EDISON

OSE Immunotherapeutics

Initiation of coverage

Immunotherapy research engine

Pharma & biotech

OSE Immunotherapeutics (OSE) is a drug developer that focuses on both oncology and immune disorders, with an R&D pipeline diversified across different indications and mechanisms of action. Long-term collaborations with top research institutions enable the company to identify novel targets in a cost-effective and time-efficient manner, and develop products for R&D and out-licensing. The success of this model is demonstrated by several commercial partnerships, including a deal with Boehringer Ingelheim (BI) in April 2018 for a total value of €1.1bn plus royalties. OSE's most advanced internal programme is Tedopi for NSCLC (Phase III), with results expected in 2021. We value OSE at €171m or €11.7/share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/16	0.4	(6.9)	(0.30)	0.0	N/A	N/A
12/17	6.7	(12.6)	(0.72)	0.0	N/A	N/A
12/18e	20.6	0.8	0.06	0.0	N/A	N/A
12/19e	0.0	(20.0)	(1.36)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles and exceptional items.

€27m in potential licensing income in 2019

OSE has commercial deals in place with Boehringer Ingelheim (OSE-172, SIRPα antagonist, late preclinical) and Servier (OSE-127, IL-7R antagonist, Phase I). A €15m milestone payment is expected from BI in H119 on the initiation of Phase I in multiple solid tumours with OSE-172, and a €12m fee could be received from Servier in H119 if it exercises its option to proceed to a Phase II trial with OSE-127. The combined value of the deals is €1.37bn in milestones plus royalties, so there is potential for significant licensing income over the next few years. OSE had a deal with Janssen Biotech for FR104 (CD28 antagonist, Phase II ready), but in November 2018 Janssen returned the rights due to reprioritizing its pipeline. OSE is now considering development options including re-partnering.

Tedopi Phase III cancer vaccine for 2L/3L NSCLC

OSE is conducting its own Phase III study (Atalante 1) with off-the-shelf cancer vaccine Tedopi in advanced NSCLC patients in 2L/3L. Atalante 1 is the only trial currently fully financed by OSE. Following a pause in recruitment in June 2017, the trial design was modified (with a narrower patient population to meet the changing standard of care), and is on track for interim data readout in H219 and final readout in 2021. This and the initiation of the Phase I studies with partnered products represent key near-term catalysts, which should be reached with no external fund-raising if both milestone payments are received (cash runway into early 2021).

Valuation: €171m or €11.7/share

We value OSE at €171m or €11.7/share (estimated net cash of €7.5m at end 2018). We currently value four assets in four indications, but further additions are possible depending on a future strategic decision from OSE. The company's value drivers are diversified, with Tedopi accounting for 31% of our rNPV. Overall, we see OSE's R&D programmes as cost-effective due to low out-of-pocket R&D costs, and well diversified, with different mechanisms of action and specific indications.

6 December 2018

Price	**€3.3**
Market cap	**€48m**
Net cash (€m) including current financial assets at end-H118	13.9
Shares in issue	14.4m
Free float	24%
Code	OSE
Primary exchange	Euronext Paris
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(1.8)	(15.6)	(8.8)
Rel (local)	1.8	(9.4)	(0.8)
52-week high/low		€4.69	€3.21

Business description

OSE Immunotherapeutics is an immunotherapy company based in Nantes and Paris, France and listed on the Euronext Paris exchange. OSE is currently developing immunotherapies for the treatment of solid tumours and autoimmune diseases and has established several partnerships with large pharma companies.

Next events

Initiation of OSE-127 Phase I study	H119
Initiation of OSE-172 Phase I study	H119
Initiation of Tedopi Phase II study in pancreatic cancer	H119
Updated strategy for FR104	2019

Analysts

Jonas Peciulis +44 (0)20 3077 5728

Alice Nettleton +44 (0)20 3077 5700

healthcare@edisongroup.com

Edison profile page

Investment summary

Company description: From research to licensing-ready assets

OSE Immunotherapeutics is a biotechnology company based in Nantes and Paris, France and listed on the Euronext Paris exchange. The company was created in May 2016 through the merger of OSE Pharma and Effimune. It specialises in the identification of immunotherapy targets, the generation of product candidates and early- to mid-stage development before out-licensing for late-stage development and commercialisation. OSE is able to benefit from strong research partnerships, especially with Inserm in Nantes. OSE's research headquarters are in Nantes and benefit from these extensive networks developed over the years. OSE's lead asset in clinical development is Tedopi, a cancer vaccine in development for non-small cell lung cancer (NSCLC, Phase III) and pancreatic cancer (Phase II). Other interesting assets include Phase II-ready FR104, OSE-127 (partnered with Servier) and OSE-172 (in late preclinical studies, partnered with BI).

Valuation: €171m or €11.7/share

We value OSE based on a risk-adjusted NPV analysis using a 12.5% discount rate, including estimated net cash of €7.5m at end-2018. This results in a value of €171m or €11.7/share. We include four assets in our valuation, namely Tedopi in NSCLC, OSE-172, FR104 and OSE-127. We have not included Tedopi in pancreatic cancer until the commercial strategy is clearer. We assume a licensing deal for Tedopi in NSCLC after the Phase III study. The two near-term milestone payments from Servier and BI are dependent on the respective assets moving from late preclinical stage to Phase I. Typically, this is a low-risk transition but, to reflect any remaining R&D risk and the fact that ultimately this will be a third-party decision, we include the €12.0m payment from Servier and the €15.0m payment from BI due in 2019 with a 90% risk adjustment.

Financials: Two milestone payments to expand cash runway

In its H118 financial results, OSE reported €20.6m in revenues (vs €2.8m in H117). This includes the upfront payment from BI for OSE-172 received in April 2018. Total operating expenses for H118 were €10.2m vs €7.3m in H117. R&D expenses are the company's largest expense: €8.0m in H118 vs €7.9m in H117. The largest contributor is the Tedopi Atalante 1 Phase III study. We expect R&D costs to remain largely constant at €8m per six months of operation until the end of the trial in 2021. As of 30 June 2018, OSE had cash of €18.6m (includes 'current financial assets'). With cash burn around €15m per year, cash is expected to last into H219. If both milestone payments totalling €27m are received in H119 (from Servier and BI), the cash runway should extend into early 2021.

Sensitivities: Out-licensing and own R&D model

OSE is subject to typical biotech company development risks. We see the largest part of its value coming from Tedopi in NSCLC due to the late stage of this project. Therefore, the outcome of the Atalante 1 Phase III trial will be important. The licensing deals with BI and Servier substantially diversify this risk, but the risk remains if any of those partnerships are discontinued. If OSE does not receive the expected licensing income in 2019 (up to €27m), it might have to raise money from elsewhere to fund its operations. The main patent of Tedopi expires in 2024 with potential to extend the protection for five years. OSE filed for fresh patents in 2014/15, which are yet to be granted. However, market exclusivity after the launch of Tedopi could be secured if OSE receives orphan drug designation in the US, and a biologicals licence in the US and Europe. Finally, Janssen decided to discontinue the licensing deal related to FR104 asset. Once OSE regains the rights and data, it will have to clarify its future development plans.

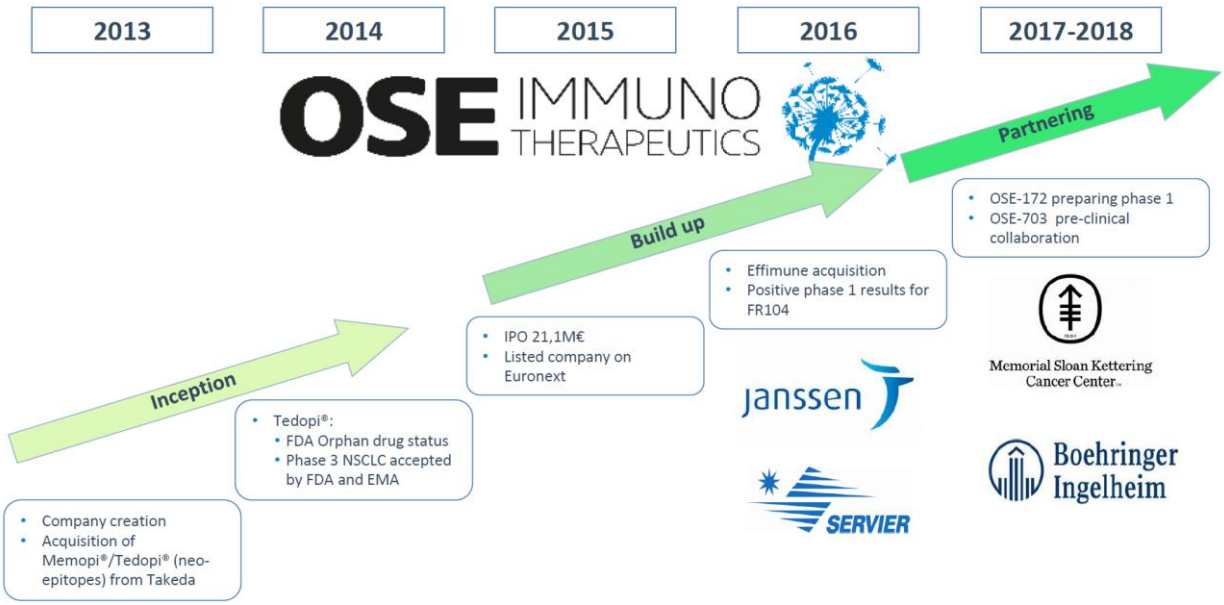
Immunotherapy R&D and out-licensing model

OSE Immunotherapeutics (OSE) is an immunotherapy company created in May 2016 through the merger of OSE Pharma and Effimune, as both companies saw potential synergies between their business models and asset portfolios:

- **OSE Pharma** was created in 2013 around the Tedopi asset, which was acquired from Takeda. It then began a Phase III clinical trial with Tedopi in NSCLC and listed in 2015.
- **Effimune** was a private company, which was spun out from the Nantes Institute of Transplantation, Urology and Nephrology (ITUN) in December 2007. It was focused on the discovery and development of drugs, mainly for transplantation and autoimmune diseases. Effimune's pipeline included FR104, Effi-7 (now OSE-127, Effi-DEM [OSE-172] and Effi-3 [OSE-703]) and had a unique position terms of access to research through its longstanding collaborations with the research institutions in Nantes. These include ITUN, Inserm, Nantes University, University of Maryland in Baltimore and Seattle's Children's Institute.

After the merger, OSE Pharma held 71% of the shares of the merged entity, OSE Immunotherapeutics, which has been operating since 2016 and is listed on Euronext Paris. The founders of both OSE Pharma and Effimune are still involved, eg CEO Alexis Peyroles was CFO at OSE Pharma previously. Dominique Costantini, currently chairman of OSE Immunotherapeutics, co-founded OSE Pharma and was its CEO. Maryvonne Hiance, who was co-founder and CEO of Effimune, is now serving as vice chairman and director of strategy for OSE, and Bernard Vanhove, who was co-founder and COO of Effimune, is now COO of OSE. Nicolas Poirier, PhD, is CSO of OSE and was also previously at Effimune. Emile Loria, a former chairman of OSE, and Dominique Costantini are majority shareholders in OSE and have been working on the Tedopi asset. Emile Loria has been involved with Tedopi asset since 2001.

Exhibit 1: History of OSE



Source: OSE company presentation April 2018

OSE's business model involves the identification of immunotherapy targets, the generation of product candidates, early-stage development and, finally, out-licensing for late-stage development and commercialisation. OSE has a somewhat unique position in the immunotherapy landscape in that it can benefit from immunotherapy research in Nantes through its longstanding relationship with Inserm and other institutions.

