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Immunotherapy in MSS/pMMR Metastatic Colorectal Cancer – Insights from the KEYNOTE-651

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Abstract

Microsatellite stable (MSS)/mismatch repair-proficient (pMMR) colorectal cancer (CRC) accounts for the majority of CRC cases and generally respond poorly to immunotherapy alone. This mini-review integrates findings from the KEYNOTE-651 study with current knowledge of frontline immunotherapy in MSS/pMMR metastatic CRC and explores the implications for clinical practice and future research directions.

Keywords: Chemotherapy, Colorectal cancer , Immunotherapy, KEYNOTE-651, Tumors

Introduction

Colorectal cancer (CRC) is a major public health concern, being the third most commonly diagnosed cancer and the second most common cause of cancer death both worldwide and in the United States [1-3]. Only a small proportion of CRCs is classified as microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR), which is characterized by a high tumor mutation burden (TMB) and increased expression of neoantigens, leading to robust immune responses. These tumors are often responsive to immune checkpoint inhibitors (ICIs), particularly those targeting the programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) axis [4-9]. Additionally, CRCs harboring germline or somatic pathogenic variants in DNA polymerase ε (POLE) and δ (POLD1) demonstrate a hypermutated phenotype with an extremely high TMB and numerous neoantigens produced because of aberrant proofreading function, and also tend to respond well to ICI therapy [10-12]. In contrast, microsatellite stable (MSS)/mismatch repair-proficient (pMMR) tumors are more common, accounting for approximately 95% of CRC cases. They are typically considered as "immune cold" tumors with limited responsiveness to immunotherapy [13-15]. The challenge of treating MSS/pMMR CRC has driven research toward innovative strategies that combine immunotherapy with other therapies of distinct mechanism to enhance antitumor responses.

The KEYNOTE-651 study (ClinicalTrials.gov Identifier: NCT03374254) offers valuable insights into the potential role of pembrolizumab in the treatment of MSS/pMMR metastatic CRC (mCRC) [16,17]. This mini-review aims to integrate findings from the KEYNOTE-651 study with current knowledge of frontline immunotherapy in MSS/pMMR mCRC, exploring the implications for clinical practice and future research directions. The use of immunotherapy in refractory setting is beyond the scope of this review.

The Role of Immunotherapy in MSS/pMMR mCRC

The application of immunotherapy with ICIs in MSS/pMMR mCRC has been less straightforward, with historically poor responses. MSS/pMMR tumors typically exhibit a low mutational burden, resulting in fewer neoantigens that can be recognized by the immune system and therefore a lack of robust immune activation. Moreover, these tumors generally

show low levels of tumor-infiltrating lymphocytes (TILs) and an immune-excluded microenvironment, characterized by the absence or inactivity of cytotoxic T lymphocytes and decreased expression of checkpoint proteins. This immune-suppressive environment further hinders the effectiveness of ICIs [13-15]. Recent studies have explored various combination strategies to enhance the efficacy of immunotherapy in MSS/pMMR CRC. The underlying rationale is that anticancer therapies, e.g. cytotoxic drugs, targeted therapies, and radiotherapy etc., can modulate the tumor microenvironment, enhance immune activation, and leverage synergistic effects [13,18,19]. Ongoing research has also been focusing on identifying predictive biomarkers to optimize treatment strategies. These approaches have the potential to overcome the inherent resistance of these tumors to ICIs alone and improve treatment outcomes in a patient population that has limited therapeutic options.

The KEYNOTE-651 Study

The phase 1b KEYNOTE-651 study investigated the combinations of pembrolizumab with or without binimetinib (MEK1/2 inhibitor) in addition to standard chemotherapy regimens across different lines of therapy in MSS/pMMR mCRC [16,17]. There were 5 cohorts including pembrolizumab plus binimetinib as later line (cohort A), mFOLFOX7 and pembrolizumab as first-line therapy (cohort B), mFOLFOX7 and pembrolizumab plus binimetinib as first line (cohort C), FOLFIRI and pembrolizumab as second-line therapy (cohort D), and FOLFIRI and pembrolizumab plus binimetinib as second line (cohort E). Despite the tolerability of pembrolizumab plus binimetinib in cohort A, the rate of dose-limiting toxicity was higher in cohort C and E, and the response rate with pembrolizumab plus binimetinib adding into chemotherapy was lower than standard chemotherapy. Therefore, the results did not support further enrollment in cohort C and E [17].

Overall, the combinations of chemotherapy with pembrolizumab alone were well-tolerated, with grade 3 or 4 adverse events (AEs) reported in 58% of patients in cohort B and 53% in cohort D. Importantly, no grade 5 treatment-related AEs were observed, underscoring a favorable safety profile. The most common AEs included neutropenia and decreased neutrophil counts, reflective of the hematologic toxicity associated with chemotherapy. Immune-mediated AEs were consistent with the known safety profile of pembrolizumab [16].

