LUNG CANCER UPDATES

AACR HIGHLIGHTS

14-18 ABRIL 2018, CHICAGO

# Terapias dirigidas (III)


## Dr. Manuel Dómine

## Fundación Jiménez Díaz



Con el patrocinio de

Bristol-Myers Squibb

Iniciativa científica de:

GECP

Grupo Español de Cáncer de Pulmón

Spanish Lung Cancer Group

# Poziotinib overcomes de novo resistance of HER2 exon 20 mutations in NSCLC and other cancers: Preclinical studies and initial clinical testing J. P. Robichaux



- POZIOTINIB es un inhibidor con actividad en Inserciones del exon 20 de EGFR (73% RR. Elamin et al IASLC 2017)
- HER2 está mutado en el 2% de NSLC la mayoría por inserciones en el exon 20
- POZIOTINIB inhibe in vitro e in vivo las inserciones de HER2 en exon 20
- Basados en estos datos preclínicos y en los resultados del estudio previo en inserciones del 20 de EGFR actualmente hay 2 estudios fase I de poziotinib en inserciones del 20 en EGFR y HER2 y otro estudio basket para otros tumores

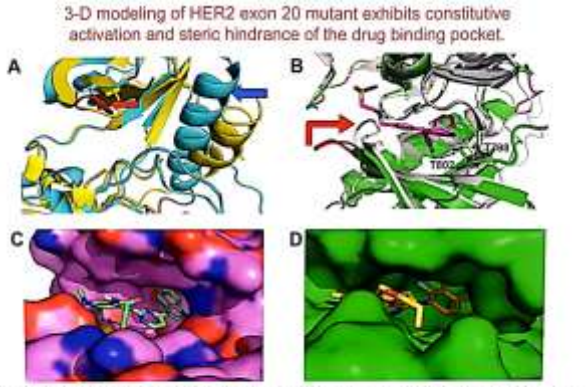


**Figure 2:A.** 3D modeling of HER2 A775insYVMA (blue) and HER2-WT (yellow), the P-loop (red arrow), and the α-C helix (blue arrow). **B.** 3-D modeling of HER2 A775insYVMA (green) and WT (grey) shows constitutive activation and rigid placement of the α-c-helix in the inward position, reducing the binding of lapatinib (pink). **C.** HER2 WT (pink) with osimertinib (green) has a much larger binding pocket compared to **D.** HER2 A775insYVMA (green) with poziotinib (yellow).

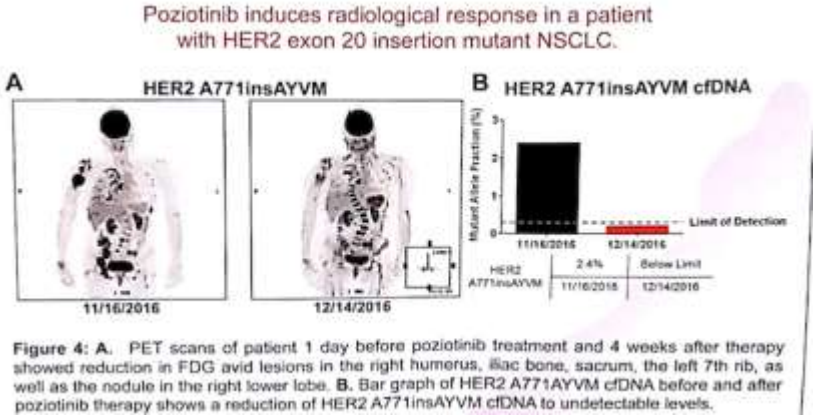


**Figure 4: A.** PET scans of patient 1 day before poziotinib treatment and 4 weeks after therapy showed reduction in FDG avid lesions in the right humerus, iliac bone, sacrum, the left 7th rib, as well as the nodule in the right lower lobe. **B.** Bar graph of HER2 A771AYVM cfDNA before and after poziotinib therapy shows a reduction of HER2 A771insAYVM cfDNA to undetectable levels.

# Nuevos inhibidores de EGFR



## 4788 / 17 - Preclinical evaluation of E-191, a highly selective EGFR T790M inhibitor. L. Xile

- E-191 as a novel irreversible inhibitor that shown in vitro and in vivo a selective inhibitor of the resistance mutant forms of EGFR, potently inhibiting EGFRT790M but not EGFRWT.
- These results make us believe that E-191 has a good potential in the clinic for the treatment of resistant EGFR driven NSCLC.

## 4789 / 18 - Clinical candidate DBPR112: A novel EGFR inhibitor as a promising treatment for non-small cell lung cancer. H. Hsieh

- DBPR112 a potent EGFR-TKI showing excellent inhibitory ability on EGFRL858R/T790M and EGFR exon 20 insertion.
- DBPR112 was orally effective against the growth of human lung H1975 tumors subcutaneously xenografted in nude mice showing dramatic reduction in tumor size.
- DBPR112 was approved by US FDA in 2016 and the Phase I clinical trial has been initiated since July 2017 in Taiwan.

