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FDA approvals for mismatch repair deficiency in metastatic colorectal cancer and non-metastatic colorectal cancer: a next-generation oncology treatment based on biomarker expression

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Abstract

Colorectal, gastric and hepatocellular cancers have been traditionally considered to be poorly immunogenic; however, increasing evidence now suggests that these tumors are recognized by the immune system. Immune checkpoint blockade is showing promising clinical activity in multiple tumors including colorectal and non-colorectal. In fact, one of the most significant achievements witnessed in the field of immunotherapy has been the success of immune checkpoint inhibitors (CPIs) in microsatellite instability-high colorectal and non-colorectal tumors. For this reason, the US FDA has granted accelerated approval to Pembrolizumab and Nivolumab as monotherapies and Nivolumab plus Ipilimumab as combined therapy. These new findings open the door to a next-generation oncology treatment based on biomarker expression.

The average tumor displays dozens of mutations; however, tumors with DNA deficient mismatch repair (dMMR) may harbor thousands of them, especially in the regions of repetitive DNA known as microsatellites [1]. Tumors that are found to harbor mutations in select microsatellite sequences called microsatellite instability (MSI) regions are referred to as "microsatellite instability-high (MSI-H)." It is now understood that two distinct immunologic subtypes of cancer tumors exist according to the dMMR status, namely, MSI and microsatellite stable (MSS) subtypes, which are mutually exclusive [2, 3].

Recently, on May 23, 2017, the US Food and Drug Administration (FDA) granted accelerated approval to Pembrolizumab (Keytruda®, Merck & Co) for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-high or dMMR solid tumors that have progressed after prior treatment and who have no satisfactory alternative treatment options, as well as for patients with MSI-high or dMMR metastatic CRC (mCRC) following progression on a fluoropyridine, oxaliplatin and irinotecan regimen [4]. The approval was based on the data from 149 patients with MSI-H or dMMR cancers enrolled across five uncontrolled multi-cohort, multi-center, single-arm clinical trials (KEYNOTE-16, -164, -012, -028, and -158). Ninety patients had mCRC and the remaining 59 patients suffered from one of 14 other cancer types. The objective response rate (ORR) was 39.6 % (95% CI: 31.7, 47.9) including 11 (7.4 %) complete responses (CRs) and 48 (32.2 %) partial responses (PRs).

On July 31, 2017, the FDA granted accelerated approval to another CPI, Nivolumab (Opdivo®, Bristol-Myers Squibb Company), for the treatment of patients aged 12 years and older with dMMR and MSI-H mCRC and on September 22, 2017 the FDA granted 2 accelerated approvals to non-colorectal cancers (non-CRC). The first one was for Nivolumab in hepatocellular carcinoma (HCC) patients previously treated with sorafenib and the second one for Pembrolizumab in advanced gastric cancer patients. The Nivolumab approval for treatment of mCRC patients was based on the data from study CHECKMATE-142, a multi-center, open-label study where 53 patients received Nivolumab 3 mg/kg by intravenous infusion every two weeks until unacceptable toxicity or radiographic progression. The ORR as assessed by an independent radiographic review committee was 28 % (n=15) (95% CI: 17, 42). Responses lasted six or more months for 67 % (95% CI: 38, 88) of the patients [5]. The Nivolumab approval for HCC patients who progressed on or were intolerant to sorafenib was based on the results from a subgroup of 154 patients enrolled in the phase I/II CHECKMATE-040 clinical trial. Patients received nivolumab 3 mg/kg by intravenous infusion every two weeks. The confirmed ORR, as assessed by blinded independent central review, was 14.3 % (95% CI: 9.2, 20.8), with three CRs and 19 PRs. The duration of response (DOR) ranged from 3.2 to 38.2+ months; 91 % of responders had responses lasting six months or longer and 55 % had responses lasting 12 months or longer [6]. The Pembrolizumab aapproval is based on the results of KEYNOTE 059, an open-label, multicenter, non-comparative, multi-cohort trial that enrolled 259 patients with gastric or gastroesophageal junction (GE) adenocarcinoma. Among the 259 patients enrolled, seven (3%) had tumors that were determined to be MSI-high. Responses were observed in four of these seven patients (ORR 57%), with one complete response. The response duration ranged from 5.3+ to 14.1+ months [7].

