Xintela

Healthcare

12 July 2021

Advancing integrins as innovation engine

Xintela, backed by its integrin biomarker technology platform XINMARK, is a potential disrupter in the regenerative stem cell and oncology areas. Initial targets are osteoarthritis (OA), glioblastoma (GBM) and triple negative breast cancer (TNBC), all areas with significant unmet need. 2021 could be a transformational year with an expected start for a Phase I/IIa trial for OA and the planned spinoff of the oncology arm. ARDS optionality in the COVID-19 world presents an outside opportunity too. Potential deals or partnerships in animal OA and oncology are near-term triggers.

Integrin-based platform provides competitive edge

With a focus on 'off-the-shelf' adipose derived allogeneic mesenchymal stem cells (MSCs), Xintela's competitive advantage stems from its integrin α10β1 biomarker platform, which facilitates the selection of a homogeneous preparation of MSCs (forming the stem cell therapy platform XSTEM), providing greater differentiation capacity and ability to home to damaged cartilage, as well as consistency (both functional and regulatory advantages). A GMP-certified facility provides the company with full control and flexibility in the manufacturing of XSTEM. The biomarker is also found to be expressed in a number of 'aggressive' tumours where Xintela's antibody-based immunotherapy platform XINMAB presents a potential add-on to current standard of care.

Targeting areas with c $10bn commercial potential

OA, GBM and TNBC have all been the focus of significant R&D by the industry but there has been limited success in delivering effective treatment options. Current OA treatments offer only symptomatic relief (they do not halt disease progression), creating a sizeable opportunity for a potential disease-modifying OA drug (DMOAD), a void avidly eyed by Xintela. A first-in-class targeted antibody therapy in the chemotherapy-dominated GBM space carries significant potential too.

2021 to be a year of validation

With preclinical trials complete and the crucial GMP certification achieved (May 2021), timely commencement of the clinical Phase I/IIa knee OA study and successful conclusion of the planned Targinta spin-off (potentially unlocking untapped value) should be the next catalysts for Xintela. Concerns around funding needs have been alleviated to a degree by the SEK28m directed share issue in June 2021, with the company seeking to secure various forms of long-term financing for both Xintela and Targinta.

Historical financials

Year end	Revenue (SEKm)	PBT (SEKm)	EPS (SEK)	DPS (SEK)	P/E (x)	Yield (%)
12/17	0.0	(21.9)	(0.79)	0.0	N/A	N/A
12/18	1.6	(26.3)	(0.83)	0.0	N/A	N/A
12/19	5.7	(38.1)	(1.10)	0.0	N/A	N/A
12/20	14.9	(36.6)	(0.68)	0.0	N/A	N/A

Source: Company filings

Price	SEK2.30
Market cap	SEK205m

Share price graph

Share details

Code	XINT
Listing	Nasdaq First North Growth
Shares in issue	89.1m
Net cash at 31 March 2021	SEK15.5m

Business description

Xintela is a Swedish preclinical-stage biotechnology company with focus on stem-cell based therapies and oncology, based on its proprietary integrin marker technology platform XINMARK. Its lead candidate is XSTEM-OA, an MSCs based treatment for osteoarthritis (OA), expected to commence Phase I/IIa trials in 2021. While the veterinary OA business is seeking out-licencing opportunities following proof of principle, the oncology business is being primed for a spin-off under subsidiary Targinta in 2021.

Bull

- Unique technology platform with first-in-class potential.
- Serving markets with high unmet need and significant commercial opportunity.
- Scope for expansion into other musculoskeletal and oncology indications.

Bear

- Difficulty securing funding for clinical trials.
- Challenges in finding partners/out-licensing opportunities.
- Regulatory hurdles in different geographies.

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Investment summary

Company description: Integrins driving therapeutic strategy

Xintela is a Swedish biotech company, founded in 2009 and listed on the Nasdaq First North Exchange since 2016. It is focused on stem cell-based regenerative solutions for degenerative joint diseases as well as targeted therapies for multiple indications in oncology. XINMARK, its technology platform, based on the biomarker integrin α10β1, is the cornerstone of the company's development programme. The marker technology is used to select high-quality therapeutic MSCs (XSTEM) and to direct specific therapeutic antibodies to aggressive tumours. We believe that this in-house developed technology platform provides Xintela with strong IP and is a key differentiating factor versus competing therapies in the target areas, based on data from preclinical studies. Another standout aspect is its focus on its own Good Manufacturing Practice (GMP)-certified facility (approved by the Swedish Medicinal Products Agency in May 2021). This is uncommon for a company the size of Xintela and while expensive at first, this strategy could pay off in the near term, by affording greater flexibility and reducing both time and cost associated with the production process. The company is employing a two-pronged strategy in its path to commercialisation. While for its lead candidate XSTEM-OA (selected allogeneic, adipose tissue derived MSC based treatments) the plan is to independently take it to proof of concept (Phase I/IIa trials planned in 2021 for knee OA), the other programmes – EQSTEM and CANISTEM (OA in horses and dogs, respectively) and XINMAB (oncology) – have the potential to be monetised much sooner, immediately following proof of principle. If successful, this should materially reduce Xintela's financial burden.

Financials: Funded to execute its 2021 plans

Xintela is currently in pre-revenue stage and has been funding its operations through equity issues and bridge loans. Since listing in March 2016, the company has raised c SEK240m in equity, including SEK50m from a private placement with German orthopaedic player Bauerfeind in 2018 (its largest current shareholder with a c 19% stake). This is against an average annual cash burn of c SEK30–35m in the past three years, including the group contribution to Targinta. We note that the Q121 cash burn was unusually high (SEK26.7m), but this can be partially attributed to the company paying off its SEK10.9m bridge loan facility (taken as part of working capital) and should therefore be transitory. The net cash balance at the end of the Q121 stood at SEK15.5m, which has been strengthened further by a SEK28m equity injection in June 2021. These funds may potentially be sufficient to initiate the Phase I/IIa trials for XSTEM and conclude the spin-off of Targinta, although subsequent rounds of funding would be required to complete the clinical trials. Xintela has indicated that it is continuously working to secure various forms of long-term financing for both Xintela and Targinta and may seek partnerships in veterinary and oncology spaces to de-risk the pipeline.

Sensitivities: Risks typical to a development stage biotech

Xintela's risks are typical to an early-stage biotech: development, regulatory and financing risks dominate. The biggest near-term sensitivity is related to the company's flagship programme, XSTEM, given its upcoming clinical trial in knee OA patients, expected to start in 2021. The ability to finance the trial is paramount to successful execution and timely completion of the study. Moreover, XSTEM, by virtue of being a cell-based therapy, is termed as an advanced therapy medicinal product (ATMP), which is governed by a stringent and complex regulatory environment compared to other biologics and small molecule drugs. Gaining approval and subsequent reimbursement status will require the company to meet rigorous standards. Moreover, the targeted oncology areas, by nature, are highly risky and treatment resistant with the company likely to face serious competition from big pharma. Fostering partnership deals and/or out-licensing opportunities will also be critical.

Unique integrin marker technology, multiple applications

Xintela specialises in stem cell-based therapies (with an initial focus on OA) and targeted therapies for oncology indications, underpinned by its technology platform, XINMARK. The platform is based on the biomarker integrin α10β1, a cell surface protein initially discovered on cartilage cells by Xintela's CEO Evy Lundgren-Åkerlund in 1998. The integrin family are cell surface receptors that facilitate the interaction/adhesion between cells and the extracellular matrix. Integrin α10β1 was subsequently found to be expressed in both MSCs and 'aggressive' forms of tumours. In the stem cell therapy programme, the marker technology works by selecting high-quality MSCs with specific antibodies, forming the patented therapeutic stem cell platform XSTEM. In the oncology programme, the marker technology works by directing specified antibodies to target aggressive tumour cells (either through inhibiting tumour migration and proliferation or by introducing a cytotoxin to the cancer cell to induce cell death). Targeted antibodies for the platform are largely being developed in-house with a set of own antibodies as well as human antibodies in-licensed from Bioinvent.

