Claudin 18.2-Targeted Immunotherapy: a landscape analysis of stakeholders, drug modalities, pipeline and business opportunities

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and available for binding of targeted monoclonal antibodies, and CLDN18.2 expression is maintained in gastric cancers and gastric metastases (reviewed by Türeci, 2019).

Pellino et al. (2021) evaluated the immunohistochemical profile of CLDN18 in a real-world and mono-institutional series of gastric (n=280) and gastro-esophageal (n=70) carcinomas. The association of CLDN18 expression with clinicopathological features and survival outcomes was investigated. Cases were dichotomized according to a cut-off of 2+ or 3+ intensity in ≥75% of the tumor cells, which is the IHC cut-off being used for eligibility in ongoing zolbetuximab studies. High membranous CLDN18 expression (2+ and 3+ intensity ≥75%) was found in 117/350 (33.4%) tissue samples analyzed. CLDN18 expression correlated with age <70 ($p = 0.0035$), positive EBV status ($p = 0.002$), high stage (III, IV) at diagnosis ($p = 0.003$), peritoneal involvement ($p < 0.001$) and lower incidence of liver metastases ($p = 0.013$). CLDN18 did not correlate with overall survival.

A recent tissue microarray study from the same institution including a large series of 523 primary gastric carcinomas (GCs; n = 408), gastroesophageal carcinomas (GECs; n = 115) and 135 matched and synchronous nodal metastases, detected high claudin expression in 29.4% of patients with primary GCs/GECs (Coati, 2019). High membranous CLDN18 expression was present in 150/510 (29.4%) primary cases and in 45/132 (34.1%) metastases. An abnormal expression (i.e. nuclear and/or cytoplasmic) was observed in 115 (22.5%) primary cases and in 33 (25.0%) metastases. A 38.8% of the cases showed significant CLDN18 intratumoral variability among the different tissue microarray cores obtained from the same tumor. Positive membrane CLDN18 expression was statistically associated with non-antral GCs ($p = 0.016$), Lauren diffuse type ($p = 0.009$), and with EBV-associated cancers ($p < 0.001$).

CLDN18 moderate-to-strong membranous expression was always observed in non-neoplastic gastric mucosa. In cancer cells, CLDN18 was considered as positive only if membranous staining was present.

Overall, <u>any</u> CLDN18 expression was present in the 61.6% (327/510) of primary cases and in 55.3% (73/132) of nodal metastases. <u>High</u> CLDN18 expression (i.e. *H*-score >51) was present in the 29.3% (150/510) of primary cases and in 34.1% (45/132) of nodal metastases.

In 108/510 (21.2%) primary tumors, only a <u>weak</u> (i.e. 1+) CLDN18 expression was observed, and only 26 (5.1%) of these cases were classified as high CLDN18 tumors. <u>Moderate</u> (i.e. 2+) membranous staining was observed in 101/510 (19.8%), whereas <u>strong</u> CLDN18 expression

each product for ex-China development and commercialization. The first product candidate from the collaboration to enter clinical studies was IBI345, an IgG-based universal "modular" CLDN18.2-targeting CAR T-cell product candidate. IBI389 is Innovent's proprietary recombinant bispecific monoclonal antibody targeting CLDN18.2 and CD3, discovered and developed by Innovent. Innovent did not disclose whether IBI389 is based on Roche's TCB technology.

7.2 Other Biopharmaceutical Companies outside of China with CLDN18.2 Programs

Ten small biopharmaceutical companies headquartered outside of China with a stake in the field of claudin 18.2 have been identified, described and analyzed (Table 4). Seven of the ten companies are based in North America (six US companies and one Canadian/US company). Two South Korean companies are active in the CLDN18.2 field and only one European biotech company, headquartered I the Czech Republic is developing an anti-CLDN18.2 ADC.

The ten companies have 14 CLDN18.2 assets based on nearly equally distributed drug modalities: three naked antibodies, three ADCs, three BiTEs, two T-cell based construcs and three other bispecific antibodies with 4-1BB or CD47 as second target. The companies hold global rights for their CLDN18.2 assets except Elevation Oncology and Leap Therapeutics which acquired ex-China rights from CSPC Pharmaceutical Group. SOTIO licensed ADC technology from NBE Therapeutics to generated the SOT102 ADC. The CLDN18.2 assets from TORL Biotherapeutics are based on work conducted at the University of California Los Angeles.

