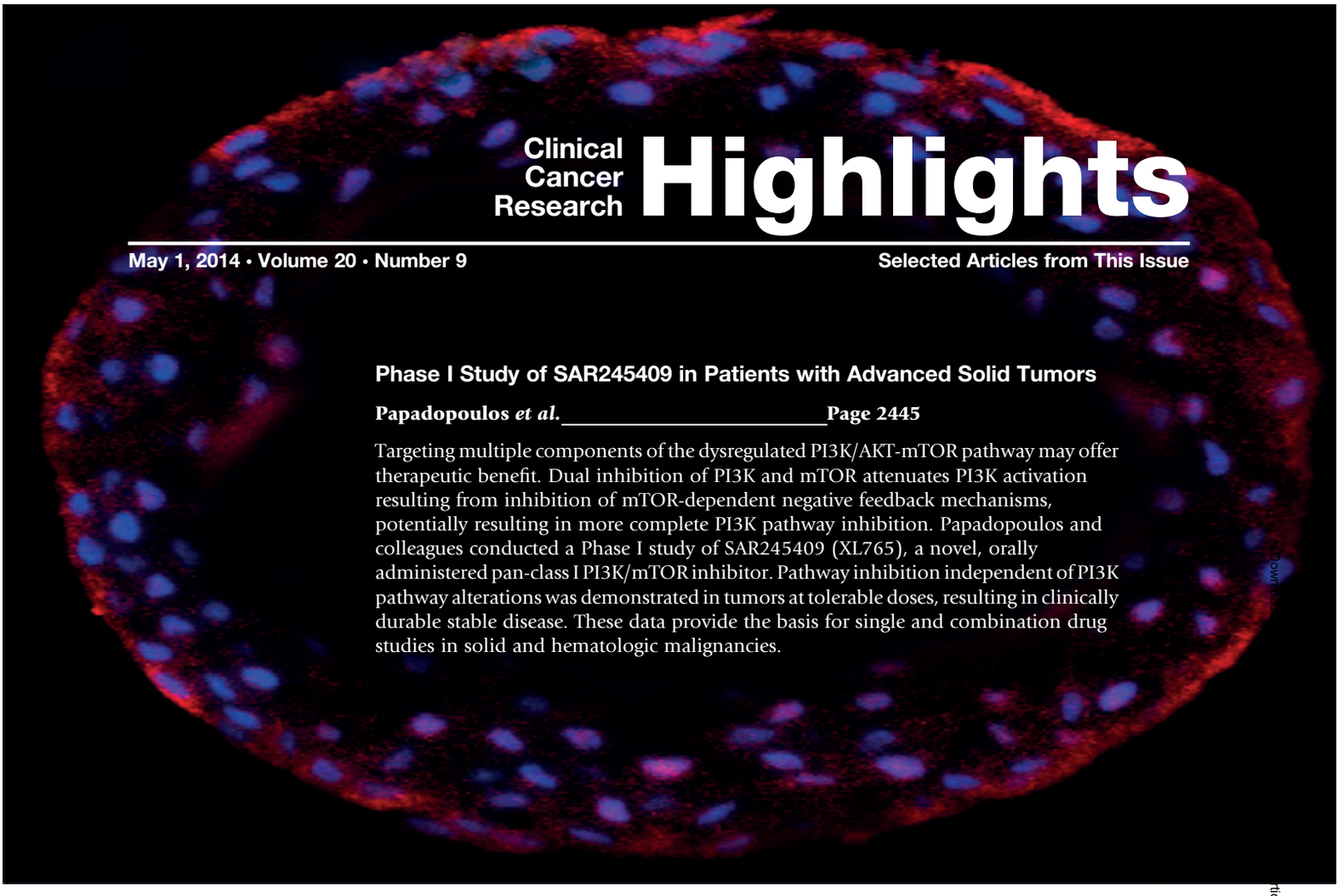
Clinical Cancer Research **Highlights**

May 1, 2014 • Volume 20 • Number 9

Selected Articles from This Issue



Phase I Study of SAR245409 in Patients with Advanced Solid Tumors

Papadopoulos *et al.* **Page 2445**

Targeting multiple components of the dysregulated PI3K/AKT-mTOR pathway may offer therapeutic benefit. Dual inhibition of PI3K and mTOR attenuates PI3K activation resulting from inhibition of mTOR-dependent negative feedback mechanisms, potentially resulting in more complete PI3K pathway inhibition. Papadopoulos and colleagues conducted a Phase I study of SAR245409 (XL765), a novel, orally administered pan-class I PI3K/mTOR inhibitor. Pathway inhibition independent of PI3K pathway alterations was demonstrated in tumors at tolerable doses, resulting in clinically durable stable disease. These data provide the basis for single and combination drug studies in solid and hematologic malignancies.

Regulation of IL-32 in Gastric Cancer

Tsai *et al.* **Page 2276**

The role of IL-32 in gastric cancer (GC) progression and metastasis is still unknown. This study shows that IL-32 contributes to GC progression by increasing the metastatic potential resulting in worse patient survival. We found that IL-32 increase cell invasion ability both *in vitro* and *in vivo* by inducing IL-8 and VEGF expression via phosphor-AKT and active β-catenin/HIF-1α signaling pathways. These results demonstrate a novel function and regulation of IL-32 in GC and imply that it might be advantageous to target IL-32 for cancer therapy.

Increased KIT Inhibition in GIST

Kim *et al.* **Page 2350**

Although targeted therapies have revolutionized the treatment of oncogene-addicted cancers such as gastrointestinal stromal tumor (GIST), they rarely achieve cure. In a transgenic mouse model of GIST and human GIST xenografts, Kim and colleagues demonstrate that increased KIT inhibition can cause substantially more tumor regression than the first-line agent imatinib. PLX3397 was a more potent KIT inhibitor and eliminated more tumor cells than imatinib, but also induced intratumoral fibrosis, which appeared to impair further drug delivery. The results warrant investigation of more potent KIT inhibitors in human GIST and identify the stromal response as a potential barrier to optimal therapy.

Pancreatic TICs in a Syngenic Murine Model

Banerjee *et al.* **Page 2388**

Relapse of any tumor is largely attributed to the presence of tumor-initiating cells (TIC), which are quiescent cells within a tumor that evade conventional chemotherapy. In this study we have isolated and identified CD133+ TICs in an immune-competent, genetic mouse model for pancreatic cancer. It further shows that these TICs, though resistant to most standard chemotherapeutic agents like paclitaxel, gemcitabine and 5FU, respond to minnelide (under phase I clinical trial) and undergo apoptotic cell death both *in vivo* and *in vitro*. We show that minnelide decreases the CD133+ TICs in this extremely aggressive model for pancreatic cancer that is more clinically relevant, compared with the immune-compromised TIC models reported earlier.