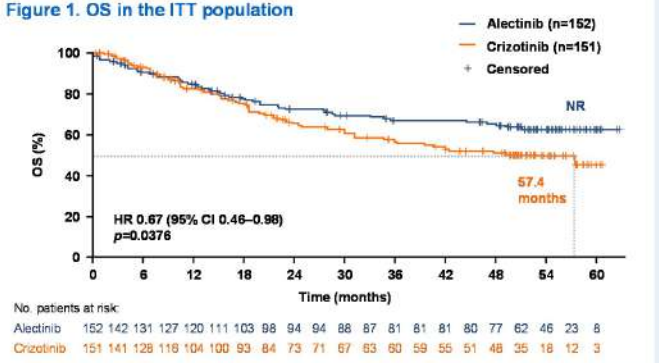
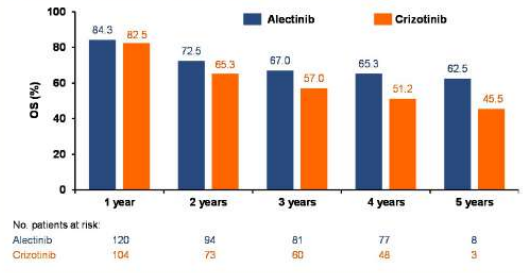


Figure 2. OS event-free rate in the ITT population



Peters S ASCO 2020

Brigatinib: perfil molecular

ALK Mutations

Table 1. *ALK* Fusions Detected in Plasma

	Brigatinib n=124	Crizotinib n=127
ALK fusion detected at screen, n (%)	68 (54.8)	71 (55.5)
EML4-ALK fusion detected at screen, n (%)	57 (46.0)	64 (50.4)
EML4-ALK variant detected		
V1	25 (43.9)	30 (46.9)
V2	6 (10.5)	5 (7.8)
V3	23 (40.4)	21 (32.8)
V5	1 (1.8)	0
V5'	2 (3.5)	7 (10.9)
EML4-ALK variant undetermined	0	1 (1.6)

Table 2. Efficacy in Patients With Known *EML4-ALK* Fusions by Variant at Baseline

EML4-ALK variant	Brigatinib	Crizotinib	*P* value, log rank
V1, n	25	30	
ORR, %	84.0 (63.9–95.5[a])	73.3 (54.1–87.7[a])	
mPFS, mo	NR (18.0–NR[a])	13.0 (7.4–24.0[a])	0.0143
V2, n	6	5	
ORR, %	83.3 (35.9–99.6[a])	60.0 (14.7–94.7[a])	
mPFS, mo	16.0 (6.3–NR[a])	11.0 (7.4–NR[a])	0.661
V3, n	23	21	
ORR, %	82.6 (61.2–95.0[a])	66.7 (43.0–85.4[a])	
mPFS, mo	16.0 (7.6–NR[a])	7.4 (3.7–12.0[a])	0.0019

[a]95% CI

Camidge DR ASCO 2020

eXalt3

Ensaritinib

- Stage IIIB/IV NSCLC
- ALK+ by local FDA-approved assays or central confimration by FISH by Abbott
- ECOG PS 0-2
- No prior ALK inhibitor
- ≤ 1 Prior chemotherapy regimen

NCT02767804

→ Randomized 1:1

→ Ensartinib 225 mg QD

→ Crizotinib 250 mg BID

Stratified by:
- Prior chemotherapy
- ECOG PS
- Asia Pacific vs ROW
- Brain metastases at BL

