



cancers



Editorial

Unlocking the Potential of Biomarkers for Immune Checkpoint Inhibitors in Cancer Therapy

Giada Dal Collo and Paul Takam Kamga

Special Issue

Immune Checkpoint Inhibitor-Based Immunotherapy in Cancer: Predictive Biomarkers and Mechanisms of Resistance

Edited by
Dr. Paul Takam Kamga



<https://doi.org/10.3390/cancers15184503>

Editorial

Unlocking the Potential of Biomarkers for Immune Checkpoint Inhibitors in Cancer Therapy

Giada Dal Collo ¹  and Paul Takam Kamga ^{2,*} 

¹ Department of Immunology, Erasmus University Medical Center, 3015 GD Rotterdam, The Netherlands; giada.dalcollo@gmail.com

² EA4340 BECCOH, Université Paris-Saclay, UVSQ92100 Boulogne-Billancourt, France

* Correspondence: takam.paul@gmail.com

Immune checkpoint inhibitors (ICIs) are pharmaceutical agents capable of disrupting immune checkpoint signaling, leading to T-cell activation and a robust anti-tumor response [1]. The first anti-cancer ICI was aimed at targeting Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA4) (Ipilimumab). It showed promising outcomes in pre-treated patients with melanoma, including anticancer response rates and improved overall survival (OS) [1]. Subsequent advancements yielded a range of ICIs focusing on Programmed cell death protein-1/Programmed death-ligand 1 (PD1/PDL1) (i.e., Pembrolizumab, Atezolizumab, Durvalumab, and Nivolumab), which have been utilized as primary treatments for refractory melanoma, advanced and metastatic NSCLC, and other malignancies encompassing solid tumors and hematological malignancies. All these ICIs have demonstrated clinical advantages in terms of objective response rate (ORR) and survival, resulting in first-line therapeutic options administered alone or in conjunction with complementary strategies such as chemotherapy or radiotherapy [2–4]. Nonetheless, not all patients respond equally to these treatments, prompting the need for predictive biomarkers to optimize treatment selection and elevate patient outcomes. In addition, ICIs are associated with immune-related adverse events (IRAEs). These events not only induce patient discomfort but can also compel the temporary or permanent halt of immunotherapy [5]. Because many of these IRAEs are intricately tied to the mechanisms underlying ICIs, the pursuit of predictive biomarkers for IRAEs holds immense significance and often intersects with biomarkers used to evaluate ICIs' effectiveness [6–8]. Notably, evidence from studies suggests that IRAEs correlate with substantial enhancements in ORR and patient survival, underscoring their predictive value [9].

PDL-1 expression, as assessed through immunohistochemistry (IHC), was the first marker to gain approval and practical application in conjunction with ICIs. Patients with high PDL-1 expression (PDL-1 > 50%) tend to exhibit a more favorable response to the treatment. However, intriguingly, certain patients with lower PDL-1 expression (PDL-1 < 10%; PDL-1 < 5%; PDL-1 < 1%) have demonstrated enhanced ORR and prolonged survival, while some with elevated PDL-1 expression exhibited resistance to therapy [10–12]. Furthermore, it is noteworthy that the predictive value of PDL-1 expression does not remain consistent across all types of ICIs and cancer varieties [13]. This disparity arises, in part, from the spatiotemporal heterogeneity of the tumor, the variations in the methods utilized to assess PDL-1 expression, including techniques for IHC, the types of cells analyzed (cancer cells, immune cells, or both), and the specific antibody type employed [14]. As a result, there is a pressing need to standardize and refine the methods for analyzing PDL-1 expression. Circulating soluble PDL-1 (sPDL-1) has displayed encouraging potential. Despite certain contrasting findings, systematic reviews and meta-analyses provided evidence for a positive correlation between high levels of sPDL-1 and worse survival in individuals undergoing ICI treatment for solid cancer, including NSCLC and gastric cancer [15–17]. As previously mentioned, it is evident that PDL-1 expression alone is insufficient for patient stratification.



