LUNG CANCER UPDATES
ASCO HIGHLIGHTS
1-5 JUNIO 2018, CHICAGO

"Immunotherapy for Oncogene-Driven Non-Small Cell Lung Cancer"

Rosario García Campelo
Medical Oncology Unit
University Hospital A Coruña, Spain

GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

Study design

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Safety and clinical activity results from a phase 1b study of alectinib plus atezolizumab in *ALK*+ advanced NSCLC

Dong-Wan Kim,[1] Shirish Gadgeel,[2] Scott Gettinger,[3] Gregory J. Riely,[4] Geoffrey Oxnard,[5] Tarek Mekhail,[6] Peter Schmid,[7] Afshin Dowlati,[8] Rebecca Heist,[9] Antoinette J. Wozniak,[10] Genevive Hernandez,[11] Indrani Sarkar,[11] Emmanuel Mitry,[12] Paul Foster,[11] Carol O'Hear,[11] Jessica Spahn,[11] Sai-Hong Ignatius Ou[13]

1. Seoul National University Hospital, Seoul, South Korea; 2. University of Michigan, Ann Arbor, MI, USA; 3. Yale Cancer Center, Yale New Haven Hospital, New Haven, CT, USA; 4. Memorial Sloan Kettering Cancer Center, New York City, NY, USA; 5. Dana-Farber Cancer Institute, Boston, MA, USA; 6. Florida Hospital Cancer Institute, Orlando, FL, USA; 7. Barts Cancer Institute, London, UK; 8. UH Cleveland Medical Center, Cleveland, OH, USA; 9. Massachusetts General Hospital, Boston, MA, USA; 10. Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA; 11. Genentech Inc., South San Francisco, CA, USA; 12. F. Hoffmann-La Roche Ltd, Basel, Switzerland; 13. Chao Family Comprehensive Cancer Center, University of California, Irvine School of Medicine, Orange, CA, USA

Study design

Key eligibility
- Treatment-naïve
- *ALK*+ advanced NSCLC
- ECOG PS 0–1
- Measurable disease
- Asymptomatic brain metastases allowed

Stage 1*†
Safety evaluation (n=7)
(on-treatment and post-progression biopsies optional)
Alectinib: 600mg BID PO‡
Atezolizumab: 1200mg q3w IV (Cycle 1, Day 8 of 28; Cycle ≥2, Day 1 of 21)

No DLTs observed with alectinib 600mg after 28 days; therefore, all patients received the same dose and dosing schedule (n=21)

Stage 2†
Expansion (n=14)
(on-treatment and post-progression biopsies mandatory)
Alectinib: 600mg BID PO
Atezolizumab: 1200mg q3w IV (Cycle 1, Day 8 of 28; Cycle ≥2, Day 1 of 21)

Alectinib 7-day run-in

Cycle 1: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Cycle ≥2: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

▼ Alectinib
● Atezolizumab

*Unless MTD is exceeded
†Discontinued in patients with disease progression or unacceptable toxicity
‡Starting dose of alectinib

BID, twice daily; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MTD, maximum tolerated dose; PO, by mouth; q3w, every three weeks

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Presented By Dong-Wan Kim at 2018 ASCO Annual Meeting

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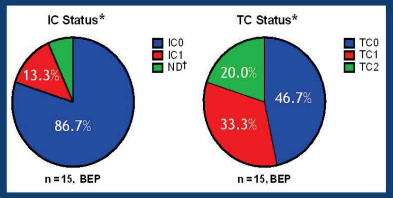
Baseline characteristics

n (%)		All patients (n=21)
Age, years	Median (range)	53.0 (36–75)
Sex, n (%)	Female	9 (42.9)
	Male	12 (57.1)
Race, n (%)	Asian	9 (42.9)
	White	12 (57.1)
Smoking status, n (%)	Current	2 (9.5)
	Prior	6 (28.6)
	Never	13 (61.9)
Histology type, n (%)	Squamous	2 (9.5)
	Non-squamous	19 (90.5)
ECOG PS, n (%)	0	8 (38.1)
	1	13 (61.9)
CNS metastasis, n (%)	Present	6 (28.6)
	Absent	15 (71.4)

