2020–2021 Drug Updates: Investigational Therapeutics in the Pipeline

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Presenter's disclosure of conflicts of interest is found at the end of this article.

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Abstract

During JADPRO Live Virtual 2021, Donald C. Moore, PharmD, BCPS, BCOP, DPLA, discussed investigational therapeutic agents in the drug development pipeline. Dr. Moore highlighted agents that represent either a new drug class, a novel mechanism of action, a rethinking of how to approach treating a disease, or those that have recently received FDA Breakthrough Designation status that advanced practitioners should be aware of.

Investigators are currently evaluating many new agents in the hematology/oncology pipeline, including novel immunotherapies that can potentially complement existing immunotherapies. Emerging therapeutics are also being evaluated in very difficult-to-treat patient populations, such as *TP53*-mutant acute myeloid leukemia (AML), heavily pretreated multiple myeloma, platinum-resistant/PARP inhibitor–resistant ovarian cancer, and treatment refractory B-cell lymphomas.

During JADPRO Live Virtual 2021, Donald C. Moore, PharmD, BCPS, BCOP, DPLA, of Levine Cancer Institute, Atrium Health, described the pharmacology of novel investigational therapeutics currently under development and discussed the literature supporting the ongoing evaluation of these agents.

SOLID TUMORS

Bempegaldesleukin for Melanoma

As Dr. Moore explained, interleukin-2 (IL-2) plays an important role in promoting tumor cell death by enhancing the survival and expansion of CD4-positive and CD8-positive T-cells and natural killer cells (Figure 1). Although high-dose IL-2 is indicated for melanoma and renal cell carcinoma, its clinical use is limited by a short half-life that necessitates higher doses, which leads significant toxicities.

Bempegaldesleukin, a first-in-class CD122-preferential IL-2 pathway agonist, leverages clinically validated IL-2 pathway to stimulate antitumor response. A phase II study of bempegaldesleukin plus

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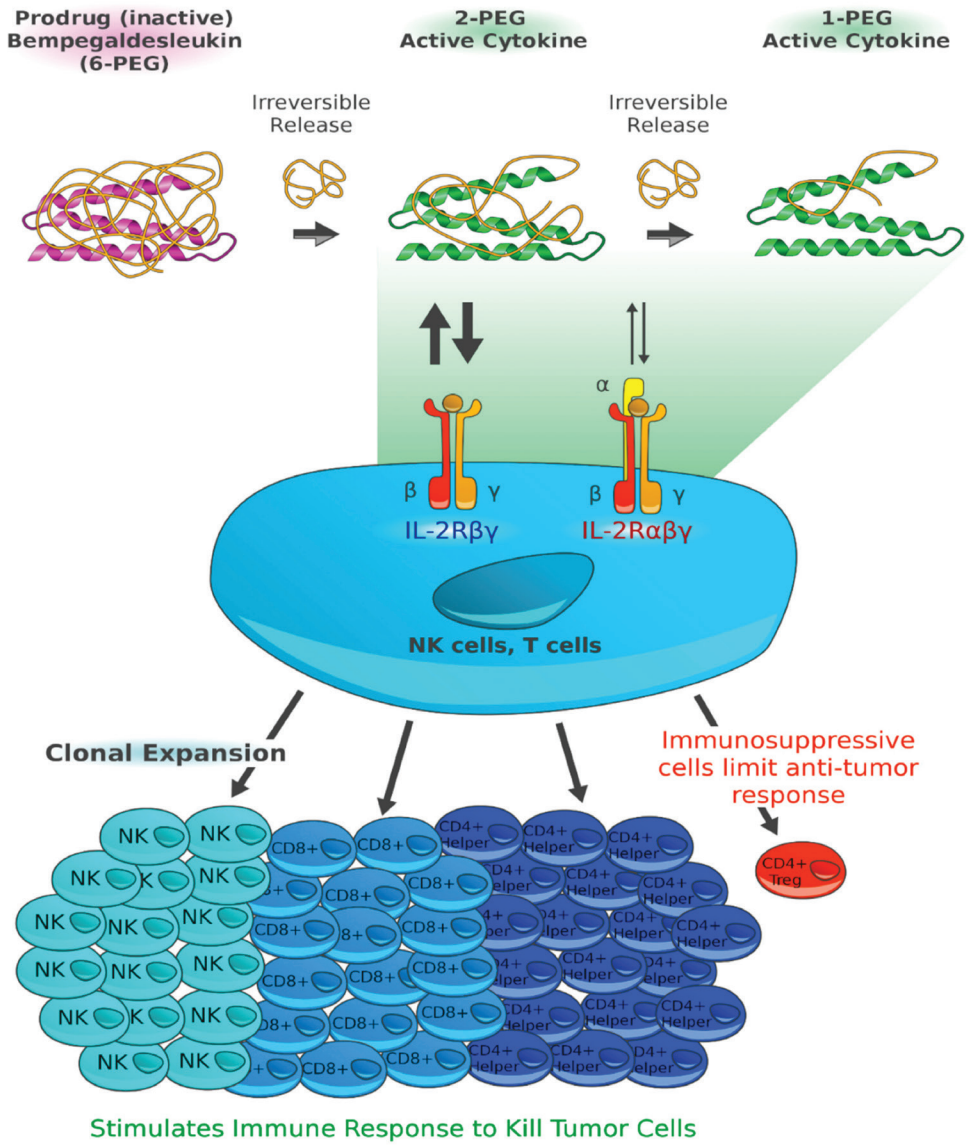

