



Molecular Partners Presents Preclinical Proof-of-Concept for CD3 Switch-DARPin T Cell Engager, Clinical Biomarker Analyses for MP0317 at SITC 2024

November 7, 2024

Preclinical proof-of-concept data supports the potential of CD3 Switch-DARPin platform to activate and boost T cells in the presence of tumor targets only

MP0317's ability to activate CD40 in a variety of tumor types further evidenced by comprehensive clinical biomarker analyses

ZURICH-SCHLIEREN, Switzerland and CONCORD, Mass., Nov. 07, 2024 (GLOBE NEWSWIRE) -- [Molecular Partners](#) AG (SIX: MOLN; NASDAQ: MOLN), a clinical-stage biotech company developing a new class of custom-built protein drugs known as DARPin therapeutics ("Molecular Partners" or the "Company"), today announced the presentation of data pertaining to two programs, including preclinical proof-of-concept for a novel T cell engager Switch-DARPin in solid tumors, and comprehensive biomarker analyses from the completed Phase 1 clinical trial of MP0317. Posters will be presented at the 2024 Annual Meeting of the Society for Immunotherapy of Cancer (SITC), being held November 8–10 in Houston, TX, with the following details:

Title: *Unlocking precision: a next generation multi-specific CD3 Switch-DARPin with enhanced function to tackle the current limitations of T cell engagers in ovarian cancer*

Abstract & Poster Number: 842

Title: *Comprehensive biomarker analyses from a Phase 1 study reveals marked tumor microenvironment modulation in patients with advanced solid tumors treated with MP0317, a FAP-localized CD40 agonistic DARPin*

Abstract & Poster Number: 612

Timing & Location: November 9, 2024 at 9 am – 8:30 pm CT; Exhibit Halls AB

Both posters will be made available on Molecular Partner's website in the [Scientific Documents section](#).

"Our Switch-DARPin platform provides a novel approach to tumor-localized T-cell engagement and costimulation through its logic-gated on/off Switch mechanism. We are excited to have the opportunity to add this MoA to our validated CD3 T cell engager approach," said Patrick Armstutz, Ph.D., CEO of Molecular Partners. "We hope to open therapeutic avenues for co-stimulating T-cell engagers, by rendering them silent in the circulation and activating them at the tumor site."

CD3 Switch-DARPin: Preclinical proof-of-concept for T cell engager with enhanced function in solid tumors

The Switch-DARPin platform provides a logic-gated "on/off" function (the "Switch") to multispecific DARPin candidates leading to immune activation only in the presence of defined antigens. This allows targeting the immune activation to tumors, increasing both efficacy and safety and opening up new opportunities for cancer treatment. T cell engagers (TCE) are a powerful class of immuno-oncology therapies but have faced a range of challenges such as high toxicity and limited specificity, particularly against solid tumors. By employing a multi-specific Switch-DARPin, Molecular Partners aims to bring additional dimensions of safety and potency to the fundamental TCE mechanism.

The data to be presented at SITC provide further validation of the Company's Switch-DARPin platform and preclinical proof-of concept that conditional T cell activation in solid tumors is feasible, as exemplified in preclinical ovarian cancer models. The presented multi-specific Switch-DARPin molecule comprises DARPins targeting:

1. CD3, to engage and activate T cells
2. CD2, a co-stimulator of CD3 on T cells
3. Mesothelin, a notable tumor antigen overexpressed across several cancer types, including ovarian cancer, and used as anchoring target for the Switch-DARPin
4. And the Switch-DARPin, which binds either to the tumor antigen EpCAM or to the CD3 DARPin mentioned above. In a default state, the whole molecule is in closed state (or Switched off), masking the CD3 DARPin and preventing immune activation. When tumor antigens mesothelin and EpCAM are present, the Switch-DARPin "switches" to bind EpCAM instead of the CD3 DARPin, thereby freeing the CD3 DARPin and allowing it to bind and activate T cells. T cell activation is further enhanced through co-stimulation by the CD2 DARPin.

This CD3 Switch-DARPin molecule effectively induces potent tumor regression *in vivo*, with reduced cytokine release, a significant toxicity event for TCEs in the clinic, compared to an unmasked CD3 with CD2 co-stimulation. In addition, co-engagement of CD2 leads to sustained T cell activation and cytotoxic capacity. Finally, masking of CD3 prevents T cell activation in the absence of tumor antigens, hence potentially allowing for "silent" TCEs outside of tumors. Taken together, masking CD3 may reduce the risk of CRS and provide a better safety profile to TCEs.

MP0317: Comprehensive biomarker data further support CD40 activation locally in tumor microenvironment

MP0317 is a CD40 agonist designed to activate immune cells specifically within the tumor microenvironment (TME) by anchoring to fibroblast activation protein (FAP) which is expressed in high amounts in the stroma of various solid tumors. This tumor-localized approach has the potential to

deliver greater efficacy with fewer side effects compared to systemic CD40-targeting therapies.

