LUNG CANCER
UPDATES
ASCO HIGHLIGHTS
31 MAYO - 4 JUNIO 2019

Iniciativa científica de:
GECP
lung cancer research

Cómo revertir la resistencia a las terapias dirigidas EGFR, ROS1

Dr. Delvys Rodríguez-Abreu

Día 1

Con la colaboración de:

Bristol-Myers Squibb
illumina
Lilly

Revertir resistencia a EGFR

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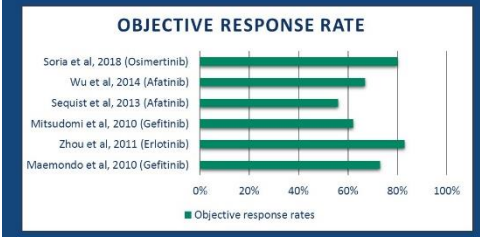
Background: EGFR TKIs

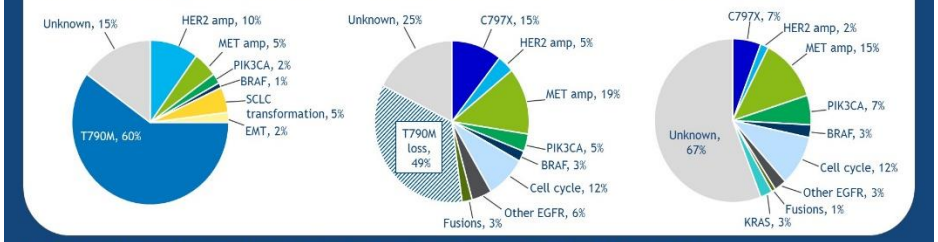
While targeting an oncogenic driver in NSCLC usually leads to robust initial responses, emergence of resistance is inevitable and limits clinical benefit

EGFR mutated NSCLC



Targeting HER3 to Address Multiple EGFR TKI Resistance Mechanisms

Mechanisms of resistance to EGFR TKIs in EGFR-mutant NSCLC

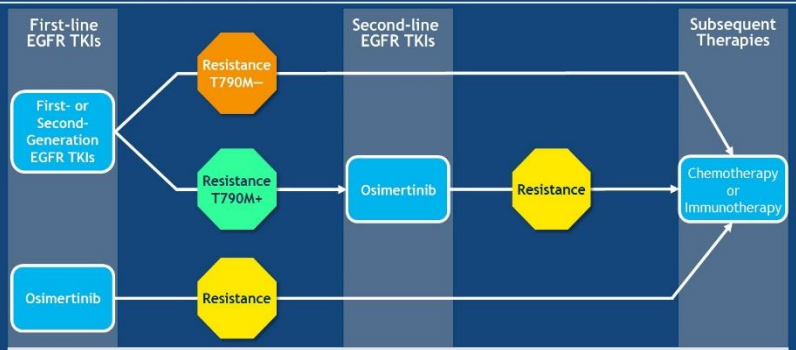


- Developing therapies to combat all individual resistance mechanisms is likely impractical
- Resistance mechanisms may overlap in an individual patient
- 57%–67% of EGFR-mutant NSCLCs show some level of HER3 expression[4,5]

Targeting HER3 with an antibody drug conjugate may be an alternative treatment strategy for advanced NSCLC

1. Wu, et al. *Mol Cancer*. 2018;17:38. 2. Papadimitrakopoulou, et al. *Ann Oncol*. 2018;29. 3. Ramalingam, et al. *Ann Oncol*. 2018;29. 4. Yi, et al. *Mod Pathol*. 1997;10:142-148. 5. Kawano, et al. *J Surg Res*. 2008;146:43-48.

EGFR TKI Resistance Creates a Significant Unmet Need in Metastatic EGFR-mutant NSCLC

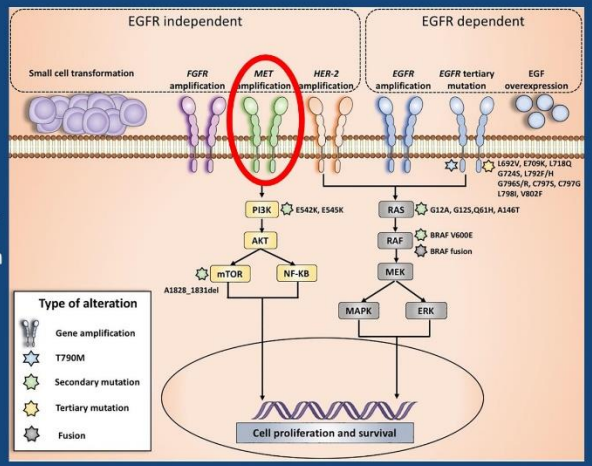


Overall survival is approximately 22–36+ months[a]

[a]Estimates of patients who have progressed on EGFR TKIs and chemotherapy from Tan CS, et al. *Mol Cancer*. 2018;17:29. References: Planchard D, et al. *Ann Oncol*. 2018;29:iv192-iv237. Ettinger DS, et al. *J Natl Compr Canc Netw*. 2017;15:504-535. Jänne PA, et al. *Lancet Oncol*. 2014;15:1433-1441. EGFR, epidermal growth factor receptor; NSCLC, nonsmall cell lung cancer; TKI, tyrosine kinase inhibitor.