# Nuevos inhibidores de EGFR de 3ª generación

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4790 / 19 - YH25448, an irreversible 3rdgeneration EGFR TKI, exhibits superior anticancer effects with potent brain BBB penetration in NSCLC. J. Yun

YH25448, a highly mutant-selective and irreversible 3rd generation EGFR TKI potently penetrating blood-brain barrier (BBB) penetration, targets both activating EGFR mutations Del19, L858R and T790M mutation while sparing wild type

Superior in vitro potency and selectivity over osimertinib

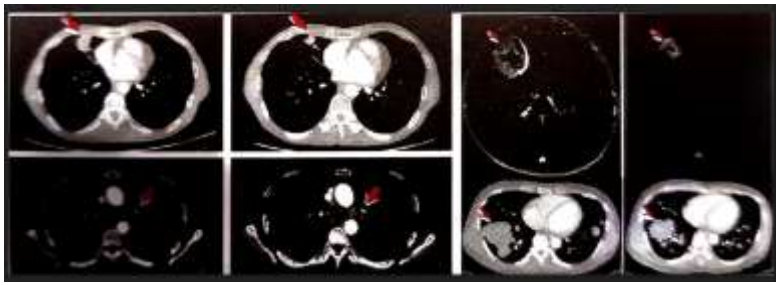
Superior in vivo efficacy over osimertinib in both(del19, L858R) and double (L858R/T790M) mutant xenograft models

Excellent BBB penetration and superior in vivo efficacy over osimertinib in a brain metastasis model

Lower skin toxicity over osimertinib

Phase I/II clinical trial in EGFR mutant NSCLC patients are underway (NCT03046992)

**63 y old male T790M**

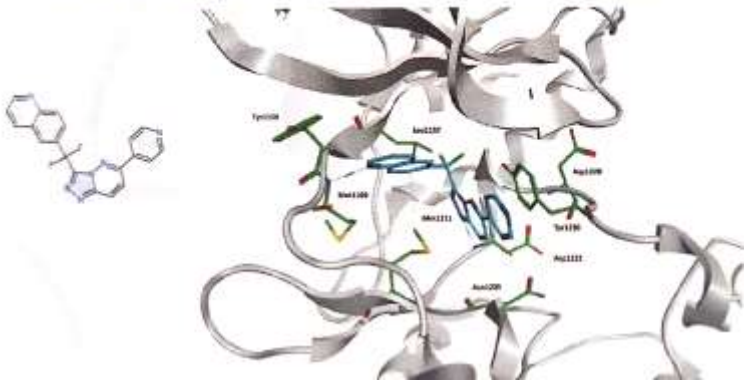


**37 y old male T790M**

# 4791 / 20 - OMO-1, a potent, highly selective, orally bioavailable, MET kinase inhibitor with a favorable preclinical toxicity profile, shows both monotherapy activity, against MET pathway-driven tumors, and EGFR TKI combination activity in acquired resistance models. M. Libouban



## OMO-1 adapts a high affinity binding mode



## OMO-1 a highly selective and potent MET kinase inhibitor

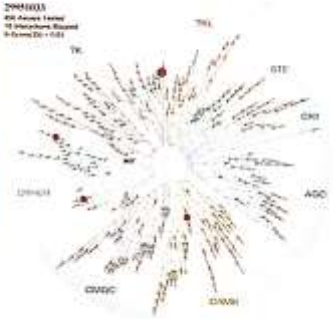
DiscoverX binding assay against 456 kinases in the absence of ATP

| ENZYME | OMO-1 Kd [nM] |
|---|---|
| MET | 1.2 |
| MET (M1250T) | 2.1 |
| MET (Y1235D) | 21 |
| ABL1 (H396P)-nonphosphorylated | 260 |
| ABL1 (F317L)-phosphorylated | 800 |
| YSK4 | 1100 |

Millipore in vitro enzyme activity assay using recombinant enzymes at 10μM ATP

| Kinase | OMO-1 $IC_{50}$ [nM] | crizotinib $IC_{50}$ [nM] |
|---|---|---|
| MET | 2 | 11.7 |
| Abl | 1210 | 61.8 |
| Arg | 7590 | 121 |
| TrkA | 9480 | 4.05 |

$IC_{50}$ >10μM against 250 kinases
crizotinib inhibits 35 more kinases with $IC_{50}$ of less than 1μM



Kinase profile of OMO-1.

- Induced regression of large MET amplified EBC-1 SqNSCLC
- Combination treatments were well tolerated and improved EGFR targeted therapy. Although single agent OMO-1 had no effect on NSCLC HCC827 EGFR, combination with Erlotinib led to delayed onset of tumor recurrence.