Exhibit 2: OSE Immunotherapeutics' R&D pipeline

Product	Indication, status	Deal comments, upcoming events
Tedopi *Peptide vaccine*	NSCLC (Phase III)	■ OSE is fully funding the Phase III study and plans to out-license after its completion. ■ **Phase III study ongoing, first data expected in H219, final data 2021.**
Tedopi *Peptide vaccine*	Pancreatic cancer (Phase II)	■ Phase II study sponsored by GERCOR, a physician network. No financial commitment from OSE. ■ **Phase II study expected to start in H119**
FR104 *CD28 antagonist*	Rheumatoid arthritis (Phase II-ready)	■ Janssen had worldwide development and commercialisation rights in autoimmune diseases and transplantation for €155m in potential milestone payments + royalties (includes €10m upfront payment as option exercise fee received in August 2016), but returned the rights to OSE on 2 November 2018. ■ **OSE is considering options for further development**
OSE-127 (Effi-7) *IL-7Rα (CD127) antagonist*	Ulcerative colitis, Sjögren's syndrome (Phase I)	■ License option agreement between OSE and Servier in December 2016. Worldwide licence option agreement in autoimmune diseases. €272m total deal value including €10.3m upfront payment (received 2016), two-step €30m option exercise fee (if option is exercised) and development and commercial milestones. Plus double-digit royalties on sales. ■ OSE is developing the asset until Phase II, which is currently financed by a Bpifrance grant of €9.1m. Servier will continue the development of the asset afterwards. Servier plans to study OSE-127 in ulcerative colitis and potentially in Sjögren's syndrome. ■ **If option is exercised (first step) a €12m fee expected in H119**
OSE-172 (Effi-DEM) *Myeloid checkpoint inhibitor*	Multiple cancer indications (preclinical)	■ Licence agreement with Boehringer Ingelheim in April 2018. Worldwide rights in multiple cancer indications. €1.1bn potential development and commercial milestones, including €15m upfront payment (received April 2018) and up to €15m milestone payment on initiation of Phase I study (expected H119). Plus royalties on worldwide net sales. ■ Boehringer Ingelheim bears all R&D costs (including Phase I). OSE will finish the Phase I study (Phase Ia/Ib) and Boehringer Ingelheim will take over for the subsequent trials and commercialisation. ■ **Up to €15m milestone payment on initiation of Phase I study (expected H119)**
OSE-703 (Effi-3) *IL-7R Mab*	Solid tumours (preclinical)	■ Cytotoxic monoclonal antibody against IL-7R being developed in collaboration with the Memorial Sloan Kettering Cancer Center (CAR-T expertise). ■ OSE-703 is engineered to improve three types of antibody mediated cytotoxicity: Antibody Dependent Cell-mediated Cytotoxicity (ADCC), Antibody-dependent cellular phagocytosis (ADCP) and Complement-dependent cytotoxicity (CDC). ■ Next step: development strategy in solid tumours.

Source: Edison Investment Research; OSE Immunotherapeutics

OSE's most advanced asset is Tedopi, a synthetic peptide cancer vaccine which was in-licensed from Takeda in 2013 by OSE Pharma and which OSE is developing internally for NSCLC (Phase III), and in collaboration with GERCOR for pancreatic cancer (Phase II). OSE has also demonstrated a track record of establishing partnerships with large pharma (Exhibit 3):

- The option deal with **Janssen Biotech** for FR104 in rheumatoid arthritis was secured by Effimune before the merger, and the option was exercised following positive Phase I results for a total deal value of up to €155m plus royalties on net sales. In November 2018, Janssen returned the rights to OSE citing a strategic review and reprioritisation of its portfolio, which is not uncommon in the industry. OSE is now considering all options for further development of FR104.
- The deal with **Servier** was secured in 2016 for OSE-127 which is currently in Phase I. Total milestone payments amount to €272m plus double-digit royalties on sales. A €12m option exercise fee (first step) is expected in H119.
- The deal with **BI** was signed in 2018 for OSE-172, which is expected to enter Phase I in the coming months triggering a payment to OSE of €15m. The total deal value is €1.1bn plus royalties on net sales.

€27m licensing income expected in 2019

Milestone payments from commercial deals will help to fund the company's R&D, the majority of which is the ongoing Tedopi Atalante 1 trial. Up to €27m could be generated from milestone payments in the near term, which includes €15m from BI for OSE-172 and €12m from Servier for OSE-127. OSE is in the final stages of preparing to submit the Phase I clinical trial application studying OSE-172, and expects to receive the milestone payment once the first patient has been

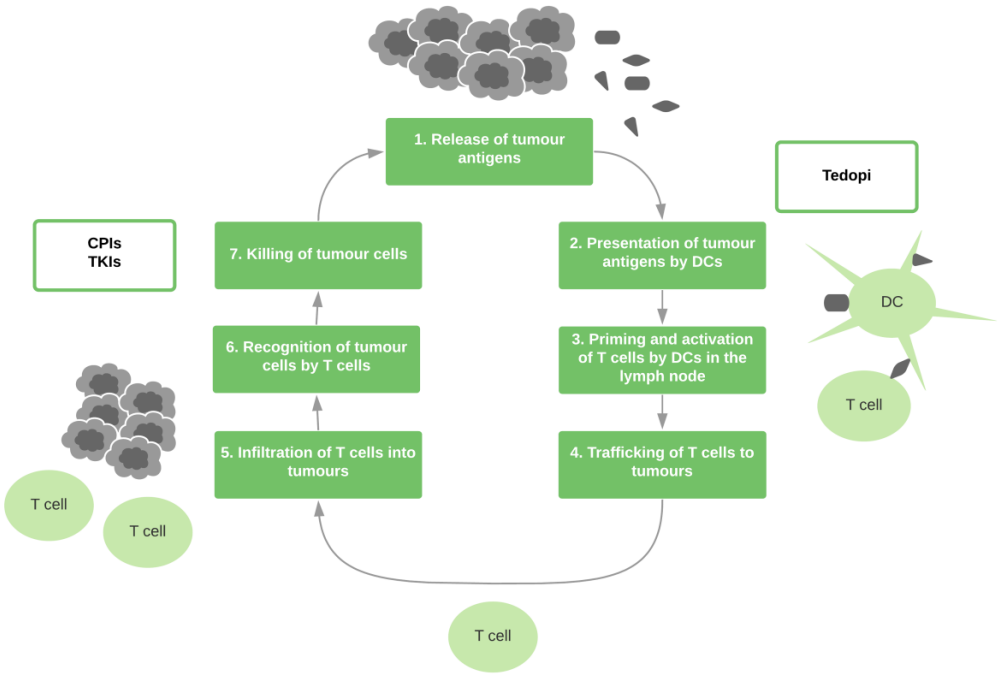
enrolled in **H119**. OSE is also undertaking Phase I preparation work for OSE-127, which should be ready to move into a Phase I trial in **H119**, which is when the Servier option can be exercised. Current cash burn is around €15m/year, so these payments would add roughly two years of runway assuming OSE maintains a similar level of R&D work.

Overall, we see OSE's R&D programmes as very cost-effective due to low out-of-pocket R&D costs, and well diversified, with different mechanisms of action and specific indications.

Tedopi: Peptide vaccine for NSCLC + pancreatic cancer

Tedopi is OSE's lead asset, a cancer vaccine in development for NSCLC (Phase III) and pancreatic cancer (Phase II). In June 2017, recruitment for Atalante 1, the Phase III trial in NSCLC, was halted following a recommendation by the Independent Data Monitoring Committee, but later resumed in February/March 2018 after a redesign of the study to include only patients who have progressed after a IL/2L checkpoint inhibitor. OSE plans to complete its Phase III study in NSCLC then out-license for the final stage of development and commercialisation. The first readout from this trial is expected in 2019. Management believes that a positive outcome of this study will allow for at least conditional, or even full approval, in this patient group. Another key direction that management envisions for Tedopi is to test its use in combination with other immunoncology drugs, primarily checkpoint inhibitors. The next nearest opportunity to explore this is the investigator-led Phase II trial in pancreatic cancer patients in combination with nivolumab.

Exhibit 3: Cancer immunity cycle and positioning of Tedopi



Source: Based on research by Chen and Mellman

What are cancer vaccines?

In a malignant process, cancer cells die and proteins/antigens are released (step 1 in Exhibit 3). These are then taken up by the patient's own antigen-presenting cells, or dendritic cells (DCs) and in lymph nodes they present these antigens to T-cells (step 2). This leads to an activation and production of populations of T-cells, which can now recognise and destroy cancerous cells that display the same antigens as those previously presented (steps 3 to 7). However, this process is

not perfect, which is why not every malignant process is stopped. Once a tumour develops, it often also has multiple ways to suppress the immune response and enable the tumour to 'hide' from the immune cells. The goal of cancer immunotherapies is to expose the tumour microenvironment as foreign to the patient's immune system so the tumour is recognised and immunologically attacked (step 7), ie turn from 'cold' to 'hot'.

Cancer vaccines are one such immunotherapy strategy – they aim to elicit an immune response that will lead to the selective destruction of tumour cells. So far, Dendreon's Provenge (dendritic cell vaccine, approved in 2010) and Amgen's Imlygic (oncolytic virus, approved in 2015) are the only approved cancer vaccines and there is no lack of research being conducted in this area. The relative lack of more successful examples, however, could be explained by variability in design of the vaccine, the selection of antigens and the understanding of the inhibitory tumour microenvironment. In addition, more and more preclinical studies are supporting the idea that the backbone strategy in immunoncology should be combination treatments exploiting different steps in the immunity cycle (Schlom and Gulley, 2018).

The most popular cancer vaccine technologies include peptide vaccines, oncolytic viruses and dendritic cell vaccines. Peptide vaccines are a type of cancer vaccine and work by presenting peptides to the patient's immune system that are likely to be expressed by the patient's tumour. Compared with other approaches such as dendritic cell vaccines and other *ex vivo* approaches, peptide vaccines are more straightforward.

Getting cancer peptide vaccines right

Historically, vaccines were first developed against infective diseases (first virus, then bacteria) and were made from live attenuated pathogens, inactivated organisms or purified whole antigens. However, live vaccines can cause the disease itself, while non-living vaccines were effective in inducing humoral immunity (antibodies produced by B-cells), but not effective in inducing cell-mediated immunity (T-cells directly destroy 'foreign' cells), which are the two major types of adaptive immunity that generate an antigen-specific immune response.[1] With advancing knowledge of antigen processing and presentation, an epitope-based vaccine emerged that demonstrated the potential to initiate a cell-mediated, antigen-specific immune response and quickly gained popularity in cancer vaccine research. This approach aims to develop vaccines from highly conserved epitopes that are present in large proportions of the population and would elicit a cell-mediated immune response.

