BRYAN, GARNIER & CO

INDEPENDENT RESEARCH

13th June 2016

Morphosys

"Back for MORe"

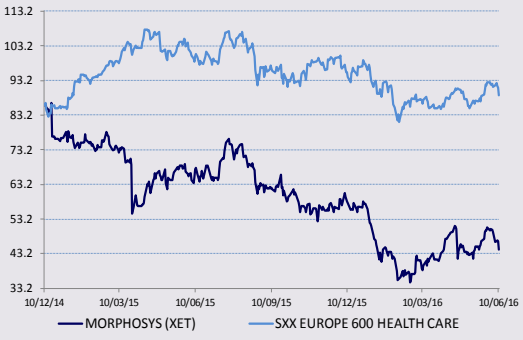
Healthcare

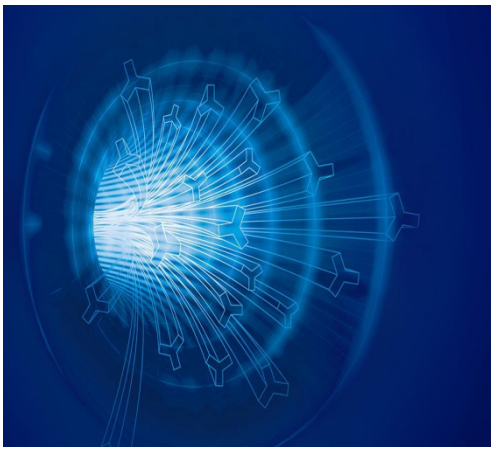
Fair Value EUR62 (Price EUR44.47)

BUY
Coverage initiated

Bloomberg	MOR GR
Reuters	MORG.DE
12-month High / Low (EUR)	76.3 / 35.0
Market capitalisation (EURm)	1,180
Enterprise Value (BG estimates EURm)	937
Avg. 6m daily volume ('000 shares)	143.5
Free Float	92.0%
3y EPS CAGR	NM
Gearing (12/15)	-78%
Dividend yields (12/16e)	NM

YE December	12/15	12/16e	12/17e	12/18e
Revenue (EURm)	106.20	55.00	79.63	15.27
EBIT(EURm)	17.17	-64.20	-60.17	-145.18
Basic EPS (EUR)	0.57	-1.63	-1.53	-3.80
Diluted EPS (EUR)	0.57	-1.63	-1.53	-3.80
EV/Sales	8.45x	17.03x	12.34x	71.36x
EV/EBITDA	43.5x	NS	NS	NS
EV/EBIT	52.3x	NS	NS	NS
P/E	78.0x	NS	NS	NS
ROCE	16.0	-47.9	-42.3	-98.9





We are initiating coverage of Morphosys with a Buy recommendation and a FV of EUR62, representing c.35% upside potential. The stock has significantly underperformed both its peers and the wider market, following disappointing late-stage data for MOR202 and bimagrumab plus Celgene's decision to end the partnership agreement for the latter. We believe that upcoming Phase III data for guselkumab, an anti-IL23p19 (partnered with JNJ) in development for the treatment of plaque psoriasis, could lead to a rerating of the shares.

- **Low-risk business model.** Morphosys, a German biotech company focused on the discovery and development of monoclonal antibodies, has a two-pronged business model: 1/ Discovery agreements with major laboratories who assume all the development costs as soon as a project is created, with MOR receiving royalty rates of 4-6% on average; 2/ More profitable partnership agreements for proprietary candidates following proof of concept data. Of note, Morphosys has already signed over a dozen partnership agreements with big pharmas and smaller laboratories.

- **Significant near-term catalyst.** While consensus is focused on anticancer agents like MOR202 and MOR208, we see guselkumab as the key share price driver. Headline Phase III data in plaque psoriasis is due in H2 16. We anticipate launch in late 2017 and forecast peak sales of EUR1.5Bn in 2025.

- **Initiating at Buy with a FV of EUR62.** Recent share price weakness has led to an attractive entry point for MOR shares, in our view, since Morphosys' pipeline is sufficiently rich and diverse for investors to play significant near-term clinical catalysts with limited downside risk. In a best case scenario, we see upside of 50%, vs. downside of only 2%. The main risk to our FV would be guselkumab missing its primary endpoint in a Phase III trial (-EUR18 all other things being equal, assuming we completely remove this compound from our valuation).

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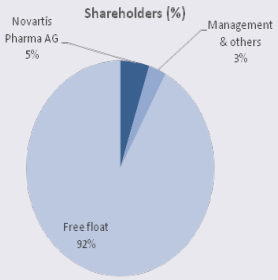

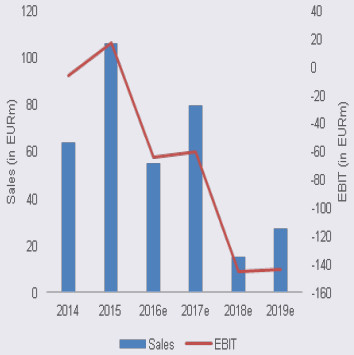

Company description

Morphosys is a biopharmaceutical company focused on the development of monoclonal antibodies

Simplified Profit & Loss Account (EURm)	2014	2015	2016e	2017e	2018e	2019e	2020e
Revenues	64.0	106	55.0	79.6	15.3	27.3	115
Change (%)	*-%*	*66.0%*	*-48.2%*	*44.8%*	*-80.8%*	*79.1%*	*319%*
Adjusted EBITDA	(1.8)	20.6	(60.2)	(56.2)	(141)	(140)	(63.2)
EBIT	(6.0)	17.2	(64.2)	(60.2)	(145)	(144)	(67.2)
Change (%)	*-%*	*-%*	*-474%*	*-6.3%*	*-141%*	*-1.0%*	*-53.3%*
Financial results	1.6	3.4	3.0	2.5	2.0	1.5	1.0
Pre-Tax profits	(4.4)	20.6	(61.2)	(57.7)	(143)	(142)	(66.2)
Exceptionals	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tax	(1.3)	5.7	(18.4)	(17.3)	(43.0)	(42.7)	(19.8)
Net profit	(3.1)	14.8	(42.8)	(40.4)	(100)	(99.6)	(46.3)
Restated net profit	(3.1)	14.8	(42.8)	(40.4)	(100)	(99.6)	(46.3)
Change (%)	*-%*	*-%*	*-389%*	*-5.8%*	*-148%*	*-0.6%*	*-53.5%*
Cash Flow Statement (EURm)							
Operating cash flows	(26.3)	(46.5)	(38.8)	(36.4)	(96.2)	(95.6)	(42.3)
Change in working capital	(12.1)	(22.9)	(9.4)	0.0	0.0	0.0	0.0
Capex, net	20.5	8.8	10.0	10.0	10.0	10.0	10.0
Financial investments, net	(6.5)	112	0.0	0.0	0.0	0.0	0.0
Dividends	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net debt	(303)	(283)	(243)	(197)	(90.7)	14.9	67.2
Free Cash flow	(34.7)	(32.3)	(39.4)	(46.4)	(106)	(106)	(52.3)
Balance Sheet (EURm)							
Tangible fixed assets	3.6	3.5	9.5	15.5	21.5	27.5	33.5
Intangibles assets	46.0	79.6	79.6	79.6	79.6	79.6	79.6
Cash & equivalents	303	283	244	197	90.9	(14.7)	(67.0)
current assets	19.6	17.2	5.7	5.7	5.7	5.7	5.7
Other assets	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total assets	426	400	355	315	215	115	68.7
L & ST Debt	0.25	0.23	0.23	0.23	0.23	0.23	0.23
Others liabilities	77.4	37.1	35.1	35.1	35.1	35.1	35.1
Shareholders' funds	349	363	320	280	179	79.7	33.4
Total Liabilities	426	400	355	315	215	115	68.7
Capital employed	91.8	92.8	89.4	95.4	101	107	113
Ratios							
Operating margin	(9.30)	16.17	(117)	(75.56)	(951)	(526)	(58.57)
Tax rate	29.71	27.85	30.00	30.00	30.00	30.00	30.00
Net margin	(4.79)	13.97	(77.89)	(50.70)	(657)	(364)	(40.39)
ROE (after tax)	(0.88)	4.09	(13.39)	(14.44)	(55.90)	(125)	(139)
ROCE (after tax)	(3.34)	15.98	(47.94)	(42.33)	(98.88)	(92.76)	(40.85)
Gearing	(86.73)	(77.94)	(76.06)	(70.46)	(50.59)	18.67	201
Pay out ratio	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Number of shares, diluted	26.19	26.24	26.58	26.58	26.58	26.58	26.58
Data per Share (EUR)							
EPS	(0.12)	0.57	(1.63)	(1.53)	(3.80)	(3.78)	(1.76)
Restated EPS	(0.12)	0.57	(1.63)	(1.53)	(3.80)	(3.78)	(1.76)
% change	*-%*	*-%*	*-385%*	*-5.8%*	*-148%*	*-0.6%*	*-53.5%*
BVPS	13.32	13.82	12.04	10.52	6.75	3.00	1.26
Operating cash flows	(1.01)	(1.77)	(1.46)	(1.37)	(3.62)	(3.60)	(1.59)
FCF	(1.32)	(1.23)	(1.48)	(1.74)	(4.00)	(3.97)	(1.97)
Net dividend	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Source: Company Data; Bryan, Garnier & Co ests.

