#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

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BARCELONA
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Targeted Therapies
NRG1, ALK TKI resistant, EGFR TKI resistant, Kras mut and (CAR)-T

Rosario García Campelo

Servicio de Oncología Médica

Hospital Universitario A Coruña, INIBIC

Con la colaboración de:
Bristol-Myers Squibb
illumina
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Outline

- NRG1
- ALK TKI resistant
- EGFR TKI resistant
- EGFR mut with Brain Mts
- Kras mut
- Relevance of molecular testing

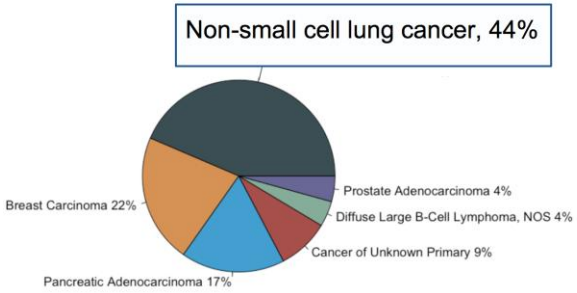
OA14.03 – Clinical Rationale and Preclinical Evidence for Chimeric Antigen Receptor (CAR) T Cell Therapy Clinical Trial in KRAS-Mutant Lung Cancer

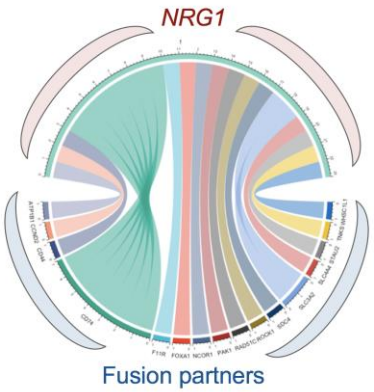
ID	CAR T	Adjunct Therapy	Phase	N	Status	Location
NCT04025216	CART-TnMUC1	Cyclophosphamide Fludarabine	1	80	Not yet recruiting	TBA
NCT03932565	4th Gen. CAR-T cells (IL7 and CCL19 or / and IL12) targeting Nectin4/FAP	None	1	30	Recruiting	China
NCT03638206	Multi-target Gene-modified CAR-T/TCR-T Cell	None	1/2	73	Recruiting	China
NCT03525782	anti-MUC1 CAR-T Cells	Pembrolizumab	1/2	60	Recruiting	China
NCT03356808	CAR T cells	None	1/2	20	Recruiting	China
NCT03						
NCT03						
NCT03	MUC1, Lewis-Y, or CD80/86					
NCT03054298	huCART-meso cells	None	1	30	Recruiting	USA – UPenn
NCT02862028	HerinCAR-PD1 cells	None	1/2	20	Recruiting	China
NCT02713984	anti-HER2 CAR-T	None	1/2	60	Recruiting	China
NCT02587689	anti-MUC1 CAR T Cells	None	1/2	20	Recruiting	China
NCT02414269	iCasp9M28z T cell infusions	Cyclophosphamide Pembrolizumab	1	66	Recruiting	USA – MSKCC
NCT02349724	anti-CEA-CAR T	None	1	75	Recruiting	China
NCT01583686	anti-mesothelin CAR transduced PBL	Fludarabine Cycolphosphamide Aldesleukin	1/2	15	Terminated	USA – NCI

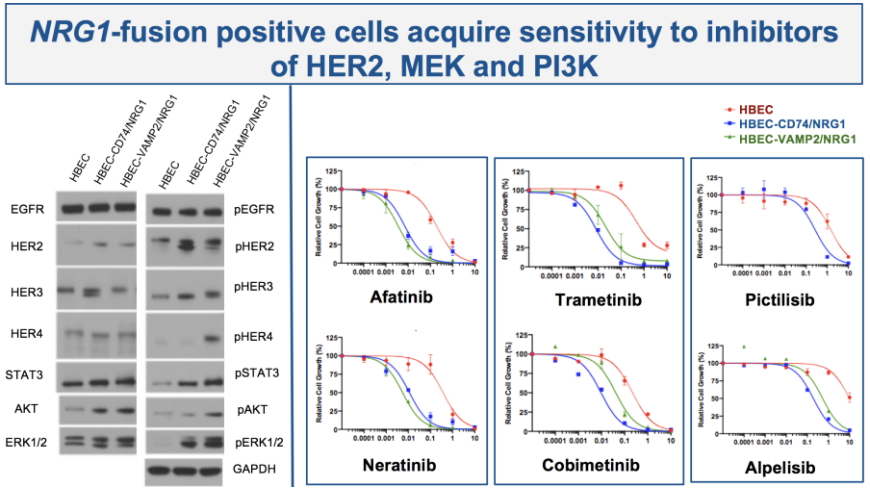
CAR T in lung cancer:
Promising but premature

MA21.01 – Generation and Characterization of Novel Preclinical Disease Models of NSCLC with NRG1 Rearrangements to Improve Therapy

NRG1 fusion, a new player?







