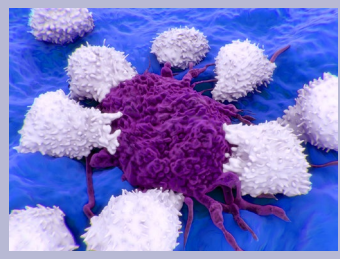

Future ONCOLOGY

Abstract Book 2015–2016

The next few decades will see dramatic changes within the field of oncology. Whilst the burden of disease is set to increase, the available armamentarium to the oncologist will be greater, more robust and offer the potential to focus on individual needs. ***Future Oncology*** provides a forum for a new era of cancer care. The journal focuses on the most important advances and highlights their relevance in the clinical setting. Furthermore, ***Future Oncology*** delivers essential information in concise, at-a-glance article formats – vital in delivering information to an increasingly time-constrained community.

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Drug Evaluation

Nivolumab: targeting PD-1 to bolster antitumor immunity

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www.futuremedicine.com/doi/full/10.2217/fon.15.52

Nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, blocks PD-1 and can restore anticancer immune responses by abrogating PD-1 pathway-mediated T-cell inhibition. Nivolumab is approved in Japan and the USA for the treatment of patients with advanced melanoma. A Phase I trial reported overall objective response rates of 17, 32 and 29% in patients with advanced non-small-cell lung cancer, melanoma and renal cell carcinoma, respectively, which included many heavily pretreated patients. 1-/2-year overall survival rates were 42%/24%, 63%/48% and 70%/50% for non-small-cell lung cancer, melanoma and renal cell carcinoma, respectively. Nivolumab significantly improved survival versus dacarbazine in previously untreated patients with metastatic melanoma in a Phase III trial. Nivolumab is associated with a manageable adverse event profile. Numerous clinical trials are investigating nivolumab alone or in combination with other therapies in multiple cancer settings. This article summarizes the development of nivolumab as of November 2014.

02

Clinical Trial Protocol

The HELIOS trial protocol: a Phase III study of ibrutinib in combination with bendamustine and rituximab in relapsed/refractory chronic lymphocytic leukemia

Michael Hallek[1], Neil E Kay[2], Anders Osterborg[3], Asher A Chanan-Khan[4], Michelle Mahler[5], Mariya Salman[5], Ying Wan[5], Steven Sun[5], Sen Hong Zhuang[5] & Angela Howes[6]

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Future Oncology 11(1), 51–59 (2015).

www.futuremedicine.com/doi/abs/10.2217/fon.14.119

Ibrutinib is an orally administered, covalent inhibitor of Bruton's tyrosine kinase with activity in B-cell malignancies based on Phase I/II studies. We describe the design and rationale for the Phase III HELIOS trial (trial registration: EudraCT No. 2012-000600-15; UTN No. U1111-1135-3745) investigating whether ibrutinib added to bendamustine and rituximab (BR) provides benefits over BR alone in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. Eligible patients must have relapsed/refractory disease measurable on CT scan and meet ≥1 International Workshop on Chronic Lymphocytic Leukemia criterion for requiring treatment; patients with del(17p) are excluded. All patients receive BR (maximum six cycles) as background therapy and are randomized 1:1 to placebo or ibrutinib 420 mg/day. Treatment with ibrutinib or placebo will start concomitantly with BR and continue until disease progression or unacceptable toxicity. The primary end point is progression-free survival. Secondary end points include safety, objective response rate, overall survival, rate of minimal residual disease-negative remissions, and patient-reported outcomes. Tumor response will be assessed using the International Workshop on Chronic Lymphocytic Leukemia guidelines.

