Editorial Commentary

Breaking barriers: patient-derived xenograft (PDX) models in lung cancer drug development—are we close to the finish line?

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The epidermal growth factor receptor (EGFR) gene was discovered in 1978 (1) but only later in 2004 was the role of EGFR activating mutations in lung cancer identified (2). EGFR mutations (EGFRm) are seen in 15–25% of patients with non-small cell lung cancer (NSCLC), especially adenocarcinomas, never smokers, females, and Asians. Activating EGFRm occur in exons 18–21. Deletions in exon 19 and L858R missense mutation in exon 21 represent the classical mutation types, whereas mutations in exons 18 and 20 are relatively rare. In addition to their rarity, exon 20 mutations are also resistant to EGFR tyrosine kinase inhibitors (TKIs) approved for the treatment of lung cancer with classical EGFRm (3). First-generation EGFR TKIs (e.g., erlotinib and gefitinib) are reversible and non-selective. Second-generation (e.g., afatinib and dacomitinib) are irreversible and non-selective (4). Osimertinib, which is a highly selective 3rd generation EGFR TKI, is characterized by its smaller molecular size, irreversible binding to EGFR TKI, ability to cross blood brain barrier, and better tolerability. In addition, it is effective in targeting T790M mutations, a well-known resistance mechanism to earlier generation EGFR TKI (5). This has led to a wide spectrum of indications for osimertinib both in advanced and early stage EGFR-driven NSCLC, encompassing second-line therapy after progression on an earlier generation TKI with T790M mutation (6), first-line therapy as a single agent (7), or in combination with chemotherapy (8), and adjuvant therapy for resected EGFR-driven localized NSCLC stages IB–IIIA (9).

In patients with advanced stage NSCLC, treatment with EGFR TKIs results in an excellent initial response but resistance does eventually develop, and a wide variety of resistance mechanisms have been identified. Resistance mechanisms to osimertinib is different from that of earlier generation TKIs (10). On-target resistance usually is the result of secondary mutations in the TK domain of the *EGFR* gene, whereas, the common off-target mechanisms involve MET (5–24%), HER2 (2–5%), HER3, RAS/RAF (1–3%), AKT/mTOR (4–11%), and epithelial-to-mesenchymal transition (11). Amplification or over-expression of the MET gene as a resistance mechanism to osimertinib, is relatively common with a reported frequency of 5–24% (11). Single agent capmatinib has shown activity in patients with MET-amplified NSCLC (12). Therefore, combining osimertinib with an MET TKI presents a rational choice to overcome MET-mediated resistance (*Table 1*).

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Table 1 Early-phase trials investigating combined MET TKIs with osimertinib after progression on first-line osimertinib

Trial	Phase	Year	Experimental arm
TATTON	Ib	2020	Savolitinib (or durvalumab) + osimertinib
SAVANNAH	II	2022	Savolitinib + osimertinib
ORCHARD (MET cohort)	II	2019	Savolitinib + osimertinib
INSIGHT 2	II	2022	Tepotinib + osimertinib

TKIs, tyrosine kinase inhibitors.

Table 2 Results of early-phase trials investigating combined MET TKIs with osimertinib

Study	N	ORR (%)	mPFS (months)
TATTON-cohort B1 (prior EGFR TKI)	69	33	5.5
TATTON-cohorts B2, B3 & D (EGFR TKI naïve)	51 (cohort B2)	65 (cohort B2)	9.1 (cohort B2)
	18 (cohort B3)	67 (cohort B3)	11.0 (cohort B3)
	42 (cohort D)	62 (cohort D)	9.0 (cohort D)
SAVANNAH	193	49	7.1
ORCHARD (MET cohort)	20	20	N/A
INSIGHT 2	122	43.9	5.4

EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; ORR, overall response rate; mPFS, median progression-free survival; N/A, not available.

