

New Targets & Strategies in Focus at AACR

Mounting Concerns About BRAF Inhibitor Resistance

Companies:

Amgen (AMGN)
Array (ARRY)
AstraZeneca (AZN)
ArQule (ARQL)
Bristol-Myers Squibb (BMY)
Curis (CRIS)
Daiichi Sankyo
Eisai
Eli Lilly (LLY)
Epizyme (privately held)
GlaxoSmithKline (GSK)
Infinity (INFI)
Novartis (NVS)
Pervasis (privately held)
Pfizer (PFE)
Roche (RHHBY)
Sanofi-Aventis (SNY)
Takeda

Products:

AMG 820 (Amgen)
ARRY 382 (Array)
ARQ 736 (ArQule)
BMS-833923 (Bristol)
EZH2-inhibitor (Epizyme)
GDC-0449 (Curis / Roche)
GSK1120212 (Glaxo)
GSK2118436 (Glaxo)
Iniparib (Sanofi)
IPI-926 (Infinity)
LDE 225 (Novartis)
LY2940680 (Lilly)
Olaparib (AstraZeneca)
PF 4449913 (Pfizer)
PLX3397 (Daiichi Sankyo)
PLX4032 (Daiichi Sankyo)
PVS-30200 (Pervasis)
TAK-441 (Takeda)

- The 102nd Annual Meeting of the **American Association for Cancer Research (AACR)** last week in Orlando gave glimpses into new approaches to treat cancer, including updates on a number of important molecular targets.
- Hot topics at this year's meeting were therapies targeting **BRAF, hedgehog, EML4-ALK, and PARP**.
- Especially for BRAF and hedgehog, drug-resistant variants will be an issue, opening the door to follow-on compounds, as has been the case with Novartis's (NVS) Gleevec.
- Attendees anticipate good results for **Plexxikon** (a subsidiary of Daiichi Sankyo) and **Roche (RHHBY) BRAF^{V600E} inhibitor PLX4032** but are also looking for solutions to potential resistance and toxicity issues.
- **Targeting the immune system, the tumor microenvironment, and other cellular compartments that interact with tumor cells** are emerging topics of great promise.
- Intriguing preclinical data were presented by two private companies, **Epizyme** and **Pervasis**. The former is developing histone methyltransferase inhibitors while the latter is developing a cell therapy.

We attended the 102nd Annual Meeting of the American Association for Cancer Research (AACR) in Orlando, Florida. Although there were no high-profile clinical data presentations, the meeting featured updates on several emerging molecular targets, setting the stage for ASCO in early June.

BRAF

The molecular target *du jour* is clearly BRAF. The BRAF inhibitor PLX4032 has generated impressive top-line data in the BRIM3 metastatic melanoma trial. Despite the elegance of a biomarker (BRAFV^{600E} mutation) driven development program, there is increasing concern about early and widespread resistance to PLX4032. The mechanisms of resistance do not appear to involve additional BRAF mutations, but rather residual RAF-RAF-MEK-ERK pathway activity or signalling via other molecules (e.g. PI3K, CRAF, COT). Plexxikon is working on second-generation BRAF inhibitors, including those that do not stimulate RAF signalling in the setting of wildtype BRAF (the “Raf inhibitor paradox”). This phenomenon is incompletely understood. It is thought to explain some of the skin toxicities seen with PLX4032, such as the rapid and extensive development of squamous cell carcinomas, and may also facilitate resistance.

Other BRAF inhibitors in the clinic include Glaxo’s GSK2218436, in phase III for melanoma, and ArQule’s ARQ 736, currently in phase I testing.

One way to improve on the PLX4032 results might be simultaneous administration of BRAF and MEK inhibitors. Results from a Glaxo phase I combination study of GSK2118436 and GSK1120212, a BRAF and MEK inhibitor, respectively, will be featured at ASCO.

Hedgehog

Efforts to target the hedgehog / patched / smoothed pathway continue to gain momentum. The most advanced compound is Curis / Genentech (Roche)’s GDC-0449 for basal cell carcinoma (BCC). Given the high incidence of hedgehog pathway mutations in BCC, it is unlikely that GDC-0449 will require a companion diagnostic. Full details on the reportedly successful pivotal phase II BCC study will be presented at ASCO. As with BRAF inhibitors, resistance is a liability for this program, and second-generation compounds are being developed

by Eli Lilly and Takeda. Presentations by Eli Lilly and Takeda scientists mentioned that their compounds (LY2940680 and TAK-441, respectively) are active against GDC-0449 resistant tumors. Other hedgehog pathway inhibitors in the clinic include phase II programs at Infinity (IPI-926) and Novartis (LDE 225) as well as Bristol’s BMS-833923 (XL139) and Pfizer’s PF 4449913, both in phase I.

PARP

Inhibition of the DNA repair enzyme poly (ADP-ribose) polymerase (PARP) remains an accepted therapeutic strategy, despite the recent high-profile phase III failure of Sanofi’s iniparib in triple-negative breast cancer (TNBC; ER-, PR-, and HER2-negative). AACR attendees speculated that iniparib may not be an especially potent PARP inhibitor, based in part on a lack of significant new toxicity when added to standard chemotherapy and on the failed TNBC study. Patients with germline BRCA1 and -2 mutations remain the most readily identifiable candidates for PARP inhibition.

A fascinating phase II trial involving the PARP inhibitor olaparib (AstraZeneca) is underway. This trial enrolls only patients with BRCA1/2 mutant tumors (and not tumor organ site). Such a study would be expected to include subjects with not only breast and ovarian tumors, but also pancreatic, prostate, and possibly other forms of cancer.

Tumor Microenvironment

The role of the tumor microenvironment (extracellular matrix, fibroblasts, infiltrating immune cells) is increasingly thought to be important in cancer progression and metastasis. Targeting elements of the tumor microenvironment (rather than the actual tumor cells) could therefore be a viable clinical strategy. An example of a microenvironment targeted therapy is the Plexxikon FMS/Kit inhibitor PLX3397. An ongoing phase I trial is evaluating PLX3397 in advanced Hodgkin lymphoma. Amgen (AMG 820), Array (ARRY 382) and ImClone (a subsidiary of Eli Lilly; IMC RON8) have phase I programs targeting various aspects of macrophage signaling pathways, such as the c-FMS receptor and RON.

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Epizyme & Pervasis: Early But Intriguing

Epizyme is developing inhibitors of histone methyltransferases (HMTs), which could emerge as a significant epigenetic target class primarily, but not exclusively, for cancer. Epizyme's lead compound, an inhibitor of the HMT EZH2, is partnered with Eisai and may be uniquely suited to treating follicular lymphoma and some diffuse large B cell lymphomas. Other (undisclosed) Epizyme compounds are partnered with GlaxoSmithKline.

Intriguing preclinical data stemming from the Pervasis cell therapy PVS-30200 were presented at AACR. This approach is based on viewing endothelial cells as paracrine biochemical regulators that can control tumor biology via so-called angiocrine effects. PVS-30200 consists of matrix-embedded endothelial cells that are injected into primary tumors.

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