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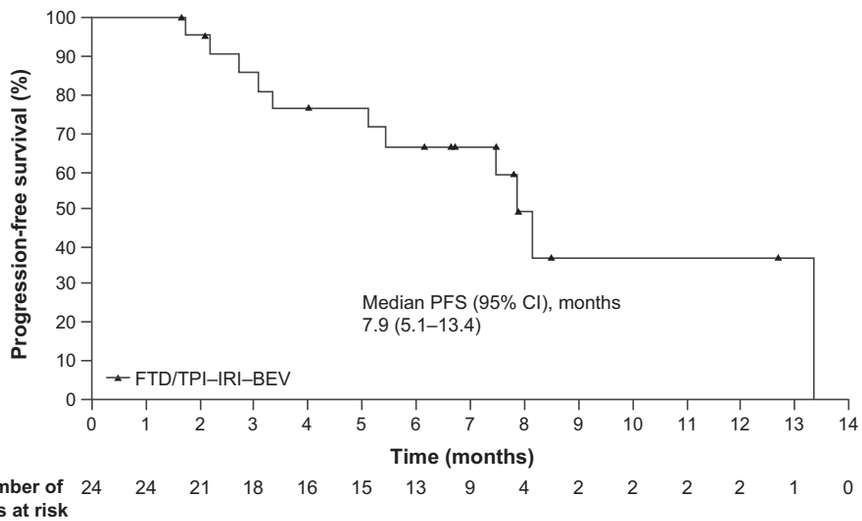
CLINICAL CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

Trifluridine/Tipiracil, Irinotecan, and Bevacizumab in mCRC



Varghese *et al.* | Page 1555

Trifluridine/tipiracil (FTD/TPI), an oral cytotoxic agent, has previously led to improved survival in patients with pretreated, refractory metastatic colorectal cancer. Varghese and colleagues conducted a phase I evaluation of the combination of FTD/TPI, irinotecan, and bevacizumab in patients with advanced previously treated gastrointestinal tumors, including mCRC. No unexpected adverse events were observed with this combination. FTD/TPI, irinotecan, and bevacizumab demonstrated promising antitumor activity, with 12% and 16% of patients experiencing partial responses or stable disease, respectively. These results provide justification for further investigation of this regimen in mCRC.

Cyclophosphamide Exposure-Toxicity Association in Pediatrics

Campagne *et al.* | Page 1563

Infants and young children with brain tumors are a vulnerable population who often encounter severe chemotherapy-related toxicities, which could be reduced with adjusted drug dosages. In this patient population, Campagne and colleagues developed a population-based pharmacokinetic model characterizing the cyclophosphamide and metabolites disposition and investigated the associations among drug exposures and drug-induced hematological toxicities. They found higher metabolite exposures in infants (<1 year) vs. older children, which were associated with worse myelosuppression events. The investigators proposed to reduce the cyclophosphamide dosage for infants by ∼20% to decrease myelosuppression and allow these patients to safely receive this very active drug.

Capivasertib Rapidly Targets Key AKT Pathway Biomarkers

Robertson *et al.* | Page 1574

Window-of-opportunity (WOO) studies provide a unique opportunity to monitor drug mechanism(s) *in vivo*. Robertson and colleagues report on the STAKT study, a triple blind randomized controlled WOO trial in ER+ primary breast cancers. In this trial, treatment with the recommended monotherapy dose of capivasertib, an oral selective AKT1–3 inhibitor, modulated the AKT pathway after 4.5 days. This was evidenced by significant decreases in biomarkers of the AKT pathway (including pGSK3β and pPRAS40) and reduced cell proliferation (Ki67). The biological data obtained from STAKT indicate the potential for capivasertib to be an effective oral anticancer therapy due to its impact on proliferative AKT signaling. Further trials of this agent in advanced breast cancer are warranted.

Combined SHP2 and KRAS G12C Inhibition

Ryan *et al.* | Page 1633

KRAS is the most commonly mutated oncogene in human cancer. Recently, mutant-specific inhibitors of KRAS, such as covalent inhibitors of $KRAS^{G12C}$, have challenged the notion that KRAS is an undruggable target. However, adaptive feedback reactivation of pathway signaling remains a concern for resistance. Ryan and colleagues confirmed the reactivation of wild-type KRAS following treatment with G12C inhibitors. Importantly, the authors noted that inhibition of SHP2, upstream of RAS, prevented the reactivation of RAS signaling. Preclinical assessment of the combination of $KRAS^{G12C}$ and SHP2 inhibition revealed sustained RAS inhibition and improved efficacy. Similar strategies to target the upstream RAS pathway concurrently with RAS inhibition represent a promising therapeutic approach.

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