EDISON

Medigene

Outlook

New assets, new partnerships

Pharma & biotech

Medigene continues to position itself as a leader in cellular therapies by the expansion of both its internal pipeline (MDG1021) and external partnerships (Roivant/Cytovant). The company has announced MDG1021 (HA-1 targeting TCR) will start its clinical programme in 2020. A new partnership with Roivant/Cytovant (total deal terms >$1bn) demonstrates the ongoing value third parties see in Medigene's technology and expertise. Medigene's MDG1011 trial in multiple myeloma (MM), acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS) is ongoing and the first patient has been treated; we now forecast initial data in H120. We have added the Roivant/Cytovant deal to our valuation and have removed Veregen following the sale of remaining rights and inventory to Aresus Pharma. We now value Medigene at €460m (previously €470m).

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/17	8.9	(15.1)	(0.72)	0.0	N/A	N/A
12/18	7.8	(16.5)	(0.70)	0.0	N/A	N/A
12/19e	10.7	(25.9)	(1.05)	0.0	N/A	N/A
12/20e	9.7	(24.7)	(1.01)	0.0	N/A	N/A

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

Roivant/Cytovant: $10m upfront with $1bn+ potential

Under the terms of the deal with Roivant/Cytovant (rights in Greater China, South Korea and Japan), Medigene has been awarded $10m as an upfront payment, in addition to over $1bn in potential future milestone payments and royalties on future net sales. Medigene has granted Roivant/Cytovant exclusive licence to an NY-ESO-1 targeting TCR and a dendritic cell (DC) vaccine targeting Wilms Tumour-1 (WT-1) and preferentially expressed antigen of melanoma (PRAME). An additional discovery agreement has been made covering TCRs for two undisclosed targets.

TCR and DC clinical trials mark major milestones

Medigene has enrolled its first patient (12 expected in Phase I) in its Phase I/II clinical trial for MDG1011 TCR in patients with refractory/relapsed (r/r) MM, AML or MDS. Due to the complexities of enrolment, we expect initial data are possible in H120, not late 2019. New treatment centres are being added in an effort to speed up patient enrolment. Positive top-line interim data were announced at the end of 2018 for the Phase I/II DC vaccine trial, which is expected to complete by year end.

MDG1021: HA-1 into the clinic

Medigene has announced it will take a TCR targeting HA-1 (MDG1021) into the clinic in 2020 for patients with relapsed/persistent hematologic malignancies after allogeneic haematological stem cell transplantation. The trial will be sponsored by Medigene and conducted by partners at Leiden University Medical Center.

Valuation: €460m (€18.72/share)

We value Medigene at €460m (€18.72/share) vs €470m (€19.16/share). We now include the Roivant/Cytovant deal in our valuation and have updated our launch timelines for MDG1011. We have also rolled our model forward and updated for FX.

19 June 2019

Price	**€7.56**
Market cap	**€186m**
	$1.12/€
Net cash (€m) at 31 March 2019 (including time deposits) – does not include $10m Cytovant upfront	65.5
Shares in issue	24.6m
Free float	80.3
Code	MDG1
Primary exchange	Frankfurt (Xetra)
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(10.0)	(13.0)	(39.2)
Rel (local)	(10.7)	(17.8)	(36.8)
52-week high/low		€15.29	€7.29

Business description

Medigene is a German biotech company with complementary technology platforms in cancer immunotherapy. Its lead T-cell receptors (TCRs) and dendritic cell vaccines are both in Phase I/II clinical studies.

Next events

H119 results	7 August 2019
DC vaccine full clinical data	End 2019
MDG1011 initial clinical data	Early 2020

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Edison profile page

Medigene is a research client of Edison Investment Research Limited

Investment summary

Company description: Focus on immunotherapy

Medigene, an immunotherapy focused clinical company, is developing its three technologies, DC vaccines, adoptive TCR therapy and T-cell specific antibodies (TABs), for use in cancers. The purchase of privately-held Trianta Immunotherapies in January 2014 was a transformational transaction, positioning Medigene as an emerging cancer immunotherapy player. Originally founded in 1994 as a spin-out of the Munich Gene Center, Medigene raised €125m in its Frankfurt Stock Exchange IPO in 2000, and its legacy assets – Eligard (prostate cancer), EndoTAG-1 (breast cancer), RhuDex (autoimmune) and Veregen (genital warts) – have now been sold or out-licensed. It retains a stake in Immunocore (valued at €5.4m as of 31 December 2018). Medigene employs 118 staff (at end December 2018) and its headquarters are in Munich, Germany.

Valuation: €460m (€18.72/share)

We value Medigene at €460m (€18.72/share) based on a risk-adjusted NPV. Our model includes MDG1011, AML DC vaccine, deal metrics for the bluebird bio collaboration and Imlygic royalties. Following the sale of the remaining rights of Veregen to Aresus Pharma we have now removed the asset from our valuation. We now include the Roivant/Cytovant deal in our valuation and value the NY-ESO-1 TCR, PRAME and WT-1 DC vaccine and the two undisclosed TCR discovery programmes. We have adjusted timelines for MDG1011 and the bluebird collaboration. We now expect first MDG1011 data in 2020 (previously 2019) and have pushed back our forecast out-license and launch of MDG1011 into 2020 (previously 2019) and 2023 (previously 2021), respectively. For bluebird, we now expect the first product (MAGE-A4 TCR) from the partnership to enter a Phase I trial in 2020 (previously 2018).

Financials: Funded past full TCR and DC readouts

Boosted by a gross €32.3m raise in May 2018 and the expanded partnership with bluebird ($8m, upfront), Medigene reported a 31 March 2019 net cash position of €65.5m. This was recently improved further by the $10m (c €9m) upfront received from the Roivant/Cytovant partnership. We forecast a cash runway into FY21, which should enable full readouts of its Phase II DC vaccine trial and TCR trial. We have updated our forecasts to reflect the Roivant/Cytovant deal, Veregen deal and new financial guidance by Medigene. We forecast revenue of €10.7m in 2019, which includes approximately $3.3m of the $10m Roivant/Cytovant upfront (deferred over three years). We have increased our FY19 R&D forecasts to €27.4m vs €21.7m previously, as clinical trial costs continue to ramp following the initiation of the MDG1011 clinical trial. We forecast SG&A will rise year-on-year to €11.5m (vs FY18 €7.6m) driven by a non-cash loss of c €4.5m from the sale of Veregen rights (compensated by income interest receipts from 2021). We now forecast an FY19 EBITDA loss of €27.6m vs a loss of €17.9m previously.