The poster presents the results of a comprehensive biomarker analyses from the completed Phase 1 multi-center, open label, dose-escalation trial of MP0317 monotherapy in patients with advanced solid tumors. The research further demonstrates the ability of MP0317 to induce a targeted, tumor-localized CD40 activation and its suitability for Q3W (every three weeks) and Q1W (weekly) dosing. The CD40 pathway is activated in a broad-spectrum of cancer types and various tumor locations. Evidence of TME remodeling in patients treated with pharmacologically active doses is exemplified by increases in dendritic cells, M1 macrophages, plasma cells, and T follicular helper cells, as well as IFN γ downstream activation and an increased dendritic cell maturation gene signature score. Peripheral pharmacodynamic effects aligned with the MP0317 mode of action are also seen, including increases in CXCL10 chemoattractant, transient B-cell reduction, and activation in blood.

Molecular Partners is in discussion with leading academic centers regarding potential investigator-initiated combination trials of MP0317.

About DARPin Therapeutics

DARPin (Designed Ankyrin Repeat Protein) therapeutics are a new class of custom-built protein drugs based on natural binding proteins that open new dimensions of multi-functionality and multi-target specificity in drug design. The flexible architecture, intrinsic potential for high affinity and specificity, small size and high stability of DARPins offer benefits to drug design over other currently available protein-based therapeutics. DARPin candidates can be radically simple, with a single DARPin unit acting as the delivery vector to a specific target; or multispecific, with the possibility of engaging more than five targets, and combining multiple and conditional functionalities in a unique DARPin drug candidate. The DARPin platform is designed to be a rapid and cost-effective drug discovery engine, producing drug candidates with optimized properties and high production yields. DARPin therapeutics have been clinically validated across several therapeutic areas and developed through to the registrational stage.

About Molecular Partners AG

Molecular Partners AG is a clinical-stage biotech company pioneering the design and development of DARPin therapeutics for medical challenges other drug modalities cannot readily address. The Company has programs in various stages of pre-clinical and clinical development, with oncology as its main focus. Molecular Partners leverages the advantages of DARPins to provide unique solutions to patients through its proprietary programs as well as through partnerships with leading pharmaceutical companies. Molecular Partners was founded in 2004 and has offices in both Zurich, Switzerland and Concord, MA, USA. For more information, visit www.molecularpartners.com and find us on LinkedIn and Twitter/X [@MolecularPrtnrs](https://twitter.com/MolecularPrtnrs)

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Any statements contained in this press release that do not describe historical facts may constitute forward-looking statements as that term is defined in the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation: implied and express statements regarding the clinical development of Molecular Partners' current or future product candidates; expectations regarding timing for reporting data from ongoing clinical trials or the initiation of future clinical trials; the potential therapeutic and clinical benefits of Molecular Partners' product candidates and its RDT and Switch-DARPin platforms; the selection and development of future programs; Molecular Partners' collaboration with Orano Med including the benefits and results that may be achieved through the collaboration; and Molecular Partners' expected business and financial outlook, including anticipated expenses and cash utilization for 2024 and its expectation of its current cash runway. These statements may be identified by words such as "aim", "expect", "guidance", "intend", "outlook", "plan", "potential", "will" and similar expressions, and are based on Molecular Partners' current beliefs and expectations. These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements. Some of the key factors that could cause actual results to differ from Molecular Partners' expectations include its plans to develop and potentially commercialize its product candidates; Molecular Partners' reliance on third party partners and collaborators over which it may not always have full control; Molecular Partners' ongoing and planned clinical trials and preclinical studies for its product candidates, including the timing of such trials and studies; the risk that the results of preclinical studies and clinical trials may not be predictive of future results in connection with future clinical trials; the timing of and Molecular Partners' ability to obtain and maintain regulatory approvals for its product candidates; the extent of clinical trials potentially required for Molecular Partners' product candidates; the clinical utility and ability to achieve market acceptance of Molecular Partners' product candidates; the potential that Molecular Partners' product candidates may exhibit serious adverse, undesirable or unacceptable side effects; the impact of any health pandemic, macroeconomic factors and other global events on Molecular Partners' preclinical studies, clinical trials or operations, or the operations of third parties on which it relies; Molecular Partners' plans and development of any new indications for its product candidates; Molecular Partners' commercialization, marketing and manufacturing capabilities and strategy; Molecular Partners' intellectual property position; Molecular Partners' ability to identify and in-license additional product candidates; unanticipated factors in addition to the foregoing that may impact Molecular Partners' financial and business projections and guidance; and other risks and uncertainties that are described in the Risk Factors section of Molecular Partners' Annual Report on Form 20-F for the fiscal year ended December 31, 2023, filed with Securities and Exchange Commission (SEC) on March 14, 2024 and other filings Molecular Partners makes with the SEC. These documents are available on the Investors page of Molecular Partners' website at www.molecularpartners.com. In addition, this press release contains information relating to interim data as of the relevant data cutoff date, results of which may differ from topline results that may be obtained in the future. Any forward-looking statements speak only as of the date of this press release and are based on information available to Molecular Partners as of the date of this release, and Molecular Partners assumes no obligation to, and does not intend to, update any forward-looking statements, whether as a result of new information, future events or otherwise.