Citation: Dal Collo, G.; Takam Kamga, P. Unlocking the Potential of Biomarkers for Immune Checkpoint Inhibitors in Cancer Therapy. *Cancers* **2023**, *15*, 4503. <https://doi.org/10.3390/cancers15184503>

Received: 12 August 2023

Accepted: 8 September 2023

Published: 10 September 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Hence, in addition to PD-L1 expression, several other biomarkers are currently in the process of being developed.

Tumor mutational burden (TMB) quantifies the number of mutations harbored by tumor cells within a specific neoplasm. This mutational burden is closely associated with antigen processing and load in MHC-I, consequently impacting anti-tumoral immunity. For this instance, the study of Robert M. Samstein et al. demonstrated a positive correlation between high TMB and efficacy of ICIs across diverse cancer types and for different types of ICIs, as revealed by better ORR and longer survival in a robust cohort of 1662 cancer patients treated with different ICIs (Atezolizumab, Avelumab, Durvalumab, Ipilimumab, Nivolumab, Pembrolizumab, or Tremelimumab) [18]. This conclusion was further confirmed in several studies, as demonstrated by the systematic analysis of Kim et al., who examined 26 studies focused on immune checkpoint inhibitors (ICIs) in cancer. All these studies converge to show a correlation between high TMB, better response, longer overall survival (OS), and progression-free survival (PFS). This collective evidence supports the idea that TMB could serve as an effective biomarker associated with the use of ICIs [19,20].

The genetic variation in the DNA mismatch repair (MMR) pathway is one source of a high TMB load, which can lead to genome instability and microsatellite instability (MSI). For instance, as revealed by the Phase II CheckMate 142 Study, the application of ICIs in metastatic colorectal cancer (mCRC) demonstrated that defects in MMR and/or MSI (dMMR/MSI-H) are predictive indicators for the effectiveness of Pembrolizumab, Nivolumab, and Nivolumab in combination with low-dose Ipilimumab [21,22]. Notably, this correlation has also been observed across various other cancer types, including lung cancer, melanoma, renal cell carcinoma, and many others [23,24]. Additionally, as suggested by Schrock et al. and validated by emerging data, the utilization of TMB in conjunction with dMMR/MSI-H enhances the predictive value for ICIs compared to using dMMR/MSI-H alone [24]. Nevertheless, the pragmatic implementation of TMB in the clinical care of patients poses challenges. For instance, the use of genome sequencing or advanced next-generation sequencing tools to assess TMB load, though informative, can introduce complexity and prove burdensome when integrating them into everyday clinical routines [25]. Although the use of next-generation sequencing for targeted gene panels has somewhat alleviated this burden, the lack of a well-defined consensus on the cutoff ratio across various studies underscores the need for harmonization efforts [26].

In the pursuit of identifying alternative biomarkers, researchers have directed their efforts towards analyzing intermolecular interactions within tumor cells [27]. This exploration has extended to encompass the evaluation of various molecules, i.e., signaling molecules, cytokines/chemokines, and different cell types present in the tumor microenvironment, including tumor-associated fibroblasts (CAF), tumor-associated macrophages (TAM), mesenchymal stroma cells, and infiltrating immune cells. Additionally, it encompasses the examination of circulating and systemic markers within the host [4,28,29]. These encompass immune gene signatures [30], tumor-infiltrating lymphocytes (TILs), diverse T cell populations (such as CD8+, regulatory T cells, and T helper cells) [24,25], myeloid-derived suppressor cells (MDSCs) [31], and even the composition of the gut microbiome [32]. Thanks to advanced omics techniques, advancements in computational tools, the application of artificial intelligence, and a systems biology approach, emerging studies combine multiple markers to define expression patterns or nomograms that may accurately predict the outcomes of ICIs [30,33,34]. However, while the clinical feasibility of such an approach, as well as the utilization of single markers, necessitate further investigation, the validation and standardization of these methodologies across different cancer types and treatment contexts remain crucial challenges.

