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

Celia D'Cruz1, Garry Beran2, Yongxin Ren3, Ammar Adam4, Evan Barry5, Minhui Shen5, Paul Gavin6, Melanie Frigault7, Shiming Fan8, Feng Zhou9, Weiguo Qing10, Mike Zinda11, Weiguo Su12, and Edwin Clark13

Oncology iMED, AstraZeneca, Gatehouse Park1, Waltham MA, Alderley Park2, Macclesfield, UK, Asia and Emerging Markets iMED1, Shanghai China and Hutchison MedPharma3, Shanghai China

#3114

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

Introduction:

- Met is a receptor tyrosine kinase that is deregulated (amplification, mutation and over-expression) across multiple cancer types
- Azi is partnering with Hutchison MedPharma in the development of AZD6094/HMPL-504 (Volitinib) a potent (IC50 4 nM) and selective 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.

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

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

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

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.cancerforsx.com http://srs.sanger.ac.uk/journals/content/11T/1/055