Figure 1. Bempegaldesleukin. Image republished from Gellrich et al. (2020) under terms of Creative Commons Attribution License (CC BY).

nivolumab (Opdivo) in first-line metastatic melanoma (stage III unresectable or stage IV) has demonstrated a median progression-free survival of approximately 31 months, with the potential for deepening responses over time (Diab et al., 2021).

"At 24 months, when treatment is ending, progression-free survival is 53%," said Dr. Moore. "One year later, progression-free survival is 46%, which shows that some durability of the response is maintained in these patients."

The median overall survival has not yet been reached, and at 36 months, 71% of patients are still alive, said Dr. Moore.

The most common adverse event noted has been flu-like symptoms, including chills, pyrexia, and influenza-like illness. Rates of cytokine related–adverse events were highest in cycle 1, but the incidence decreased with continued dosing.

Bempegaldesleukin was granted breakthrough designation by the U.S. Food and Drug Administra-

tion (FDA) in 2019 in combination with nivolumab for melanoma. A confirmatory phase III trial evaluating bempegaldesleukin plus nivolumab vs. nivolumab alone in the first line of previously untreated metastatic melanoma is currently ongoing.

Tiragolumab for Lung/Esophageal Cancers

TIGIT (T-cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory domains) is an inhibitory checkpoint receptor primarily expressed on T cells and natural killer cells. Preclinical studies suggest that TIGIT may be a complementary pathway with PD-1/PD-L1 blockade (Yeo et al., 2021; Figure 2).

Tiragolumab, a novel anti-TIGIT monoclonal antibody, was recently evaluated in the randomized, placebo-controlled, phase II CITYSCAPE trial (Rodriquez-Abreu et al., 2020). Chemotherapy-naive patients with PD-L1–positive non–small cell lung cancer (NSCLC) were randomized to receive tiragolumab in combination with atezolizumab (Tecentriq) every 3 weeks or atezolizumab plus placebo.

The addition of tiragolumab to atezolizumab nearly doubled the overall response rate vs. atezolizumab alone along with a significant improvement in median progression-free survival. Although treatment-related adverse events were higher in the combination arm compared with the control arm, said Dr. Moore, there was actually a lower rate of grade 3 or higher adverse events and a lower rate of discontinuations due to adverse events in the combination arm.

Tiragolumab was recently granted breakthrough designation by the FDA in combination with atezolizumab for PD-L1–high NSCLC. A confirmatory phase III trial evaluating atezolizumab with or without tiragolumab in metastatic PD-L1–selected NSCLC is currently ongoing. Tiragolumab is also being evaluated in esophageal cancer.