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Recently, on July 10, 2018 the FDA also granted an accelerated approval to the combination of Nivolumab and Ipilimumab (Yervoy®, Bristol-Myers Squibb Company) for the treatment of adult and pediatric patients 12 years and older MSI-H or dMMR mCRC following progression on a fluoropyrimidine, oxaliplatin, and irinotecan combination. The approval is based on the results from a cohort of 119 patients with MSI-H or dMMR mCRC treated with the combination in the phase II CHECKMATE-142 study. The ORR was 46 % (95% CI, 35-58). Among the 38 responders, there were three CRs and 35 PRs. The DOR was not reached (range, 1.9-23.2+ months). Eighty-nine percent of the responders had a response of ≥6 months, with 21 % having a response ≥12 months [8].

Table 1 shows detailed efficacy data from dMMR/MSI-H mCRC and non-CRC patients extracted from the studies used for the Pembrolizumab, Nivolumab and Ipilimumab approvals. The combination Nivolumab + Ipilimumab demonstrates superior efficacy results than the nivolumab monotherapy in pretreated mCRC patients.

Table 1: Efficacy data of CPIs in dMMR/MSI in mCRC and non-CRC

Drug Name	**No. of subjects**	**ORR.**	**CR**	**PR**	**SD**	**PD**	**NE/ND**	**DCR**
Dose		**No. (%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**No. (%)**
Study name								
Study identifier		**95% CI**						**95% CI**
dMMR/MSI mCRC								
Pembrolizumab	28	16 (57)	11	46	32	4	7	25 (89)
10 mg/kg Q2W KEYNOTE-016 (NCT01876511)*		39 - 73						73 - 96
Pembrolizumab	61	17 (28)	0	28	23	46	NA	NA
200 mg Q3W KEYNOTE-164 (NCT0260198)		17 - 41						
Nivolumab 3 mg/ kg	53	19 (36)	0	36	37	21	6	39 (74)
CHECKMATE-142 (single arm) (NCT02060188)		23-50						60 -65
Nivolumab 3 mg/ kg +	119	65 (55)	3	51	31	12	3	95 (80)
Ipilimumab 1 mg/kg CHECKMATE-142 (combination arm) (NCT02060188)		45 - 64						72 -87
dMMR/MSI non-CRC								
Nivolumab*	154	14.3	2	12	-	-	-	-
3 mg/kg CHECHMATE-040 (NCT01658878)								
Pembrolizumab**	7	4 (57)	1	3	-	-	-	-
200mg Q3W KEYNOTE 059 (NCT02335411)								

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE/ND, not evaluable/not determined; dMMR, deficient mismatch repair; MSI, microsatellite instability; MSS microsatellite stable; HCC, hepatocellular carcinoma; NA; not available; *in hepatocellular carcinoma patients and **in gastric or gastroesophageal junction patients

To date, three CPIs (two anti-PD-1 and one CTLA-4 inhibitors) have been approved based on the tumor biomarker regardless of the tumor original location. The regulatory approvals for Keytruda®, Opdivo® and Yervoy® for patients with MSI-H and dMMR tumors marked an important milestone for cancer treatment. The indication of the approvals is based on a common biomarker rather than the anatomic location (tissue or organ) in the body where the tumor originated. Recently, the National Comprehensive Cancer Network (NCCN) guidelines 2017 have incorporated the recommendation for universal testing for dMMR/MSI-H and the use of nivolumab or pembrolizumab in dMMR/MSI-H metastatic CRC after previous adjuvant FOLFOX/CAPEOX within 12 months [9]. With increasing accessibility to genetic analysis tools such as next-generation sequencing, it may expect that identification of more dMMR/MSI-H patients will continue to grow. In addition, other CPIs are also being tested in clinical trials along with a new strategy combining CPI with other therapies in different tumor types.

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