The efficacy of pembrolizumab in combination with chemotherapy in cohort B seemed comparable with historical data for current standard of care in the first line setting [20-22]. In cohort B, the objective response rate (ORR) was reported at 61%, which was numerically higher in KRAS wild-type (WT, 71%) than KRAS mutant (53%) subpopulations. Median progression-free survival (PFS) and overall survival (OS) were 8.6 months (95% CI, 7.2-14.1) and 28.6 months (95% CI, 18.0-36.3), respectively. In cohort D, the ORR was lower at 25%, with KRAS WT tumors demonstrating an ORR of 47%, while KRAS mutant tumors exhibited only an ORR of 6%. Median PFS and OS were 8.3 months (95% CI, 2.2-15.6) and 25.1 months (95% CI, 19.0-not reached), respectively [16].

The study also explored potential biomarkers associated with treatment response with chemotherapy plus pembrolizumab. Responders tended to exhibit higher PD-L1 combined positive score (CPS) and T-cell inflamed gene expression profiles, alongside lower HER2 expression. The study did not observe any correlation between TMB and response [16]. These insights emphasize the importance of identifying molecular characteristics that may inform patient selection and treatment strategies.

Combinations of Immune Checkpoint Inhibitors with Chemotherapy in MSS/pMMR mCRC

Along with KEYNOTE-651 study there are many other studies conducted in first-line advanced MSS/pMMR CRC including single arm and randomized studies.

A phase 1b study of first-line pembrolizumab plus mFOLFOX6 (n = 30, most were MSS/pMMR) reported a median PFS of 8.8 months, with stable disease (SD), partial response (PR), and complete response (CR) observed in 43.3%, 50.0%, and 6.7% of patients, respectively [23]. The phase 2 POCHI study screened unresectable MSS/pMMR mCRC patients for a high immune infiltrate, defined by at least one positive immune score (Immunoscore® and/or TuLIS) on primary tumor resection specimens, and evaluated the efficacy of first-line pembrolizumab in combination with CAPOX and bevacizumab (n = 28). Preliminary analysis demonstrated a high efficacy and good safety profile of this combination in this selected MSS/pMMR mCRC patient population, with CR of 21%, PR of 54%, 12-month PFS of 68%, grade ≥ 3 treatment related adverse events of 64%, and no toxic death [24].

First-line nivolumab combined with FOLFOXIRI and bevacizumab was explored in RAS/BRAF mutated mCRC (n = 73) in the phase 2 NIVACOR study. Promising activity was seen in 52 MSS patients, with an objective response rate (ORR) of 78.9% and median PFS of 9.8 months [25]. The phase 2 CheckMate 9X8 study of nivolumab plus mFOLFOX6 and bevacizumab (n = 127, 121 MSS/pMMR) versus mFOLFOX6 and bevacizumab (n = 68, 61 MSS/pMMR) in previously untreated mCRC did not meet its primary end point of PFS. However, higher PFS rates after 12 months, higher ORR, and durable responses were observed with nivolumab plus mFOLFOX6/bevacizumab. Among MSS/pMMR patients, median PFS was 11.8 months *vs.* 11.9 months. PFS trends were maintained when MSI-H/dMMR patients (n =13) were excluded. Numerically longer PFS was observed with nivolumab plus mFOLFOX6/bevacizumab in the consensus molecular subtype 3 (CMS3) subgroup in MSS/pMMR patients. After 12 months, PFS also favored nivolumab plus mFOLFOX6/bevacizumab in MSS/pMMR patients with CMS1 and CMS3 at baseline. No associations were observed between baseline TMB or PD-L1 expression (CPS ≥ 1) and PFS [26].

The phase 2 AVETUX trial evaluated first-line avelumab in combination with FOLFOX plus cetuximab in RAS/BRAF WT mCRC (n = 39, 36 MSS, 1 MSI-low) and reached a final median PFS of 11.1 months and median OS of 32.9 months. Out of 33 evaluable patients, there were 4 CRs and 4 others with no evidence of disease (NED) after secondary resection (CR + NED, 24.2%), 22 PRs (66.7%), and 3 SDs (9.1%). TIL diversity and clonality correlated with treatment response [27]. Avelumab combined with mFOLFOXIRI plus cetuximab was evaluated as first-line therapy in RAS WT unresectable mCRC (n = 62, all pMMR) in the phase 2 AVETRIC trial. The study met its primary endpoints with median PFS of 14.1 months and ORR of 82%, respectively. Grade 3-4 immune-related adverse events occurred in 6% of patients [28].

The phase 2 ATEZOTRIBE study investigated the combination of atezolizumab with FOLFOXIRI and bevacizumab in the first-line setting. In the pMMR cohort, median OS was 30.8 and 29.2 months for experimental (n = 134) and control (n = 68) groups, respectively (HR, 0.80; P = 0.117). Median PFS was 13.0 and 11.5 months in the experimental and control groups, respectively (HR, 0.80; P = 0.088). TMB-high (≥ 10 mutations per Mb) and Immunoscore Immune-Checkpoint (IC) high status (with high density and proximity of CD8 and PD-L1 cells) were independently associated with higher OS and PFS benefit from the addition of atezolizumab [29]. No PFS difference was observed according to TILs and PD-L1 expression [30]. An immune-related 27-gene expression signature DetermaIO with an exploratory optimized cut-off point (IO^{OPT}) predicted PFS benefit of adding atezolizumab in pMMR tumors as well as the overall population [31]. The results suggest that specific genetic profiles may help identify patients who could benefit from immunotherapy.

