Targeted drug combinations: avant-garde oncology

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Combination therapies take stage

In this year's most prominent oncology conferences, an emerging theme amongst leading abstracts was the increasing use of combination targeted therapy. Spurred by a presidential call for precision medicine, leading researchers are now exploring the use of a combination of targeted agents to simultaneously attack multiple cancer pathways. This strategy has been most exemplified in the case of cancer immunotherapy, as a number of groundbreaking studies in the clinical arena have demonstrated the promise and superiority of combination therapy.

Combined PD-1 and CTLA-4 inhibition in newly diagnosed metastatic melanoma: a new standard of care?

At the American Association for Cancer Research (AACR) Annual Meeting in Philadelphia, PA, this year, Dr. Stephen Hodi and colleagues presented initial data from a phase II, double-blind trial in which 142 patients were enrolled testing the combination of anti-CTLA4-antibody ipilimumab with the anti-PD-1 antibody nivolumab (1). The objective-response rate was found to be 61% in the group that received both ipilimumab and nivolumab (combination group) *vs.* 11% in patients receiving ipilimumab alone. The data for progression-free survival was similarly impressive, with a hazard ratio (HR) of 0.40 in favor of the combination arm. Combination therapy was noted to have increased adverse events, with 54% of patients in the combination arm having grade 3 or 4 treatment-related adverse events *vs.* 24% in the monotherapy arm.

The results of the larger confirmatory phase III trial, CheckMate 067, were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting by Dr. Jedd Wolchok and colleagues. Results from this trial continued to demonstrate the benefit of combination therapy, with patients receiving both ipilimumab and nivolumab having significantly longer progression-free survival and higher objective response rates than treatment with ipilimumab or nivolumab alone. In fact, the combination therapy had an overall response rate (ORR) of 57.6% compared to 43.7% in the nivolumab alone group and 19% in the ipilimumab alone group. The median progression-free survival was 11.5 months with both nivolumab and ipilimumab, as compared with 2.9 months with ipilimumab, and 6.9 months with nivolumab. Interestingly, in this study, investigators found that the greatest benefit with the combination therapy may occur in the context of negative PD-L1 tumor expression. Toxicity was increased in patients receiving nivolumab plus ipilimumab with 55% of patients having a grade 3-4 toxicity reported (95.5% any grade), but no treatment-related deaths were reported. The majority (85-100%) of grade 3-4 toxicity resolved with administration of immunomodulatory agents with the exception of endocrine events. Despite 1/3 of patients stopping treatment due to treatment related toxicity, 67.5% who discontinued treatment continued to have a response to treatment (half of whom developed the response after treatment stoppage). However, caution must be exercised as final results regarding overall survival, the co-primary endpoint, has not yet been reported (2).

New immunomodulatory combinations

In other developments at the AACR Annual Meeting,

Dr. David Bajor and colleagues presented early results of a phase I clinical trial testing the combination of anti-CTLA-4 blockade with tremelimumab in addition to an investigational immunostimulatory anti-CD40 monoclonal antibody (CP-870,893). In this small study of 24 pre-treated patients with metastatic melanoma, combination therapy was found to be safe, with three patients experiencing dose-limiting toxicities. Clinical response rates were encouraging with ORR was 27%, which included complete responses in two patients and partial responses in four patients (3).

The combination of anti-CTLA-4 blockade with tremelimumab was also tested with the PD-1 inhibitor MEDI4736 in the setting of previously treated non-small cell lung cancer (NSCLC). At the ASCO annual meeting, Dr. Scott Antonia and colleagues presented data from a phase Ib open label study demonstrating that the combination of the PD-L1 and CTLA-4 blockade had encouraging response rates in both PD-L1 positive and negative patients. In the subgroup of patients with PD-L1 negative expression, ORR was 27% and overall disease control rate was 48%. Adverse events were acceptable and within range of similar combination treatments (4).

Targeting DNA-repair pathways

The increasing use of multiple targeted agents was not only limited to immunomodulatory agents. At the AACR Annual Meeting, several early-phase trials reported safety and efficacy with the combination of PARP inhibitors and other targeted agents. A growing body of evidence has suggested PARP activity even in patients without BRCA mutations. Dr. Ursula Matulonis and colleagues presented data from an open able phase I trial in women with advanced triple negative breast cancer and refractory ovarian cancer. In this study, two PI3K inhibitors, BKM120 or BYL719, were tested in combination with olaparib, a PARP inhibitor previously approved for use in the BRCA-mutated ovarian cancer. Evidence of clinical benefit by RECIST criteria was observed on all dose levels in both BRCA mutated and wild-type patients (5). Similarly, in the ComPAKT trial, the investigational AKT inhibitor AZD5363 was evaluated for safety in combination with olaparib. Dr. Timothy Yap and colleagues used a novel clinical trial design to investigate the safety and activity of the combination treatment in breast, ovarian, and prostate cancers, regardless of BRCA1/2 mutation status. Investigators found objective responses in 20% (4/20) of patients with minimal toxicity (6).

Targeting BRAF pathways

At the ASCO annual meeting, mature results of the COMBI-d study, a randomized, double-blinded, phase III study comparing the combination of dabrafenib and trametinib with dabrafenib and placebo as first-line therapy in patients with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma were revealed. This encouraging study demonstrated a statistically significant improvement in overall survival among patients with BRAF V600E/K mutation-positive metastatic melanoma receiving the combination of BRAF inhibitor and a MEK inhibitor when compared to a BRAF inhibitor alone (median of 25.1 *vs*. 18.7 months, P=0.0107). The improvement in overall survival establishes the combination of dabrafenib and trametinib as the standard targeted treatment for BRAF mutation-positive melanoma (7).

These encouraging results were reinforced by results from a single-arm, 2-stage, phase II study in patients advanced BRAFV600E mutant NSCLC. Data from Dr. David Planchard and colleagues presented at ASCO this year suggested that this combination treatment may be useful in other disease sites. Patients in this study with metastatic NSCLC, who had failed at least one line of chemotherapy, demonstrated an ORR of 63%. Toxicity was manageable, with Grade 3 AEs occurring in 39% of patients, however, there was one patient with a fatal pleural effusion (8).

Future directions

As new pathways continue to become better characterized the opportunities for targeted therapy combinations will increase. By engaging multiple pathways, non-overlapping toxicities from each targeted treatment may allow for greater ability to improve the therapeutic ratio while minimizing the development of resistance pathways. Innovative clinical trial designs, such as umbrella and bucket studies like the ALCHEMIST, FOCUS 4, BATTLE and Lung-MAP trials, will be necessary to take advantage of the increasing number of agents available for various genetic alterations that are available across multiple disease sites.

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