Targeted therapies were tested including inhibitors of HER2, MEK and PI3K, demonstrating effectiveness.

Studies exploring the efficacy of these agents alone or in combination, along with additional targeted agents are ongoing

Gladstone E, et al. MA 21.01

MA21.05 – Phase II Trial of the Combination of Alectinib with Bevacizumab in ALK-Positive Nonsquamous Non-Small Cell Lung Cancer

Methods

Patients with *ALK*+ Nonsquamous NSCLC who had progressed after alectinib treatment (n=12)

↓

Alectinib 600 mg PO QD
Bevacizumab 15 mg/kg Q3W

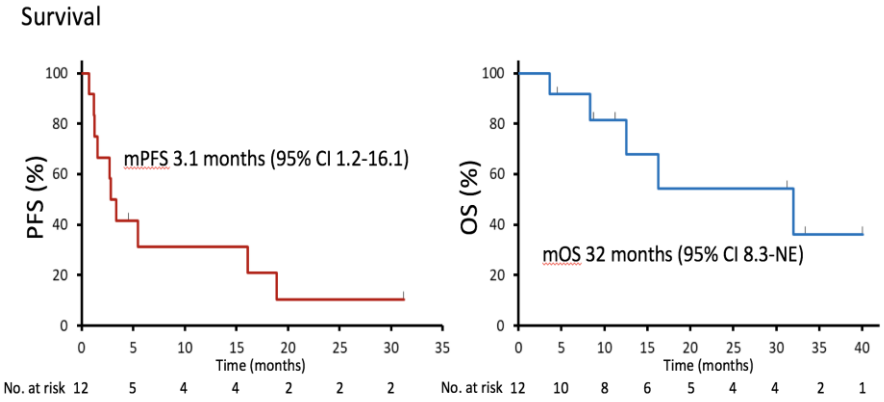
Primary endpoint
- PFS

Secondary endpoints
- OS, ORR, DCR, safety

Patient characteristics

Demographic and baseline characteristics		
Age	years, range	67, 30-77
Sex	Female / Male	10/2
ECOG-PS	0 / 1 / 2	1/10/1
Smoking status	Never smoked / smoker	9/3
Stage (UICC ver.7)	IV / post operative	10/2
Prior ALK-TKIs	Alectinib	12
	Crizotinib	9
	Ceritinib	2
Response to alectinib	CR / PR / SD	1/7/4
Treatment line	2	3
	≥3	9

Survival



The combination of bevacizumab and alectinib demonstrated clinical activity in *ALK*-positive NSCLC with acquired resistance to alectinib

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Watanabe et al. MA 21.05

MA21.06 – Preliminary Phase 1 Results of U3- 1402 – A Novel HER3-Targeted Antibody Drug Conjugate – In EGFR TKI-Resistant, EGFR-Mutant NSCLC

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U3-1402 Phase 1 Dose Escalation Study Design

Eligibility Criteria

- **Metastatic/unresectable *EGFR*-mutant NSCLC and:**
  - T790M-negative after progression on erlotinib, gefitinib, or afatinib; *OR*
  - Progressed on osimertinib
- **Stable brain metastases allowed**
- **Pretreatment tumor tissue (after progression on TKIs) was required for retrospective analysis of HER3 expression**

U3-1402 Dose Escalation (N = 30)

Received ≥ 1 dose of U3-1402 IV Q3W

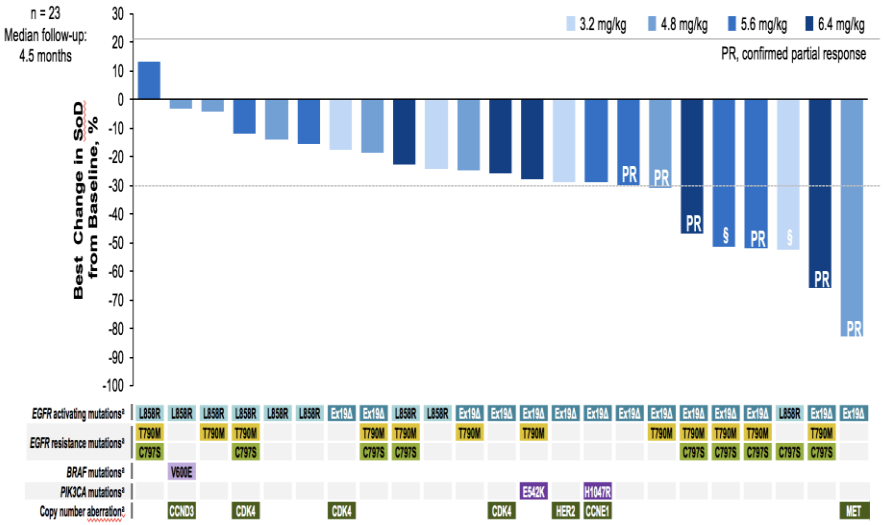
- 6.4 mg/kg (n = 5)
- 5.6 mg/kg (n = 12)
- 4.8 mg/kg (n = 9)
- 3.2 mg/kg (n = 4)

