## *Keynote lecture* (Tue, 25 Sep, 11:15–12:00)
## A systems approach to predictive markers and therapeutic targets

**71** INVITED

**A systems approach to predictive markers and therapeutic targets**

J.W. Gray. *USA*

Abstract not received.

## *Special session* (Tue, 25 Sep, 13:30–14:30)
## Novel targeted therapies using predictive markers in lung cancer

**72** INVITED

**Novel agents targeting the Wnt pathway in lung cancer**

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**Background:** Aberrant activation of the Wnt signaling pathway is implicated in the development of a broad spectrum of human tumors. We previously demonstrated that Dishevelled (DVL), a Wnt pathway modulator, was overexpressed in lung tumors and cell lines. Wnt signaling in the β-catenin pathways seems to be induced by DVL overexpression. In this study we aimed to design small-molecule inhibitors to block the interaction between the Frrzzled-7 Wnt receptor and the PDZ domain of DVL and to test whether it inhibits down-stream Wnt signaling and suppresses tumor cell growth.
**Materials and Methods:** Small-molecule inhibitor FJ9 was chemically synthesized using structural design of indole-2-carbinol-based chemical scaffold. AlphaScreen energy transfer assays and nuclear magnetic resonance spectrometer were used to test the binding of Frz-7 and DVL. Changes of downstream Wnt signaling after FJ9 treatment were analyzed using quantitative RT-PCR, Western blot, and β-catenin-dependent Tcf transcription with luciferase assay. Inhibition of tumor cell growth of FJ9 was tested in cultured cell lines as well as in a mouse xenograft model bearing H460 cells.
**Results:** Our study showed that the small-molecule inhibitor FJ9 specifically disrupted the interaction between the Frz-7 Wnt receptor and the PDZ domain of Dishevlled. FJ9 inhibited the Tcf transcriptional activity by directly suppressing DVL-mediated nuclear translocation of β-catenin. Results from Western and RT-PCR reveal that FJ9 significantly down-regulates canonical Wnt signaling molecules (c-myc, cyclin D1), and the inhibitor of apoptosis protein Survivin. The effects of FJ9 on the growth of tumor cells were assayed in the cells with intact β-catenin signaling. We showed that FJ9 caused significant apoptosis in the H460 and H1703 non-small cell lung cancer cell lines, and LOX melanoma cell line, as compared with normal primary cultures of NHBE or SAEC. Results from in vivo testing showed that FJ9 significantly inhibited the growth of the tumor xenografts after daily administration of FJ9 (50 mg/kg) for 14 days as compared with control groups ($p = 0.02$).
**Conclusions:** Our study demonstrates that small-molecule inhibitors of the PDZ domain of DVL can down-regulate the β-catenin-dependent Wnt signaling pathway and induce apoptosis in human lung cancer cells. Further study is warranted for development of small molecule-based targeted therapies for lung cancer.