Sensitivities: Competing in a hot sector

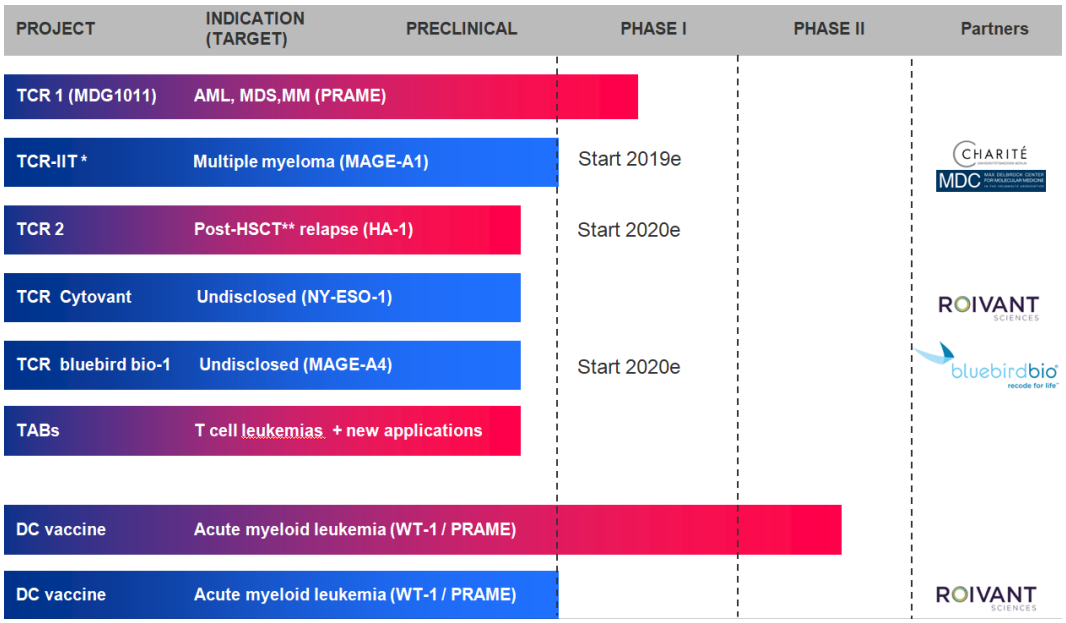
Medigene is subject to the risks typically associated with biotech company drug development, including the possibility of unfavourable outcomes in clinical trials, success of competitors and commercial decisions by partners or potential partners. Cancer immunotherapy has become a highly competitive landscape and Medigene's technology platforms are still in relatively early stages of development. The outcomes of the DC vaccine trial and the PRAME TCR trial are therefore key sensitivities. Equally, multiple companies have more advanced DC vaccines and TCRs in development, which could limit the market opportunity for Medigene's candidates and restrict the cancer targets that may be pursued.

A growing list of assets and partnerships

Medigene is positioning itself at the forefront of the next wave of cell and gene therapies that aim to genetically alter a patient's cells to combat cancer. Medigene's most advanced technologies are its TCR therapies and DC vaccines. Key assets (Exhibit 1) are MDG1011 (TCR that targets PRAME), which has just enrolled the first patient in its Phase I trial in AML, MM and MDS; and its DC vaccine (presenting the WT-1 and PRAME antigens), which has recently presented positive interim data from its Phase I/II trial in AML. Both technologies aim to utilise a patient's immune system to target cancer cells, whether directly or indirectly. In the case of TCR therapies, ex-vivo (cells removed from a patient) genetic modification of a patient's T-cell to include a specific cancer antigen targeting T-cell receptor (TCR) enable a direct approach (once modified cells are administered back into a patient) to generate an immune response to a cancer cell. T-cell receptors are a T-cell's natural receptors; in the body these recognise and bind to antigens presented by cells. While indirectly DC cancer vaccines aim to present cancer associated antigens to the immune system in the hope they will train the body's T-cells to attack cancer cells that present these antigens.

TCR therapies hold the greatest potential of the two technologies as similar CAR-T cellular therapies have demonstrated the power of direct cancer targeting. TCRs additionally have a theorised advantage over CAR-Ts in that they can target a wider range of antigens, particularly intracellular antigens, which get presented on the surface of a cell by the MHC (major histocompatibility complex). The ability to target the antigens that CAR-Ts cannot could prove a major advantage, particularly in solid cancers where tumour exclusive targets remain allusive. However, it should be noted that TCRs are incredibly complex and to date no TCR product has been clinically approved. The engineering of the cell product, particularly the TCR, in addition to the selection of the right cancer antigen are likely to be critical to any success. Medigene additionally has an earlier-stage TAB platform that utilises its recombinant TCR technologies in order to produce, isolate and characterise monoclonal antibodies specific to TCR structures. TABs recognise T-cells based on their unique T-cell receptors and can therefore distinguish between different T-cells expressing different TCRs.

Exhibit 1: Medigene pipeline



Source: Medigene

Medigene's expertise with these technologies continues to rapidly evolve as evidenced by numerous scientific achievements in 2018 and 2019. This technology is beginning to transition

towards the clinic with HA-1 targeting TCR for post-HSCT (haematopoietic stem cells transplant) relapse patients now expected by Medigene to enter the clinic in 2020. External validation of Medigene's technology continues to grow with the expansion of the bluebird partnership in September 2018 and the recent announcement of the partnership with Roivant/Cytovant. Partner bluebird continues to see significant value in Medigene's TCR technology and has recently announced the target (MAGE-A4) of the first TCR product candidate developed in the partnership. It expects to take the MAGE-A4 TCR product candidate into the clinic in 2020.