A majority of the biomarkers currently under investigation encompass cellular factors or molecules intricately engaged in immune evasion. These components operate within a coordinated framework, either fostering an environment favoring anti-inflammatory processes or contributing to the creation of a suppressive tumor niche that hampers anticancer immunity, ultimately culminating in resistance to ICIs [35,36]. The current challenges

reside in effectively implementing experimental models that replicate interactions among immune, stromal, and cancer cells. For instance, the classic two-dimensional (2D) coculture models often entail cultivating immune effector cells (T, B, and NK cells) on monolayers of cancer or stromal cells, encompassing various components such as MSCs, fibroblasts, and macrophages [37]. This model is frequently complemented by animal models or three-dimensional (3D) culture systems and organs-on-chips, offering the advantage of emulating the intricate cellular dynamics and mechanical complexity observed in patients [38–40]. By integrating these preclinical models with advanced high-resolution imaging and real-time monitoring, a complete comprehension of the dynamic interactions can be achieved, not only deepening our understanding of the mechanisms underlying resistance to ICIs, but also highlighting potential drug targets that could enhance the efficacy of ICIs [40,41].

In conclusion, the collaborative efforts of researchers and clinicians in deciphering the intricacies of immune responses offer a pathway to personalized treatment strategies driven by biomarkers. This holds the potential to enhance the effectiveness of cancer therapy and ultimately lead to better patient outcomes. A holistic endeavor towards validating, standardizing, and incorporating biomarkers will pave the road towards achieving precision medicine within the realm of immune checkpoint inhibitors and cancer treatment.

Author Contributions: Conceptualization; writing—original draft preparation, writing—review and editing: G.D.C. and P.T.K. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Lipson, E.J.; Drake, C.G. Ipilimumab: An Anti-CTLA-4 Antibody for Metastatic Melanoma. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2011**, *17*, 6958–6962. [[CrossRef](#)]
2. Brahmer, J.; Reckamp, K.L.; Baas, P.; Crinò, L.; Eberhardt, W.E.E.; Poddubskaya, E.; Antonia, S.; Pluzanski, A.; Vokes, E.E.; Holgado, E.; et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2015**, *373*, 123–135. [[CrossRef](#)] [[PubMed](#)]
3. Brahmer, J.R.; Tykodi, S.S.; Chow, L.Q.M.; Hwu, W.-J.; Topalian, S.L.; Hwu, P.; Drake, C.G.; Camacho, L.H.; Kauh, J.; Odunsi, K.; et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N. Engl. J. Med.* **2012**, *366*, 2455–2465. [[CrossRef](#)] [[PubMed](#)]
4. Mehlman, C.; Takam Kamga, P.; Costantini, A.; Julié, C.; Duménil, C.; Dumoulin, J.; Ouaknine, J.; Giraud, V.; Chinet, T.; Emile, J.-F.; et al. Baseline Hedgehog Pathway Activation and Increase of Plasma Wnt1 Protein Are Associated with Resistance to Immune Checkpoint Inhibitors in Advanced Non-Small-Cell Lung Cancer. *Cancers* **2021**, *13*, 1107. [[CrossRef](#)]
5. Conroy, M.; Naidoo, J. Immune-related adverse events and the balancing act of immunotherapy. *Nat. Commun.* **2022**, *13*, 392. [[CrossRef](#)] [[PubMed](#)]
6. Lee, D.J.; Lee, H.J.; Farmer, J.R.; Reynolds, K.L. Mechanisms Driving Immune-Related Adverse Events in Cancer Patients Treated with Immune Checkpoint Inhibitors. *Curr. Cardiol. Rep.* **2021**, *23*, 98. [[CrossRef](#)]
7. Berner, F.; Bomze, D.; Diem, S.; Ali, O.H.; Fässler, M.; Ring, S.; Niederer, R.; Ackermann, C.J.; Baumgaertner, P.; Pikor, N.; et al. Association of Checkpoint Inhibitor-Induced Toxic Effects With Shared Cancer and Tissue Antigens in Non-Small Cell Lung Cancer. *JAMA Oncol.* **2019**, *5*, 1043–1047. [[CrossRef](#)]
8. Das, S.; Johnson, D.B. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. *J. Immunother. Cancer* **2019**, *7*, 306. [[CrossRef](#)] [[PubMed](#)]
9. Foster, C.C.; Couey, M.A.; Kochanny, S.E.; Khattri, A.; Acharya, R.K.; Tan, Y.-H.C.; Brisson, R.J.; Leidner, R.S.; Seiwert, T.Y. Immune-related adverse events are associated with improved response, progression-free survival, and overall survival for patients with head and neck cancer receiving immune checkpoint inhibitors. *Cancer* **2021**, *127*, 4565–4573. [[CrossRef](#)]
10. Liu, X.; Guo, C.-Y.; Tou, F.-F.; Wen, X.-M.; Kuang, Y.-K.; Zhu, Q.; Hu, H. Association of PD-L1 expression status with the efficacy of PD-1/PD-L1 inhibitors and overall survival in solid tumours: A systematic review and meta-analysis. *Int. J. Cancer* **2020**, *147*, 116–127. [[CrossRef](#)]
11. Chen, Y.; Fu, J.; Li, Z.; Chen, Q.; Zhang, J.; Yang, Y.; Yang, P.; Wang, J.; Liu, Z.; Cao, Y.; et al. Cutoff values of PD-L1 expression in urinary cytology samples for predicting response to immune checkpoint inhibitor therapy in upper urinary tract urothelial carcinoma. *Cancer Cytopathol.* **2023**, *131*, 179–187. [[CrossRef](#)] [[PubMed](#)]
12. Horn, L.; Spigel, D.R.; Vokes, E.E.; Holgado, E.; Ready, N.; Steins, M.; Poddubskaya, E.; Borghaei, H.; Felip, E.; Paz-Ares, L.; et al. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). *J. Clin. Oncol.* **2017**, *35*, 3924–3933. [[CrossRef](#)] [[PubMed](#)]