Epitopes are the antigenic determinant sections of antigens, ie smaller peptide sequences of the proteins that can be recognized by the immune system as foreign, when presented on the surface of antigen-presenting cells (step 2 in Exhibit 3). The epitopes that are recognized by CD8+ T-cells (cytotoxic T-cells) are bound to major histocompatibility complex (MHC) class I molecules on the surface of APCs. CD4+ T-cell ('helper') epitopes are bound by the MHC class II molecules. In humans, MHC is also called human leukocyte antigen (HLA) and MHC class I molecules are encoded by HLA-A, -B and -C genes. There are many specific HLA types, but due to substantial overlap three peptide specificities HLA-A2, A3, and B7 cover around 90% of the population.[1]

Tedopi antigens

Tedopi is a subcutaneously deliverable combination of 10 synthetic peptides/neoepitopes, nine of which have been optimised from five antigens commonly expressed on tumour cells, known as tumour-associated antigens (TAAs). These TAAs are CEA, p53, HER-2/neu, MAGE-2 and MAGE-3, and are part of HLA-A2, therefore restricted to HLA-A2 positive subjects, around 45% of total

[1]. L Zhao et al. Advances in the study of HLA-restricted epitope vaccines. *Hum Vaccin Immunother. 2013 Dec 1; 9(12): 2566–2577*

population. Tedopi includes a tenth peptide (pan-DR epitope or PADRE), which is a CD4+ T-cell (helper) epitope included to augment the magnitude and duration of CTL responses. 90% of malignant tumours express at least one of these five tumour antigens. The patient's antigen presenting cells (eg dendritic cells) take up the antigens, process them and present them on their cell surface through HLA-A2. The dendritic cells then prime T-cells in the lymph node (both CD4+ "helper" cells and CD8+ "cytotoxic" cells). These T-cells can now recognise tumour cells as foreign and kill them. Several steps were taken during the development of the vaccine with expectations to increase its potency:

- A proprietarily epitope screening technology, Memopi, was used to optimise and identify epitopes that bind strongly with the HLA-A2;
- A multi-epitope approach with several epitopes used, which bind key CD8+ T-cell receptors (TCRs); and
- The additional PADRE peptide was included to induce CD4+ T-cell activation in addition to CD8+, which theoretically should 'expand' the immune reaction.

NSCLC still a challenge in checkpoint inhibitor era

Lung cancer is the leading cause of cancer-related deaths globally (19.4% of total cancer-related deaths); 2.1 million new cases were reported worldwide in 2018. NSCLC is the most common type of lung cancer, accounting for 85-90% of all cases. Five-year survival rates for NSCLC remain poor despite progress over the last 15 years; only 15% of patients diagnosed with all stages of lung cancer survive more than five years. The more recent availability of new treatment options as described below has improved outcomes and survival for patients, but there is still a great need for more effective treatments across first-line (1L), second-line (2L) and third-line (3L) settings.

NSCLC is not a single entity but a number of pathologies with different molecular abnormalities; subsets of NSCLC can be further defined at the molecular level by identification of driver mutation that occurs across multiple oncogenes (Exhibit 4). Therefore, in the clinical setting, treatment of NSCLC depends on the stage at which it is diagnosed and the molecular status of the tumour. Common treatable oncogene mutations in NSCLC include the EGFR mutation (19%, according to GlobalData) and ALK translocation (5%, GlobalData). Recently introduced targeted therapies against these mutations (eg crizotinib, gefitinib, erlotinib, afatinib) have improved progression-free survival in patients to 10-12 months versus six months on platinum doublet treatment in a clinical trial setting.

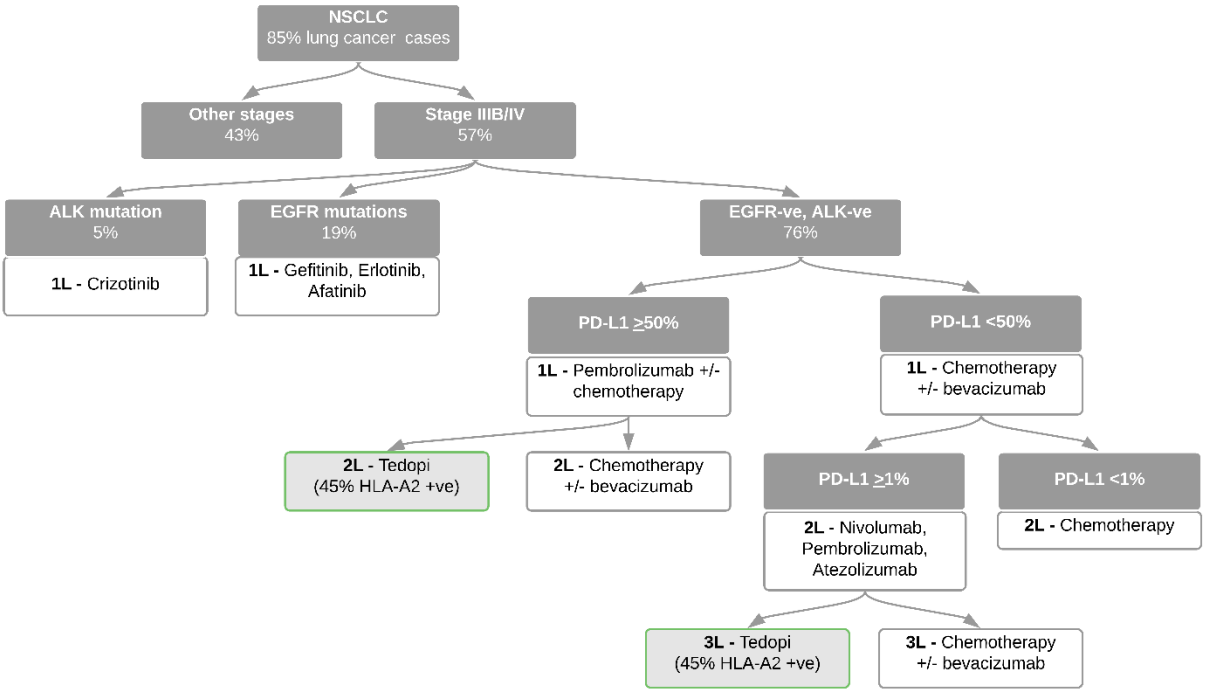
A standard of care has emerged based on the molecular status of a patients' tumour in the US and Europe for 1L treatment of advanced NSCLC (Exhibit 4). Particularly the advent of immunotherapy has changed the treatment of NSCLC. The first- and second-line space for these patients is currently dominated by targeted therapies in ALK or EGFR mutated patients or PD-1/PD-L1 inhibitors in ALK/EGFR negative patients. Opdivo (nivolumab, Bristol Myers Squibb) and Keytruda (pembrolizumab, Merck) are approved for the treatment of second-line NSCLC patients who have progressed after platinum-based chemotherapy. Additionally, Keytruda is indicated for first-line patients with metastatic NSCLC whose tumours have high PD-L1 expression (≥ 50%). More recently, Tecentriq (atezolizumab, Roche) was approved for second-line NSCLC patients who have progressed after platinum-based chemotherapy.

However, a large proportion of patients do not respond to currently available checkpoint inhibitors (c 80%) and patients that do respond will acquire drug resistance and experience disease progression. According to the American Society of Clinical Oncology Clinical Practice Guideline Update (2017), the only recommended treatment after treatment with a checkpoint inhibitor and chemotherapy is single-agent pemetrexed or docetaxel as a salvage therapy. Initially, Tedopi is positioned as a therapy for this patient group. This is based on its Phase III Atalante 1 trial, where it is being studied as a 2L/3L treatment for patients with stage IIIB or IV NSCLC, with disease

recurrence or progression after treatment with a checkpoint inhibitor and platinum-based chemotherapy and who are HLA-A2 positive. The trial excludes patients with EGFRmt, or ALK rearrangements. From our calculations, we estimate this addressable population for Tedopi to be 32,000 patients in the US and Europe (combined), which we use in our model:

- 464k total lung cancer cases in the US and EU (top 14 countries used in our model).
- NSCLC accounts for 85%.
- Stage IIIb/IV at diagnosis 57%.
- EGFR and ALK negative patients comprise 76%.
- No reliable standardised approach to test for PD-L1 yet, and we therefore assume majority (90%) of EGFR and ALK negative stage IIIb/IV patients will receive CPIs.
- 50% progress after CPI treatment.
- HLA-A2 positive 45%.

Exhibit 4: Potential positioning of Tedopi in 2L/3L, advanced stage HLA-A2+ve NSCLC based on guidelines



Source: Edison Investment Research, American Society of Clinical Oncology Clinical Practice Guideline Update 2017; Management of non-small cell lung cancer: The era of immunotherapy. Note: Some patients may also be addressable from other groups, eg checkpoint inhibitors are recommended as a second-line treatment for patients with BRAF mutations (ASCO guidelines), drugs approved since the guidelines were last updated have not been included in this figure.

Several other drugs are in late-stage trials for this patient population (Exhibit 5) including Opdivo, which is being studied in four Phase III trials. Many other earlier Phase I and II stage trials explore various combinations of approved therapies, but also novel drugs targeting new mutations including FGFR tyrosine kinase, RET, MET and ROS1.

Exhibit 5: Phase III trials in advanced NSCLC that progressed after CPI and chemotherapy (EGFRwt, ALK-ve)

Product	Company	Pharmacological class	Phase III trial(s)	No. patients	Est. primary completion date	Estimated study completion date
Selumetinib in combination with docetaxel	AstraZeneca		NCT01933932	510	June 2016	December 2018
Abemaciclib (LY2835219)	Eli Lilly		NCT02152631	450	September 2017	November 2018
Opdivo (nivolumab)	Bristol-Myers Squibb		NCT02066636	1380	January 2022	January 2022
			NCT02713867	350	June 2022	June 2022
			NCT01642004	352	November 2014	December 2018
			NCT01673867	792	February 2015	December 2018
Ilaris (canakinumab) + docetaxel	Novartis	IL-1 beta MAb	NCT03626545	240	March 2021	August 2021
Tedopi	OSE Immunotherapeutics	Cancer vaccine	NCT02654587	325	2021	2021

Source: EvaluatePharma, clinicaltrials.gov. Note: Estimated primary completion date = according to clinicaltrials.gov, meaning the earliest possible date that a primary outcome will be announced.

Tedopi Phase III Atalante 1 trial readout in 2021 (interim 2019)

The Atalante 1 trial was initiated at the beginning of 2016 by OSE. It was a multi-centre Phase III clinical trial for patients diagnosed with advanced NSCLC who are HLA-A2 positive and who had failed on at least the first line of therapy. The trial planned to enrol 500 patients in 70 centres in Europe and the US and was expected to complete in 2018. The first review in January 2017 by the Independent Data Monitoring Committee (IDMC) recommended that OSE continued the trial without modification. However, following the second review in June 2017, recruitment was halted following a recommendation by the IDMC, but later resumed in February/March 2018 after the study was redesigned. The trial has an updated protocol and is now focusing on a subgroup of patients in the original design (Exhibit 7). These patients are post-checkpoint inhibitor failures, ie patients who progressed after 1L/2L treatments with EGFR- or ALK-targeted therapies, or checkpoint inhibitors. This new focus could represent an interesting opportunity since no drug is currently registered for post-checkpoint failure and it represents an area of unmet need.