The core inflection point for Medigene remains the readout of Medigene's first internal TCR product candidate (MDG1011), which we now expect will readout early Phase I data in early 2020 (delayed from our original forecast of 2019 due to complexities in patient recruitment). We note other potential major inflection points over the next 12–18 months in the progression of the bluebird bio collaboration, the Roivant/Cytovant collaboration, the full readout of the DC vaccine Phase II trial (trial completion expected by end 2019) and the initiation of the investigator (Charité and Max Delbrück Centre) led melanoma-associated antigen 1 (MAGE-A1) TCR trial (forecast by Medigene to be initiated in 2019) in MM patients.

Roivant/Cytovant: $10m upfront with $1bn+ potential

Medigene has announced a new partnership with Roivant and Sinovant, which have launched Cytovant, a new biopharmaceutical company focused on developing cellular therapies in Asia. Under the terms of the deal with Roivant/Cytovant (rights in Greater China, South Korea and Japan), Medigene has been awarded $10m as an upfront payment, in addition to over $1bn in potential future milestone payments and royalties on future net sales. The deal grants Roivant/Cytovant exclusive licence (in the aforementioned Asia regions) to an NY-ESO-1 targeting TCR and a DC vaccine targeting WT-1 and PRAME. An additional discovery agreement has been made covering TCRs for two undisclosed targets.

Medigene's NY-ESO-1 TCR is believed to be HLA-A*02 restricted, which could limit the patient population in Asia, as HLA-A*02 is typically more common in western populations. However, it is likely Roivant/Cytovant would look to develop an NY-ESO-1 TCR that is relevant for the local population. Human leukocyte antigen (HLA) system is a gene complex that encodes MHC (major histocompatibility complex presents antigens on both healthy and cancerous cells) proteins in humans and there are known to be hundreds of HLA types, which occur in different frequencies in humans. The correct identification of a patient's HLA type is needed for a TCR to work effectively.

The most advanced NY-ESO-1 asset globally is GSK3377794, which is in development by GSK (licensed in August 2018 from partner Adaptimmune). GSK3377794 utilises GSK's SPEAR T-cell technology and is HLA-A*02 specific. Most recent clinical data were published in May 2018 on 12 patients with synovial sarcoma, who demonstrated an overall response rate (ORR) of 50% (6/12) with one confirmed complete response (CR) and five confirmed partial responses (PRs). Duration of response (DoR) was 30.9 weeks with median time to initial response of 6.2 weeks. Median progression-free survival (PFS) was 15 weeks (range 8–38 weeks) with an estimated median OS of 120 weeks. GSK is expected to rapidly advance the asset towards commercialisation with a launch potentially in 2021/22 in the US and the EU.

Bluebird expansion and first collaboration asset named

Medigene's expansion of the bluebird partnership (see our update note, bluebird bio back for more) to include an additional two TCRs takes the total to six ongoing programmes. The expansion includes a one-off payment of €8m to Medigene and up to €250m in potential milestone payments per candidate. The original deal was signed in September 2016 to cover four targets and we believe this expanded agreement further validates Medigene's expertise in this area, particularly Medigene's unique platform for identifying and characterising specific TCRs to target antigens.

bluebird has recently announced the target (MAGE-A4) of the first TCR product candidate developed in the partnership and it plans to take the MAGE-A4 TCR product candidate into the clinic in 2020. MAGE-A4 is a member of the melanoma antigen gene (MAGE) protein family and is highly expressed in a number of cancer types (melanoma, breast, colon and ovarian) while retaining low expression in healthy tissues.

One of the most advanced assets in the sector is in development by Adaptimmune, which is developing a TCR targeting MAGE-A4 (ADP-A2M4). ADP-A2M4 is being tested in a Phase I, open-label trial in a range of cancer patients who are HLA-A*02 positive. The trial is expected to enrol 42 patients and has to date completed three dose expansion groups (100 million, 1 billion and 5 billion cells) and is in an ongoing expansion group (up to 10 billion cells). The first two cohorts (100 million and 1 billion) were in six ovarian patients and demonstrated limited efficacy (one patient initially had 27% reduction but progressed at week 12). In cohort 3 (5 billion cells) and the expansion phase (up to 10 billion cells) a total of 10 synovial patients were treated (five of whom received the maximum dose of 10 billion cells), of which 4 of 5 at the highest dose (10 billion cells) demonstrated a partial response. Responses in other tumour types to date have been minimal. Adverse events for all tumour types have been typical of patients treated with other cell therapies.

As shown by Adaptimmune's data, selecting the correct indications and dose will be critical to the success of any MAGE-A4 TCR product. However, arguably the correct T-cell/TCR design is more important. Using Medigene's technology, a TCR has been selected that Medigene and bluebird believe has the highest possible avidity needed to drive tumour response. In tumour xenograft models, the MAGE-A4 TCR demonstrated durable tumour elimination beyond that of a NY-ESO-1 TCR. Additionally, the TCR has been shown to be co-receptor independent and able to generate cytotoxicity in both CD8 and CD4 T-cell populations. Both bluebird and Medigene carried out significant work to ensure limited cross-reactivity of the TCR with other antigens.

In addition to selecting the correct TCR, bluebird is designing extra features into the T-cells to promote the best response in solid tumours. Solid tumours have an immunosuppressive environment that often prevents T-cells acting. TGFβ is a key example of this and is believed to be a master regulator of T-cell response. It is expressed by a range of cancers and will stimulate a reduction in T-cell cytokine production, proliferation and activity when bound by T-cell receptors. To combat this, bluebird has edited the TGFβ T-cell receptor to reverse this suppression of T-cell activity and instead stimulate cytokine production, proliferation and activity ('signal converter technology'). Thus, cancer cells would now provide T-cells with a stimulatory factor that aids their own destruction. In a CAR-T model using signal-converter technology, complete reduction in tumour volumes were demonstrated in mouse models, contrasted with minimal reduction in tumour volume when using only a CAR-T. When the mice were re-challenged with a new tumour on the opposite side of the body, the cancer was quickly eliminated.

The Mage-A4 TCR is expected to enter the clinic in 2020 in a range of cancers.

MDG1011: PRAME+ TCR treats first patient

Medigene's MDG1011 is an adoptive TCR therapy targeting PRAME that aims to directly attack a cancer in an approach similar to that of other approved cell therapies such as Kymriah (Novartis) and Yescarta (Kite/Gilead). A Phase I/II clinical trial testing MDG1011 in r/r MM, AML and MDS is ongoing and the first patient (MM) has been treated.