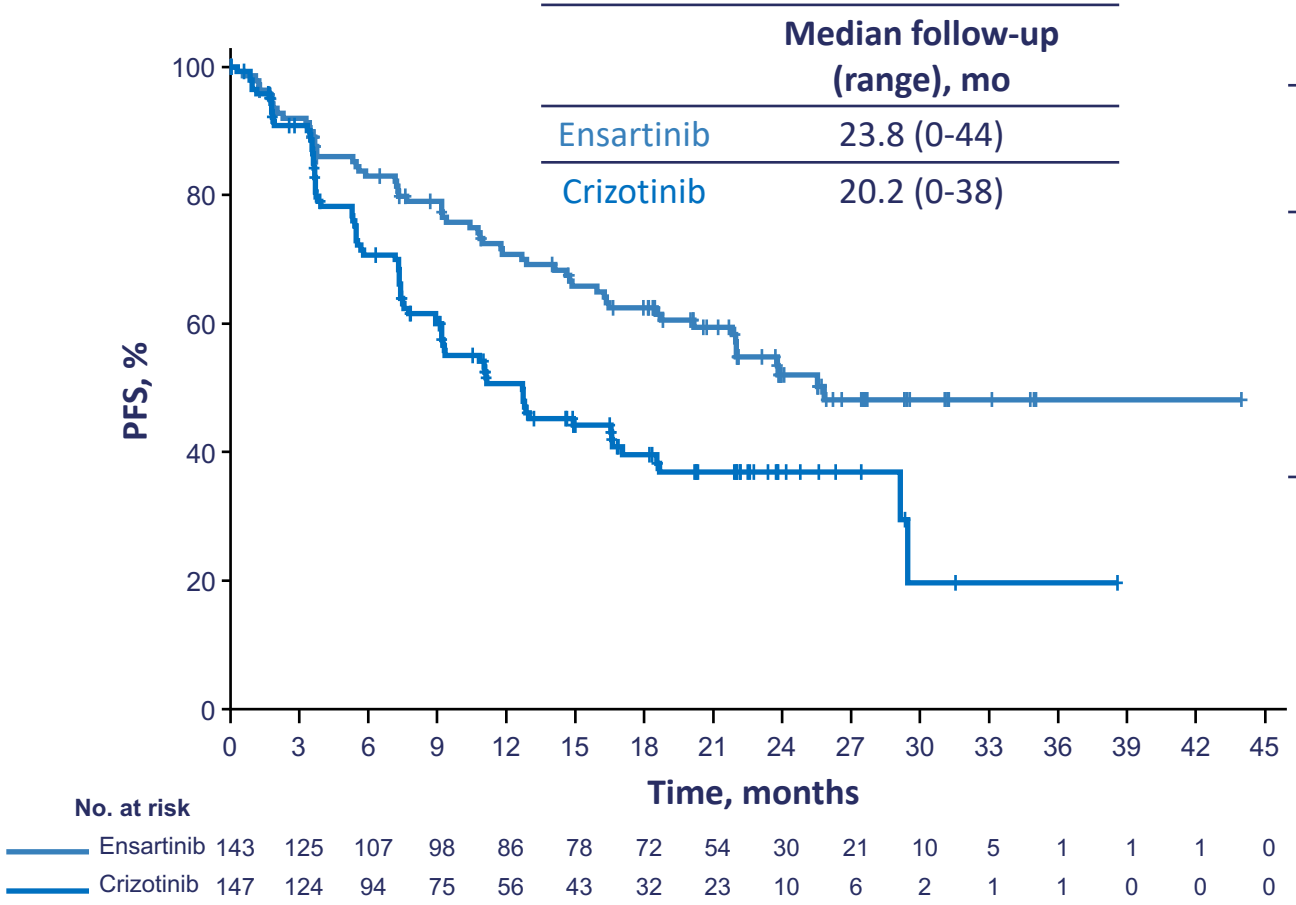
- No crossover allowed
- Trial fully accrued as of Nov 2018

Objetivo principal: PFS (BIRC) en la población por ITT

Horn, WCLC, 2020

eXalt3

Objetivo principal: PFS (BIRC) en la población por ITT



	Ensartinib (n = 143)	Crizotinib (n = 147)
mPFS (95% CI), mo	**25.8** (21.8-NR)	**12.7** (9.2-6.6)
Hazard ratio (95% CI)	**0.51** (0.35-0.72)	
P value (log-rank test)	**.0001**	

