Tratamientos dirigidos II

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Iniciativa científica de:

GECP

Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

Update of crizotinib activity in METex14 skipping mutations (phase 1)

PROFILE 1001 Study Design

- Multicenter phase 1 trial (NCT00585195) – *MET* exon 14-altered NSCLC subgroup
- Key Objective: investigate the safety and antitumor activity of crizotinib in *MET* exon 14-altered NSCLC

Eligibility	Advanced NSCLC *MET* exon 14 alteration No prior MET-directed targeted therapy Treated brain metastases allowed if stable for ≥2 weeks
Diagnosis of *MET* exon 14 alteration	Local molecular profiling
Treatment	Crizotinib at 250 mg twice daily
Response Assessment	Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 Imaging at baseline and every 8 weeks
Adverse Events	Common Terminology Criteria for Adverse Events (CTCAE) v3.0
Biomarker Analysis	Retrospective analysis for *MET* exon 14 status was performed by: • Central testing of available tumor tissue (FoundationOne CDx, FMI) • Circulating cell free DNA analysis (PlasmaSELECT-R 64, PGDx)

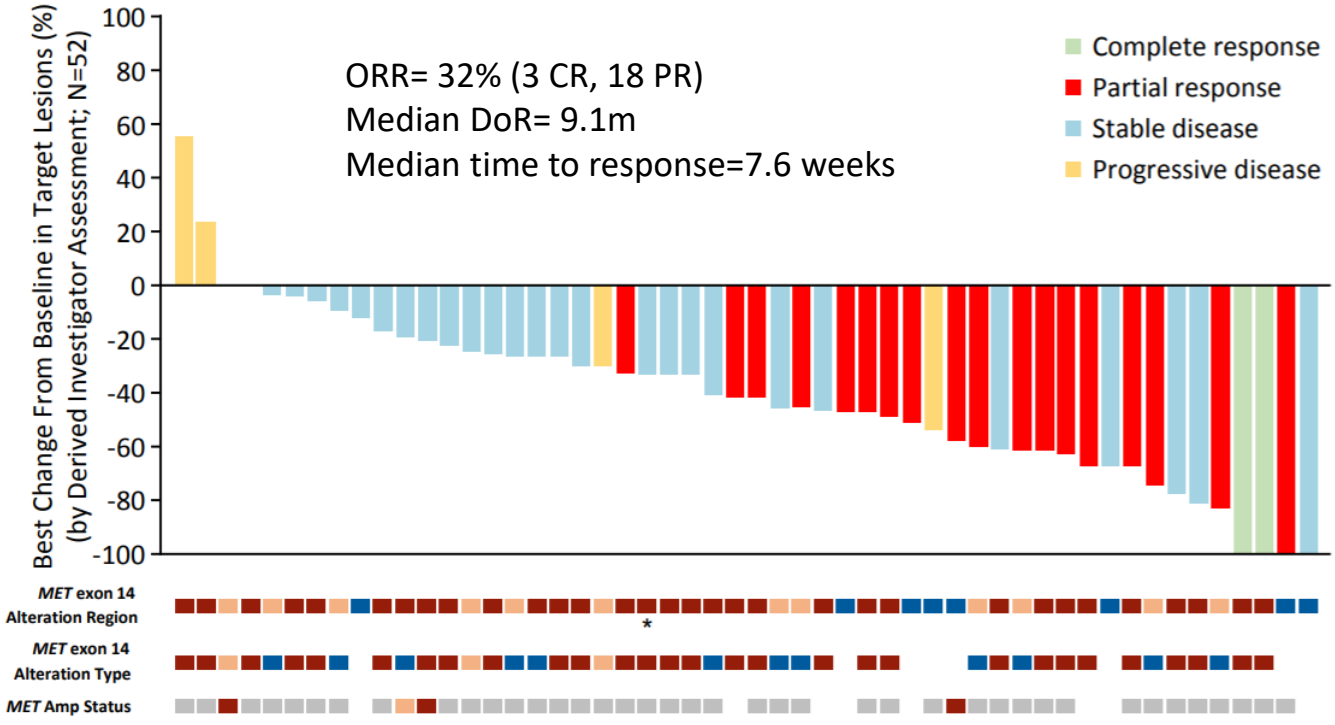
Drilon et al.

