Hematological malignancies:
- Publications on 3 drugs, which are pan-Aurora inhibitors targeting also Bcr-Abl kinase, described hematological responses in early clinical trials in patients with T315I or other Bcr-Abl mutated CML (and Philadelphia positive ALL in 2 cases) relapsing on imatinib and other c-Abl therapies. Partial and complete cytogenetic responses were reported, with undetectable T315I in one case.
- In AML, reduction of bone marrow blasts was observed. This preliminary antileukemic activity was not sustained enough and led to investigate new regimens with dose-intensifications and more prolonged administrations. Similarly more frequent administrations/intakes of drugs targeting also FLT3 aim at maintaining a sufficient inhibition for a prolonged diminution of blasts.
- Myeloproliferative disorders: cross-reactivity with JAK2 was explored with one compound and is expected to be investigated for other Aurora inhibitors.

Potential other targets: The different cancer relevant cross-reactivities of some compounds might be at the origin of specific developments, such as inhibition of FGFRs for example in T(4−14) positive Multiple Myeloma, or in subsets of patients with bladder, breast, endometrial and cervix cancers, or Ret in thyroid cancers.
Combinations: Preclinical studies support a wide spectrum of combinations with classical chemotherapeutic agents or targeted drugs. Phase I combination studies are ongoing and might represent the most promising future of Aurora kinase inhibitors.
Updated results on these compounds will be given during the lecture.

244 INVITED

Polo-like kinase inhibition in oncology: from bench to bedside

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Background: *polo* is a gene encoding for an enzyme present in *Drosophila melanogaster*, discovered and cloned in 1991 by Llamazares *et al.* Mutations in *polo* were found to induce abnormal mitoses in *Drosophila*. Clay *et al.* identified and cloned gene sequences in murine hematopoietic progenitor cells encoding for a protein kinase, which shares extensive homology with the enzyme encoded by *Drosophila*'s *polo* gene. The mouse gene was named *Plk*, the protein encoded by *Plk* is polo-like kinase, which belongs to a family of serine/threonine kinases with critical involvement in cell growth and differentiation in various species. Hamanaka *et al.* cloned in 1994 both murine and human complementary DNAs that were homologous to *Drosophila*'s *PlkIT*> gene and the related kinase. The human counterpart of the mouse gene was named P*LK*. Up to 80% of human tumors of various origin express high levels of *PLK* transcripts, whereas the according mRNA is mainly absent from surrounding healthy tissue, as described first by Holtrich *et al.* in 1994. Polo-like kinase expression is associated with poor prognosis in some tumor types.
Materials and Methods: Polo-like kinases 1, 2 and 3 are key regulators of multiple steps in mitosis and obviously an attractive target for anticancer drug development. The current state-of-the-science presentation will briefly describe the biology of polo-like kinases and the basic principles of inhibiting these enzymes. Polo-like kinase inhibitors interfere with different stages of mitosis, with centrosome maturation, spindle formation, chromosome separation and cytokinesis. They induce mitotic chaos and severe pertubation of the cell cycle, ultimately leading to cancer cell death. Various drugs in advanced stages of preclinical and early clinical testing will be reviewed. Non-confidential safety and efficacy data from the first dose-finding Phase I studies and the earliest screening Phase II trials with polo-like kinase inhibitors will be presented. The pharmacology of the most advanced agents will be summarized briefly. The presentation will cover information on drugs such as BI-2536, BI-6727, GSK461364, LC-445, various pyrazoloquininazolines, ON 01910, amongst others.
Conclusions: Small-molecule inhibitors of polo-like kinases are new and promising tools in the treatment of human cancers, some of them having passed the transition from bench to bedside and now reaching the critical Phase I/early Phase II stage of clinical development in solid tumors, lymphoma and hematological malignancies.

245 INVITED

PARP inhibitors in cancer treatment

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Poly(ADP-ribose) polymerases (PARPs) are a family of highly conserved enzymes, the most abundant being PARP-1, a nuclear DNA-binding enzyme that is activated by DNA strand breaks. PARP-1 has a key role in binding to and the signalling of DNA single strand breaks as part of the base excision repair process.
Recent evidence shows that BRCA-1 or BRCA-2 defective cell lines are exquisitely sensitive to PARP inhibition compared to BRCA wild-type or heterozygous cell lines [1,2]. This is because single strand breaks accumulate following PARP inhibition, which result in stalled replication forks and DNA double strand breaks during S-phase. These lesions are normally repaired by homologous recombination repair, which is dependent on BRCA functionality. BRCA functionality may be lost in a significant proportion of cancers by epigenetic mechanisms as well as by hereditary mutations, increasing the population potentially sensitive to treatment with PARP inhibitors.
AG014699, a potent tricyclic indole inhibitor of PARP-1 and 2, was the first in class to undergo a Phase I trial in cancer patients [3]. AZD2281 (KU-0059436) has undergone a Phase I trial in cancer patients with BRCA mutations [4]. Phase I data have been reported on BSI-201 and Phase 0 data on ABT-888. A Phase II study of AG014699 in patients with breast or ovarian cancer and known mutations of BRCA-1 or BRCA-2 is being conducted in UK centres.

References

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246 INVITED

Targeting Her: Can resistance to EGFR inhibitors be overcome?

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Background: The epidermal growth factor receptor (Her1) is a receptor tyrosine kinase with an extensively described role in mediating pleiotropic cellular responses. Upon binding by a number of ligands, the receptor enters into ligand-receptor dimers and is autophosphorylated. The phosphorylated receptor recruits docking proteins and signal transduction molecules, resulting in activation of cascades which are anti-apoptotic, proliferative, and contribute to metastasis and angiogenesis. Targeting of Her is therapeutic in lung, head and neck and colon cancer, but de novo and acquired resistance are common, attributed to mutation in downstream effectors, upregulation of redundant receptors, mutation in the receptor, and alteration in receptor trafficking, among other mechanisms.
Materials and Methods: A systems biology approach defined an siRNA library targeting the extended EGFR signaling network. High throughput screening of this library identified candidate genes that sensitize cells to EGFR inhibition. This dataset is used to map elements of the EGFR signaling network responsible for sensitivity.
Results: 110 primary hits sensitized to one or both of the EGFR-targeting agents, with significant overlap within the groups. Sensitization effects are confirmed with 4 separate siRNAs targeting each hit, establishing that the degree of sensitization correlates with potency of the siRNA in knocking down expression of its target. Approximately 45% of the initial hits pass validation. A number of the hits are quite distant from EGFR in the protein interaction networks, including novel candidates for regulating the EGFR pathway.
Conclusions: siRNA targeting of a library of candidate genes identifies novel targets for sensitization to EGFR inhibition, and provides a tool for drug discovery and design of trials for patients with cetuximab or erlotinib resistant head and neck, colon and lung cancer.