CRM1/BRAF Inhibition in Melanoma
Salas Fragomeni et al. __Page 1171
The CRM1 receptor mediates the nuclear export of critical proteins that are required for cancer cell proliferation, survival, and drug resistance. Salas Fragomeni and colleagues evaluated the effects of novel inhibitors of CRM1 in melanoma and found that selective inhibitors of nuclear export (SINE) decrease melanoma cell proliferation independent of BRAF mutation status and synergistically enhance the cytotoxic effects of BRAF inhibition in BRAF-mutant melanoma. These SINE compounds also induce complete regression of BRAF V600E tumors when combined with BRAF inhibition. Clinical studies to explore the use of SINE compounds in combination cancer therapy are underway.

DCDT2980S for the Treatment of Non-Hodgkin Lymphoma
Li et al. __Page 1255
Antibody-drug conjugates (ADC), potent cytotoxic drugs linked to antibodies via chemical linkers, allow for the targeting of chemotherapy to tumors. Here, Li and colleagues describe the preclinical data for DCDT2980S, an anti-CD22 ADC that targets the potent microtubule inhibitor monomethyl auristatin E to B-cell malignancies. DCDT2980S is active in xenograft models of lymphoma at clinically relevant exposures. Notably, surface expression of CD22 had little correlation to efficacy of DCDT2980S. These data suggest that DCDT2980S could be used to treat a wide variety of B-cell malignancies. DCDT2980S is currently being evaluated in patients.

mTORC2-Targeted Therapy for Ovarian Clear Cell Carcinoma
Hisamatsu et al. __Page 1367
Clear cell carcinoma (CCC) of the ovary is characterized by poor sensitivity to standard chemotherapy; thus, new treatments are critically needed. Hisamatsu and colleagues found that mTORC2 is frequently activated in CCC and that CCC cells are highly sensitive to mTORC2 inhibition. These findings have significant implications for the future design of clinical trials of first-line therapies for CCC. They also discovered that RAD001-mediated mTORC2 activation is involved in the mechanism responsible for RAD001 resistance and that mTORC2 inhibition has profound antitumor effects in RAD001-resistant CCC. Therefore, an mTORC2-targeting therapy represents a novel treatment option for recurrent CCC developing after mTORC1-inhibition.

Superagonists of TRAILR2-Induced Apoptosis
Swers et al. __Page 1235
Induction of programmed cell death through tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors has shown significant promise in preclinical studies as a therapeutic approach for cancer. However, early attempts at targeting this axis in the clinic have not yielded significant benefit to patients. By driving significantly greater activity, including in models refractory to TRAIL, the novel scaffold offers new hope in targeting this axis for cancer therapy and may provide insights to maximize therapeutic benefits for other members of the TNFR superfamily.