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1. Investment Case

Why the interest now?

The reason for writing now

MOR shares have been weak in recent months following negative news for 1/ MOR202 (an anti-CD38 in Phase II for multiple myeloma) and 2/ bimagrumab (an anti-ActRIIb which failed in its first indication). However, in our view Morphosys' rich and diversified pipeline includes other valuable assets with upcoming clinical catalysts that can lead to significant share price upside with a highly attractive risk-reward profile.

Cheap or Expensive?

Valuation

Our EUR62 Fair Value stems from a Sum-of-the-Parts valuation in which the net present value (NPV) of each drug candidate is based on free cash flow forecasts through to 2030.

When will I start making money?

Catalysts

The key catalyst for MOR shares is Phase III results for guselkumab in psoriasis, which could add EUR8 to our FV (c.55% upside). Other major catalysts are outlined on page 6.

What's the value added?

Difference from consensus

While consensus has been focusing on MOR208 (anti-CD19), we believe that the majority of value lies in the company's immunology franchise, particularly guselkumab. We also see multiple valuable projects in Morphosys' oncology pipeline, such as the anti-4-1BB (partnered with Pfizer) and Anetumab ravtansine (partnered with Bayer). We see limited potential for MOR208 and MOR202 given changes in the competitive landscape in haematological tumours (e.g. ibrutinib and venetoclax in chronic lymphocytic leukemia [CLL], daratumumab and isatuximab in myeloma).

Could I lose money?

Risks to our investment case

Negative clinical results and/or non-approval of products could have a significant impact on our valuation. However, the diversity of Morphosys' portfolio limits the downside risk over the next 12 months, in our view.

2. Why initiate coverage now?

2.1. Attractive entry point due to recent weakness

MOR shares have underperformed its peers by 8% over the past 12 months, due largely to 1/ disappointing clinical data involving MOR202 and bimagrumab, along with 2/ the loss of a partner (Celgene). This has been exacerbated by the poor performance of the wider equity market, particularly with regard to the biotech sector. In our view, the share price decline is overdone and has created an attractive entry point for investors in light of our positive stance on Morphosys' late-stage pipeline. Hence, we expect upcoming catalysts to trigger a re-rating of the shares.

2.2. FV of EUR62 represents c.35% upside

Our valuation is derived from a sum-of-the-parts calculation valuing each major project using a DCF model. In all cases, our free cash flows have been factored in on the basis of an 10% discount rate and over an explicit period from 2016 to 2030 (the aim is to incorporate the potential lifespan of each product candidate). We have then applied a probability of success rate depending on the project's clinical progress in the indication and setting concerned.

Fig. 1: BG valuation

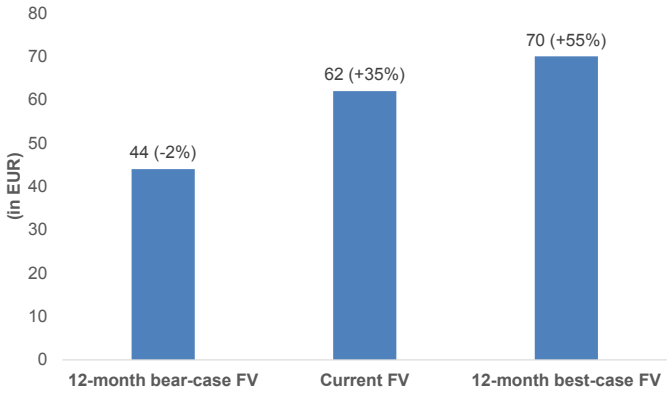
Drug candidates	Target	Indications	Stage	Peak sales (EURBn)	NPV (EURm)	PoS (%)	r-NPV (EURm)	Per share (EUR)
Unpartnered programs								
MOR208	CD19	DLBCL	Phase 2	0.6	540	35%	189	7
MOR202	CD38	Multiple myeloma	Phase 2	0.0	0	0%	0	0
MOR209	PSMA/CD3	Prostate cancer	Phase 1	0.8	1,000	20%	200	8
Partnered programs								
Guselkumab (JNJ)	IL23p19	Plaque psoriasis	Phase 3	1.6	494	60%	296	11
Guselkumab (JNJ)	IL23p19	Pustular psoriasis	Phase 3	0.6	175	60%	105	4
Guselkumab (JNJ)	IL23p19	Psoriatic arthritis	Phase 2	0.7	186	35%	65	2
Bimagrumab (NVS)	ActRIIB	sIBM & others	Phase 3	0.0	0	0%	0	0
Gantenerumab (ROG)	Amyloid-β	Mild Alzheimer's disease	Phase 3	0.0	0	0%	0	0
MOR103 (GSK)	GM-CSF	Rheumatoid arthritis	Phase 2	0.7	658	35%	230	9
Anetumab (BAY)	Mesothelin	Mesothelioma	Phase 2/3	0.6	241	60%	144	5
PF-05082566 (PFE)	4-1BB	Cancers	Phase 1	0.0	0	20%	0	0
Others	Diverse	Diverse	Phase 2	na	314	35%	110	4
= Enterprise Value					**3,608**	**37%**	**1,340**	**51**
(+) Net cash					298	100%	298	11
= Equity Value					**3,906**	**42%**	**1,638**	**62**

Source: Bryan, Garnier & Co ests.

2.3. Best-case scenario yields FV of EUR70 (c.55% upside)

At current levels, the risk-reward profile over the next 12 months looks attractive. In a best case scenario, we see upside of nearly 55%, yielding a FV of EUR70 (+EUR8 if guselkumab is approved). In a worst case scenario, we see downside potential of only 2%. Of note, we do not attribute any value to several projects in late-stage development, since they have failed Phase III trials or because we are very cautious about their prospects.

Fig. 2: Potential change in our FV depending on the results of guselkumab



Source: Bryan, Garnier & Co. ests.

2.4. Multiple upcoming catalysts

As shown below, there are multiple near-term catalysts across Morphosys's rich pipeline.

