#IASLCUPDATES

Iniciativa científica de:

GECP lung cancer research

LUNG CANCER UPDATES

IASLC HIGHLIGHTS

7-10 DE SEPTIEMBRE 2019

Con la colaboración de:

Bristol-Myers Squibb

illumina

Lilly

LUNG CANCER UPDATES
IASLC HIGHLIGHTS
7-10 DE SEPTIEMBRE 2019
BARCELONA
Iniciativa científica de:
GECP lung cancer research

Targeted Therapies

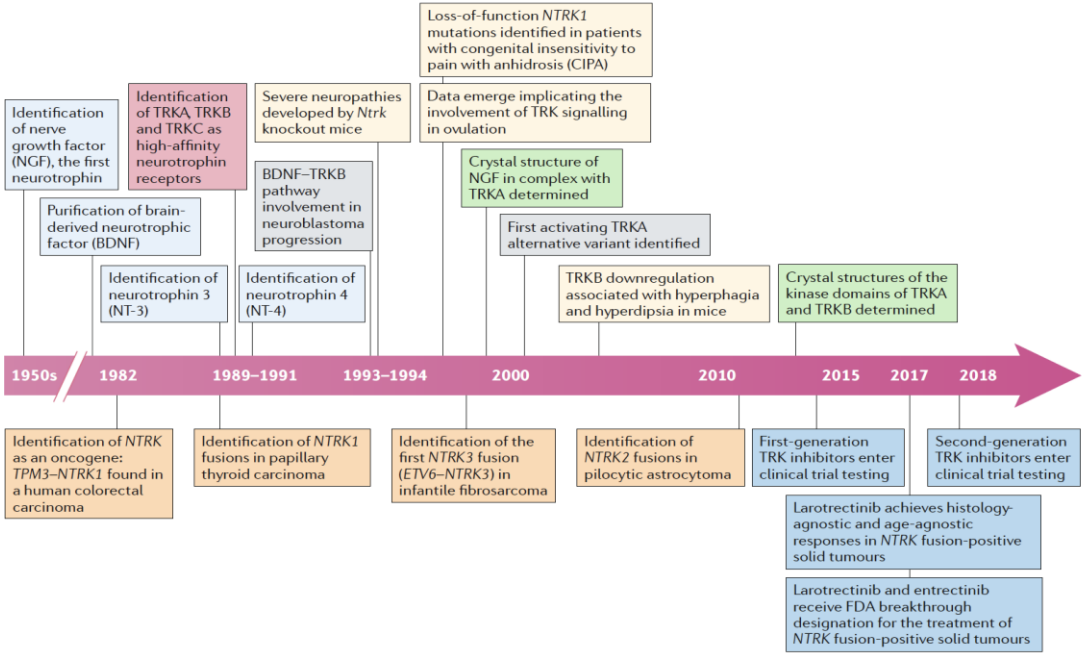
Beyond EGFR and ALK

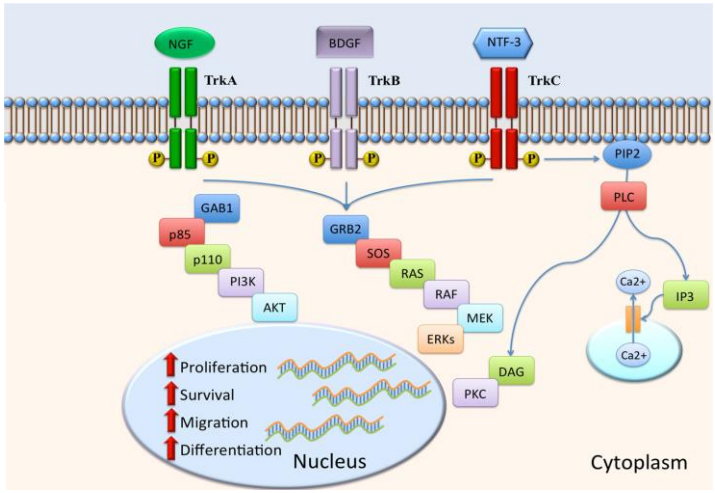
Rosario García Campelo

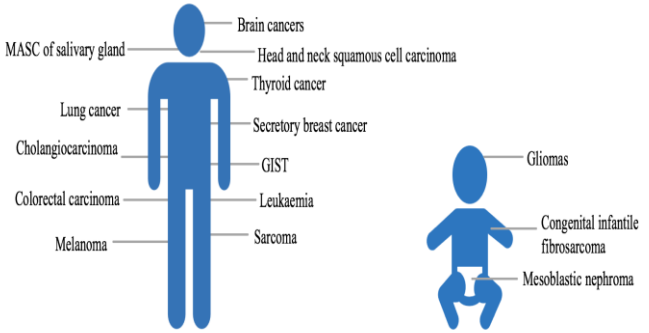
Servicio de Oncología Médica
Hospital Universitario A Coruña, INIBIC

Con la colaboración de:
Bristol-Myers Squibb
illumina
Lilly

A not so new target… but the best example of agnostic target: NTRK







Cocco E et al. Nat Reviews 2018
Ricciuti et al. Med Oncol 2017

Activity of Larotrectinib in TRK Fusion Lung Cancer

Adult phase I trial (NCT02122913)
- Age ≥18 years
- Advanced solid tumours

N=1

Adult/adolescent phase II 'basket' trial (NAVIGATE; NCT02576431)
- Age ≥12 years
- Advanced solid tumours
- TRK fusion cancer

N=11

12 patients with TRK fusion lung cancer

Patient characteristics

Median age, range	**49.0 (25–76) years**
Sex, n (%)	
Male	**6 (50)**
Female	**6 (50)**
NTRK fusion, n (%)	