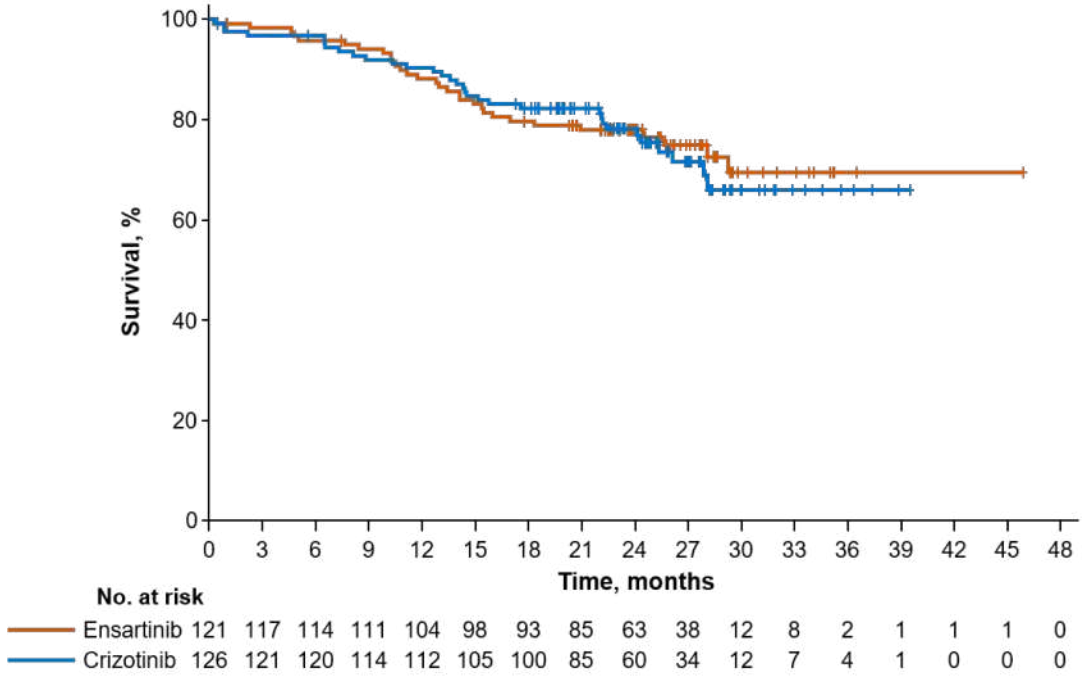
Horn, WCLC, 2020

BIRC-assessed confirmed systemic ORR: ensartinib = 75%; crizotinib = 67%

CR rates: ensartinib = 14%; crizotinib = 6%

eXalt3

Supervivencia global



	Ensartinib (n = 121)	Crizotinib (n = 126)
Median OS (95% CI), mo	NR (NR-NR)	NR (NR-NR)
Hazard ratio (95% CI)	**0.88** (0.52-1.50)	
P value (log-rank test)	**.6470**	
24-mo OS (95% CI), %	78 (69-84)	78 (69-84)