MET amplification

- Post-osimertinib: 15%
- Pre-clinical models show synergy between EGFR and MET inhibition and targeting MET can reverse resistance
- Treatment strategy: dual inhibition



Lim, et al, *Cancer Treatment Reviews* 2018

Revertir resistencia a EGFR

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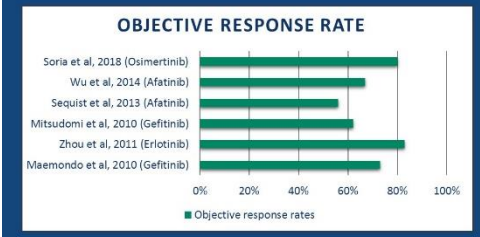
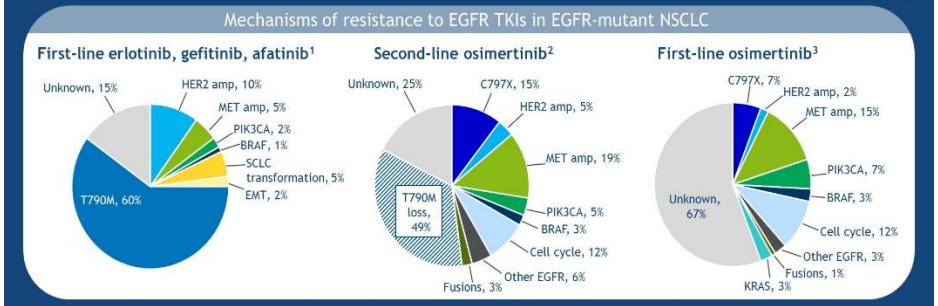


Targeting HER3 to Address Multiple EGFR TKI Resistance Mechanisms



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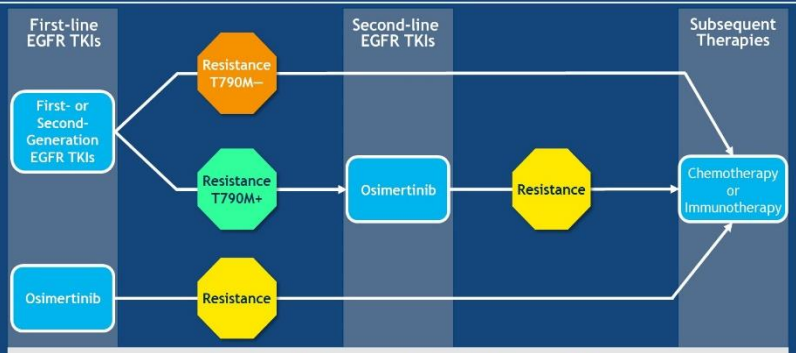

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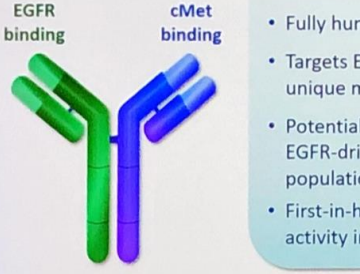
JNJ-61186372 (JNJ-372), an EGFR-cMet bispecific antibody, in EGFR-driven advanced non-small cell lung cancer (NSCLC)

Eric B. Haura,[1] Byoung Chul Cho,[2] Jong-Seok Lee,[3] Ji-Youn Han,[4] Ki Hyeong Lee,[5] Rachel E. Sanborn,[6] Ramaswamy Govindan,[7] Eun Kyung Cho,[8] Sang-We Kim,[9] Karen L. Reckamp,[10] Joshua K. Sabari,[11] Catherine A. Shu,[12] Dong-Wan Kim,[13] Jorge E. Gomez,[14] Aaron S. Mansfield,[15] Alexander Spira,[16] Pasi A. Jänne,[17] Santiago Viteri,[18] Jose Manuel Trigo,[19] Martin Curtis,[20] Patricia A. Lorenzini,[20] Meena Thayu,[20] Amy Roshak,[20] Kyounghwa Bae,[20] Roland E. Knoblauch,[20] Joshua C. Curtin,[20] Nahor Haddish-Berhane,[20] Matthew V. Lorenzi,[20] Keunchil Park,[21] Joshua M. Bauml[22]

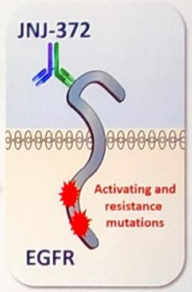
[1]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [2]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Seoul National University Bundang Hospital, Gyeonggi-do, Republic of Korea; [4]National Cancer Center, Gyeonggi-do, Republic of Korea; [5]Chungbuk National University Hospital, Cheongju, Republic of Korea; [6]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA; [7]Washington University School of Medicine, St. Louis, MO, USA; [8]Gachon University Gil Medical Center, Incheon, Republic of Korea; [9]Asan Medical Center, Seoul, Republic of Korea; [10]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [11]NYU School of Medicine, New York, NY, USA; [12]Columbia University Medical Center, New York, NY, USA; [13]Seoul National University Hospital, Seoul, Republic of Korea; [14]Icahn School of Medicine at Mt. Sinai, New York, NY, USA; [15]Mayo Clinic, Rochester, MN, USA; [16]Virginia Cancer Specialists, Fairfax, VA, USA; [17]Dana Farber Cancer Institute, Boston, MA, USA; [18]Hospital Universitari Dexeus, Barcelona, Spain; [19]Hospital Universitario Virgen de la Victoria, Malaga, Spain; [20]Janssen R&D, Spring House, PA, USA; [21]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [22]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