Fig. 3: 2016-2017 newsflow

Date	Clinical stage	Program	Indication
2016			
H1 16	Phase III	Bimagrumab	Sporadic inclusion body myositis
H1 16	Phase III	Guselkumab	Psoriasis (VOYAGE 1)
H1 16	Phase II	LGF316	Panuveitis
H1 16	Phase II	LGF316	Paroxysmal nocturnal hemoglobinuria
H1 16	Phase II	LJM716	Esophageal cancer + BYL716
H1 16	Phase I	Anetumab Ravtansine	Advanced malignancies
H2 16	Phase III	Guselkumab	Psoriasis (VOYAGE 2)
H2 16	Phase III	Guselkumab	Psoriasis (NAVIGATE)
H2 16	Phase II	MOR202	Multiple Myeloma
H2 16	Phase II	MOR208	Non-Hodgkin Lymphomas
H2 16	Phase II	Tarextumab	Pancreatic cancer
H2 16	Phase I	MOR209	Prostate cancer
H2 16	Phase I	LJM716	BYL716 + trastuzumab (anti-HER2)
2017			
H1 17	Phase III	Bimagrumab	Sporadic inclusion body myositis (extension)
H1 17	Phase III	Guselkumab	Pustular/Erythrodermic psoriasis
H1 17	Phase II	Bimagrumab	Sarcopenia
H1 17	Phase II	Bimagrumab	Hip fracture surgery
H1 17	Phase II	Guselkumab	Psoriatic arthritis
H1 17	Phase II	MOR103	Rheumatoid arthritis
H1 17	Phase II	MOR202	Multiple Myeloma
H1 17	Phase II	MOR208	Chronic Lymphocytic Leukemia
H2 17	Phase II	MOR208	Chronic Lymphocytic Leukemia (+ idelalisib)
H2 17	Phase II	MOR208	DLBCL (+ lenalidomide)
H2 17	Phase II	PF05082566	Solid tumors + avelumab
H2 17	Phase II	Tarextumab	Small cell lung cancer
H2 17	Phase II	VAY736	Pemphigus vulgaris
H2 17	Phase II	VAY736	Primary Sjögen's Syndrome
H2 17	Phase I	PF05082566	Non-Hodgkin Lymphomas (+ rituximab)
H2 17	Phase I	PF05082566	Solid tumors + pembrolizumab
H2 17	Phase I	VAY736	Primary Sjögen's Syndrome

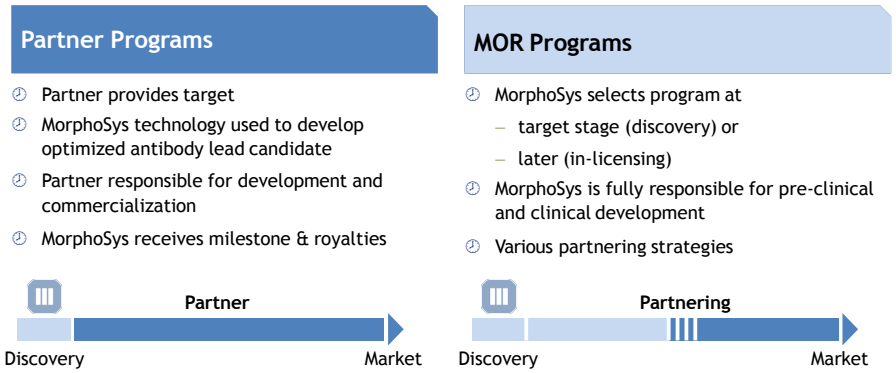
Source: Company Data

2.5. Company Background

Created in 1992, Morphosys is a German biotech company specialised in the discovery and development of monoclonal antibodies (similar to its peers Genmab and Ablynx). The company has a two-pronged business model: 1/ Discovery agreements with major laboratories who assume all the development costs as soon as a project is created, with MOR receiving royalty rates of 4-6% on average; 2/ More profitable partnership agreements for proprietary candidates following proof of concept data.

Morphosys has already signed over a dozen partnership agreements with big pharmas and smaller laboratories, which is testament to the relevance of its offer. This has created a rich and diversified development pipeline, which covers a broad range of therapeutic areas, including oncology, auto-immune diseases and neurodegenerative diseases. This compares favourably to the majority of other listed European biotechs. In this report, we have focused our analysis on candidates (proprietary or not) for which we 1/ see significant sales potential, and 2/ have identified short-term catalysts (clinical results, approvals, agreement signings, potential sector read-across etc.).

Fig. 4: Morphosys – Business structure



Source: Morphosys

Fig. 5: Morphosys – Development pipeline

Program	Partner	Target	Indication	Clinical stage
Bimagrumab	Novartis	ActRIIb	Sporadic inclusion body myositis (sIBM)	Phase III
Guselkumab	JNJ	IL23p19	Psoriasis	Phase III
Gantenerumab	Roche	Amyloid-β	Alzheimer's disease	Phase III
MOR208	Ø	CD19	Blood cancers (CLL, NHL)	Phase II
MOR202	Ø	CD38	Multiple Myeloma	Phase II
BHQ880	Novartis	DKK-1	Multiple Myeloma	Phase II
MOR103	GSK	GM-CSF	Inflammation	Phase II
CNTO3157	JNJ	TLR3?	Inflammation	Phase II
CNTO6785	JNJ	Nd	Inflammation	Phase II
Anetumab Ravtansine	Bayer	Mesothelin (ADC)	Solid tumours	Phase II
LJM716	Novartis	HER3	Cancer	Phase II
LGF316	Novartis	C5	Eye diseases	Phase II
BPS804	Mereo/Novartis	Sclerostin	Brittle bone syndrome	Phase II
Tarextumab	Oncomed	Notch 2	Solid tumours	Phase II
VAY736	Novartis	BAFF-R	Inflammation	Phase II
MOR209	Emergent	PSMA/CD3	Prostate cancer	Phase I
BAY1093884	Bayer	TFPI	Haemophilia	Phase I
BI-836455	BI	IGF-1	Solid tumours	Phase I
NOV-7	Novartis	Nd	Eye diseases	Phase I
NOV-8	Novartis	Nd	Inflammation	Phase I
NOV-9	Novartis	Nd	Diabetic eye diseases	Phase I
NOV-10	Novartis	Nd	Cancer	Phase I
NOV-11	Novartis	Nd	Blood disorders	Phase I
PF-05082566	Pfizer	4-1BB	Solid tumours	Phase I
Vantictumab	Oncomed	Fzd7	Solid tumours	Phase I
MOR106	Galapagos	Nd	Inflammation	Phase I
MOR107	Ø	AT2-R	Fibrosis	Preclinical
Immuno-oncology program	Merck KGaA	Nd	Cancer	Preclinical
Immuno-oncology program	Immatics	Nd	Cancer	Preclinical

Source: Company Data; Bryan, Garnier & Co ests.

3. Guselkumab: an underestimated asset

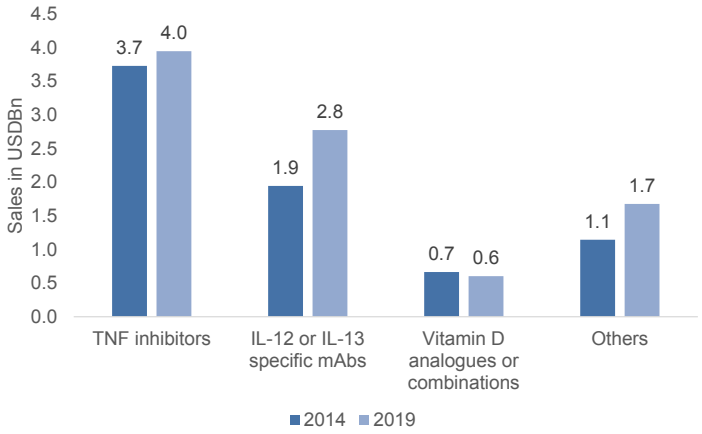
Guselkumab, a humanised anti-IL23p19 in Phase III development for plaque psoriasis, is MOR's key value driver, in our view. The antibody, which is being developed by partner JNJ, has demonstrated promising efficacy and a clean safety profile in the Phase II X-PLORE trial. Two Phase III registration trials (VOYAGE 1 and VOYAGE 2) testing the 100mg/kg dose against both placebo and the active comparator adalimumab (the current market leader) in moderate to severe anti-TNF treatment naïve patients are due to report headline data in H2 16.

We think there is a 60% probability of positive data, which could lead to US and European approval in late 2017. And although the plaque psoriasis market is competitive, we forecast peak sales of EUR1.5Bn in 2025, driven by guselkumab's favourable administration schedule.