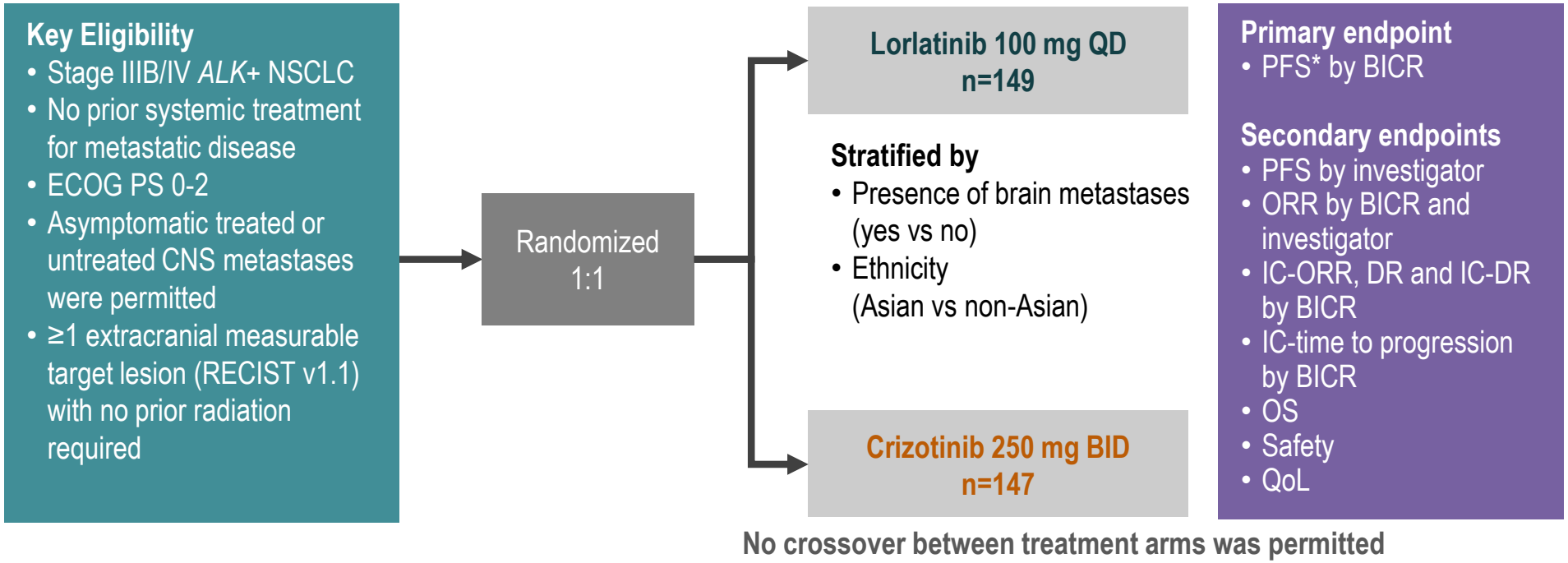
Horn, WCLC, 2020

Crown

Lorlatinib

VIRTUAL 2020 ESMO congress

CROWN Study Design



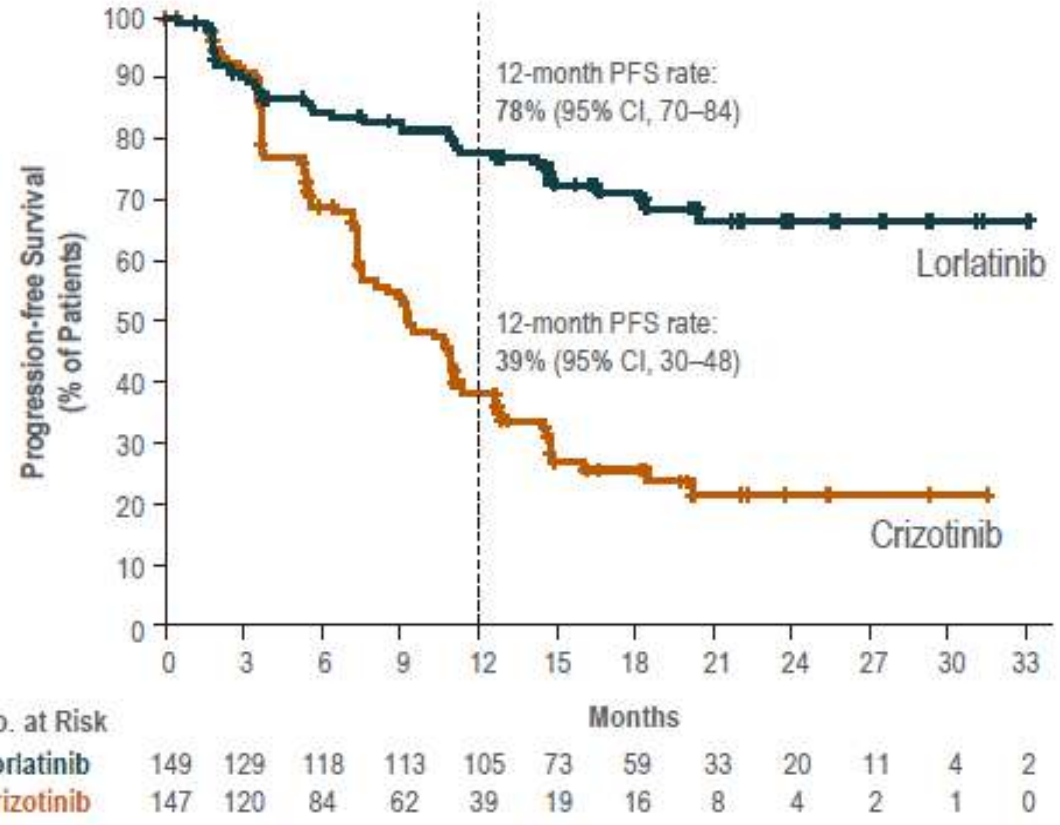
No crossover between treatment arms was permitted

Solomon, ESMO, 2020

CROWN

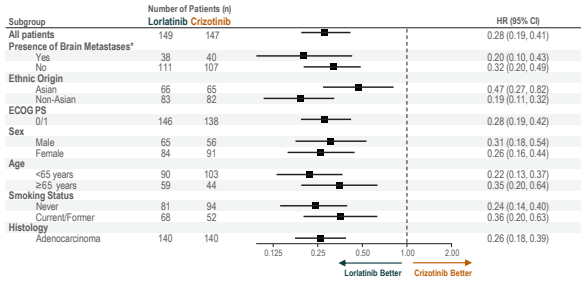
Primary endpoint
- PFS* by BICR

Median duration of follow up for PFS was 18.3 months and 14.8 months,



	Lorlatinib (n=149)	Crizotinib (n=147)
Patients with event, n (%)	41 (28)	86 (59)
Median PFS, months (95% CI)	NE (NE–NE)	9.3 (7.6-11.1)
HR (95% CI) 1-sided P value*	0.28 (0.19-0.41) <0.001	

*By stratified log-rank test.



	Lorlatinib (n=149)	Crizotinib (n=147)
CR, n (%)	4 (3)	0 (0)
PR, n (%)	109 (73)	85 (58)

Solomon, ESMO, 2020

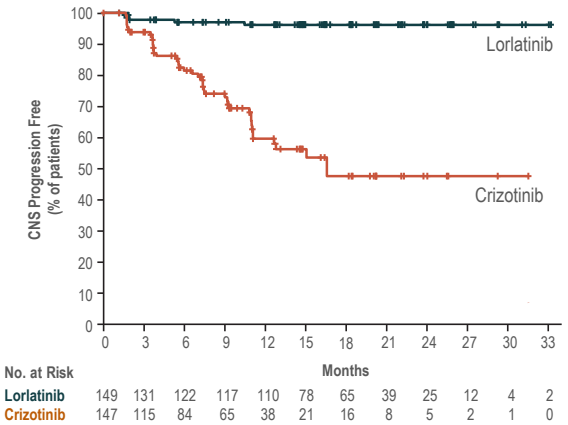
Crown

lorlatinib

Intracranial-OR by BICR

	Patients with measurable or non-measurable brain metastases at baseline		Patients with measurable brain metastases at baseline	
	Lorlatinib (n=38)	Crizotinib (n=40)	Lorlatinib (n=17)	Crizotinib (n=13)
IC-responders, n (%)	25 (66)	8 (20)	14 (82)	3 (23)
(95% CI)	(49-80)	(9-36)	(57-96)	(5-54)
Odds ratio (95% CI)	8.41 (2.59-27.23)		16.83 (1.95-163.23)	
IC-CR, n (%)	23 (61)	6 (15)	12 (71)	1 (8)
Median DR, months (95% CI)	NE (NE–NE)	9.4 (6.0-11.1)	NE (NE–NE)	10.2 (9.4-11.1)