JNJ-372 Fase 1

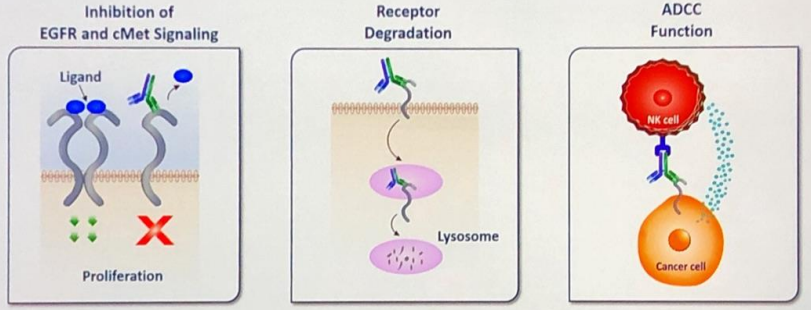
Overview: JNJ-61186372 (JNJ-372)



- Fully humanized, bispecific IgG1 antibody
- Targets EGFR and cMet receptors through unique mechanisms of action
- Potential to provide clinical benefit in EGFR-driven NSCLC, including TKI-resistant populations
- First-in-human study currently evaluating activity in EGFRmut-driven NSCLC



Preclinical Data Consistent With 3 Proposed Mechanisms of Action



JNJ-372 has demonstrated activity in multiple EGFRmut NSCLC models of EGFR- and cMet-mediated TKI resistance

Moores et al. 2016 *Cancer Res*; 76 (13)

Study Design: Objectives and Eligibility

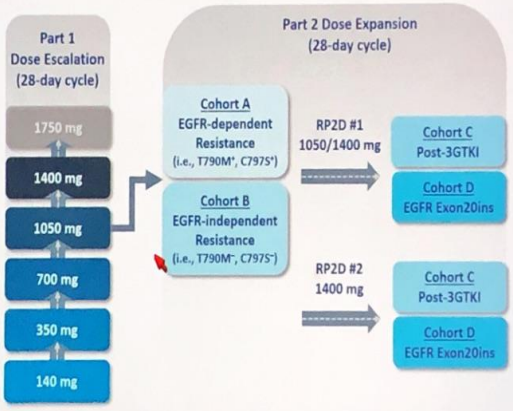
N-142

Dr. Keunchil Park
Samsung Medical Center
Sungkyunkwan University School of Medicine

WCLC 2018
J Thorac Oncol 2018;13:S344-5

Dr. Byoung Chul Cho
Yonsei Cancer Center
Yonsei University College of Medicine

ESMO 2018
Ann Oncol 2018;29:viii493-viii547



Dosing: intravenous; once weekly in cycle 1 and biweekly thereafter

Demographic and Baseline Disease Characteristics

	Total (N=142)
Median age, years (range)	63 (33–82)
Male/Female, n (%)	52/90 (37/63)
Race, n (%)	
Asian	100 (70)
Black	4 (3)
White	33 (23)
Not reported	5 (4)
ECOG PS, n (%)	
0	37 (26)
1	104 (73)
2	1 (1)
Median prior lines of treatment, n (range)	3 (0–10)
Median prior lines of EGFR TKI, n (range)	2 (0–6)
NSCLC subtype, n (%)	
Adenocarcinoma	139 (98)
Squamous cell carcinoma	3 (2)

	Total (N=142)
EGFR mutation subtype, n (%)[a]	
wtEGFR	11 (8)
Primary EGFR mutation[b]	131 (92)
Exon 19 deletion	60 (46)
Exon 21 L858R	34 (26)
Exon 20 insertion	33 (25)
Exon 18 G719A	3 (2)
Exon 20 S768I	1 (1)
Exon 20 T790M	1 (1)
V769L	1 (1)
TKI resistance mutation[b,c]	
T790M	49 (37)
C797S	28 (21)
cMet amplification (≥6 copies)[d]	10 (8)

JNJ-372 Fase 1

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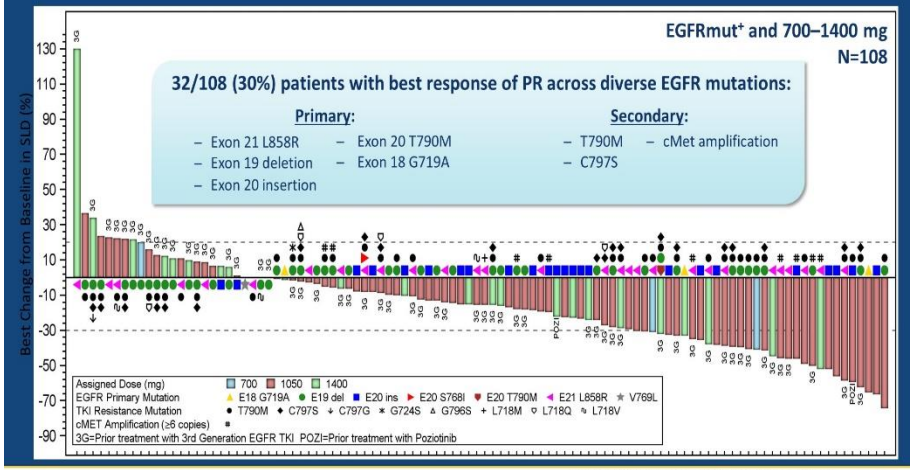
Results – highlights



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6 patients had best overall response of PD and non-evaluable target lesion measurements or new lesions in the first postbaseline assessment and are not included in the plot but are included in the N; SLD=sum of target lesion diameters

