Molecular Cancer Therapeutics

Highlights

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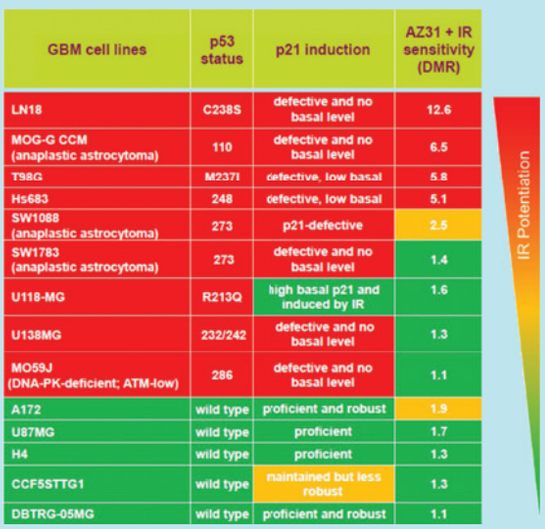
Selected Articles from This Issue



GBM cell lines	p53 status	p21 induction	AZ31 + IR sensitivity (DMR)
LN18	C238S	defective and no basal level	12.6
MOG-G CCM (anaplastic astrocytoma)	110	defective and no basal level	6.5
T98G	M237I	defective, low basal	5.8
Hs683	248	defective, low basal	5.1
SW1088 (anaplastic astrocytoma)	273	p21-defective	2.5
SW1783 (anaplastic astrocytoma)	273	defective and no basal level	1.4
U118-MG	R213Q	high basal p21 and induced by IR	1.6
U138MG	232/242	defective and no basal level	1.3
MO59J (DNA-PK-deficient; ATM-low)	286	defective and no basal level	1.1
A172	wild type	proficient and robust	1.9
U87MG	wild type	proficient	1.7
H4	wild type	proficient	1.3
CCF5STTG1	wild type	maintained but less robust	1.3
DBTRG-05MG	wild type	proficient and robust	1.1

Novel Orally Bioavailable ATM Inhibitor Radiosensitizes Glioma

Karlin and Allen *et al.* Page 1637

Surgery and chemoradiation are the standard of care for glioblastoma multiforme (GBM), a devastating and incurable cancer with few clinical options. Small molecule inhibitors targeting ATM, a master regulator of the DNA damage response, are currently in clinical development. Karlin, Allen, and colleagues report an experimental, blood-brain barrier penetrating ATM kinase inhibitor that prolongs the survival of mice with orthotopic tumors in combination with radiation. The enhanced response seen with tumors having dysfunctional p53 signaling is attributed to increased mitotic catastrophe. These results define a mechanism for preferential responses in p53-defective cancers and may lead to improved, selective treatment of GBM.

TAS6417 as a Novel EGFR-TKI Specific to Exon 20 Insertions

Hasako *et al.* Page 1648

Development of EGFR-tyrosine kinase inhibitor (TKI) with selectivity against exon 20 insertion mutations over wild-type is a major challenge for the treatment of non-small-cell lung cancer (NSCLC) driven by EGFR harboring such mutations. Hasako and colleagues identified TAS6417 which is a novel small molecule EGFR-TKI and exhibits selective inhibition of exon 20 insertion mutations over wild-type *in vitro* and *in vivo*, achieving remarkable antitumor efficacy in preclinical model including NSCLC patient-derived xenograft model. These findings support clinical evaluation of TAS6417 as an efficacious drug candidate for patients with NSCLC harboring EGFR exon 20 insertion mutations.

EYA3 and Tumor Angiogenesis

Wang *et al.* Page 1659

EYA3 is a protein tyrosine phosphatase that promotes survival of cells after DNA damage. In this study, Wang and colleagues show that host vascular endothelial cell EYA3 promotes tumor angiogenesis, and that tumor cell EYA3 promotes survival and proliferation of tumor cells. Pharmacological inhibition of the EYA3 protein tyrosine phosphatase activity attenuates tumor growth and tumor angiogenesis by targeting both host and tumor cells. Simultaneously targeting the tumor vasculature and tumor cells is an attractive therapeutic strategy since it could counter the development of the more aggressive phenotype known to emerge from conventional anti-angiogenic agents.

AZD6738 Synergizes with Gemcitabine to Inhibit PDAC

Wallez *et al.* Page 1670

Rising incidence and extreme mortality rate of PDAC, engender a major unmet clinical need that urgently requires novel therapeutic strategies. Small molecule inhibitors targeting DNA damage response pathways hold promise, but rational combinations with conventional therapies require investigations. Here, Wallez and colleagues report that the ATR inhibitor, AZD6738, and gemcitabine potently synergize to inhibit proliferation of PDAC cell lines, and demonstrate that this combination is well tolerated, inducing tumor regression in preclinical cancer models. Together, these data support clinical testing of this innovative combination in patients with PDAC, and more generally in solid tumors with high levels of replication stress.