Iniciativa científica de:

GECP lung cancer research

# LUNG CANCER UPDATES

## ASCO HIGHLIGHTS

**31 MAYO - 4 JUNIO 2019**


Con la colaboración de:

Bristol-Myers Squibb

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UPDATES
ASCO HIGHLIGHTS
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# Mutaciones de MET

Dra. Ana Laura Ortega

Con la colaboración de:

Bristol-Myers Squibb
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# Fase II GEOMETRY: capmatinib en METΔex14



## Capmatinib in *METΔex14*-mutated advanced non-small cell lung cancer (NSCLC): Efficacy data from the phase II GEOMETRY mono-1 study

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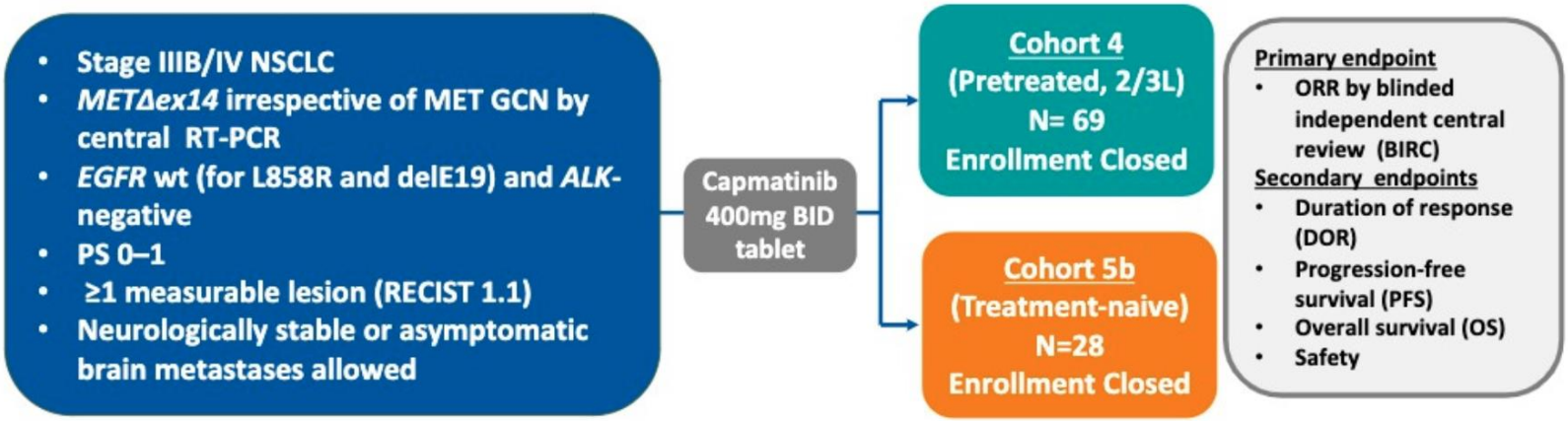
PRESENTED BY: Prof. Juergen Wolf

Abstract No 9004

# Fase II GEOMETRY: capmatinib en METΔex14



## GEOMETRY mono-1: A phase II trial of capmatinib in patients with advanced NSCLC harboring *MET exon14 skipping* mutation




Study methodology:

- Cohort 4 and 5b are each analyzed separately and have independent statistical hypothesis
- Primary (ORR) and key secondary (DOR) endpoints based on BIRC including 2 parallel independent radiology reviewers (+ additional one for adjudication)
- Efficacy endpoints based on BIRC and investigator assessment per RECIST 1.1

Data cut off: April 15, 2019; median duration of follow-up for DOR: 9.7 months in Cohort 4 and 9.6 months in Cohort 5b
Additional data on *MET* mutated patients will be generated in Cohort 6 (2L; N~30) and Cohort 7 (1L; N~27)