Pie-charts to be redrawn

Baseline biomarkers

- PD-L1 expression was observed in 8/15 patients with evaluable tumors at baseline
  - 6 patients had PD-L1 expression on tumor cells only
  - 2 patients had PD-L1 expression on both immune cells and tumor cells
- CD8 T-cell count were evaluable in 17/20 patients at baseline
  - CD8 levels ranged from 0.2–15% of central tumor area, with a median of 0.8%



*PD-L1-positive cells defined as: IC0 or TC0 (<1%), IC1 or TC1 (≥1% but <5%); TC2 (≥5% but <50%)
†One patient had a pre-treatment sample taken >2 years before C1D1; all others had pre-treatment samples taken within one month of C1D1
BEP, biomarker evaluable population; IC, tumor-infiltrating immune cell; TC, tumor cell

Safety overview

Note: Number of alectinib withdrawals to be confirmed, details of alectinib modifications to be added, and DLT definition to be added at next draft

n (%)	All patients (n=21)
Any AE	21 (100)
Grade 3*	14 (66.7)
Serious AEs	7 (33.3)
Any treatment-related AE	19 (90.5)
Treatment-related grade 3 AEs	12 (57.1)
AE leading to atezolizumab withdrawal†	5 (23.8)
AE leading to alectinib withdrawal	0 (0.0)
AE leading to alectinib dose modification/interruption‡	15 (71.4)
No dose-limiting toxicities occurred§	

Investigator-assessed, safety evaluable population (patients received ≥1 dose of any study drug; data cut-off 1 February 2018, median follow-up: 16.9 months)

*No grade 4–5 AE events; †Liver function test increased, neutrophil count decreased, nausea, pneumonitis, rash (AEs did not fall under DLT criteria); ‡xxx ; §DLTs were defined as xxx

Most frequent treatment-emergent AEs (any grade)

n (%) (in ≥20% of patients)	All patients (n=21)
Constipation	11 (52.4)
Fatigue	10 (47.6)
Rash	10 (47.6)
Pyrexia	9 (42.9)
Dizziness	7 (33.3)
Headache	7 (33.3)
Cough	6 (28.6)
Myalgia	6 (28.6)
Aspartate aminotransferase increased	6 (28.6)
Alanine aminotransferase increased	5 (23.8)
Diarrhea	5 (23.8)
Dyspnea	5 (23.8)

Most frequent treatment-emergent AEs (grade 3)

Most frequent treatment-emergent AEs (grade 3)

Alectinib-related AE n (%)	All patients (n=21)
Alanine aminotransferase increase	2 (9.5)
Blood bilirubin increased	1 (4.8)
Liver function test increased	1 (4.8)
Rash	1 (4.8)
Rash maculo-papular	1 (4.8)
Hypophosphatemia	1 (4.8)
Neutropenia	1 (4.8)
Hyperbilirubinemia	1 (4.8)
Dyspnea	1 (4.8)

Atezolizumab-related AE n (%)	All patients (n=21)
Rash	3 (14.3)
Alanine aminotransferase increase	2 (9.5)
Dyspnea	2 (9.5)
Liver function test increased	1 (4.8)
Meningitis aseptic	1 (4.8)
Neutropenia	1 (4.8)
Pneumonitis	1 (4.8)
Rash maculo-papular	1 (4.8)

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ORR

ORR

	All patients (n=21)
Responders, n (%)	18 (85.7)
CR, n (%)	2 (9.5)
PR, n (%)	16 (76.2)
SD, n (%)	2 (9.5)
PD, n (%)	0 (0.0)
Missing/unevaluable, n (%)	1 (4.8)
Median DoR, months*	20.3
DCR (CR + PR + SD >24 weeks), %	19 (90.5)

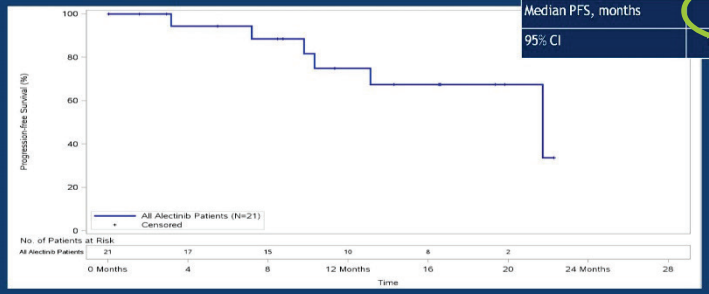
Investigator-assessed; data cut-off 1 February 2018 (median follow-up: 16.9 months)
*For alectinib monotherapy, the ALEX study reported a DoR of 'not evaluable' at the primary cut-off with a follow-up of 18.6 months
CR, complete response; ORR, objective response rate; PR, partial response; PD, progressive disease; SD, stable disease

