Insulin-Like Growth Factor Pathway

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The insulin-like growth factor (IGF) pathway is a key mechanism for growth and survival in human cancers, including lung cancer. Because of the high expression of components of IGF signaling in lung cancer and early evidence of clinical activity in lung cancer, development of several novel agents targeting the IGF-1 receptor (IGF-1R) and the IGF pathway have included programs in lung cancer.1,2 Current agents in development are categorized as either anti-IGF-1R monoclonal antibodies (mAbs) or small molecule tyrosine kinase inhibitors (TKI), which as a class are earlier in clinical development.3 The agents discussed at the meeting are summarized in Table 1.

**SUMMARY OF PRESENTATIONS**

**Science**

A brief overview of the IGF-1R signaling pathway was provided by Dr. Pollak to put into context its role in non-small cell lung cancer (NSCLC). Our understanding of the role of IGF-1 and insulin signaling is expanding from their initial roles in skeletal growth and glucose metabolism. It is becoming more clear that IGF/insulin signaling play key roles in the proliferation and survival of number of malignancies, including lung cancer.4 Further studies are necessary to understand the complex feedback and regulatory systems to maximize the safety and efficacy of targeting this pathway.

**MAbs Targeting IGF-1R**

Each of the mAbs described have demonstrated evidence of blocking ligand activation of IGF-1R, induce IGF-1R down-regulation, can induce hyperglycemia, but do not bind the insulin receptor (InsR).

**Figitumab (CP-751,871)**

Figitumab is a fully human IgG2 mAb against the IGF-1R with a relatively long half life of 20 days, both of which are features that set it apart from other IgG1 mAb agents in development described later.5 A phase II randomized study demonstrated a significant increase in the response rate (54%) and progression-free survival for patients receiving paclitaxel/carboplatin plus figitumumab at 20 mg/kg compared with paclitaxel/carboplatin alone.1 The antitumor activity was highest in the squamous subset of NSCLC, with a response rate of 78% and 12-week progression-free survival of 89% for paclitaxel, carboplatin, and figitumumab at 20 mg/kg. These data led to A4021016, a phase III randomized clinical trial of paclitaxel, carboplatin with or without figitumumab at 20 mg/kg as front-line treatment for advanced NSCLC nonadenocarcinomas. The study was halted after the Data Safety Monitoring Committee identified an imbalance in the number of deaths in the experimental arm and concerns regarding increased cardiac and metabolic adverse events. The study was later permanently closed due to failure of survival hazard ratio to exceed the prespecified futility threshold. Dr. Scagliotti presented data attempting to explain the apparently discordant results of the reported phase II study and the recent results of the phase III trial. The biomarker analyses performed as part of A4021016 demonstrated that treatment tolerability and survival correlated with plasma-free IGF-1 levels. In particular, patients with the lowest quartile of free IGF-1 had poor overall survival and had a higher incidence of cardiovascular events on study. Free IGF-1 selection criterion is being considered to future figitumab investigations.

**Cixutumumab (IMC-A12)**

Cixutumumab, an IgG1 mAb against IGF-1R from ImClone, is currently being investigated in five clinical trials in lung cancer.6,7 The front line treatment studies include gemcitabine, cisplatin, cetuximab with or without (1:1) cixutumumab in NSCLC; paclitaxel, carboplatin, bevacizumab with or without (1:1) cixutumumab in nonsquamous NSCLC; paclitaxel, carboplatin with (1:1:1) cixutumumab, cetuximab, or both in NSCLC; and VP-16, cisplatin with or without (1:1:1) cixutumumab or the Hedgehog antagonist, GDC-0449 in extensive stage small cell lung cancer (ESSCLC). An additional study is ongoing evaluating erlotinib with or without (1:1) cixutumumab in second-line or greater NSCLC. No interim results are available at this time.