Results of the phase 1b/2 MEDITREME trial showed that the first-line durvalumab plus tremelimumab (anti-CTLA-4) combined with mFOLFOX6 chemotherapy was tolerable with promising clinical activity in RAS-mutant MSS mCRC. Among the 48 patients with MSS tumors, the ORR was 64.5% with 25 PRs and 6 CRs. Median PFS was 8.2 months. Higher TMB (> 5.8) and lower homologous recombination deficiency (HRD) score (< 29) were associated with better PFS. Integrated transcriptomic analysis underlined that high immune signature and low epithelial-mesenchymal transition were associated with better outcome. Immunomonitoring showed induction of neoantigen and NY-ESO1 and TERT blood tumor-specific T cell response were associated with better PFS [32]. The phase 1b/2 COLUMBIA-1 trial part 2 compared FOLFOX and bevacizumab with and without durvalumab and oleclumab (anti-CD73) in patients with treatment-naïve MSS mCRC (n = 26 in each arm). The safety profile was manageable. The confirmed ORR was numerically higher with the addition of durvalumab and oleclumab (61.5% vs. 46.2%) but did not meet the statistically significant threshold in either arm. Median PFS was 10.9 vs. 11.1 months. Biomarker analysis showed that patients with CD73-high tumors achieved a numerically higher ORR in the durvalumab and oleclumab arm. Median PFS was similar [33].

Implications for Clinical Practice and Future Directions

While the findings of the KEYNOTE-651 study are modestly promising, they highlight significant challenges and areas for further research in the management of MSS/pMMR mCRC. Several key areas warrant further investigation to optimize treatment strategies and improve patient outcomes.

1. Optimizing immunotherapy combinations in MSS/pMMR mCRC:

The KEYNOTE-651 study demonstrates that combining ICIs like pembrolizumab with standard chemotherapy results in comparable, but not superior, antitumor activity in MSS/pMMR mCRC. This underscores a critical limitation: immunotherapy alone, or in combination with standard chemotherapy, has not shown the transformative outcomes observed in MSI-H or dMMR cancers.

Although the combination did achieve an ORR of 61% in the first-line setting (cohort B), this outcome is similar to what is expected from chemotherapy (alone or with bevacizumab or cetuximab), based on historical data [20-22]. However, the imbalances in the molecular characteristics, e.g. KRAS mutation status, of patient cohorts in this non-randomized study could have skewed the overall efficacy data. In cohort B, the ORR was numerically higher in KRAS WT (10/14, 71%) than KRAS mutant (9/17, 53%) patients. Current evidence shows that these combinations do not consistently improve OS or PFS over standard chemotherapy in randomized studies. For example, trials like CheckMate 9X8 also failed to demonstrate a statistically significant PFS benefit when adding nivolumab to chemotherapy in this patient population. However, certain patient subgroups, like those with specific molecular subtypes (e.g., CMS3), may derive more benefit from immunotherapy-chemotherapy combinations [26]. It is well established that liver metastasis is associated with suppressed antitumor immunity and several early-phase studies of ICI combinations in refractory setting suggested that patients with non-liver metastases seemed to have higher response and improved survival [34-38]. The same concept may be worth further exploration in the first-line setting.

2. The differential responses observed based on KRAS mutation status, PD-L1 CPS, T-cell-inflamed gene expression profiles, and HER2 highlight the importance of molecular profiling in guiding treatment decisions. Targeting specific molecular alterations may enhance treatment outcomes and lead to more personalized therapeutic strategies. Continued efforts to identify predictive biomarkers for response to immunotherapy in larger patient populations are essential. Stratifying the data by molecular characteristics and exploring them as true predictors versus confounding factors in future analyses among larger patient cohorts are expected to provide more robust conclusions. Research should focus on genomic, transcriptomic, and proteomic profiling to uncover potential markers that can inform patient selection and treatment outcomes.

3. Investigating the mechanisms of resistance to immunotherapy in MSS/pMMR CRCs is essential for developing strategies to overcome resistance. Understanding why certain patients respond while others do not can lead to the identification of novel therapeutic targets and combination strategies.

Conclusion

The findings from the KEYNOTE-651 underscore the potential of immunotherapy as a transformative approach in the management of MSS/pMMR mCRC. However, immunotherapy in the first-line setting is not ready for prime time, since there is a lack of robust evidence on its additive efficacy. Continued research, innovation, and a focus on personalized medicine will be essential in refining treatment strategies, identifying predictive biomarkers, and ultimately improving outcomes for patients with MSS/pMMR mCRC.

Disclosure

Richard D Kim received honoraria from Incyte, Pfizer and Astra Zeneca; received consulting fee from Astra Zeneca, Bayer, Roche, Pfizer, Abbvie, Eisai, Exelixis, Merck and Ipsen. Ruoyu Miao reports no conflict of interest.

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