Biomarkers Continue to Show Promise in Predicting Response to Immunotherapy: Tumor Mutational Burden (TMB)

Novel Biomarkers Lead to Better Treatments

Options for cancer treatment have exploded in the last decade, partly due to the discovery of cellular biomarkers and the development of Immune Checkpoint Inhibitor (ICI) therapies. In 2011 ipilimumab became the first ICI approved in Europe for the treatment of advanced melanoma improving survival at both one and two years by nearly 50%[1],[2]. Immune Checkpoint Inhibitors work by stimulating the body's own immune system to recognize cellular abnormalities, attack and eliminate the threat. They have also shown promise across a wide range of tumour types including melanoma, urothelial carcinoma, SL and NSCLC, and TNBC to name a few difficult to treat cancers. [3] With a better understanding of how tumour cells work, their unique cellular signals, or biomarkers, (such as PD-1, PD-L1, TMB, and DMMR) and how histologically identical tumours can behave and respond very differently among individuals, treatment options have gone from broad and generalized based only on tumour type, to very personalized and increasingly effective and durable.

Until recently little was understood about tumour markers, and what was known was not yet translated into actionable treatment options. Like PD1 and PDL1 biomarkers that gained extensive research attention in 2011, Tumour Mutation Burden (TMB) is now an increasingly useful tumour marker used to predict tumour response to ICI treatment for many types of solid tumours.[4] Among other biomarkers, TMB studies look to target cancer cells and predict efficacy of immunotherapy before it is offered as a treatment option. By targeting these mutations and leveraging the body's innate ability to recognize defects in cellular function, science is getting closer and closer to truly personalized cancer treatment — and eventually a cure.

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[1] Hodi F, O'Day S, McDermott D et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. New England Journal of Medicine. 2010;363(8):711-723. doi:10.1056/nejmoa1003466

[2] YERVOY™ (ipilimumab) Approved for the Treatment of Previously-Treated Advanced Melanoma in the EU. FierceBiotech. https://www.fiercebiotech.com/biotech/yervoy%E2%84%A2-ipilimumab-approved-for-treatment-of-previously-treated-advanced-melanoma-eu. Published 2011. Accessed April 1, 2021.

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Cellular Mutations May Predict Response

Mutations in the DNA of replicating cells is how tumour cells achieve this unregulated growth. Normal cells that continue to grow and replicate outside their original function in the body, and without regard for their surrounding structures eventually leads to a malignancy. Normal cells are able to repair their DNA along the way, but malignant cells lose this ability in what is called deficient DNA mismatch repair (dMMR) or MSI-H[5]. These errors in coding that would normally be fixed or destroyed by the immune system, are no longer regulated in the body and eventually lead to tumours that then evade the immune system's normal control. Retrospectively we are learning that certain tumours, melanoma and NSCLC in one review, had higher response rates and better outcomes after receiving immunotherapy[6]. It is hypothesized that the more mutations a cell has the more targets there may also be for either developing new therapies or predicting a better response to existing ICIs.

Measuring TMB

Tumours with high TMB are defined by the estimated number of somatic mutations per megabase (mut/Mb) of interrogated genomic sequences[7]. Debate is ongoing as to what constitutes high mutational burden. Studies continue to try and answer what number of mutations predict increased response to ICIs. In one analysis by Guatam, TMB-High was defined as >/ 10 mut/Mb, while other analyses have ranged from 2-200 mut/Mb[8][9]. A separate analysis has found that high microsatellite instability (MSI-H), which is currently predicted to have increased ICI responsiveness, also correlates in some cases up to 74% with TMB high tumours numbering >/17 mut/Mb[10].

Predicting Tumor Response with High TMB

Some tumour types exhibiting high TBM are also showing promising responses to ICIs. An analysis by McNamara found high TMB in a wide range of tumour types, including bladder,

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[5] Sinicrope F, Yang Z. Prognostic and predictive impact of DNA mismatch repair in the management of colorectal cancer. Future Oncology. 2011;7(3):467-474. doi:10.2217/fon.11.5

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[7] Merino D, McShane L, Fabrizio D et al. Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project. J Immunother Cancer. 2020;8(1):e000147. doi:10.1136/jitc-2019-000147

[8] The QuIP Study Attempts to Harmonise the Use of TMB Panels. Esmo.org. https://www.esmo.org/oncology-news/the-quip-study-attempts-to-harmonise-the-use-of-tmb-panels. Published 2019. Accessed April 1, 2021.

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[10] Salem M, Puccini A, Grothey A, et al. Comparative molecular analysis between microsatellite instability-high (MSI-H) tumors with high tumor mutational burden (TMB-H) versus MSI-H tumors... | OncologyPRO. Oncologypro.esmo.org.

breast, colorectal, esophagogastric, glioma, head and neck, melanoma, NSCLC, and renal cell showed greater survival after receiving ICIs[11]. In another 2015 analysis of clinical benefit from ICI, the group with the higher number of mutations, averaging in the 300s, had a more durable response to treatment lasting greater than six months, compared to the group with an average of just 148 mutations which had little to no durable response at six months[12]. This Supports the theory that more mutations offer more targets for the immunotherapy to attack and provide lasting effect.

Conclusion

Undoubtedly more analysis is needed to establish the threshold and tumour type that is likely to be most predictable in response to ICIs, but there is promising evidence that it may soon be a useful tool in predicting patient outcomes, possibly up to 50% benefit in outcomes[13]. In addition to identifying high TMB, a framework needs to be established for a more precise number of mutations that correlate to better and more durable patient response[14]. While science delves further into the exact mechanism and significance of cellular biomarkers and predicting their responsiveness to novel therapies for multiple types of cancer, one thing is sure we are inching closer to full understanding of cancer behavior and by predicting their response, we may eventually find a cure for many previously evasive cancers.

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[13] Hodi F, O'Day S, McDermott D et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. New England Journal of Medicine. 2010;363(8):711-723. doi:10.1056/nejmoa1003466

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