NTRK1	**9 (75)**
NTRK2	**0 (0)**
NTRK3	**3 (25)**
Brain metastases at baseline, n (%)	
Yes	**6 (50)**
No	**6 (50)**

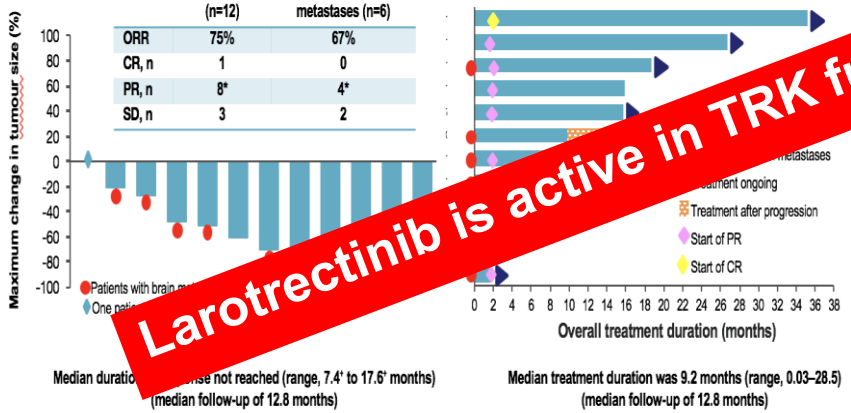
Dosing
- Larotrectinib, 100 mg BID continuously
- 28-day cycles

Endpoints
- **Primary endpoint**
  - Best objective response rate (RECIST 1.1)
- **Secondary endpoints**
  - Duration of response
  - Progression-free survival
  - Overall survival
  - Safety

Farago A, et al. MA09.07
Data cut off February 19 2019
TRK fusion status determined by local CLIA (or similar accredited laboratories)
BID, twice daily; NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase.
Presented by: Dr Anna F. Farago, Massachusetts General Hospital Cancer Center, Boston, USA

Larotrectinib is active in TRK fusion lung cancer

	All patients (n=12)	Patients with brain metastases (n=6)
ORR	75%	67%
CR, n	1	0
PR, n	8*	4*
SD, n	3	2



Median duratio… …se not reached (range, 7.4+ to 17.6+ months)
(median follow-up of 12.8 months)

Median treatment duration was 9.2 months (range, 0.03–28.5)
(median follow-up of 12.8 months)

*PR pending confirmation in 1 patient. Investigator assessments as of 19 February 2019.
CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.