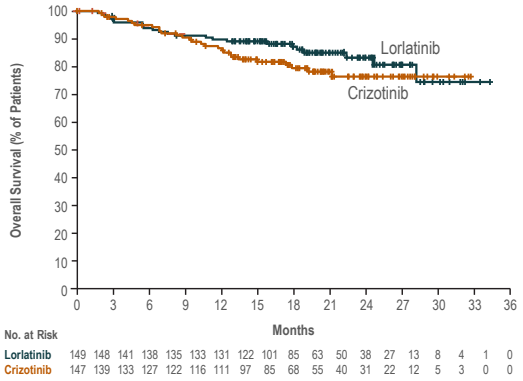
Intracranial Time to Progression by BICR



	Lorlatinib (n=149)	Crizotinib (n=147)
Patients with event, n (%)	5 (3)	45 (31)
Median time to CNS progression, months (95% CI)	NE (NE–NE)	16.6 (11.1-NE)
HR (95% CI) 1-sided P value*	0.07 (0.03-0.17) <0.001	

*By stratified log-rank test.

Overall Survival



	Lorlatinib (n=149)	Crizotinib (n=147)
Patients with event, n (%)	23 (15)	28 (19)
Median OS, months (95% CI)	NE (NE–NE)	NE (NE–NE)
HR (95% CI)	0.72 (0.41-1.25)	

Solomon, ESMO, 2020

Crizotinib frente a inhibidores de ALK de 2º y 3º generación

La distribución de pacientes asiáticos, no fumadores y pacientes con PS 0-1 fue similar en los 4 ensayos. Datos de eficacia.

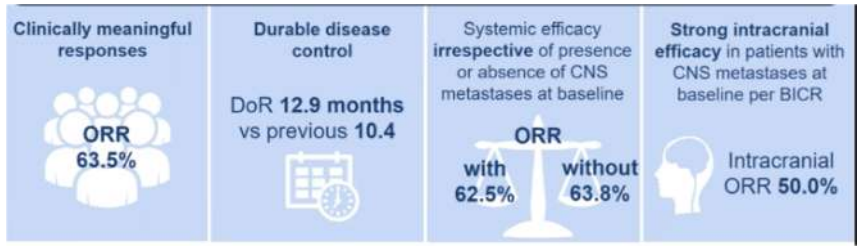
Drug	Trial	N	Previous QT	CNS met baseline	Brain RT	ALK Assessment	Crossover
Lorlatinib (100mg/d)	CROWN	296	NO	Lorlatinib: 26% Crizotinib: 27%	Lorlatinib: 6% Crizotinib: 7%		NO
Alectinib (600mg x 2)	ALEX	303	NO	Alectinib: 38% Crizotinib: 42%	Alectinib: 14% Crizotinib: 17%	Central IHQ (D5F3)	NO
Brigatinib (90 mg x1 7d, 180 mg x 1)	ALTA-1L	275	Brigatinib: 26% Crizotinib: 27%	Brigatinib: 29% Crizotinib: 30%	Brigatinib: 13% Crizotinib: 14%	Local (approved assays)	YES
Ensartinib (225 mg x 1)	eXalt-3	290	Ensartinib: 24% Crizotinib: 29%	Ensartinib: 33% Crizotinib: 39%	Ensartinib: 5% Crizotinib: 5%	Local (approved assays) Or Central (FISH Abbot)	NO

Drug	Trial	N	ORR %	CNS RR %	PFS BIRC Months (95%CI)	PFS INV Months (95%CI)
Lorlatinib (100mg/d)	CROWN	296	Lorlatinib: 76% Crizotinib: 58%	Lorlatinib: 82% Crizotinib: 23%	Lorlatinib: NE (NE-NE) Crizotinib: 9.3m (7.6-11.1) **HR: 0.28 (0.19-0.41)**	Lorlatinib: NE (NE-NE) Crizotinib: 9.1m (7.4-10.9) HR: 0.21 (0.14-0.31)
Alectinib (600mg x 2)	ALEX	303	Alectinib: 82.9% Crizotinib: 75.5%	Alectinib: 81% Crizotinib: 50%	Alectinib: 25.7m (19.9-NE) Crizotinib: 10.4m (7.7-14.6) HR: 0.50 (0.36-0.70)	Alectinib: 34.8m (17.7- NE) Crizotinib: 10.9m (9.1-12.9) **HR: 0.43 (0.32-0.58)**
Brigatinib (90 mg x1 7d, 180 mg x 1)	ALTA-1L	275	Brigatinib: 74% Crizotinib: 62%	Brigatinib: 78% Crizotinib: 26%	Brigatinib: 24m (18.5-NE) Crizotinib: 11 m (9.2-12.9) **HR: 0.49 (0.35-0.68)**	Brigatinib: 29.4 (21.2-NE) Crizotinib: 9.2 (7.4-12.9) HR: 0.43 (0.31-0.61)
Ensartinib (225 mg x 1)	eXalt-3	290	Ensartinib: 75% Crizotinib: 67%	Ensartinib: 64% Crizotinib: 21%	Ensartinib: 25.8m (21.8-NE) Crizotinib: 12.7m (9.2-6.6) **HR: 0.51(0.35-0.72)**	NA