Adavosertib for Ovarian Cancer

Adavosertib is a Wee1 inhibitor, which is a critical regulator of the G2/M checkpoint in the cell cycle that helps to prevent the entry of damaged

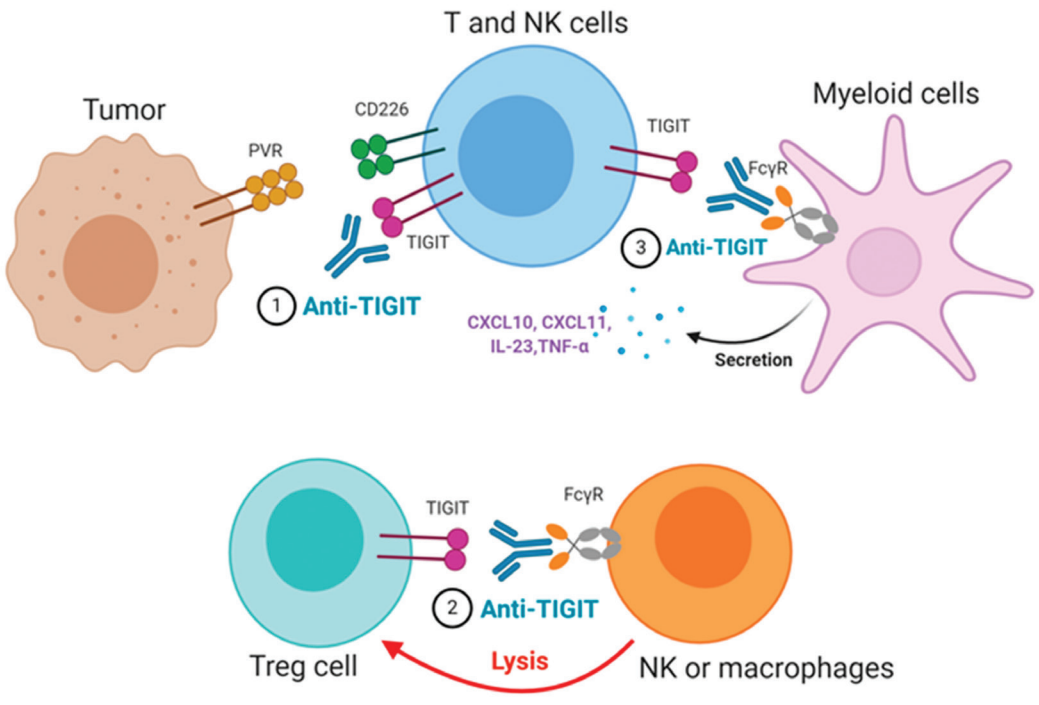

Figure 2. Tiragolumab. Image republished from Yeo et al. (2021) under terms of Creative Commons Attribution License (CC BY).

DNA into mitosis. As Dr. Moore explained, Wee1 has been found to be altered in several cancers, including breast, ovarian, and sarcomas (Rodriquez-Abreu et al., 2020). Research also suggests that *TP53* mutations may also lead to an increase in the dependency of this G2-phase checkpoint. Wee1 inhibition could limit that dependency and help to induce G2 checkpoint escape, said Dr. Moore.

Adavosertib was recently evaluated in combination with gemcitabine in a randomized, double-blind, placebo-controlled phase II trial that included patients with platinum-resistant or platinum-refractory, high-grade serous ovarian cancer (Lheureux et al., 2021). Patients were randomized to receive adavosertib plus gemcitabine vs. placebo plus gemcitabine.

Results of the study showed a statistically significant improvement in median progression-free survival and overall survival as well as a significant improvement in the overall response rate (23% in the investigational arm vs. 6% percent in the control).

The most common side effects in the combination arm were high-grade hematologic toxicity, including neutropenia, thrombocytopenia, and anemia. There was also a significantly higher incidence of grade 3 or higher fever and neutropenia with the addition of adavosertib to gemcitabine compared with gemcitabine alone. In addition, maculopapular rash occurred in 39% of patients in the combination arm vs. just 9% in the control arm.