# Fase II GEOMETRY: capmatinib en METΔex14



## Baseline characteristics

| Baseline characteristics | | Cohort 4 (2/3L) N = 69 | Cohort 5b (1L) N = 28 |
|---|---|---|---|
| **Age (years)** | Median (range) | 71 (49-90) | 71 (57-86) |
| **Race, n (%)** | Caucasian | 49 (71.0) | 24 (85.7) |
| | Asian | 19 (27.5) | 4 (14.3) |
| | Other | 1 (1.4) | 0 |
| **Sex, n (%)** | Female/Male | 40 (58.0)/29 (42.0) | 18 (64.3)/10 (35.7) |
| **Smoking history, n (%)** | Never smoker | 40 (58.0) | 18 (64.3) |
| | Former smoker | 27 (39.1) | 9 (32.1) |
| | Current smoker | 2 (2.9) | 1 (3.6) |
| **ECOG status, n (%)** | 0 | 16 (23.2) | 7 (25.0) |
| | 1 | 52 (75.4) | 21 (75.0) |
| | 2 | 1 (1.4) | 0 |
| **Histology, n (%)** | Adenocarcinoma | 53 (76.8) | 25 (89.3) |
| | Squamous | 6 (8.7) | 2 (7.1) |
| | Others* | 10 (14.5) | 1 (3.6) |
| **Key metastatic site of cancer, n (%)** | Brain† | 11 (15.9) | 3 (10.7) |
| | Liver | 16 (23.2) | 4 (14.3) |
| | Bone | 41 (59.4) | 16 (57.1) |
| | Adrenal | 11 (15.9) | 6 (21.4) |
| **Concurrent MET amplification, n (%)** | <4 GCN | 18 (26.1) | 4 (14.3) |
| | ≥4-6 GCN | 15 (21.7) | 10 (35.7) |
| | ≥6-<10 | 17 (24.6) | 3 (10.7) |
| | ≥10 GCN | 11 (15.9) | 4 (14.3) |
| | Missing | 8 (11.6) | 7 (25.0) |

*all other histologies including 5 sarcomatoid/carcinosarcoma
†12 identified in medical history and 2 identified at baseline CT scan

# Fase II GEOMETRY: capmatinib en METΔex14



## Best overall response (pretreated cohort 4)

***All responses confirmed per RECIST 1.1***

***Response rates consistent between BIRC and investigator assessment***

| | Cohort 4 (2/3L) N=69 | |
|---|---|---|
| | **BIRC** | **Investigator** |
| **Best overall response, n (%)** | | |
| Complete Response | 0 | 1 (1.4) |
| Partial Response | 28 (40.6) | 28 (40.6) |
| Stable Disease | 25 (36.2) | 22 (31.9) |
| Non-CR/non-PD | 1 (1.4) | 2 (2.9) |
| Progressive Disease | 6 (8.7) | 7 (10.1) |
| Not evaluable* | 9 (13.0) | 9 (13.0) |
| **Overall response rate (ORR) %, (95% CI)** | **40.6 (28.9, 53.1)** | **42.0 (30.2, 54.5)** |
| **Disease control rate (DCR) %, (95% CI)** | **78.3 (66.7, 87.3)** | **76.8 (65.1, 86.1)** |

*not qualifying for confirmed CR or PR and without SD after more than 6 weeks or progression within the first 12 weeks

BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; DCR, disease control rate (CR+PR+SD+non-CR/non-PD); ORR, overall response rate (CR+PR); PD, progressive disease; PR, partial response; SD, stable disease

# Fase II GEOMETRY: capmatinib en METΔex14



## Best overall response (treatment naive cohort 5b)

***All responses confirmed per RECIST 1.1***
***Response rates consistent between BIRC and investigator assessment***

| | Cohort 5b (1L) N=28 | |
|---|---|---|
| | **BIRC** | **Investigator** |
| **Best overall response, n (%)** | | |
| Complete Response | 1 (3.6) | 0 |
| Partial Response | 18 (64.3) | 17 (60.7) |
| Stable Disease | 8 (28.6) | 10 (35.7) |
| Progressive Disease | 1 (3.6) | 1 (3.6) |
| **Overall response rate (ORR) %, (95% CI)** | **67.9 (47.6, 84.1)** | **60.7 (40.6, 78.5)** |
| **Disease control rate (DCR) %, (95% CI)** | **96.4 (81.7, 99.9)** | **96.4 (81.7, 99.9)** |