3.1. What is plaque psoriasis?

Plaque psoriasis is an auto-immune skin disease affecting around 2-4% of the population in mature markets (with 10% of cases considered severe). In a few words, we would say the disease is characterised by 1/ a proliferation and an abnormal differentiation of skin cells (otherwise known as keratinocytes), 2/ an infiltration of the dermis and epidermis by diverse immunity cells and 3/ the emergence of red and painful plaques in various places (the scalp, knee and elbow are the areas most often affected).

Fig. 6: Psoriasis market (2014-2019)



Source: The Psoriasis Market, Nature Reviews Drug Discovery (2015)

The factors causing the disease are not all well-known. However, a consensus seems to have formed considering that 1/ the primitive anomaly at the origin is probably found in skin cells and especially keratinocytes and that 2/ activation of various lymphocyte populations is necessary to reveal this anomaly and cause the pathology. The fact that immunosuppressive T lymphocyte treatments such as cyclosporine and tacrolimus have shown a beneficial effect in this indication is not meaningless in any case. This is the reason why research has converged on T cells.

A specific focus has been placed on T helpers (Th) given their role as conductor in the construction of the immune response. These cells are indeed known for stimulating/activating other immunocompetent cells and each subset is defined by its cytokine production profile. For example,

those primarily secreting IFN-γ, TNF-α and IL-2 are known as Th1 and prompt pro-inflammatory responses against foreign bodies. A few years ago, lymphocyte Th1s were still considered as being the most important players in the process. This is probably why mAbs targeting TNF-α were developed in this indication.

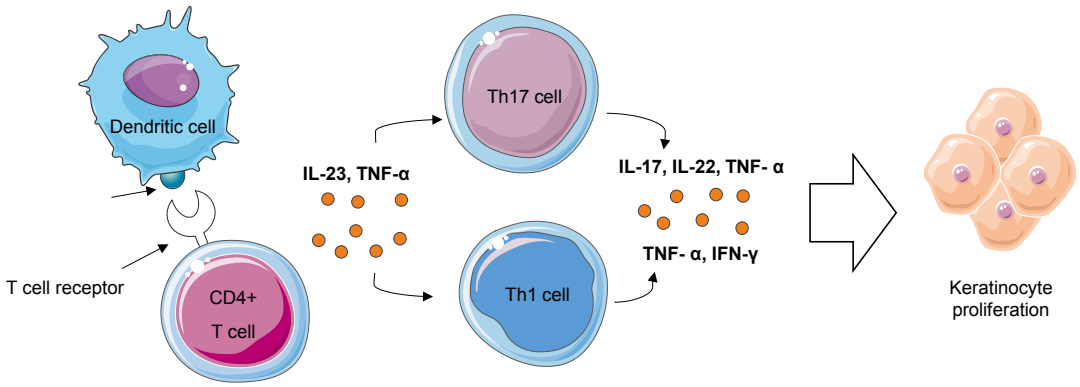
As time has gone by, research has naturally widened to include other cytokines and other immune pathways. IL-17 and IL-23 in particular showed up on the radar following the discovery of the Th17 subset and works on their eventual role in the pathogenesis of various auto-immune diseases.

Fig. 7: Different T helper subsets

T cell subset	Upstream inducers	Transcription factors	Signature cytokines	Immune activities
Th1 cell	IL-12	STAT4, T-Bet	IFN-γ and TNF-α	Pro-inflammatory antimicrobial activity Suppression of Th2 responses Autoimmunity
Th2 cell	IL-4	STAT6, GATA3	IL-4, IL-5, IL-10 and IL-13	Anti-nematode immunity, tissue repair Suppression of Th1 responses Asthma and allergy
Tregs	TGF-β	SMADs and FoxP3	IL-10	Immunosuppression
Th17 cell	IL-1, IL-6, IL-23 and TGF-β	STAT3, SMADs and RORγ	IL-17, IL-21, IL-22 and TNF-α	Bactericidal activity and antifungal immunity Autoimmunity

Source: Bryan, Garnier & Co ests.

Fig. 8: Main immune pathways implied in psoriasis



- Upon antigenic stimulation, naïve CD4+ T cells differentiate into different subsets (Th1, Th2, Th17, etc.), characterized by different cytokine production profiles and effector functions
- Differentiation into specific subtypes depend mainly on the cytokine milieu of the microenvironment
- Among others IL-23 (which exhibits the p23 and p40 subunits) induces the differentiation of CD4+ T cells into Th17 cells that produce IL-17, IL-6 and TNF-α

Source: Bryan, Garnier & Co ests.

3.2. Anti-IL-17: a standard in the making

This progress in understanding the immunological mechanisms of the disease has enabled a number of therapeutic targets to emerge in recent years. A number of these have proved superior to anti-TNF's in widescale clinical studies (see Fig. 9). A first stone was laid in 2009 with the approval of JNJ's anti-IL12/IL23p40 ustekinumab. However far more recently, the focus was placed on anti-IL17As such as secukinumab by Novartis (also marketed under the name of Cosentyx) and ixekizumab by Lilly (which was also approved at the end of March 2016 by the US regulator).

Cosentyx (secukinumab) looks well on the way to becoming part of the treatment's paradigm. Approved by the FDA at the end of January 2015, the rising momentum of this Novartis drug looks pretty promising in terms of volumes bearing in mind that 1/ the first rebates granted were apparently fairly significant in order to open a maximum number of doors before the arrival of ixekizumab 2/ dermatologists are known for their conservatism.

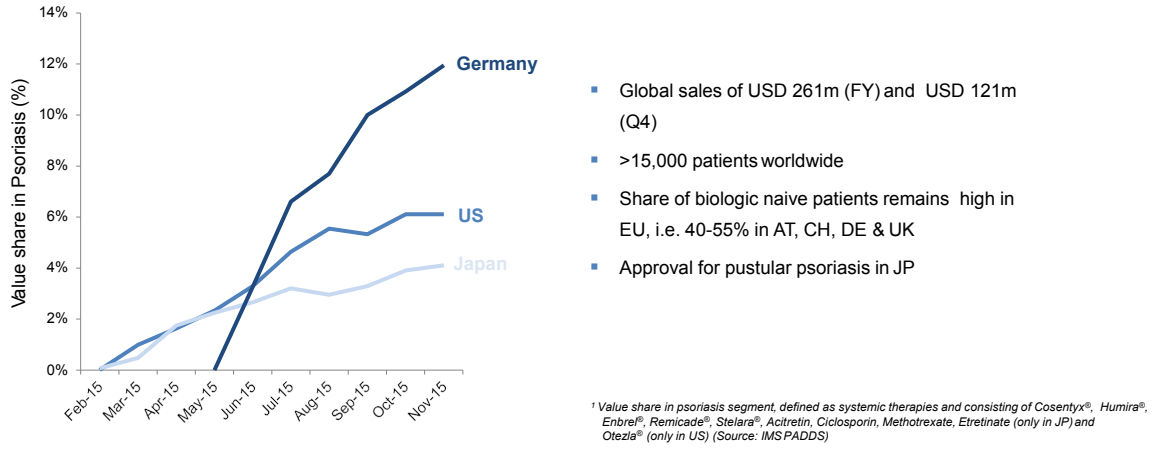
The story of brodalumab (anti-IL17R) by AstraZeneca has been slightly more turbulent. In May 2015, and contrary to all expectations, Amgen withdrew from the project due to the emergence of suicidal thoughts in a small number of patients, although it remained to be seen whether these side effects were really related to the treatment, whether this was a class effect or specifically linked to receptor targeting (whereas secukinumab and ixekizumab target the ligand protein). AZN did not think so and this enabled it to sign another agreement with Valeant in September 2015.