The first regulatory approvals of Kymriah (Novartis) and Yescarta (Kite/Gilead), which are approved to treat paediatric acute lymphoblastic leukaemia (ALL) and adult diffuse large B-cell lymphoma (DLBCL) respectively have demonstrated an appetite for cellular therapies. Limited initial commercial success of these therapies (Kymriah FY18 sales: $76m, Yescarta: $264m), due to

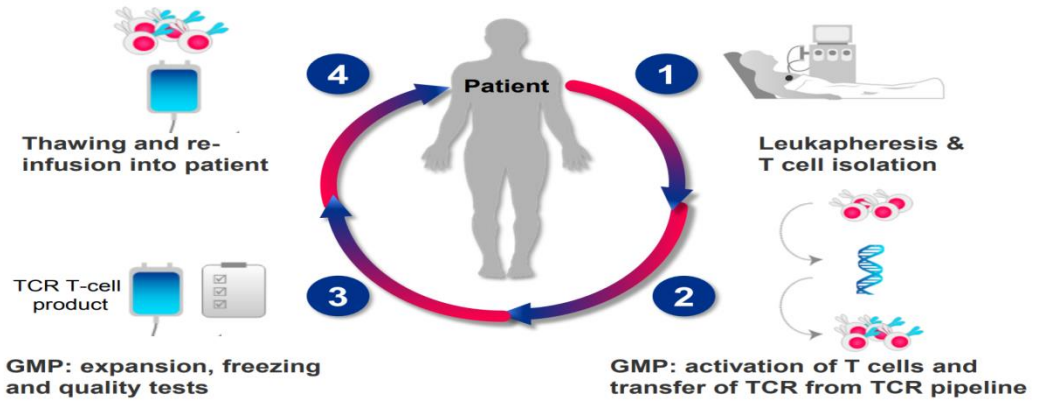
complexities in manufacturing, logistics, reimbursement and patient access has dampened original excitement; however, we continue to believe the long-term potential of cellular therapies remains valid. As such, the treatment of patients in Medigene's MDG1011 Phase I/II TCR trial is a major inflection point for the company. If early signs of strong efficacy are observed, data from the Phase II component of the trial could form part of an accelerated regulatory filing. However, we note that commercial success is no longer guaranteed by a regulatory approval. New therapies need to beat the current standard of care and also need to be competitive with any new treatments in development. Additionally, ease of use and affordability is critical to the success of cellular therapies.

Due to slower than expected patient enrolment, we now expect first MDG1011 data in 2020 (previously 2019) and have pushed back our forecast out-license and launch of MDG1011 to 2020 and 2022 respectively.

MDG1011: Expansive Phase I/II trial

Each treatment (Exhibit 2) is personalised to a patient (autologous) by removing and isolating their T-cells (leukapheresis), modifying these cells to express the relevant TCR/HLA complex (HLA-A*2:01 restricted TCR specific to PRAME) by incubation with a viral vector, expanding the cells and then reinfusing them into the patient. Patient screening is ongoing with one patient having received treatment to date. Strict enrolment criteria (eg PRAME+ and HLA-A*02:01+) mean that only 10–20% of potential patients are eligible for treatment and patient enrolment has been slower than originally expected. Medigene has chosen PRAME as its first target to test clinically as it is believed to be prevalent on tumour cells and show limited expression on most healthy cells (except for abundance in the testis). In melanomas, PRAME expression is thought to occur in c 90% of cancerous tissue and up to c 50–65% in AML, whereas expression has been demonstrated to exist across other cancers including, but not limited to, non-small cell lung cancer, Hodgkin's lymphomas and breast carcinomas.

Exhibit 2: TCR manufacturing process



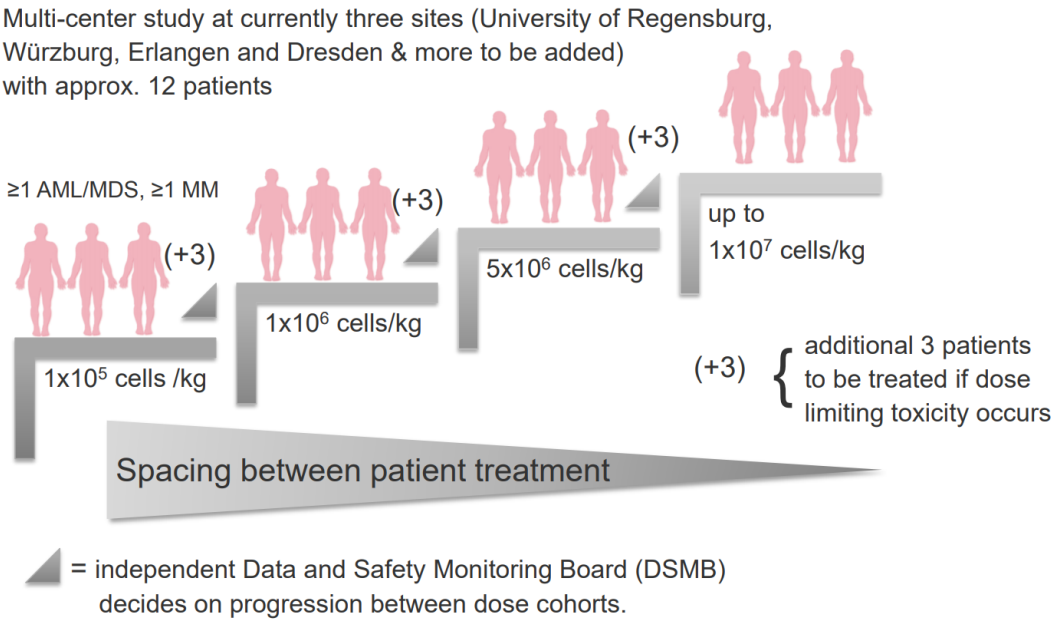
Source: Medigene

Medigene continues to implement a variety of procedures to increase patient enrolment speed, including changing enrolment criteria for each dose cohort to at least one MM patient and at least one patient with either AML or MDS (instead of one of each). MM has a higher incidence rate than AML or MDS, so this change should be beneficial for enrolment speed as it could enable the inclusion of two MM patients per cohort. To date, the clinical trial is running at four university hospitals (Regensburg, Erlangen, Würzburg and Dresden) and Medigene is opening an additional four centres (total of eight), which will begin screening patients within the coming months. Finally, to expand the eligible patient population, Medigene has optimised its analytical method for determining whether a patient is PRAME positive so lower levels of clinically relevant PRAME expression can now be detected.