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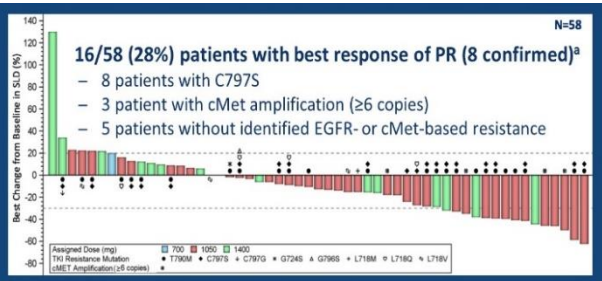
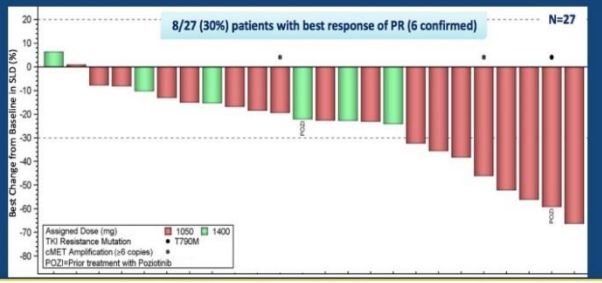
Post 3GTKI: RR 28%



exon20ins: RR 30%



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Clinical trials - EGFR + cMET inhibitors … the world of TKIs

Population	Drugs	Met-selected?	Result
EGFR-mutant, TKI resistant NSCLC	Erlotinib + tivatinib[1]	no	ORR 6.7% (3/45 patients) 3 responders: + Met IHC, + HGF
	Gefitinib + savolitinib[2]	no	ORR 18% - (2/11) neither with MET amplification
	Gefitinib + capmatinib[3]	Yes	ORR 29% ORR 47% in highest MET GCN
	Gefitinib + tepotinib[4]	Yes	ORR 33%
	Osimertinib + savolitinib[5]	Yes	Prior 1st/2nd gen: ORR – 52% Prior 3rd gen: ORR 25%

1. Azuma et al ESMO Open 2018. 2. Yang et al ASCO Meet Abstr 2016. 3. Wu et al JCO 2019. 4. Wu et al ASCO Meet Abstr. 2016. 5. Sequist et al AACR 2019

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19 PRESENTED BY: Jessica R. Bauman, MD

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Conclusions

- JNJ-372 activity observed across diverse EGFR-mutated NSCLC, including those with unmet need
  - Patients with EGFR C797S-mediated resistance to 3GTKI (osimertinib)
  - Patients with cMet-mediated resistance to 3GTKI (osimertinib)
  - Patients with TKI-naïve Exon20ins disease
- JNJ-372 has a manageable safety profile consistent with EGFR inhibition
  - Low ≥Grade 3 toxicity rate (9%)
  - Frequent IRR, but primarily limited to first dose (C1D1)
- 1050 mg and 1400 mg currently being explored as RP2D
- Enrollment of patients with high unmet need is ongoing (NCT02609776)

U3-1402 Fase 1

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Safety and preliminary antitumor activity of U3-1402, a HER3-targeted antibody drug conjugate, in EGFR TKI-resistant, EGFRm NSCLC

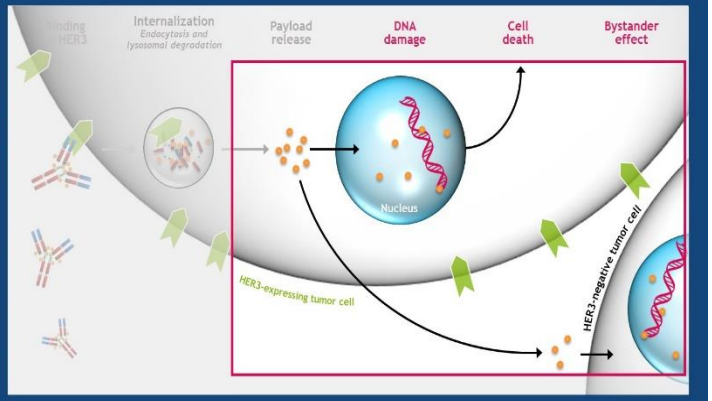
Pasi A. Jänne[1], Helena Alexandra Yu[2], Melissa Lynne Johnson[3], Conor Ernst Steuer[4], Michele Vigliotti[5], Corinne Iacobucci[5], Shuquan Chen[5], Channing Yu[5], Dalila Sellami[5]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Sarah Cannon Research Institute, Nashville, TN; [4]Winship Cancer Institute of Emory University, Atlanta, GA; [5]Daiichi Sankyo Inc., Basking Ridge, NJ

U3-1402, a Novel Antibody Drug Conjugate Designed to Target HER3 Expression in EGFR-mutant NSCLC

U3-1402 Design Features

- Payload MOA: Topo I inhibitor
- High potency of payload
- High drug-to-antibody ratio (~8:1)
- Payload with short systemic half-life
- Stable linker-payload
- Tumor-selective cleavable linker
- Bystander effect



U3-1402 Phase 1 Dose Escalation and Expansion Study

Eligibility

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 TKI) required for retrospective analysis of HER3 expression

Dose Escalation[a]

Received ≥1 dose of U3-1402 IV Q3W: N = 23

N-23

- 6.4 mg/kg, n = 5
- 5.6 mg/kg, n = 6
- 4.8 mg/kg, n = 8
- 3.2 mg/kg, n = 4

Ongoing n = 16

Discontinued[b] n = 7

Dose Expansion

Will enroll additional patients at the recommended dose for expansion

Study Objectives

- **Primary:** Safety and tolerability of U3-1402
- **Secondary:** Antitumor activity of U3-1402
- **Exploratory:** Biomarkers of U3-1402 antitumor activity

Data cutoff of February 25, 2019. [a]Dose escalation was guided by the modified continuous reassessment method with escalation with overdose control. Additional doses may be added. [b]Reasons for discontinuation included progressive disease per RECIST v1.1, n = 5; clinical progression (definitive clinical signs of disease progression, but did not meet RECIST criteria), n = 1; and adverse event, n = 1. clinicaltrials.gov NCT03260491.

