Adagene Presents Two Posters with New Insights on Increased Therapeutic Index for Masked Anti-CTLA-4 SAFEbody® ADG126 (Muzastotug) and Data Reinforcing Clinical Safety and Efficacy for ADG126 as Monotherapy and in Combination with Anti-PD-1 Therapy at Society for Immunotherapy of Cancer (SITC) 39th Annual Meeting

November 7, 2024

- Improved safety and efficacy profiles for ADG126 versus ipilimumab driven by precision masking, novel epitope-dependent antibody-dependent cellular cytotoxicity (ADCC) and partial CTLA-4 blockade -

- Clinical data show benefit of combining immune checkpoint inhibitors in MSS CRC and essential role of CTLA-4 to prime PD-L1 pathway -

- Clinical poster selected by SITC as a 'Top 100' abstract out of 1439 regular abstracts -

SAN DIEGO and SUZHOU, China, Nov. 07, 2024 (GLOBE NEWSWIRE) -- Adagene Inc. ("Adagene") (Nasdaq: ADAG), a company transforming the discovery and development of novel antibody-based therapies, today announced data at the SITC 39th Annual Meeting, taking place in Houston, Nov. 6 – 10, 2024. The two poster presentations provide new insights on the increased therapeutic index (TI) for ADG126 and reinforce its clinical safety and efficacy profiles in combination with pembrolizumab* including in advanced Metastatic Microsatellite-stable (MSS) Colorectal Cancer (CRC).

"CTLA-4 has an essential role in harnessing the immune system to improve outcomes for patients with cold and PD-L1 low or negative tumors, and CTLA-4 inhibition has been shown to prime T cells contributing to enhanced combination therapy activity," said Daneng Li, MD, Associate Professor in the Department of Medical Oncology & Therapeutics Research at the City of Hope Comprehensive Cancer Center, and a study investigator. "With its increased therapeutic index (TI), ADG126 has demonstrated in clinic that a unique epitope and masking technology can be deployed to deplete CTLA-4 mediated intratumoral T regulatory cells (Tregs), as anti-PD-1 alone has a minimum effect."

In the first poster, *Deciphering Improved Clinical Therapeutic Index (TI) of Muzastotug (ADG126), a Masked Anti-CTLA-4 SAFEbody® over its Unmasked Form (ADG116) as Monotherapy or in Combination with anti-PD-1 Therapy (toripalimab),* data demonstrate how the improved TI of ADG126 allows for higher and repeat dosing to unleash its efficacy to the maximum potential, while maintaining an improved safety profile. Analyses of the masked ADG126 SAFEbody and its unmasked version, ADG116, show the improved TI relative to commercially available anti-CTLA-4 therapies (e.g., ipilimumab) via enhanced epitope-dependent ADCC and T cell priming. By targeting the constitutively over-expressed CTLA-4 on T regulatory cells (Tregs) in the tumor microenvironment (TME) for potent CTLA-4 mediated intratumoral Treg depletion, ADG126 achieves tumor-specific targeting with minimal on-target off-tumor toxicities.

Key highlights include:

- The unique epitope of ADG126 and its activated form (ADG116) drives species cross-reactivity enabling the same antibody to be used across mice, monkey and human studies, with a unified set of physiologically relevant parameters for population pharmacokinetic (PK) modeling. Analyses show a significantly higher and sustained steady state tumor-specific engagement of CTLA-4 with the masked ADG126, suggesting increased exposure in the TME and a stronger ADCC effect.
- New analyses show the seamless translation of preclinical PK analyses to clinical PK data, including:
    - head-to-head comparison of ADG126 to ipilimumab in MC38 mice (colon cancer model), a single dose of ADG126 showed a three-fold increased active (e.g., cleaved) drug exposure in homogenized tumor tissue samples at 10 mg/kg versus a single dose of ipilimumab at 1 mg/kg while maintaining similar plasma active drug exposures.
    - A second analysis in the MC38 mice model showed two consecutive doses of ADG126 at 20 mg/kg increased the tumor cleaved and total PK versus a single dose, demonstrating continuous intratumoral cleavage of intact ADG126 and accumulation within the TME. This reflects the effectiveness of ADG126 repeat dosing to increase drug exposure within the TME, supporting its mechanism with CTLA-4 mediated intratumoral Treg depletion.

The second poster, *Phase 1b/2, Multicenter Dose Escalation and Expansion Study of Muzastotug (ADG126, a Masked Anti-CTLA-4 SAFEbody®) in Combination with Pembrolizumab in Advanced/Metastatic MSS CRCs*, presents additional follow up data from an ongoing trial showing the best-in-class therapeutic potential of ADG126 in combination with anti-PD-1 therapy in patients with the most common form of colorectal cancer, MSS CRC.

The trial, conducted in patients with advanced MSS CRC without liver metastases, showed that ADG126 administered at 10 mg/kg Q6W or Q3W in combination with pembrolizumab (200 mg/Q3W) demonstrated an encouraging efficacy signal, durable disease control and an early survival benefit in MSS CRC patients, with dose-dependent efficacy and objective responses per RECIST criteria observed for the Q3W schedule.

