High- Versus Low-Dose Lenalidomide Maintenance in Myeloma

**Fenk et al. | Page 5879**

High-dose chemotherapy and autologous blood stem-cell transplantation (ASCT) followed by lenalidomide maintenance (LenMT) is the current standard of care for patients with multiple myeloma (MM). However, dose reductions of LenMT are often necessary. Fenk and colleagues performed a clinical trial of MM patients after ASCT and high-dose lenalidomide consolidation therapy (CT) at 25 mg/day were randomized to receive LenMT at either 25 or 5 mg/day. Patients receiving high dose LenMT showed improved PFS compared with patients receiving low dose. Adverse events were more common in patients in the high-dose arm but decreased after dose-adjustments. Therefore, the maximum tolerated dose of LenMT varied among patients and needs to be individually tailored. Long-term follow-up studies may further refine the dosing implications of LenMT.

Palbociclib and Trastuzumab in HER2-Positive Breast Cancer

**Ciruelos et al. | Page 5820**

CDK4/6 inhibitors plus endocrine therapy improves overall survival in women with estrogen receptor (ER)-positive HER2-negative advanced breast cancer. However, this combination has not been studied in HER2+ disease. Ciruelos and colleagues report the results of the SOLTI-1303 PATRICIA clinical trial in which women with HER2+ advanced breast cancer who were heavily pretreated were administered palbociclib in combination with trastuzumab with or without endocrine therapy. This combination showed evidence of activity in these patients, especially in the context of hormone receptor-positive disease. Genomic analysis of tumor samples revealed that the Luminal subtype by the PAM50 assay is a biomarker that might better select patients for palbociclib treatment, regardless of hormone receptor status. Based on these findings, the PATRICIA trial has been amended, and a new randomized cohort is currently recruiting.

Anti-Tumor Responses Mediated by Tebentafusp in Melanoma

**Middleton et al. | Page 5869**

Metastatic uveal melanoma (mUM) carries a poor prognosis and is not responsive to checkpoint inhibition. In a phase I/II trial in patients with melanoma, Middleton and colleagues assessed tebentafusp, a first-in-class bispecific fusion protein containing a high-affinity T-cell receptor binding domain targeting and an anti-CD3 T-cell-engaging domain which redirects T cells to kill gp100-expressing tumor cells. Tebentafusp was well tolerated in both mUM and metastatic cutaneous melanoma (mCM) patients, and a 65% overall survival rate was observed in both patient groups. Treatment activated IFNγ signaling, as well as an increase in serum CXCL10, and a reduction in circulating CXCR3+ CD8+ T cells together with an increase in cytotoxic T cells in the tumor microenvironment. Furthermore, increased serum CXCL10 was associated with prolonged patient survival. These data support further investigation of tebentafusp as a promising new anticancer therapy for metastatic melanoma.

Single-Cell PI3K Pathway Assessment in Archival Tumor Tissue

**Stopsack et al. | Page 5903**

The PI3K pathway is activated in a large proportion of cancers, and activation may predict sensitivity to PI3K/Akt inhibitors. Stopsack and colleagues describe a novel multiplex immunofluorescence approach to quantify PI3K pathway activity in archival formalin-fixed, paraffin-embedded tumor specimens based on three PI3K pathway markers on a single-cell level. High PI3K scores identified men with primary prostate cancer from two prospective cohort studies who were increased risk of metastatic progression and cancer death over long-term follow-up. This measure of PI3K activation warrants assessment as a predictive biomarker in clinical trials of PI3K inhibitors.