13. Gong, J.; Chehrrazi-Raffle, A.; Reddi, S.; Salgia, R. Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: A comprehensive review of registration trials and future considerations. *J. Immunother. Cancer* **2018**, *6*, 8. [[CrossRef](#)]
14. Zhao, X.; Bao, Y.; Meng, B.; Xu, Z.; Li, S.; Wang, X.; Hou, R.; Ma, W.; Liu, D.; Zheng, J.; et al. From rough to precise: PD-L1 evaluation for predicting the efficacy of PD-1/PD-L1 blockades. *Front. Immunol.* **2022**, *13*, 920021. [[CrossRef](#)] [[PubMed](#)]
15. Ando, K.; Hamada, K.; Watanabe, M.; Ohkuma, R.; Shida, M.; Onoue, R.; Kubota, Y.; Matsui, H.; Ishiguro, T.; Hirasawa, Y.; et al. Plasma Levels of Soluble PD-L1 Correlate With Tumor Regression in Patients With Lung and Gastric Cancer Treated With Immune Checkpoint Inhibitors. *Anticancer. Res.* **2019**, *39*, 5195–5201. [[CrossRef](#)]
16. Scirocchi, F.; Strigari, L.; Di Filippo, A.; Napoletano, C.; Pace, A.; Rahimi, H.; Botticelli, A.; Rughetti, A.; Nuti, M.; Zizzari, I.G. Soluble PD-L1 as a Prognostic Factor for Immunotherapy Treatment in Solid Tumors: Systematic Review and Meta-Analysis. *Int. J. Mol. Sci.* **2022**, *23*, 14496. [[CrossRef](#)] [[PubMed](#)]
17. Cheng, Y.; Wang, C.; Wang, Y.; Dai, L. Soluble PD-L1 as a predictive biomarker in lung cancer: A systematic review and meta-analysis. *Future Oncol.* **2022**, *18*, 261–273. [[CrossRef](#)]
18. Samstein, R.M.; Lee, C.-H.; Shoushtari, A.N.; Hellmann, M.D.; Shen, R.; Janjigian, Y.Y.; Barron, D.A.; Zehir, A.; Jordan, E.J.; Omuro, A.; et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nat. Genet.* **2019**, *51*, 202–206. [[CrossRef](#)]
19. Kim, J.Y.; Kronbichler, A.; Eisenhut, M.; Hong, S.H.; van der Vliet, H.J.; Kang, J.; Shin, J.I.; Gamerith, G. Tumor Mutational Burden and Efficacy of Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. *Cancers* **2019**, *11*, 1798. [[CrossRef](#)]
20. Sha, D.; Jin, Z.; Budzgies, J.; Kluck, K.; Stenzinger, A.; Sinicrope, F.A. Tumor Mutational Burden (TMB) as a Predictive Biomarker in Solid Tumors. *Cancer Discov.* **2020**, *10*, 1808–1825. [[CrossRef](#)]
21. André, T.; Shiu, K.-K.; Kim, T.W.; Jensen, B.V.; Jensen, L.H.; Punt, C.; Smith, D.; Garcia-Carbonero, R.; Benavides, M.; Gibbs, P.; et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N. Engl. J. Med.* **2020**, *383*, 2207–2218. [[CrossRef](#)] [[PubMed](#)]
22. Lenz, H.-J.; Van Cutsem, E.; Luisa Limon, M.; Wong, K.Y.M.; Hendlisz, A.; Aglietta, M.; García-Alfonso, P.; Neyns, B.; Luppi, G.; Cardin, D.B.; et al. First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2022**, *40*, 161–170. [[CrossRef](#)]
23. Rizzo, A.; Ricci, A.D.; Gadaleta-Caldarola, G. MSI-H/dMMR and cancer immunotherapy: Current state and future implications. *Expert. Rev. Precis. Med. Drug Dev.* **2021**, *6*, 345–347. [[CrossRef](#)]