Baseline Characteristics of Patients Treated with U3-1402

Baseline clinical characteristics		Dose escalation (N = 23)[a]
Age, median (range), years		63.0 (51.0–80.0)
Sex, n (%)	Female	14 (60.9)
	Male	9 (39.1)
Race, n (%)	White	13 (56.5)
	Asian	7 (30.4)
	Black or African American	1 (4.3)
	Other	2 (8.7)
ECOG performance status, n (%)	0	9 (39.1)
	1	14 (60.9)
Prior therapies, n (%)	Any EGFR TKI	23 (100.0)
	Osimertinib[b]	21 (91.3)
	Chemotherapy	10 (43.5)

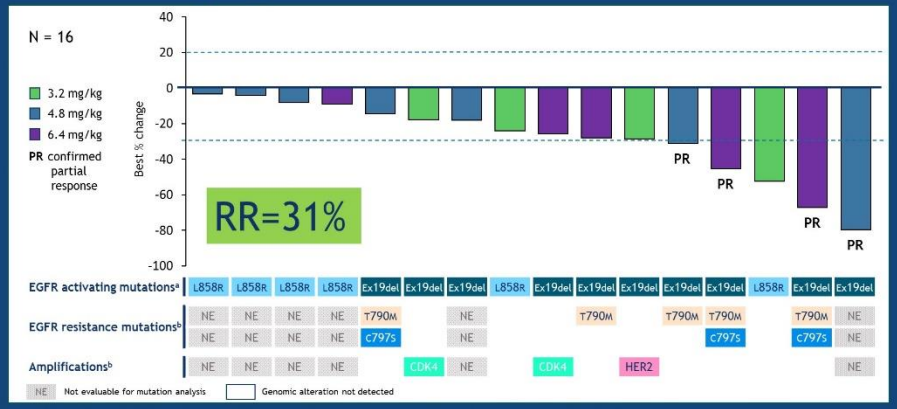
Baseline disease characteristics		Dose escalation (N = 23)[a]
Sites of metastases, n (%)	CNS[c]	14 (60.9)
	Liver	9 (39.1)
	Lung	4 (17.4)
Tumor stage, n (%)	IV	23 (100.0)
Sum of diameters of target lesions, median (range), mm		69 (20–143)

Baseline molecular characteristics		Dose escalation (N = 23)[a]
HER3 expression[d]		
Evaluable patients[e]	n/n (%)	19/19 (100.0)
Membrane H-score[f] *composite score of 0–300*	median (range)	193 (150–290)
EGFR mutation[g], n (%)	Ex19del	13 (56.5)
	L858R	9 (39.1)
	L861Q	1 (4.3)

Data cutoff date of February 25, 2019. [a]Safety analysis set included all patients who received ≥1 dose of U3-1402. [b]Additional subject with prior osimertinib reported after snapshot date, not shown. [c]Includes brain and spinal metastases as reported by investigators. [d]Based on central analysis of tumor tissue collected prior to first dose of U3-1402. [e]Includes patients with tumor samples that have completed retrospective analysis. [f]Membrane H-score is a composite of percentage of positively staining cells and intensity of individual cell staining. For patients with multiple H-scores, the highest number was used. [g]As reported locally by the investigator.

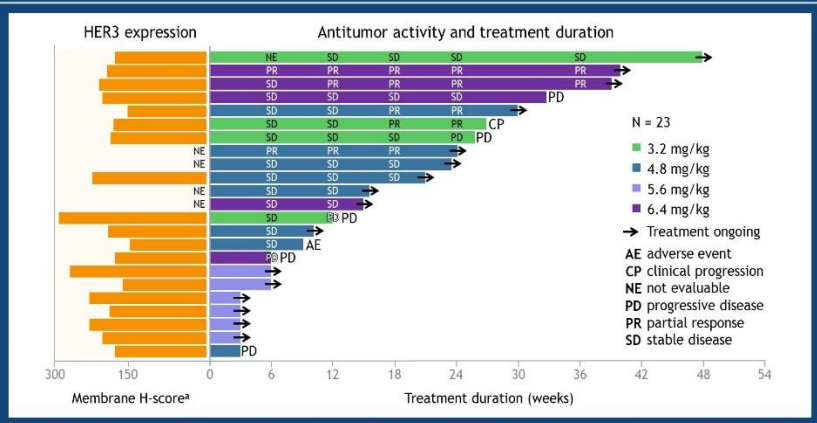
U3-1402 Fase 1

Results – highlights



Data cutoff date of February 25, 2019. Dotted lines denote 20% increase and 30% decrease in tumor size. Sixteen patients received ≥1 dose of U3-1402 and had pre- and post-treatment evaluable tumor assessments. [a]Local testing as reported by the investigator. [b]Performed centrally using Oncomine Comprehensive assay v3 from formalin-fixed, paraffin-embedded tumor tissue.