PFS

Graph to be redrawn

PFS

	All patients (n=21)
Patients with events, n (%)	6 (28.6)
Median PFS, months	21.7
95% CI	13.1, NE



Investigator-assessed; data cut-off 1 February 2018 (median follow-up: 16.9 months)
NE, not evaluable

Avelumab (anti–PD-L1) in combination with crizotinib or lorlatinib in patients with previously treated advanced NSCLC: phase 1b results from JAVELIN Lung 101

Alice T. Shaw,[1] Se-Hoon Lee,[2] Suresh S. Ramalingham,[3] Todd M. Bauer,[4] Michael J. Boyer,[5] Enric Carcereny Costa,[6] Enriqueta Felip,[7] Ji-Youn Han,[8] Toyoaki Hida,[9] Brett G. M. Hughes,[10] Sang-We Kim,[11] Makoto Nishio,[12] Takashi Seto,[13] Patrick I. Ezeh,[14] Debasis Chakrabarti,[15] Jing Wang,[16] Andrew Chang,[16] Luca Fumagalli,[17] Benjamin J. Solomon[18]

[1]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [2]Samsung Medical Center, Seoul, South Korea; [3]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [4]Tennessee Oncology, Nashville, TN, USA; [5]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [6]Institut Catala d'Oncologia de Badalona, Servicio de Oncologia Medica, Badalona, Spain; [7]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [8]Center for Lung Cancer, National Cancer Center, Goyang-si, South Korea; [9]Aichi Cancer Center Central Hospital, Nagoya, Japan; [10]The Prince Charles Hospital, Cancer Care Services, Chermside, QLD, Australia; [11]Asan Medical Center, Seoul, South Korea; [12]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [13]National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [14]Pfizer Inc, Cambridge, MA, USA; [15]Pfizer Inc, Collegeville, PA, USA; [16]Pfizer Inc, San Diego, CA, USA; [17]Pfizer Inc, Milan, Italy; [18]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Study design: JAVELIN Lung 101

Phase 1b/2, open-label, multicenter, dose-finding trial

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Key eligibility criteria	Initial dose level	Key assessments
Group A • *ALK*-negative NSCLC • No known *ROS1* gene rearrangement, *c-MET* gene amplification, or *c-MET* exon 14 skipping • ≥1 prior regimen of systemic therapy • No prior antibody/drug targeting a T-cell coregulatory protein (eg, anti-PD-1/PD-L1)	**Group A** Avelumab 10 mg/kg (1h IV) Q2W + crizotinib 250 mg PO BID	Maximum tolerated dose (MTD) and recommended phase 2 dose
Group B • *ALK*-positive NSCLC • Any number of prior regimens, including zero • No prior antibody/drug targeting a T-cell coregulatory protein (eg, anti-PD-1/PD-L1) • Asymptomatic untreated brain metastases allowed	**Group B** Avelumab 10 mg/kg (1h IV) Q2W + lorlatinib 100 mg PO QD	Dose-limiting toxicities Safety and tolerability Antitumor activity

Data cutoff, October 27, 2017.
BID, twice a day; **IV,** intravenous; **PO,** by mouth; **Q2W,** every 2 weeks

Patient characteristics

	Avelumab + Crizotinib *ALK*– (n=12)	Avelumab + Lorlatinib *ALK*+ (n=28)
Median age (range), years	59.5 (43.0-76.0)	54.0 (30.0-77.0)
Sex, n (%)		
Male	6 (50.0)	12 (42.9)
Female	6 (50.0)	16 (57.1)
ECOG PS, n (%)		
0	3 (25.0)	10 (35.7)
1	9 (75.0)	15 (53.6)
2	0	3 (10.7)
Measurable brain metastases at baseline, n (%)		
Yes	0	4 (14.3)
No	12 (100.0)	24 (85.7)