The company is initially targeting 92 patients (12 patients in Phase I, 80 patients split 40 each into treatment and control groups in Phase II) with one of three r/r blood cancers: AML, MDS and MM. Patients will be genotyped to ensure they are HLA-A*02:01 positive and they will undergo a cyclophosphamide and fludarabine preconditioning regimen. The Phase I component of the trial is designed to test up to three dose cohorts (optional fourth dose cohort may be used) in a 3+3 design (12 patients in total) (Exhibit 3). The trial will test dose ranges from 100,000 to 10 million transduced T-cells per kg of body weight. At each dosing level, once all patients have been treated, a four-week safety follow up will be observed before an independent data and safety monitoring board decides if the next dosing level should be done. In our view, the first dose level is unlikely to prove efficacious and will instead be a safety check. However, any signs of efficacy at the lowest dose level would provide upside to our assumptions for MDG1011's efficacy.

Primary endpoints of the Phase I component are safety, ORR, maximum tolerated dose (MTD) and/or recommended Phase II dose (RPD2). In addition, the number of patients who receive the planned target dose will be assessed. These endpoints, in addition to other secondary endpoints, will be assessed at three and 12 months after dosing.

Exhibit 3: MDG1011 Phase I trial design



Source: Medigene

Phase II will expand the dose cohort from Phase I and include a control group, which will contain PRAME patients who are HLA-A*02:01 negative and treated according to physician's discretion. Only two of three indications will be taken forward into the Phase II part of the trial and 40 patients each (split equally between indications) will be enrolled into the treatment and control arm. Co-primary endpoints of the Phase II component include the assessment of safety and evaluation of the ORR at three months (12-month total follow up). Overall survival (OS), PFS and DoR will be also be measured at three, six and 12 months.

HA-1: Into the clinic in 2020 with MDG1021

Medigene has announced it will take a TCR targeting HA-1 (MDG1021) into the clinic in 2020 for patients with relapsed/persistent hematologic malignancies after allogeneic haematological stem cell transplantation. The trial will be sponsored by Medigene and conducted by partners at Leiden University Medical Center (LUMC). Medigene sees significant commercial and clinical opportunity with this antigen because of its broad HA-1 expression in liquid and solid tumours and its de-risked

clinical profile (tested in humans). To date, an HA-1 specific TCR has been tested by LUMC in five patients (clinical trial registry).

Data are yet to be published from the five patients, but Medigene reports the therapy was well tolerated. The trial was originally meant to enrol 20 patients but was halted early due to slow enrolment as a result of complications in the trial design and manufacturing. Medigene will implement its own manufacturing processes and use the experience it is gaining with the MDG1011 clinical trial to try and bypass many of these previous issues. We note although LUMC has clinically tested the HA-1 TCR, Medigene will have to start the clinical trial development from scratch with a dose-escalation Phase I study. This is because Medigene is using its own manufacturing processes, which will classify the HA-1 TCR as a new product. We await the publication of efficacy data from the LUMC trial to further assess the potential of an HA-1 TCR. At this time we do not include HA-1 TCR in our valuation or financials and await more details on the product development strategy; once they are available we will reassess the situation.

MAGE-A1 TCR: Initiation of Phase I expected in 2019

Medigene is collaborating with Charité and Max Delbrück Centre (MDC) on a MAGE-A1 TCR. The collaboration aims to begin enrolling a Phase I study in MM in 2019; however, the initiation of the trial has been slower than expected and we have no information on the potential start date (once it receives regulatory approval – the clinical trial application was submitted in mid-2017).

The research project is funded by the German Federal Ministry of Education and Research with funding directed towards Charité, which will be conducting the clinical trial, and MDC, which will run the analytics and ensure good manufacturing practice (GMP). Medigene is supporting both organisations by managing regulatory affairs associated with trial approval and providing advice on the development of the analytics and GMP production. Medigene holds a first right of negotiation for the TCR product candidate in MM once study results are available from the Phase I study. Additionally, Medigene is entitled to undisclosed profit participation if a third party subsequently acquires the rights to the MAGE-A1 TCR.

Early DC vaccine data impresses

Medigene's most advanced clinical cancer immunotherapy technology is its autologous DC vaccines. Its lead candidate is a WT-1 and PRAME DC vaccine, which is in a Phase I/II trial for maintenance of patients who are in remission from AML. Medigene has reported top-line interim data from its Phase I/II clinical trial testing its DC vaccine in AML patients (n=20) who were in complete remission (CR). After a 12-month treatment period, OS was 89% (n=18/20) and PFS was 60% (n=12/20). These early data are comparable to those of patients treated with allogeneic stem cell transplants. However, relapses are common in AML and long-term data are needed to determine the sustainability of the responses. The trial is expected to complete by the end of the year with top-line two-year data expected.

Patients had AML that was positive for the WT-1 antigen in addition to with/without PRAME positivity and were treated monthly (with a higher frequency in the first six weeks) with the DC vaccine that expressed these antigens. To be enrolled in the trial, patients had to have morphologic CR or CR with incomplete hematologic recovery (CRi) after initial therapy. Although the majority of patients who are diagnosed with AML will go into CR/CRi following initial therapy, most will relapse within six months without further treatment. Stem cell transplant remains the gold standard for AML patients in remission. However, many patients are ineligible and are left with less-effective maintenance options.

Competition remains intense in MM

Medigene's pipeline of cellular therapies is focused on some of the most competitive disease areas in cancer. Multiple myeloma is a key indication for both the MDG1011 TCR and the MAGE-A1 TCR and we note that the treatment paradigm across all lines of therapy continues to shift dramatically. Medigene's trials are initially focused on r/r (often third-line and above) patients, a known strategy for experimental therapies. Often these patients have limited survival prospects and any advances, however small, are welcome. However, the treatment paradigm continues to shift as other cellular therapies and more classical treatments demonstrate significant survival improvements in these challenging patient populations.