† Nontarget PD in asymptomatic leptomeningeal focus

AEs in … overall dataset (n=207)

	Treatment-emergent AEs (%)					Treatment-related AEs (%)		
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
…zziness	18	15	3	–	36	<1	–	18
Nausea	25	3	1	–	29	<1	–	21
Constipation	24	3	1	–	29	1	–	15
Anaemia	22	5	<1	–	27	–	–	12
ALT increased	10	7	10	–	27	2	–	11
AST increased	17	5	3	<1	26	2	<1	21
Cough	18	5	3	–	26	1	–	19
Diarrhoea	23	3	<1	–	26	–	–	1
Vomiting	16	6	1	–	23	–	–	5
Pyrexia	17	6	<1	–	23	–	–	10
Dyspnoea	12	5	<1	<1	18	–	–	1
Headache	10	6	2	–	18	–	–	1
Myalgia	13	4	–	–	16	–	–	4
Peripheral oedema	12	3	1	–	16	<1	–	7
	12	4	–	–	15	–	–	7

Dose Reduction: 9% (n=11/122 patients with TRK fusion cancer) – all maintained tumour regression on reduced dose.
Discontinue due to AE: <1% (n=1/122 patients with TRK fusion cancer)

ORR 75%
mDOT 9.2 m

Farago A, et al. MA09.07

Alectinib in previously treated RET-rearranged advanced NSCLC: a Phase I/II trial ALL-RET.

Methods/Design

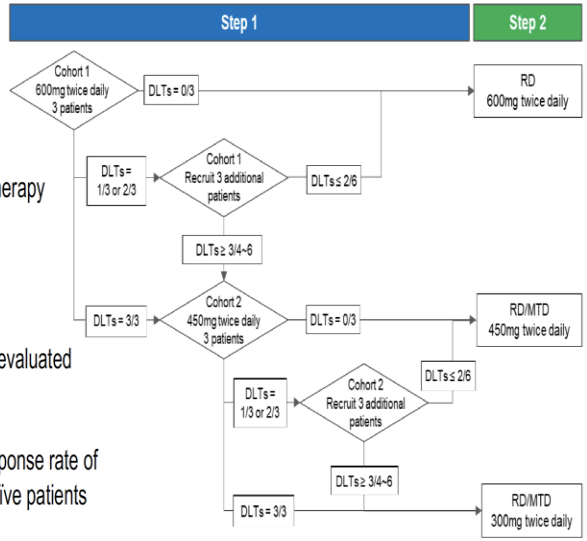
Single-arm,
multi-institutional phase 1/2 trial

Key Eligibility:

- *RET* fusion-positive NSCLC
- At least one regimen of chemotherapy
- Screened by LC-SCRUM-Japan

Step 1 (Phase 1)
Primary endpoint : safety.
Dose-limiting toxicity (DLT) was evaluated during the first cycle.

Step 2 (Phase 2)
Primary endpoint : Objective response rate of RET-TKI naïve patients



Dose-limiting toxicities in Step1 (Phase 1)

