AACR 2022

New Outfit for Current Targets

Anupam Goyal, PhD.

Current targeted therapies (approved or late phase) have shown moderate durable response. The need for long-term remission and safety concerns are driving clinical research to develop next-generation therapies with high specificity and affinity for the existing targets. The advancing science and development of these next-generation therapies was highlighted at AACR 2022.

Power of two in one: New immunotherapies broadening the therapeutic index by targeting multiple tumor antigens

- While indoleamine-2,3 dioxygenase (IDO) inhibitors such as Epacadostat (Incyte) and BMS-986205 (BMS) failed to take off[1,2], IO Biotech is developing a vaccine targeting two immunotherapeutics IDO and PD-L1. IO102-IO103 helps in the modulation of the TME into an enhanced pro-inflammatory environment and helps in killing IDO and PD-L1 expressing cells. This is different from the previous approaches that target single immunosuppressive pathways or direct the immune system against specific antigens expressed by tumor cells.[3]
- IO Biotech presented results of the IDO/PD-L1 peptide vaccine in combination with nivolumab from a Phase II study in poor prognosis (1L+) metastatic melanoma patients. An ORR of 80% (46.7% CR) and mPFS of 25.3 months were observed (N=30), which is significantly more than the standard treatment of care without additional toxicity.[4] Currently, it is in Phase III trials with pembrolizumab in 1L stage III/IV melanoma patients.

Masked CD47 inhibitor, ADG153, likely to have a lower incidence of anemia

- CD47, a cell surface protein, forms a signaling complex with macrophage signal regulatory protein-α (SIRPα) and helps these cells escape macrophage-driven phagocytosis. Anti-CD47 antibodies block the interaction between SIRPα and tumor surface CD47 and enhance the phagocytosis of tumor cells by macrophages. Preclinical research has shown that CD47 antagonist monoclonal antibodies enable the phagocytosis and elimination of acute myeloid leukemia (AML), non-Hodgkin's lymphoma (NHL), and many solid tumors in xenograft models. However, adverse effects (AEs) such as on-target anemia (CD47 antibodies tend to induce hemagglutination) continue to plague the development of anti-CD47 antibodies.
- ADG153 is a masked anti-CD47 antibody and has shown strong antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) activity in both hematologic and solid tumor indications. Preclinical data showed that ADG153 IgG1 is well-tolerated, did not induce human hemagglutination, and significantly reduced anemia. ADG153 had an 8% decrease in red blood cell counts, compared to 49% decrease with magrolimab, the class-leading antibody (Gilead, Phase III in AML 1L and MDS 1L).[5,6]
- Adagene is preparing to submit an IND for ADG153 during 2022.

Next-gen cytokine-mediated therapy (SOT101) with selective binding to T and NK cells may have a better AE profile and enhanced efficacy

- SOT101 is a fusion protein and agonist containing IL-15 and the Sushi+ domain of IL-15Rα. It selectively binds to cytotoxic T and NK cells while avoiding other cell types thus reducing AEs and optimized half-life will likely improve efficacy by limiting T-cell exhaustion. SOT101 has demonstrated strong preclinical efficacy in various tumor models. It showed an increase in long-term survival and tumor regression as well as a favorable toxicology profile. SOT101 has also demonstrated potential for a combination approach with checkpoint inhibitors and ADCC monoclonal antibodies.
- Sotio presented the interim results of Phase I AURELIO-03 study of SOT101 in combination with pembrolizumab for patients with advanced metastatic tumors. Clinical benefit was observed in 12 of 16 patients (CR = 1 and PR = 4) with a favorable safety profile. The majority of treatment-emergent adverse events were Grade 2 or less and transient. No added safety signals were observed by combining SOT101 with pembrolizumab compared to SOT101 monotherapy. More mature data from the Phase I study will confirm the efficacy and safety profile.[7]

Next-gen CD137 agonist, ADG206, may further increase antitumor activity with better safety