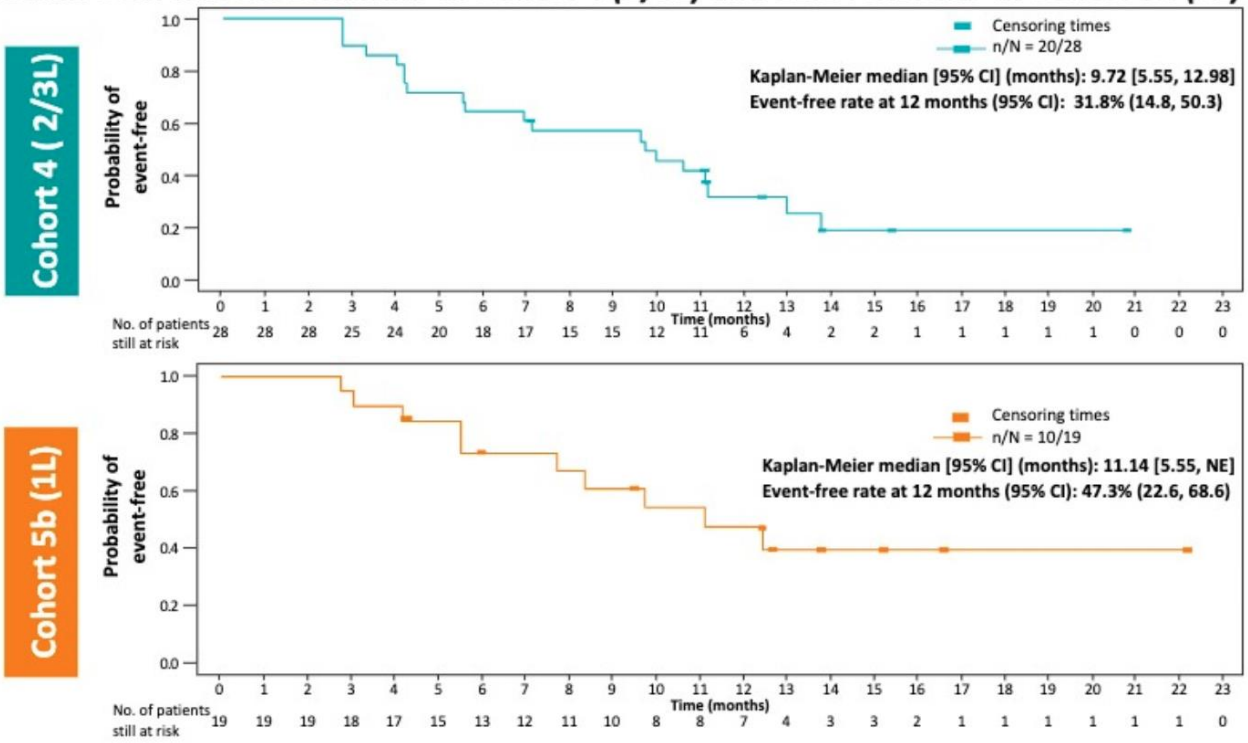
BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; DCR, disease control rate (CR+PR+SD+non-CR/non-PD); ORR, overall response rate (CR+PR); PD, progressive disease; PR, partial response; SD, stable disease

# Fase II GEOMETRY: capmatinib en METΔex14



## Duration of Response per BIRC

***Median DOR was 9.72 months in Cohort 4 (2/3L) and 11.14 months in Cohort 5b (1L)***




***Median DOR per investigator was 8.31 months (95% CI: 4.34, 12.06) in Cohort 4 and 13.96 months (95% CI: 4.27, NE) in Cohort 5b***



