# Targeting MET in preclinical models to support the clinical development of AZD6094/HMPL-504 (Volitinib) in NSCLC

#3114

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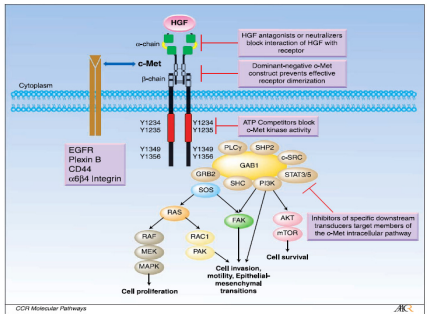
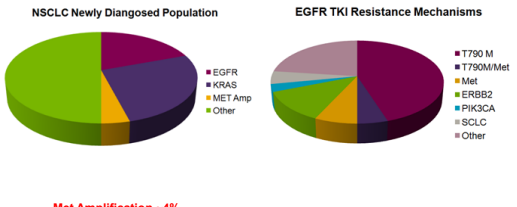



Schematic of Met Signaling (Eder et al. Clin Cancer Research 2009)

## Introduction:

- Met is a receptor tyrosine kinase that is deregulated (amplification, mutation and over-expression) across multiple cancer types
- Aberrant HGF/Met pathway activation leads to uncontrolled tumor cell growth, invasion and survival
- AZ is partnering with Hutchison MediPharma in the development of **AZD6094/HMPL-504 (Volitinib)** a potent (IC50 4 nM) and selective (>650 fold selectivity over 265 kinases) small molecule inhibitor of Met
- AZD6094/HMPL-504 is a monotherapy for Met-amplified cancers (e.g. subsets of gastrointestinal and lung cancers), with opportunities to combine with EGFRi or chemotherapy in Met-driven cancers
- AZD6094/HMPL-504 is active in both HGF dependent and independent disease settings. AZD6094/HMPL-504 activity in these settings is distinct from Met and HGF antibodies (onartuzumab and rilotumumab) that are only active in HGF dependent disease. In addition, AZD6094/HMPL-504 selectivity may provide a more favorable therapeutic index than multi-kinase inhibitors (crizotinib and cabozantinib).
- Recent evaluation of AZD6094/HMPL-504 across a panel of cancer cell lines demonstrated selectivity for Met-driven disease, with Met amplified cell lines being most sensitive.
- Using patient-derived xenograft (PDX) and cell lines models, we demonstrate that AZD6094/HMPL-504 has significant anti-tumor activity as a monotherapy or in combination with taxotere or gefitinib.

## Met Prevalence in NSCLC and EGFRm TKI Resistant Disease




Met Amplification ~4%
Met expression ~50%

Met Amplification 15-25% (+/-T790m)

## AZD6094/HMPL-504 is a potent and selective Met inhibitor active in HGF dep and indep models

### Figure 1. Sanger cell line pharmacology

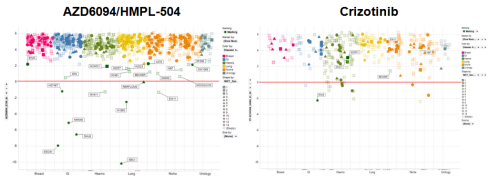



**Figure 1: A)** 972 cell lines collapsed by disease type and shaped by MET copy number, lines with <10uM (~ln2.4) are highlighted for AZD6094/HMPL-504; **B)** Crizotinib, a multi-kinase inhibitor (AnLK, Met, Ros) appears far less potent than AZD6094/HMPL-504. Cell lines marked are those that overlap with AZD6094/HMPL-504 <10uM cell lines. Red line, ln0=1uM.

### Figure 2. Gastric and lung cancer cell lines are sensitive to AZD6094/HMPL-504

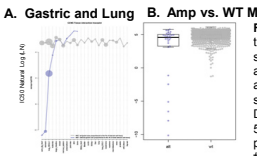



**Figure 2. A)** Average drug sensitivity by tissue type based on MET aberration status. **B)** Distribution of MET amplification (alt) vs non-amplified (wt) across 972 lines demonstrates that most sensitive lines harbor Met amplifications. Development plans for AZD6094/HMPL-504 in gastric cancer were previously presented (Gavine et al. AACR poster #928, 2013)