**Dalotuzumab (MK-0646)**

Dalotuzumab is a humanized IgG1 mAb against the IGF-1R from Merck.8 The dose-limiting toxicity have not been identified at maximum tolerated dose (MTD) of 20 mg/kg/wk, and the recommended phase II dosing is 10 mg/kg/wk. Three ongoing clinical trials in lung cancer were discussed. The IMPACT study is a randomized phase II study investigating pemetrexed and cisplatin with or without dalotuzumab in previously untreated nonsquamous NSCLC. Vanderbilt is conducting a phase II study of erlotinib with and without dalotuzumab in previously treated NSCLC. A single-
for greater than 5 months. A case was presented demonstrat-
two patients with NSCLC experienced control of their disease
glycemia than the intermittent dosing. In the phase I studies,
dosing seems to stimulate more hyperinsulinemia and hyper-
tyrosine kinase inhibitors

Monoclonal antibodies
Gigitumumab (CP-751, 871) 20 d Pfizer Phase III
Cixutumumab (IMC-A12) 6–9 d ImmClone Phase II
Dalotuzumab (MK-0646) 4–5 d Merck Phase II/III
AMG479 7–11 d Amgen Phase II

Tyrosine kinase inhibitors
OSI-906 2–5 h (t1/2) OSI Phase III (ACC)
BMS-754807 Not reported Bristol-Myers Squibb Phase I/II

TABLE 1. IGF Targeted Therapies Presented

<table>
<thead>
<tr>
<th>Agent</th>
<th>Half Life (t1/2)</th>
<th>Company</th>
<th>Phase of Development</th>
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<tr>
<td>Monoclonal antibodies</td>
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<td>Phase I/II</td>
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arm phase I/II study is also being conducted in ESSCLC with
cisplatin, etoposide, and dalotuzumab. Interim results are not
available.

AMG-479

AMG-479 is a fully human IgG1 mAb antagonist of the
IGF-1R from Amgen. Dose-limiting toxicity is thrombocyto-
penia at the 20 mg/kg dose.\(^9\) A phase I/II clinical trial is being
collected with two doses (12 and 18 mg/kg) in combination
with paclitaxel and carboplatin given on day 1, every 3
weeks. After safety evaluation of the two, the second part of
the study will evaluate the efficacy of a single dose of
AMG-479 with paclitaxel and carboplatin. An additional
phase I/II study is evaluating either AMG-479 or AMG-102
(antihepatocyte growth factor mAb) in combination with
etoposide and carboplatin (or cisplatin) in ESSCLC. Both
studies are ongoing, without any available clinical data to
report.

IGF-1R/InsR TKIs

Both TKIs described are potent orally bioavailable
inhibitors of the IGF-1R and InsR kinases. It is unclear
whether blockade of the InsR will be an advantage of TKIs
over the anti-IGF-1R mAbs due to the involvement of InsR in
IGF signaling or whether this will be a metabolic liability that
hinders the development of these agents.\(^3\)

OSI-906

The MTD of OSI-906 has been established at either 150
mg twice daily for continuous dosing or 600 mg daily on an
intermittent 1 week on/1 week off schedule.\(^10\) Continuous
dosing seems to stimulate more hyperinsulinaemia and hyper-
glycemia than the intermittent dosing. In the phase I studies,
two patients with NSCLC experienced control of their disease
for greater than 5 months. A case was presented demonstrat-
ing tumor regression in a patient failing two lines of chemo-
therapy and erlotinib. Phase II and III studies are being
planned in combination with erlotinib in NSCLC for 2010.

BMS-754807

Phase I studies identifying the MTD of BMS-754807 as
a single agent and in combination with paclitaxel/carboplatin,
cetuximab, or trastuzumab are ongoing. No clinical investi-
gations in lung cancer have been announced for this agent.\(^11\)
Initial clinical data from the phase I studies report that
fluorodeoxyglucose PET imaging may be a good pharmaco-
dynamic marker for this agent. Serum insulin also seemed to
increase in a dose-response fashion to BMS-754807.

FUTURE DIRECTIONS

Targeting the IGF signaling pathway remains a prom-
ising area of clinical investigation in lung cancer. The enthui-
siasm, nonetheless, is blunted by the unexpected safety and
efficacy results in phase III investigations with figitumumab.
To date, no other major safety concerns have emerged for
IGF targeting in lung cancer. Nevertheless, it has become
more clear that patient selection will be important, possibly
through free IGF-1 and/or other assessments, to identify the
optimal patient population for targeting IGF signaling in lung
cancer.

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