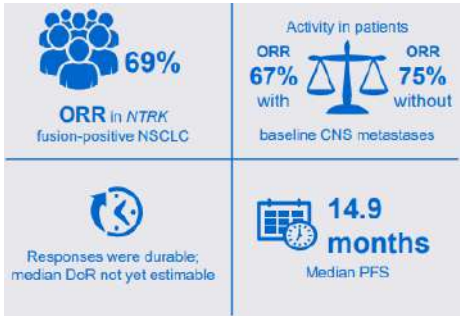
Solomon, ESMO, 2020
Peters, N Engl J Med, 2017
Camidge, N Engl J Med, 2018
Horn, WCLC, 2020

NTRK

Entrectinib



Rolfo C ASCO 2020

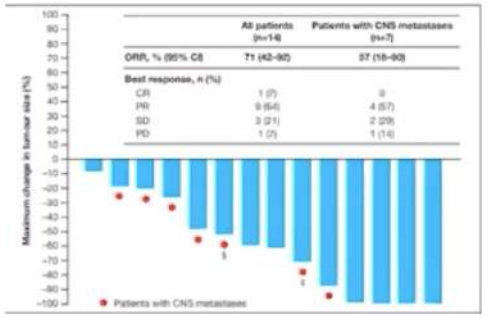


Drilon A Esmo 2020

Larotrectinib

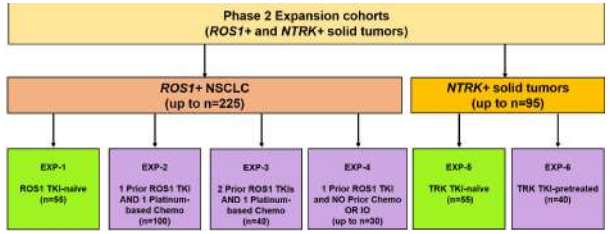
	All patients (n=116)	Patients with brain metastases (n=14)
ORR, % (95% CI)	71 (62–79)	71 (42–92)
Best response, n (%)		
CR	12 (10)	0
PR	70 (60)[1]	10 (71)
SD	19 (16)	2 (14)
PD	11 (9)	2 (14)
Not determined	4 (3)	0

Drilon A. ASCO 2020



Drilon A ESMO 2020

Repotrectinib



Doebetle RC ASCO 2020

ROS1

Lorlatinib

Baldacci S
ASCO 2020

Table 3: Overall response to lorlatinib.

	ALK+ (n=143)	ROS1+ (n=57)
Best overall response		
Number of patients with available data	130 (90.9%)	51 (89.5%)
Complete response	10 (7.7%)	0 (0.0%)
Partial response	50 (38.5%)	24 (47.1%)
Stable disease	52 (40.0%)	21 (41.2%)
Progressive disease	16 (12.3%)	5 (9.8%)
Objective response rate	*60 (46.2%)*	*24 (47.1%)*
Disease control rate	*112 (86.2%)*	*45 (88.2%)*
Not evaluable	2 (1.5%)	1 (2%)
Central nervous system objective response rate (available data; %)*	*55 (/132; 41.7%)*	*20 (/53; 37.7%)*
Median duration of response (range, months)	*8.3 (0-29.3)*	*5.7 (0-34.5)*
Median follow up (IC95%, months)	15.6 (14.0-17.9)	14.5 (13.5-25.1)
Median lorlatinib duration (range, months)	7.4 (0.2-41.2)	7.3 (0.85-34.7)
Median lorlatinib duration beyond progression (range, months)	1.7 (0.1-22.1)	1.15 (0.03-25.3)

* Defined as the rate of intracrancial tumor response according RECIST v1.1

Figure 2: PFS for the ROS1+ cohort.

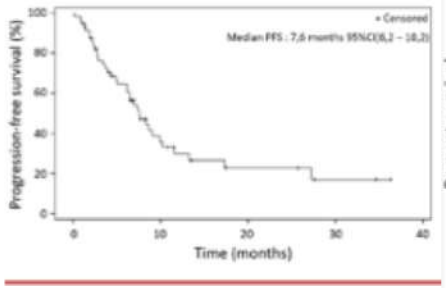
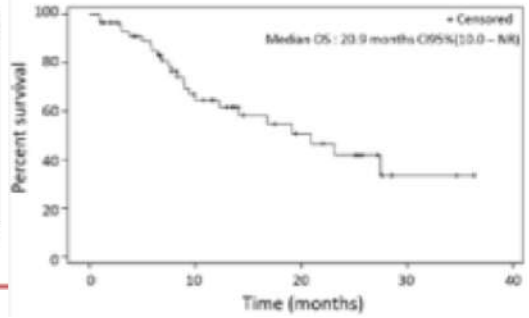


Figure 4: OS from lorlatinib initiation for the ROS1+ cohort.