Patient Disposition[a]

- **Ongoing**, n = 17
- **Discontinued**, n = 13
  - Progressive disease: 9
  - Consent withdrawal: 2
  - Clinical progression: 1
  - AE: 1

Objectives	Primary:	Secondary:	Exploratory:
	Safety and tolerability of U3-1402 and RDE determination	Antitumor activity of U3-1402	Biomarkers of U3-1402 antitumor activity

Antitumor Activity of U3-1402 Across Diverse EGFR TKI Resistance Mechanisms



Targeting HER3 with U3-1402 may provide clinical benefit to patients with *EGFR*-mutant NSCLC with diverse mechanisms of TKI resistance

Yu H, et al. MA 21.06

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MA21.10 – Phase II Study of 160mg of Osimertinib in EGFR T790M Positive NSCLC with Brain or Leptomeningeal Metastases Who Progressed on Prior EGFR TKI

STUDY OVERVIEW:

- Patients with activating EGFR mutation
- Resistance to EGFR tyrosine kinase inhibitor
  (For those who treated with 3rd generation EGFR TKI, extracranial lesion has to be stable)
- Brain metastases or leptomeningeal metastases
- Confirmed EGFR T790M from the tissue or the plasma

BM cohort (n=40)

- Radiologically confirmed brain metastases lesion
- No leptomeningeal metastases
- Previous radiotherapy or gamma knife surgery is allowed

LM cohort (n=40)

- Leptomeningeal metastases with or without brain metastases
- Cytology confirmed by CSF study

→ Osimertinib 160mg qd

Multi-center, Open-label, Phase 2 study

Primary endpoint
BM cohort: Overall response rate (H0: 10% vs. H1: 30%)
LM cohort: Overall survival (H0: 3 months vs. H1: 5months)

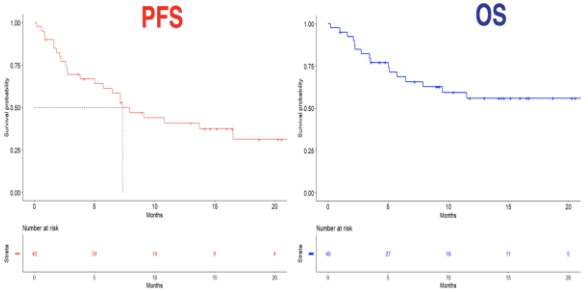
First patient received treatment: May, 18th, 2017
Data cut off date: March, 31st, 2019

CLINICAL OUTCOMES: Brain Metastases Cohort (N=40)

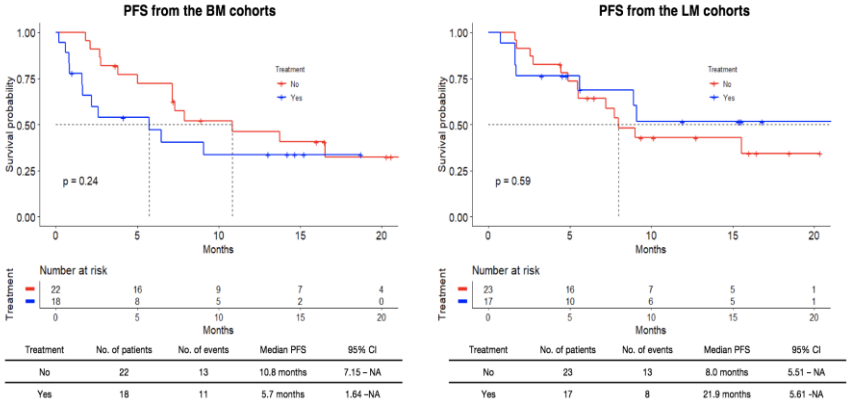
Overall best intracranial response	
Complete response	n= 3 (7%)
Partial response	n= 18 (45%)
Stable disease	n= 10 (25%)
Progressive disease	n= 4 (10%)
Not evaluable	n= 5 (13%)
Number of events†	
Intracranial progression only	n= 1 (3%)
Extracranial progression only	n= 11 (28%)
Intra & extra cranial progression	n= 3 (7%)
Clinical disease progression	n=2 (5%)
Death events without disease progression	n= 7 (18%)
Overall PFS events	n= 24 (60%)
Overall Death events	n= 16 (40%)
Other reason for study discontinuation*	
Adverse event	n= 1 (4%)
Consent withdrawal	n= 2 (7%)