- CD137 agonists enhance antitumor immunity mediated by cytotoxic T lymphocytes. Urelumab, the lead drug within the class (BMS), has shown modest efficacy but liver inflammation-related side effects plague its development.[8] To achieve improved safety and efficacy, the next-gen CD137 agonist, ADG206, uses precision masking of antigen-binding sites that get activated in the TME. In addition, T-cell response and antitumor activity of ADG206 is further enhanced by incorporating Fc mutations with increased FcγR-mediated cross-linking.
- At AACR, Adagene presented data from preclinical models and showed that ADG206 (monotherapy) had 4 times stronger antitumor activity as compared to Urelumab. Adagene is preparing to submit an IND or equivalent filing for ADG206 in 2022.[9]

References

1. N. P. Taylor. Incyte Wipes Out Late-phase Epacadostat Program After Pivotal Failure of Keytruda Combination. Fierce Biotech. May 1, 2018.
2. N. P. Taylor. Bristol-Myers Squibb drops phase 3 trials of $800M IDO drug. Fierce Biotech. May 1, 2018.
3. IO Biotech. IO Biotech Corporate Presentation. Last updated on May 3, 2022.
4. J. W. Kjeldsen, C. L. Lorentzen, E. Martinenaite, et al. High clinical efficacy in poor prognosis patients with metastatic melanoma treated with an IDO/PD-L1 peptide vaccine in combination with nivolumab [ABS#CT535]. In: AACR 2022; April 8-13; New Orleans, LA. Available at: https://www.abstractsonline.com/pp8/#!/10517/presentation/20274.
5. Adagene. Adagene Presents Data Demonstrating First and Best-in-Class Potential for Differentiated Preclinical Antibody Candidates at American Association for Cancer Research (AACR) Annual Meeting 2022. Accessed April 8, 2022.
6. B. Cai, A. N. Nguyen, S. Zheng, et al. ADG153-G1, a highly differentiated anti-CD47 IgG1 SAFEbody, demonstrates potent in vivo anti-tumor activities with enhanced ADCC/ADCP effects and significantly reduced RBC-related and antigen sink liabilities [Abs# 4257 / 16]. In: AACR 2022; April 8-13; New Orleans, LA. Available at: https://www.abstractsonline.com/pp8/#!/10517/presentation/16968.
7. S. Champiat, A. Marabelle, V. Galvao, et al. SOT101, an IL-2/IL-15 Rβγ superagonist, in combination with pembrolizumab in patients with advanced solid tumors: Interim safety and efficacy results from the AURELIO-03 dose escalation trial [Abs# CT040]. In: AACR 2022; April 8-13; New Orleans, LA. Available at: https://www.abstractsonline.com/pp8/#!/10517/presentation/20383.
8. H. Zhang, D. He, M. Zhang, et al. Evaluation of efficacy and toxicity of CD137 immunotherapy with urelumab-mIgG1 chimeric antibody in CD137 HuGEMM™. J Immunother Cancer. 2020;8(Suppl 3):A1–A559
9. G. Liu, Z. Dai, J. Qu, et al. ADG206, an anti-CD137 agonistic POWERbody™ with tailor-made efficacy and safety profiles by strong crosslinking and tumor selective activation for single and combinational cancer immunotherapy [Abs# 2868 / 11]. In: AACR 2022; April 8-13; New Orleans, LA. Available at: https://www.abstractsonline.com/pp8/#!/10517/presentation/16901

Please Contact:
John.L'Ecuyer@smartanalyst.com

GLOBAL HEADQUARTERS
(New York, USA)
285 Madison Ave
22nd Floor, New York
NY 10017
Mobile: +1 (646) 852-5097

EUROPE
(London, UK)
1.04 Power Road Studios
114 Power Road, Chiswick
London W3 5PY
Mobile: +44-(0)-752-163-8242
Mobile: +44-(0)-772-574-4296

ASIA PACIFIC
(Gurgaon, India)
First Floor, DLF Plaza Tower
DLF Qutub Enclave, DLF City
Phase-I, Gurgaon 122002
Haryana, India
Tel: 91-124-4313800