Exhibit 6: Tedopi Phase III NSCLC trial design, trial conducted by OSE Immunotherapeutics (NCT02654587)

Summary design	Randomised, parallel group Phase III study designed to evaluate Tedopi (OSE-2101) compared with standard treatment (docetaxel or pemetrexed) in HLA-A2 positive patients (n=325) with locally advanced (stage IIIb) unsuitable for radiotherapy or metastatic (stage IV) NSCLC in second- or third-line treatment after failure of immune checkpoint inhibitor regimens.
Dosing schedule (study drug)	Tedopi arm: subcutaneously, a total of 13 doses over the course of two years until disease progression (using RECIST 1.1 criteria), unacceptable toxicity or consent withdrawal. Active comparator: either docetaxel or pemetrexed standard of care.
Endpoints	Primary endpoint: Overall survival (OS) Secondary endpoints: Disease control rate (DCR); QLQ-C30 (EORTC QLQ questionnaire); QLQ-LC13 (lung cancer module from EORTC QLQ questionnaire); Progression Free Survival (PFS); safety and tolerability profile compared to the control group Other: Objective Response Rate (ORR); Disease Control Rate (DCR); Duration of Response (DR); Time to deterioration (TTD); Time to next lung cancer therapy
Timelines	Study start: Q116; results expected: 2021

Source: Clinicaltrials.gov, ECOG = Eastern Cooperative Oncology Group

The new patients recruited into the trial will only be checkpoint inhibitor failure patients, but OSE will continue to treat patients who have already started treatment from other groups. Exhibit 7 shows the new design graphically. According to management, 100 patients will be recruited in addition to the patients already recruited from the checkpoint failure group (step 1). If a certain percentage (required by the IDMC) are still alive after 12 months, this will be regarded as clinically meaningful then the trial will be allowed to enrol an extra 225 patients to a total of 325, at which point OS will be measured (step 2). This pause of approximately nine months led to a delay in the expected data readout (previously 2018, now 2021). The readout from step 1 mentioned above is expected end of 2019 and these data will be published. The final results from step 2 are expected in 2021. Management believes that a positive outcome of this study will allow for at least conditional or even full approval in this patient group.

Exhibit 7: Atalante 1 trial overview

Source: OSE company presentation November 2018

Tedopi Phase II data

A Phase II study was carried out by Epimmune, a previous developer of Tedopi, between 2004 and 2007. The study design is shown in Exhibit 8.

Exhibit 8: Phase II design (NCT00104780)

Summary design	Open-label, multicentre, single-arm, Phase II study designed to evaluate safety, efficacy and immunogenicity of Tedopi in patients (n=64) with advanced NSCLC who were HLA-A2 positive
Comparator group	Those patients, who were screened for the study, but had HLA-A2 negative status (n=72) were used as a retrospective comparator group
Dosing schedule	Vaccine administered subcutaneously, a total of 13 doses over the course of 2 years
Endpoints	Survival, safety, immune response (measured by the interferon gamma enzyme-linked immunosorbent spot assay)
Timelines	Patients enrolled between February 2005 and March 2006

Source: ASCO Journal of Clinical Oncology. Note: NSCLC = non-small cell lung cancer; ECOG = Eastern Cooperative Oncology Group.

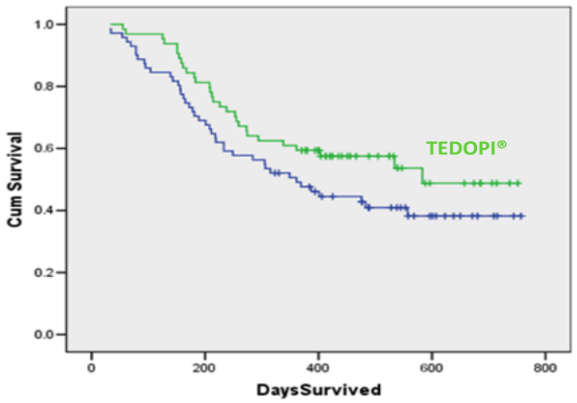
This study was designed as an open-label, single-arm that enrolled 64 HLA-A2 positive patients, who received Tedopi for two years. For comparison, patients who were screened for this trial but had HLA-A2 negative status were followed for one year. Therefore, only short-term survival comparison data ares available. The Tedopi group was followed for a longer period. Results included:

- Overall, the drug was **well tolerated** with just one grade 3 adverse event in relation to the study drug (fever/chills), and 63 grade 1-2 adverse events, which included injection site erythema (21%), fatigue (16%), injection site pain (14%) and fever (14%).
- **Median overall survival** in Tedopi group was 17.3 months versus 12 months in the comparator group (HLA-A2 negative patients who received standard of care) (Exhibit 9). **One-year survival** was 59% in Tedopi group versus 49% in the comparator arm. While numerically both endpoints were better in the Tedopi group, p values were 0.086 and 0.063 respectively, and therefore showed a trend, but did not reach required statistical significance. There is some evidence that HLA-A2 negative status may underpin a better survival rate, ie HLA-A2 negative patients may have not been the best comparator arm. The strategy of using HLA-A2 negative patients from the screening in the same trial was chosen according to the practice of other similar cancer vaccine trials by other parties. Presumably, this was the case because of cost-effectiveness as true randomization would have required large additional investments. However, increasing evidence now shows that HLA-A2 positivity is actually a negative prognostic factor (Nagata et al 2009, Bulut et al 2009, Kiewe et al 2008, Gamzatova et al 2006), therefore the comparison with HLA-A2 negative patients may have increased the efficacy hurdle for Tedopi. From this perspective, trending p values appear interesting enough to explore Tedopi in a better designed trial.
- **Long-term survival** analysis showed that 25% of patients in the Tedopi group were still alive after four years (Exhibit 10). No long-term survival data are available from the same HLA-A2

comparison group, but the historical five-year survival rate for stage IV is less than 10% (the Tedopi arm includes stage IIIB/IV patients of whom 67% were most difficult to treat with metastatic disease).

- In terms of **immune response**, all nine vaccine epitopes (excluding PADRE) were immunogenic in at least one patient, and T-cell responses to the epitopes were demonstrated in the majority of patients, where 91% had a response to at least one epitope, and 18% had a response to at least five epitopes.
- An interesting and significant ($p<0.001$) correlation was observed:
  - If there was a response to at least one Tedopi epitope, patients' average survival period was 406 ± 58 days;
  - If to two to three epitopes, then the survival period was 778 ± 72 days; and
  - If four to five epitopes, then 875 ± 67 days.

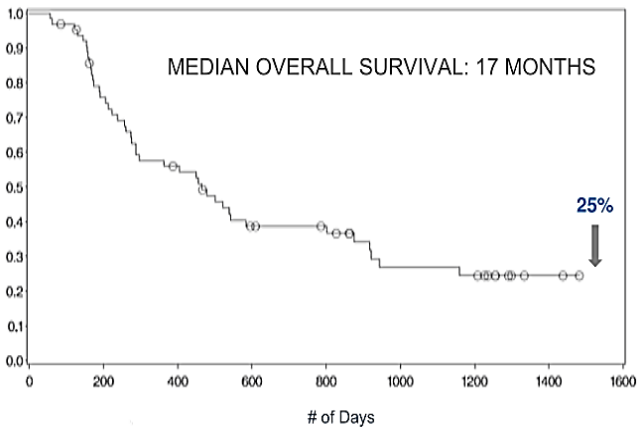
Exhibit 9: Tedopi Phase II short-term survival data



MEDIAN OVERALL SURVIVAL (p=0.086)
- **TEDOPI®: 17.3 MONTHS** vs. CONTROL* (HLA-A2-) : **12 months**

ONE YEAR SURVIVAL (p=0.063)
- **TEDOPI®: 59%** vs. CONTROL* (HLA-A2-) : **49%**

Exhibit 10: Tedopi Phase II long-term survival data

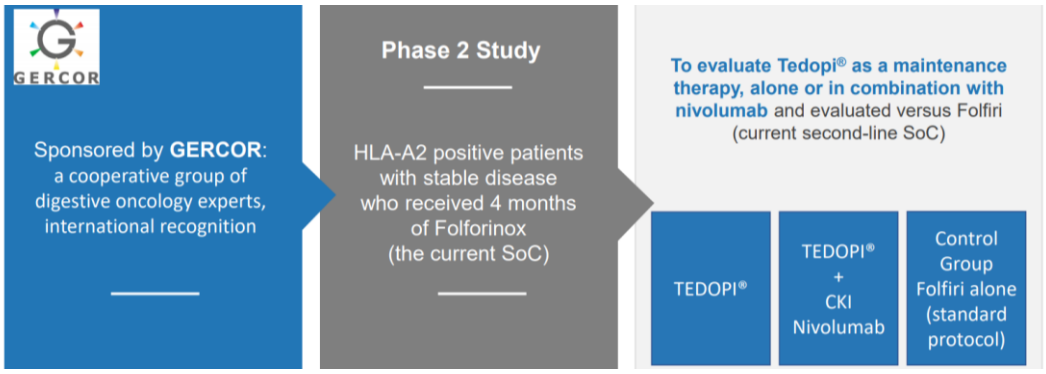


Source: OSE Immunotherapeutics. Note Tedopi in HLA-A2 positive vs retrospective analysis of standard of care in HLA-A2 negative patients

Investigator-led Phase II trial to be initiated in pancreatic cancer

As discussed above, increasing knowledge of immunotherapeutics suggests there is a strong case for combining treatment methods that affect different parts of the cancer immunity cycle. Outside the Atalante 1 trial, OSE sees combinations with checkpoint inhibitors as another key direction for Tedopi. OSE was approached by GERCOR, an association of physicians, to carry out an exploratory Phase II study with Tedopi in combination with nivolumab in pancreatic cancer. Since GERCOR is sponsoring the study and OSE only contributes limited financial support, this represents a cost-effective opportunity for Tedopi to be studied in combination. The trial protocol has not been finalised yet, but GERCOR plans to study Tedopi in combination with a checkpoint inhibitor and initiate the trial in H119. The preliminary trial design is shown in Exhibit 11. Management will evaluate options for further development and commercialisation depending on results from this study, which is when we will also reassess the opportunity. The insights from this trial could lead to further development for pancreatic cancer or a Phase III trial in NSCLC in combination with a checkpoint inhibitor.

Exhibit 11: Planned Phase II in pancreatic cancer (sponsored by GERCOR)



Source: OSE company presentation November 2018

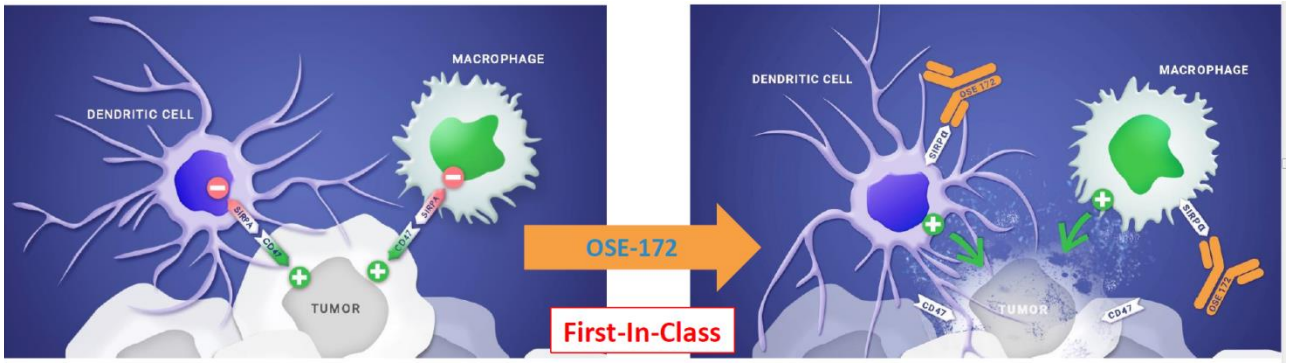
Keeping IP fresh and expected market exclusivity

The main patent protecting Tedopi was filed in 2004 (PCT application WO2004094454); the expiry date is therefore 2024 with potential to extend by five years. OSE has since filed new patent applications – two PCTs filed in 2014 (PCT/EP14/73975 for brain metastasis) and 2015 (PCT/EP2015/064746 method for inducing early T memory response with a short peptides antitumour vaccine). Tedopi was granted orphan drug designation in 2013 by the FDA for the treatment of NSCLC in patients expressing HLA-A2. This means that if Tedopi reaches the market before similar products, this could provide seven years of exclusivity from the date of approval. In addition, the biologicals licence in the US and Europe would give 12 and 10 years of market exclusivity respectively.