03

Research Article

Neoadjuvant breast cancer treatment as a sensitive setting for trastuzumab biosimilar development and extrapolation

Christian Jackisch[1], Frank A Scappaticci[2], Dominik Heinzmann[3], Fabio Bisordi[3], Thomas Schreitmüller[3], Gunter von Minckwitz[4] & Javier Cortés[5]

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Future Oncology 11(1), 61–71 (2015).

www.futuremedicine.com/doi/full/10.2217/fon.14.187

Aims: Identify sensitive end points and populations for similarity studies of trastuzumab and biosimilar monoclonal antibodies. **Methods:** We performed meta-analyses of trastuzumab clinical trials data: overall response rate (ORR) and progression-free survival in metastatic breast cancer (MBC), and total pathologic complete response (tpCR) and event-free survival in the neoadjuvant setting. Fitted models predicted the maximum loss in long-term efficacy for different similarity trial designs. Immunogenicity rates were investigated in different early breast cancer (EBC) study phases. **Results:** Using the same equivalence margins for ORR (MBC) and tpCR (EBC), the predicted maximum loss in long-term efficacy with a biosimilar candidate versus the reference product is smaller for tpCR than for ORR. In EBC this predicted loss could be controlled with feasible patient numbers for a typical clinical trial. Analyses suggested that a treatment-free follow-up phase is preferable for immunogenicity characterization. **Conclusion:** Treatment of patients with neoadjuvant breast cancer represents a sensitive setting for establishing biosimilarity of efficacy and immunogenicity. tpCR is a sensitive end point in this setting to establish biosimilarity between a biosimilar candidate and its reference product.

04

Perspective

A periodic table for cancer

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Future Oncology 11(5), 785–800 (2015).

www.futuremedicine.com/doi/full/10.2217/fon.14.315

Cancers exhibit differences in metastatic behavior and drug sensitivity that correlate with certain tumor-specific variables such as differentiation grade, growth rate/extent and molecular regulatory aberrations. In practice, patient management is based on the past results of clinical trials adjusted for these biomarkers. Here, it is proposed that treatment strategies could be fine-tuned upfront simply by quantifying tumorigenic spatial (cell growth) and temporal (genetic stability) control losses, as predicted by genetic defects of cell-cycle-regulatory gatekeeper and genome-stabilizing caretaker tumor suppressor genes, respectively. These differential quantifications of tumor dysfunction may in turn be used to create a tumor-specific 'periodic table' that guides rational formulation of survival-enhancing anticancer treatment strategies.

05

Review

A review of conventional and drug-eluting chemoembolization in the treatment of colorectal liver metastases: principles

David M Liu[1], Avnesh S Thakor[2], Mark Baerlocher[3], Mohammed T Alshammari[1], Howard Lim[4], Sebastian Kos[5], Andrew S Kennedy[6] & Harpreet Wasan[7]

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Future Oncology 11(9), 1421–1428 (2015).

www.futuremedicine.com/doi/full/10.2217/fon.15.3

The management of colorectal liver metastasis has undergone a significant change since the development of novel ablation and embolization. Drug-eluting microsphere platforms, designed to deliver targeted concentrations of systemic therapy directly into the tumor via its arterial vasculature, have garnered interest and gained in popularity in recent years. Based on in vitro and in vivo data, multiple factors contribute to locoregional exposure including carrier base, smaller particle size (larger surface area), chemotherapeutic and chemotherapeutic intensity. Based on the current published clinical data, therapy appears well tolerated but the questions remain as to the ideal technique, patient population and overall efficacy. The purpose of this article is to provide a perspective on the scientific basis, and clinical review of the current data supporting the use of this platform in the setting of metastatic colorectal carcinoma.

06

Research Article

Prognostic role of *KRAS*, *NRAS*, *BRAF* and *PIK3CA* mutations in advanced colorectal cancer

Luisa Foltran[1], Giovanna De Maglio[1], Nicoletta Pella[1], Paola Ermacora[1], Giuseppe Aprile[1], Elena Masiero[1], Mariella Giovannoni[1], Emiliana Iaiza[1],Giovanni Gerardo Cardellino[1], Stefania Eufemia Lutrino[1], Micol Mazzer[1], Manuela Giangreco[1], Federica Edith Pisa[1], Stefano Pizzolitto[1] & Gianpiero Fasola[1]

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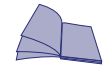
Future Oncology 11(4), 629–640 (2015).