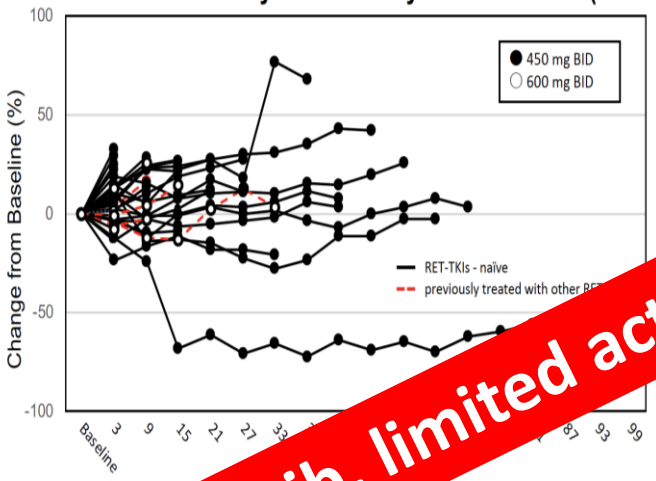
Cohort (Alectinib dose)	Age (years)	Sex	Smoking Status	Type of *RET* fusion	Histology	ECOG PS	Body weight (kg)	Previous RET-TKI treatment	Previous ICI treatment	Number of previous regimens	Dose-limiting toxicities (DLTs)
Cohort 1 (600 mg BID)	53	F	Never	*KIF5B-RET*	Adeno	0	67	-	-	2	-
	64	F	Former	*KIF5B-RET*	Adeno	1	45	Vandetanib	-	3	-
	47	F	Never	*KIF5B-RET*	Adeno	1	60	-	Nivo	5	Rash, AST increased
	39	F	Never	*KIF5B-RET*	Adeno	1	55	-	Nivo	8	Erythema multiforme , Thromboembolic event
	61	F	Never	*KIF5B-RET*	Adeno	1	46	Vandetanib	-	3	-
	73	M	Former	Unknown	Adeno	1	54	-	-	2	CPK Increased
Cohort 2 (450 mg BID)	68	F	Never	*KIF5B-RET*	Adeno	0	58	-	-	1	-
	58	M	Never	*KIF5B-RET*	Adeno	0	53	-	-	4	-
	75	M	Former	*KIF5B-RET*	Adeno	1	63	-	-	2	-

On the basis of DLTs we determined alectinib 450 mg BID as the recommended dose (RD) for phase 2.

Yanagitani N, et al. OA02.01

Alectinib, limited activity in RET-TKI naive NSCLC...

Efficacy assessed by central review (RECIST v1.1)



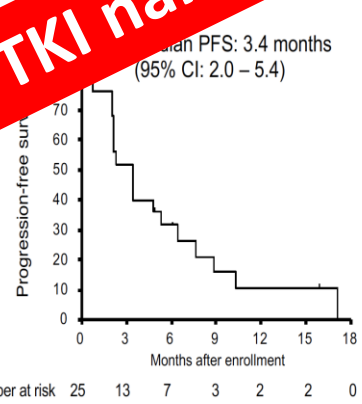
	RET-TKI naïve (n=25)
Best overall response	n (%)
CR	0
PR	
	2 (8.0)

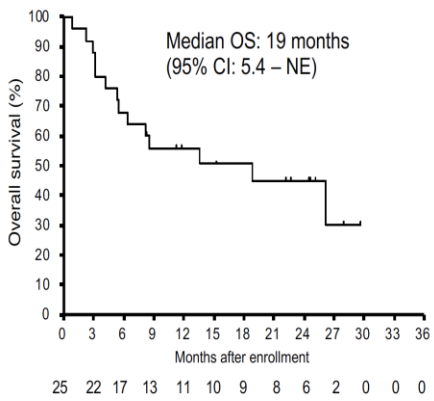
[95 % CI]: 4.0 % [0.1-20.4]

DCR* [95 % CI]: 52.0 % [31.3-72.2]