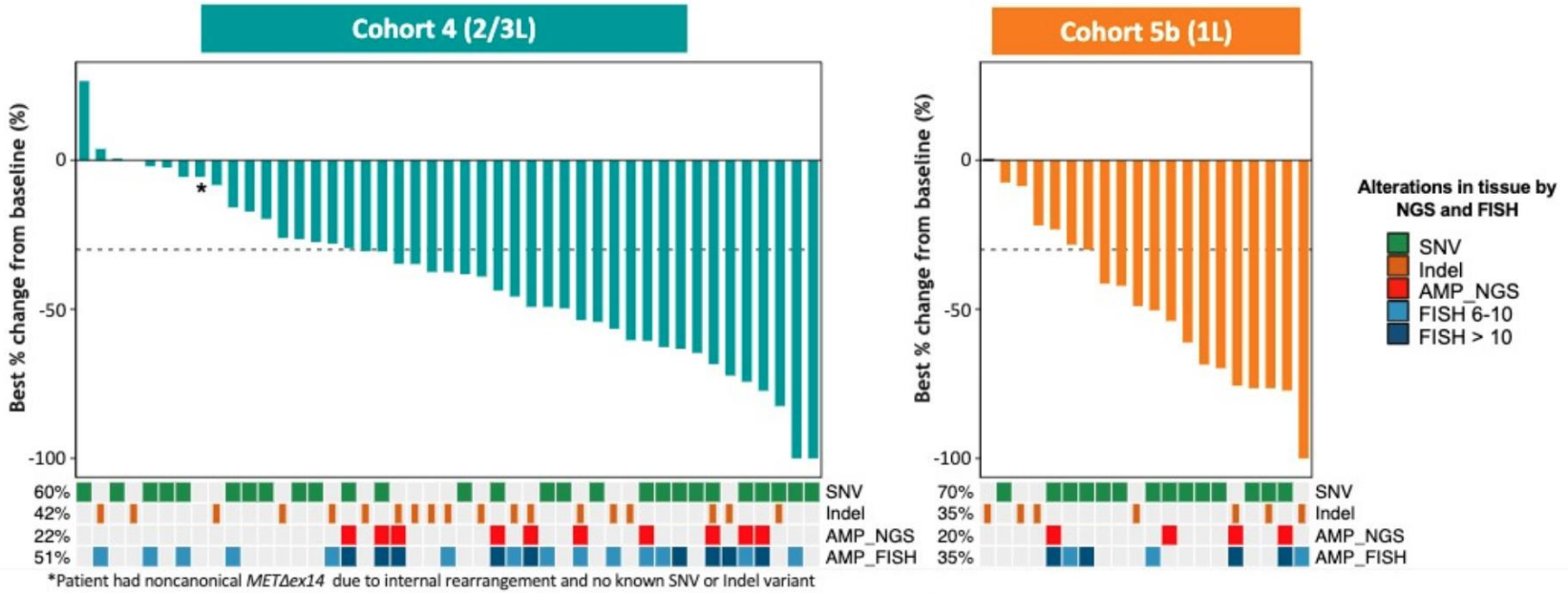
n is the number of events, N is the number of patients

# Fase II GEOMETRY: capmatinib en METΔex14



## Tumor shrinkage by *MET* alterations

- ***Deep responses and DOR were observed independently of type of MET mutation (SNV, Indel) leading to METΔex14 or co-occurrence of MET amplification.***
- ***MET mutations could be detected by both RT-PCR and NGS***
  - High concordance (99%) between NGS and RT-PCR† in detection of *METΔex14* in tumor tissue




*Patient had noncanonical *METΔex14* due to internal rearrangement and no known SNV or Indel variant

†73 tissue samples, Cohort 4=53 (Including 1 patient with a noncanonical METΔex14 rearrangement and no canonical variants), Cohort 5b=20.

SNV, Single nucleotide variant in MET leading to Ex14 skipping; Indel, Insertion or deletion leading to METEx14; AMP_NGS, amplification detected by FM NGS panel ≥ 6 *GCN*; AMP_FISH, MET FISH copy number

# Fase II VISION: tepotinib en METΔex14



# Phase II study of tepotinib in NSCLC patients with *MET*ex14 mutations

**Paul K. Paik[1], Remi Veillon[2], Alexis B. Cortot[3], Enriqueta Felip[4], Hiroshi Sakai[5], Julien Mazieres[6], Frank Griesinger[7], Leora Horn[8], Helene Senellart[9], Jan Van Meerbeeck[10], Javier de Castro Carpeño[11], Jyoti Patel[12], Marina Chiara Garassino[13], Masahiro Morise[14], Niels Reinmuth[15], Santiago Viteri[16], Takaaki Tokito[17], Tomohiro Sakamoto[18], Jürgen Scheele[19], Xiuning Le[20], on behalf of the VISION Study Group**

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PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Paul K. Paik

Abstract no. 9005

# Fase II VISION: tepotinib en METΔex14



## VISION study design

VISION is a single-arm, phase II trial of tepotinib in patients with NSCLC harboring MET alterations (NCT02864992)

### Study Design

- **Stage IIIB/IV NSCLC**
  - **All histologies** (including squamous and sarcomatoid)
  - Exclusion of active brain metastases or brain as only measurable lesion
- **Tissue- or blood-based *MET* alterations** (central lab testing)
  - A. *MET*ex14 skipping mutations detected:
    - OR
      - **Plasma,** LBx (DNA based)
      - **Tissue,** TBx (RNA based)
  - B. *MET* amplification only
- **1st , 2nd , 3rd line of therapy**
  - Prior anti-MET therapy was not allowed
  - Prior immunotherapy was allowed