The lead candidate, XSTEM-OA, is an MSC product for OA in humans under development and preparing to enter clinical trials (Phase I/IIa) in H221. A patent application covering XSTEM (product and method) was approved by the European Patent Office in March 2021. The approval covers all uses of XSTEM for therapeutics or prevention in Europe (including veterinary indications) and confers protection through 2038. The stem cells for the study will be produced in the company's own GMP facility, which the company claims will both assure full control and flexibility and reduce costs of the clinical study (running costs are likely to be lower than outsourced production). The plan is to go solo for the Phase I/IIa study and out-license following proof of concept, with the goal of maximising value. With its proof of principle results in the horse study the company is ready to discuss partnerships with animal health companies regarding the veterinary (an area with a less rigid regulatory environment and shorter route to the market) products EQSTEM and CANISTEM.

The COVID-19 pandemic has encouraged the company to repurpose its platform to explore treatment for acute respiratory distress syndrome (ARDS), a life-threatening lung disease affecting severely ill COVID-19 patients. Following promising results from an early preclinical study (improved lung function in a pig model), the project received an additional SEK2.3m grant from the Swedish R&D funding agency Vinnova in April 2021 (the SEK1m grant was received earlier) to advance the study further. Xintela is also planning to expand XSTEM's applicability to chronic wounds where the company claims promising wound healing capability (less scarring, healed tissue more 'normal' looking) in a preclinical, pig model study conducted in collaboration with The Burn Center at Linköping University Hospital.

The oncology application XINMAB, which commenced development in 2015, is currently being investigated for GBM and TNBC, with the company considering both antibody-drug conjugates (ADC) and function-inhibiting antibodies as potential treatment options. Vinnova has granted SEK2m in funding for glioblastoma research. Given the scale of the market, the company has ongoing plans to establish the oncology segment as an independent entity under its wholly owned subsidiary Targinta. The goal is to spin-off Targinta in 2021. To this effect, the company has been identifying a new management team for the business. In December 2020, industry veteran Jeffrey Abbey was appointed senior management advisor for Xintela and in May 2021, Per Norlén was recruited as Targinta's CEO (effective September 2021). A summary of Xintela's programmes is listed in Exhibit 1 below.

Exhibit 1: Xintela key assets

Product	Cell source/type	Indication	Market	Delivery method	Status	Comments
XSTEM - OA	Selected Allogeneic MSC, Adipose derived	OA	Human	Intra-articular injection	Phase I/IIa in 2021	Phase I/IIa likely in H221 in knee OA in Australia, plan to out-license after proof-of-concept
XSTEM - ARDS	Selected Allogeneic MSC, Adipose derived	ARDS	Human	Intravenous injection	Preclinical	Plan to complete preclinical studies in 2021
XINMAB-GBM	ADC/ Function-blocking antibody	Glioblastoma	Human	N/D	Preclinical	Planned spin-off in 2021, followed by out-licensing/partnership for clinical development
XINMAB-TNBC	ADC/Function-blocking antibody	TNBC	Human	N/D	Preclinical	Planned spin-off in 2021, followed by out-licensing/partnership for clinical development
EQSTEM	Selected Allogeneic MSC, Adipose derived	OA	Veterinary (horse)	Intra-articular injection	Preclinical	Seeking partners to support clinical development and commercialisation plans
CANISTEM	Selected Allogeneic MSC, Adipose derived	OA	Veterinary (dogs)	Intra-articular injection	Preclinical	Seeking partners to support clinical development and commercialisation plans

Source: Company filings, Edison Investment Research. Note: ADC – Antibody-drug conjugate.

Harnessing MSCs' multipotent promise…

The regenerative properties of MSCs are being investigated in a range of diverse indications such as cardiovascular diseases, musculoskeletal disorders, oncology, diabetes, immune disorders and central nervous system (CNS) disorders. MSCs are multipotent (have the ability to differentiate into various cell types) and can be extracted from different sources, including bone marrow, adipose tissue, dental pulp, synovium, muscle and other tissues (Exhibit 2).[1] Adipose tissue derived MSCs (AT-MSCs) have been gaining traction as they yield 500x more MSCs than bone marrow (BM-MSCs) and are easier to aspirate.[2] Moreover, AT-MSCs can be sourced from discarded adipose deposits from liposuction clinics – versus BM-MSCs, which need to be specially drawn from donors – an advantage from an ethical point of view. They also display similar characteristics and gene expression to BM-MSCs and while somewhat inferior typically in terms of differentiation into chondrocytes (cartilage cells) and osteoblasts (bone cells), they compensate by having a higher proliferation rate (cell division and growth). In addition, AT-MSCs have been found to have a higher immunomodulatory capacity than BM-MSCs.

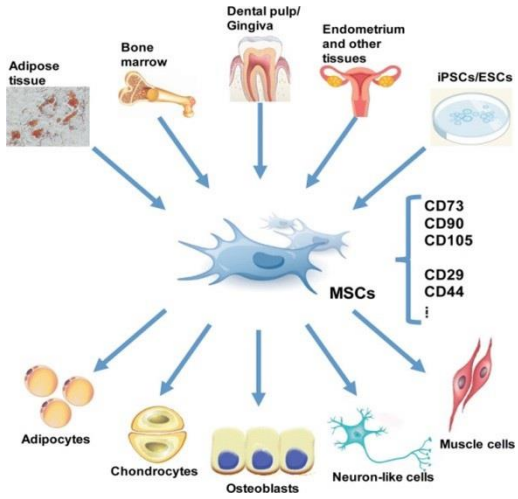
In addition to their regenerative potential, an exciting aspect of MSCs is their anti-inflammatory and immunomodulatory property, making them particularly promising in autoimmune and degenerative diseases such as OA. MSCs are termed 'immune-privileged' as they inhibit unwanted immune response by regulating immune cells (natural killer cells, cytotoxic T cells, macrophages). They also secrete signalling molecules (called secretome), which enhances their anti-inflammatory properties via improved communication between cells (paracrine activity)[3] (Exhibit 3).

1 Elahi, Kourosch C et al. Human Mesenchymal Stromal Cells from Different Sources Diverge in Their Expression of Cell Surface Proteins and Display Distinct Differentiation Patterns. *Stem cells international* vol. 2016

2 Debnath, T., & Chelluri, L. K. (2019). Standardization and quality assessment for clinical grade mesenchymal stem cells from human adipose tissue. *Hematology, transfusion and cell therapy*, 41(1), 7–16.

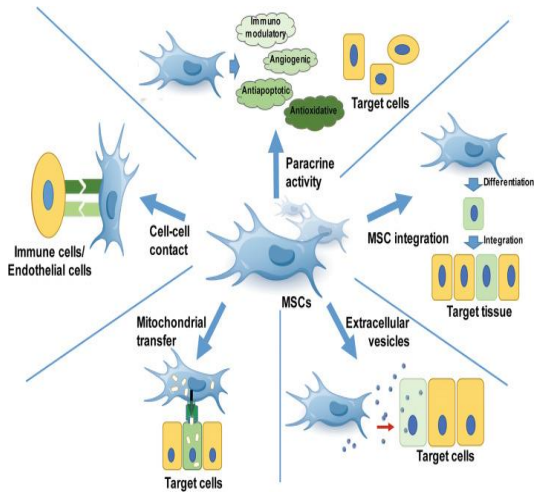
3 Fan, XL., Zhang, Y., Li, X. et al. Mechanisms underlying the protective effects of mesenchymal stem cell-based therapy. *Cell. Mol. Life Sci.* 77, 2771–2794 (2020)

Exhibit 2: MSC characteristics



Source: Fan, XL., Zhang, Y., Li, X. et al. Mechanisms underlying the protective effects of mesenchymal stem cell-based therapy. *Cell. Mol. Life Sci*. 77, 2771–2794 (2020). Note: MSC definition based on the three-point criteria laid down by the International Society for Cellular Therapy (ISCT).