We highlight recent CAR-T data from bluebird bio (in a collaboration and licence agreement with Celgene), antibody drug conjugate (ADC) data from GSK and Bispecific T-Cell Engager data from Amgen. We note all these programmes are focused on developing treatments that target B-cell maturation antigen (BCMA) and success with other targets could provide a competitive advantage if clinically successful.

Exhibit 4: Key competitors in relapsed/refractory multiple myeloma

Company/Product/ /Technology	Potential US/ EU launch	Data
bluebird (Celgene)/ bb2121/ CAR-T	2020/2021	May 2019: Phase I trial in 33 patients. ORR was 85%, with 45% (n=15) of patients achieving a complete response.
GSK/ GSK2857916/ ADC	2020/2021	March 2019: Phase II trial in 35 patients. ORR was 60%, CR was 15% and PFS was 12 months (95% CI (3.1-Not Estimable/NE)). However, in a subgroup of patients who had not previously received anti-CD38 antibody, daratumumab, the ORR was 71% (95% CI (47.8%,88.7%)) with a median PFS of 15.7 months, (95% CI (2.3-NE)). In those patients who had previously been treated with daratumumab, the ORR was 38.5%; (95% CI (13.9-68.4)) with a mPFS of 7.9 months (95% CI (2.3-NE)). The most common grade three and four events were thrombocytopenia (35%) and anaemia (17%), which were manageable.
Amgen/ AMG 420/ BiTE	2021/2022 Granted FDA fast track designation	ASCO 2019: Phase I trial in 42 patients. Patients dosed between 0.2 and 800ug/day. At 400ug/day, seven out of 10 patients responded (ORR: 70%) with five patients achieving minimal residual disease negative (no detectable cancer). One patient had a dose-limiting toxicity observed at 400ug/day and 800 ug/ml was determined not to be tolerable.

Source:bluebird, GSK, ASCO 2019

We believe the most relevant non-TCR competition for Medigene will be these BCMA-targeting product candidates. However, it will face competition mainly from stem cell transplants along with more traditional treatments (antibodies and chemotherapy) that are approved in r/r patients either alone or in combination. These include Janssen's Darzalex (daratumumab), Takeda's Ninlaro (ixazomib), Bristol Myer's Empliciti (elotuzumab) and Celgene's Pomalyst (pomalidomide). Additionally, Celgene's first-line blockbuster Revlimid (lenalidomide) and the generic steroid dexamethasone are commonly used across treatment lines in various combinations.

Pricing and reimbursement in the limelight

It is widely recognised by payors and prescribers that cell and gene therapies could provide huge clinical benefit and in some conditions be curative, but the high potential cost of such therapies remains of concern. In August 2017, the FDA approved Novartis's CAR-T Kymriah for use in paediatric patients with ALL, priced at $475,000. This initiated a debate on how much these innovative therapies are worth and subsequent approvals of other costly cell and gene therapies such as Luxturna ($425,000 for one eye), Yescarta ($373,000) and Zolgensma ($2.1m) have fuelled these discussions.

With regards to pricing and reimbursement of most relevance to Medigene are CAR-T treatments such as Kymriah and Yescarta where the principles of the treatment are similar (remove a patient's cells, modify them then reinfuse them back into the patient to kill a specific cancer). Kymriah faces

ongoing discussions with payors over what is the appropriate pricing model for the treatment. A recent example is Novartis securing a contract in Germany for an outcomes-based payment structure with GWQ ServicePlus, which represents approximately 13 million medical insurance policyholders. The contract is arranged so that Novartis will repay part of the drug cost to GWQ if certain undisclosed survival outcomes are not reached. We note this is a temporary pilot programme until the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband), which represents 90% of the population of Germany, concludes its negotiations with Novartis. In the UK, after extensive discussions NICE approved Kymriah in paediatric ALL in September 2018 and more recently (February 2019) in DLBCL. Originally NICE did not deem Kymriah cost effective in DLBCL; however, further negotiations have led to a lower price.

In the US, the fragmented healthcare system has generated varied and distinct reimbursement challenges for cell and gene therapies. The Centres for Medicare and Medicaid Services (CMS) has recently revealed new guidelines for the coverage of CAR-T therapies and has only committed to partial coverage of the total cost (including hospitalisation costs) of treatment with CAR-T therapies, with significant cost being put on the hospitals and the patients. Additionally, in the case of Medicaid, all states have their own authority with negotiations needed for each.

As the sector grows and systems are put in place, we believe many of the reimbursement challenges faced by cell and gene manufactures will be addressed; however, it remains one of the key sensitives for the sector as whole. This is particularly so in the context of a growing number of cell/gene therapies, which will continue to take a greater share of healthcare budgets.

Legacy assets divested

Medigene's strategy is now focused on its TCR and DC platforms and it has divested all of its legacy assets (Veregen, EndoTAG, RhuDex and Eligard). However, it still receives royalties on Imlygic (following Medigene's sale of its stake in Catherex to Amgen in 2015). Medigene recently completed its transition to an immunotherapy-focused company with the sale of the remaining rights and inventories of Veregen (topical treatment for genital warts) to Aresus Pharma. Medigene received €300,000 upfront and will receive approximately €7.75m over 10 years as revenue-based earnout payments from 2021 onwards.

Medigene's legacy assets Eligard (prostate cancer), EndoTAG-1 (breast cancer) and RhuDex (autoimmune diseases) have been sold or out-licensed. In 2012 Medigene received income of $17.68m from Cowen Healthcare Royalty Partners for Eligard (in the past it was treated in the accounts as a financing arrangement although it has since been restated to be fully recognised in 2012). EndoTAG is now owned by SynCore Biotechnology (deal signed in December 2015). Medigene is entitled to €5m in milestone payments, which are paid out in five annual €1m instalments, in addition to potential milestone payments and royalties. RhuDex is owned by Dr Falk Pharma (deal signed in 2014). It is being developed in hepatology and gastroenterology. Falk Pharma is responsible for development, marketing and resultant costs.