**N = up to 120**

**Cohort A** *MET*ex14 skipping mutations → **Tepotinib 500 mg QD** (21 day cycles until progressive disease [PD])

**Cohort B** *MET* amplification → Tepotinib 500 mg QD (21 day cycles until PD)

### Selected Endpoints

**Primary endpoint**

- Objective response rate (ORR) by independent review

**Secondary endpoints**

- ORR by investigator assessment
- Duration of response
- Objective disease control
- Progression-free survival
- Overall survival
- Safety
- Health-related quality of life

The trial aims for an ORR based on independent review in the range of 40–50% with a lower limit of the corresponding exact 2-sided 95% confidence interval (according to Clopper–Pearson) to exceed an ORR of 20%.

**We now report interim data including ORR assessed by independent review and select secondary endpoints**

# Fase II VISION: tepotinib en METΔex14



## Baseline patient and tumor characteristics

| Characteristic, n (%) | | Tepotinib (N=87)* |
|---|---|---|
| Median age, years (range) | | 74.0 (39–89) |
| Sex | Male | 47 (54.0) |
| Race† | White | 66 (75.9) |
| | Asian | 17 (19.5) |
| Smoking history‡ | Never smoker | 38 (43.7) |
| | Former smoker | 38 (43.7) |
| | Regular smoker | 2 (2.3) |
| Prior lines of anticancer therapy | 0 | 33 (37.9) |
| | 1 | 31 (35.6) |
| | 2 | 20 (23.0) |
| | 3 | 3 (3.4) |

| Characteristic, n (%) | | Tepotinib (N=87)* |
|---|---|---|
| *MET*ex14-skipping mutation§ | Positive in ctDNA (L+) | 57 (65.5) |
| | Positive in tissue (T+) | 58 (66.7) |
| Histopathological classification‖ | Adenocarcinoma | 75 (86.2) |
| | Squamous | 7 (8.0) |
| | Sarcomatoid | 1 (1.1) |
| Disease stage at study entry‡ | IIIB | 2 (2.3) |
| | IV | 83 (95.4) |
| Brain metastases¶ | Present | 8 (9.2) |
| ECOG PS | 0 | 22 (25.3) |
| | 1 | 65 (74.7) |

*All tepotinib-treated patients. †Other n=1; race not collected at site n=3. ‡Smoking history and Disease stage at study entry were missing for 9 and 2 patients, respectively. §Numbers do not add up to 100% due to overlap of patients with both L+ and T+. Of 53 patients that were tested both with LBx and TBx, 29 were positive in both. ‖Non-small cell lung cancer not otherwise specified n=1; poorly differentiated carcinoma n=1; adenosquamous n=1; missing n=1. ¶Non-target lesions. ECOG PS, Eastern Cooperative Oncology Group performance status.

# Fase II VISION: tepotinib en METΔex14



## Efficacy: Best overall response (IRC/Investigator)

Efficacy analysis includes patients having ≥2 post-baseline assessments or who discontinued treatment for any reason.

| Tepotinib 500 mg QD | Liquid biopsy (L+) | | Tissue biopsy (T+) | |
|---|---|---|---|---|
| | IRC (n=48) | Investigator (n=47) | IRC (n=51) | Investigator (n=51) |
| **BOR by RECIST 1.1**, n (%) | | | | |
| Complete response | 0 (0) | 3 (6.4) | 0 (0) | 3 (5.9) |
| Partial response | 24 (50.0) | 23 (48.9) | 23 (45.1) | 25 (49.0) |
| Stable disease | 8 (16.7) | 5 (10.6) | 14 (27.5) | 11 (21.6) |
| Progressive disease | 7 (14.6) | 10 (21.3) | 8 (15.7) | 6 (11.8) |
| Not evaluable | 9 (18.8) | 6 (12.8) | 6 (11.8) | 6 (11.8) |
| **ORR**,* n (%) [95% CI] | 24 (**50.0**) [35.2, 64.8] | 26 (**55.3**) [40.1, 69.8] | 23 (**45.1**) [31.1, 59.7] | 28 (**54.9**) [40.3, 68.9] |
| **mDOR**, months [95% CI] | **12.4** [5.8, ne] | **17.1** [7.1, ne] | **15.7** [9.0, ne] | **14.3** [5.7, ne] |
| **DCR**,† n (%) [95% CI] | 32 (**66.7**) [51.6, 79.6] | 31 (**66.0**) [50.7, 79.1] | 37 (**72.5**) [58.3, 84.1] | 39 (**76.5**) [62.5, 87.2] |

*ORR, objective response rate: confirmed complete response/partial response.