Exhibit 3: MSC mechanism of action



Source: Fan, XL., Zhang, Y., Li, X. et al. Mechanisms underlying the protective effects of mesenchymal stem cell-based therapy. *Cell. Mol. Life Sci*. 77, 2771–2794 (2020).

…while circumventing the heterogeneity limitation

Despite their regenerative potential, one aspect that has impeded clinical progression in MSCs is their apparent heterogeneity resulting in non-uniformity in data/results between clinical studies. Features of MSCs can differ based on donor characteristics (both age and gender) and the underlying tissue used. Cell microenvironment and differences in cell isolation and expansion can also produce varied outcomes. This is the key reason why the robust preclinical data has not translated as strongly into clinical efficacy (while generally showing a high safety profile), with many late-stage trials failing to meet primary endpoints. With only 10 currently approved MSC therapies (out of >1,000 registered and c 300 completed trials),[4] the conversion rate remains low. These path-to-commercialisation issues highlight the need for more selective biomarkers to identify and isolate the required MSC cells. This will be required to meet the safety, efficacy and regulatory standards to qualify as an off-the-shelf ATMP treatment option. Xintela, with its integrin-based marker platform, could be well placed to bridge this gap and navigate the issue of MSC heterogeneity as well as differentiation potential in relation to BM-MSCs, provided these claims are validated in clinical trials.

XINMARK's homogenous solution…

Xintela offers a solution to the heterogeneity issue through its unique biomarker technology XINMARK, which uses specific antibodies to select integrin α10β1 expressing MSCs from the heterogeneous preparation of MSCs. These selected MSCs are expanded multi-fold in a culture and then cryopreserved for administration. Xintela presents a persuasive argument on the high differentiation capacity of integrin α10β1 selected MSCs, including into chondrocytes. Intuitively, therefore, bone and joint related disorders will be the primary focus for the management, with initial development work catering to OA, an area lacking in any currently approved disease modifying alternatives. The company's products under this platform include XSTEM-OA (OA in humans) and EQSTEM/CANISTEM (OA in horses/dogs).

In addition to promising MSC homogeneity, high differentiation capacity and consistency in quality between donors, the company also contends high immunomodulatory capacity and improved homing to damaged cartilage. These aspects were enunciated in two preclinical studies conducted by the company: 1) an in vitro study with selected equine stem cells; and 2) an in vivo study of post

4 Clinicaltrials.gov; search keywords – Mesenchymal stem cells (targeted search); additional criteria – completed.

traumatic OA in an equine model of impact-induced talar injury. More recently (in May 2021), the company reported observations from another preclinical animal model (conducted in association with Professor Casper Lindegaard at the Department of Veterinary Clinical Science at Copenhagen University), indicating that XSTEM contributes to repairing joint cartilage damage by differentiating into chondrocytes and producing new cartilage tissue (details to be published at a later date). This may strengthen XSTEM's case as a potential DMOAD.

…XSTEM poised to enter the clinic

Xintela's lead product candidate XSTEM-OA is an investigative MSC based treatment for OA, based on its stem cell platform XSTEM of integrin α10β1-selected MSCs. Unlike autologous therapies, XSTEM provides allogeneic 'off-the shelf' MSCs, which are cryopreserved until use. Moreover, MSCs extracted from a donor can be expanded homogeneously to treat multiple patients, suggesting significantly lower treatment costs. Xintela has positioned XSTEM as a one-shot treatment (intra-articular injection in the affected joint), a potential advantage when seeking reimbursement. However, given the paucity of marketed products, repeat administration every few years may be a more plausible scenario, in our opinion. A sense of the final treatment cost can be gauged from Regeneus's Progenza (another stem cell therapy for OA, currently in Phase II) which is targeting a reimbursement price of $5,000–7,000.[5] Another potential competitor, the anti-NGF product, Pfizer's Tanezumab, was anticipated to be priced at c $11,000 annually[6] but has since received a negative recommendation by the FDA advisory committee in March 2021.

By virtue of its regenerative capability, XSTEM-OA can be a DMOAD alternative to traditional pain alleviation therapies. With no currently approved DMOADs, the opportunity for the company is sizeable. A first clinical trial is planned to commence in H221 with an initial focus on knee OA. Moreover, with no significant safety issues highlighted for MSCs in preclinical studies, Xintela can directly proceed to a combined Phase I/IIa proof-of-concept study, which will analyse preliminary efficacy in addition to safety and tolerability of the treatment and administration. Given that the company plans to produce the stem cells for the study in its own facility, we estimate the earliest start date of H221 for the study with a total trial duration of 18–24 months.

While the details of the study structure and enrolment have not been disclosed yet, the decision to choose Australia as the study destination looks strategic. In addition to first-class logistics and a conducive regulatory environment, trial costs are significantly lower in Australia.[7] Moreover, it provides a gateway to key Asian markets, such as Japan, which passed laws back in 2014 (Safety of Regenerative Medicine ACT), allowing for fast-track approval (after Phase II) of cell-based therapies, provided efficacy is re-iterated in post-marketing studies. A look at currently approved MSC-based therapies highlight the Asia-dominated distribution (see Exhibit 4). Western economies have been tougher to break into as highlighted by Prochymal, which was approved in Canada and New Zealand in 2012 but is yet to be marketed (due to lack of reimbursement). However, the 2018 EU approval and subsequent reimbursement nod for TiGenix's/Takeda's Alofisel could herald a change in this sentiment.

5 www.bioworld.com/articles/496801-aussie-stem-cell-company-regeneus-out-licenses-progenza-to-kyocera-for-japan-market?v=preview

6

7 ww2.frost.com/frost-perspectives/australia-preferred-destination-early-phase-clinical-trials/

Exhibit 4: Approved MSC products as of 2020

Product	Company	Type	Indication	Approval
Queencell	Anterogen	Autologous, Adipose derived	Subcutaneous tissue defects	South Korea (2010)
Cellgram-AMI	Pharmicell Co.	Autologous, Bone marrow derived	Acute myocardial infarction	South Korea (2011)
Cartistem	Medipost	Allogeneic, Umbilical cord derived	Knee articular cartilage defects	South Korea (2012)
Cupistem	Anterogen	Autologous, Adipose derived	Crohn's fistula	South Korea (2012)
Prochymal (remestemcel-L)	Osiris Therapeutics/ Mesoblast	Allogeneic, Bone marrow derived	Graft-vs-Host disease	Canada (2012), New Zealand (2012)
Neuronata-R	Corestem	Autologous, Bone marrow derived	Amyotrophic lateral sclerosis	South Korea (2014)
TEMCELL	JCR Pharmaceuticals/Mesoblast	Allogeneic, Bone marrow derived	Graft-vs-Host disease	Japan (2015)
Stempeucel	Stempeutics Research PVT	Allogeneic, Bone marrow derived	Critical limb ischemia	India (2017)
Stemirac	Nipro Corp.	Autologous, Bone marrow derived	Spinal cord injury	Japan (2018)
Alofisel	TiGenix NV/Takeda	Allogeneic, Adipose derived	Complex perianal fistulas in Crohn's disease	Europe (2018)

Source: Edison Investment Research

A look at licensing deals in the space also highlights significant attention to cell-based therapies from Asian biopharmas. It also provides a sense of the kind of partnership terms Xintela can expect for XSTEM, although deal terms typically vary based on a product's clinical phase (see Exhibit 5).