OSE-172 – SIRPα antagonist

OSE-172 is a first-in-class SIRPα antagonist and is currently in preclinical stage with a Phase I study in collaboration with BI expected to start in H218 (fully funded by BI). The drug is expected to work in a similar way to T-cell immune checkpoint inhibitors in the tumour microenvironment, but instead of T-cells it inhibits the checkpoints between tumour cells and myeloid cells (Exhibit 12): myeloid-derived suppressor cells (MDSCs) and tumour-associated macrophages (TAMs). It binds to signal regulatory peptide alpha (SIRPα) on myeloid cells, which inhibits the SIRPα/CD47 interaction (CD47 on the surface of cancer cells). CD47 acts as 'a don't eat me' signal to macrophages of the immune system, so when blocked this increases the likelihood that the myeloid cell recognises the cancer cell as foreign, then attacks and digests the cancer cell. Phagocytosis leads to presentation of cancer antigens on the surface, which stimulates the immune system.

Exhibit 12: OSE-172 mechanism of action



Source: OSE

OSE licensed OSE-172 to BI in April 2018. Under the terms of the agreement, BI will fund all future development including the Phase I trial, which is expected to initiate in 2018. This Phase I trial (design not released yet) will study OSE-172 in multiple solid tumour indications. BI will take over development and commercialisation completely after Phase I.

This is OSE's largest deal in terms of total deal value (€1.1bn potential development, regulatory and sales milestones plus royalties). According to management, this is broken down roughly as 30% development milestones and 70% sales milestones, plus a 10% royalty on worldwide net sales. For context, there have been other preclinical SIRPα/CD47 inhibitor deals in the past few years:

- Celgene in-licensed its CC-90002 (anti-CD47 antibody) from InhibRx in 2012 at preclinical stage for over $500m total deal value including upfront and milestone payments but not including royalties.
- TG Therapeutics in-licensed its anti-CD47 & CD19 antibody TG-1801 from Novimmune also at preclinical stage in June 2018 for $185m in upfront and milestones plus tiered royalties on net sales. This deal was not a straight licence though since both companies will continue to develop the product.

OSE-172 a first-in-class myeloid checkpoint inhibitor

Assets in the CD47 and SIRPα pathway landscape are early stage (Exhibit 13). CD47, which is present in tumour cells, is the more studied target and six companies are studying CD47 monoclonal antibodies in Phase I/II clinical trials. Forty Seven is leading the way with its asset Hu5F9-G4, which is currently being studied in six Phase I/II trials including monotherapy and combinations with targeted therapies or T-cell checkpoint inhibitors. Its most advanced trial is a Phase II trial in non-Hodgkin lymphoma in combination with rituximab in 72 patients and, according to clinicaltrials.gov, has a primary completion date of March 2020. Forty Seven is also developing a SIRPα inhibitor FSI-189, which is in preclinical stage. The only SIRPα inhibitor which is in clinical stage is ALX148, so the data from ALX Oncology will be relevant for OSE.

Exhibit 13: CD47 and SIRPα inhibitors

Pharmacological class	Drug	Company	Indications, stage of development
Anti-CD47 MAb	Hu5F9-G4	Forty Seven	Non-Hodgkin lymphoma [Phase II, in combination with rituximab], solid tumour indications [Phase II], ovarian cancer [Phase I], acute myeloid leukaemia [Phase I], general blood malignancies [Phase I]
	CC-90002	Celgene	Solid tumour indications [Phase I], Acute myeloid leukaemia [Phase I], Myelodysplastic syndrome [Phase I], Multiple myeloma [Phase I], Non-Hodgkin lymphoma [Phase I]
	SRF231	Surface Oncology	General cancer indications [Phase I]
	Anti-CD47 MAb	BIOCAD	Solid tumour indications [Phase I]
	TTI-621	Trillium Therapeutics	Non-Hodgkin lymphoma [Phase I], general blood malignancies [Phase I], solid tumour indications [Phase I], acute lymphocytic leukaemia [Phase I], small cell lung cancer [Phase I]
	TTI-622	Trillium Therapeutics	Non-Hodgkin lymphoma [Phase I], general blood malignancies [Phase I], solid tumour indications [Phase I], acute lymphocytic leukaemia [Phase I], small cell lung cancer [Phase I]
SIRPα inhibitor	ALX148	ALX Oncology	Solid tumour indications [Phase I], Non-Hodgkin lymphoma [Phase I]
	Effi-DEM	OSE Immunotherapeutics	Solid tumour indications [preclinical], hepatoma [preclinical], breast cancer [preclinical], melanoma [preclinical]
	FSI-189	Forty Seven	Solid tumour indications [preclinical]
	DSP107	KAHR Medical	Solid tumour indications [preclinical]

Source: Evaluate Pharma, Clinicaltrials.gov, Edison Investment Research. Note: MAb = monoclonal antibody.

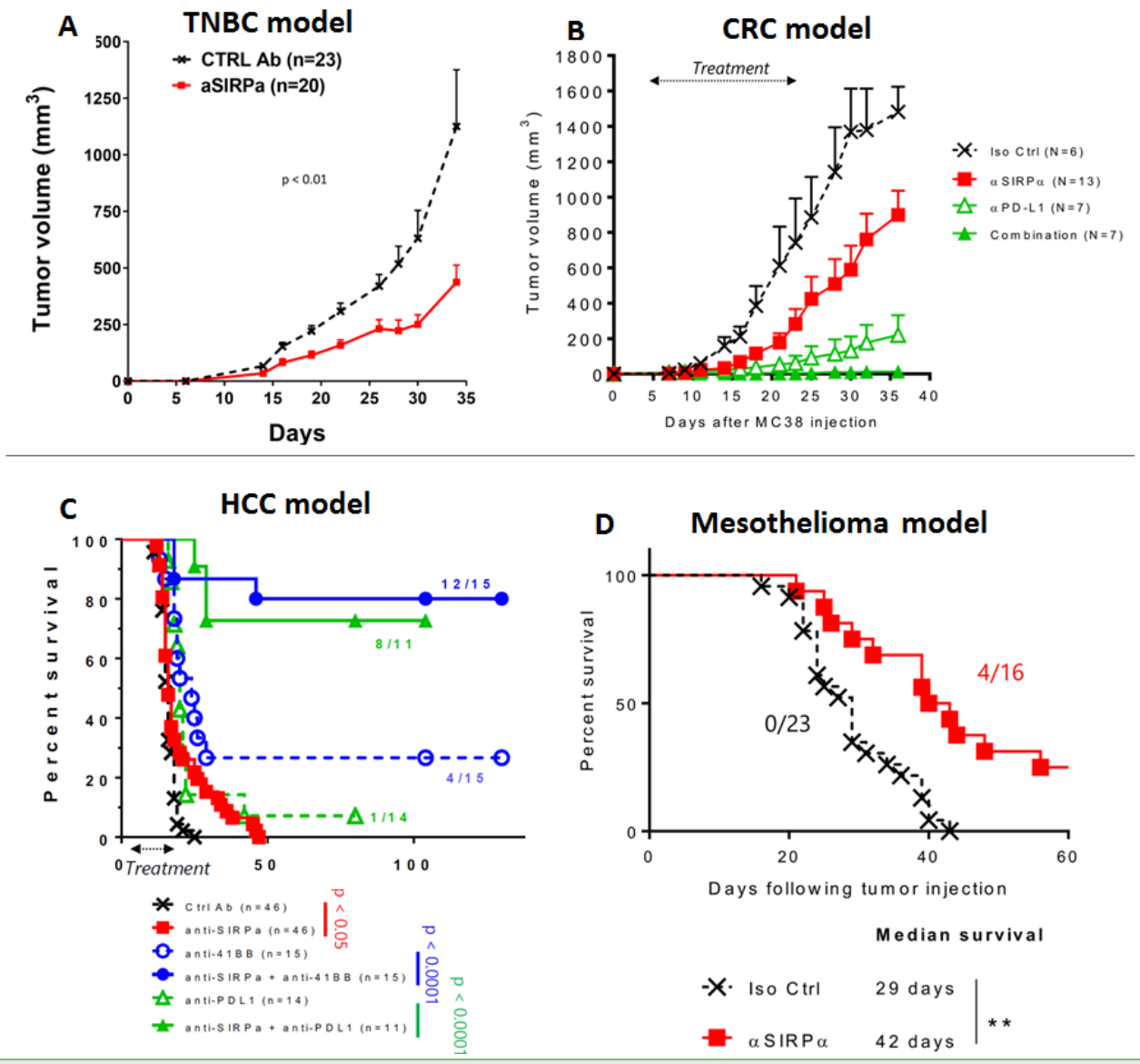
OSE-172 preclinical data

OSE has accumulated proof-of-concept data in various *in vivo* models, which were recently presented at the AACR conference in April 2018. OSE's SIRPα antagonist antibody demonstrated:

- Reduced tumour growth and significantly increased survival in several orthotopic tumour models (Exhibit 14).

- Additional key findings included prevention of tumour lung and liver metastasis in some of the models and positive rebalance in the tumour microenvironment by switching M2 pro-tumorigenic macrophages into M1 anti-tumorigenic macrophages while increasing effector memory CD8 T-cells.
- Interestingly, some of the *in vivo* data suggested that the SIRPα antagonist antibody could act synergistically in combination with checkpoint inhibitors, since it was able to increase overall survival when combined with anti-PDL1 or anti-4-1BB (CD137, a co-stimulatory immune checkpoint receptor).

Exhibit 14: OSE-172 proof-of-concept preclinical data in different *in vivo* models



Source: OSE Therapeutics 2018, Monotherapy with a SIRPα CKI leads to dramatic change in solid tumour microenvironment and prevents metastasis development

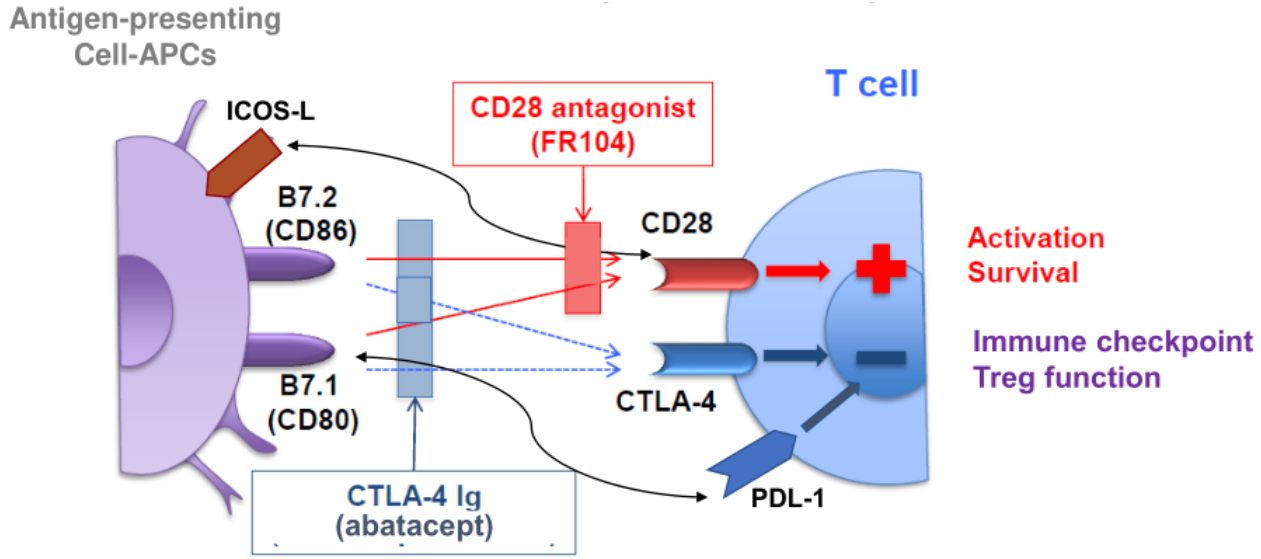
The next step for OSE-172 is a first-in-human study. This Phase I study, for which OSE will be reimbursed by BI, is expected to start in early 2019. The study design and timelines have not been made public yet. A milestone payment will be triggered on Phase I initiation.