†DCR, disease control rate: confirmed complete response/partial response or stable disease lasting at least 12 weeks.

L+, *MET*ex14-skipping mutation-positive in ctDNA; T+, *MET*ex14-skipping mutation-positive in tissue.

BOR, best overall response; CI, confidence interval; IRC, independent review committee; mDOR, median duration of response; ne, not estimable.

# Fase II VISION: tepotinib en METΔex14

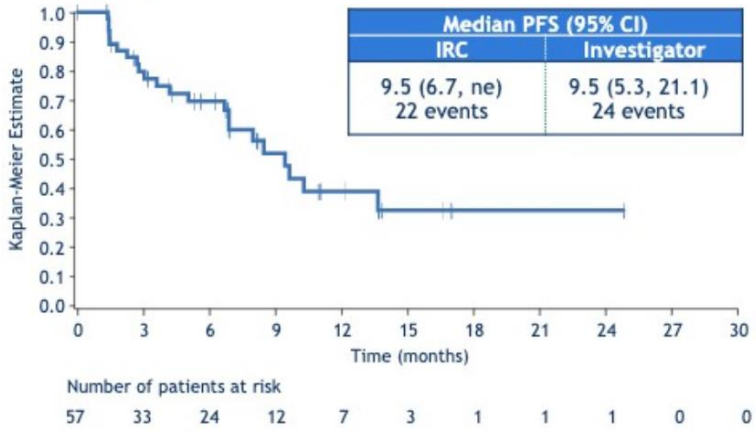


## Efficacy: Progression-free survival

PFS across all treatment lines

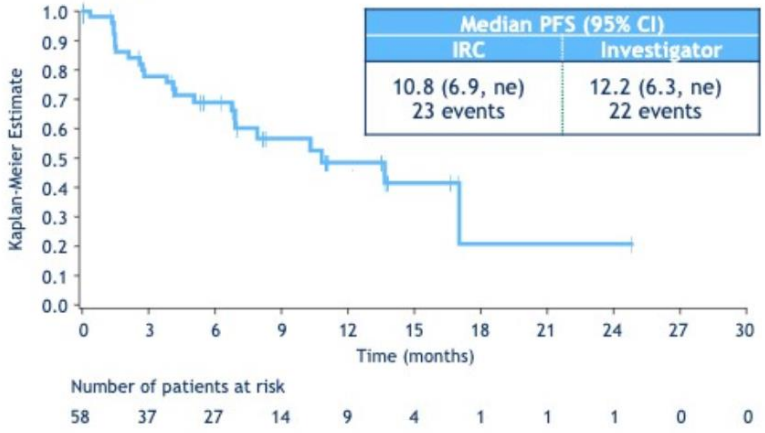
### Liquid biopsy (L+) (n=57)

PFS by IRC




### Tissue biopsy (T+) (n=58)

PFS by IRC




33/57 L+ patients and 31/58 T+ patients remain on treatment.

Median follow-up for PFS (IRC): 6.9 months (95% CI 5.5, 11.0).

L+, *MET*ex14-skipping mutation-positive in ctDNA; T+, *MET*ex14-skipping mutation-positive in tissue.
IRC, independent review committee; ne, not estimable; PFS, progression-free survival.

# Resistencias a MET



## Primary and acquired resistance to MET inhibition in patients with *MET* exon 14-altered lung cancers

**Robin Guo**, Michael Offin, A. Rose Brannon, Andrew Chow, Lukas Delasos, Romel Somwar, Olivia Wilkins, Kerry Scott, Yuan Tian, Fabiola Cecchi, Todd A. Hembrough, Bob T. Li, Charles M. Rudin, Mark G. Kris, Maria E. Arcila, Natasha Rekhtman, Paul K. Paik, Marc Ladanyi, Ahmet Zehir, Alexander Drilon

Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY; NantOmics, LLC, Rockville, MD; UConn Health, Farmington, CT