Exhibit 5: Selected licensing deals in cell therapies

Date	Company	Partner	Cell type	Asset/ clinical phase	Indication	Deal value
November 2020	Mesoblast	Novartis	Mesenchymal stem cells	Remestemcel-L/ Phase II completed	ARDS	Worldwide rights - $25m upfront + $25m equity investment+ upto $1.25bn milestone payment+ double-digit royalties
August 2020	Regeneus	Kyocera	Mesenchymal stem cells	Progenza/ Phase I completed	Knee OA	Japanese rights - $9m upfront + $10m milestone payments+ double-digit royalties
September 2019	Cynata	Fujifilm	Mesenchymal stem cells	CYP-001/ Phase I completed	Graft-versus-host disease (GvHD)	Worldwide rights - $3m upfront + $4m milestone payments+ 10% royalties
July 2016	TiGenix	Takeda	Adipose-derived stem cells	Cx601/ Phase III	Complex perianal fistulas in Crohn's disease	Ex-US rights - €25m upfront+ €10m equity investment+ upto €355m milestone payment+ double-digit royalties
January 2016	Athersys	Healios	Multipotent Adult Progenitor Cells	Multistem/ Phase II completed	Ischemic stroke	Japanese rights - $15m upfront + $215m milestone payments+ double-digit royalties

Source: Company newsflow; Edison Investment Research

OA market in hunt of a DMOAD

OA is a degenerative joint ailment and is the most common form of arthritis, accounting for 50% of the total musculoskeletal disease burden. It is also estimated to be the fourth leading cause of disability worldwide. The onset of OA is generally associated with ageing, but other risk factors – obesity, trauma, occupational hazards (athletes, military personnel), lack of exercise, genetics and gender – predispose even younger population to its debilitating effects. According to the WHO, 9.6% of men and 18.0% of women aged over 60 years suffer from symptomatic OA.[8] In Europe 40 million people are affected by OA while the figure stands at 32.5 million in the US (c 240 million globally).

OA is characterised by the progressive deterioration or thinning of articular cartilage (covering over the bones providing lubrication and smooth movement of the joints), resulting in bones rubbing together leading to stiffness, pain, inflammation and decreased mobility. The disease most commonly affects the joints in the knees, hips, spine and extremities (hands and feet). The current treatment algorithm is often unsatisfactory, offering only palliative care (focus on reducing inflammation and pain management) without targeting the underlying structural deterioration. The standard of care begins with analgesics and nonsteroidal anti-inflammatory drugs (NSAIDS), followed by corticosteroids and opioids as the disease progresses. Some other options include intra-articular injections of Hyaluronic acid/viscosupplements (provides lubrication to joints) and antidepressant Duloxetine (Cymbalta) to treat chronic pain. However, none of these treatments have conclusively been shown to arrest or reverse the progression of the disease. Worse still, the earlier lines of treatment are also often contra-indicated for long-term use due to toxicity and serious cardiovascular and gastrointestinal side-effects (analgesics, NSAIDs), further cartilage

8 www.who.int/chp/topics/rheumatic/en/

erosion (corticosteroids) or habit-forming properties (opioids). In severe OA cases, the only option left is surgical joint replacement/arthroscopy. However, as the lifespan of the prostheses is limited (10–15 years), repeat surgery may be required in younger patients.

Under the present scenario, there is significant unmet need for a restorative therapy. Candidate DMOADs aim to fill this gap, seeking to regenerate the underlying structure, thereby improving clinical outcomes. However, there are no currently approved DMOADs, although a number of regenerative investigational therapies are in clinical development. Of these, MSC based therapies look to be the most promising, in terms of both safety and efficacy (see Exhibit 6).

Exhibit 6: Candidate DMOADs advance-stage pipeline

Company	Programme	Mechanism of action	Administration	Efficacy data, concluded studies			Status
				Pain relief	Cartilage improvement	Notes	
Cell-based							
Regeneus	Progenza	Patented MSC and secretome therapy	Intra-articular injection (single dose)	Positive	Positive	Statistically significant improvement in WOMAC* pain score and cartilage formation	Phase II successfully completed in March 2018. Signed out-licensing partnership with Kyocera in August 2020
Kolon/ Tissuegene	Invossa	Chondrocytes genetically modified to produce Transforming Growth Factor β1	Intra-articular injection (single dose)	Positive	Positive	Statistically significant improvement in pain and function. Indications of improved cartilage structure	Phase III trials to resume in the US after lifting of clinical hold in April 2020 for false ingredient claims
Stempeutics	Stempeucel	Bone-marrow derived allogeneic MSCs	Intra-articular injection (single dose)	Positive	Mild	Pain reduction statistically significant on WOMAC, VAS** and ICOAP** scores. Slight improvement in cartilage thickness	Phase III trial dates unavailable. Signed co-development agreement with Alkem Labs in February 2018
Cellular Biomedicine	AlloJoin	Allogeneic mesenchymal progenitor cells	Intra-articular injection (2 doses at 3-week interval)	Positive	Mild	Statistically significant improvement on WOMAC pain score; minor improvement in cartilage thickness	Phase II commenced in September 2019 in China
Cynata	CYP-004	MSCs using patented Cymerus technology platform	Intra-articular injection (3 injections over one year)	N/A	N/A	N/A	Phase III trials initiated in November 2020; designed to evaluate CYP-004's disease modifying potential
Others							
Samumed	Lorecivivint	Small-molecule CLK/DYRK1A inhibitor of the Wnt pathway	Intra-articular injection (single dose)	Mild	Positive	Improvement in WOMAC pain score not statistically significant. Cartilage regeneration positive	Phase III initiated in May 2019
Merck KGaA	Sprifermin	Recombinant human fibroblast growth factor-18	Intra-articular injection (administered every 6 to 12 months)	Mild	Positive	Cartilage regeneration positive in highest dose. Change in WOMAC pain score not statistically significant	Phase II successfully completed in October 2019. Seeking partners for Phase III
Paradigm Biopharma	Zilosul	Repurposed Pentosan Polysulfate Sodium (PPS)	Intra-muscular injections (6 injections across 3 weeks)	Positive	Positive	Statistically significant reduction in KOOS**** pain score. Positive results in inhibiting cartilage loss.	Phase IIb completed in 2018. Phase III to commence in Q2/Q321

Source: Company newsflow; Edison Investment Research. Note: *WOMAC: Western Ontario and McMaster Universities Arthritis Index; **VAS: Visual Analog Scale for Pain; ***ICOAP: Intermittent and Constant Pain Score; ****KOOS: Knee Injury and Osteoarthritis Outcome Score.

While DMOADs offer a compelling solution, the path to approval continues to involve risk, highlighted by the recent suspension/failure of some promising prospects such as Galapagos/Servier's ADAMTS-5 inhibitor GLPG1972 and Ampio's albumin-derived Ampion. Reimbursement is another issue to be cognisant of, but Alofisel's success in landing reimbursement status bodes well for other MSC-based therapies, such as the one Xintela is developing.

Rapidly growing addressable market

Rising life expectancy and increasing incidence of obesity means that the OA therapeutics market will continue to grow rapidly. According to Markets and Markets, the global OA market is expected to grow from $7.3bn in 2020 to $11bn in 2025, at a CAGR of 8.7%. The biggest chunk (c 75%) will be attributed to the US, while the EU5 and Japan will make up 15% and 10% of the opportunity, respectively. Knee OA is the predominant sub-set of the total OA market and is the focus of current clinical investigations.

