Heterogeneity Underlies the
Emergence of EGFR T790M
Wild-Type Clones Following
Treatment of T790M-Positive
Cancers with a Third-Generation
EGFR Inhibitor

Z. Piotrowska, M.J. Niederst, C.A. Karlovich,
H.A. Wakelee, J.W. Neal, M. Mino-Kenudson,
L. Fulton, A.N. Hata, E.L. Lockerman, A. Kalsy,
S. Digumarthy, A. Muzikansky, M. Raponi,
A.R. Garcia, H.E. Mulvey, M.K. Parks,
R.H. DiCecca, D. Dias-Santagata, A.J. IafRATE,
A.T. Shaw, A.R. Allen, J.A. Engelman,
and L.V. Sequist

Précis: Baseline intratumor heterogeneity
for the EGFR T790M mutation is associated
with outgrowth of resistant EGFR T790M–
wild-type subclones and predicts clinical
response to the EGFR T790M-specific
inhibitor rociletinib.

See commentary, p. 694

Germline Mutations in the
CDKN2B Tumor Suppressor
Gene Predispose to Renal
Cell Carcinoma

M. Jafri, N.C. Wake, D.B. Ascher, D.E.V. Pires,
D. Gentle, M.R. Morris, E. Rattenberry,
M.A. Simpson, R.C. Trembath, A. Weber,
E.R. Woodward, A. Donaldson, T.L. Blundell,
F. Latif, and E.R. Maher

Précis: Germline inactivating mutations
in CDKN2B were identified in patients
with inherited renal cell carcinoma and
predicted to impair its tumor suppressive
activity.

INPP4B Is a Tumor
Suppressor in the Context
of PTEN Deficiency

T.-T.T. Vo and D.A. Fruman

Précis: Loss of INPP4B in mice promotes
enhanced AKT2 activation and PI(3,4,5)P3
accumulation to induce metastatic thyroid
tumors in the context of PTEN deficiency.

See commentary, p. 697
See article, p. 740

INPP4B Is a PtdIns(3,4,5)P3
Phosphatase That Can Act as a
Tumor Suppressor

S. Kofuji, H. Kimura, H. Nakanishi, H. Nanjo,
S. Takasuga, H. Liu, S. Eguchi, R. Nakamura,
R. Itoh, N. Ueno, K. Asanuma, M. Huang,
A. Koizumi, T. Habuchi, M. Yamazaki,
A. Suzuki, J. Sasaki, and T. Sasaki

Précis: Loss of INPP4B in mice promotes
enhanced AKT2 activation and PI(3,4,5)P3
accumulation to induce metastatic thyroid
tumors in the context of PTEN deficiency.

See commentary, p. 697
See article, p. 740
In Vivo Role of INPP4B in Tumor and Metastasis Suppression through Regulation of PI3K–AKT Signaling at Endosomes .......... 740
Précis: Loss of INPP4B drives localized activation of PI3K–AKT2 in early endosomes and cooperates with PTEN inactivation to promote aggressive and metastatic thyroid tumor formation.
See commentary, p. 697
See article, p. 730

ARID1A Deficiency Impairs the DNA Damage Checkpoint and Sensitizes Cells to PARP Inhibitors ...... 752
Précis: The identification of a role of ARID1A in the DNA damage response suggests a potential therapeutic vulnerability of ARID1A-mutant cancers.

Shen and colleagues identified ARID1A, a subunit of SWI/SNF chromatin remodeling complexes, as a binding partner of ATR, a key regulator of the DNA damage response. ARID1A is recruited to DNA double-strand breaks (DSB) in an ATR-dependent manner and promotes efficient DSB end resection, which is necessary for activation of ATR and subsequent initiation and maintenance of the G2/M checkpoint. ARID1A loss impaired homologous recombination and single-strand annealing DSB repair mechanisms and, similar to loss of BRCA1 or BRCA2, conferred sensitivity to DSB-inducing PARP inhibitors. Given that inactivating mutations in ARID1A are among the most frequent genetic events in human cancers, these findings suggest that PARP inhibitors may be effective in a broader spectrum of cancers than previously appreciated. For details, please see the article by Shen and colleagues on page 752.