* CR, PR, 8 weeks or more of SD sustained (non-PD)

s treated with alectinib 450mg BID





Number at risk 25 13 7 3 2 2 0

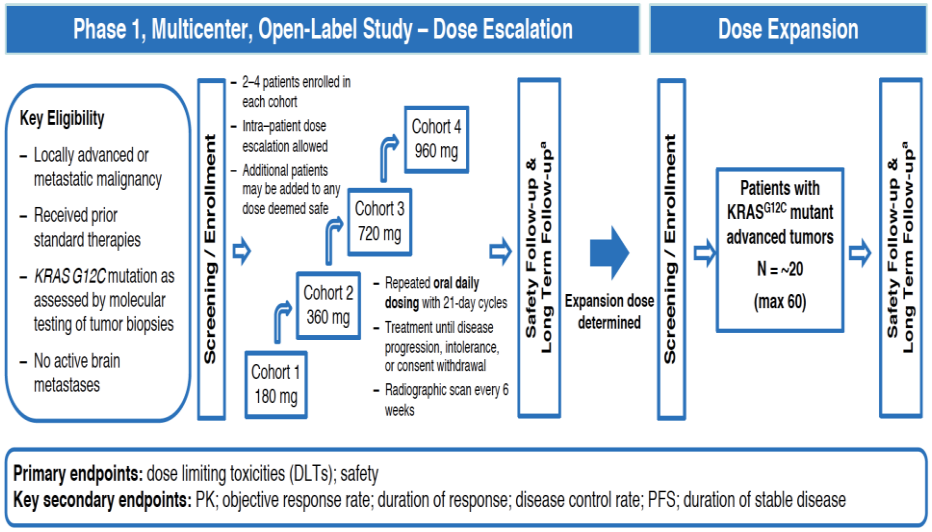
25 22 17 13 11 10 9 8 6 2 0 0 0

ORR 4%
mPFS 3.4m
mOS 19m

Yanagitani N, et al. OA02.01

Phase I study of safety, tolerability, PK and Efficacy of AMG 510, a novel KRAS G12 inhibitor evaluated in NSCLC

AMG 510 First-in-Human Study Design



[a]30 (+7) days after end of treatment for safety follow-up; every 12 weeks for long term follow-up. PK: pharmacokinetics; PFS: progression-free survival.

Baseline Characteristics

Baseline Characteristics	N = 34
Median age (range) – year	67.5 (49.0–77.0)
Female – n (%)	18 (52.9)
ECOG performance status score – n (%)	
0	5 (14.7)
1	26 (76.5)
2	3 (8.8)
Prior lines of systemic anticancer therapy – n (%)	
1	2 (5.9)
2	3 (8.8)
> 2	29 (85.3)
Median No. of prior systemic anticancer therapy – n (range)	3.5 (1–8)