Baldacci S
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Table 3: Overall response to lorlatinib

	ROS1+ (n=71)
Best overall response	
Number of patients with available data	66 (92.9%)
Complete response	0 (0.0%)
Partial response	30 (45.5%)
Stable disease	26 (39.4%)
Progressive disease	8 (12.1%)
Objective response	*30 (45.5%)*
Disease control	*56 (84.8%)*
Not evaluable	2 (3%)
Central nervous system objective response rate (available data; %)*	*28 (/57; 41.8%)*
Median duration of response (range, months)	*6.1 (0-34.5)*
Median follow up (IC95%, months)	14.8 (12.5-25.7)
Median lorlatinib duration (range, months)	7.4 (3.49-34.7)
Median lorlatinib duration beyond progression (range, months)	0.7 (3.03-25.3)

* Defined as the rate of intracrancial tumor response according RECIST v1.1

Figure 1: Progression-free survival

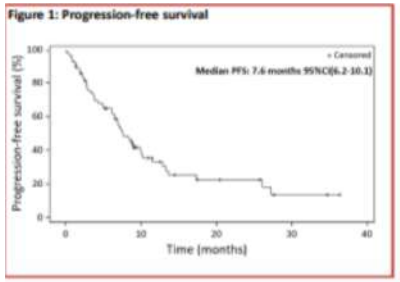
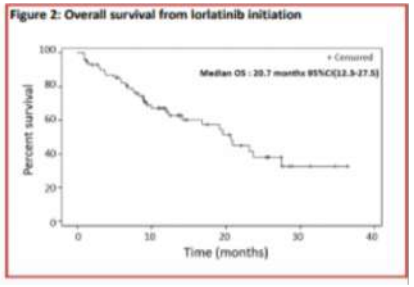


Figure 2: Overall survival from lorlatinib initiation



Entrectinib

Krebs MG ESMO 2020
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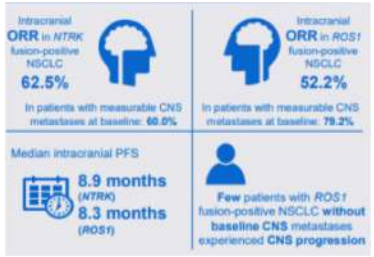
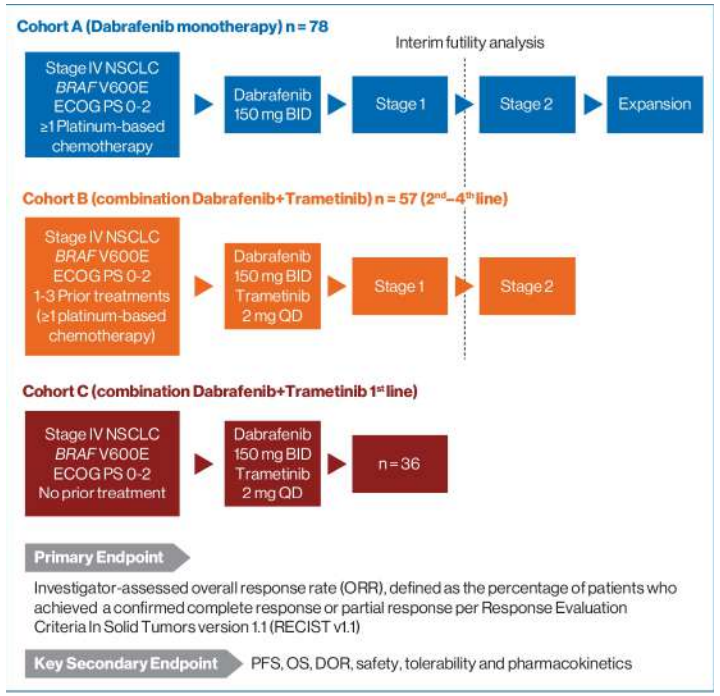
Liu S ESMO 2020