Fig. 9: Anti-IL17 – PASI and PGA at 12 weeks vs anti-TNF-α

Company	Compound	Target	PASI75	PASI90	PASI100	PGA 0-1
AstraZeneca	Brodalumab (210 mg/kg qw2)	IL17R	85-86%	70%	37-41%	79-80%
Eli Lilly	Ixekizumab (80 mg/kg qw2)	IL17	87-90%	68-71%	38-41%	83%
Novartis	Secukinumab (300 mg/kg qw4)	IL17	77-82%	54-59%	24-28%	62-65%
Amgen	Etanercept	TNF-α	41%	19%	5%	34%

Source: Companies Data

Fig. 10: Market share of Cosentyx (secukinumab) in value terms in psoriasis



Source: Novartis Q4 15 results presentation

3.3. A candidate underestimated by the market

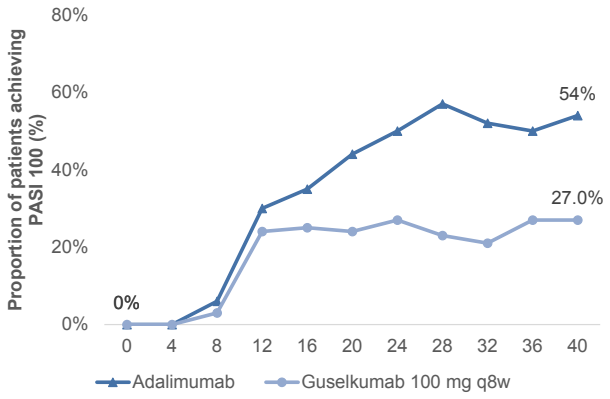
Guselkumab is a humanised anti-IL23p19, administered subcutaneously and developed by JNJ. A Phase II trial named X-PLORE helped test this antibody in anti-TNF-α treatment-naïve patients suffering from moderate or severe psoriasis. In general, we would say that this compares very well to the 100mk/kg dose.

- The PASI 90 at 16 weeks (which measures the proportion of patients having benefited from an improvement of at least 90% on the basis of a severity score) showed a statistically significant improvement relative to the placebo (62% vs. 2%, p<0.001). In addition, the PASI 100, showed a rate of 33% after 16 weeks of treatment (vs. 10% and 26% for the placebo and adalimumab), gradually improving to 54% after 40 weeks (vs. 27% for adalimumab).

- Results of PGA 0-1 at 16 weeks were also interesting, with 86% of patients having reached a score of 0 or 1 (including 45% at 0) vs. 58% in the adalimumab arm.

- The percentage of patients having suffered at least one side effect is seemingly fairly similar between the various arms. Cardiovascular events and a case of cancer were noted in the experimental group, but in view of the low frequency, we consider it too early to draw any real conclusions (see Fig. 12).

Fig. 11: Guselkumab vs rivals - Score PGA 0-1 (12-16 weeks)



Source: Duffin et al, AAD 2014

Fig. 12: Guselkumab –Phase II results – Toxicity analysis

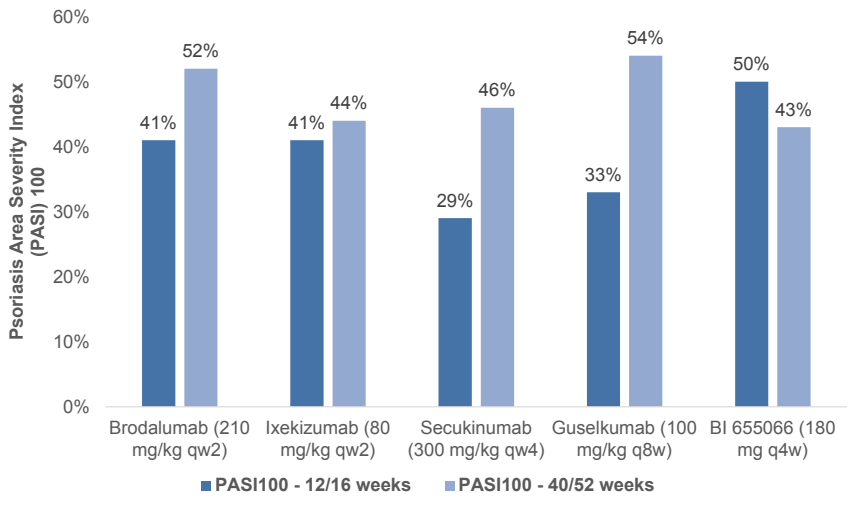
Outcome	Placebo (n=42)	Guselkumab (n=207)	Adalimumab (n=43)
Weeks 0-16			
Patients in whom study agent was discontinued because of≥ 1 AE	3 (7%)	5 (2%)	3 (7%)
Patients with ≥ 1 adverse events	22 (52%)	103 (50%)	24 (56%)
Patients with ≥ 1 serious adverse events	1 (2%)	3 (1%)	1 (2%)
Patients with ≥ 1 infections	6(14%)	41 (20%)	5 (12%)
Patients with ≥ 1 serious infections	0 (0%)	2 (1%)	0 (0%)
Patients with ≥ 1 infections requiring treatment	3 (7%)	14 (7%)	2 (5%)
		Guselkumab (n=235)	**Adalimumab (n=38)**
Weeks 16-52			
Patients in whom study agent was discontinued because of ≥ 1 AE		3 (1%)	1 (3%)
Patients with ≥ 1 adverse events		115 (49%)	23 (61%)
Patients with ≥ 1 serious adverse events		4 (2%)	1 (3%)
Patients with ≥ 1 infections		70 (30%)	14 (37%)
Patients with ≥ 1 serious infections		0 (0%)	1 (3%)
Patients with ≥ 1 infections requiring treatment		21 (9%)	6 (16%)
Patients with ≥ 1 cancers		1 (<1%)	0 (0%)
Patients with ≥ 1 major adverse cardiovascular events		3 (1%)	0 (0%)

Source: Gordon et al, NJEM 2015

Whether for PASI 90 or PASI 100, we admit voluntarily that the 16 week scores are slightly below those noted for IL17 blocking antibodies. However, the analysis is totally different if we include a wider duration since **PASI 100 at 40 weeks for guselkumab is fairly similar to that of brodalumab at 52 weeks.** A look at the PGA 0-1 score at 16 weeks (which seems to be increasingly favoured by the FDA) shows that guselkumab also compares well with its main rivals (see Fig. 13/14).

The fact that the beneficial effect of guselkumab takes slightly longer to materialise (at least in terms of PASI 100) is not really an Achilles' heel from our viewpoint. Indeed, we believe that this aspect could be widely offset by its **more patient-friendly administration schedule (once every two months compared with once or twice a month for anti-IL-17).**

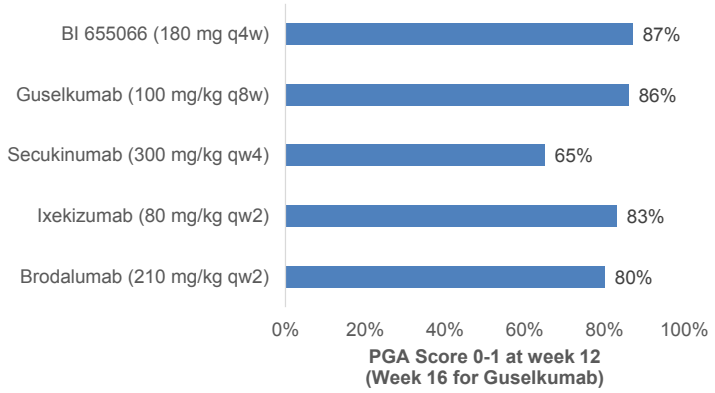
Fig. 13: Guselkumab vs rivals – PASI100



* Guselkumab: PASI 100 at 16 weeks and 40 weeks (vs 12 and 52 weeks for the other compounds)

Source: Companies Data; Bryan, Garnier & Co ests.

Fig. 14: Guselkumab vs rivals - Score PGA 0-1 (12-16 weeks)



Source: Companies Data; Bryan, Garnier & Co ests.

- **Positive read-across from AbbVie/Boehringer Ingelheim deal**

Testifying to interest in this therapeutic class, AbbVie recently acquired the rights to BI 655066 (guselkumab rival also in Phase III, and which has proved its efficacy vs. ustekinumab) and a CD40 antagonist from Boeringher Ingelheim. The financial terms of the deal were not fully unveiled, although we would nevertheless note that 1/ the first payment made totalled USD595m and that 2/ development costs for BI 655066 are to be shared, whereas AbbVie should be fully responsible for its marketing in the main indications (plaque psoriasis, arthritic psoriasis, Crohn's disease).