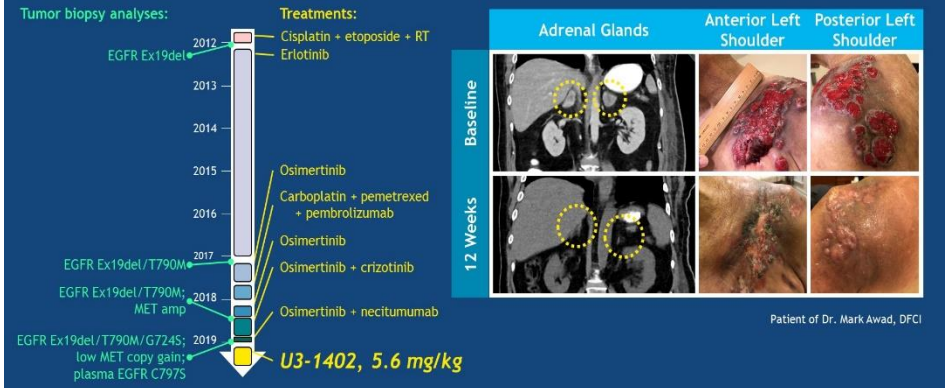
U3-1402 Treatment Duration



Data cutoff date of February 25, 2019. Safety analysis set included all patients who received ≥1 dose of U3-1402. [a]Membrane H-score is a composite of percentage of positively staining cells and intensity of individual cell staining. Scores range from 0–300. For patients with multiple H-scores, the highest number was used.

U3-1402 Patient Case

65-year-old male NSCLC patient



Patient of Dr. Mark Awad, DFCI

Conclusions

- U3-1402, a HER3 ADC, displayed a manageable safety profile in this phase 1 study
  - The majority of TEAEs were grade 1 or 2 events
  - The majority of discontinuations were due to progressive disease (n = 5); only 1 patient discontinued due to an AE, and there were no TEAEs leading to death
  - DLTs were grade 4 platelet count decreased (n = 4) and grade 3 febrile neutropenia (n = 1)
- Antitumor activity with U3-1402 was observed in patients with EGFR-mutant TKI-resistant NSCLC, with a median follow-up of 4.2 months
- The 5.6 mg/kg dose cohort is ongoing, and a dose expansion is planned for Q3 of 2019

Targeting HER3 with U3-1402 may be a practical approach to treat EGFR-mutant NSCLC with diverse mechanisms of resistance to EGFR TKIs

Data cutoff February 25, 2019.

Revertir resistencia a ALK y ROS1

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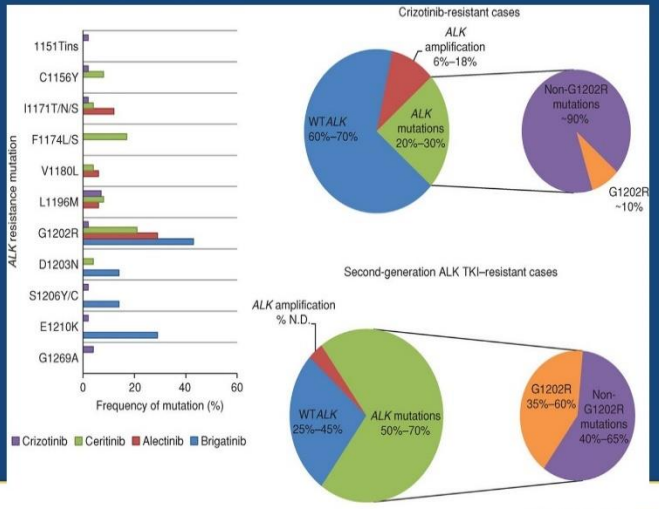
Background: ALK TKIs

NSCLC with ALK rearrangement

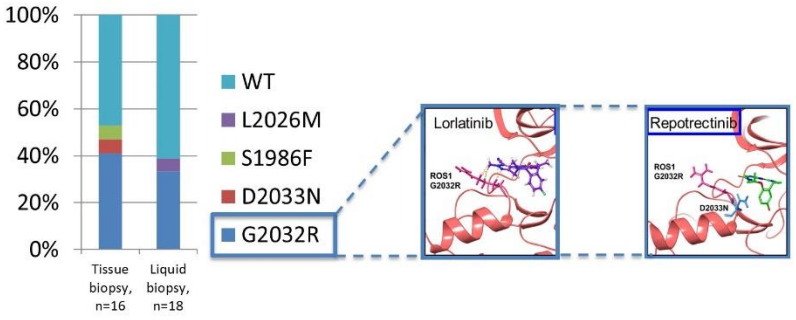
Acquired resistance to ALK inhibitors



Gainor et al, Cancer Discov 2016; Lin et al, Cancer Discov 2017

Secondary mutations in ROS1

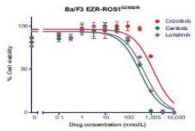
***ROS1*, ~50% 2nd mutations**



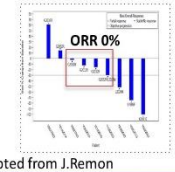
Lin Cancer Discovery 2017, CCR 2018, Dagogo-Jack JTO 2019

ROS1 TKI against G2032R

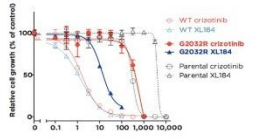
Lorlatinib

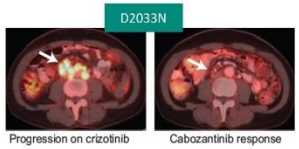


IC_{50} ~500 nmol/L for block G2032R



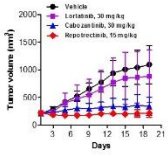
Cabozantinib

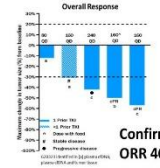




NCT01639508 ph II ongoing in *RET / ROS1 / NTRK* fusions

Repotrectinib





Confirmed ORR 40%

Adapted from J.Remon

Cho ASCO 2019, Chong CCR 2017, Facchinetti CCR 2016, Katayama CCR 2015
Solomon ESMO 2018, Drilon CCR 2016, Kato Cancer Sci 2018

