Presentation Summary: Evolving role of PD-1 blockade as the primary treatment for dMMR locally advanced rectal cancer

Mismatch repair deficiency has been increasingly recognized as a subgroup across numerous tumor sites that predicts sensitivity to immune checkpoint inhibition as a therapeutic strategy. The majority of dMMR cases are associated with Lynch syndrome and germline loss of function mutations in most commonly MSH2 and MSH6. Hypermethylation of the MLH1 promotor and PMS2 loss of function mutations also incur the phenotype but are less likely to be associated with germline mutations. The presence of coexisting BRAF V600E mutation strongly suggests a sporadic loss of MMR and not the heritable. Over the last few years a significant number of Phase II studies evaluating activity of immune checkpoint inhibitors including PD-1/PD-L1 and CTLA4 axis agents have shown promising responses and have even begged the question whether surgery can even be avoided in some dMMR diseases. Incidence of dMMR/MSI is lower in rectal cancer compared to colon (5.7% vs 19.7%).[1-2]

Chemotherapy pitfalls in dMMR disease:

It is generally accepted that dMMR colorectal cancers are for all intents and purposes resistant to fluropyrimidine monotherapy. Data supports combination chemotherapy with oxaliplatin has a maintained benefit in the adjuvant setting.[3] The radiosensitizing capability of fluoropyrimidine with radiation has not been formally tested against radiotherapy alone, leaving a question of how radiation should be approached in the dMMR cohort of rectal adenocarcinoma cases.

PD-1 axis inhibition in colon and metastatic CRC:

A number of phase II and more recently some Phase III trials have demonstrated significant activity of PD-1 axis inhibition, and in some cases in combination with CTLA4 inhibition, for dMMR colon and rectal cancers. Most of this data has come from metastatic colon cancers however includes rectal cases as well. KEYNOTE 177 has thus far been the largest phase III trial conducted and established Pembrolizumab as first line therapy superior to chemotherapy in MMR deficient metastatic colorectal cancer.[4-8]

Checkpoint inhibition in Neoadjuvant Colorectal Cancer:

The NICHE trial included 20 patients with dMMR locally advanced colorectal cancer who received a single dose of Ipilimumab and two doses Nivolumab prior to surgery. All twenty proceeded to surgery with 19/20 showing a major pathologic response defined as >10% tumor viability. 12/20 (60%) had a pCR at time of surgery.[9] The PICC trial was a single center parallel-group randomized non-comparative Phase II trial consisting of 2 groups of 17 patients harboring dMMR locally advanced colorectal cancer. 15/17 (88%) and 11/17 (65%) in the Toripalimab + Celecoxib and Toripalimab alone respectively had pCR at time of surgery.[10] In 2022, two major publications have significantly furthered excitement that immune checkpoint inhibition is likely poised to become the most integral component of treatment in dMMR LARC. First, Cercek et. al presented data at ASCO 2022 from a Phase II single arm trial of the PD-1 inhibitor Dostarlimab. 12 evaluable patients received Dostarlimab on 3-weekly cycle for 6 months, to be followed by Chemoradiotherapy and Surgery for non-complete clinical response. 12/12 (100%) patients experienced complete clinical response with no evidence of residual disease on magnetic resonance imaging, ^{18}F-fluorodeoxyglucose–positron-emission tomography, endoscopic evaluation, digital rectal

examination, or biopsy. There were no grade 3 AEs reported and at time of publication (median follow up 6-25 months). No recurrences had been reported and no patients had gone on to receive chemoradiotherapy or surgery.[11] The NICHE-II trial presented at ESMO 2022 was a colon and not rectal cancer trial, however given the significant similarity in disease characteristics is nonetheless very encouraging and far larger numbers than the Cercek trial with Dostarlimab in dMMR rectal adenocarcinoma. NICHE-II enrolled 112 patients with cT3+ and/or N+ dMMR disease in the ITT population that received 3 mg/kg of Nivolumab plus 1 mg/kg of Ipilimumab in the first cycle, then only Nivolumab in the second cycle 2 weeks later, followed by surgery within 6 weeks of enrolling. Pathologic responses defined as <50% residual viable tumor (RVT), with Major Pathologic response (MPR) defined as <10% RVT, including those with pCR in the tumor and <10% viable cells in positive lymph nodes. Pathologic complete response (pCR) was defined as 0% viability in both tumor and lymph nodes. Only 2/112 patients had immune related events delaying surgery by >2 weeks. 74% of participants had radiographic Stage III disease. Of 107 Evaluable patients 99% had a pathologic response, and 95% MPR rate. The pCR rate was 67%, and Grade 3 or greater irAE occurred in only 4 patients, 2 of which were asymptomatic elevations in amylase/lipase.[12]

How long should neoadjuvant immunotherapy be:

The Cercek trial with dostarlimab noted complete responses were not seen before 3 months. This would contrast with the data presented from the NICHE-II trial suggesting that 2 doses of immune checkpoint inhibitor and surgery within 6 weeks of first treatment showed a tremendous rate of complete pathologic responses. It is possible the combination immunotherapy with the addition of a single dose of CTLA4 led to faster responses than dostarlimab monotherapy did, however impossible to say comparing the two trials. Further data is needed to support the optimal approach including mono or combination immune checkpoint therapy, as well as duration prior to definitive resection, as well as whether resection can be safely omitted in those with complete clinical responses with long term outcomes comparable to other current standard therapy.

Surgery for those with excellent response to neoadjuvant therapy:

It has been an increasingly common question in the pMMR rectal cancer cohort with recent evolution of data supporting that some patients can be spared surgery with reasonable outcomes, however long-term confirmation of this approach is still awaited, and patient selection is critical to this approach. With the phenomenal and deep responses seen with neoadjuvant checkpoint inhibition in the dMMR cohort one can only believe a similar watch and wait strategy used in the OPRA trials could be employed following neoadjuvant immunotherapy in LARC for patients experiencing a complete clinical response. The Cercek trial has had reassuring findings omitting tradition chemoradiation and surgery thus far for all 12 patients that had clinical complete response to 6 months of Dostarlimab. This approach is analogous to the OPRA trial which showed superiority of chemoradiotherapy followed by neoadjuvant chemotherapy compared to the reverse sequencing, however did not have a comparator arm of standard of care.[13] It did however establish reasonable outcomes with an organ preservation approach in rectal cancer and thus we can glean from this that a similar strategy in the dMMR is not unreasonable.

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