From our viewpoint, clinical data for BI 655066 differs to that of guselkumab in two ways: 1/ the AbbVie and Boehringer antibody seems more powerful during the first weeks of treatment (PASI 100: 50.0% after 12 weeks for the 180mg dose), but 2/ its efficacy seems slightly below that of mAb by JNJ/MOR when observed over a longer period (indeed we could even say it deteriorates over time) and 3/ its administration scheme is slightly more restrictive (once every four weeks vs. eight weeks for r guselkumab).

- **What place within the JNJ portfolio?**

As always, it is important to see to what extent a project can be critical for partners shouldering the development. Indeed, we have the impression that the planets are fairly well aligned. A number of observers have already noted that JNJ currently markets two treatments for use in psoriasis, Remicade (etanercept) and Stelara (ustekinumab)… and for which we believe sales are at risk in psoriasis (apart from the arrival of anti-TNF-alpha biosimilars, we consider that prescriptions should rapidly shift in favour of anti-IL-17 and anti-IL-23 given the therapeutic benefits they provide). In this context, we consider that the sales focus should gradually slide towards Morphosys' antibody, at least for the psoriasis market (and for which a big pharma already has the doors open).

An early-stage project such as **COVA-322**, a bispecific targeting both TNF-α and IL-17A, looks very attractive on paper. The two targets have been validated in this disease and are recognised for acting in synergy (Wang *et al*, 2013). This is very likely why JNJ bought Covagen, the company developing the drug, in 2014. That said, we would note that 1/ no clinical data has been presented so far, whereas a Phase Ib/II trial in psoriasis theoretically ended a few months ago, and 2/ the principal indication is more rheumatoid arthritis (at least according to the company's latest slides). Plus, Lilly also develops a similar antibody (named LY3232094)… And here again, psoriasis is not on the agenda (the focus being rather on ulcerative colitis and Crohn's disease).

Fig. 15: JNJ development portfolio in psoriasis

Compound	MoA	Status	Total sales
Remicade (infliximab)	Anti-TNF-α	Marketed	USD6.6Bn
Stelara (ustekinumab)	Anti-IL12/23p40	Marketed for plaque psoriasis, filed for paediatric psoriasis	USD2.5Bn
Guselkumab	Anti-23p19	Phase III in plaque psoriasis, Phase II in psoriatic arthritis	N/A
Simponi (golimumab)	Anti-TNF-α	Filed for psoriatic arthritis	N/A
Toreforant (JNJ-168)	H4R antagonist (oral)	Phase II in plaque psoriasis	N/A
COVA-322	Bispecific TNF-α and IL-17	Phase I/II in plaque psoriasis (terminated)	N/A

Source: JNJ; Bryan, Garnier & Co ests.

3.4. EUR1.5bn in plaque psoriasis

No fewer than two publications of Phase III trials are expected in H1 2016 or H2 at the latest (the first should be VOYAGE1 theoretically), and both of these aim to assess Guselkumab at the 100 mg/kg dose in moderate to severe plaque psoriasis and more precisely 1/ against two comparison arms, one being a pure placebo and one an active component (adalimumab), 2/ in anti-TNF treatment naïve patients.

Demonstration of the superiority of guselkumab compared with adalimumab is clearly a prerequisite, although potential will above all be determined by its amplitude. In absolute terms, we would say that our vision could be confirmed 1/ if PASI 100 and PGA 0-1 at 16 weeks prove to be 30% and 80% higher respectively, and 2/ if the safety profile turns out to be similar to anti-TNFs, whether for opportunist infections, in cancer cases, or cardiovascular events. Assuming that these various factors are validated, we believe the MOR/JNJ antibody will clearly have a role to play in a market that is nevertheless increasingly competitive (and once again, we believe its administration schedule and JNJ's backing will be key to its advent).

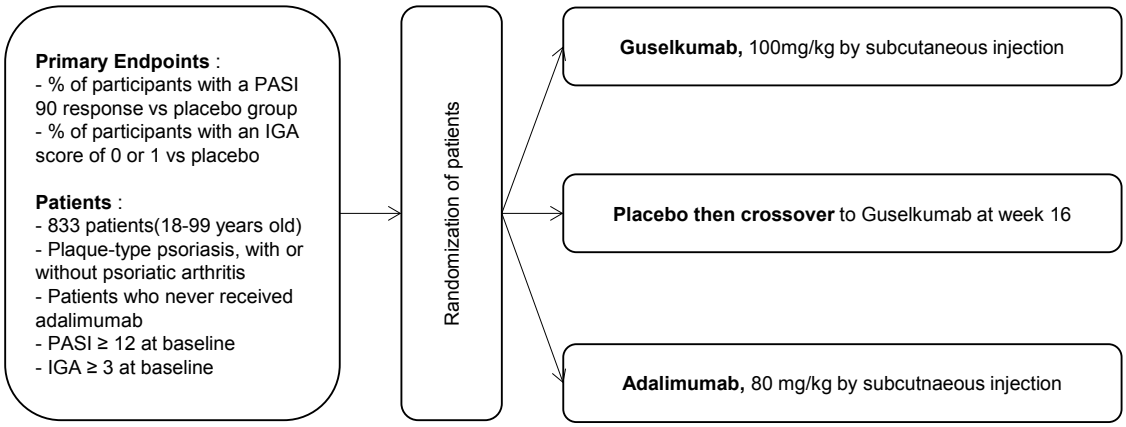
That said, we remain fairly conservative in our assumptions for sales penetration in that two anti-IL-17s are already on the market and that the two pharma companies behind their marketing seem fairly ambitious/aggressive. This is why our market share estimate is for 4.5% further out for a pricing in line with these new therapies.

Fig. 16: Sales forecasts for Guselkumab in plaque psoriasis

	2017	2018	2019	2020	2021	2022	2023	2024	2025
Psoriasis incidence (in M)	**20.6**	**20.8**	**21.0**	**21.2**	**21.4**	**21.6**	**21.8**	**22.0**	**22.3**
- USA	6.4	6.5	6.6	6.6	6.7	6.8	6.8	6.9	7.0
- Europe	9.1	9.2	9.3	9.4	9.5	9.6	9.6	9.7	9.8
- ROW	5.1	5.1	5.2	5.2	5.3	5.3	5.4	5.4	5.5
% Plaque Psoriasis	80%								
% Moderate to severe disease	30%								
% Treated with biologics	20%								
Pricing per patient - US (USD)	35,000								
Pricing per patient - Europe & ROW (EUR)	20,000								
Guselkumab - Market shares - US (%)	0.5%	1.5%	2.5%	3.5%	4.0%	4.5%	5.0%	5.5%	6.0%
Guselkumab - Market shares - Europe (%)	0.5%	1.5%	2.5%	3.5%	4.0%	4.5%	5.0%	5.5%	6.0%
Guselkumab - Market shares - ROW (%)	0.0%	0.5%	1.5%	2.5%	3.5%	4.0%	5.0%	5.5%	6.0%
Guselkumab - Sales (EURm)	**93**	**305**	**547**	**793**	**948**	**1,081**	**1,241**	**1,379**	**1,519**
% var y-o-y		229%	79%	45%	20%	14%	15%	11%	9%

Source: Bryan, Garnier & Co ests.

Fig. 17: Design of VOYAGE1 trial



* IGA: Investigator's global assessment
PASI: Psoriasis Area and Severity Index

Source: ClinicalTrials.gov

4. MOR208: an overly optimistic consensus?

MOR208 is a monoclonal antibody targeting CD19, a protein with an expression pattern fairly similar to that of CD20 (which is one of the cornerstones of success for Roche and rituximab in haematological cancers). Bearing this in mind, it is hardly surprising that indications such as chronic lymphoid leukaemia (CLL) or non-Hodgkin's lymphoma (NHL) are among the first addressed.

