LBA – 004 Phase 2 study results of murlentamab, a monoclonal antibody targeting the Anti-Mullerian-Hormone-Receptor II (AMHRII), acting through Tumor-Associated Macrophage engagement in advanced/metastatic colorectal cancers

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Introduction: Membranous expression of AMHRII is present in about 80% of colorectal adenocarcinomas. Murlentamab is a glycoengineered mAb binding with high affinity both AMHRII on the tumor cell membrane and CD16 via its low-fucose Fc on macrophages, inducing phagocytosis. Murlentamab reprograms TAMs, restoring their antitumoral functions, also resulting in cytotoxic T lymphocyte activation.

Methods: Patients with pretreated advanced/metastatic colorectal adenocarcinoma, measurable disease, performance status $\leq$1, adequate organ function, baseline tumor biopsy, and agreeing to a subsequent biopsy under treatment, received murlentamab single agent (SA) or in combination with trifluridine/tipiracil (FTD/TPI) in two parallel non-randomized cohorts.

Antitumor activity (objective response by RECIST 1.1, Tumor Growth Rate (TGR), progression-free survival (PFS), overall survival), pharmacodynamics (circulating immune cells and tumor microenvironment) and safety were to be assessed in 30 patients (15 in each cohort) evaluable for efficacy (having completed at least two 28-day cycles of treatment and with at least one tumor assessment under treatment).

Results: Thirty-nine heavily pretreated patients were enrolled and received murlentamab, SA or in combination with FTD/TPI. Fourteen patients in SA and 15 patients in combination with FTD/TPI (after a median of 4 and 2 prior therapy lines, respectively) were evaluable for efficacy. No objective responses were observed. A 1.7-fold and 3.6-fold TGR decrease was observed with murlentamab SA and murlentamab combined with FTD/TPI, respectively.

In the murlentamab SA cohort, 21% (3/14) of patients were progression-free at 2 months. In combination with FTD/TPI, 53% (8/15), 40% (6/15) and 31% (4/13) of patients were progression-free at 2, 4 and 6 months, respectively. Among patients with more than 20% AMHRII-positive tumor cells, 5/6 and 3/4 patients were stabilized at 4

and 6 months, respectively. In contrast, the 7 patients progressing at their first tumor evaluation (2 months) had less than 20% of AMHRII-positive tumor cells.

In the 7 paired biopsies analyzed, tumor microenvironment immune activation (staining positive area increase) under murlentamab was observed: CD16 in 6/7 tumors reflecting macrophage activation; granzymeB/CD16 co-localisation in 5/7 tumors reflecting phagocytosis. In the paired biopsies from 2 patients stabilized at 4 months in combination with FTD/TPI, CD86 on antigen presenting cells and CD8 on T cell increased, reflecting activation.

In the peripheral blood (samples from 20 patients analyzed), a significant activation of monocytes (CD69+) and neutrophils (CD64+) was observed under murlentamab SA and in combination with FTD/TPI.

No serious adverse events related to murlentamab were reported. All 36 reported murlentamab toxicities experienced by 10 patients in combination with FTD/TPI cohort were G1-2, the most common being: decreased appetite (9 events), vomiting, nausea, constipation and asthenia (3 events each). No overlapping toxicities were observed when combining murlentamab with FTD/TPI.

Conclusion: This pilot study suggests longer than expected PFS for murlentamab and FTD/TPI in advanced mCRC, especially in patients with high AMHRII expression. Immune activation of the macrophage / cytotoxic T cell cascade was observed in tumor microenvironment as well as in peripheral blood. These results together with murlentamab's innovative immunological mode of action support its further development in combination with standard chemotherapies and/or immunological agents in colorectal cancers.