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Response to Immunotherapy in Cancer Patient One Biomarker is not Enough

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ABSTRACT

Immunotherapy have led to astronomic changes in cancer treatment with several approval by the Food and Drug Administration for varied cancers. In the era of precision oncology, medical oncologist needs biomarkers to guide their prescription of these new treatments, and to select the right patient for these high-cost drugs. in this article we describe the available predictors biomarkers for Immune checkpoint therapies response and their limitations. Immunotherapy have led to monumental changes in cancer treatment with several approval by the Food and Drug Administration (FDA) for varied cancers [1]. In the era of precision oncology, medical oncologist needs biomarkers to guide their prescription of these new treatments to select the right patient for these high-cost drugs.

Many studies reinforce programmed death-ligand 1 (PD-L1) expression, tumor-infiltrating lymphocytes (TILs), mismatch repair deficiency (MMRd) and tumor mutational burden (TMB) as predictive biomarkers to instruct the prescription of Immune Checkpoint Blockade (ICB) therapies [2]

But Many questions remain without any clear response; what is the more accurate biomarker for ICB use?

- Is TMB a more accurate, comprehensive biomarker since it is obtained throw NGS comparing to the others biomarkers obtained by IHC?
- Is there any relationship between the different biomarkers?
- Is ICB therapy advised for patients with MMRp / MSS, but with high TMB or PDL1 positive
- Should we do extensive analysis of MMRd / MSI-H, PD-L1, TMB and TILs for each tumor and prescribe ICB if one of them returned positive?
- Why some tumors didn't response to ICB despite they are expressing PDL1?

Therefore, it is mandatory continuing investigation for suitable biomarkers to predict the efficacy of immunotherapy and thus identify the patients who are most likely to respond to ICBs

Abbreviations: FDA: Food and Drug Administration; TMB: tumor mutational burden; PD-L1: Programmed Death-Ligand 1; TILs: Tumor-Infiltrating Lymphocytes; ICB: Immune Checkpoint Blockade; EC: endometrial cancer; CRC: colorectal cancer; GC: Gastric Cancer

Tumor-Infiltrating Lymphocytes (TILs)

TILs represent the important constituent of the tumor environment. Increased levels of TILs were associated with increased rates of response to neoadjuvant chemotherapy and improved prognosis for the molecular subtypes of TNBC and HER2-positive breast cancer, but not for patients with HR positive breast cancer. A threshold of 20% TILs was the most powerful outcome prognosticator of pathological completer response. In the literature patients with elevated infiltration density of TILs had an excellent prognosis after immunotherapy. Many studies suggest that immune-inflamed tumors (hot tumors) than immune-desert tumors (cold tumors), can inspire a robust immune response especially in Lung cancers [3,4]

Mismatch Repair Deficiency (MMRd)

MSI/ MMRd, is the consequence of the inactivation of mismatch repair genes, MSI detection can be done by immunohistochemistry (IHC) but NGS has also recently emerged. MSI-high status correlates with higher neoantigen expression which helps the immune system recognize tumors. MMRd have been identified in multitude of solid tumors, MMRd/MSI high have the particularity to predict the response for ICB regardless the type and site of tumor [5]. This biomarker is considered as a presage of response to ICB in stage IV colorectal cancer (CRC), stomach cancer and endometrial cancer (EC), in localized CRC it is a prognostic factor as well with a benefit in the OS 6. in stage IV EC MMRd combination of immunotherapy and chemotherapy is the standard of care on first line, the second line of treatment is dictated by the MMR status to use ICB as monotherapy or combined with TKI [6-9]. The FDA approved the use of pembrolizumab in all MSI tumors regardless the status of the others biomarkers, which is meaning that you can still prescribe ICBs even if the tumor is TMB low or PDL1 negative. PDL1+ expression was higher in MMRd CRC then in MMRp [10,11]. A study of 393 patients with advanced gastrointestinal cancers, genitourinary cancers or rare cancers showed that PD-L1+ expression was 38.9% in MMRd solid tumors compared with 15.2% in pMMR tumors [12]. In other studies, [13,14] the PD-L1+ rate varied from 12.1–35.2% in pMMR Gastric Cancer (GC) and from 46.7–60.0% in MMRd GC

Programmed Death-Ligand 1 (PD-L1)

PD-L1 is a biomarker correlated with immune system inhibition. PD-L1 positivity is a presage to response to immunotherapy. However, the heterogeneity of this biomarker emphasizes the need for further implements to predict the right patient for immunotherapy. The PDL1 status is considerably different among varied cancers, but also inside the same tumor (spatial heterogeneity)

Precise evaluation of PD-L1 status is important for proper treatment judgements. Misclassification of PD-L1 expression can be established by different factors such as expression heterogeneity [15].