Fig. 18: MOR208 – Clinical trials underway

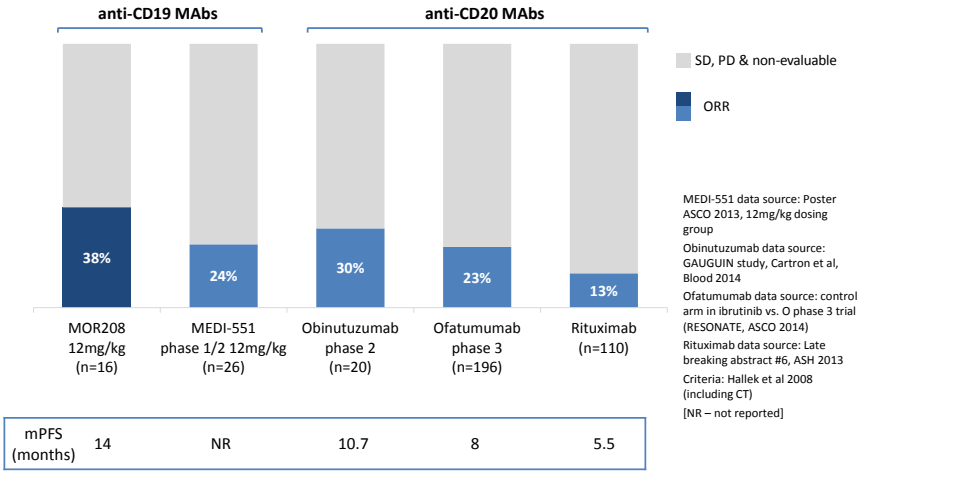
Indication	Patients	Setting	Clinical stage
Non-Hodgkin Lymphomas (NHL)	92	Monotherapy, R/R patients	Phase II
Diffuse Large B cell Lymphomas (DLBCL)	80	Combo with lenalidomide (IMiD), 2nd line	Phase II
Diffuse Large B cell Lymphomas (DLBCL)	320	Combo with bendamustine, 2nd line	Phase II/III
Chronic Lymphocytic Leukaemia (CLL)	120	Combo with idelalisib (PI3K), BTKi failures	Phase II
Chronic Lymphocytic Leukaemia (CLL)	80	Combo with lenalidomide (IMiD) R/R, naïve and Richter's transformation patients; With ibrutinib (BTKi) in ibrutinib-refractory patients	Phase II

Source: Morphosys

4.1. CLL: a new challenging therapeutic paradigm

The consensus of analysts seems fairly optimistic in terms of the group's ability to sign a partnership agreement with a mid-size/big pharma group. The first set of clinical data obtained by the candidate admittedly bode well, especially if we compare it with other antibodies currently being developed/marketed in these indications. A small Phase I/IIa (n=16) study indeed helped provide first indications on the efficacy and safety profile of MOR208 in refractory or relapse patients: 1/ 38% of these benefited from partial responses at the 12mg/kg dose (which compares more beneficially with the 30% obtained by obinutuzumab in a similar setting, 2/ MOR208 was fairly well tolerated with the main side effects being reactions at the injection point, neutropenia and thrombocytopenia cases, as well as an increase in certain enzymes (nothing surprising for a cytotoxic antibody depleting B cells).

Fig. 19: MOR208 – Response rate in CLL (R/R)

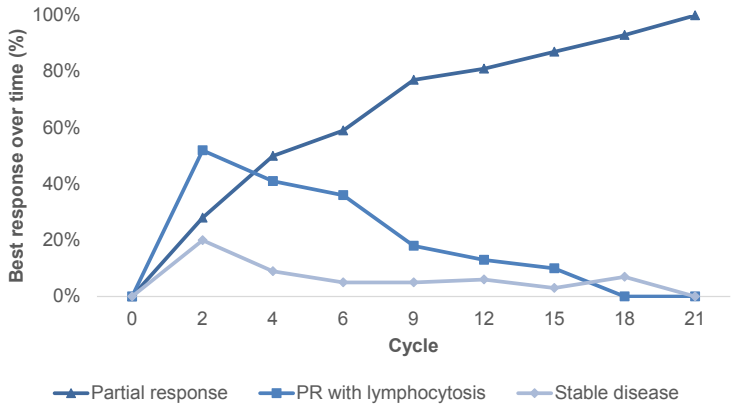


Source: Morphosys

However, the real question is to know whether MOR208 could be more efficient or safer than an anti-CD20, which clearly remains a very significant component of the CLL therapeutic landscape. However, we also estimate that the standard should rapidly change to benefit from new therapeutic classes, and notably:

- **BTK inhibitors** such as Imbruvica (ibrutinib) by JNJ/Pharmacyclics, given their clear superiority in terms of efficacy faced with different references and in diverse settings. The most obvious example stems from the Phase III RESONATE study involving refractory or relapse patients for more than one therapy, and ofatumumab (anti-CD20) as comparison (ORR: 90% vs 25%, 90% reduction in risk of progression or death after 16 months of survival).
- As proof of the rising interest in this new class, AstraZeneca recently acquired Acerta in order to get its hands on acalabrutinib, a second-generation inhibitor boasting greater selectivity for BTK and benefiting potentially from a better safety profile, but also greater efficacy compared with ibrutinib (for CLL in any event).

Fig. 20: Phase I results for acalabrutinib in CLL (R/R)



Source: AstraZeneca, Acerta Pharma acquisition (Dec 2015)

- **BCL2 inhibitors,** and especially venetoclax by Roche/AbbVie, looks just as promising. Like ibrutinib, the compound was designated a Breakthrough Therapy thanks to the excellent tumour regressions that it managed to generate in pre-treated patients harbouring the chromosomic p17 deletion (ORR: 90% of which 31% complete responses).

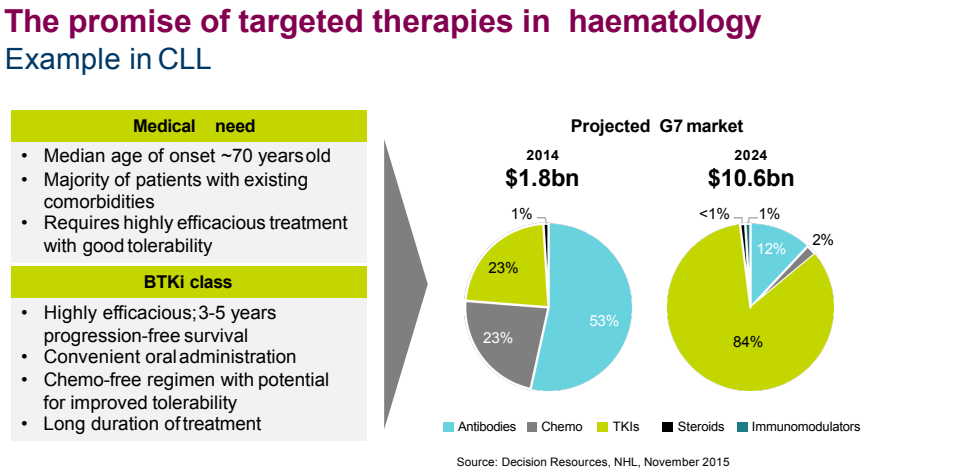
- **Combinations between these two new approaches,** but also with classes just as promising as PD-1/PD-L1 inhibitors are currently being assessed (interest stemming from the fact that ibrutinib is thought to favour a Th1 type response given its ITK inhibiting action, although this all remains very theoretical). Triple combinations are also being considered and some of these continue to imply therapeutic antibodies such as obinutuzumab… However, we doubt whether this type of cocktail could become a genuine standard, if only for cost reasons.