Sensitivities

Medigene is subject to the risks typically associated with biotech company drug development, including the possibility of unfavourable outcomes in clinical trials, success of competitors and commercial decisions by partners or potential partners. Cancer immunotherapy has become a highly competitive landscape and Medigene's technology platforms are still in relatively early stages of development. The outcomes of the investigator and company-initiated trials with the DC vaccines and PRAME TCR are therefore key sensitivities. Equally, multiple companies have more advanced

DC vaccines and TCRs in development, which could limit the market opportunity for Medigene's candidates and restrict the cancer targets that may be pursued.

Valuation: €460m (€18.72/share)

We value Medigene at €460m (€18.72/share) based on a risk-adjusted NPV. We have rolled our model forward and updated it for exchange rates. Our model includes MDG1011, AML DC vaccine, deal metrics for the bluebird bio collaboration and Imlygic royalties. For a summary of our valuation and assumptions, please see Exhibit 5. Following the sale of remaining rights of Veregen to Aresus Pharma, we have removed the asset from our valuation. We additionally now include the Roivant/Cytovant deal in our valuation and value the NY-ESO-1 TCR, PRAME and WT-1 DC vaccine and the two undisclosed TCR discovery programmes. We have assumed €250m potential milestones per product split between Phase I, Phase II, Phase III, NDA filing and approval. We forecast that Phase I trials will start in 2020 for the NY-ESO-1 TCR and the PRAME & WT-1 DC vaccine and that the undisclosed TCR programmes will enter the clinic in 2021 and 2022. We do not model any indications or sales-related income included at this time. However, we will reassess this once the assets enter the clinic.

Exhibit 5: rNPV valuation and assumptions

Product	Status	Launch	NPV (€m)	Peak sales ($m)	Probability of success	Royalty rate	rNPV (€m)	rNPV/ share (€)	Key assumptions
DC vaccine - AML	Phase I/II	2022	108	347	30%	15%	32	1.28	50% AML patients eligible (~20,000 in US/EU); 15% peak penetration; $7,500 per dose, 10 doses/patient.
DC vaccine deal metrics				200	25%		41	1.68	$50m upfront, post Phase II (2019 / 50% chance); $25m on NDA filing (2022 / 25% chance); $125m on regulatory approval (2023 / 25% chance).
MDG1011 TCR	Preclinical	2023*	1306	4,033	15%	20%	193	7.87	MM and AML patients who are r/r (c 50,000 in EU/EU), 20% peak penetration, $350,00 prince in US, 20% discount in Europe
MDG1011 TCR deal metrics				500	15%		50	2.02	2x indications included; $100m upfront post Phase II (2020 / 25% chance); $50m on NDA filing (2022/2023 / 5% chance); $150m on regulatory approval (2023/2024 / 5% chance).
bluebird bio TCR deal	Preclinical	2027 onwards	436	N/A	10% (product 1 & 2), 7% product (3 & 4)	N/A	36	1.47	$15m upfront, total milestones $272m split between Phase I, Phase II, Phase III, NDA filing and approval. Six products included reaching the clinic one year apart, starting in 2020. No sales-related income included at this time.
Roivant/ Cytovant deal	Preclinical	2028 onwards	320	N/A	10% (NY-ESO-1 TCR and DC vaccine), 7% (undisclosed TCRs)	N/A	23	0.93	$10m upfront. Include NY-ESO-1, DC vaccine and two undisclosed TCRs. Assume €250m potential milestones per product split between Phase I, Phase II, Phase III, NDA filing and approval. All four products reaching the clinic one year apart, starting in 2020. No sales-related income included at this time.
Imlygic	Marketed	2015	11	230	100%	1%	11	0.43	1% royalty, Evaluate product consensus figures, peak after seven years post launch.
Portfolio total			2,179				385	15.69	
Net cash as of 31 March 2019 +$10m (€8.92m) Roivant/Cytovant upfront							74.4	3.03	
Overall valuation							460	18.72	

Source: Edison Investment Research. Note: *In our previously published outlook note this was mistakenly shown as 2024 rather than 2021.

We have adjusted timelines for MDG1011 and the bluebird collaboration. We now expect initial MDG1011 data in 2020 (previously 2019) and have pushed back our forecast out-licence and launch of MDG1011 to 2020 (previously 2019) and 2023 (previously 2021), respectively. For bluebird, we now expect the first product (MAGE-A4 TCR) from the partnership to enter a Phase I trial in 2020 (previously expected in 2018).

Financials: Funded past TCR and DC readouts

Boosted by a gross €32.3m raise in May 2018 and the expanded partnership with bluebird ($8m, upfront), Medigene reported a 31 March 2019 net cash position of €65.5m. This was recently improved further by the $10m upfront received from the Roivant/Cytovant partnership. We forecast a cash runway into FY21, which should enable full readouts of its Phase II DC vaccine trial and TCR trial. We have updated our forecasts to reflect the Roivant/Cytovant and Veregen deals and new financial guidance by Medigene.

In Q119, immunotherapy revenues from the bluebird collaboration remained essentially flat at €1.39m (2016: €1.38m) of which €525k was reimbursement of R&D costs. Total revenue also remained essentially flat and consisted in the main of revenue from Veregen of €687k (Q118: €727k) although as a result of its sale to Aresus Pharma no further revenue will be recognised. We forecast revenue of €10.7m in 2019, mainly driven by bluebird revenue of €5.7m. Additionally, this now includes approximately $3.3m (€3.0m) of the $10m Roivant/Cytovant upfront (deferred over three years) and we have also forecast €1m in R&D funding in FY19 and FY20 (€4m total).

We have increased our FY19 R&D forecasts to €27.4m vs €21.7m previously, as clinical trial costs continue to ramp following the initiation of the MDG1011 clinical trial. We forecast SG&A will rise to €11.5m (vs FY18 €7.6m) driven by a non-cash loss of c €4.5m from the sale of Veregen rights (compensated by income interest receipts from 2021). We now forecast an FY19 EBITDA loss of €27.6m vs a loss of €17.9m previously.

We now forecast an FY19 EBITDA loss of €27.6m vs a loss of €17.9m previously and a net loss of €25.9m vs €17.2m previously.