www.futuremedicine.com/doi/full/10.2217/fon.14.279

Aim: To explore the prognostic value of extended mutational profiling for metastatic colorectal cancer (mCRC). **Materials & methods:** We retrospectively reviewed survival results of 194 mCRC patients that were assigned to four molecular subgroups: BRAF mutated; KRAS mutated codons 12-13 only; any of KRAS codons 61-146, PIK3CA or NRAS mutations and all wild-type. Point mutations were investigated by pyrosequencing. **Results:** BRAF (5.2%) and KRAS 12-13 (31.9%) mutations were associated with poorer survival (HR 2.8 and 1.76, respectively). Presenting with right-sided colon cancer, not resected primary tumor, WBC >10 × 109/l, receiving less chemotherapy or no bevacizumab were all associated with inferior outcome. The all-wild-type subgroup (39.2%) reported the longest survival. **Conclusion:** Extended mutational profile combined with clinical factors may impact on survival in mCRC.



07

Perspective

Chemotherapy options for patients suffering from heavily pretreated metastatic breast cancer

Guy Jerusalem[1], Andrée Rorive[1] & Joëlle Collignon[1]

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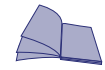
Future Oncology 11(12), 1775–1789 (2015).

www.futuremedicine.com/doi/full/10.2217/fon.15.80

The identification of additional chemotherapy agents for anthracycline- and taxane-pretreated advanced breast cancer (ABC) is an urgent medical need. Single agent chemotherapy is most times administered because combined therapy is only associated with modest, if any, improvement in median progression-free survival. Randomized trials failed to show overall survival benefit compared with single agent chemotherapy. We hope to modify the natural history of ABC by the consecutive use of treatments with documented activity in heavily pretreated patients. Quality of life remains an important end point as cure is in general not possible. We first review the activity of the approved and the most frequently used agents in heavily pretreated ABC. Thereafter, the potential role and safety profile of etirinotecan pegol is discussed given the results recently released of a Phase III trial comparing this agent to Treatment of Physician's Choice.



08

Short Communication

Incidence rates of chronic lymphocytic leukemia in US states are associated with residential radon levels

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Future Oncology 12(2), 165–174 (2016).

www.futuremedicine.com/doi/abs/10.2217/fon.15.275

Aim: Environmental risk factors for chronic lymphocytic leukemia (CLL) have not been consistently identified. An etiologic role for ionizing radiation in CLL is controversial. Because most of the ionizing radiation to which individuals are exposed comes from radon at home, we examined CLL incidence rates in relation to residential radon levels. **Methods:** We used population-based rates for CLL for US states from 2007 to 2011 and measurements of residential radon made by the US Environmental Protection Agency. **Results:** Incidence rates for CLL were significantly correlated with residential radon levels among whites (both genders together and each gender separately; $p < 0.005$) and among blacks ($p < 0.05$). **Conclusion:** We speculate that radon increases CLL risk and that the mechanisms may be similar to those by which radon causes lung cancer.

09

Research Article

Feasibility, efficacy and safety of tyrosine kinase inhibitor treatment in hemodialyzed patients with renal cell cancer: 10 years of experience

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[1]Military Institute of Medicine, Warsaw, Poland

Future Oncology 11(16), 2267–2282 (2015).

www.futuremedicine.com/doi/full/10.2217/fon.15.112

Aims: Sine efficiency of tyrosine kinase inhibitor (TKI) therapy in dialyzed patients is still unclear we aim to analyze the outcome of treatment in such cohort. **Patients & methods:** We analyzed treatment outcomes of patients with clear cell renal cell carcinoma (ccRCC) with special focus on those who were also treated with hemodialysis and described treatment safety and progression-free survival of eight patients treated with TKIs and hemodialysis. **Discussion & conclusion:** Our report supports statement that TKI treatment of dialyzed patients is safe and effective. ccRCC increases risk of developing renal insufficiency as well as end-stage renal disease that require dialysis. Introduction of multitargeted receptor kinase inhibitors (TKIs), including sunitinib, sorafenib and pazopanib significantly expanded life time expectancy of metastatic renal clear cell carcinoma. The advance also applies to patients with ccRCC and end-stage renal disease who undergo dialyses.