Adavosertib is also being evaluated in the setting of PARP inhibitor-resistant ovarian cancer. Data from the phase II EFFORT trial of adavosertib with or without olaparib showed an overall response rate of 29%, with a clinical benefit rate of 89% in the combination arm (Westin et al., 2021).

HEMATOLOGIC MALIGNANCIES

Teclistamab (Multiple Myeloma)

B-cell maturation antigen (BCMA), a cell-surface receptor expressed on myeloma cells but not on naïve and memory B cells, has been shown to be a relatively selective and attractive therapeutic target. As Dr. Moore explained, BCMA promotes the maturation and long-term survival of normal plasma calls and has been found to be essential in the proliferation and survival of malignant plasma cells in the setting of myeloma (Tai & Anderson, 2015).

Teclistamab is a BCMA CD3 bispecific antibody currently under development. It was evaluated in the two-part phase I MajesTEC-1 study, which included patients with multiple myeloma that was relapsed/refractory or intolerant to established therapies (Krishnan et al., 2021). Patients enrolled had not received prior BCMA-targeted therapy.

"This was a heavily pretreated patient population with some high-risk features, including high-risk cytogenetics and extramedullary disease, and patients had a median of five prior lines of therapy," said Dr. Moore, who noted that most patients were triple-class refractory, and 38% were penta-drug refractory.

With a median follow-up of 6 months, results of the study demonstrated an overall response rate of 65%, which was largely very good partial responses or better, and a complete response or better rate of 40%.

"A good overall response rate with single agents in heavily relapsed/refractory myeloma is typically in the 20% to 30% range," said Dr. Moore. "The response rate from this trial has created optimism and enthusiasm for bispecific antibodies in the setting of myeloma."

Treatment-related toxicities were mostly hematologic and included neutropenia, anemia, and thrombocytopenia. Cytokine release syndrome (CRS) occurred in 70% of patients but was only grade 1 or 2. No grade 3 or higher CRS was observed.

Teclistamab recently received breakthrough designation by the FDA and is currently being evaluated in an international, open label, phase II study in relapsed/refractory myeloma.

Talquetamab for Multiple Myeloma

Talquetamab is a bispecific antibody designed to target G protein coupled family C group 5-member D (GPRC5D) and CD3. As Dr. Moore explained, GPRC5D is a highly expressed receptor in multiple myeloma that has limited expression in healthy human tissue, including normal plasma cells and other immune cells, which makes it a relatively specific target for multiple myeloma (Verkleij et al., 2021).

Talquetamab was evaluated in the phase I MonumenTAL study, which included a heavily pretreated population of patients with multiple

myeloma (Berdeja et al., 2021). Approximately one third of patients had extramedullary disease and had received a median of six prior lines of therapy.

With a median follow-up of 6 months, the overall response rate was 70%, which was largely very good partial responses or better, and a complete response or better rate of 10%. According to Dr. Moore, a similar overall response rate was seen in the triple-class refractory and penta-drug refractory patient cohorts.

Like teclistamab, treatment-related adverse events on talquetamab were mostly hematologic toxicities. Cytokine release syndrome was observed in 73% of patients but was mostly grade 1 or 2. One patient had a grade 3 or higher CRS event. Dermatologic adverse events, including skin exfoliation, pruritus, rash, and nail disorders, were also reported. No immune effector cell-associated neurotoxicity syndrome (ICANS) was observed with talquetamab.

Talquetamab is currently undergoing a phase II expansion study in relapsed/refractory multiple myeloma.

Glofitamab for Non-Hodgkin Lymphoma

Glofitamab is a CD20-targeting, T-cell-engaging, bispecific antibody with a novel two-to-one bivalent structure. As Dr. Moore explained, the full-length antibody has a longer half-life than non-Fc-bearing bispecific T-cell engagers like blinatumomab (Blincyto), which gives it the potential for more convenient administration with no need for continuous infusion (Zhu et al., 2016).

