sequencing (ChIP-seq). Resminostat’s effect on global gene expression was analysed by RNA-seq focusing on CTCL-relevant pathways and genes.

Results and discussions Resminostat increased total lysine acetylation in CTCL cell lines. The active epigenetic mark H3K27ac dose-dependently accumulated on a genome-wide level as detected by ChIP-seq analysis. Global gene expression profiling revealed both gene induction and repression by resminostat. First data showed a regulation of T helper (Th) 1 and 2 specific genes implying that resminostat normalises the Th1/Th2 imbalance in CTCL which is discussed to be associated with disease progression. Moreover, expression of skin-homing receptor genes was reduced by resminostat indicating a potential effect of resminostat on the cutaneous tropism of malignant T cells. Furthermore, the pruritus mediator IL-31 was downregulated by resminostat suggesting an attenuation of itching and thus indicating an important benefit for CTCL patients regarding their health-related quality of life.

Conclusion First results from a genome-wide study suggest a promising impact of resminostat on different targets relevant for the pathogenesis of CTCL. These data broaden our understanding of resminostat’s molecular mechanism of action in CTCL and support our current clinical phase II trial evaluating resminostat for maintenance treatment of patients with advanced stage CTCL (RESMAIN, NCT02953301).

Results and discussions Of the ALK inhibitors, alectinib was more selective than ceritinib and brigatinib. Cell lines harbouring the NPM-ALK translocation were potently inhibited by all three inhibitors. There was a strong correlation between drug sensitivity and high ALK expression levels. Furthermore, elevated expression of JAK3 and other JAK-STAT signalling genes correlated with drug sensitivity, indicating a potential role of JAK-STAT signalling in response to ALK inhibitors. Elevated expression of the transcription factor MYCN was indicative of the sensitivity of NPM-ALK negative cell lines for ceritinib and brigatinib.

Conclusion By profiling all clinically approved kinase inhibitors, we were able to compare their selectivity and identify novel response biomarkers. These data will be important in guiding novel applications of these inhibitors as well as future drug development in the kinase field.

PO-457 IS 8-AZAGUANINE SELECTIVELY ACTIVE AGAINST ANEUPLOID ACUTE MYELOID LEUKAEMIA?

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Introduction Aneuploidy, the presence of an abnormal number of chromosomes within a cell, is a recurrent characteristic of both solid and haematological tumours. A substantial number of patients with acute myeloid leukaemia (AML) harbour a complex karyotype, which consists in three or more aberrations, including numerical chromosome abnormalities in the absence of prognostically favourable rearrangements. The prognosis of these patients is dismal due to the poor response to the conventional therapy, a combination of the nucleoside analogue cytarabine and the anthracycline daunorubicin. For this reason compounds that specifically cause lethality in karyotypically abnormal cells with numerical chromosome aberrations could provide a novel treatment approach.

Material and methods With the aim to identify compounds that are more cytotoxic against aneuploid versus diploid AML cells, we tested a group of chemicals on 36 primary human AML samples (18 with a euploid karyotype, 18 with an aneuploid karyotype) derived from either bone marrow or peripheral blood. We further established an isogenic AML cell line model to confirm the observations made on primary cells and to gain insight into the aneuploidy-specific mechanisms of action of the drugs.

Results and discussions We identified 8-azaguanine as a compound that causes lethality in aneuploid primary cells more efficiently than in euploid cells. In the cell line model, both viability and apoptosis assays suggest that the aneuploid clones at earlier differentiation levels respond better to 8-azaguanine than the euploid cells, with the tetraploid clone responding the best.

Conclusion Our results provide an initial clue to proceed with further investigations on the therapeutic application of 8-aza-guanine against aneuploid AML.

PO-456 CELL LINE PANEL PROFILING OF ALL CLINICALLY APPROVED KINASE INHIBITORS FOR CANCER TREATMENT

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Introduction Profiling of drugs on cancer cell line panels can uncover new insights into the mechanisms of drug response. We have established a panel of 102 genetically well-characterised cell lines from distinct tumour origins, called Oncolines. Earlier work on kinase inhibitor profiling showed that our workflow generates highly reproducible data. Here we present the profiling of seventeen kinase inhibitors which have been approved since November 2014 in the Oncolines panel.

Material and methods The profiled agents include the ALK inhibitors ceritinib, brigatinib, and alectinib, the CDK4/6 inhibitors palbociclib, abemaciclib, and ribociclib, the BTK inhibitors ibrutinib, and acalabrutinib, and nine other novel marketed inhibitors that were not profiled earlier. The cell lines were screened in parallel in a high-throughput proliferation assay based on ATP-lite read-out, at 9 duplicate concentrations of each inhibitor. Drug response was expressed as IC50 and GR50 values.

Drug response metrics were associated with genomic alterations in the cell lines. These were retrieved from the Catalogue of Somatic Mutations in Cancer database and filtered for relevance in primary patient tumours.

In addition, we calculated correlations between the log IC50 and basal gene expression levels of 18,900 genes, retrieved from the Cancer Cell Line Encyclopaedia. Correlations were filtered by the Oncolines database of 150 previously profiled anti-cancer agents.