New findings in the poster at SITC 2024 include:

- In MSS CRC patients, a lower rate of key TRAEs (i.e., diarrhea, colitis, etc.) with ADG126 at the 10 mg/kg dosing level in combination with pembrolizumab relative to lower doses of 1-2 mg/kg of an Fc engineered anti-CTLA-4 antibody in clinical development when used in combination with anti-PD-1. Clinical PK, particularly the monitoring of active species of ADG126 in peripheral blood, supports long-term safety of the combination therapy.

- The rate of Grade 3 and higher TRAEs for ADG126 in combination with pembrolizumab was also shown to be much lower than historically reported with currently approved standard of care combinations. In the combination cohort, there was no Grade 3 or higher colitis, which is common with other anti-CTLA-4 therapies.
- A case study of one responder who received two prior lines of therapy before receiving ADG126 in combination with pembrolizumab showed an 80% decrease in target lesions (50 mm at baseline). This confirmed partial response (PR) correlated with a 100% decrease in carcinoembryonic antigen (CEA) levels versus baseline. Individualized PK data also demonstrated the correlation of tumor shrinkage and plasma exposure. After five cycles, the patient experienced TRAEs, after which dosing was modified and treatment resumed, showing durable clinical benefit for over 12 months. This response is one of four PRs reported from the ongoing 10 mg/kg Q3W combination cohort of MSS CRC patients without liver metastases (n=24).
- Repeat doses of ADG126 10 mg/kg in combination with pembrolizumab shows encouraging dose-dependent clinical efficacy and well-tolerated safety in accordance with plasma cleaved ADG126 concentrations. These data support that ADG126 may be a potential best-in-class anti-CTLA-4 and may be considered as a backbone therapy.

Follow up continues for MSS CRC patients treated with ADG126 10 mg/kg doses in combination with pembrolizumab. In addition, Adagene is evaluating a single dose of ADG126 at 20 mg/kg followed by a 10 mg/kg Q3W maintenance dose in combination with pembrolizumab in a cohort of 12 enrolled patients with data expected in 2025.

Poster Presentation Details
Both posters can be viewed during SITC on Saturday, November 9 at the George R. Brown Convention Center (Level 1, Exhibit Halls AB). They will also be available on the Publications page of the company's website here.

About Adagene
Adagene Inc. (Nasdaq: ADAG) is a platform-driven, clinical-stage biotechnology company committed to transforming the discovery and development of novel antibody-based cancer immunotherapies. Adagene combines computational biology and artificial intelligence to design novel antibodies that address globally unmet patient needs. The company has forged strategic collaborations with reputable global partners that leverage its SAFEbody® precision masking technology in multiple approaches at the vanguard of science.

Powered by its proprietary Dynamic Precision Library (DPL) platform, composed of NEObody™, SAFEbody, and POWERbody™ technologies, Adagene's highly differentiated pipeline features novel immunotherapy programs. The company's SAFEbody technology is designed to address safety and tolerability challenges associated with many antibody therapeutics by using precision masking technology to shield the binding domain of the biologic therapy. Through activation in the tumor microenvironment, this allows for tumor-specific targeting of antibodies in tumor microenvironment, while minimizing on-target off-tumor toxicity in healthy tissues.

Adagene's lead clinical program, ADG126 (muzastotug), is a masked, anti-CTLA-4 SAFEbody that targets a unique epitope of CTLA-4 in regulatory T cells (Tregs) in the tumor microenvironment. ADG126 is currently in phase 1b/2 clinical studies in combination with anti-PD-1 therapy, particularly focused on Metastatic Microsatellite-stable (MSS) Colorectal Cancer (CRC). Validated by ongoing clinical research, the SAFEbody platform can be applied to a wide variety of antibody-based therapeutic modalities, including Fc empowered antibodies, antibody-drug conjugates, and bi/multispecific T-cell engagers.

For more information, please visit: https://investor.adagene.com.
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Safe Harbor Statement
This press release contains forward-looking statements, including statements regarding certain clinical results of ADG126, the potential implications of clinical data for patients, and Adagene's advancement of, and anticipated preclinical activities, clinical development, regulatory milestones, and commercialization of its product candidates. Actual results may differ materially from those indicated in the forward-looking statements as a result of various important factors, including but not limited to Adagene's ability to demonstrate the safety and efficacy of its drug candidates; the clinical results for its drug candidates, which may not support further development or regulatory approval; the content and timing of decisions made by the relevant regulatory authorities regarding regulatory approval of Adagene's drug candidates; Adagene's ability to achieve commercial success for its drug candidates, if approved; Adagene's ability to obtain and maintain protection of intellectual property for its technology and drugs; Adagene's reliance on third parties to conduct drug development, manufacturing and other services; Adagene's limited operating history and Adagene's ability to obtain additional funding for operations and to complete the development and commercialization of its drug candidates; Adagene's ability to enter into additional collaboration agreements beyond its existing strategic partnerships or collaborations, and the impact of the COVID-19 pandemic on Adagene's clinical development, commercial and other operations, as well as those risks more fully discussed in the "Risk Factors" section in Adagene's filings with the U.S. Securities and Exchange Commission. All forward-looking statements are based on information currently available to Adagene, and Adagene undertakes no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as may be required by law.

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