Repotrectinib (TRIDENT) Fase 1

LUNG CANCER UPDATES
ASCO HIGHLIGHTS
31 MAYO - 4 JUNIO 2019

Safety and Preliminary Clinical Activity of Repotrectinib in Patients with Advanced *ROS1* Fusion-Positive Non-Small Cell Lung Cancer (TRIDENT-1 STUDY)

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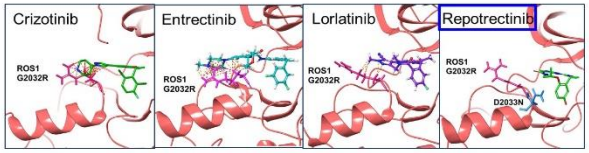
Targeting *ROS1* Fusion Positive Non-Small Cell Lung Cancer

- *ROS1* rearrangement is an oncogenic driver in 1-2% of NSCLC
- Crizotinib is the only approved targeted therapy for patients with advanced *ROS1*+ NSCLC
- G2032R is the most common *ROS1* resistance mutation after crizotinib treatment[1]
- **Repotrectinib is a next-generation ROS1/TRKA-C/ALK inhibitor, designed to overcome TKI resistance mutations, especially solvent front *ROS1* G2032R[2]**

[1]Gainor JF et al., ICO Precis Oncol 2017
[2]Drilon A et al., Cancer Discov 2018

Repotrectinib is a Small, Rigid Macrocycle Designed to Overcome the *ROS1* G2032R Solvent Front Mutation



CD74-ROS1 Ba/F3 Cell Proliferation IC_{50} (nM)*

ROS1	Crizotinib	Ceritinib	Cabozantinib	Entrectinib	Lorlatinib	Repotrectinib
WT	14.6	42.8	0.5	10.5	0.2	<0.2
G2032R	266.2	1391	11.3	1813	160.7	3.3

*Data based on evaluation of comparable proxy chemical reagents purchased from commercial sources except repotrectinib

N-33

TRIDENT-1 Design

Study Design/Eligibility (Phase 1)
- Advanced solid tumors harboring *ROS1/NTRK1-3/ALK* fusions
- No limit on prior lines of therapy
- Asymptomatic CNS metastases allowed

Phase 1 Primary Objective
- Determine the MTD and RP2D

Phase 1 Secondary Objectives
- Safety and tolerability
- Preliminary objective response rate and clinical benefit rate

	Number of patients per dose cohort									
	40 mg QD	80 mg QD	160 mg QD	240 mg QD	160 mg BID	200 mg BID[1]	120 mg QD w/ Food	160 mg QD w/ Food	160 mg QD/BID w/Food[2]	Total
Safety population (*ROS1+, NTRK1-3+, ALK+* solid tumors)	13	12	23	10	12	2	3	5	3	83**
Efficacy population (*ROS1+* NSCLC)	5	5	10	2	6	0	2	3	0*	33

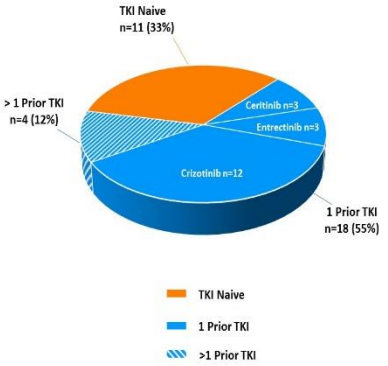
[1] 2 ALK patients enrolled
[2] 160 mg QD for one week followed by 160 mg BID
* Not yet evaluable for efficacy by BICR
** N=83 patients: 31 were *ALK+*, 9 were *NTRK+*, and 43 were *ROS1+* (of which 33 *ROS1+* NSCLC were evaluable for efficacy by BICR)
BICR: Blinded Independent Central Review

TRIDENT-1: *ROS1+* NSCLC Patient Demographics

Characteristics	N=33
Age, median (range)	57 (30, 79)
Sex, female n (%)	23 (70)
Race, Asian n (%)	20 (61)
Median lines of prior systemic therapy (range)	2 (1, 8)
Prior chemotherapy, n (%)	28 (85)
CNS metastases at baseline n (%)*	18 (55)
Median # of prior ROS1 TKIs (range)	1 (0, 3)
TKI Naive, n (%)	11 (33)
TKI Pretreated, n (%)	22 (67)
1 prior TKI	18 (55)
Crizotinib only	12 (67)
Ceritinib or entrectinib	6 (33)
>1 prior TKI	4 (12)

*Assessed by Investigator

Distribution of Prior ROS1 TKIs



Repotrectinib (TRIDENT) Fase 1

LUNG CANCER UPDATES
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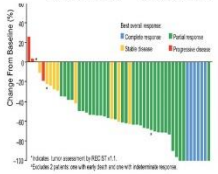
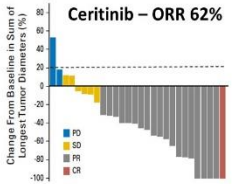
ROS1 inhibitors in TKI naive patients