**73** INVITED

**Management of lung cancer based on genetic abnormalities – easy and practical for patients and oncologists**

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Increased receptor tyrosine kinase (RTK) signalling in lung cancer is often caused by gene amplification, increased transcription/translation, or mutations that promote ligand-independent autophosphorylation. The failure of RTKs to be appropriately deactivated can cause neoplastic growth and resistance to EGFR tyrosine kinase inhibitors (TKIs). We reason that defective RTK downregulation can also be related to CHFR and 14-3-3σ methylation status and therefore intervene in resistance to EGFR TKIs. We carried out an ERCC1-customized trial of cisplatin in stage IV non-small-cell lung cancer (NSCLC). One hundred and seventy-nine of a total of 365 patients included in the trial received second-line therapy (105 chemotherapy, 74 EGFR TKIs). Overall median survival, calculated from the start of first-line treatment, for patients with unmethylated CHFR was 21.4 months with EGFR TKIs and 11.2 months with chemotherapy ($P = 0.0001$). No differences were observed in patients with methylated CHFR. Median survival for patients with methylated 14-3-3σ was 21 months with EGFR TKIs and 10 months with chemotherapy ($P = 0.0004$). The subgroup of patients with methylated 14-3-3σ and unmethylated CHFR attained a median survival of 24.6 months with EGFR TKIs, in contrast with 9 months with chemotherapy ($P = 0.003$). The genetic causes underlying these results are being investigated in experimental models.
Similar findings have been observed in 52 NSCLC patients with EGFR mutations treated with second-line erlotinib. Progression-free survival (PFS) was 20 months for patients with methylated 14-3-3σ versus 15 months for those with unmethylated 14-3-3σ, and 20 months for patients with unmethylated CHFR versus 10 months for those with methylated CHFR. PFS for patients with EGFR exon 19 deletion and methylated 14-3-3σ has not been reached, while it is 15 months for those with exon 19 deletion and unmethylated 14-3-3σ. For patients with EGFR L858R mutation and methylated 14-3-3σ, PFS was 20 months while it has not been reached for those with L858R mutation and unmethylated 14-3-3σ. PFS for patients with EGFR exon 19 deletion and unmethylated CHFR was 16 months versus 4 months for those with exon 19 deletion and methylated CHFR. PFS for patients with EGFR L858R mutation and unmethylated CHFR was 20 months versus 10 months for those with L858R mutation and methylated CHFR.
Simple guidelines for customizing chemotherapy will be presented.

**74** INVITED

**How to exploit the apoptic machinery**

G. Giaccone. *National Cancer Institute, Medical Oncology Branch, Bethesda, USA*

The apoptosic machinery is defective in many common tumors, and the unraveling of the pathways that lead to apoptosis has allowed the possibility of targeting apoptosis as a valuable way to kill tumor cells selectively. There are several molecules involved in the two major pathways of apoptosis (intrinsic and extrinsic) that are being targeted by drugs. In the extrinsic pathway, there are drugs that target the death receptors. Tumor Necrosis Factor (TNF) was the first one to be targeted; however recombinant TNF is too toxic when given systemically and TNF is still being used as part of limb perfusion treatments together with melphalan for patients with extremity sarcomas or malanomas that are no longer treatable by surgery. Fas-L has not entered the clinic because of several liver toxicity in preclinical animal models. Recombinant Trail has undergone phase I testing without major side effects and is now being investigated in combination with chemotherapy. A major advantage of Trail as a target, compared to the other death receptor members is that Trail is by far more expressed in tumors than in normal cells. Striking synergy has also been observed with several chemotherapeutic drugs and irradiation. Agonistic antibodies against Trail are also being investigated. They have been found to be devoid of major toxicities and phase II studies are ongoing with two antobodies (mapatumumab and lexatumumab) used as single agents and in combination, in several tumor types. Although hints of antitumor activity has been shown with single agents, the most promise probably comes from combinations.
in the intrinsic pathway, the mitochondial membrane molecules that belong to the Bcl-2 family have been targeted by several agents, mostly small molecules. Several agents have been developed that have differential activities against the many molecules that belong to the Bcl-2 family, and early studies demonstrate some activity in lymphocytic leukemia (e.g. GX15–07). The antisense oligonucleotide Oblimersen sodium has undergone extensive development, but it demonstrated insufficient activity in leukemia and melanoma in phase III studies.
A growing family of proteins called IAPs (inhibitors of Apoptosis proteins) is also bein targeted by small molecules and antisense strategies. Among these are inhibitors of XIAP and survivin that are most advanced. Antisense oligonucleotides have been tested in phase I and are now moving into phase II trials. The putative survivin small molecule inhibitor YM-155 has been tested in phase II studies in non-small cell lung cancer, prostate cancer and melanoma, with some activity.
Several other molecles may be of interest in the apoptosis machinery, for the development of effective agents and this represents a field of intense research.