### Figure 3. Lung cancer cell lines with Met amplification validated for AZD6094/HMPL-504

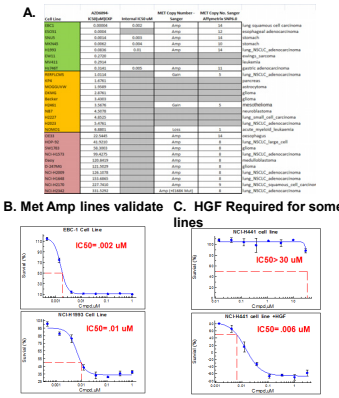



**Figure 3. A)** Table rank ordered by IC50 values for most sensitive lines (<1uM IC50) with Met status indicated (green). Lines with IC50's between 1-10uM (orange) may be more sensitive in the presence of HGF. Met amplified lines not demonstrating senstivity to AZD6094/HMPL-504 indicated by red. **B)** Validation of select NSCLC cell lines (EBC-1 and H1993) both with Met amplification. **C)** Additional NSCLC line H441, was tested +/- HGF, demonstrating increased sensitivity in the presence of HGF. NB. Sanger cell panel run in FBS, no HGF added.

### Figure 4. AZD6094/HMPL-504 demonstrates potent anti-tumor efficacy in cMET-amplified NSCLC xenograft model, EBC-1

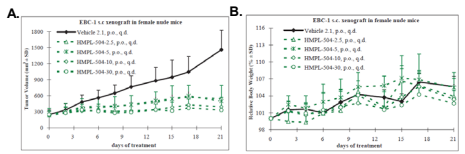
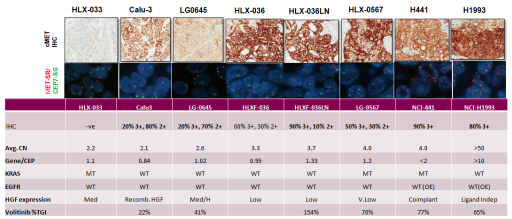



**Figure 4. A)** Anti-tumor activity in EBC-1 xenografts is shown at 4 doses, 2.5, 5, 10 and 30 mpk qd. Maximal anti-tumor activity of 93% is achieved with 30 mpk AZD6094/HMPL-504. **B)** Body weight measurements throughout study demonstrate that AZD6094/HMPL-504 is well tolerated.

## AZD6094/HMPL-504 is efficacious in panel of NSCLC xenografts

### Figure 5. Panel of cell line and patient derived xenografts characterized for Met status




| | HLX-033 | Calu3 | LG-0645 | HLXF-036 | HLXF-036LN | LG-0567 | NCI-441 | NCI-H1993 |
|---|---|---|---|---|---|---|---|---|
| IHC | -ve | 20% 3+, 80% 2+ | 20% 3+, 70% 2+ | 60% 3+, 30% 2+ | 90% 3+, 10% 2+ | 50% 3+, 30% 2+ | 90% 3+ | 80% 3+ |
| Avg. CN | 2.2 | 2.1 | 2.6 | 3.3 | 3.7 | 4.0 | 4.0 | >50 |
| Gene/CEP | 1.1 | 0.84 | 1.02 | 0.95 | 1.33 | 1.2 | <2 | >10 |
| KRAS | MT | WT | WT | WT | WT | MT | MT | WT |
| EGFR | WT | WT | WT | WT | WT | WT | WT (OE) | WT(OE) |
| HGF expression | Med | Recomb. HGF | Med/H | Low | Low | V.Low | Coimplant | Ligand Indep |
| Volitinib %TGI | | 22% | 41% | | 154% | 70% | 77% | 65% |

### Figure 6. H1993 efficacy correlates with p-Met inhibition

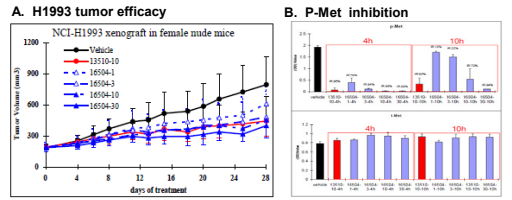



**Figure 6. A)** Anti-tumor activity in H1993 xenografts is shown at 4 doses; 1, 3, 10 and 30 mpk qd. Maximal anti-tumor activity of 65% is achieved with 30 mpk AZD6094/HMPL-504 . **B)** Pharmacodynamic marker, p-Met was measured by ELISA and demonstrates maximal inhibition at 4 hrs with continued inhibition at 10 hrs with 30 mpk, the most efficacious dose.