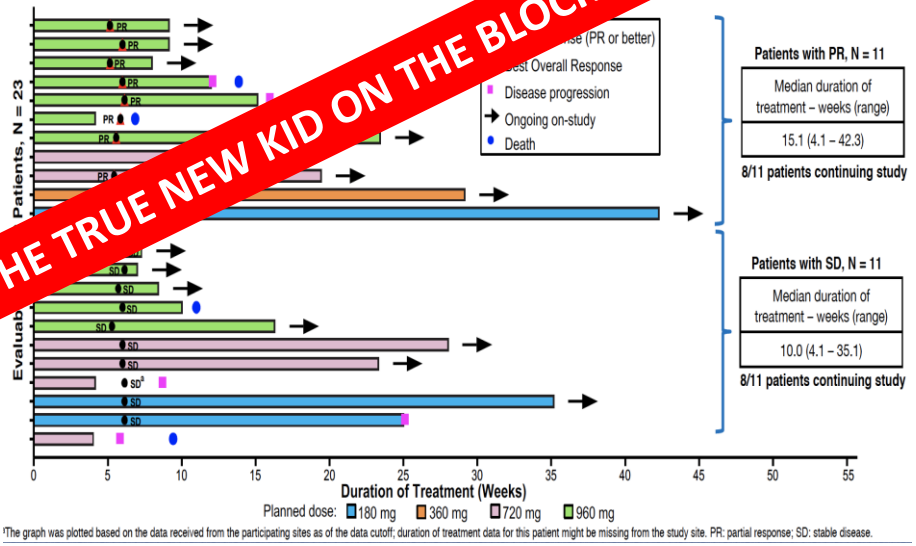
Govindan R, et al. OA02.02

Best Tumor Response and Change in Tumor Burden From Baseline

Efficacy outcomes	All evaluable patients N = 23	Evaluable patients treated with 960mg N = 13
Best overall response		
Partial response – No. (%)	11 (48)	7 (54)
Stable disease – No. (%)	11 (48)	6 (46)
Progressive disease – No. (%)	1 (4)[a]	0 (0)
Objective response rate – %	48%	54%
Disease control rate[b] – %	96%	100%

1 patient discontinued study due to PD prior to the 1st assessment, and the
g; [b]PR or SD at week 6; [c]Patient had complete response to the target lesions.
Evaluable patients: patients who have been followed up for at lea
disease; PD: progressive disease.

Time to Response and Duration of Treatment f… Levels



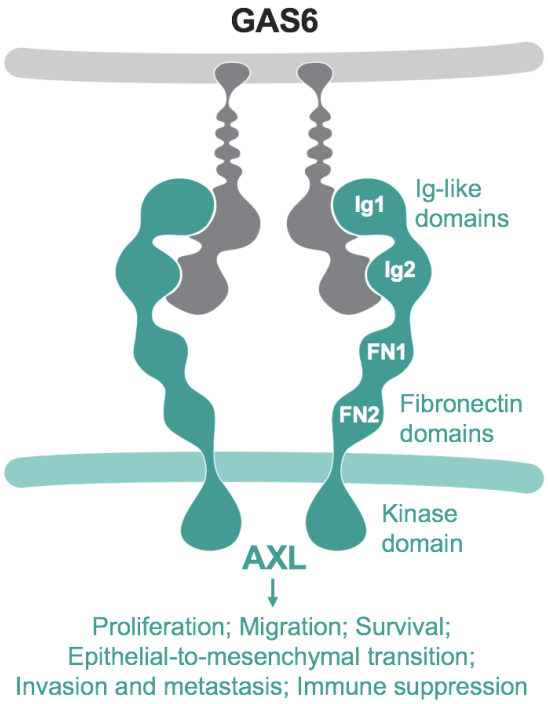
[a]The graph was plotted based on the data received from the participating sites as of the data cutoff; duration of treatment data for this patient might be missing from the study site. PR: partial response; SD: stable disease.

AFTER SO MANY FAILURES…AMG 510, THE TRUE NEW KID ON THE BLOCK

ORR 48%
mDOT 10-15.1weeks

Govindan R, et al. OA02.02

First-in-human phase 1/2 trial of anti-AXL antibody-drug conjugate (ADC) Enapotamab Vedotin (EnaV) in advanced NSCLC



Phase 1
Dose Escalation[1]
N=47

NSCLC (n=8)
Ovarian cancer (n=22)
Melanoma (n=9)
Endometrial cancer (n=5)
Cervical cancer (n=3)

Study Endpoints

MTD
Safety
Anti-tumor activity
Biomarkers

RP2D
EnaV
2.2 mg/kg
1Q3W

Phase 2a
Dose Expansion
N=102

Cohort 1: NSCLC with EGFR mutations (n=11)

Cohort 2: NSCLC without activating EGFR mutations or ALK rearrangements (n=24)

Cohorts 3 to 7: Melanoma, sarcoma, or ovarian cancer (n=67)