24. Schrock, A.B.; Ouyang, C.; Sandhu, J.; Sokol, E.; Jin, D.; Ross, J.S.; Miller, V.A.; Lim, D.; Amanam, I.; Chao, J.; et al. Tumor mutational burden is predictive of response to immune checkpoint inhibitors in MSI-high metastatic colorectal cancer. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **2019**, *30*, 1096–1103. [[CrossRef](#)]
25. Zhang, W.; Wang, R.; Fang, H.; Ma, X.; Li, D.; Liu, T.; Chen, Z.; Wang, K.; Hao, S.; Yu, Z.; et al. Influence of low tumor content on tumor mutational burden estimation by whole-exome sequencing and targeted panel sequencing. *Clin. Transl. Med.* **2021**, *11*, e415. [[CrossRef](#)]
26. Merino, D.M.; McShane, L.M.; Fabrizio, D.; Funari, V.; Chen, S.-J.; White, J.R.; Wenz, P.; Baden, J.; Barrett, J.C.; Chaudhary, R.; 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*, e000147. [[CrossRef](#)] [[PubMed](#)]
27. Talb, J.; Takam Kamga, P.; Mayenga, M.; Costantini, A.; Julié, C.; Dumenil, C.; Dumoulin, J.; Ouaknine, J.; Giraud, V.; Dujon, C.; et al. Gene expression profile of high PD-L1 non-small cell lung cancers refractory to pembrolizumab. *Cancer Immunol. Immunother.* **2022**, *71*, 2791–2799. [[CrossRef](#)]
28. Takam Kamga, P.; Swalduz, A.; Costantini, A.; Julié, C.; Emile, J.-F.; Pérol, M.; Avrillon, V.; Ortiz-Cuaran, S.; de Saintigny, P.; Leprieur, E.G. High Circulating Sonic Hedgehog Protein Is Associated With Poor Outcome in EGFR-Mutated Advanced NSCLC Treated With Tyrosine Kinase Inhibitors. *Front. Oncol.* **2021**, *11*, 747692. [[CrossRef](#)]
29. Fujimura, T. Stromal Factors as a Target for Immunotherapy in Melanoma and Non-Melanoma Skin Cancers. *Int. J. Mol. Sci.* **2022**, *23*, 4044. [[CrossRef](#)]
30. Hu, X.; Guo, J.; Shi, J.; Li, D.; Li, X.; Zhao, W. A 20-gene mutation signature predicts the efficacy of immune checkpoint inhibitor therapy in advanced non-small cell lung cancer patients. *BMC Pulm. Med.* **2023**, *23*, 223. [[CrossRef](#)] [[PubMed](#)]
31. Peranzoni, E.; Ingangi, V.; Masetto, E.; Pinton, L.; Marigo, I. Myeloid Cells as Clinical Biomarkers for Immune Checkpoint Blockade. *Front. Immunol.* **2020**, *11*, 1590. [[CrossRef](#)] [[PubMed](#)]
32. Lee, K.A.; Thomas, A.M.; Bolte, L.A.; Björk, J.R.; de Ruijter, L.K.; Armanini, F.; Asnicar, F.; Blanco-Miguez, A.; Board, R.; Calbet-Llopart, N.; et al. Cross-cohort gut microbiome associations with immune checkpoint inhibitor response in advanced melanoma. *Nat. Med.* **2022**, *28*, 535–544. [[CrossRef](#)]
33. Balachandran, V.P.; Gonen, M.; Smith, J.J.; DeMatteo, R.P. Nomograms in Oncology—More than Meets the Eye. *Lancet Oncol.* **2015**, *16*, e173–e180. [[CrossRef](#)] [[PubMed](#)]
34. Yoon, S.J.; Lee, C.B.; Chae, S.U.; Jo, S.J.; Bae, S.K. The Comprehensive “Omics” Approach from Metabolomics to Advanced Omics for Development of Immune Checkpoint Inhibitors: Potential Strategies for Next Generation of Cancer Immunotherapy. *Int. J. Mol. Sci.* **2021**, *22*, 6932. [[CrossRef](#)] [[PubMed](#)]

