AHFS Final Determination of Medical Acceptance: Off-label Use of Dostarlimab-gxly as Neoadjuvant Therapy for Adult Patients with Locally Advanced, dMMR/MSI-H Rectal Cancer

Drug: Dostarlimab-gxly

Off-label Use: Neoadjuvant therapy for adults with locally advanced, dMMR/MSI-H rectal cancer

Criteria Used in Selection of Off-label Use for Review:

- Initial results from a clinical trial, and updated analysis of trial data, demonstrating a significant clinical complete response in the neoadjuvant setting

Strength of Evidence: Level 2 (Moderate strength/quality)

Grade of Recommendation: Reasonable choice (accepted, with possible conditions)

Narrative Summary:

Use as Neoadjuvant Therapy for Adults with Locally Advanced, dMMR/MSI-H Rectal Cancer

In patients with locally advanced rectal cancer, neoadjuvant chemotherapy and radiation with subsequent surgical resection of the rectum is a standard treatment approach.[10001] However, 5-10% of patients with rectal cancer have mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease, which is often resistant to chemotherapy.[10001,10002] Dostarlimab-gxly has been evaluated as a potential treatment option in this setting in a prospective, single-group, single-center, phase 2 study.[10001,10002,10003]

Adult patients (≥18 years of age) with dMMR/MSI-H stage II or III rectal cancer, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and no

evidence of distant metastases were eligible for study enrollment.[10001] Additionally, eligible patients were *without* active autoimmune or infectious disease conditions, receipt of immunosuppressive therapy within the prior 7 days, or prior administration of immunotherapy, chemotherapy, or radiation for the rectal tumor.[10001] Patients received dostarlimab-gxly at a dose of 500 mg IV every 3 weeks for 6 months (9 cycles), potentially followed by standard radiation therapy with concurrent administration of capecitabine at usual recommended doses, and subsequently total mesorectal excision.[10001] Patients who experienced a clinical complete response, defined as the absence of residual disease on digital and endoscopic rectal examination and rectal MRI, with no restricted diffusion on T2-weighted imaging, after completion of either dostarlimab-gxly induction therapy or chemoradiotherapy underwent nonoperative follow-up.[10001] Digital and endoscopic rectal examinations were conducted at baseline, 6 weeks, 3 months, 6 months, and then every 4 months after treatment initiation.[10001] Clinical imaging (T2- and diffusion-weighted MRI, FDG-PET, and CT) of the chest, abdomen, and pelvis was also conducted at baseline, 3 months, 6 months, and every 4 months.[10001] With each endoscopy, biopsies of the tumor were performed.[10001]

Of the initial 16 patients (of a planned enrollment of 30 patients), 12 were enrolled for >6 months and completed all 9 cycles of dostarlimab-gxly therapy; the median follow-up time for these patients was 12 months (range, 6 to 25 months).[10001] The other 4 patients were administered at least a single dostarlimab dose and continued to receive treatment at the time of preliminary data publication.[10001] Of all enrolled patients, 62% were female and the median age was 54 years (range, 26 to 78 years).[10001] Most patients (75%) enrolled in the study had a baseline ECOG performance status of 0 and stage III disease was present in 15 patients.[10001] The most commonly occurring presenting symptoms of disease included rectal bleeding (88%), constipation (31%), and abdominal pain (25%).[10001] The primary study end points included: 1) sustained clinical complete response 12 months after completion of dostarlimab-gxly therapy (in patients who did not undergo surgery) or pathological complete response (in patients who underwent surgery) with or without chemoradiotherapy and 2) overall response to dostarlimab-gxly therapy with or without chemoradiotherapy.[10001]

The overall response rate was evaluated using a one-sample hypothesis.[10001] The null hypothesis was that the percentage of patients with an overall response would be <25%; this was established based on a study in which the observed chemotherapy response among patients with mismatch repair-deficient rectal cancers was 7%.[10001] Successful rejection of the null hypothesis required 6 or more patients with an overall response by the end of the initial stage of the study (after 15 patients were enrolled) and 11 or more patients with an overall response by the end of the second stage of the study (after 30 patients were enrolled).[10001] Initial results revealed that all 12 patients who completed treatment with dostarlimab-gxly and underwent at least 6 months of follow-up experienced a clinical complete response (100%; 95% confidence interval: 74-100), with no evidence of tumor on MRI or PET scans, endoscopic evaluation, digital rectal examination, or biopsy.[10001] Additionally, no patients had been administered chemoradiotherapy or underwent surgery and no cases of progression or recurrence were reported during follow-

up.[10001] A rapid therapeutic response was seen, with symptom resolution within 9 weeks after dostarlimab-gxly initiation in 81% of patients.[10001] Regarding safety, no adverse events of grade 3 or higher were reported.[10001] Adverse events of any grade were observed in 12 (75%) of the 16 enrolled patients; the most common grade 1 or 2 adverse events were rash or dermatitis (31%), pruritus (25%), fatigue (25%), and nausea (19%).[10001] A single patient was noted to experience thyroid-function abnormalities.[10001]

An updated analysis of data involving 23 patients who completed 6 months of dostarlimab-gxly therapy has been presented since publication of initial results.[10003] The rate of clinical complete response was 100% in these 23 consecutive patients.[10003] During the median follow-up period of 9.3 months (range, 0.0-36.3 months), no patients were administered chemoradiotherapy and none underwent surgical resection.[10003] No grade 3 or 4 adverse events were observed in the updated data analysis.[10003]

Based on current evidence, dostarlimab-gxly as neoadjuvant therapy for adult patients with locally advanced, dMMR/MSI-H rectal cancer has Level 2 (moderate strength/quality) evidence supporting its use.[10001,10003] Currently available data show a complete clinical response to dostarlimab-gxly therapy in 100% of patients, with none requiring chemoradiotherapy or surgery and no grade 3 or 4 adverse events observed.[10001,10003] However, the number of patients enrolled in the only prospective, single-center, phase 2 study is small (n=23) and data on survival and the duration of complete response are not available to date.[10001,10003]

Dosage

When dostarlimab-gxly is used as neoadjuvant therapy for adult patients with dMMR/MSI-H locally advanced rectal cancer, the usual dosage is dostarlimab-gxly 500 mg IV every 3 weeks for 6 months (9 cycles).[10001]

References:

10001. Cercek A, Lumish M, Sinopoli J, et al. PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. *N Engl J Med*. 2022;386:2363-76.