Cohort 2 Key Inclusion Criteria

- Advanced (stage IIIA/B) or metastatic (stage IV) NSCLC without activating EGFR mutations or ALK rearrangements
- Progressive disease following last prior treatment, which includes PD-1/PD-L1 inhibitor and/or chemotherapy
- ECOG PS 0–1
- Measurable disease (RECIST v1.1)
- Acceptable renal and liver function and hematological status
- Signed informed consent

https://clinicaltrials.gov/ct2/show/NCT02988817

1. Ameratunga M, *et al. J Clin Oncol* 2019;37:2525.

Data cut-off: 31-JAN-2019

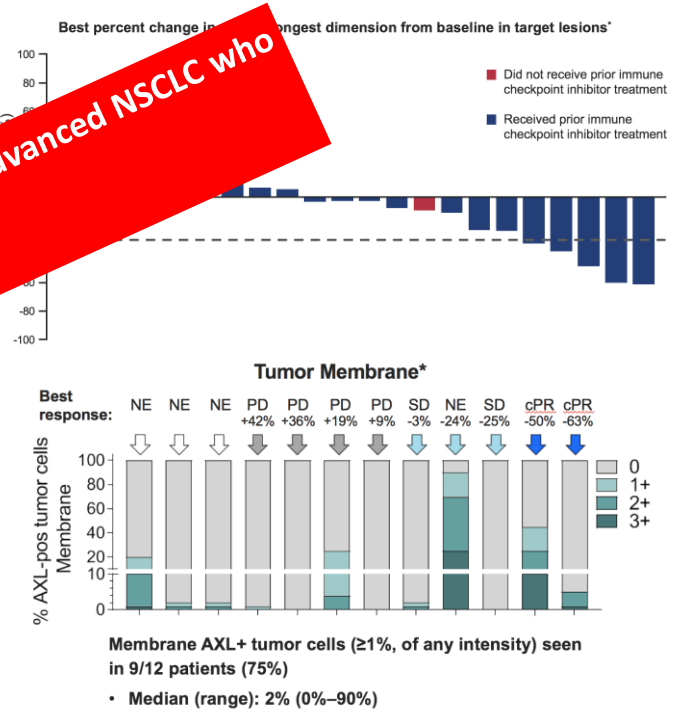
Ramalingam S, et al OA 02.05

Patient characteristics	
Male, n (%)	15 (58%)
Age, median (range), years	65.5 (38–74)
≥70 years, n (%)	8 (31%)
Smoking history, n (%)	
Non-smoker	3 (12%)
Race, n (%)	
White	24 (92%)
ECOG PS, n (%)	
0	3 (12%)
1	23 (88%)
Tumor stage at screening, n (%)	
Stage IV	25 (96%)
NSCLC histology, n (%)	
Adenocarcinoma	15 (58%)
Squamous cell carcinoma	6 (23%)

Disease characteristics	N=26*
Prior lines of treatment, median (range)	2 (1–4)
Prior treatments, n (%)	
Platinum doublet chemotherapy	20 (77%)
Immune checkpoint inhibitor	17 (65%)
Docetaxel	6 (23%)
Gemcitabine	5 (19%)
Immediate prior treatment, n (%)†	
Immune checkpoint inhibitor	12 (46%)
Immune checkpoint inhibitor plus chemotherapy	6 (23%)
Docetaxel	3 (12%)
Platinum doublet chemotherapy	2 (8%)
Gemcitabine	1 (4%)
Best response to last prior treatment, n (%)	
PR	
SD	
PD	13 (50%)

Best overall response (confirmed)	N=26
ORR, n (%)	5 (19%)
CR	
PR	
SD	
onset of response	
Median, weeks	11.0
95% CI	5.0–17.0
Duration of response	
Median, weeks	18.1

EnaVed monotherapy: encouraging preliminary activity in patients with advanced NSCLC who failed ICIs and platinum-based chemotherapies AXL expression: a potential predictive biomarker



Membrane AXL+ tumor cells (≥1%, of any intensity) seen in 9/12 patients (75%)

- **Median (range): 2% (0%–90%)**

Phase II trial of Bemcentinib with pembrolizumab

Study overview

2nd line advanced NSCLC
- Adenocarcinoma histology
- IO naïve
- Progressed on a platinum based chemotherapy in 1L
- AXL and PD-L1 All comers
- Fresh tissue biopsy

