

with a point mutation. Two patients with point mutations eventually experienced progression of their disease. Tumor progression was not observed in the patients with exon 19 deletions. The mean progression free interval was 430 days (CI [294,567]) for the whole series.

Conclusions: The observations add support to the importance of EGFR status as predictors of response to TKIs. Exon 19 deletions seem to predict the best responses to TKIs.

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S30. ANTI-TUMOR APPLICATIONS OF ACTIVATING TOLL-LIKE RECEPTOR 9 WITH PF-3512676 (FORMERLY CPG 7909)

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Unmethylated CpG dinucleotides are relatively common in viral and bacterial DNA, but are rare in vertebrate DNA. Toll-like receptor 9 (TLR9) detects these "CpG motifs" as a sign of infection, and can be activated for therapeutic purposes by CpG motifs in synthetic oligodeoxynucleotides (CpG ODN), such as PF-3512676 (formerly called CPG 7909, or CpG 2006). PF-3512676 engages TLR9 in B cells and plasmacytoid dendritic cells (pDC), thereby stimulating innate and adaptive immunity, including antigen-specific Th1-like T cell responses. Murine studies showed anti-tumor activity of PF-3512676 as a monotherapy for relatively small tumors. Tumor regression was associated with the induction of a tumor-specific CTL response. PF-3512676 has been administered at various dose levels to more than 1000 humans, and has shown activity as a monotherapy in phase I human clinical trials when administered by intratumoral injection in basal cell carcinoma, by subcutaneous injection in cutaneous T cell lymphoma (CTCL), melanoma, and renal cell carcinoma, and by intravenous injection in non-Hodgkin's lymphoma.

Although the demonstrated activity as a monotherapy provides some proof-of-concept for the use of PF-3512676 in cancer therapy, we considered that combination approaches may provide greater efficacy. We theorized that disruption of the tumor using conventional anti-tumor therapies may reduce the tumors' resistance to immune mediated attack induced through TLR9 activation with PF-3512676. In murine models regression of larger tumors could be induced when PF-3512676 was used in combination with other therapies, including radiotherapy, surgical resection, monoclonal anti-tumor antibodies, and chemotherapy. The combination of PF-3512676 or other CpG ODN with certain chemotherapy regimens, including paclitaxel or gemcitabine, increased the generation of tumor antigen-specific CTL and/or improved tumor regression and survival in metastatic tumor models. These studies also demonstrated the involvement of T cells in the synergy between CpG and paclitaxel, consistent with the hypothesis that this combination induces enhanced tumor specific adaptive immune responses. These encouraging results in mouse models have been extended into human therapy in a controlled Phase II trial, where 112 patients with locally advanced or metastatic non-small cell lung cancer were randomized to receive either chemotherapy alone, or in combination with PF-3512676. The combination with che-

motherapy provided a statistically significant improvement in objective response rate, and a trend to prolonged survival (1 year survival 33% vs. 50%, $P=0.08$). The safety and tolerability of these TLR9 agonists has generally been good, with the major adverse events being transient injection site reactions and flu-like symptoms. Phase III trials of PF-3512676 in combination with 2 doublet chemotherapy regimens (paclitaxel plus carboplatin or gemcitabine plus cisplatin) for first-line therapy of locally advanced or metastatic NSCLC in 1600 patients were initiated in late 2005.

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S31. GENE PROFILING IN MELANOMA – WHAT HAVE WE GAINED?

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In the mid 1990s one of the first targets of DNA microarray analysis was melanoma. For over a decade researchers have made increasing use of this technology in their efforts to understand the molecular biology underlying this disease. Most work has concentrated on class-comparison approaches which assess the transcriptional differences between aggressive and less aggressive variants, or explored the consequences of activating mutations in members of the MAPK pathway. Other studies examined the effects of various in vitro treatments including UV, retinoids, demethylation and hypoxia. The general outcome of these studies have been the generation of ever longer lists of genes nearly all of which are guilty through association. But who are the master criminals in the crowd? Where are the strings which draw these multitudinous factors together and who are the puppetmasters behind them? DNA microarrays may have brought us closer to the facts, but what they all mean is not at all obvious to the majority of researchers. Just where in these details lies the devil of malignancy?

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S32. TUMOR STROMA-ASSOCIATED ANTIGENS FOR ANTI-CANCER IMMUNOTHERAPY

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Immunotherapy has been widely investigated for its potential use in cancer therapy and it becomes more and more apparent that the selection of target antigens is essential for its efficacy. Indeed, limited clinical efficacy is partly due to immune evasion mechanisms of neoplastic cells, e.g. downregulation of expression or presentation of the respective antigens. Consequently, antigens contributing to tumor cell survival seem to be more suitable therapeutic targets. However, even such antigens may be subject to immune evasion due to impaired