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# Overcoming resistance and bypassing checkpoints—possible new therapeutic frontiers in oncology

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The armamentarium of systemic oncological therapies has constantly increased in recent years and in addition to standard chemotherapy now includes targeted therapies, anti-hormonal therapies, anti-angiogenic therapies and immunotherapy. All these therapeutic approaches have been proven a clinical success, often significantly prolonging the lives of cancer patients. However, mostly tumours progress as resistance to these therapies develops biologically, defined by either primary or secondary resistance mechanisms.

In the guest editor edition "Overcoming resistance and bypassing checkpoints—possible new therapeutic frontiers in oncology", we review the major biological mechanisms of resistance by which cancer cells can evade targeted therapy, chemotherapy, anti-angiogenic therapy, anti-hormonal therapy and immunotherapy in various oncological diseases and discuss new avenues to overcome or bypass resistance situations.

The advent of genomics led to the identification of specific "driver" mutations in oncogenic kinases as well as to the development of targeted small molecule inhibitors to block their tumour-driving functions. Important examples are activating mutations in the epidermal growth factor receptor (EGFR) in non-small cell lung cancer (NSCLC) and KIT mutations in gastrointestinal stromal tumours (GIST). Absenger [1] summarizes the current treatment landscape of EGFR-mutated NSCLC and discusses new perspectives on novel EGFR tyrosine kinase inhibitors (TKI) focussing on primary resistance as well as on new potential combinations strategies to overcome secondary resistance.

In general, 80% of GIST harbour mutations in KIT gene and imatinib is the mainstay of therapy for high-risk adjuvant and advanced stage disease. Seeber et al. [2] critically analyse strategies to overcome imatinib resistance in GIST and provide an overview of promising new agents currently evaluated in trials.

Ovarian cancer (OC) shows high genetic and tumour microenvironmental heterogeneity. Advanced stage OC therapy consists of chemotherapy/anti-angiogenic therapies and development of therapy resistance poses a major therapeutic challenge. Wieser et al. [3] discuss novel approaches as PARP (poly ADP ribose polymerase) inhibition and forecast that therapy may require different approaches depending on the molecularly defined subgroups of OC ("differentiated", "immunoreactive", "mesenchymal" and "proliferative"). Furthermore, Fuereder [4] gives an overview on immunotherapy resistance and focuses on the molecular background of resistance to checkpoint inhibition (CPI) and outlines current clinical data of CPI combination studies. Future potential strategies to overcome CPI resistance might also depend on the immune phenotype. Kauffman-Guerrero et al. [5] report on their experience with monitoring CPI efficacy in NSCLC with PET-CT imaging (PERCIST criteria). Thereby the authors show that PET-CT has the ability to identify non-responders (not detected via RECIST criteria) early, thus finally leading to the prevention of overtreatment and govern an early switch to a more effective therapy. Culig [6] reports on resistance to anti-androgen therapy in prostate cancer. Anti-androgen resistance maybe mediated by mutations in the androgen receptor itself or their co-activators, but also other players like stromal factors or stem cells have been associated with therapy resistance.

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In summary this edition intends to highlight the heterogeneity of therapy resistance depending on each therapeutic strategy and tumour type. For the future, to successfully overcome resistance a deep understanding of genetic driver alterations as well as of the tumour microenvironmental factors is necessary. Concluding, resistance may never be entirely prevented; however the development of new inhibitors and combination approaches may help to treat common drivers of resistance or delay progressive disease.

**Conflict of interest** A. Pircher declares that he has no competing interests.

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