FR104: T-cell co-stimulation inhibitor for RA

FR104 is a fragment antigen-binding (Fab) region of an antibody that acts as CD28 antagonist. Currently it is in development for rheumatoid arthritis but could be used in other immune disorders. CD28 acts as co-receptor in the T cell receptor (TCR) and delivers stimulatory signals from antigen presenting cells to T cells. FR104 has a similar mechanism of action to Orencia (abatacept), which blocks T-cell binding to antigen-presenting cells via blocking CD80/86 on antigen-presenting cells, preventing it from binding to the CD28 receptor on the T-cell. In a similar way, Orencia normalises inflammatory mediators in rheumatoid arthritis patients. FR104 blocks the other side, ie the CD28 receptor. The differentiating aspect of FR104 is that, while abatacept blocks both stimulatory and inhibitory signals via CD28 and CTLA-4 respectively, FR104 selectively blocks only the stimulatory signal via CD28 (Exhibit 15).

Orencia is marketed by Bristol-Myers Squibb for RA and peak sales are expected to be $2.8bn in 2020 (source: EvaluatePharma). It is also marketed for juvenile idiopathic arthritis and psoriatic arthritis, and in clinical trials for various other immune disorders. Orencia was the first FDA-approved agent for RA that blocks activation of T-cells, and there are still no other drugs targeting T-cells; nor biosimilars yet for abatacept. We believe there is room for another T-cell co-stimulation inhibitor in RA, and so FR104 has potential. Belatacept is a marketed CD28 antagonist marketed for kidney transplantation in the US with $100m in sales in 2017 (EvaluatePharma). A private Russian biopharmaceutical company TheraMAB is developing an anti-CD28 antibody, albeit it has been described as having an agonistic action. The product is in early stages of development.

Exhibit 15: FR104 mechanism of action



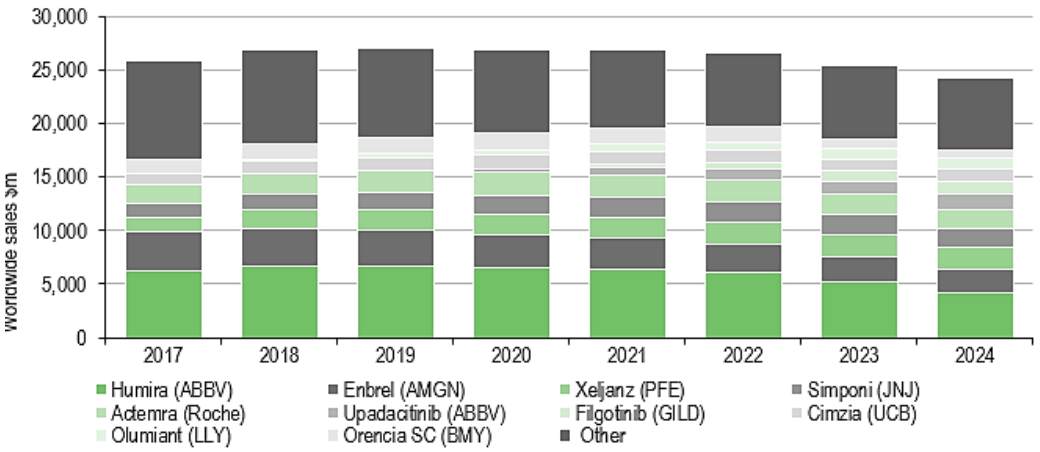
Source: OSE

Rheumatoid arthritis is a chronic autoimmune disease characterised by inflammation in the joints. It affects approximately 1.8 million patients in the US and 1.4 million in Europe (EU14). Patients are treated according to disease severity: mild (23%), moderate (45%) and severe (32%) (GlobalData). Patients with mild RA are usually treated with disease-modifying, anti-rheumatic drugs (DMARDS) as monotherapy such as methotrexate plus steroid therapy if needed. Moderate disease is treated with DMARD monotherapy followed by biologics such as an anti-TNF or non-TNF biologic if required, and finally severe patients may be treated with DMARD combination therapy, anti-TNF or non-TNF biologics.[2]

[2] 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis.

Due to the chronic nature of the disease, high prevalence and introduction of higher priced biologic drugs, RA is a large market. According to EvaluatePharma, the RA market in 2017 was $26.0bn. Anti-TNFs have been the most successful class of RA drug in terms of revenues including Humira (AbbVie), which reached $6.2bn in sales in 2017; Enbrel (Amgen), which reached $4bn peak sales in 2016,[3] and Remicade (J&J) which reached $2.5bn peak sales in 2013. Newer classes of drugs include JAK inhibitors, and anti-IL-6 MAbs.

Exhibit 16: RA market consensus forecasts (total branded drug sales)



Source: EvaluatePharma

However, the market is changing with the introduction of biosimilars, which suggests that the branded market is likely to remain flat and somewhat decline later on. Longer-term dynamics will depend on the novel drug launched, its health benefit and achieved pricing. A GlobalData survey of physicians carried out in 2018 found that biosimilars are already being prescribed extensively for RA, especially in Europe. 69% of physicians surveyed from EU5 countries reported prescribing biosimilars to at least half of their patients. In the US this is much lower at 24%. Marketed and late-stage biosimilars in RA are for anti-TNFs (ie Infliximab, adalimumab, etanercept). However, the introduction of biosimilars is causing pricing pressure in the whole market. For example, Orencia (BMS) costs around $50,000 per patient per year but has many discounts to remain competitive, so only bringing in around $10,000 per patient per year (EvaluatePharma).

So far, FR104 has been studied in Phase I in healthy subjects and OSE has not indicated which subpopulation will be targeted. We assume at this stage that FR104 would be most suitable for moderate/severe RA patients as a 2L/3L therapy similar to Orencia before its label extension in 2008.

FR104 is safe and well tolerated in healthy volunteers

In 2016, OSE completed a Phase I study with FR104, which showed a good safety profile. The study was a first-in-human, randomized, double-blind, placebo-controlled, single centre study evaluating single and multiple ascending intravenous doses of FR104 in healthy subjects. In total, 65 subjects were enrolled and received FR104 intravenously. The endpoints included safety and PK/PD analysis.

The study found that FR104 was well tolerated and the recommended Phase II dose was determined. There were no discontinuations and no deaths. There was only one serious adverse event, nephrolithiasis, which was not deemed to be related to FR104. There were 42 treatment

[3] EvaluatePharma.

emergent adverse events (TEAE, related to the treatment), of which 0 were categorised as severe, 15 were mild, 14 were moderate and 13 were categorised as 'at least possibly treatment-related'.

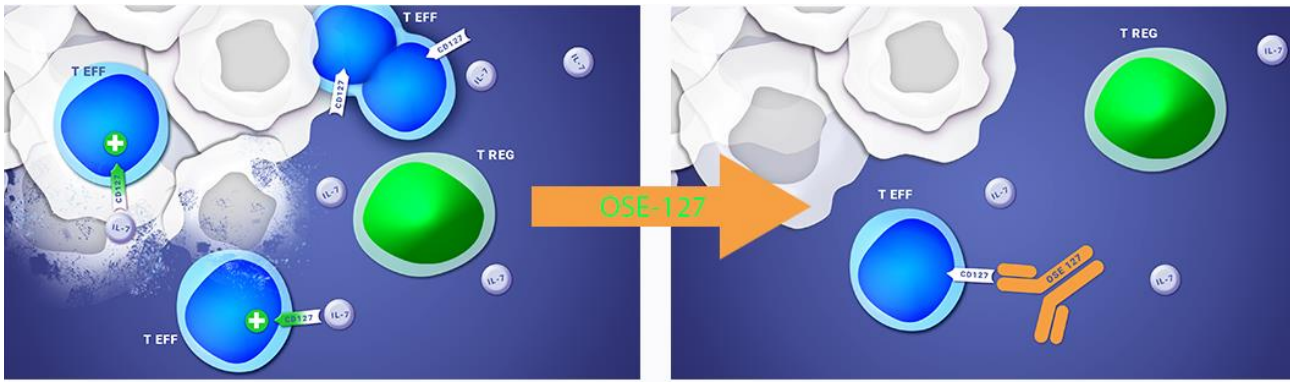
Rights returned from Janssen

In November 2018, Janssen returned the licensing rights to OSE. According to OSE's press release, this was not related to the product itself, since no red flags had been identified, but rather the result of a strategic review and reprioritisation of its immunotherapy portfolio away from rheumatoid arthritis. OSE is now considering all options for further development of FR104, which include developing the asset itself (it has all the necessary data to start the Phase II study) and partnerships. Most likely, the company will try to find a partner as a first step so that it can focus on the Tedopi trial and on its research platform. OSE will receive data from Janssen by the end of 2018, and we therefore expect the company to initiate the business development activities with regard to this asset in early 2019, so an update on this programme could come in later in 2019.

OSE-127: IL-7Rα antagonist for ulcerative colitis

OSE-127 is a humanised monoclonal antibody against IL-7Rα, specifically CD127, in late-stage preclinical development for ulcerative colitis and other autoimmune diseases. IL7 is a cytokine that controls the proliferation, apoptosis and activation of CD4 and CD8 T-cells in humans. OSE-127, a humanized monoclonal antibody, is an antagonist of the IL7 receptor (IL-7R) present on T-cells (CD127), thus down regulating the immune activity.

Exhibit 17: OSE-127 mechanism of action



Source: OSE

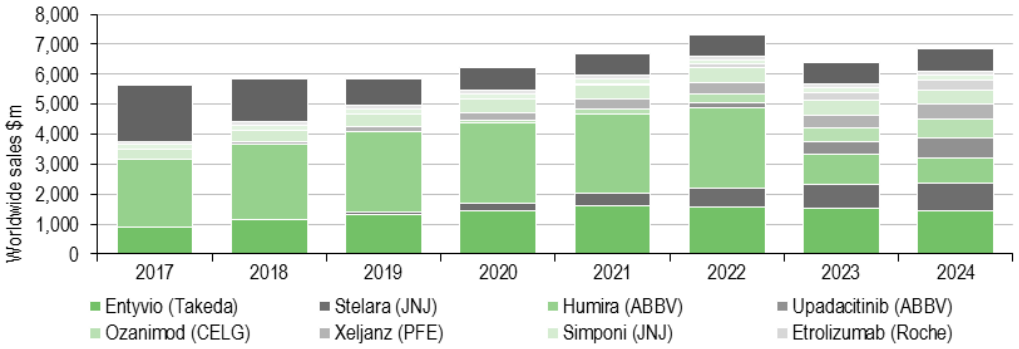
OSE has a commercial agreement with Servier, signed in December 2016. The potential deal value is €272m, including a €10.3m upfront payment (received 2016). The deal involves a two-step €30m option exercise, development/commercial milestones later on and double-digit royalties on sales. OSE is developing the asset until Phase II (each phase will trigger an options exercise fee). Servier will then continue the development of the asset. Servier plans to study OSE-127 in ulcerative colitis and potentially in Sjögren's syndrome. A €12m option exercise fee (first step) is expected in H119.