# Resistencias a MET

## Methods

### Patients

- Advanced non-small cell lung cancers
- *MET* exon 14 alteration
  - DNA/RNA-based next-generation sequencing (NGS) of tumor
- Received 1 or more MET tyrosine kinase inhibitors

### Tumor NGS

- Targeted DNA NGS (MSK-IMPACT™/FoundationOne)
  - Before MET TKI (n=74)
  - Paired NGS at progression (n=14)
- Targeted RNA NGS (n=16, MSK-Solid Fusion™ Assay)

### Tumor Protein Assessment

- Mass Spectrometry (NantOmics)
  - **MET** protein (n=16)
  - **KRAS** protein (n=16)
- **MET** Immunohistochemistry (n=8, SP44 Clone)

# Resistencias a MET



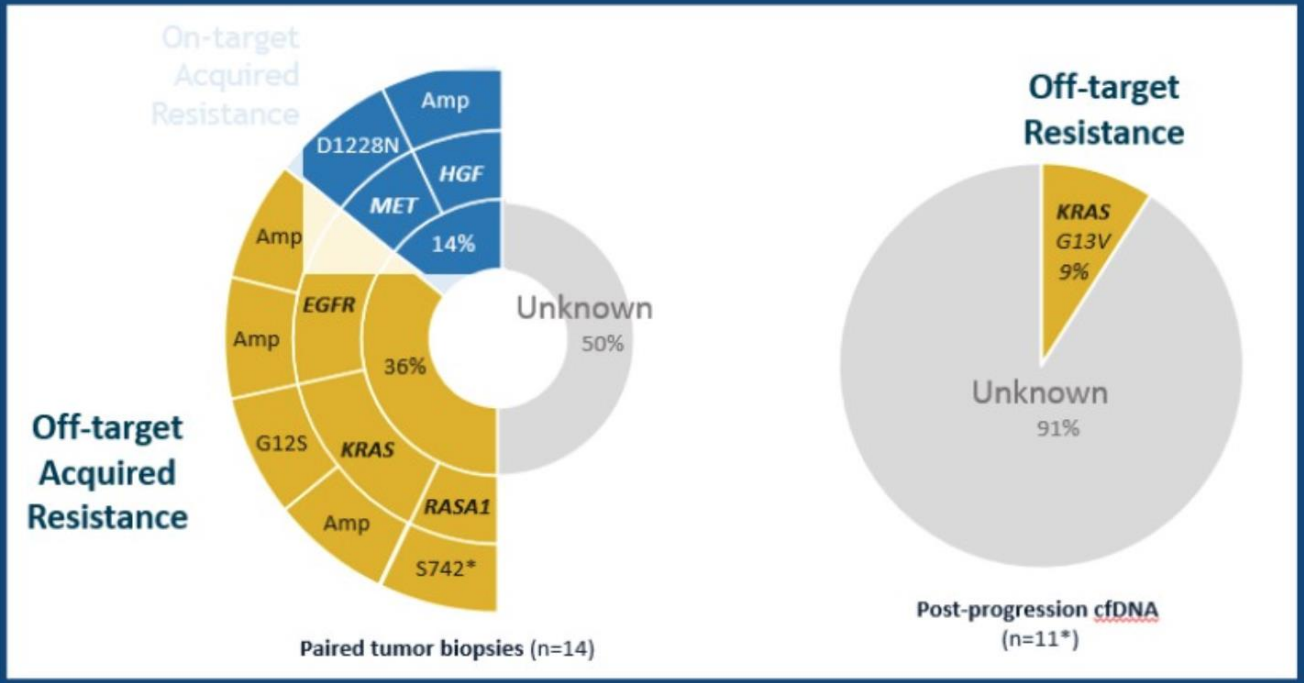
## Clinicopathologic features of patients with advanced *MET* exon 14-altered lung cancers

| All patients (n=75) | | |
|---|---|---|
| Age, median (range) | | 73 years (44-91 years) |
| Sex, % (n) | Female | 52% (39) |
| Cigarette smoking, % (n) | Never<br>Former or Current | 44% (33)<br>56% (42) |
| Histology | Adenocarcinoma<br>Sarcomatoid<br>Other | 77% (58)<br>11% (8)<br>12% (9) |
| Number of TKIs | 1<br>2 or more | 76% (57)<br>24% (18) |
| MET TKI received | Crizotinib<br>Other TKIs (never Crizotinib) | 91% (68)<br>9% (7) |