According to the official Kellgren and Lawrence system, OA is classified into five severity grades, ranging from grade 0 (no OA, full joint function) to grade IV (severe OA with near complete cartilage erosion). Since XSTEM-OA has not undertaken clinical studies of its own yet, we cull our estimates of Xintela's target market from results of existing MSC trials. A 2020 study that evaluated over 20 clinical trials on MSC-based treatment for OA concluded that these therapies were most effective for grades II and III OA (mild-to-moderate),[9] when there is still some cartilage left to 'home' on to. This subset accounts for c 50% of all OA cases and is likely to be Xintela's addressable market, albeit a highly competitive one. The company is likely to face stringent competition from existing standard of care (NSAIDs; genericised market), alternate lines of treatments (such as viscosupplements/hyaluronic acid, for example Sanofi's Synvisc and J&J's Monovisc) and other novel therapies under development (such as platelet rich plasma-PRP). On the other hand, demonstrated efficacy in severe OA in clinical trials (a less crowded market and therefore a proportionately larger opportunity) could expand the market potential materially. Competition in this area was expected to come from anti-NGFs – Pfizer/Eli Lilly's Tanezumab and TEVA/Regeneron's Fasinumab – although a negative recommendation for Tanezumab from the FDA advisory committee in March 2021 on safety/toxicity concerns may ease the competitive threat for the likes of Xintela. Although Pfizer has indicated that it would continue to advance its talks with the FDA, the overwhelming 19:1 committee vote against Tanezumab reduces the chances of an eventual approval, in our view.

In terms of geographic focus, Japan and home market Europe are likely to be a key initial focus, the former due to its high incidence of OA (25.3 million people)[10] and a favourable regulatory and market environment for cell-based therapies. It is also demographically attractive, given the high proportion of geriatric population (>33% of population is above the age of 60).

EQSTEM, CANISTEM: Veterinary solutions to OA

Xintela's marker technology also finds application in the veterinary space, where the company is specifically focusing on therapeutic integrin α10β1selected allogeneic MSCs for horses (EQSTEM) and dogs (CANISTEM). In addition to the typical age and weight related reasons, trauma (due to racing/training/competing) is a main reason for OA in these animals. The prevalence of OA in equine and canine animals is much higher than humans, with surveys indicating that 25% of horses and 20% of dogs suffer from the debilitating effects of the disease. In fact, 60% of lameness issues in horses are attributed to OA. As in humans, the clinical symptoms are characterised by a progressive worsening of pain and joint function.

Traditional therapy options are also restricted to palliative care (pain and inflammation management), with NSAIDS and corticosteroid injections as the mainstays. Stem cell-based autologous therapies while available since 2003 for horses and 2007 for dogs, have been unable to find widespread traction, likely due to absence of both standardisation and reimbursement (autologous therapies have, until now, been exempt from regulatory rigours, being classified as in-

9 Ip H, Nath D, Sawleh S H, et al. (September 21, 2020) Regenerative Medicine for Knee Osteoarthritis – The Efficacy and Safety of Intra-Articular Platelet-Rich Plasma and Mesenchymal Stem Cells Injections: A Literature Review. *Cureus* 12(9): e10575

10 Yoshimura N. Epidemiology of osteoarthritis in Japan: the ROAD study. *Clinical Calcium*. 2011 Jun;21(6):821–825.

hospital treatments rather than medicinal biologics). Allogeneic MSCs therefore are a viable alternative, without the above-mentioned limitations of their autologous counterparts.

According to Grand View Research, the global veterinary pain management market is expected to grow from $1.15bn in 2018 to $1.74bn in 2026, a CAGR of 5.3%. The growth is attributed to the rising trend of pet adoption (68% of US households keep pets), increasing awareness of pet care and growing incidence of pet obesity (56% of pet dogs are obese in the US). The COVID-19 pandemic has also fuelled pet adoption as a means to companionship and reduced stress. OA is the largest segment, accounting for >70% of the market (c 15m dogs and c 2.5m horses have been diagnosed with OA in the US). Increasing penetration of regenerative therapies should fuel the market growth further.

It is reasonable to assume that Xintela's exposure to the animal OA space could allow it a faster market entry (vs for humans) given the relatively flexible regulatory environment with the possibility of smaller and expedited clinical trials. With two allogeneic MSC-based therapies already approved in Europe for horses – 1) Boehringer Ingelheim's/GST's chondrogenic induced peripheral blood-derived Arti-Cell Forte (approved in April 2019) and 2) Equicord's umbilical cord derived Horstem (approved in June 2019) – the prospects seem high for other similar therapies in the pipeline. There are currently no approved canine MSC-based products although clinical studies are underway.

Xintela's strategy is to develop and commercialise the veterinary products in partnership with animal health companies. A minor use minor species (MUMS) designation status in Europe for EQSTEM (granted in 2018), should afford greater negotiation power with potential partners due to a lower regulatory overhang. According to management guidance, a clinical trial is likely to commence once a partner is on-board.

XSTEM-ARDS: Creating opportunity out of adversity

The anti-inflammatory and immunomodulatory properties of MSCs have also been acknowledged in ARDS associated with COVID-19. ARDS is a serious respiratory condition, characterised by fluid build-up in the air sacs that prohibits the lungs from filling up with air, causing oxygen deprivation in the bloodstream. This leads to shortness of breath, low blood pressure and eventual organ failure, if not controlled in time. ARDS typically afflicts patients who are already critically ill, as is the case with severe COVID-19. The SARS-CoV-2 virus, once it reaches the respiratory tract, triggers a hyperactive immune response leading to a cytokine storm, inflammation and pneumonia, which can manifest into ARDS. According to studies, 42% of COVID-19 patients with pneumonia go on to develop ARDS, with 61–81% of those requiring ICU care. COVID-19 ARDS has been observed to have worse outcomes compared to ARDS from other causes with mortality ranging from 65.7–94.0% for those on ventilator support.[11] Typical ARDS mortality rate stands at 34–40%.

While antivirals (remdesivir) and other drugs (corticosteroid dexamethasone, convalescent plasma) have being examined as potential treatments (with varied degrees of success), MSC-based therapies have attracted significant interest, particularly due to their anti-inflammatory and immunomodulatory properties. Several trials are underway, with encouraging data from early studies (reduced mortality, less ICU time). However, replication of these robust results in large-scale studies continues to be tricky, as highlighted by the recent Phase III failure of Mesoblast's MSC-based treatment for ARDS (related to COVID-19 and otherwise).

Xintela has also completed a preclinical study utilising XSTEM-ARDS in a pig model of ARDS, claiming promising results (improved lung function and stabilised blood circulation), although details are currently unavailable. The company argues that its platform's ability to maintain purity and consistency of stem cell preparations accords it an advantage over peers in terms of efficacy and regulatory compliance. Notwithstanding these claims, it is difficult to ascribe a value to Xintela's

11 Gibson, Peter G et al. COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. *The Medical Journal of Australia* vol. 213,2 (2020): 54–56.e1. doi:10.5694/mja2.50674

ARDS opportunity at this stage related to COVID-19, given that the uptake may be affected by the effectiveness of the COVID-19 vaccines across the various strains of the virus, However, ARDS from causes other than COVID-19 is also a possible focus for XSTEM-ARDS as the medical need for these patients remains significant.

GMP facility a risk mitigator?