Glofitamab was evaluated in the NP30179 study, a first-in-human, three-part, phase I study in relapsed/refractory B-cell non-Hodgkin lymphoma (NHL). Part two is a multiple-patient dose escalation that included adult patients with histologically confirmed B-cell NHL expected to express CD20 who had received at least one prior therapy with no available life-extending treatment options (Hutchings et al., 2021).

Response has been seen in approximately 70% of patients, with complete responses in more than half of patients. Importantly, said Dr. Moore, responses have been seen in a variety of different B-cell lymphoma subtypes, including diffuse large B-cell lymphoma, follicular lymphoma, transformed follicular lymphoma, and mantle cell lymphoma.

Like many other bispecific antibodies, the main safety event of interest with glofitamab is CRS, which occurred in 71% of patients receiving glofitamab. According to Dr. Moore, however, lower starting doses were associated with lower rate of CRS. Neurologic adverse events also occurred in approximately one third of patients.

Glofitamab is undergoing a phase III trial in relapsed/refractory diffuse large B-cell lymphoma in combination with gemcitabine and oxaliplatin vs. rituximab plus gemcitabine and oxaliplatin.

Magrolimab for AML and MDS

Magrolimab is an anti-CD47 monoclonal antibody currently under investigation for AML and myelodysplastic syndromes. CD47 is a transmembrane protein that functions as an anti-phagocytic signal and has been found to be overexpressed in both AML and high-risk myelodysplastic syndrome (MDS; Chao et al., 2020).

Magrolimab was recently evaluated in a phase 1b study with azacitidine in patients with treatment-naïve AML who are unfit for intensive induction chemotherapy (Sallman et al., 2019). The objective response rate in the entire cohort was 65%, with a complete response rate of 44%. The median overall survival for *TP53*-wild-type patients was approximately 19 months, with a median time to response of 2 months.

"The onset of response to magrolimab is more rapid than what we would expect with azacitidine alone," said Dr. Moore.

In the *TP53*-mutant patients, which will be the cohort of interest going forward, the objective response rate was 72%, with a complete response rate of 48%. The median duration of response in *TP53*-mutant patients was approximately 10 months, and the median overall survival was 13 months.

The most common adverse events were anemia, fatigue, hyperbilirubinemia, neutropenia, thrombocytopenia, and nausea. Treatment-related febrile neutropenia occurred in two patients, and there were no immune-related adverse events observed in the study.

Magrolimab is currently being evaluated in a single-arm, MDS cohort, registration study, and there are several ongoing phase III trials evaluating magrolimab in combination with azacitidine.

Disclosure

Dr. Moore reported advisory board participation and consulting fees from Oncopeptides.

References

Berdeja, J. G., Krishnan, A. Y., Oriol, A., van de Donk, N. W. C. J., Rodriguez-Otero, P., Askari, E.,...Chari, A. (2021). Updated results of a phase 1, first-in-human study of talquetamab, a G protein-coupled receptor family C group 5 member D (GPRC5D) × CD3 bispecific antibody, in relapsed/refractory multiple myeloma (MM). *Journal of Clinical Oncology, 39*(15), 8008. https://doi.org/10.1200/JCO.2021.39.15_suppl.8008

Chao, M. P., Takimoto, C. H., Feng, D. D., McKenna, K., Gip, P., Liu, J.,...Majeti, R. (2020). Therapeutic targeting of the macrophage immune checkpoint CD47 in myeloid malignancies. *Frontiers in Oncology*, *9*, 1380. https://doi.org/10.3389/fonc.2019.01380

Diab, A., Tykodi, S. S., Daniels, G. A., Maio, M., Curti, B. D., Lewis, K. D.,... Hurwitz, M. E. (2021). Bempegaldesleukin plus nivolumab in first-line metastatic melanoma. *Journal of Clinical Oncology, 39*(26), 2914–2925. https://doi.org/10.1200/JCO.21.00675

Gellrich, F., Schmitz, M., Beissert, S., & Meier, F. (2020). Anti-PD-1 and novel combinations in the treatment of melanoma—an update. *Journal of Clinical Medicine*, *9*(1), 223. https://doi.org/10.3390/jcm9010223