PDL1 is not an accurate biomarker for many reasons:

1/several studies have described the efficacy of ICBs in PDL1- tumor of the cervix, lung and melanoma [16-18]

2/other study showed more percentages of PD-L1 positivity in the resected specimens compared to diagnostic biopsies [19].

3/Biopsies containing less than 100 cancer cells or older than three years may conduct to an underestimation of PD-L1 status [20].

4/ changeability between pathologist and over the different anatomical sites and variability during disease progression may play a role as well [21,22]

5/Also, this difference may be due to the antibodies used in the assessment of the PDL1 status. Antibody clone SP142 showed lower levels of PD-L1 expression compared with the 22C3 assay [23,24].

Tumor Mutational Burden (TMB)

TMB estimates the frequency of somatic mutation in cancer patient. high TMB correlates with elevated neoantigen status and recognition of cancer cells by T cells. It has been described in many cancers and has been correlated with improved response rate and prolonged survival for patients on ICBs [25]. TMB enlarges the proportion of patients who can be candidates for immunotherapy. TMB has been extensively considered in melanoma, lung and bladder cancers [26-29].

But what are the benchmarks to distinguish between low and high TMB? Some authors are using the threshold of 10 somatic mutations per mega base, some others 16 others 6 [30-32]. Relationship between TMB and PD-L1 expression may vary among different cancers, there are discrepant data regarding the relationship between PD-L1 expression and TMB. A study in the Bloomberg-Kimmel Institute for Cancer Immunotherapy [33] showed that PD-L1 expression and TMB are not absolutely correlated within most cancer subtypes, and they show only a marginal relationship. Across distinct cancers, PD-L1 expression and TMB have distinct effects on the response rate to ICBs. further study are necessary to analyze the correlation between TMB and PD-L1 expression in different cancers.

Yoonet all [34] showed that in various cancers, a correlation between TMB and PD-L1 status. This Relationship may differ among different cancer site, with a high compatibility found in Gastric Cancers and EC and a frail association with pancreatic cancer and kidney cancer [35-37].

Conclusion

Ther is an unmet need to presage patients' responses to ICBs using biomarkers to select the right patients for this treatment, there is a discrepant result between the available biomarkers used in the clinic. Researchers need to investigate for predictive clinically trustworthy biomarkers, practically in the daily practice, by merging all the available markers you can be more confident not excluding your patients from responding to immunotherapy drugs.