Update of crizotinib activity in METex14 skipping mutations (phase 1)

Patients with *MET* exon 14-altered lung cancers (N=69)		
Age, years	Median (range)	72 (34–91)
Sex, n (%)	Female Male	40 (58) 29 (42)
Race, n (%)	White Asian Black Other	50 (73) 11 (16) 2 (3) 6 (9)
Smoking history, n (%)	Former smoker Never smoker Smoker	42 (61) 26 (38) 1 (1)
Tumor histology, n (%)	Adenocarcinoma Sarcomatoid carcinoma Squamous cell carcinoma Adenosquamous carcinoma	58 (84) 6 (9) 3 (4) 2 (3)
ECOG performance status, n (%)	0 1 2	19 (28) 49 (71) 1 (1)
Prior treatments for advanced disease, n (%)	0 ≥1	26 (38) 43 (62)

Drilon et al.

Update of crizotinib activity in METex14 skipping mutations (phase 1)



Biomarker Data Key§

	MET exon 14 alteration region	*MET* exon 14 alteration type	*MET* amp status
	Splice donor	Base substitution	Detected
	Splice acceptor†	Large indel (>35 bp)	UIF
	Canonical‡	Indel	–
	Not detected	–	Not detected

Benefit regardless of heterogeneity in mutation type and absence or presence of concurrent MET amplification

Drilon et al.

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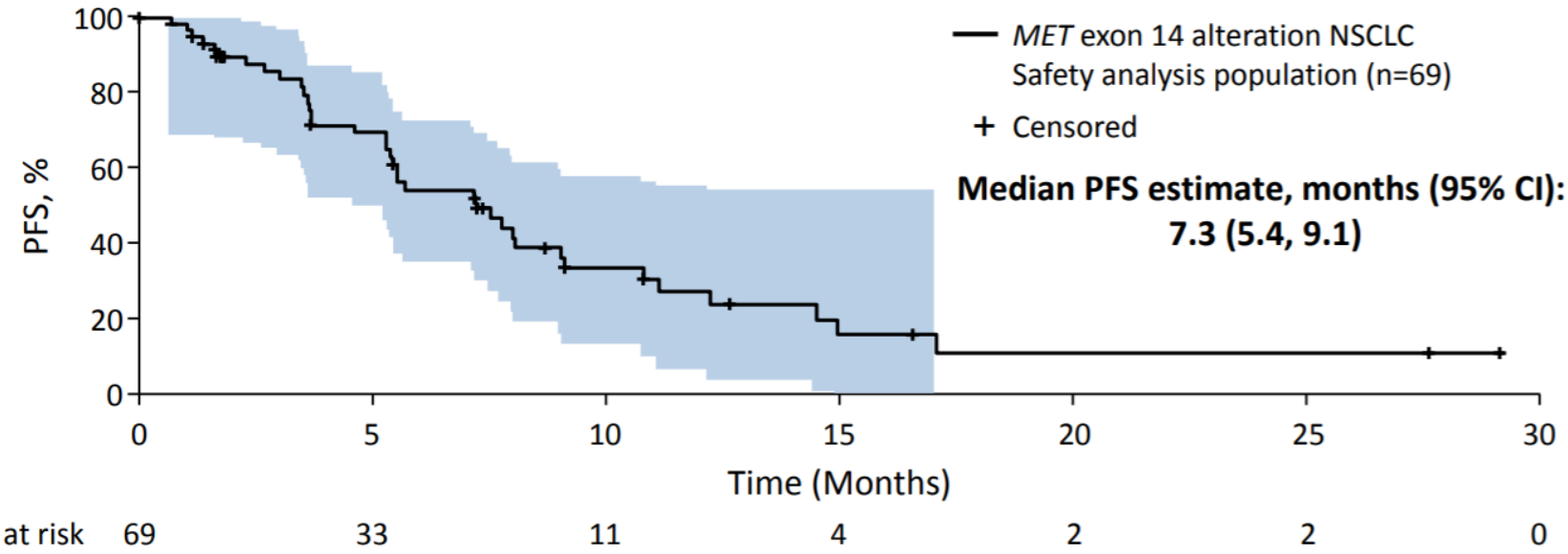


- OS data were not mature at time of data cutoff: 34.8% patients had died; 40.6% still in follow-up
- Median Overall Survival (OS) estimate, months (95% CI): 20.5 (14.3, 21.8)

Drilon et al.