35. Weng, C.-Y.; Kao, C.-X.; Chang, T.-S.; Huang, Y.-H. Immuno-Metabolism: The Role of Cancer Niche in Immune Checkpoint Inhibitor Resistance. *Int. J. Mol. Sci.* **2021**, *22*, 1258. [[CrossRef](#)] [[PubMed](#)]
36. Park, K.; Veena, M.S.; Shin, D.S. Key Players of the Immunosuppressive Tumor Microenvironment and Emerging Therapeutic Strategies. *Front. Cell Dev. Biol.* **2022**, *10*, 830208. [[CrossRef](#)]
37. Di Trapani, M.; Bassi, G.; Ricciardi, M.; Fontana, E.; Bifari, F.; Pacelli, L.; Giacomello, L.; Pozzobon, M.; Féron, F.; De Coppi, P.; et al. Comparative Study of Immune Regulatory Properties of Stem Cells Derived from Different Tissues. *Stem Cells Dev.* **2013**, *22*, 2990–3002. [[CrossRef](#)]
38. Dal Collo, G.; Adamo, A.; Gatti, A.; Tamellini, E.; Bazzoni, R.; Takam Kamga, P.; Tecchio, C.; Quaglia, F.M.; Krampera, M. Functional dosing of mesenchymal stromal cell-derived extracellular vesicles for the prevention of acute graft-versus-host-disease. *Stem Cells Dayt. Ohio* **2020**, *38*, 698–711. [[CrossRef](#)]
39. Li, Y.; Fan, H.; Ding, J.; Xu, J.; Liu, C.; Wang, H. Microfluidic devices: The application in TME modeling and the potential in immunotherapy optimization. *Front. Genet.* **2022**, *13*, 969723. [[CrossRef](#)]
40. Wei, S.C.; Meijers, W.C.; Axelrod, M.L.; Anang, N.-A.A.S.; Screever, E.M.; Wescott, E.C.; Johnson, D.B.; Whitley, E.; Lehmann, L.; Courand, P.-Y.; et al. A genetic mouse model recapitulates immune checkpoint inhibitor-associated myocarditis and supports a mechanism-based therapeutic intervention. *Cancer Discov.* **2021**, *11*, 614–625. [[CrossRef](#)]
41. Chen, M.; Zhou, K.; Dai, S.-Y.; Tadepalli, S.; Balakrishnan, P.B.; Xie, J.; Rami, F.E.I.; Dai, T.; Cui, L.; Idoyaga, J.; et al. In vivo bioluminescence imaging of granzyme B activity in tumor response to cancer immunotherapy. *Cell Chem. Biol.* **2022**, *29*, 1556–1567.e6. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.