### Figure 7. AZD6094/HMPL-504 is efficacious in PDX model with <4 copies Met, HLXF-036LN

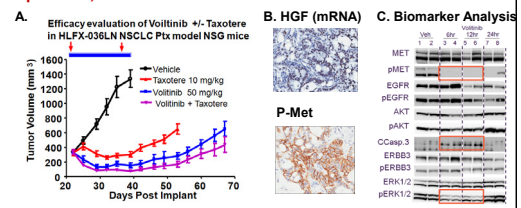



**Figure 7.** HLXF-036LN (Met 3.72 copies, Met/CEP ratio 1.33) **A)** Tumor regressions with AZD6094/HMPL-504 therapy alone in model with <4 copy number and 90% 3+ IHC for Met. **B)** Tumor HGF (mRNA, RNAscope) and p-Met (IHC) expression are both detectable **C)** Analysis of tumor samples shows maximal inhibition of p-Met after 6-12 hrs AZD6094/HMPL-504 with simultaneous down-regulation of pERK1/2 signaling and caspase 3 induction.

### Figure 8. AZD6094/HMPL-504 and Taxotere provide durable anti-tumor response in PDX model with < 4 copies Met, LG0645

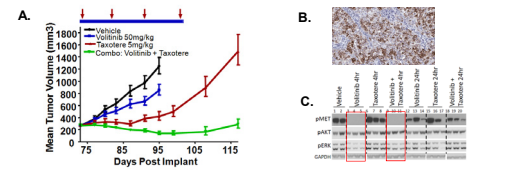



**Figure 8.** LG0645 (Met 2.64 copies, Met/CEP 1.02) **A)** Tumor regressions and durable responses are demonstrated with AZD6094/HMPL-504/Taxotere combination **B)** Tumor HGF (mRNA, RNAScope) expression is high **C)** Tumor samples shows inhibition of p-Met at 4 hrs and back by 24 hrs.

## AZD6094/HMPL-504 is active in a model of EGFR TKI resistance

### Figure 9. Xenograft of EGFRm, TKI-R, Met-Amp responds to AZD6094/HMPL-504 and gefitinib combination

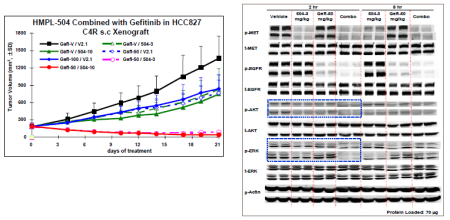



**Figure 9.** HCC827-C4R, EGFR TKI resistant (Met 4 GCN). A) Efficacy study demonstrates tumor regressions with AZD6094/HMPL-504 and Gefitinib in combination. B) Analysis of tumor samples shows inhibition of p-Met at 2-4 hrs with down regulation of pMET, p-EGFR and greater inhibition of pERK in the combination group. Additional data to support AZD6094/HMPL-504 in EGFRm Met Amp TKI resistance were previously reported (F. Zhou, AACR 2013 #971)

## Summary:

We have provided a platform of evidence for AZD6094/HMPL-504(Volitinib) treatment in NSCLC by selecting preclinical models representative of selected patient Met FISH or IHC scores to inform design of clinical trials and support development of rational combinations.

- Response to AZD6094/HMPL-504 monotherapy in WT EGFR NSCLC is seen in a subset of cell lines and patient derived xenografts with Met amp or over expression.
- Preclinical data support the combination of AZD6094/HMPL-504 and taxotere for reducing tumor burden in EGFR WT NSCLC.
- AZD6094/HMPL-504, in combination with gefitinib, is efficacious in EGFRm relapsed disease, supporting Met's role in resistance in this setting. Preclinical support, internal and external, for combining with EGFR TKI is strong.
- AZD6094/HMPL-504 is more potent and selective than other Met inhibitors (Crizotinib) and may have activity in subsets of NSCLC that may not respond to HGF and Met antibodies (onartuzumab and rilotumumab) due to the ability to inhibit constitutively active, non HGF dependent disease.

## References:

Sanger Institute:
Website ref is http://www.cancerRxgene.org
http://nar.oxfordjournals.org/content/41/D1/D955

1) Genomics of Drug Sensitivity in Cancer (GDSC): a resource for therapeutic biomarker discovery in cancer cells. *Nucl. Acids Res.* (1 January 2013) 41 (D1): D955-D961.
2) Systematic identification of genomic markers of drug sensitivity in cancer cells. *Nature.* Volume:483, Pages:570–575 (29 March 2012).

AstraZeneca