Exhibit 6: Financial summary

€'000s	2017	2018	2019e	2020e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	8,882	7,754	10,725	9,739
of which: Veregen revenues (royalties/milestones/supply)	2,790	1,596	987	0
R&D partnering (SynCore/Falk Pharma/grants)	0	0	0	0
Non-cash income (Eligard)	1,206	178	0	0
Bluebird bio partnership	4,886	5,980	5,738	5,739
Roivant/Cytovant partnership	0	0	4,000	4,000
Cost of sales	(1,621)	(849)	(275)	0
Gross profit	7,261	6,905	10,450	9,739
Selling, general & administrative spending	(8,266)	(7,613)	(11,451)	(7,333)
R&D expenditure	(14,877)	(17,117)	(27,387)	(29,578)
Other operating spending	0	0	0	0
Operating profit	(15,882)	(17,825)	(28,388)	(27,173)
Goodwill & intangible amortisation	(524)	(523)	(522)	(521)
Exceptionals	0	0	0	0
Share-based payment	0	0	0	0
EBITDA	(14,615)	(16,253)	(27,641)	(26,426)
Operating Profit (before amort. and except.)	(15,358)	(17,302)	(27,866)	(26,652)
Net interest	(435)	74	467	74
Other (forex gains/losses; associate profit/loss)	672	747	1,546	1,849
Profit Before Tax (norm)	(15,121)	(16,481)	(25,853)	(24,728)
Profit before tax (reported)	(15,645)	(17,004)	(26,375)	(25,249)
Tax	(344)	(45)	(45)	(45)
Profit/(loss) from discontinued operations	0	0	0	0
Profit after tax (norm)	(15,465)	(16,526)	(25,898)	(24,773)
Profit after tax (reported)	(15,989)	(17,049)	(26,420)	(25,294)
Average number of shares outstanding (m)	21.5	23.7	24.6	24.6
EPS - normalised (c)	(71.93)	(69.82)	(105.46)	(100.88)
EPS - Reported (€)	(0.74)	(0.72)	(1.08)	(1.03)
Dividend per share (c)	0.0	0.0	0.0	0.0
BALANCE SHEET				
Fixed assets	48,595	67,394	82,206	82,572
Intangible assets & goodwill	36,292	36,225	42,903	42,382
Tangible assets	4,329	4,261	5,097	5,984
Other non-current assets	7,974	26,908	34,206	34,206
Current assets	63,342	62,196	45,629	16,242
Stocks	7,724	7,298	0	0
Debtors	1,699	787	787	787
Cash	51,724	51,408	42,139	12,752
Other	2,195	2,703	2,703	2,703
Current liabilities	(8,124)	(8,821)	(8,821)	(8,821)
Trade accounts payable	(725)	(1,358)	(1,358)	(1,358)
Short-term borrowings	0	0	0	0
Deferred income	(3,575)	(3,474)	(3,474)	(3,474)
Other	(3,824)	(3,989)	(3,989)	(3,989)
Long-term liabilities	(10,315)	(13,344)	(10,007)	(6,669)
Pension provisions	(405)	(414)	(414)	(414)
Long-term borrowings	0	0	0	0
Other liabilities (Deferred taxes; Trianta milestones)	(4,548)	(4,246)	(4,246)	(4,246)
Deferred revenues (Eligard non-cash income & bluebird bio)	(5,362)	(8,684)	(5,347)	(2,009)
Net assets	93,498	107,425	101,807	83,325
CASH FLOW				
Operating cash flow	(20,729)	(10,013)	(9,430)	(29,102)
Net interest	(45)	(26)	1,267	874
Tax	(75)	(103)	(45)	(45)
Capex	(1,533)	(1,010)	(1,061)	(1,114)
Expenditure on intangibles	0	0	0	0
Acquisitions/disposals	480	537	0	0
Equity financing	19,329	29,923	0	0
Other	1,667	(19,624)	0	0
Net cash flow	(906)	(316)	(9,269)	(29,387)
Opening net debt/(cash)*	(52,630)	(51,724)	(51,408)	(42,139)
HP finance leases initiated	0	0	0	0
Other (foreign exchanges differences)	0	0	(0)	0
Closing net debt/(cash)*	(51,724)	(51,408)	(42,139)	(12,752)

Source: Company data, Edison Investment Research. Note: *Net cash includes cash in addition to both long- and short-term time deposits.

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Management team

CEO and CSO: Dolores Schendel	CFO and CBDO: Axel-Sven Malkomes
Professor Dr Dolores Schendel joined Medigene as chief scientific officer in 2014 with the acquisition of Trianta Immunotherapies (now Medigene Immunotherapies) where she was a majority founding member and has been managing director since 2013. She was appointed CEO with effect from April 2016. From 1998-2013, Professor Schendel was director of the Institute of Molecular Immunology of the German Research Center for Environmental Health at the Helmholtz Center in Munich. Previously she served as a university professor for immunology at the Ludwig-Maximilian university, focusing on human cellular immunology and T-cell responses within the field of oncology.	Axel-Sven Malkomes joined Medigene in April 2019. Most recently, he was Managing Director of the Life Sciences Practice for Barclays in Europe. He has additionally served as Global Head of Healthcare & Chemicals Investment Banking at Société Générale and as an investor at private equity firm 3i as co-head of European Healthcare Investments. Previously, he had leading operational and corporate roles at Merck KGaA, as CEO of a Merck KGaA group company and as head of strategic planning as well as mergers and acquisitions/business development, where he participated in the initial set-up and build-out of the company's oncology business.
CMO & CDO: Dr Kai Pinkernell	
Dr Kai Pinkernell has been responsible for the clinical advancement of Medigene's immunotherapy platforms since February 2016. Before joining Medigene, he held leading positions at Miltenyi Biotech, Bergisch Gladbach, Germany, most recently as global head of clinical business and head of clinical development. Previously, Dr Pinkernell was with Cytori Therapeutics, San Diego, US, as senior director of regenerative cell technology. He studied medicine and received his MD from the Westfaelische-Wilhems University in Muenster, Germany.	

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Tongyang Networks Co.	6.7%
Aviva	4.9%
QVT Financial, L.P.	4.4%
DJSMontana	3.4%
Shares held by executive and supervisory board	3.6%

Companies named in this report

Amgen (AMG), Bluebird (BLUE), GlaxoSmithKline (GSK), Roivant Sciences, Sinovant Sciences

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