Given the promising preclinical and early-stage headline data for MSC-based therapeutics, we believe the low success/conversion rate can be partially attributed to issues in the handling and processing side of the supply chain, particularly while scaling up the production process. Research suggests that c 80% of early-stage cell therapy companies outsource their manufacturing from pre-investigational new drugs through stage II studies. This could potentially mean less flexibility and control over processing cell samples and the resultant quality and consistency thereof. By virtue of having its own GMP manufacturing facility, Xintela should be able to realise the benefits of its early investment (although the scale-up and running costs have not been disclosed publicly) in the form of complete control of the manufacturing process as well as the associated time and cost savings. With stem cells for its upcoming clinical trials supplied from its own facility, the company can ensure better oversight on quality/consistency of its products during the trials, potentially enhancing the prospects of a favourable outcome. Moreover, given that there are only a handful of cell therapy players with their own GMP facility, having this tangible asset should help Xintela garner interest from potential investors and partners.

Another benefit of having its own manufacturing facility and one that could be monetised quickly is the option of contract manufacturing (although we note that Xintela's manufacturing capacity is currently undisclosed). The influx of cell and gene therapies in trials (c 1,100 clinical trials underway at the end of 2020)[12] has pushed up the demand for contract manufacturing materially. The 130 certified contract development and manufacturing organisations (CDMOs) servicing the cell and gene therapy innovators are small-scale (the market is fairly fragmented).[13] Capacity therefore is limited, with ramping up a time-consuming process. This creates a vital opportunity for Xintela, should it decide to go down that path. The need to gain capacity has also fuelled major M&A activity in this space, with some big-ticket deals in the last couple of years, concluded at significant premiums (Exhibit 7).

Exhibit 7: Recent acquisitions in the CDMO/CMO space

Announcement date	Acquirer	Target	Deal value	EV/sales multiple	EV/EBITDA multiple
February 2021	Charles River Laboratories	Cognate BioServices	$875m	NA	NA
November 2019	Recipharm	Consort Medical	$650m	NA	NA
August 2019	Fujifilm Diosynth Biotechnologies	Biogen's biomanufacturing facility	$890m	NA	NA
April 2019	Catalent	Paragon Bioservices	$1.2bn	6x	>20x*
March 2019	Thermo Fisher	Brammer Bio	$1.7bn	7x	>20x*

Source: Edison Investment Research. Note: *Results Healthcare 'Outsourced Pharmaceutical Manufacturing 2020'.

Optimising the oncology opportunity

Within oncology, Xintela is employing its biomarker technology, XINMARK, to develop antibody-based first-in-class targeted therapies (XINMAB) for aggressive tumours, with initial focus on GBM and TNBC, both areas with significant unmet need. The antibodies will target Xintela's in-house biomarker, integrin α10β1, which the company asserts is highly expressed in aggressive tumour types. There are two products under development:

1. **Antibody-Drug Conjugates (ADCs):** Cell toxin attached to an antibody; this works by utilising the antibody to deliver a cytotoxic load to the tumour cell, inducing cell death.

12 Alliance for Regenerative Medicine

13 www.pharmasalmanac.com/articles/visualizing-the-future-of-contract-development-and-manufacturing-for-cell-and-gene-therapies

2. **Function-blocking antibodies:** These antibodies inhibit certain functions related to the integrin α10β1, such as tumour cell viability, migration and proliferation, leading to suppressions of tumour growth.

In addition to GBM and TNBC, integrin α10β1 is found to be expressed in other aggressive cancers, including prostate, pancreatic and lung cancer, indicating opportunity for expansion into other indications. The company has received approval from both Europe and the US patent offices for its patent application on antibody treatment of GBM using integrin α10β1 (protection until 2036, once granted). This patent also covers other cancers of the CNS. Given the scope and scale of the oncology business and the level of oversight required (both in terms of funding and intellectual capital), the goal is to spin-off the segment in 2021 under fully owned subsidiary Targinta.

The GBM landscape

GBM is the most invasive malignant form of brain tumour, defined as a grade IV glioma by the WHO. It is also the most common, accounting for over 50% of all gliomas and >15% of all brain tumours (primary and metastatic).[14] Latest figures from the American Cancer Society peg the incidence of brain and other nervous system cancer in the US at 24,530. The corresponding figure stands at 64,600 for Europe and 156,200 for Asia. More than half of these are GBM cases. 120,000 deaths per year globally are attributed to GBM, highlighting the aggressive nature of the cancer.[15] According to Global Data, the GBM therapeutics market is expected to grow from $662m in 2017 to $1.4bn in 2027 across the US, EU5, Japan and China at a CAGR of 7.5%.

Unlike most other cancers, the GBM treatment modality is severely restricted, with only three drugs currently approved for treatment: Temozolomide (chemotherapy), bevacizumab (anti-VEGF monoclonal antibody; not approved in Europe) and Nitrosourea/gliadel wafer (chemotherapy). The present standard of care for newly diagnosed cases comprises maximal surgical resection of the tumour (complete resection is extremely difficult) followed by radiotherapy and chemotherapy with Temozolomide. Bevacizumab (Avastin) is additionally prescribed in recurrent GBM and although it has shown increased progression fee survival (PFS), overall survival (OS) remains unchanged. Even with treatment, the average survival rate stands at just 15 months (four months without treatment) with a five-year survival rate of c 5%.

Despite these aggressive therapeutic regimens, the cancer relapses for a majority of patients within a few months. Therapeutic challenges for GBM arise from its molecular heterogeneity as well as the difficulty in drug delivery across the blood-brain barrier (BBB), particularly for large molecule drugs. GBM tumours can be made up of different tumour cell types; glioblastoma stem-like cells (GSCs) are one highly tumorigenic cellular subtype, believed to be responsible for treatment resistance and cancer reoccurrence. They also express a variation of biomarkers (see Exhibit 8), an example being MGMT, which, if unmethylated, negates the therapeutic effects of Temozolomide. In addition to the commonly tested biomarkers, a number of other molecular biomarkers, including integrins, are under evaluation as targeted therapies for GBM.

Exhibit 8: Common biomarkers for glioblastoma

Name	Expression	Primary glioblastoma*	Secondary glioblastoma**
MGMT	Methylated	36%	75%
EGFR	Amplified/mutated	30–60%	8%
TP53	Mutated	28%	65%
PTEN	Mutated	25%	4%
CDKN2A	Deleted	31–78%	8%
IDH1	Mutated	5%	75%

Source: Wojciech Szopa et al., Diagnostic and Therapeutic Biomarkers in Glioblastoma: Current Status and Future Perspectives. *BioMed Research International.* February 2017. Note: *80–90% of GBM cases; originates from glial cells. **Progresses from lower-grade astrocytoma; slower growing and less aggressive than primary GBM.

14 www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Glioblastoma-Multiforme

15 Globocan 2018

Given the challenging GBM space, the risk/reward trade-off for under development therapeutics remains high. Recent failure of promising therapies such as BMS's checkpoint inhibitor Opdivo and AbbVie's EGFR targeting ADC Depatux-M are indicators of this difficult-to-treat disease. Currently, seven drugs are in late-stage clinical trials, with BMS's proteasome inhibitor Marizomib expected to report headline Phase III data in late 2022. Several other therapies in are early-stage trials.

Xintela's early promise in GBM

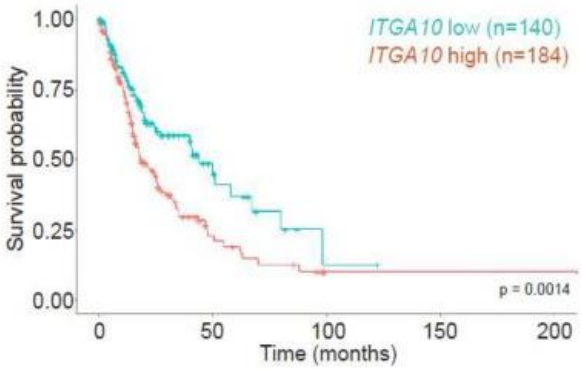
With studies highlighting the role of GSCs in the tumour's aggressiveness, therapies targeting this sub-population are potentially attractive. Integrins, which are overexpressed in GSCs, have been a focus of multiple studies due to their involvement in cell migration, proliferation and angiogenesis in GBM tumours. Xintela has reported promising results from its preclinical studies investigating integrin α10β1 as a therapeutic target in GBM. The company investigated two different aspects: 1) expression levels and role of integrin α10β1 in patient extracted GBM tissue and cells; and 2) the effect of integrin α10β1 targeting ADC (using saporin as the cytotoxin) on GBM cells (in-vitro) and in a xenograft mouse model (in-vivo). The study concluded that integrin α10β1's distribution increased with higher grades of gliomas, with negligible expression on normal brain cells (Exhibit 9). Moreover, it was also observed that survival probability increased with lower level of integrin α10β1 expression in tumours (based on analysing ITGA10 gene expression using the cancer genome atlas (TCGA) for gliomas) (see Exhibit 10).