Ghelli Luserna di Rorà, A., Cerchione, C., Martinelli, G., & Simonetti, G. (2020). A WEE1 family business: Regulation of mitosis, cancer progression, and therapeutic target. *Journal of Hematology & Oncology*, *13*(1), 126. https://doi.org/10.1186/s13045-020-00959-2

Hutchings, M., Morschhauser, F., Iacoboni, G., Carlo-Stella, C., Offner, F. C., Sureda, A.,... Dickinson, M. J. (2021). Glofitamab, a novel, bivalent CD20-targeting T-cell-engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: A phase I trial. *Journal of Clinical Oncology*, *39*(18), 1959–1970. https://doi.org/10.1200/JCO.20.03175

Krishnan, A. Y., Garfall, A. L., Mateos, M-V, van de Donk, N. W. C. J., Nahi, H., San-Miguel, J. F.,...Usmani, S. Z. (2021). Updated phase 1 results of teclistamab, a B-cell maturation antigen (BCMA) × CD3 bispecific antibody, in relapsed/refractory multiple myeloma (MM). *Journal of Clinical Oncology*, 39, 2021(suppl 15), 8007. https://doi.org/10.1200/JCO.2021.39.15_suppl.8007

Lheureux, S., Cristea, M. C., Bruce, J. P., Garg, S., Cabanero, M., Mantia-Smaldone, G.,...Oza, A. M. (2021). Adavosertib plus gemcitabine for platinum-resistant or platinum-refractory recurrent ovarian cancer: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet*, *397*(10271), 281–292. https://doi.org/10.1016/S0140-6736(20)32554-X

Rodriquez-Abreu, D., Johnson, M. L., Hussein, M. A., Cobo, M., Patel, A. J., Secen, N. M.,...Cho, B. C. (2020). Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first-line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE). *Journal of Clinical Oncology,* 38(15_suppl), 9503. https://doi.org/10.1200/JCO.2020.38.15_suppl.9503

Sallman, D. A., Asch, A.S., Kambhampati S., Al Malki, M. M., Zeidner, J. F., Donnellan, W.,...Daver, N. (2019). The first-in-class anti-CD47 antibody magrolimab (5F9) in combination with azacitidine is effective in MDS and AML patients: Ongoing phase 1b results. *Blood*, 134(1), 569. https://doi.org/10.1182/blood-2019-126271

Tai, Y. T., & Anderson, K. C. (2015). Targeting B-cell maturation antigen in multiple myeloma. *Immunotherapy*, *7*(11), 1187–1199. https://doi.org/10.2217/imt.15.77

Verkleij, C., Broekmans, M., van Duin, M., Frerichs, K. A., Kuiper, R., de Jonge, A. V.,...van de Donk, N. (2021). Preclinical activity and determinants of response of the GPRC5DxCD3 bispecific antibody talquetamab in multiple myeloma. *Blood Advances*, *5*(8), 2196–2215. https://doi.org/10.1182/bloodadvances.2020003805

Westin, S. N., Coleman, R. L., Fellman, B. M., Yuan, Y., Sood, A. K., Soliman, P. T.,...Liu, J. F. (2021). EFFORT: EFFicacy Of adavosertib in parp ResisTance: A randomized two-arm non-comparative phase II study of adavosertib with or without olaparib in women with PARP-resistant ovarian cancer. *Journal of Clinical Oncology*, 39(no. 15_suppl), 5505. https://doi.org/10.1200/JCO.2021.39.15_suppl.5505

Yeo, J., Ko, M., Lee, D. H., Park, Y., & Jin, H. S. (2021). TIGIT/CD226 axis regulates anti-tumor immunity. *Pharmaceuticals*, *14*(3), 200. https://doi.org/10.3390/ph14030200

Zhu, M., Wu, B., Brandl, C., Johnson, J., Wolf, A., Chow, A., & Doshi, S. (2016). Blinatumomab, a bispecific T-cell engager (BiTE(®)) for CD-19 targeted cancer immunotherapy: Clinical pharmacology and its implications. *Clinical Pharmacokinetics*, *55*(10), 1271–1288. https://doi.org/10.1007/s40262-016-0405-4