Table 4a: Overview of Other Biopharmaceutical Companies outside of China with CLDN18.2 Programs

Company	HQ	Drug Code / INN	Drug Modality	Origin / Rights	R&D Phase
ABL Bio	S-Korea	Givastomig	4-1BB bsAb	Partnered with I-Mab Biopharma / global	I (US & China)
Abpro	USA	ABP-150	BiTE	In house / global	0
CARTEXEL	S-Korea	CLDN18.2 CAR-T	CAR T-cells	mAb from Integral / global	Preclinical
Elevation Oncology	USA	SYSA1801 (EO-3021)	ADC	CSPC Pharma / global ex-China	I (China)
Integral Molecular	USA	High-affinity mAbs	Naked mAb	In house / global	Preclinical
			BiTE	In house / global	Preclinical
Leap Therapeutics	USA	NBL-015	Fc-modified mAb	CSPC Pharma / global ex-China	I
		NBL-016	4-1BB bsAb		Preclinical

"strong" or "enhanced" ADCC and ADCP or CDC, but without benchmarking with zolbetuximab. The Fc functions ADCC and CDC of SPX-101 and GB7004 are claimed to be better than those of zolbetuximab, but without disclosure of the mechanism of action.

8.4.1 Clinical Experience with Anti-CLDN18.2 Naked Monoclonal Antibodies

In the previous paragraph, the benchmark pivotal clinical study results of zolbetuximab were described, Briefly, in the active comparator controlled SPOTLIGHT trial, zolbetuximab treatment showed a significant reduction in the risk of disease progression or death compared with placebo (hazard ratio [HR] 0.75, 95% CI 0.60-0.94; p=0.0066). The median progression-free survival was **10.61 months** (95% CI 8.90-12.48) in the zolbetuximab group versus **8.67 months** (8.21-10.28) in the placebo & mFOLFOX group. Zolbetuximab treatment also showed a significant reduction in the risk of death versus placebo (HR 0.75, 95% CI 0.60-0.94; p=0.0053). Overall survival was significantly improved (median **18.23** vs **15.54 months**, HR 0.750, *P*=0.0053).

In the active comparator controlled GLOW trial, zolbetuximab plus CAPOX reduced the risk of progression or death by **31.3%** (n=507; hazard ratio [HR]=0.687; [95% confidence interval [CI]: (0.544-0.866)]; p=0.0007) compared to placebo plus CAPOX. Median PFS was **8.21 months** (95% CI: 7.46–8.84) in the treatment arm and **6.80 months** (95% CI: 6.14–8.08) in the placebo & CAPOX arm. Zolbetuximab plus CAPOX significantly prolonged overall survival (OS) reducing the risk of death by 22.9% (HR=0.771; 95% CI: 0.615-0.965; p=0.0118). Median OS was **14.39 months** (95% CI: 12.29-16.49) and **12.16 months** (95% CI: 10.28-13.67) for the treatment arm and placebo arm, respectively.

Osemitamab

Transcenta presented progression free survival (PFS) data by CLDN18.2 expression level from the Phase I/II study in China (Cohort C of TranStar102) of Osemitamab plus Capecitabine and Oxaliplatin (CAPOX) as first-line treatment of advanced gastric/gastroesophageal junction (G/GEJ) cancer which will support the upcoming global Phase III pivotal trial. A proprietary Claudin18.2 companion diagnostic assay has also been developed to support patient screening in the pivotal trial. Pivotal trial material has been manufactured and cleared by regulatory agencies such as the U.S. FDA and the Center for Drug Evaluation (CDE) in China. CLDN18.2 positive was required, which is defined as IHC membrane staining ≥10% tumor cells with ≥1+ intensity per LDT assay, selecting approximately 55% of the screened patients.

9.2.3 CARTEXEL

Cartexell is a subsidiary of Helixmith, that researches and develops CAR-T cell therapies against solid tumor. Cartexell developed a proprietary new CAR-T 2.0 technology, which controlls CAR-T cells and reinforce its anti-cancer activity. CAR-T 2.0 technology expresses a functional gene to block immune checkpoints, enhance infiltration of T cell, increase recruitment of immune cells or improve survival of T cell as well as CAR gene in T-cells concomitantly. Cartexell possesses multiple CAR-T cell therapy candidates targeting solid tumors.