VISION: Tepotinib in pts with METex14 skipping mutations (phase 2)

VISION: A Phase II, Single-arm Trial to Investigate Tepotinib in Advanced NSCLC With *MET*exon14-Skipping Alterations

- Advanced/metastatic NSCLC
  - all histologies
- *MET*exon14-skipping mutation-positive by NGS
  - tissue and blood based
- 1st, 2nd, 3rd line of therapy
- N = up to 120
- Regions: EU, US, Japan

→ **Tepotinib 500 mg QD** →

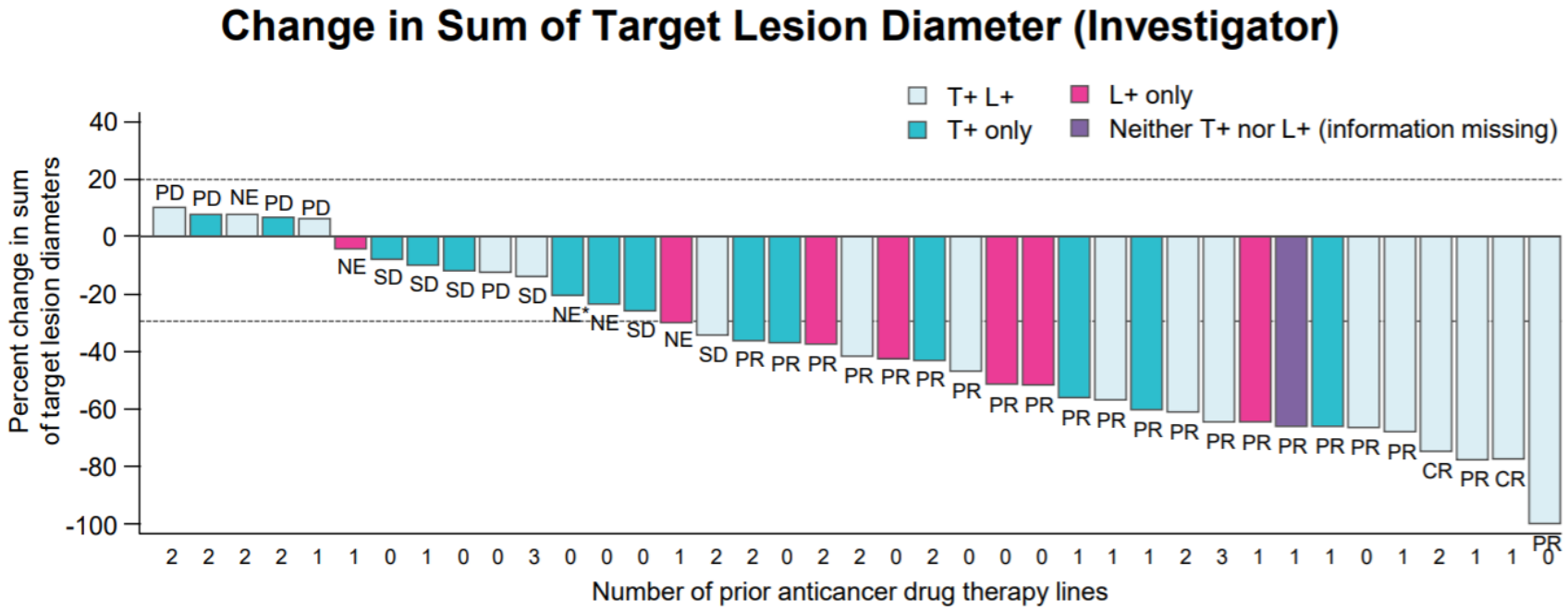
Primary endpoint
- ORR; RECIST v1.1 (independent review, IRC)*

Secondary endpoints
- ORR (investigator assessment)
- Safety
- Duration of response
- Progression-free survival
- Overall survival

Characteristic		Tepotinib 500 mg (N=46)*
Median age, years (range)		73.0 (39–89)
Sex, n (%)	Male	30 (65.2)
Race,† n (%)	White	32 (69.6)
	Asian	11 (23.9)
Smoking history,‡ n (%)	Never smoker	16 (34.8)
	Former smoker	21 (45.7)
	Regular smoker	1 (2.2)
Prior lines of anticancer therapy, n (%)	0	16 (34.8)
	1	16 (34.8)
	2	12 (26.1)
	3	2 (4.3)

Characteristic		Tepotinib 500 mg (N=46)*
*MET*exon14-skipping mutation status,‖ n (%)	Positive in ctDNA (L+)	28 (60.9)
	Positive in tumor (T+)	37 (80.4)
	Positive in both L+ and T+	20 (43.5)
Brain metastases,§ n (%)	Present	3 (6.5)
Histopathological classification, n (%)	Adenocarcinoma	43 (93.5)
	Other¶	3 (6.5)
Disease stage, n (%)	IIIB	3 (6.5)
	IV, IVa or IVb	43 (93.5)

VISION: Tepotinib in pts with METex14 skipping mutations (phase 2)