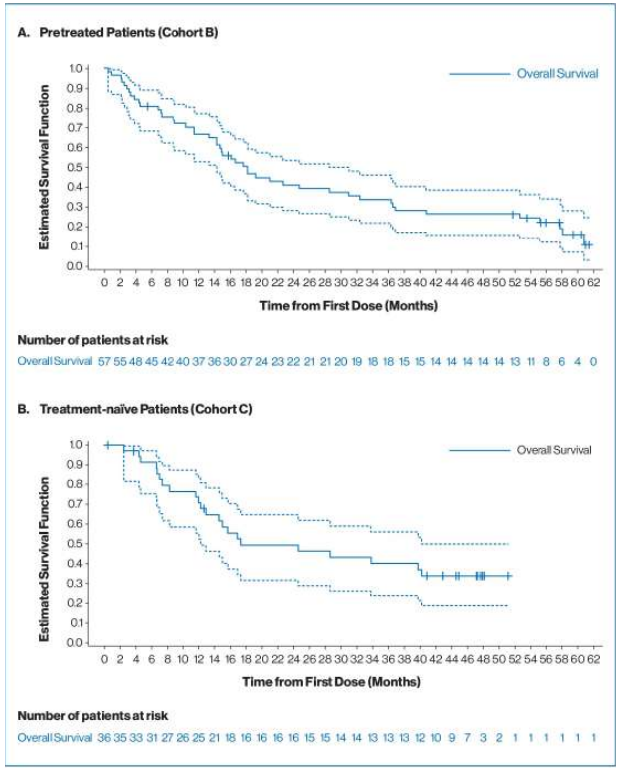


	Prior LOT: 0*	Prior LOT: 1	Prior LOT: 2	Prior LOT: ≥3
	NTRK+ solid tumours†			
ORR, % (n/N)	80.0 (16/20)	61.9 (13/21)	65.0 (13/20)	38.5 (5/13)
95% CI	56.3–94.3	38.4–81.9	40.8–84.6	13.9–68.4
Median DoR, months (responders n/N)	NE (16/20)	15.1 (13/21)	11.1 (13/20)	9.4 (5/13)
95% CI	5.6–NE	10.4–15.1	7.9–15.0	2.8–NE
	ROS1+ NSCLC‡			
ORR, % (n/N)	71.7 (43/60)	60.9 (39/64)	66.7 (12/18)	73.7 (14/19)
95% CI	58.6–82.6	47.9–72.9	41.0–86.7	48.8–90.9
Median DoR, months (responders n/N)	16.5 (43/60)	14.8 (39/64)	28.6 (12/18)	15.7 (14/19)
95% CI	11.0–NE	9.2–NE	24.6–28.6	9.1–20.5

BRAF

Dabrafenib trametimib





Pretratados

18.2 m

1º línea

17.3 m

- Fifty seven of 62 tumor samples retrieved from 93 patients were centrally confirmed to have *BRAF* V600E mutation; 5 non-confirmed BRAF tumors (3 patients had PR) were positive for *c-MET T1010I, KRAS G12V, ALK* fusion and 2 *JAK3* S493C with median PFS of 13.8 months while OS was not estimable due to limited data points
- Eleven (22%) of 50 NSCLC patients analyzed for additional genomic alterations had concomitant somatic mutations and/or genetic alterations in addition to *BRAF* V600E mutation (**Table 4**)
- Log Rank test and Cox proportional hazards regression were used to test the significance
- NSCLC patients whose tumors had concomitant genetic alterations in the PI3K pathway showed a trend toward decreased OS
  - Median OS for patients with co-activated MAPK and PI3K pathways and single *BRAF* V600E mutation was 5.4 and 22.7 months, respectively ($P = 0.0660$ by the log-rank test)
- Landscape of baseline DNA alterations for *BRAF* V600E NSCLC patients with available data where patients are ranked according to OS is shown in **Figure 3**

Table 4. Genomic Alterations Detected by NGS in Archival Biopsies of Metastatic *BRAF* V600E–mutant NSCLC Patients and their Association with Clinical Outcome

Cohort	Genetic alterations	Cohort	Best response	PFS, months	OS, months
D + T (Cohort B) (ORR, 68.4%; mPFS, 10.2 months; mOS, 18.2 months)	*BRAF* V600E + *IDH1* R132C	B	CR	6.9	40.7
	BRAF V600E + *KRAS* G13C	B	PR	58.1	58.1
	BRAF V600E + *IDH1* R132L*§	B	PR	32.4	32.4
	BRAF V600E + *PIK3CA* E542K	B	PR	16.7	55.2
	BRAF V600E + *cMET* ex 14 skipping	B	PR	10.2	18.2
	BRAF V600E + *PIK3CA* E545K	B	NE	1.4**	3.8
	BRAF V600E + *PIK3CA* E545K	B	PD	1.4	3.1
	cMET T1010I^	B	PR	27.6	59.4
	JAK3 S493C^	B	PR	5.6	10.3
	KRAS G12V^	B	PD	2.9	4.4
D + T (Cohort C) (ORR, 63.9%; mPFS, 10.8 months; mOS, 17.3 months)	*BRAF* V600E + *mTOR* T1977K	C	PR	7.0	7.0
	BRAF V600E + *IDH1* R132C	C	PR	10.4	17.3
	BRAF V600E + *IDH1* R132L	C	PR	5.5	8.2
	BRAF V600E + *BRAF* G466V	C	SD	19.4	40.2
	ALK fusion^	C	SD	13.8	40.9‡
	JAK3 S493C^	C	PR	19.3	51.2‡

CR, complete response; D, Dabrafenib; mOS, median overall survival; mPFS, median progression-free survival; NE, not evaluable; NGS, next-generation sequencing; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; T, Trametinib. *Patient reported no history of former or current smoking at baseline (never smoker). ^These patients are reported as BRAFV600E wild type after central lab testing. ‡Censored, follow-up ongoing. **Censored due to follow up ended. §A *CTNNB1* S33C mutation was also detected in this patient.

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Muchas gracias y feliz navidad