Supplemental Table 1. Immunotherapeutic Approaches Tested in Clinical trials for Pediatric Solid Tumors at the Crossroads

|  |  |  |  |
| --- | --- | --- | --- |
| Immunotherapeutic Approach | Target | Disease Evaluated | Ref |
| mAb | HER2 (Trastuzumab) | Osteosarcoma | (1) |
| mAb | Anti-glycoprotein non-metastatic B (CDX-011) | Osteosarcoma | (2) |
| mAb | Tumor necrosis factor related apoptosis-inducing ligand (lexatumumab) | Pediatric sarcomas | (3) |
| mAb | Insulin-like growth factor 1 receptor (cixutumumab) | Pediatric sarcomas | (4) |
| CAR-T | GD2 (3rd generation) | Neuroblastoma | (5) |
| CAR-T | HER2 (2nd generation) | Pediatric sarcomas | (6) |
| ICI | CTLA4 (ipilimumab) | Pediatric solid tumors | (7) |
| ICI | PD-1 (nivolumab) | Pediatric solid tumors | (8) |
| ICI | PD-1 (pembrolizumab) | Pediatric solid tumors /lymphoma | (9) |
| ICI | PD-L1 (atezolizumab) | Pediatric solid tumors | (10) |
| Vaccine therapy | Wilms tumor gene 1 | Pediatric tumors | (11) |
| Vaccine therapy | NeuGcGM3 (racotumomamb) | Neuroblastoma and other pediatric tumors | (12) |
| Vaccine therapy | Dendritic cell vaccines (Review) | Pediatric tumors | (13) |

Supplemental Table 2. Promising Immunotherapeutic Approaches Beyond Traditional Checkpoint Blockade with Examples of Successful Clinical Application in Adult Solid T umors

|  |  |  |  |
| --- | --- | --- | --- |
| Biologic Approach | Target / Modality | Agents utilized | Clinical Application (Ref) |
| T cell based therapies | Co-inhibitory pathways | Anti-LAG3; anti-TIM-3; anti-TIGIT | (14) |
| T cell based therapies | Tumor reactive (TCR-driven) T cells | Viral specific T cells (i.e. autologous EBVSTs); Autologous and normal donor-specific T cells; Autologous TAA-specific T cells; T cells with vaccines; TILs enriched for mutation-specific T cells | (15) |
| T cell based therapies | CAR-T cells | CAR-T cells | (16) |
| NK cells | NK cells | NK cells | (17) |
| Vaccine therapy | Vaccine therapy | Synthetic peptides, messenger RNA, DNA plasmids, viral vectors, engineered attenuated bacterial vectors, ex vivo antigen-loaded dendritic cells | (18) |
| TME | Vasculature, hypoxia | Anti-angiogenics (i.e. anti-VEGF); anti-hypertensives targeting the renin-angiotensin system; anti-CXCR4 agents | (19,20) |
| TME | Regulatory T cells (Tregs) | Depletion of Tregs (anti-CD25, anti-CCR4); Reprogramming of Tregs (OX40, GITR, IDO1 inhibitors) | (21) |
| TME | Myeloid cells | Tumor associated macrophage reprogramming agents (i.e. Anti-CSF-1/R+, CCL2, IL-6, CD40) | (22) |

Supplemental References

1. Ebb D, Meyers P, Grier H, Bernstein M, Gorlick R, Lipshultz SE*, et al.* Phase II trial of trastuzumab in combination with cytotoxic chemotherapy for treatment of metastatic osteosarcoma with human epidermal growth factor receptor 2 overexpression: a report from the children's oncology group. J Clin Oncol **2012**;30(20):2545-51 doi 10.1200/JCO.2011.37.4546.

2. Kopp LM MS, Karilo M, et al. Phase 2 trial of the GPNMB-targeted antibody-drug conjugate, CDX-011 (glembatumumab vedotin) in recurrent/refractory osteosarcoma (OS): a report from the Children’s Oncology Group (COG). . Connective Tissue Oncology Society (CTOS) 2017 Annual Meeting. Maui, Hawaii.

3. Merchant MS, Geller JI, Baird K, Chou AJ, Galli S, Charles A*, et al.* Phase I trial and pharmacokinetic study of lexatumumab in pediatric patients with solid tumors. J Clin Oncol **2012**;30(33):4141-7 doi 10.1200/JCO.2012.44.1055.

4. Malempati S, Weigel B, Ingle AM, Ahern CH, Carroll JM, Roberts CT*, et al.* Phase I/II trial and pharmacokinetic study of cixutumumab in pediatric patients with refractory solid tumors and Ewing sarcoma: a report from the Children's Oncology Group. J Clin Oncol **2012**;30(3):256-62 doi JCO.2011.37.4355 [pii]

10.1200/JCO.2011.37.4355.

5. Heczey A, Louis CU, Savoldo B, Dakhova O, Durett A, Grilley B*, et al.* CAR T Cells Administered in Combination with Lymphodepletion and PD-1 Inhibition to Patients with Neuroblastoma. Mol Ther **2017**;25(9):2214-24 doi 10.1016/j.ymthe.2017.05.012.

