IN BRIEF

BREAST CANCER

Obesity associated with resistance to anti-angiogenic therapy

Anti-angiogenic therapy, predominantly with the anti-VEGF antibody bevacizumab, has not been shown to improve the survival of patients with breast cancer. 70% of patients with this disease are overweight or obese; now, data from 99 patients treated with bevacizumab indicate that a high BMI (≥25) is associated with tumours that are typically larger at diagnosis, hypovascular, hypoxic, and insensitive to bevacizumab. Interestingly, patients with a high BMI had high circulating levels of IL-6 and FGF2. In obese mice with breast cancer, elevated expression of FGF2 or IL-6 by adipocytes and other cells of the tumour microenvironment was likewise associated with resistance to anti-VEGF therapy, which could be overcome through pharmacological antagonism of the FGF2 or IL-6 axes.

ORIGINAL ARTICLE Incio, J. et al. Obesity promotes resistance to anti-VEGF therapy in breast cancer by up-regulating IL-6 and potentially FGF-2. *Sci. Transl Med.* **10**, eaag0945 (2018)

HEAD AND NECK CANCER

Postoperative chemoradiotherapy versus radiotherapy for high-risk cutaneous disease

In the phase III TROG 05.01 trial, 310 patients with resected high-risk cutaneous squamous cell carcinoma of the head and neck received either chemoradiotherapy with carboplatin (area under the curve 2) or radiotherapy alone, in the adjuvant setting; 89% versus 88% of patients were free of locoregional relapse at 2 years, and the respective rates were 87% and 83% at 5 years (HR 0.84, 95% CI 0.46–1.55; $P = 0.58$). Similarly, no statistically significant differences in disease-free survival or overall survival were reported. Thus, postoperative radiation therapy is highly efficacious in this population and incorporation of carboplatin to postoperative treatment, although mostly well tolerated, provides no additional benefit.

ORIGINAL ARTICLE Porceddu, S. V. et al. Postoperative concurrent chemoradiotherapy versus postoperative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck: the randomized phase III TROG 05.01 trial. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.2017.77.0941 (2018)

LUNG CANCER

New subtypes of high-grade neuroendocrine tumours revealed

Large-cell neuroendocrine carcinoma (LCNEC) is a rare and aggressive form of lung cancer. Confusingly, LCNEC has molecular and pathological features in common with not only neuroendocrine small-cell lung cancers (SCLCs) but also adenocarcinomas and squamous cell carcinomas, and can sometimes co-occur with any of these other cancer types. Now, comprehensive integrative genomic and transcriptomic profiling of 75 LCNECs has revealed two molecular subgroups: type I LCNECs, characterized by biallelic *TP53* and *STK11* and/or *KEAP1* alterations, and a neuroendocrine differentiation phenotype (*ASLC1*^{high}*DLL3*^{high}*NOTCH*^{low}); and type II tumours, which have biallelic inactivation of *TP53* but also *RB1*, are *ASLC1*^{low}*DLL3*^{low}*NOTCH*^{high}, and have upregulation of immune-related pathways. These findings have implications for clinical trials: patients with type I LCNECs might be candidates for DLL3-directed therapies that have promising activity against SCLC, whereas those with type II LCNECs might respond to Notch-targeted agents or immunotherapy.

ORIGINAL ARTICLE George, J. et al. Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors. *Nat. Commun.* **9**, 1048 (2018)

HAEMATOLOGICAL CANCER

Venetoclax–rituximab holds substantial promise in CLL

The single-agent activity of venetoclax, an antagonist of the apoptotic protein BCL-2, in patients with chronic lymphocytic leukaemia (CLL) has been established in three nonrandomized clinical studies. Now, results of the first reported international, randomized trial of venetoclax strengthen this evidence base and demonstrate the promise of combination therapy with rituximab.

In the open-label, phase III MURANO trial, 389 patients with relapsed or refractory CLL received venetoclax plus rituximab or chemoimmunotherapy with bendamustine plus rituximab (BR). The estimated 2-year progression-free survival (PFS) was 84.9% with venetoclax–rituximab versus 36.3% with BR; the PFS benefit was similar across all patient subgroups, in particular, 2-year PFS in patients with high-risk del(17p) disease was 81.5% versus 27.8%. "This markedly superior efficacy was supported by consistent superiority across the spectrum of secondary end points, including a signal for improved overall survival, despite a modest follow-up duration and widespread access to novel targeted agents at progression in the BR arm," adds lead investigator John Seymour. "The high rate of peripheral blood minimal residual disease (MRD) negativity [83.5% with venetoclax–rituximab versus 23.1% with BR] is particularly notable, and sets this chemotherapy-free regimen apart from other highly active novel treatments of CLL, such as ibrutinib, which despite protracted PFS in most patient subsets, has a very low rate of bone marrow clearance and rarely leads to deep MRD-negative responses," Seymour emphasizes.

Importantly, the frequency of tumour-lysis syndrome (TLS), a

MELANOMA

Encorafenib — a new agent for advanced-stage disease

Patients with advanced-stage *BRAF*^{V600E}-mutant melanoma are often treated with the V600E-selective *BRAF* inhibitor vemurafenib in combination with a MEK inhibitor, such as binimetinib. However, the risk of adverse events and the inevitability of acquired resistance and disease progression associated with this approach highlight the need for novel agents.

Now, data from a phase III trial demonstrate the superiority of a new ATP-competitive inhibitor, encorafenib, that is specific for the V600E, V600D, and V600K forms of BRAF. In the COLUMBUS trial, a total of 577 patients with *BRAF*^{V600}-mutant melanoma were randomly assigned to receive either vemurafenib, encorafenib (300 mg per day), or binimetinib plus encorafenib (450 mg per day) owing to the toxicity-limiting effects of binimetinib observed in phase II studies.

After a median follow-up duration of 16.6 months, patients in the binimetinib plus encorafenib group had a median progression-free survival (PFS) duration of 14.9 months versus 7.3 months with vemurafenib (HR 0.54; $P < 0.001$) and 9.6 months with encorafenib (HR 0.75; $P = 0.051$). These differences in PFS were supported by similar improvements in overall response rates: 63% versus 51% and 40% among patients in the binimetinib plus encorafenib, encorafenib, and vemurafenib groups, respectively.

Notably, patients receiving binimetinib plus encorafenib had a lower risk of adverse events than those in either the encorafenib or vemurafenib groups (58% versus 66% and 63%, respectively). This finding confirmed