Savolitinib, a MET TKI and osimertinib combination was evaluated in the multi-cohort phase IB TATTON trial (13,14). Patients with EGFRm NSCLC who had progressed on EGFR TKI and had overexpression or amplification of MET were enrolled in this trial. Naïve EGFR TKI cohorts had higher response rates and median progression free survival (PFS) than prior EGFR TKI cohort. In the follow-up phase II SAVANNAH trial, savolitinib was added after patients developed MET-mediated resistance to osimertinib (15,16). Preliminary findings from the ORCHARD trial further supported these results with the same combination in post-osimertinib EGFRm patients with MET alterations (*Table 2*) (17). Studies with other MET TKIs have also reported similar results. In the INSIGHT2 trial, tepotinib was added to osimertinib (18). The SAFFRON is an ongoing phase III trial further investigating the role of osimertinib plus savolitinib versus platinum-doublet chemotherapy. The GEOMETRY-E was another phase III trial that was investigating the role of osimertinib plus capmatinib against platinum-doublet chemotherapy, but unfortunately was terminated based on business considerations of the funding company (19,20).

Dating back to 1969, patient-derived xenograft (PDX) models have shown an optimum tumor "simulation", i.e., maintaining the primary tumor characteristics, since the real tumor tissue was implanted in the host (21). This differentiates PDX models from the previous cheaper and more readily available cell-line derived xenograft (CDX) models, in which tumor cell lines were synthetized in the lab. Lacking tumor heterogeneity particularly the microenvironment, and immunologic milieu, CDX models were increasingly replaced by PDX models in the drug development process, studying drug activity, and mechanisms of resistance (22). To further enhance the role of PDX models, host modifications, e.g., genome-edited mouse models (GEMMs) and humanized mouse models were introduced and increasingly used, instead of nude mice, severely combined immunodeficient (SCID) mice, and non-obese diabetic (NOD-SCID) mice (23). By mimicking the human tumor microenvironment and tumor heterogeneity, investigators will be able to address clinical questions as well as specific precision oncology concepts, e.g., target therapy, immunotherapy (24). Nonetheless, PDX models face multiple challenges as variable take rates (depending on tumor type and host), long tumor latency (4–6 months versus few weeks for CDX), need for specialized equipment,

well trained personnel and higher cost (25).

Jones and colleagues have conducted a pharmacokinetic (PK) and pharmacodynamic (PD) evaluation of savolitinib and osimertinib in a PDX model of MET-amplified and EGFRm NSCLC tumor previously treated with erlotinib (26). Treatment with single agent osimertinib was ineffective whereas single agent savolitinib had minimal antitumor activity. But savolitinib plus osimertinib combination had significantly better antitumor activity at 90% or more tumor regression confirming the efficacy of the combination. Phosphorylated MET (pMET) levels were significantly reduced by savolitinib, but not with osimertinib. Savolitinib alone did not inhibit phosphorylated EGFR (pEGFR) levels, but the combination was effective in reducing both pMET and pEGFR levels confirming the rationale to combine the two agents. PK and PD analysis were performed in the PDX model. The authors developed a PK/PD model linking savolitinib/osimertinib exposure (PK) to inhibition of pMET/pEGFR (PD) as well as to anti-tumor effects. By applying the PDX model parameters in human PK models the authors were able to simulate pEGFR and pMET inhibition in humans for different savolitinib doses while keeping osimertinib at a fixed dose of 80 mg once daily. They identified that savolitinib at either 600 mg once daily or 300 mg twice daily were the most effective dose levels.

Using PDX models to screen targeted therapies could minimize resource loss due to failed human trials and increase likelihood of success for the candidate drug. However, challenges remain, patients with MET amplification-based resistance to EGFR TKIs are quite heterogeneous with wide variability in their molecular phenotype, clinical characteristics and ability to tolerate the combination dosage. Therefore, a single model to guide treatment may be insufficient. The savolitinib and osimertinib combination has been extensively evaluated in human phase I studies and dosage levels for phase II studies have already been established. The PK and PD analysis using the PDX model by Jones and colleagues serves as a useful proof of principle.

PDX models are a key addition in the drug development pipeline, their ability to phenocopy drug resistant tumors might lead to more precise assessment of drug efficacy than conventional cell line studies. PK and PD analysis to model appropriate doses for early phase human trials is another potential advantage. At the same time there are no established protocols on incorporating PDX model studies with other preclinical studies to select the best candidates for human trials. The generalizability of PDX model study results to human studies requires further study and validation. The work by Jones and colleagues is an important step in that direction, given the ever-growing number of therapeutic targets in lung cancer and cancer in general, we expect to see more PDX model studies in the preclinical setting. Such studies could define the role of PDX model studies in drug development.

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