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Mini Review

Marker-Based Approval of Immune Checkpoint Inhibitors

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Abstract

Advanced and recurrent endometrial cancer constitutes an unmet need as there is hardly any therapy available. Recent classification based on whole genome sequencing by the cancer genome atlas (TCGA) has shown deficient mismatch repair (dMMR) to be a factor. Resultant neoantigen causing change in local immunity has attracted immunotherapy as remedy. However, approval of such therapy based on dMMR and other few such marker based therapy approval by FDA is not received well as shown in post approval data published.

Keywords: *dMMR; Immune Checkpoint Inhibitors; Endometrial Cancer; Pembrolizumab; Dostarlimab*

Introduction

More than 60000 new cases of endometrial cancer (EC) diagnosed in 2019 in USA. Over last three decades there has been 300% rise in its incidence. Moreover, advanced and metastatic EC is a common disease, affecting more than 15,000 patients per year in the United Sates where no definite treatment exists, thus creating an unmet need. In this segment till recently FDA approved drug was hormonal therapy, megestrol [1]. But immune checkpoint inhibitors (ICI) has superseded all other existing modalities. During the process of approval for the first time in history ICI was approved in tissue agnostic indication which was based on markers such deficient mismatch repair (dMMR). This according to some will bring "imprecision" in targeted therapy approach of precision medicine. Hence, in this review we will discuss the context ICI was introduced in fulfilling unmet need in advanced and metastatic EC and what could go wrong in it.

Classification

As described by the Cancer Genome Atlas (TCGA), the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) confirmed subgroups which are as follows: a) polymerase (POLE)-mutant/ultramutated, b) microsatellite instability-high (MSI-H), c) copy number low (CNL), and d) copy number high (CNH) [2]. MSI-H is the phenotype of deficient proteins in the mismatch repair (dMMR) pathway, which may be either sporadic or inherited mutations as in Lynch syndrome, 15 leading to the accumulation of high mutational loads. Tumours that are not dMMR/MSI-H are considered proficient mismatch repair (pMMR) or microsatellite stable (MSS).

Drug approval of advanced or recurrent disease

Mutations in *MMR* genes lead to mismatch repair protein deficiency (dMMR) and microsatellite instability (MSI). They have been implicated in multiple types of gynecologic malignancies. While dMMR is due to mutation in *MMR* genes MSI microsatellite instability is a

tract of repetitive DNA in which certain DNA motifs (ranging in length from one to six or more base pairs) are repeated, typically 5 - 50 times [3].

Approximately 30% of primary endometrial cancers are microsatellite instability high/hypermutated (MSI-H), whereas13% to 30% of recurrent endometrial cancers are MSI-H or mismatch repair deficient (dMMR) [4]. The high rate of mutations observed is responsible for the continued formation of neoantigens [5].

Considering MSI status as a marker of neoantigen and tumour mutational burden for response to immune checkpoint inhibition, pembrolizumab (MK-3475, Keytruda, Merck) obtained accelerated approval on May 23 in 2017 as a second-line treatment for all MSI-H (high microsatellite instability) dMMR (deficient DNA mismatch repair) metastatic solid tumour. It was based primarily on a phase II study of only 41 heavily pre-treated metastatic carcinoma two EC patients with or without dMMR (NCT01876511) containing two cases of EC [6].

This was the first time the FDA has ever approved any treatment based on a biomarker, rather than an organ-specific tumour type in May, 2017. A total of 15 cancer types were presented to FDA with 149 patients enrolled across five clinical trials (KEYNOTE-016 NCT01876511, KEYNOTE-164 NCT02460198NCT02460198, KEYNOTE-012 NCT01848834, KEYNOTE-158 NCT02628067). 39.6 percent had a complete or partial response.

On April 22, 2021, the Food and Drug Administration granted accelerated approval [7] to dostarlimab-gxly (Jemperli, GlaxoSmithKline LLC) for adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following a prior platinum-containing regimen.

Other related approvals

Another twob tissue agnostic high tumour mutational burden (TMB) which includes endometrial cancer. Second one is dostarlimab's accelerated approval for MSI-H or dMMR solid tumour in general. TMB and MSI status were analyzed on 148,803 tumour samples (Foundation Medicine (FM) dataset) where, 2,179 were MSI-high whereas 7,972 patients were MS-stable but TMB-high [8].

On June 16, 2020, the Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck and Co., Inc.) for the treatment of adult and pediatric patients with unresectable or metastatic tumour mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb) WES TMB ≥ 175mut/exome approximately equivalent to ≥ 10mut/MbbyF1CDx] solid tumours, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. The FDA also approved the FoundationOneCDx assay (Foundation Medicine, Inc.) as a companion diagnostic for pembrolizumab.

On August 17, 2021, the Food and Drug Administration granted accelerated approval to dostarlimab-gxly (Jemperli, GlaxoSmithKline LLC) for adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumours, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options [9]. The efficacy of dostarlimab was evaluated in the GARNET Trial (NCT02715284).

Controversy

Tissue agnostic approval based on markers has given rise to criticism. Pembrolizumab based on high TMB was pivotal for such adverse findings and comments. Four such recent FDA drug approvals are pembrolizumab for dMMR and TMB high solid tumours, olaparib for deleterious homologous recombination repair mutations castration-resistant prostate cancer and NTRK gene fusion based larotrectinib therapy where the FDA indication is broader than the studied population. These broad approvals stray from principles of precision oncology and can cause harm to patients [10].

Regarding TMB of 10 or more mutations per megabase, across multiple cancer types it is observed that the predictive value of it was limited, due to variability and unknown correlation with survival outcomes [11]. In breast cancer, prostate cancer, and glioma, CD8 T-cell levels and neoantigen load relationship was not clear with resultant poor ORR of below 20% [12]. They considered TMH based indication "too broad" and ICI selection should be based on cause of such increase rather than a threshold level. Approval based on response rate rather than more meaningful endpoints such as survival and quality of life and it slows further progress in therapy [13].

FDA admitted the fact of adverse criticism and defended by raising facts of durable responses, acceptable safety, favorable risk-benefit profile, unmet medical need shown in such approval. They have defended saying that these are accelerated approval with scope of further analysis and retaining or discarding or even raising threshold of TMH in later dates [14].

Conclusion

Immunotherapy is a revolutionary approach with benefit which is generally low with response above 20% is still unachieved due to many reasons. Dubiousness of diagnostic and predictive value of PD-L1 analysis is yet unresolved as only in 10% of trials PD-L1 status is a prerequisite. So, dependence on more marker based approach may dilute the situation further. In fact a single TMB threshold may fall short in detecting suitable individual for all types of cancer who can be treated by ICB. Overall survival is yet to be established. Surrogate diagnosis of TMB-high by F1CDx than by whole exome sequence due to cost is another constraint. Pharmacogenomics and personalised medicine are the goals, hence this blanket approach may need other sound ways to increase effectiveness of immunotherapy. While bright future is just ahead these shortcomings are some temporary hindrances.

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