6. Ahmed N, Brawley VS, Hegde M, Robertson C, Ghazi A, Gerken C*, et al.* Human Epidermal Growth Factor Receptor 2 (HER2) -Specific Chimeric Antigen Receptor-Modified T Cells for the Immunotherapy of HER2-Positive Sarcoma. J Clin Oncol **2015**;33(15):1688-96 doi 10.1200/JCO.2014.58.0225.

7. Merchant MS, Wright M, Baird K, Wexler LH, Rodriguez-Galindo C, Bernstein D*, et al.* Phase I Clinical Trial of Ipilimumab in Pediatric Patients with Advanced Solid Tumors. Clin Cancer Res **2016**;22(6):1364-70 doi 10.1158/1078-0432.CCR-15-0491

1078-0432.CCR-15-0491 [pii].

8. Davis KL, Fox E, Reid JM, Liu X, Minard CG, Weigel B*, et al.* ADVL1412: Initial results of a phase I/II study of nivolumab and ipilimumab in pediatric patients with relapsed/refractory solid tumors—A COG study. **2017**;35(15\_suppl):10526- doi 10.1200/JCO.2017.35.15\_suppl.10526.

9. Geoerger B, Kang HJ, Yalon-Oren M, Marshall LV, Vezina C, Pappo AS*, et al.* Phase 1/2 KEYNOTE-051 study of pembrolizumab (pembro) in pediatric patients (pts) with advanced melanoma or a PD-L1+ advanced, relapsed, or refractory solid tumor or lymphoma. **2017**;35(15\_suppl):10525- doi 10.1200/JCO.2017.35.15\_suppl.10525.

10. Geoerger B, Karski EE, Zwaan M, Casanova M, Marshall LV, DuBois SG*, et al.* A phase I/II study of atezolizumab in pediatric and young adult patients with refractory/relapsed solid tumors (iMATRIX-Atezolizumab). **2017**;35(15\_suppl):10524- doi 10.1200/JCO.2017.35.15\_suppl.10524.

11. Hashii Y, Sato E, Ohta H, Oka Y, Sugiyama H, Ozono K. WT1 peptide immunotherapy for cancer in children and young adults. Pediatr Blood Cancer **2010**;55(2):352-5 doi 10.1002/pbc.22522.

12. Cacciavillano W, Sampor C, Venier C, Gabri MR, de Davila MT, Galluzzo ML*, et al.* A Phase I Study of the Anti-Idiotype Vaccine Racotumomab in Neuroblastoma and Other Pediatric Refractory Malignancies. Pediatr Blood Cancer **2015**;62(12):2120-4 doi 10.1002/pbc.25631.

13. Elster JD, Krishnadas DK, Lucas KG. Dendritic cell vaccines: A review of recent developments and their potential pediatric application. Human vaccines & immunotherapeutics **2016**;12(9):2232-9 doi 10.1080/21645515.2016.1179844.

14. Shin DS, Ribas A. The evolution of checkpoint blockade as a cancer therapy: what's here, what's next? Curr Opin Immunol **2015**;33:23-35 doi 10.1016/j.coi.2015.01.006.

15. Leung W, Heslop HE. Adoptive Immunotherapy with Antigen-Specific T Cells Expressing a Native TCR. Cancer Immunol Res **2019**;7(4):528-33 doi 10.1158/2326-6066.CIR-18-0888.

16. Knochelmann HM, Smith AS, Dwyer CJ, Wyatt MM, Mehrotra S, Paulos CM. CAR T Cells in Solid Tumors: Blueprints for Building Effective Therapies. Front Immunol **2018**;9:1740 doi 10.3389/fimmu.2018.01740.

17. Hu W, Wang G, Huang D, Sui M, Xu Y. Cancer Immunotherapy Based on Natural Killer Cells: Current Progress and New Opportunities. Front Immunol **2019**;10:1205 doi 10.3389/fimmu.2019.01205.

18. Sahin U, Tureci O. Personalized vaccines for cancer immunotherapy. Science **2018**;359(6382):1355-60 doi 10.1126/science.aar7112.

19. Datta M, Coussens LM, Nishikawa H, Hodi FS, Jain RK. Reprogramming the Tumor Microenvironment to Improve Immunotherapy: Emerging Strategies and Combination Therapies. **2019**(39):165-74 doi 10.1200/edbk\_237987.

20. Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. Nat Rev Clin Oncol **2018**;15(5):325-40 doi 10.1038/nrclinonc.2018.29.

21. Shitara K, Nishikawa H. Regulatory T cells: a potential target in cancer immunotherapy. Ann N Y Acad Sci **2018**;1417(1):104-15 doi 10.1111/nyas.13625.

22. Ruffell B, Coussens LM. Macrophages and therapeutic resistance in cancer. Cancer Cell **2015**;27(4):462-72 doi 10.1016/j.ccell.2015.02.015.