ORR = 57.5% (2 CR, 21 PR); **ORR by IRC=35%**
DCR=72.5%
Median DoR = 14.3 months

VISION: Tepotinib in pts with METex14 skipping mutations (phase 2)

All TEAEs*	Tepotinib 500 mg (N=46) Any grade	Grade ≥3
≥1 TEAE	**44 (95.7)**	**23 (50.0)**
≥1 drug-related TEAE, n (%)	**34 (73.9)**	**9 (19.6)**
Drug-related TEAEs reported in ≥10% patients at any grade, n (%)		
Peripheral edema	27 (58.7)	2 (4.3)
Diarrhea	17 (37.0)	1 (2.2)
Blood creatine increased	10 (21.7)	0
Nausea	10 (21.7)	0
Dyspnea	9 (19.6)	0 (0.0)
Asthenia	8 (17.4)	1 (2.2)
Hypoalbuminemia	8 (17.4)	1 (2.2)
Constipation	7 (15.2)	0
Fatigue	7 (15.2)	0
Amylase increased	6 (13.0)	2 (4.3)
Decreased appetite	6 (13.0)	0
ALT increased	5 (10.9)	2 (4.3)
Back pain	5 (10.9)	1 (2.2)

*Events that are emergent during treatment having been absent pretreatment, or worsen relative to pretreatment and with onset dates occurring within the first dosing day until 33 days after the last dose of trial treatment. ALT, Alanine aminotransferase; TEAE, treatment-emergent adverse event.

Serious TEAEs	Tepotinib 500 mg (N=46) Any grade	Grade ≥3
Serious TEAEs, n (%)	**17 (37.0)**	**16 (34.8)**
≥1 serious drug-related TEAE, n (%)	**3 (6.5)**	**3 (6.5)**
Serious drug-related TEAEs, n (%)		
Generalized edema	1 (2.2)	1 (2.2)
Asthenia	1 (2.2)	1 (2.2)
Dizziness	1 (2.2)	1 (2.2)
Interstitial lung disease	1 (2.2)	0 (0.0)

- Median time on treatment: 4.7 months (range 0.03–19.2)
- Grade ≥4 TEAEs reported in 6 (13.0%) patients; all were serious TEAEs, none were drug-related
- TEAEs led to treatment discontinuation in 7 (15.2%) patients
- 10 (21.7%) patients had ≥1 dose reduction
- Twelve patients have died:
  - 4 non-treatment related AEs
  - 5 progressive disease/disease-related condition
  - 3 primary cause unknown

Early discontinuation in 7 pts due to TRAEs

Felip et al.

Acsé cohort: Crizotinib in ROS1+ & MET+

N =5407 pts (186 centers) entered the biomarker program

ROS1+ 77/4050 (2%); MET amp (IHC 2+ or 3+ confirmed by FISH) in 251/4171 (6%); MET mut* (by NGS or single seq) in 76/1007 (7%)

*Not all pts with MET mut were METex14 (also 16-19)

Advanced NSCLC progressing to >=1 standard prior therapy

N = 90 pts with advanced NSCLC received crizotinib 250 mg BID

Endpoint: ORR

	ORR	mPFS	mOS
MET amp (n=25)	32%	3.4 m	7.7 m
METex14 (n=28)	40%	2.6 m	8.1m
ROS1 fusion (n=37)	69%	5.5 m	17.2m

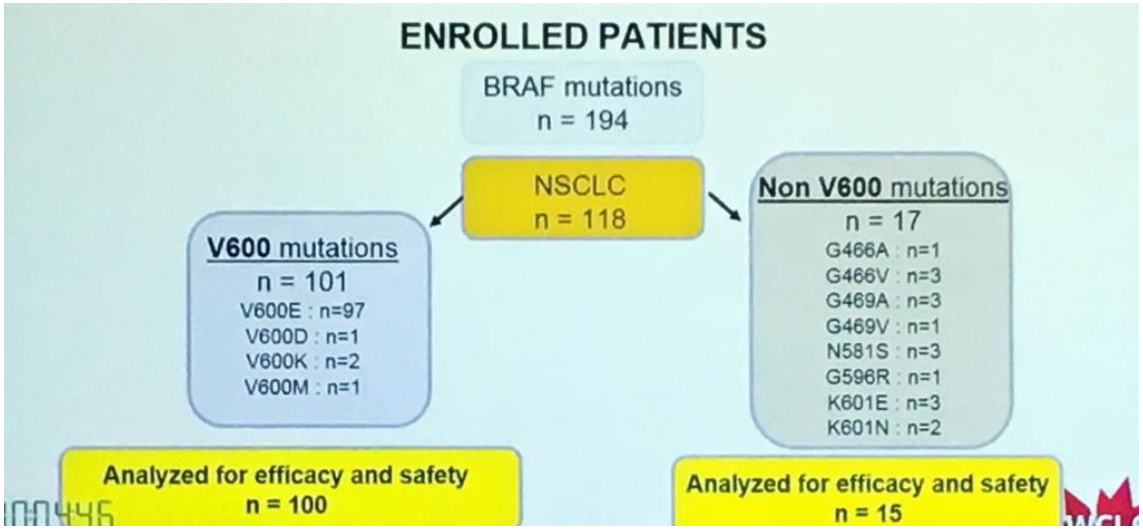
Mors-Sibilot et al.