Exhibit 9: Integrin α10β1 expression by glioma grades

		Integrin α10 IHC score			
Tissue	case no.	0	1	2	3
Normal	3	100%	0%	0%	0%
LGG	5	20%	60%	20%	0%
HGG	15	13,3%	33,3%	33,3%	20%

Source: Xintela, Lundgren-Åkerlund et. al. Integrin α10, a Novel Therapeutic Target in Glioblastoma, Regulates Cell Migration, Proliferation, and Survival. *Cancers* 2019, 11, 587. Note: Scoring of the labelling intensity of the tissues was 0 (negative), 1 (weak), 2 (moderate), and 3 (strong).

Exhibit 10: Survival probability corresponding to integrin α10β1 expression



Source: Xintela, Lundgren-Åkerlund et. al. Integrin α10, a Novel Therapeutic Target in Glioblastoma, Regulates Cell Migration, Proliferation, and Survival. *Cancers* 2019, 11, 587. Note: Kaplan–Meier curve comparing the overall survival probability of glioma patients (astrocytoma grade II, n = 59; astrocytoma grade III, n = 116; and GBM n = 149) with low vs. high ITGA10 mRNA levels.

The in-vitro studies demonstrated that the integrin α10-specific ADC induced cell death in human GBM cells. In contrast, a non-specific control ADC did not affect the viability of human GBM cells, showing that the cytotoxic effect was due to specific targeting of integrin α10.The in vivo study on a mouse xenograft model using human GBM cells also demonstrated that the integrin α10β1 specific ADC-induced cell death of the GBM cells. In this model, the ADC was administered intratumorally or intraventricularly, suggesting that the potential issue of poor BBB penetration of an ADC may be overcome by local administration resulting in a more effective treatment. However, intratumoral administration comes with its own set of challenges including consistency of drug volume distribution as well as the overall invasiveness of the procedure. The ability of Xintela's large molecule ADC to overcome these challenges and showcase efficacy will now need to be ascertained in clinic trials on humans.

In December 2019, Xintela announced that its under development function-blocking antibody also significantly suppressed the growth of GBM tumours in-vivo, reiterating the potential for the targeted therapy. The results were published in the scientific journal, Cancers. in March 2021.[16]

The company received a SEK2m grant from Vinnova (the highest sanction amount available) in March 2020 to identify an optimal ADC candidate for the treatment of GBM and other aggressive cancers. This preliminary data should provide Xintela adequate grounds to initiate and support discussions with potential partners for further development and commercialisation. It also allows the company to apply for an orphan-drug designation for its ADC and the benefit of exclusivity that comes with it.

TNBC another potential opportunity

In June 2020, Xintela announced its plans to expand its oncology franchise to include TNBC, the most aggressive form of breast cancer, accounting for 10–15% of all diagnosed breast cancer cases but a disproportionately higher number of the deaths.[17] The decision was based on positive preclinical results using function-blocking antibodies in cell lines and a validated tumour model. According to the International Agency for Research on Cancer, 2.3 million new breast cancer cases were diagnosed in 2020 globally, including 345,000 cases of TNBC (c 42,000 and c 60,000 cases in the US and Europe, respectively). According to Global Data the TNBC therapeutics market in eight major markets is expected to be worth over $2.1bn by 2025, growing at a CAGR of 11.3% between 2015 and 2025.[18]

TNBC is characterised by a high degree of metastases and probability of relapse. It is called triple negative because it does not contain any of the three receptors commonly found in breast cancer: hormones oestrogen and progesterone and the protein human epidermal growth factor (HER2). Because the cancer cells lack these proteins, treatment options are limited. Breast cancer mainstays, hormone therapy and drugs targeting HER2, generally do not work, so chemotherapy is the default treatment option. The treatment protocol for newly diagnosed TNBC comprises surgical resection (either lumpectomy or mastectomy), followed by radiation and chemotherapy (chemotherapy may be given before surgery to reduce the size of the tumour). The common chemo drugs are anthracyclines, taxanes, capecitabine, gemcitabine and eribulin. TNBC is most common in younger women (<age 40–50), African American and Hispanic people and those who have the BRCA gene mutation. 75% of TNBC patients are carriers of the BRCA1 or BRCA 2 gene mutation.[19] A sub-set of TNBC cells also express a protein called PD-L1, which is found in 20% of all TNBC cases.[20] According to the American Cancer Society, the five-year survival rate for localised TNBC is >90% but goes down to 12% for metastasised tumours.

Other therapies have made some inroads in the last couple of years, with approval of immunotherapies for advanced/metastatic TNBC targeting the above-mentioned sub-sets (Exhibit 11). The targeted therapies are gaining traction, making for a competitive landscape for both approved and pipeline therapies.

16 Masoumi KC, Huang X, Sime W, et al. Integrin α10-Antibodies Reduce Glioblastoma Tumor Growth and Cell Migration. Cancers (Basel). 2021;13(5):1184. doi:10.3390/cancers13051184

17 Tzikas, AK., Nemes, S. & Linderholm, B.K. A comparison between young and old patients with triple-negative breast cancer: biology, survival and metastatic patterns. *Breast Cancer Res Treat* 182, 643–654 (2020)

18 HER2-negative/HR+ and Triple Negative Breast Cancer – Global drug forecast and market analysis to 2025, *Global Data*

19 Caulfield, Sarah E et al. Olaparib: A Novel Therapy for Metastatic Breast Cancer in Patients With a BRCA1/2 Mutation. *Journal of the advanced practitioner in oncology* vol. 10,2 (2019): 167–174.

20 www.cancer.org/cancer/breast-cancer/treatment/treatment-of-triple-negative.html

Exhibit 11: Approved targeted therapies for TNBC

Name	Company	Description	Date of approval
Tecentriq	Roche	Checkpoint inhibitor: for unresectable or locally advanced or metastatic TNBC expressing PD-L1, in combination with chemotherapy (Abraxane); first-line treatment	March 2019 (US), August 2019 (EU)
Keytruda	Merck	Checkpoint inhibitor: for unresectable locally advanced or metastatic TNBC expressing PD-L1, in combination with chemotherapy; first-line treatment	November 2020 (US)
Lynparza	AstraZeneca/Merck	PARP inhibitor: monotherapy for locally advanced or metastatic HER2-patients with BRCA1/2 mutation who have previously been treated with chemotherapy	January 2018 (US), April 2019 (EU)
Talzenna	Pfizer	PARP inhibitor; as monotherapy for locally advanced or metastatic HER2-patients with BRCA1/2 mutation	October 2018 (US), June 2019 (EU)
Trodelvy	Gilead (Immunomedics)	ADC (rop-2-directed antibody and topoisomerase inhibitor drug conjugate); third-line treatment for metastatic TNBC patients treated with two prior therapies	April 2020 (US)

Source: Edison Investment Research

Similar to GBM, emerging evidence suggests that cancer stem-like cells could be the key reason for the recurrence, therapy resistance and metastases of TNBC. Integrins are found to be expressed in these cancer stem-like cells in TNBC and offer a potentially attractive subset for targeted therapies. A look at currently approved and pipeline therapies for TNBC shows no direct integrin-directed competitors to Xintela's TNBC programme, suggesting a potential first-in-class opportunity for its integrin-directed therapy.