Ulcerative colitis (UC) is a type of inflammatory bowel disease characterised by inflammation of the gastrointestinal tract (mainly large intestines) and associated symptoms including rectal bleeding and diarrhoea. Patients are treated according to whether they have active disease or are in remission, as well as in relation to the severity of disease, which can be mild, moderate or severe. Approximately 700,000 patients in the US and 600,000 patients in EU14 are treated every year (Global Data).

Exhibit 18 shows the UC market forecast. There are just a few of drugs that currently have blockbuster status in this market, which are Humira (AbbVie) with $2.2bn sales in 2017, and

Entyvio (Takeda) with $0.9bn in sales in 2017. Biosimilars in this market are gaining market share in a similar way to RA. The company has not reached the stage at which it can decide on positioning in this market. However, we expect OSE-127 will most likely be positioned as a 2L/3L treatment after 5-ASAs, steroids, and anti-TNFs.

Exhibit 18: UC market consensus forecasts



Source: EvaluatePharma

Sensitivities

OSE is subject to typical biotech company development risks. The largest part of OSE's value comes from Tedopi in NSCLC. Therefore, a significant risk is the outcome of the Atalante 1 Phase III trial and the success of subsequent activities. If the Phase III trial is successful, OSE plans to partner the asset, which is subject to execution and partnering risks. Our model assumes that Tedopi will be out-licensed and our valuation is therefore sensitive to potential licensing timing and actual deal terms. The main patent of Tedopi expires in 2024, with potential to extend the protection for five years. OSE filed for fresh patents in 2014/15, which are yet to be granted. However, market exclusivity after the launch of Tedopi could be secured if OSE receives orphan drug designation in the US, and the biologicals licence in the US and Europe.

Other significant risks are those relating to OSE's existing commercial partnerships with BI and Servier. As with any licensing agreement, execution is dependent on both parties working together. There is always risk from a partner's change in strategy, which could lead to deprioritisation of the asset. In this case, the asset could be returned to OSE. This was the case when Janssen returned the rights to FR104 to OSE, which is now faced with the task of re-partnering the asset or increasing investment in R&D in order to develop the asset.

OSE is due to receive up to €27m in licensing income in 2019. This is expected to finance the company to early 2021 but if these payments are not received, OSE will have to raise finance in another way to fund its operations.

Valuation

We value OSE based on risk-adjusted NPV analysis using a 12.5% discount rate, including estimated net cash of €7.5m at end-2018. This results in a value of €171m or €11.7/share. We include four assets for four indications in our valuation, namely:

- Tedopi in NSCLC for NSCLC. An investigator-led Phase II trial in pancreatic cancer could potentially be conducted and may prompt OSE to invest in this indication, which we may include in our valuation in the future.

- OSE-172 for triple negative breast cancer (TNBC). The licensing deal with BI stipulated that OSE-172 can be developed for various solid tumours. However, for modelling purposes we chose one indication and based on preclinical data TNBC is one of the potential target diseases for this asset, which we use for our valuation purposes currently. We note that since we use only one indication, we include only half of the deal economics in our model, ie €550m split across R&D and commercial milestones plus royalties.
- FR104 for rheumatoid arthritis.
- OSE-127 for UC. UC and Sjögren's syndrome are envisioned as initial indications for OSE-127. Given that it is currently progressing from preclinical to Phase I studies, we include only UC in our valuation, but will revisit its potential in the future.

Exhibit 19: Assumptions for R&D and commercial projects

Product/stage/indication	Comments
Tedopi ■ Phase III ■ NSCLC	■ Target population total lung cancer incidence rates as 223k in the US and 241k in Europe (see notes for countries) in 2017, with 85% being NSCLC. Stage IIIB/IV approximately 53% of NSCLC cases, resulting in 100k new patients in the US and 108 in Europe. 76% are EGFRwt, and no ALK rearrangements and we estimate most (90%) are treated 1L and 2L with a checkpoint inhibitor and chemotherapy either individually or in combination (Keytruda + chemo). Many of these patients (we estimate 50%) move on to 2L/3L. Of these patients, those that are HLA-A2+ve (45%) are addressable with Tedopi. This results in a target population of around 25k in US and 27k in Europe. Assumed 25% peak penetration, due to specific target population. ■ Pricing*: $70k per patient per year in the US. ■ R&D cost: €21m to complete Phase III study; then out-licensed. ■ Rights: proprietary technology; original patents expire around 2020; new patent applications filed in 2014 and 2015 could extend patent protection until 2035. Tedopi has orphan drug designation in the US (and not in Europe), which could provide 7 years market exclusivity. In addition, BLA pathway would secure 12 years exclusivity in the US and at least 10 years in Europe. ■ Licensing deal: we assume Tedopi will be out-licensed following a positive Phase III outcome in 2021. We assume no upfront or milestones, but with 20% royalties on sales.
FR104 ■ Phase II-ready ■ Rheumatoid arthritis	■ Target population: total treated RA patients is approximately 1.8m in the US and 1.4m in Europe (see notes) in 2017. We take moderate to severe patients (77%), but a conservative penetration of 2%, to reflect the likelihood that FR104 initially will be a 2L/3L therapy for more severe patients. ■ Pricing*: Orencia (BMS) is a comparable drug, and costs around $50k per patient per year but has many discounts so only bringing in around $10-15k per patient per year (EvaluatePharma). We use $15k in our model. ■ R&D cost: assume that OSE will not develop themselves, but will out-license, so we assume no cost to OSE ■ Licensing deal: we assume FR104 will be out-licensed again in 2020 with deal terms somewhat higher than those with Janssen. We assume an upfront of €20m + €180m in R&D and commercial milestones + 10% royalties.
OSE-127 ■ Phase I ■ Ulcerative colitis	■ Target population: total treated UC patients is approx. 690k in the US and 610k in Europe (see notes) in 2017. We take all severities so target population is 100% but take a low penetration of 2%, to reflect the likelihood that OSE-127 will be a 2L/3L therapy for more severe patients, and that a proportion of patients will be in remission. ■ Pricing*: We use $30k in our model to reflect likely pricing pressure from introduction of biosimilars to UC space. Average anti-TNF cost per patient per year is around $50k. ■ R&D cost: OSE financing Phase I and Phase II trial (total cost = €20m). Servier will finance subsequent trials. ■ Licensing deal: deal with Servier - modelled €261.75m in R&D and commercial milestones + 10% royalties.
OSE-172 ■ Phase I-ready ■ Multiple cancer indications	■ Target population: modelled triple negative breast cancer (TNBC) as a potential indication, combined incidence of breast cancer in the US and defined European countries is 494k. 15% of cases are TNBC. We apply a penetration rate of 30%, which gives a target patient population of around 37k in US, and similar in Europe. ■ Pricing*: $70k per patient per year. ■ R&D cost: financed by BI. ■ Licensing deal based on deal terms with BI: Worldwide rights in multiple cancer indications for €1.1bn in R&D and commercial milestones + royalties. Given the early stage of the asset we use only one indication in our model, therefore use only half of the deal economics in our model, ie €550m split across R&D and commercial milestones + royalties.

Source: Edison Investment Research, OSE. Note: Target geographies used in the model are the US, top five European countries, Benelux, Scandinavia, Austria and Switzerland. *Pricing in US; 30% discount applied in Europe, long-term price inflation is at 2.5%.

Exhibits 19 and 20 summarise our detailed assumptions for the risk-adjusted NPV valuation. The two near-term milestone payments from Servier and BI are dependent on the respective assets moving from late preclinical stage to Phase I. Typically, this is a low-risk transition but, to reflect any remaining R&D risk and the fact that ultimately this will be a third-party decision, we include the €12.0m payment from Servier and €15.0m payment from BI in 2019 with a 90% risk adjustment.

For Tedopi, we assume a licensing deal after this Phase III study for which the company may seek a commercial partner rather than building a sales organisation on its own. For FR104, we assume that OSE will not initiate the next Phase II trials on its own, but will focus on establishing a new partnership deal once the data package from Janssen is received (expected by end-2018). We assume better deal terms than those with Janssen, which were signed while the asset was still in

the preclinical stage (currently finished Phase I, more details in Exhibit 19). For OSE-172 and OSE-127, we use the deal terms announced with BI and Servier, respectively.

We have discussed the target populations for each of the assets in the relevant sections above. Once launched, pricing of the products is benchmarked to the relevant drugs currently existing on the market. We use the US, the top five European countries, Benelux, Scandinavia, Austria and Switzerland as key initial markets.

Exhibit 20: Sum-of-the-parts OSE valuation

Product	Launch	Peak sales ($m)	Unrisked NPV (€m)	Unrisked NPV/share (€)	Probability (%)	rNPV (€m)	rNPV/share (€)
Tedopi - NSCLC	2023	657	238.6	16.3	25%	48.3	3.3
FR104 – rheumatoid arthritis	2026	1,056	209.5	14.3	15%	48.1	3.3
OSE-127 – ulcerative colitis	2027	843	164.3	11.2	10%	28.6	2.0
OSE-172 – multiple cancer indications (TNBC)	2027	1,801	248.8	17.0	7.5%	38.5	2.6
Estimated net cash at end-2018			7.5	0.5	100%	7.5	0.5
Valuation			**868.7**	**59.3**		**171.0**	**11.7**

Source: Edison Investment Research. Note: WACC = 12.5% for product valuations.

Financials

In its H118 financial results, OSE reported €20.6m in revenues (vs €2.8m in H117). This includes the upfront payment from BI for OSE-172 received in April 2018. Total operating expenses for H118 were €10.2m vs €7.3m in H117. R&D expenses are the company's largest expense: €8.0m in H118 vs €7.9m in H117. The largest contributor is the Tedopi Atalante 1 Phase III study. We expect R&D costs to remain largely constant at €8m per six months of operation until the end of the trial in 2021. This is because we expect other clinical trials to be fully financed by the partner and grants for the cost will be relatively low for the preclinical and some clinical work. We do not expect OSE to initiate its own Phase II study with FR104, recently returned from Janssen, so we do not factor in any costs relating to future studies in our financial model, as we expect the company to seek a partner. Overhead expenses were €1.73m in H118 vs €1.78m in H117. OSE's operations are currently funded through its partnerships and Bpifrance grants, where some grants relate to a particular R&D project.

As of 30 June 2018, OSE had cash, cash equivalents and financial assets of €18.6m (includes 'current financial assets'). Last reported (H118) results also include debt of €4.9m, which is mainly government loans. According to management, current cash burn is around €15m per year. Therefore, current cash is expected to last into H219. If both milestone payments totalling €27m are received in H119 (from Servier and BI), the cash runway should extend into early 2021. If these payments are not received, OSE may have to raise funds in another way or adjust its R&D activities. While we expect these milestones to be paid, we do not include them in our model currently.