- Median follow-up duration: 9.15 months, 95%CI(5.08-14.43)
- Current ongoing patients: n=13 (33%)
- 6 patients received treatment as beyond progression

Median overall PFS : 7.3 months, 95% CI (5.7 – NA)
Median OS: Not reached, 95% CI (7.9 – NA)



Patients Previously treated with 3rd Generation EGFR TKI



Treatment	No. of patients	No. of events	Median PFS	95% CI
No	22	13	10.8 months	7.15 – NA
Yes	18	11	5.7 months	1.64 –NA

Treatment	No. of patients	No. of events	Median PFS	95% CI
No	23	13	8.0 months	5.51 – NA
Yes	17	8	21.9 months	5.61 -NA

- 160mg Osimertinib showed 52% of intracranial ORR including 7% complete response in BM patients. Median overall PFS was 7.3 months and median OS not reached
- In LM patients, higher intracranial DCR (90%) including 13% complete response were observed. Median overall PFS was 9.0 months and OS was 18.4 months
- Disease progression to the Osimertinib 160mg occurs more commonly in extracranial lesion compared to the intracranial lesion in both cohorts

Ahn et al. MA 21.10

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MA21.03 – The International Association for the Study of Lung Cancer (IASLC) Global Survey on Molecular Testing in Lung Cancer

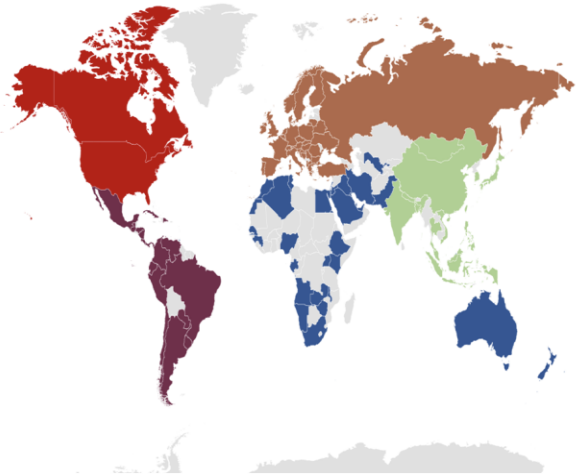
Results

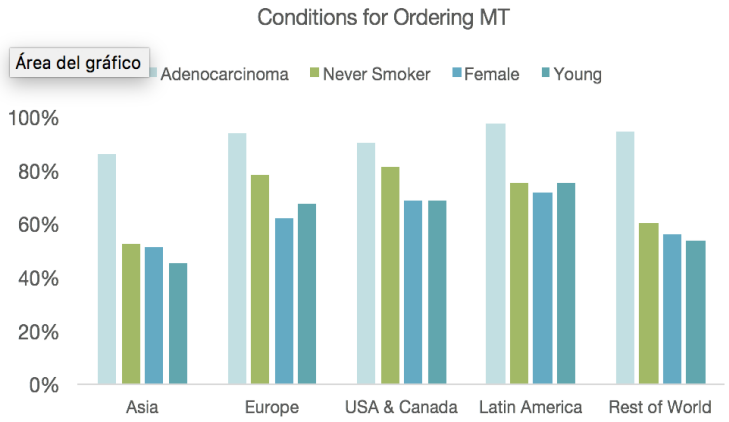
2,537 responses from 102 countries.

45% Medical Oncologists, 12% Pulmonologists, 12% Thoracic Surgeons, 9% Pathologists, and 22% scientists or other.

56% developing countries, 44% developed.

52% Asia, 19% Europe, 11% Latin America, 11% US/Canada, 7% Other.





- 94% of labs offer EGFR, 83% ALK, 69% KRAS, 68% BRAF, 64% ROS1 and 56% HER2.

Unaware of Recent Guidelines:

33% of those requesting/treating MT unaware of the most updated CAP/IASLC/AMP guidelines (Most frequently in Asia / Rest of the World) (p=0.041)

Take Home Message

Many respondents are not satisfied with the state of molecular testing

1/3 unaware of most recent evidence-based guidelines; we identified important barriers to molecular testing

Continuous education around molecular testing should be intensified on national and international levels to ensure patient receive optimal therapy