# Resistencias a MET



## Acquired resistance involves on target and bypass pathways

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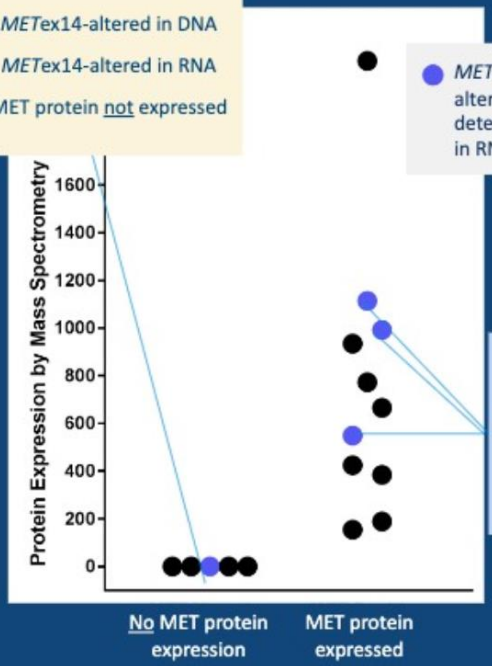
# Resistencias a MET



## Response to MET TKI by protein expression in *MET* ex14 NSCLC

**DISCORDANT**

- *MET*ex14-altered in DNA
- *MET*ex14-altered in RNA
- MET protein not expressed




*MET* exon14 alteration detected in RNA

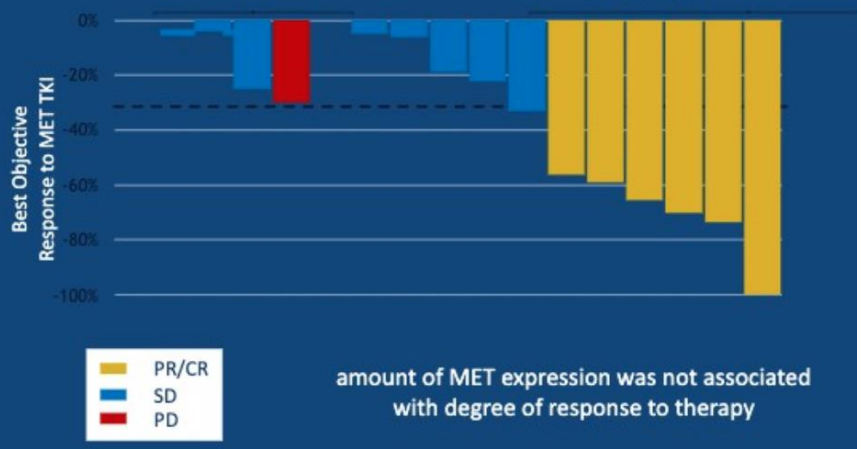
Insufficient tissue for RNA testing

**CONCORDANT**

- *MET*ex14-altered in DNA
- *MET*ex14-altered in RNA
- MET protein overexpressed

**ORR 0%, n=0/5**
**(95% CI: 0%-49%)**
No MET protein expression

**ORR 54%, n=6/11**
**(95% CI: 28%-79%)**
MET protein expression detected




amount of MET expression was not associated with degree of response to therapy

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## Increase Upfront NGS testing for NSCLC

- Growing number of actionable targets with approved therapies
- Cost effective
- Identify more patients with *MET* ex14
- Lead to additional targeted therapies for NSCLC

**TABLE 3.** Total Cost and Cost Difference Versus NGS

| | Medicare-Insured Patients (n = 2,066) | |
|---|---|---|
| **Testing Strategy** | **Total Cost** | **Cost Difference *v* NGS** |
| NGS | 2,190,499 | — |
| Sequential | 3,721,368 | 1,530,869 |
| Exclusionary | 3,584,177 | 1,393,678 |
| Hotspot panel | 4,331,295 | 2,140,795 |

NOTE. Costs are given in 2017 US dollars.
Abbreviation: NGS, next-generation sequencing.

Pennell NA et al J Clin Oncol Precision Oncology 2019

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Iniciativa científica de:
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lung cancer research

# Mutaciones de MET

Dra. Ana Laura Ortega

# ¡Muchas gracias!

Con la colaboración de:

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Lilly