References

1. Vaddepally RK; Kharel P, Pandey R, Garje R, Chandra AB, et al. (2020) Review of Indications of FDA-Approved Immune Checkpoint Inhibitors per NCCN Guidelines with the Level of Evidence. Cancers (Basel) 12(3): 738.
2. Yi M, Jiao D, Xu H, Liu Q, Zhao W, et al. (2018) Biomarkers for predicting efficacy of PD-1/PD-L1 inhibitors. Mol Cancer 17(1): 129.
3. Yu Y, Zeng D, Ou Q, Shengbo Liu, Anlin Li, et al. (2019) Association of survival andimmune-related biomarkers with immunotherapy in patients withnon-small cell lung cancer: A meta-analysis and individualpatient-level analysis. JAMA Netw Open 2(7): e196879.
4. Durgeau A, Virk Y, Corgnac S, Fathia Mami Chouaib (2018) Recent advances in targeting CD8 T-cell immunity for more effective cancer immunotherapy. Front Immunol 9: 14.
5. Lemery S, Keegan P, Pazdur R (2017) First FDA approval agnostic of cancer site - when a biomarker defines the indication. N Engl J Med 377(15): 1409-1412
6. Venderbosch S, Nagtegaal ID, Maughan TS, Smith CG, Cheadle JP, Fisher D, et al. (2014) Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res 20(20): 5322-5330.
7. Mirza MR, Chase DM, Slomovitz BM, DePont Christensen R, Novák Z, Black D, et al. (2023) Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med 388(23): 2145-2158.
8. Eskander RN, Sill MW, Beffa L, Moore RG, Hope JM, et al. (2023) Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. N Engl J Med 388(23): 2159-2170.
9. Yonemori K, Yunokawa M, Ushijima K, Sakata J, Shikama A, et al. (2022) Lenvatinib plus pembrolizumab in Japanese patients with endometrial cancer: Results from Study 309/KEYNOTE-775. Cancer Sci 113(10): 3489-3497.
10. Gatalica Z, Snyder C, Maney T, Ghazalpour A, Holterman DA, Xiao N, et al. (2014) Programmed cell death 1 (PD-1) and its ligand (PD-L1) in common cancers and their correlation with molecular cancer type. Cancer Epidemiol Biomarkers Prev 23(12): 2965-2970.
11. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. (2015) Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 348(6230): 124-128.
12. Kim ST, Klempner SJ, Park SH, Park JO, Park YS, Lim HY, et al. (2017) Correlating programmed death ligand 1 (PD-L1) expression, mismatch repair deficiency, and outcomes across tumor types: implications for immunotherapy. Oncotarget 8(44): 77415-77423
13. Inaguma S, Wang Z, Lasota J, Sarlomo Rikala M, McCue PA, et al. (2016) Comprehensive immunohistochemical study of programmed cell death ligand 1 (PD-L1): Analysis in 5536 cases revealed consistent expression in trophoblastic tumors. Am J Surg Pathol 40(8): 1133-1142.
14. Wang L, Zhang Q, Ni S, Tan C, Cai X, Huang D, et al. (2018) Programmed deathligand 1 expression in gastric cancer: Correlation with mismatch repair deficiency and HER2-negative status. Cancer Med 7(6): 2612-2620
15. Lee SJ, et al. (2015) showed that the expression of PD-L1, lymphocyte-activation gene 3 (LAG3), and indolamine 2′3′-dioxygenase 1 (IDO1) in TILs was 68.6%, 13.5%, and 28.1%, respectively, in 89 patients with MSI-H colon cancer A higher number of mutations in DNA coding sequences in MSI-H tumors have more potential to stimulate the host to generate neoantigens and trigger immune activation.
16. Schumacher TN, Schreiber RD (2015) Neoantigens in cancer immunotherapy. Science 348: 69-74. The overall mutational burden of SCC arising from MCT is high, it shares similar mutation profiles to SCC.
17. Naumann RW, Hollebecque A, Meyer T, Devlin MJ, Oaknin A, et al. (2019) Safety and Efficacy of Nivolumab Monotherapy in Recurrent or Metastatic Cervical, Vaginal, or Vulvar Carcinoma: Results from the Phase I/II 37(31): 2825-2834.
18. Kefford R, Ribas A, Hamid O, Robert C, Daud A, et al. (2014) Clinical efficacy and correlation with tumor PD-L1 expression in patients (pts) with melanoma (MEL) treated with the anti-PD-1 monoclonal antibody MK-3475. J Clin Oncol 15: 3005-3005.
19. Mehra R, Seiwert TY, Gupta S, Weiss J, Gluck I, et al. (2018) Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after longterm follow-up in KEYNOTE-012. Br J Cancer 119: 153-159.
20. M Ilie, C Bence, C Butori, S Lassalle, L Bouhlel, et al. (2015) Comparative Study of the PD-L1 Status Between Surgically Resected Specimens and Matched Biopsies of Issue for anti-PD-L1 Therapeutic Strategies, Ann Oncol 27(1): 147-153.
21. A Gagné, E Wang, N Bastien, M Orain, P Desmeules, et al. (2019) Impact of specimen characteristics on PD-L1 testing in non–small cell lung Cancer: validation of the IASLC PD-L1 testing recommendations, J Thorac Oncol 14(2019): 2062-2070.
22. H Brunnström, A Johansson, S Westbom Fremer, M Backman, D Djureinovic, et al. (2016) PD-L1 immunohistochemistry in clinical diagnostics of lung cancer: inter-pathologist variability is higher than assay variability. Mod Pathol 30(2017): 1411-1421.
23. L Hong, S Dibaj, MV Negrao, A Reuben, E Roarty, et al. (2019) Spatial and temporal heterogeneity of PD-L1 and its impact on benefit from immune checkpoint blockade in non-small cell lung cancer (NSCLC). J Clin Oncol 37(15_suppl): 9017-9017
24. Xu H, Lin G, Huang C, Zhu W, Miao Q, et al. (2017) Assessment of Concordance between 22C3 and SP142 Immunohistochemistry Assays regarding PD-L1 Expression in Non-Small Cell Lung Cancer. Sci. Rep 7: 16956.
25. Rimm DL, Han G, Taube JM, Yi ES, Bridge JA, et al. (2017) A Prospective, Multi-institutional, Pathologist-Based Assessment of 4 Immunohistochemistry Assays for PD-L1 Expression in Non-Small Cell Lung Cancer. JAMA Oncol 3: 1051-1058
26. Sha D, Jin Z, Budczies J, Kluck K, Stenzinger A, et al. (2020) Tumor Mutational Burden as a Predictive Biomarker in Solid Tumors. Cancer Discov 10(12): 1808-1825.
27. Gandara DR, Paul SM, Kowanetz M, Schleifman E, Zou W, Li Y, et al. (2018) Blood based tumor mutational burden as a predictor of clinical benefit in nonsmall-cell lung cancer patients treated with atezolizumab. Nat Med 24(9):1441-1418.
28. Hugo W, Zaretsky JM, Sun L, Song C, Moreno BH, (2016) Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. Cell 165(1): 35-44.
29. Rosenberg JE, Hoffman Censits J, Powles T, Van der Heijden MS, Balar AV, Necchi A, et al. (2016) Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 387(10031): 1909-1920
30. Carbone DP, Reck M, Paz Ares L, Creelan B, Horn L, et al. (2017) First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 376(25): 2415-2426