Helixmith was established in 1996 and is headquartered in Seoul, South Korea. The company was previously known as Byromedica Pacific Co until 1999 when it was renamed to Viromed until 2019.

In September 2022, Integral Molecular licensed a panel of monoclonal antibodies (MAbs) to CARTEXELL, enabling CARTEXELL to develop chimeric antigen receptor (CAR)-T cell therapies using Integral Molecular's CLDN18.2 MAbs (Press Release Sep 15, 2022).

Under the terms of the agreement, Integral Molecular will provide an exclusive worldwide license to CARTEXELL to use the panel of high-affinity, high-specificity, and fully humanized CLND18.2 MAbs for the development of CAR-T cell therapies against solid tumors including gastric, lung, pancreatic and esophageal cancers. CARTEXELL will be solely responsible for all research, development, and commercial activities.

9.2.4 Elevation Oncology

Based in New York, Elevation Oncology is an innovative oncology company focused on the discovery and development of selective cancer therapies to treat patients across a range of solid tumors with significant unmet medical needs.

In July 2022, CSPC Pharmaceutical Group entered into an exclusive license agreement with Elevation Oncology, Inc., a biopharmaceutical company in the U.S., to out-license the development and commercialization rights outside of Greater China of the Group’s SYSA1801 project (Claudin 18.2 ADC) (Press Release July 28, 2022). CSPC has received an upfront payment of US$ 27 million and is also eligible to receive up to US$ 148 million in potential development and regulatory milestone payments and up to US$ 1.02 billion in potential sales milestone payments, as well as royalties up to double-digit percent of sales. SYSA1801 is currently being evaluated by CSPC in a Phase 1, dose-escalation clinical trial in

In the dose escalation phase, six dose levels (0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, 20 mg/kg and 30 mg/kg, Q3W) of MIL93 were conducted for assessment. Accelerated titration was adopted for the first 2 dose levels, and the 3+3 design was used afterwards. In the dose expansion phase, patients with CLDN18.2-positive cancers received the selected RP2D. The primary objectives were the safety and tolerability, dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of MIL93. Secondary objectives included pharmacokinetics, immunogenicity and preliminary efficacy.

At the data cut-off date (August 9, 2022), 30 patients were enrolled from 6 centers in China. MIL93 was well-tolerated for the dosages tested (0.3 mg/kg through 30 mg/kg Q3W). DLT was observed in one patient during the 3-week window at 30 mg/kg. However, none of the three additional patients at 30 mg/kg had DLT, and MTD has not been reached. In further expansion study nine additional patients were enrolled into the expansion phase at the 20 mg/kg Q3W dose and 3 patients were enrolled into the dose escalation at the 10 mg/kg Q2W.

The most common TEAE occurring in ≥20% of patients were nausea (60%), hypoalbuminemia (46.7%), vomiting (43.3%), anemia (36.7%), hyponatremia (33.3%), hypocalcemia (23.3%), decreased appetite (23.3%), asthenia (23.3%), aspartate aminotransferase increased (20.0%). Serious adverse events (SAEs) were observed in nine (30%) patients, and MIL93-related SAEs occurred in six (20%) patients including hypoalbuminemia/hypoproteinemia, malnutrition, anorexia and vomiting. No treatment related Grade 4 or 5 event was reported (Huang, 2023.

Among the 25 patients who had at least one post-treatment radiological evaluation, two gastric cancer patients who progressed on multiple lines of therapies achieved a partial response (PR). The disease control rate (DCR) reached 44% (Huang, 2023).

10.1.12 NBL-015 / FL-301

NBL-015 is a fully human anti-Claudin 18.2 monoclonal antibody optimized through protein engineering to achieve enhanced antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), and antibody dependent cellular phagocytosis (ADCP) effects. NBL-015 was discovered by US-based Novarock Biotherapeutics, a indirectly hold subsidiary of Chinese major pharmaceutical company CSPC Pharmaceutical Group.

NBL-015 is a fully human antibody generated from Tranni transgenic mouse and is predicted to bear with low development and immunogenicity risks (Lei, 2020). NBL-015 demonstrates

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