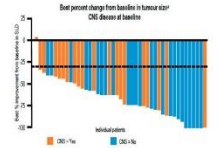
Crizotinib – ORR 72%



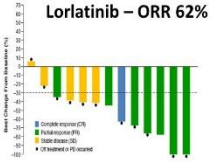
Ceritinib – ORR 62%



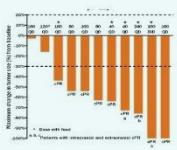
Entrectinib – ORR 77%



Lorlatinib – ORR 62%



Repotrectinib – ORR 82%



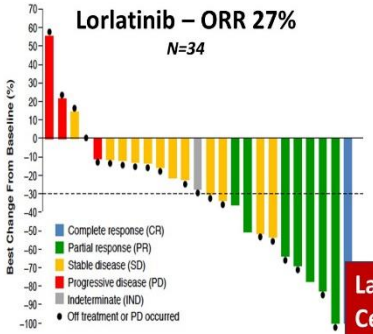
- ✓ High ORR but small n
- ✓ Dose doen't impact ORR
- ✓ PFS not available
- ✓ Efficacy vs. ROS1 fusion partner unknown

Besse – ESMO 2017 *Ou – WCLC 2018 * Solomon – ESMO 2018

Lim JCO 2017, Barlesi ELCC 2019
Shaw ELCC 2019 , Cho ASCO 2019

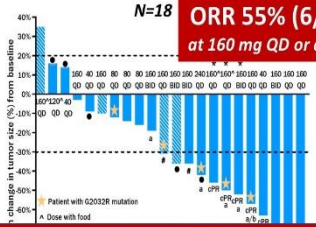
ROS1 inhibitors in TKI pretreated patients

Lorlatinib – ORR 27%
N=34



Repotrectinib – ORR 39%
N=18

ORR 55% (6/11)
at 160 mg QD or above



Last line of treatment : a ROS1 TKI (majority)
Ceritinib (n=3) : PR
Entrectinib (n=3) : no confirmed PR yet
Lorlatinib (n<4) : unknown

Besse ESMO 2017, Ou WCLC 2018, Solomon ESMO 2018, Cho ASCO 2019

Safety Summary: Treatment-Emergent and Treatment-Related AEs

Adverse Event	All Treated Patients (N=83)				
	TEAEs (≥10% of patients)			TRAEs	
	All Grades n(%)	Grade 3 n(%)	Grade 4* n(%)	Grade 3 n(%)	Grade 4 n(%)
Dizziness	47(56.6)	2 (2.4)	---	2 (2.4)	---
Dysgeusia	42 (50.6)	---	---	---	---
Dyspnea	25 (30.1)	5 (6.0)	1 (1.3)	1 (1.2)	---
Fatigue	25 (30.1)	2 (2.4)	---	---	---
Constipation	24 (28.9)	---	---	---	---
Paresthesia	24 (28.9)	---	---	---	---
Anemia	23 (27.7)	10 (12.0)	---	3 (3.6)	---
Nausea	19 (22.9)	2 (2.4)	---	---	---
Cough	17 (20.5)	---	---	---	---
Pyrexia	16 (19.3)	---	---	---	---
Headache	14 (16.9)	1 (1.2)	---	---	---
Vomiting	13 (15.7)	---	---	---	---
Upper respiratory tract infection	11 (13.3)	---	---	---	---
Ataxia	10 (12.0)	---	---	---	---
Pain in extremity	10 (12.0)	1 (1.2)	---	---	---
Abdominal pain	9 (10.8)	---	---	---	---
Muscular weakness	9 (10.8)	1 (1.2)	---	---	---

*Add'l Grade 4 TEAEs: cerebrovascular accident, dyspnea, influenza, hyperkalemia, bacterial pneumonia (n=1 each), respiratory failure (n=2); None were determined to be related to treatment
* Grade 5 TEAEs: respiratory failure (n=2), sepsis, sudden death (n=1 each); Only the case of sudden death was determined to be possibly related to treatment

- ✓ TRK inhibition? Lack of taste
- ✓ Marginal weight gain (6% all grade)
- ✓ Four DLT events:
  - ✓ Grade 2 or 3 dizziness
    - ✓ 160 mg BID (n=2)
    - ✓ 240 mg QD (n=1)
  - ✓ Grade 3 dyspnea and hypoxia
    - ✓ 160 mg BID (n=1)
- ✓ Recommended dose UNKNOWN yet

Cho ASCO 2019

Conclusions

- **TRIDENT-1 Phase 1 data support repotrectinib as a potential best-in-class *ROS1* agent in advanced NSCLC**
- **Preliminary clinical activity demonstrated across 7 dose cohorts in *ROS1+* NSCLC patients**
  - TKI-naive:
    - cORR 82% (9/11); median DOR not yet reached
  - TKI-pretreated:
    - 1 prior TKI: cORR 39% (7/18)
      - cORR 57% (4/7) in crizotinib-pretreated patients at 160 mg QD and above
  - CNS activity observed in both TKI-naïve and TKI-pretreated patients
- **Repotrectinib is a next-generation ROS1/TRKA-C/ALK inhibitor designed to overcome TKI resistant mutations**
  - All 5 *ROS1+* NSCLC patients with the G2032R SFM experienced tumor regressions with a cORR of 40%
- **Repotrectinib was well tolerated with a manageable safety profile**
  - Dizziness is an on-target AE associated with TRK inhibition and manageable
  - Most AEs managed without dose modification and rarely led to discontinuation
- **Pivotal Phase 2 portion of TRIDENT-1 planned to initiate in 2H 2019**