Acsé cohort: BRAF V600E & Non V600E Mutations

BRAF by NGS o direct sequencing

Advanced NSCLC progressing to >=1 standard prior therapy

N = 118 pts with BRAF mut advanced NSCLC



	ORR	mDoR	mPFS	mOS
BRAF V600 (n=100)	45%	6.4m	5.2m	9.3m
BRAF non V600 (n=17)	0*	2.6 m	1.8m	5.2m

(*) study was stopped

Mazières et al.

LIBRETTO-001: LOXO-292 in RET fusión + NSCLC (phase 1/2)

N=82 pts with RET+ solid tumors, NSCLC n=38

Most have KIF5B partner (61%)

Treated with LOXO-292 at distinct doses (20-240mgQD). MTD not reached

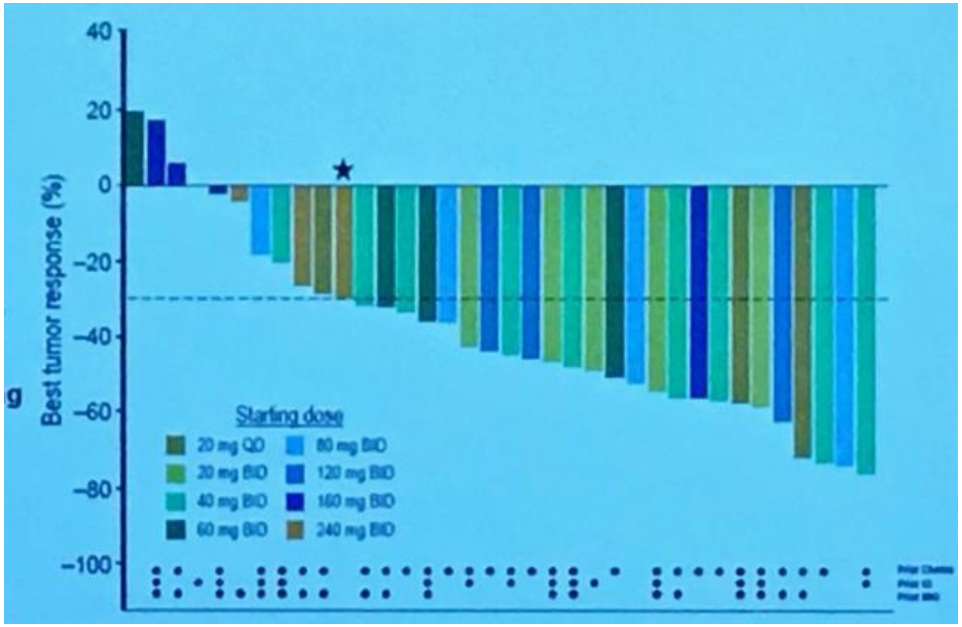
***RET*-fusion positive NSCLC**

Characteristic	Total (n=38)
Female / Male, n (%)	22 (58) / 16 (42)
Median age (range), years	62.5 (36–80)
ECOG performance status, n (%)	
0	6 (16)
1	32 (84)
Median prior systemic regimens (range)	3 (1–9)
Prior multikinase inhibitor (MKI), n (%)[3]	
0	17 (45)
≥1	21 (55)
Prior chemotherapy or immunotherapy, n (%)	33 (87)
Prior chemotherapy and immunotherapy, n (%)	15 (39)
Brain metastases, n (%)	8 (21)

Oxnard et al.

LIBRETTO-001: LOXO-292 in RET fusión + NSCLC (phase 1/2)

Efficacy (n=30). ORR = 68% (confirmed 68%), 92% ongoing
Response was independent of having received prior RET inh and fusion partner



Safety.
AEs (>20%): fatigue 20%, diarrea 16%, constipation 15%, dry mouth 12%, nausea 12%, dyspnea 11%
TRAEs G3+: tumor lysis syndrome and ALT elevation

Oxnard et al.