Single arm
Bemcentinib 200mg daily
+
Pembrolizumab 200mg q3weeks

Interim Analysis
N=24 patients

Final Analysis
N=48 patients

Endpoints
- **Primary –** ORR
- **Secondary –** DCR, DoR, TtP 12mth OS, Response by biomarker expression

Biomarker analysis
- PD-L1 and AXL expression by IHC
- Soluble protein biomarkers by liquid biopsy
- Tumor immune cell characterization

Assessments – efficacy & safety
- Response was assessed every 9 weeks per RECIST v1.1
- Adverse events were assessed by CTCAE v4.03
- Evaluable: ≥1 dose of study treatment as of data cutoff

Screened
n = 74

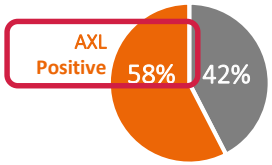
Received at least 1 dose of combination:
n = 46

35 radiologically evaluable
3 progressed without radiological assessment
8 with no response assessment

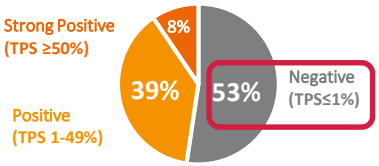
Discontinued
n = 30
- 15 PD
- 7 AE
- 3 death
- 3 investigator's decision
- 2 withdrawal of consent/ lost to follow-up

Ongoing
n = 16

AXL status
n = 33
(28 with at least 1 response assessment



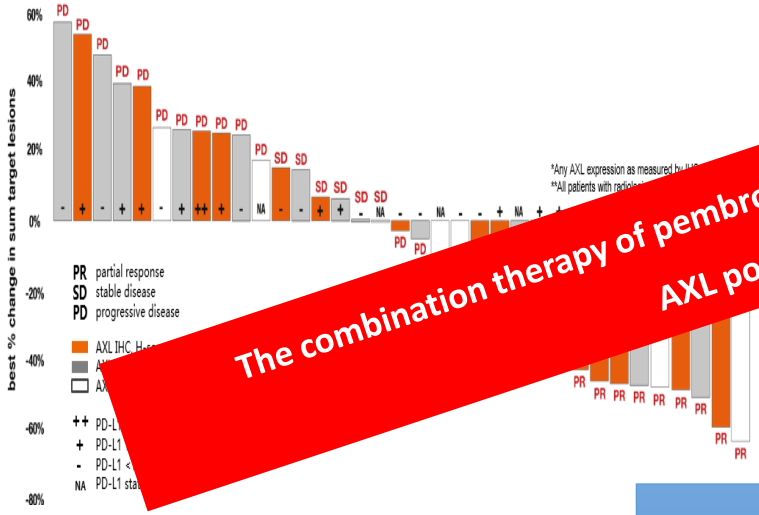
PD-L1 status
n = 38
(29 with at least 1 response assessment)



Felip et a MA 03.06

Iniciativa científica de:
GeCP lung cancer research

Bemcentinib with pembrolizumab



The combination therapy of pembrolizumab and bemcentinib is well tolerated and is benefitting AXL positive/PD-L1 low/negative patients

			SD	PD	ORR (%)	CBR (%)
	35	10	12	13	29%	63%
	28					
Positive*	15	6	4	5	40%	67%
Negative	13	2	5	6	15%	54%
PD-L1	29					
PD-L1 strong positive (TPS >50%)	2	1	0	1	50%	50%
PD-L1 weak positive (TPS 1-49%)	12	3	4	5	25%	58%
PD-L1 negative (TPS <1%)	15	4	5	6	27%	60%

ORR 29%
AXL+ pts, ORR 40% mPFS 5.9m
AXL- pts, ORR 15% mPFS 3.3m
27% ORR in PDL1 negative pts
Median OS 12.2 months

Felip et a MA 03.06