Sensitivities

Xintela's risks are typical to an early-stage biotech: development, regulatory and financing risks dominate. The biggest near-term sensitivity is related to the company's flagship programme, XSTEM, given its upcoming clinical trial. The ability to finance the trial is paramount to successful execution and timely completion of the study. Moreover, XSTEM, by virtue of being termed as an ATMP in Europe, is governed by a stringent and complex regulatory environment compared to other biologics and small molecule drugs. Gaining approval will require the company to meet rigorous regulatory standards. The reimbursement situation is also uncertain, given that regulatory authorities in the past have been reluctant to approve reimbursement for cell-based therapies. While the regulatory environment seems to be improving following TiGenix's Alofisel's realisation of reimbursement status in France, Germany and Spain, risks still remain (for example, the UK and Italy refused to grant reimbursement status and the US FDA is still unsure about the viability of cell-therapy products).

Fostering partnership deals and/or out-licensing opportunities will also be critical. Given its scale and limited financial resources, Xintela is dependent on partners to further develop and commercialise its preclinical programmes. Finding the right partner and sustaining relationships will be crucial to the company's long-term goals.

Xintela's oncology franchise is currently focusing on GBM and TNBC, both of which are highly treatment resistant. Developing oncology treatments is a challenging and expensive proposition with a long lead time to commercialisation. Plus, the risk of failure remains high. Positive headline date from clinical studies will be crucial to sustain market interest in a field dominated by big pharma.

Financials

Xintela is currently in pre-revenue stage and is therefore loss-making. The FY20 net loss stood at SEK50.3m, a 15.5% y-o-y increase over the SEK43.5m loss recorded in FY19. R&D expenses make up the bulk of the cost structure (c 80%) and stood at SEK38.2m in FY20, up 10% y-o-y over the FY19 figure of SEK34.7m. Net cash stood at SEK22.7m at the end of the period (SEK33.6m gross cash and SEK10.9m in bridge loan). The bridge loan was subsequently converted into 3.2m

shares of the company in January 2021 (leading to a further 4.15% share dilution). The Q121 net loss came in at SEK9.1m versus SEK7.5m in Q120. The net cash position at the end of March 2021 stood at SEK15.5m and was further enhanced by a SEK28m equity injection in June 2021.

Xintela has been funding its operations through equity issues and bridge loans. Since listing in March 2016, the company has raised c SEK240m in equity, including SEK50m from a private placement with German orthopaedic player Bauerfeind in 2018 (currently the largest shareholder with a 19.0% stake). This is against an average annual cash burn of c SEK30–35m in the past three years, including the group contribution to Targinta. We note that the Q121 cash burn was unusually high (SEK26.7m), but this can be attributed to the company paying off its SEK10.9m bridge loan facility (taken as part of working capital) and should therefore be transitory. Applying the normalised Q121 burn rate (adjusted to exclude the SEK10.9m bridge loan repayment) for the remainder of 2021 would result in an approximate cash burn rate of c SEK47m for covering the last three quarters of 2021. The pro forma SEK43.5m (SEK15.5m + SEK28m) of funds available at the end of Q121 may therefore be potentially sufficient to initiate the Phase I/IIa trials for XSTEM and conclude the spin-off of Targinta, although subsequent rounds of funding would be required to complete the clinical trials. The company has indicted that it is working to secure various forms of long-term financing for both Xintela and Targinta and may seek partnerships in veterinary and oncology spaces to de-risk the pipeline.

Contact details	Revenue by geography
Medicon Village SE-223 81 Lund Sweden +46 46 275 65 00 http://xintela.se/en/	N/A

Management team	
CEO: Evy Lundgren-Åkerlund	**CFO: Gunnar Telhammar**
Evy Lundgren-Åkerlund is Xintela's founder. She has extensive experience in biomedical research and development and previously held senior positions in both academia and industry. She founded Cartela and was CEO and head of research from 2000–07. She was director of operations/CEO of Ideon Bioincubator/Lund Life Science Incubator from 2008–12.	Gunnar Telhammar has held several positions as CFO, both in Sweden and abroad, and has been operating through his own consulting firm BioFinans for over 15 years. Current assignments include CEO of BioFinans, CFO of AcouSort and ImmuneBiotech. He is a member of the board of Targinta.
CBO: Thomas Areschoug	**COO: Peter Ekolind**
Thomas Areschoug has extensive experience from biomedical R&D and business development in life science, most recently in a leading role at Business Sweden. He has also been part of the board of directors at Minervax ApS and scientific advisor at Enzymatica AB.	Peter Ekolind has extensive experience of marketing, sales and leadership in several global pharmaceutical companies in various senior positions such as marketing, business and country manager. He has also been CEO of Getinge Sverige and Avidicare.
Senior management advisor: Jeffrey Abbey	**Chairman of board: Gregory Batcheller**
Jeffrey Abbey was previously CEO of Argos Therapeutics, an immuno-oncology company which he led from early-stage development through completion of a phase 3 trial, raising over $250 million in equity financing. He has also been CBO at Argos and was responsible for completing numerous deals with major biopharmaceutical companies.	Gregory Batcheller has extensive experience in pharmaceuticals, biotech and medtech. He is the chairman of the board of Saga Diagnostics, Monocl, ImmuneBiotech Medical Sweden and CarryGenes Therapeutics and a board member of CanImGuide. Previously he was chairman of the board of NeuroVive Pharmaceutical (now Abliva) and A1M Pharma (now Guard Therapeutics).
Member of board: Sven Kili	**Member of board: Karin Wingstrand**
Sven Kili has extensive experience in cell therapy. Sven is a surgeon and orthopaedic specialist with many years' experience of successful development and commercialisation of cell and gene therapy products from senior positions in pharmaceutical companies Genzyme, Sanofi Biosurgery and GlaxoSmithKline. Sven was also responsible for medical and regulatory issues in cell therapy at Geistlich Pharma. He maintains his clinical expertise in the National Health Service (NHS) in the UK.	Karin Wingstrand has been an advisor to the life sciences industry. She was previously employed as global head of AstraZeneca's clinical development, and global head of AstraZeneca's pharmaceutical and analytical R&D.
Member of board: Lars Hedbys	**Member of board: Maarten de Château**
Lars Hedbys has significant experience from leading positions and board roles in the pharmaceutical, biotech and MedTech industries with several senior positions in AstraZeneca. He currently has several board assignments including member of the boards of RhoVac, Cell Invent and Vetiqure. His previous assignments include CEO of Idogen, and Pharmiva.	Maarten de Château is CEO of Sixera Pharma and Buzzard Pharmaceuticals. He serves as chairman of the Board of Atrogi and is on the boards of OxThera, Amarna Therapeutics, Beactica and Cavis Technologies. Maarten was co-founder and CEO of Cormorant Pharmaceuticals acquired by Bristol-Myers Squibb in 2016. Prior to that, he held the position of Medical Director at Swedish Orphan Biovitrum.

Principal shareholders (as at 30 June 2021)	(%)
Bauerfiend Group	15.8
Avanza Pension	8.3
Evy Lundgren-Åkerlund	5.0
Nordnet Pensionsförsäkring	4.5
Jan Ivar Nordqvist	3.4
Pär Åke Oldentoft	2.4
Carl Fredrik Olsson	2.3
Svedala Finans	1.3
Selandia Capital	1.3
Kerstin Monsen	1.1

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