31. Gandara DR, Paul SM, Kowanetz M, Schleifman E, Zou W, et al. (2018) Blood based tumor mutational burden as a predictor of clinical benefit in nonsmall-cell lung cancer patients treated with atezolizumab. Nat Med 24(9): 1441-1448

32. Ramalingam SS, Hellmann MD, Awad MM (2018) Tumor mutation burden (TMB) as a biomarker for clinical benefit from dual immune checkpoint blockade with nivolumab (nivo) + ipilimumab (ipi) in first-line (1 L) non-small cell lung cancer (NSCLC): Identification of TMB cutoff from Check-Mate 568. In: Presented at the American Association for Cancer Research 2018 Annual Meeting; abstr CT078)

33. Wang Z, Duan J, Cai S, Han M, Dong H, Zhao J, et al. Assessment of blood tumor mutational burden as a potential biomarker for immunotherapy in patients with non-small cell lung cancer with use of a next-generation sequencing cancer gene panel. JAMA Oncol 5(5):696-702.

34. Yarchoan M, Albacker LA, Hopkins AC, Montesion M, Murugesan K, et al. (2019) PD-L1 expression and tumor mutational burden are independent biomarkers in most cancers. JCI Insight 4(6): e126908.

35. Cho YA, Lee H, Kim DG, Kim H, Ha SY, et al. (2021) PD-L1 Expression Is Significantly Associated with Tumor Mutation Burden and Microsatellite Instability Score. Cancers (Basel) 13(18): 4659.

36. Yarchoan M, Albacker LA, Hopkins AC, Montesion M, Murugesan K, et al. (2019) PD-L1 expression and tumor mutational burden are independent biomarkers in most cancers. JCI Insight 4(6): e126908.

37. Labriola MK, Zhu J, Gupta R, McCall S, Jackson J, et al. (2017) Characterization of tumor mutation burden, PD-L1 and DNA repair genes to assess relationship to immune checkpoint inhibitors response in metastatic renal cell carcinoma. J Immunother Cance 8(1): e000319.

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