Immunotherapy Advances for Colorectal Carcinoma in 2018: Newly Released Data From the Gastrointestinal Cancers Symposium in San Francisco

30 January 2018—Despite significant improvements in the management of advanced colorectal cancer (CRC), patients with chemo-refractory disease continue to have poor prognosis, with survival of only around 7 months. This indicates a high unmet need for novel treatment strategies in this patient population.

In the past few years, inhibitors of immune checkpoints (eg, PD-1, PD-L1) have revolutionized the treatment of many cancer types. The high mutational load in MSI-high (MSI-H) metastatic CRC (mCRC) resulting from deficient DNA mismatch repair (dMMR) might contribute to sensitivity to PD-1 inhibition.[1,2] Based on remarkable and durable responses from phase I and II trials, the US Food and Drug Administration (FDA) granted accelerated approval to pembrolizumab for the treatment of relapsed MSI-H tumors, including mCRC, and to nivolumab for relapsed, MSI-H mCRC.

However, in cancers such as mCRC, single-agent activity with these novel immunotherapies is limited to only the ~5% of MSI-H patients, while the vast majority (~95%) of cases are microsatellite stable (MSS), characterized by poor immunogenicity due to low tumor mutational burden and neoantigen formation, leading to negligible sensitivity to checkpoint inhibitor monotherapy.[3] Still, there is an unaddressed medical need for these 95% of patients with MSS mCRC.

At the 2018 Gastrointestinal Cancers Symposium in San Francisco, California, new data on immunotherapy in both MSS and MSI-H mCRC were presented.

Promising Efficacy of Atezolizumab and Cobimetinib Combination in MSS Advanced Colorectal Cancer

Preclinical data indicate that MEK inhibition with cobimetinib can sensitize mCRC to anti–PD-L1 targeting by promoting MHC expression and accumulation of intratumoral CD8-positive T cells, as well as by decreasing exhaustion of T cells in the tumor microenvironment.[4] This strategy was evaluated in a phase Ib trial in several solid tumor types, including heavily pretreated, advanced CRC. Patients received IV atezolizumab (800 mg q2w) and oral cobimetinib (20 mg to 60 mg daily during dose escalation and 60 mg during dose expansion either in a 21/7 or 14/14 on/off schedule). A previous report of preliminary results in 23 patients indicated that this combination was well tolerated at the maximum administered doses and yielded an objective response rate (ORR) of 17%.[5]

Johanna Bendell, MD, from the Sarah Cannon Research Institute (Nashville, Tennessee, United States), presented updated findings from the cohort of 84 patients with advanced CRC, of whom 66 (79%) had received ≥5 prior systemic therapies.[6] Among these patients, 68% were *KRAS* mutant, and 30% were *KRAS* wildtype. Microsatellite instability status was determined locally and was centrally confirmed by next generation sequencing-based scoring (50% MSS, 11% MSI-low, 1% MSI-high, 38% unknown).[6]

Key safety and efficacy findings after median follow up of 17.0 months included:

- The combination yielded a safety profile consistent with previous single-agent studies, with no unexpected increase in toxicity
- No treatment-related deaths were observed
- Grade 1/2 treatment-related adverse events (TRAEs) occurred in 58% of patients
- Grade 3/4 TRAEs occurred in 38% of patients
    - Rash, diarrhea, fatigue, and increased blood creatine phosphokinase were most frequent (5% incidence each)
- The majority of AEs were manageable
    - Adverse events leading to discontinuation of atezolizumab occurred in 13% of patients
    - Adverse events leading to discontinuation of cobimetinib occurred in 24% of patients
- Objective responses were observed in 7 patients (8%), 4 of whom had MSS disease, 1 had MSI-low, 2 had unknown MSI status
- Disease control rate (DCR) was 31%
- Responses were observed regardless of *KRAS* status
    - Median duration of response was 14.3 months
    - Median progression-free survival (PFS) was 1.9 months and 2.5 months for all patients and the MSS subgroup, respectively
- The 12-month OS rates were 43% and 51% for all patients and MSS patients, respectively, with a median OS of 9.8 months and 13.0 months, respectively

According to these findings, atezolizumab/cobimetinib represents the first potential immune-modifying combination for patients with MSS, advanced CRC. The 12-month OS rates are quite impressive and compare favorably with the 12-month OS of 24% with regorafenib, a standard option in this setting.[7] Data from the ongoing phase III IMblaze 370 (COTEZO) trial are eagerly awaited. This trial is comparing the efficacy of cobimetinib/atezolizumab with atezolizumab monotherapy and with regorafenib in patients with advanced CRC who received at least 2 prior lines of chemotherapy-based treatments.[8] Only 5% of patients with MSI-high status will be enrolled; the remaining 95% will be MSS.

Benefit of Nivolumab in MSI-H mCRC Sustained With Longer Follow-Up

Michael Overman, MD, from the MD Anderson Cancer Center (Houston, Texas, United States), presented updated efficacy and safety data with 21 months of follow-up from the nivolumab (3 mg/kg IV q2w) cohort of CheckMate-142 in patients with MSI-H mCRC.[9]

Key findings from this update included:

- ORR for all patients was 34%
    - Complete response (CR) rate increased to 9% with longer follow-up, compared with 3% after 13-month follow-up[2]
- Median PFS was 6.6 months

- Median OS was not reached; 12-month and 18-month survival rates were 72% and 67%, respectively
- No new safety signals were observed with longer follow up; 8% of patients discontinued treatment due to an any-grade AE

Ipilimumab Enhances the Clinical Benefit of Nivolumab in MSI-H mCRC

Preclinical and clinical data demonstrated that the combination of nivolumab and ipilimumab can enhance activity over nivolumab monotherapy.[10,11] Thierry André, MD, from the Hôpital Saint Antoine and Sorbonne Universités (Paris, France), presented analyses from the complete population of patients with MSI-H mCRC in the nivolumab-ipilimumab (nivolumab 3 mg/kg IV, ipilimumab 1 mg/kg q3w for 4 doses, then nivolumab 3 mg/kg q2w) cohort (N = 119) of CheckMate-142.[12]

Key findings at median follow-up 13.4 months included:

- Overall response rate was 55% (3% CR, 51% PR); DCR was 80%
- Durable responses were observed regardless of tumor PD-L1 expression, *BRAF* or *KRAS* mutational status, or history of Lynch syndrome
- Twelve-month PFS and OS rates were 71% and 85%, respectively, which were favorable compared to nivolumab monotherapy
- Statistically significant and clinically meaningful improvements in quality of life were also observed
- No new safety signals or treatment-related deaths were reported
- Any-grade TRAEs were reported in 73% of patients
    - Most common AEs included diarrhea (22%), fatigue (18%), and pruritus (17%)
- Thirty-two percent (32%) of patients experienced grade 3/4 TRAEs
    - Elevated alanine aminotransferase and/or aspartate aminotransferase (11%), elevated lipase (4%), anemia (3%), and colitis (3%) occurred in more than 2 patients
- Thirteen percent (13%) of patients discontinued treatment due to an adverse event, compared with 8% in the nivolumab monotherapy cohort

Taken together, the findings from CheckMate-142 support the use of immune checkpoint inhibition in patients with relapsed, MSI-high mCRC, and addition of ipilimumab to nivolumab may further enhance the efficacy of this approach, with acceptable toxicity.

References:

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