	Avelumab + Crizotinib *ALK*– (n=12)	Avelumab + Lorlatinib *ALK*+ (n=28)
Prior regimens for metastatic/ advanced disease*		
0	2 (16.7)	1 (3.6)
1	2 (16.7)	7 (25.0)
2	4 (33.3)	5 (17.9)
3	4 (33.3)	4 (14.3)
≥4	0	10 (35.7)
Not reported	0	1 (3.6)
Prior ALK TKIs*		
0	12 (100)	0
1	0	7 (25.0)
≥2	0	20 (71.4)
Not reported	0	1 (3.6)
Median (range)	-	2 (1-3)

Dose-limiting toxicities (DLTs)

	Avelumab + Crizotinib *ALK*– (n=12)	Avelumab + Lorlatinib *ALK*+ (n=25)†
Any DLT, n (%)	**5 (41.7)***	**0**
ALT increased	2 (16.7)	0
AST increased	2 (16.7)	0
Febrile neutropenia	1 (8.3)	0
Hepatitis	1 (8.3)	0
QT prolongation	1 (8.3)	0
Rash	1 (8.3)	0

Adverse events (any causality)

	Avelumab + Crizotinib *ALK*− (n=12)	
	Any grade	Grade ≥3
Any AE, n (%)	**12 (100)**	**7 (58.3)**
Nausea	7 (58.3)	0
Vomiting	6 (50.0)	0
Decreased appetite	5 (41.7)	0
ALT increased	4 (33.3)	2 (16.7)
Rash	4 (33.3)	1 (8.3)
Anemia	3 (25.0)	1 (8.3)
AST increased	3 (25.0)	1 (8.3)
Chills	3 (25.0)	0
Diarrhea	3 (25.0)	0
Myalgia	3 (25.0)	0
Pyrexia	3 (25.0)	0

	Avelumab + Lorlatinib *ALK*+ (n=28)	
	Any grade	Grade ≥3
Any AE, n (%)	**27 (96.4)**	**15 (53.6)**
Blood cholesterol increased	16 (57.1)	2 (7.1)
Hypertriglyceridemia	16 (57.1)	4 (14.3)
Edema peripheral	8 (28.6)	0
Arthralgia	7 (25.0)	0
Anemia	6 (21.4)	2 (7.1)
Hypothyroidism	6 (21.4)	0
Infusion-related reaction	6 (21.4)	0
Peripheral neuropathy	6 (21.4)	0
Pyrexia	6 (21.4)	1 (3.6)
GGT increased	3 (10.7)	3 (10.7)

Tables show individual adverse events (AEs) that occurred at any grade in ≥20% or at grade ≥3 in ≥10%
GGT, γ-glutamyltransferase

Avelumab + crizotinib (*ALK*–): tumor responses

	n=12
Confirmed best overall response, n (%)	
Complete response	0
Partial response	2 (16.7)
Stable disease	5 (41.7)
Progressive disease	5 (41.7)
Not evaluable	0
Objective response rate, % (95% CI)	16.7 (2.1–48.4)
Median time to response, months (range)	1.4 (1.4-1.4)
Median duration of response, months (95% CI)	4.1 (3.7–4.6)
Disease control rate, % (95% CI)	58.3 (27.7–84.8)

Avelumab + lorlatinib (*ALK+*): tumor responses

	n=28
Confirmed best overall response, n (%)	
Complete response	1 (3.6)
Partial response	12 (42.9)
Stable disease	6 (21.4)
Progressive disease	7 (25.0)
Not evaluable	2 (7.1)
Objective response rate, % (95% CI)	46.4 (27.5–66.1)
Median time to response, months (range)	1.9 (1.4-3.7)
Median duration of response, months (95% CI)	7.4 (3.7–NE)
Disease control rate, % (95% CI)	67.9 (47.6–84.1)

Some notes to conclude

- Combination therapy with ALK TKI and ICI is not the optimal therapeutic option

  NO CLEAR SIGNAL OF BETTER EFFICACY, difficult to improve actual results

- Toxicities of the combination: needs to be considered, particularly with crizotinib

- Combination CT+IO may be a path moving forward