Exhibit 21: Financial summary

€000s	2016	2017	2018e	2019e
December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	383	6,682	20,608	0
Cost of Sales	0	0	0	0
Gross Profit	383	6,682	20,608	0
Research and development	(5,149)	(14,641)	(15,000)	(15,000)
EBITDA	(6,760)	(12,502)	431	(19,870)
Operating Profit (before amort. and except.)	(87,601)	(98,146)	(6,867)	(12,625)
Intangible Amortisation	24,365	0	0	0
Exceptionals	0	0	0	0
Other	0	0	0	0
Operating Profit	17,498	(12,625)	802	(19,950)
Net Interest	0	0	9	(1)
Profit Before Tax (norm)	(6,867)	(12,625)	811	(19,951)
Profit Before Tax (reported)	17,498	(12,625)	811	(19,951)
Tax	3,074	2,238	0	0
Profit After Tax (norm)	(3,793)	(10,387)	811	(19,951)
Profit After Tax (reported)	20,572	(10,387)	811	(19,951)
Average Number of Shares Outstanding (m)	25.8	12.5	14.4	14.5
EPS - normalised (€)	(0.30)	(0.72)	0.06	(1.36)
EPS - normalised and fully diluted (€)	(4.22)	(0.30)	(0.72)	0.06
EPS - (reported) (€)	1.64	(0.72)	0.06	(1.36)
Dividend per share (€)	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	N/A
EBITDA Margin (%)	N/A	N/A	2.1	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	53,009	53,367	53,721	53,641
Intangible Assets	52,600	52,600	52,600	52,600
Tangible Assets	110	429	800	720
Investments	299	338	321	321
Current Assets	30,084	12,655	15,756	6,282
Stocks	0	0	0	0
Debtors	12,318	127	3,400	3,400
Cash	14,885	9,646	9,474	0
Other	2,881	2,882	2,882	2,882
Current Liabilities	(18,663)	(14,497)	(12,595)	(12,595)
Creditors	(18,076)	(13,908)	(12,006)	(12,006)
Short term borrowings	(587)	(589)	(589)	(589)
Long Term Liabilities	(6,358)	(7,409)	(8,043)	(17,067)
Long term borrowings	(1,197)	(4,296)	(4,296)	(13,320)
Other long-term liabilities	(5,161)	(3,113)	(3,747)	(3,747)
Net Assets	58,072	44,116	48,839	30,261
CASH FLOW				
Operating Cash Flow	682	(7,995)	(181)	(18,497)
Net Interest	0	0	9	(1)
Tax	0	0	0	0
Capex	0	0	0	0
Acquisitions/disposals	0	0	0	0
Financing	(440)	(50)	0	0
Other	4,507	(295)	(0)	0
Dividends	0	0	0	0
Net Cash Flow	4,749	(8,340)	(172)	(18,498)
Opening net debt/(cash)	(8,352)	(13,101)	(4,761)	(4,589)
HP finance leases initiated	0	0	0	0
Other	0	0	0	0
Closing net debt/(cash)	(13,101)	(4,761)	(4,589)	13,909

Source: OSE Immunotherapeutics accounts, Edison Investment Research

Contact details	Revenue by geography
22, boulevard Benoni Goullin 44200 Nantes France +33 (0)2 28 29 10 10 www.ose-immuno.com/en	N/A

Management team

CEO: Alexis Peyroles	Chairman & director of early development: Dr Dominique Costantini
Alexis Peyroles has more than 20 years of international management and financial control experience, having served in multiple related positions. Since 2013, he has been involved in OSE Pharma, both as CFO and in charge of business development. From May 2016 (the date of OSE Pharma's merger with Effimune) to April 2018, he served as COO of OSE Immunotherapeutics, in charge of finance, business development and operations. Alexis graduated from EDHEC Business School and holds an Executive MBA from Imperial College in London.	With more than 25 years of experience in management positions in the pharmaceutical industry (HMR, now Sanofi), Dr Dominique Costantini has overseen many therapeutic innovations and was involved in the development of numerous medicines. In 1997, she founded and led as CEO BioAlliance Pharma (now Onxeo), a biotech company specializing in oncology and supportive care. In 2012, Dominique founded and was CEO of OSE Pharma, a biotech company in cancer immunotherapy. She served as CEO and director of the company, subsequently renamed OSE Immunotherapeutics, until April 2018. Dominique is a medical doctor (Paris V University), specialising in immunology.
Vice chairman & director of strategy: Maryvonne Hiance	**Chief operating officer, director of R&D and international scientific collaborations: Bernard Vanhove**
Maryvonne Hiance specialises in nuclear science. Over a 20-year period, she held the position of general manager at innovative biotechnology companies including SangStat Atlantic, DrugAbuse Sciences and TcLand. In 2008, she co-founded and served as CEO for Effimune, a biotechnology company specialised in immune regulation with clinical applications in autoimmunity, transplantation and immunoncology. Since the merger of Effimune with OSE Pharma in 2016, she has been vice chairman of the board and director of strategy of OSE Immunotherapeutics. Maryvonne has an engineering degree from the Ecole Polytechnique Féminine (Paris) and a nuclear engineering degree from Polytech Grenoble (formerly the Institut des Sciences et Techniques de Grenoble).	Bernard Vanhove has extensive international scientific experience. He served as research director at the Centre National de Recherche Scientifique (CNRS, French National Scientific Research Institute), the Institut National de la Santé et Recherche Médicale (INSERM, National Institute for Health and Medical Research) and the Institut de Transplantation-Immunologie-Urologie (ITUN, Institute of Transplantation in Immuno-urology). In 2008, Bernard co-founded Effimune. On the merger of Effimune with OSE Pharma in May 2016, he was appointed COO of OSE Immunotherapeutics, in charge of R&D and international scientific collaborations. Bernard holds a PhD in Immunology from the Louvain University, Belgium.

Principal shareholders	(%)
Groupe Emile Loria	28.5
Emile Loria	18.6
Dominique Costantini	12.8
MS Medical Synergy	5.7
Debiopharm Diagnostics	2.6
Aparna Consulting	2.6
Maryvonne Hiance	2.4

Companies named in this report

Boehringer Ingelheim, Janssen, Servier

EDISON

General disclaimer and copyright

This report has been commissioned by OSE Immunotherapeutics and prepared and issued by Edison, in consideration of a fee payable by OSE Immunotherapeutics. Edison Investment Research standard fees are £49,500 pa for the production and broad dissemination of a detailed note (Outlook) following by regular (typically quarterly) update notes. Fees are paid upfront in cash without recourse. Edison may seek additional fees for the provision of roadshows and related IR services for the client but does not get remunerated for any investment banking services. We never take payment in stock, options or warrants for any of our services.

Accuracy of content: All information used in the publication of this report has been compiled from publicly available sources that are believed to be reliable, however we do not guarantee the accuracy or completeness of this report and have not sought for this information to be independently verified. Opinions contained in this report represent those of the Edison analyst at the time of publication. Forward-looking information or statements in this report contain information that is based on assumptions, forecasts of future results, estimates of amounts not yet determinable, and therefore involve known and unknown risks, uncertainties and other factors which may cause the actual results, performance or achievements of their subject matter to be materially different from current expectations.

Exclusion of Liability: To the fullest extent allowed by law, Edison shall not be liable for any direct, indirect or consequential losses, loss of profits, damages, costs or expenses incurred or suffered by you arising out or in connection with the access to, use of or reliance on any information contained on this note.

No personalised advice: The information that we provide should not be construed in any manner whatsoever as, personalised advice. Also, the information provided by us should not be construed by any subscriber or prospective subscriber as Edison's solicitation to effect, or attempt to effect, any transaction in a security. The securities described in the report may not be eligible for sale in all jurisdictions or to certain categories of investors.

Investment in securities mentioned: Edison has a restrictive policy relating to personal dealing and conflicts of interest. Edison Group does not conduct any investment business and, accordingly, does not itself hold any positions in the securities mentioned in this report. However, the respective directors, officers, employees and contractors of Edison may have a position in any or related securities mentioned in this report, subject to Edison's policies on personal dealing and conflicts of interest.

Australia

Edison Investment Research Pty Ltd (Edison AU) is the Australian subsidiary of Edison. Edison AU is a Corporate Authorised Representative (1252501) of Myonlineadvisers Pty Ltd who holds an Australian Financial Services Licence (Number: 427484). This research is issued in Australia by Edison AU and any access to it, is intended only for "wholesale clients" within the meaning of the Corporations Act 2001 of Australia. Any advice given by Edison AU is general advice only and does not take into account your personal circumstances, needs or objectives. You should, before acting on this advice, consider the appropriateness of the advice, having regard to your objectives, financial situation and needs. If our advice relates to the acquisition, or possible acquisition, of a particular financial product you should read any relevant Product Disclosure Statement or like instrument.

New Zealand

The research in this document is intended for New Zealand resident professional financial advisers or brokers (for use in their roles as financial advisers or brokers) and habitual investors who are "wholesale clients" for the purpose of the Financial Advisers Act 2008 (FAA) (as described in sections 5(c) (1)(a), (b) and (c) of the FAA). This is not a solicitation or inducement to buy, sell, subscribe, or underwrite any securities mentioned or in the topic of this document. For the purpose of the FAA, the content of this report is of a general nature, is intended as a source of general information only and is not intended to constitute a recommendation or opinion in relation to acquiring or disposing (including refraining from acquiring or disposing) of securities. The distribution of this document is not a "personalised service" and, to the extent that it contains any financial advice, is intended only as a "class service" provided by Edison within the meaning of the FAA (i.e. without taking into account the particular financial situation or goals of any person). As such, it should not be relied upon in making an investment decision.

United Kingdom

Neither this document and associated email (together, the "Communication") constitutes or form part of any offer for sale or subscription of, or solicitation of any offer to buy or subscribe for, any securities, nor shall it or any part of it form the basis of, or be relied on in connection with, any contract or commitment whatsoever. Any decision to purchase shares in the Company in the proposed placing should be made solely on the basis of the information to be contained in the admission document to be published in connection therewith.

This Communication is being distributed in the United Kingdom and is directed only at (i) persons having professional experience in matters relating to investments, i.e. investment professionals within the meaning of Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the "FPO") (ii) high net-worth companies, unincorporated associations or other bodies within the meaning of Article 49 of the FPO and (iii) persons to whom it is otherwise lawful to distribute it. The investment or investment activity to which this document relates is available only to such persons. It is not intended that this document be distributed or passed on, directly or indirectly, to any other class of persons and in any event and under no circumstances should persons of any other description rely on or act upon the contents of this document (nor will such persons be able to purchase shares in the placing).

This Communication is being supplied to you solely for your information and may not be reproduced by, further distributed to or published in whole or in part by, any other person.

United States

The Investment Research is a publication distributed in the United States by Edison Investment Research, Inc. Edison Investment Research, Inc. is registered as an investment adviser with the Securities and Exchange Commission. Edison relies upon the "publishers' exclusion" from the definition of investment adviser under Section 202(a) (11) of the Investment Advisers Act of 1940 and corresponding state securities laws. This report is a bona fide publication of general and regular circulation offering impersonal investment-related advice, not tailored to a specific investment portfolio or the needs of current and/or prospective subscribers. As such, Edison does not offer or provide personal advice and the research provided is for informational purposes only. No mention of a particular security in this report constitutes a recommendation to buy, sell or hold that or any security, or that any particular security, portfolio of securities, transaction or investment strategy is suitable for any specific person.

Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
295 Madison Avenue, 18th Floor
10017, New York
US

Sydney +61 (0)2 8249 8342
Level 4, Office 1205
95 Pitt Street, Sydney
NSW 2000, Australia