10002. Rose S. Dostarlimab: an answer for rectal cancer? *Cancer Discov*. 2022;12(8):1828-29.

10003. Cercek A. PD-1 blockade as curative-intent therapy in mismatch repair deficient locally advanced rectal cancer. Presented at the Japanese Society of Medical Oncology (JSMO) Annual Meeting, March 16-18, 2023, Fukoka, Japan.

Oncology Expert Committee Voting Results and Comments:

First-Round Vote:

Proposed Level of Evidence: Level 2 (Moderate strength/quality)
Concur with rating: 7 votes
Do not concur with rating: 0 votes

Grade of Recommendation:
Recommended use (Accepted): 4 votes
Reasonable choice (Accepted, with possible conditions): 2 votes
Not fully established (Equivocal): 1 vote
Not recommended (Unaccepted): 0 votes

Reviewer Comments in Support of Vote on Level of Evidence and Grade of Recommendation:

The patient population studied (age, identified gender, and race) is not representative of the rectal cancer patient population. Would recommend further study/evaluation in patients in the older than 65 demographic and among patients from racially diverse backgrounds.

The early results of this limited single institutional trial are promising in the dMMR/MSI-H population; however, as reported in the NEJM trial, it is limited to 12 consecutive patients in a single institution -- should be reported in a larger prospective cohort to provide support for a recommended (or even reasonable) choice. While this number is now 23 in an updated analysis, still feel like this fails to meet the level of patients to move above not fully established. I think an argument could be made for reasonable choice in dMMR/MSI-H populations only if consensus is here; would like to see more patients with longer follow-up.

Although there is some degree of scrutiny in the fact that the supporting evidence for the recommendation is based on one single-arm, single-center phase II trial, it is exceptionally compelling evidence to have a 100% complete response rate. It should also be considered that this is a very narrow patient population included in this indication - locally advanced, dMMR/MSI-high rectal cancer (which only constitutes 5-10% of all rectal cancer diagnoses). There is support and adoption within NCCN as well.

If these promising phase II results can be replicated in a double-blind RCT then dostarlimab would most certainly be recommended in this population based on high quality evidence.

I agree that the level of evidence could be improved by providing longer follow-up time and increased patient population in the trial. I do not think that a randomized clinical trial would be feasible in this case, however. Although the numbers are small, I believe there's a strong argument for the use of dostarlimab in this setting, with unprecedented 100% complete responses and low-grade toxicity reported that are much more favorable than standard of care.

Strong evidence for use of dostarlimab-gxly in rectal cancer population. However, the sample size was small and most females <54 years of age. As such, I would like to see more robust data in a sample size more representative of the rectal cancer population. There were strong data indicative of positive results with minimal impact regarding adverse events, but again, the data would benefit from exploring adverse events in a population more representative of rectal cancer patients.

Consensus Vote:

Proposed Level of Evidence: Level 2 (Moderate strength/quality)

Concur with rating: 7 votes
Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 1 vote
Reasonable choice (Accepted, with possible conditions): 6 votes
Not fully established (Equivocal): 0 votes
Not recommended (Unaccepted): 0 votes

Final Grade of Recommendation: Reasonable choice (Accepted, with possible conditions)

Reviewer Comments in Support of Vote on Level of Evidence and Grade of Recommendation:

Data remains too limited to recommend across the board, but available results are too compelling not to have this agent as an available treatment.

While small trials to support, promising early evidence along with other well-established evidence that anti-PD1 is reasonable in this population.

Study is small but data are compelling, and it should be considered as a recommended option. Larger studies would be nice to have if feasible but with a small percentage of colorectal patients having dMMR/MSI-H may not be possible to get large numbers unless its over a long period of time.

Encourage patients to enroll in ongoing clinical trials, but dostarlimab is a reasonable choice for those patients who would not qualify or are not interested in participating.

There is an unmet need for the treatment of dMMR/MSI-H locally advanced rectal cancer. Responses to neoadjuvant chemotherapy are lower in patients with dMMR compared to those without dMMR PrecdMMR/MSI-H is a biomarker that has demonstrated to be highly predictive of PD-1 clinical benefit regardless of disease/cell origin. Although recommendation is based on one single-arm, single center phase II trial, the limited data are impressive and support evidence

of the activity of immune checkpoint inhibitors in patients with dMMR/MSI-H. cCR (clinical complete response) endpoint is perceived and acceptable surrogate endpoint for long-term outcomes in rectal cancer.

Despite the small sample size, and limited patient representation from a population reflective of most patients with rectal cancer, the positive results indicate there is potential benefit in continuing use in this population. It is reasonable to continue to use dostarlimab in this setting to continue to observe efficacy and side effects. Would state there should be acknowledgement that sample size in this patient population is somewhat limited when involving patient in shared decision making.

Participants:

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Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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