Fig. 21: CLL – Potential combinations to come

Compounds	Ibrutinib	Duvelisib	Venetoclax
Mechanism of action	BTK inhibition	PI3K inhibition	BCL-2 inhibition
Indications	- Approved for use in refractory CLL, WM, second-line Mantle Cell Lymphoma - Being investigated in Multiple Myeloma, Follicular Lymphoma, and DLBCL - Being tested for Rituximab-based regimens and other anti-CD20 agents	- Being explored for use in refractory, indolent NHL and refractory CLL as monotherapy - Being tested in combination with rituximab	- Being explored for use in CLL and NHL as monotherapy treatment - Being studied in combination with Rituximab and with other agents in Multiple Myeloma and a variety of Lymphomas
Potential combos	Potential for use in combination with new immunotherapies such as PD1s, And other novel mechanisms	- Potential for combination with Ibrutinib - Potential for combination with Venetoclax	- Potential for combination with Ibrutinib - Potential for combination with Duvelisib
Launch year	2013	2017	2016

Source: AbbVie, Pharmacyclics acquisition Presentation (March 2015)

Fig. 22: Possible changes in CLL market (2014-2024)



Source: AstraZeneca, Acerta Pharma acquisition (Dec 2015)

4.1. An opportunity in DLBCL?

Before entering the heart of the matter, we would note four factors that make development of MOR208 legitimate in non-Hodgkin's lymphomas (NHL): 1/ these lymphomas are a mixed group of tumours, whether in terms of appearance, development mode or impact on the organism, but are all born in lymphocytes (B in the majority of cases), 2/ among these numerous sub-types, diffuse large B-cell lymphoma (DLBCL) is by far the most common (around 40% of cases), 3/ today, anti-CD20s are still part of the basis of treatment for this lymphoma whether under the framework of an R-CHOP regime (Cyclophosphamide, Hydroxy-doxorubicine, Oncovin, Prednisone) or in combination with bendamustine and 4/ the majority of cancer cells tend to express CD19 on their surface.

Fig. 23: MOR208 – ORR –R/R patients suffering from NHL

Best overall response	DLBCL (n=35)	iNHL (n=45)	MCL (n=12)	Total (n=92)
Complete response	2 (6%)	5 (11%)	0 (0%)	6 (7%)
Partial response	7 (20%)	8 (18%)	0 (0%)	15 (16%)
Stable disease	5 (14%)	20 (44%)	6 (50%)	32 (35%)
Progressive disease	11 (31%)	7 (16%)	5 (42%)	23 (25%)
Not evaluable	10 (29%)	5 (11%)	1 (8%)	16 (17%)
ORR (CR + PR)	9 (26%)	13 (29%)	0 (0%)	21 (23%)
ORR - Evaluable patients (CR + PR)	9 (36%)	13 (33%)	0 (0%)	21 (31%)

Source: Morphosys; Bryan, Garnier & Co ests.

Taken globally, the first clinical data for single-agent MOR208 is fairly encouraging compared with the historical base. However, like CLL, ibrutinib, venetoclax and PD-1/PD-L1 inhibitors are among the few very promising developments whose first efficacy data looks superior to that of MOR208 in FL (see Fig.25).

Fig. 24: ORR of monotherapies in R/R patients suffering from FL

Drug candidates	Median of prior lines	ORR (%)	CR (%)
MOR208 (anti-CD19)	2	26%	9%
Ibrutinib (≥ 2.5 mg/kg) (BTK inhibitor)	3	55%	27%
Venetoclax (BCL2 inhibitor)	3	34%	10%
Idelalisib (PI3K inhibitor)	4	57%	14%
Nivolumab (anti-PD-1)	3-4	40%	10%

Source: Companies Data; Bryan, Garnier & Co ests.

That said, our analysis is possibly less pessimistic in terms of DLBCL (for which MOR208 managed to generate an ORR of 26% and a complete response rate of 6%). Here again, **the new targeted therapies were capable of profound and fairly lasting responses, but only in certain types of tumour.**

- Two major sub-types of DLBCL exist with very distinct development mechanisms: (i) ABC or activated B-cell like (30-40% of cases) and (ii) GCB or germinal-centre B-cell like. Ibrutinib stood out in activated B-cell like tumours probably given the greater activity of pathways caused by BCR). A small Phase I/II study involving ibrutinib showed an ORR of 37% in R/R patients suffering from ABC type DLBCL (vs. 5% for the other sub-type).

- The first Phase I data from venetoclax seems to indicate that BCL2 inhibition could above all be efficient in patients suffering from a Richter syndrome (appearance of DLBCL in a patient suffering from CLL to start with), given that the ORR obtained stood at 43% vs. 15% for the more classic cases.

- The very first clinical results from nivolumab bode fairly well for the anti-PD-1/PD-L1 class. The "simple" fact of having generated response rates of 30-40% (including almost 10% of complete regressions) in monotherapy in widespread sub-types such as DLBCL and FL is already extremely promising. And once again, this approach stood out for the lasting nature of the responses it managed to generate.

Fig. 25: Preliminary results of nivolumab (anti-PD-1) in NHL (R/R)

Tumour	n	CR (%)	PR (%)	SD (%)	PFS 24-weeks
Diffuse Large B Cell Lymphoma (DLBCL)	**11**	**9%**	**27%**	**27%**	**24%**
Follicular Lymphoma (FL)	**10**	**10%**	**30%**	**60%**	**68%**
Other B cell Lymphoma	8	0%	0%	63%	38%
Primary Mediastinal B Cell Lymphoma	2	0%	0%	100%	0%
Mycosis Fungoid (MF)	13	0%	15%	69%	39%
Peripheral T Cell Lymphoma (PTCL)	5	0%	40%	0%	30%
Other T cell Lymphoma	5	0%	0%	20%	0%
Multiple Myeloma (MM)	27	0%	0%	67%	15%
Chronic Myelogenous Leukaemia	1	0%	0%	100%	100%

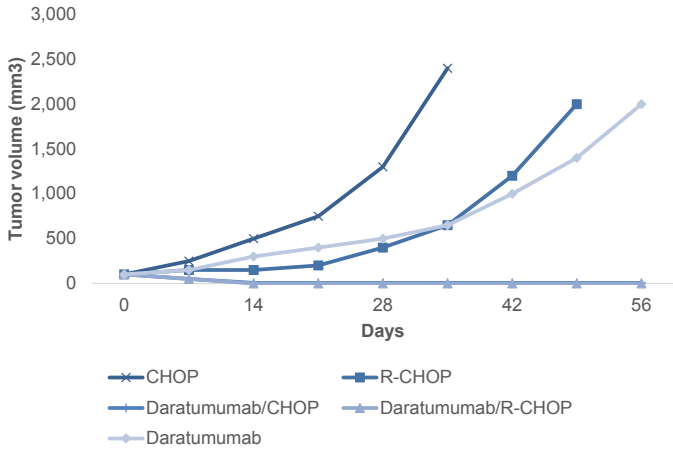
Source: Lesokhin et al, ASH 2014

In this context, we have the feeling that MOR208 could above all address patients suffering from 1/ low expression of the PD-L1 market at the time of diagnostic (70% of cases in a very conservative approach, some studies underscore overexpression in 10-20% of cases), and 2/ a GBC phenotype (55% of cases).

- **But could the landscape change?**

We should nevertheless bear in mind that several other therapeutic antibodies are currently tested in various non-Hodgkin's lymphomas, especially since some of these are fairly promising on paper such as daratumumab. We discussed this in particular under the framework of myeloma treatment, but note that several research articles have presented CD38 as a target of interest for this indication given 1/ the high number of patients over-expressing this protein (> 50% of cases), and 2/ its low variability (hence recurring parallels with CD19). We will see whether future clinical data on daratumumab will validate this theory or not, but the data obtained in pre-clinical models is nevertheless very encouraging (see Fig. 26). And if this is the case, we would not be surprised if (i) JNJ joined forces with another major laboratory in order to assess the potential of dara in combination with a checkpoint blocker in NHL and multiple myeloma and (ii) a combo with ibrutinib was also initiated. Wait and see…

Fig. 26: Daratumumab – Preclinical results in DLBCL



Source: Bryan, Garnier & Co. ests. Adpated from Genmab R&D day (Dec 2014)

4.2. Sales potential of EUR450m in second line treatment of DLBCL

We assume that the majority of value for MOR208 lies in the treatment of GCB and PD-L1-type DLBCL On this basis, we have then assumed that MOR208 could generate sales of almost EUR450m, with a market share of 35%, but solely in refractory or relapse patients.

Fig. 27: Sales estimates for MOR208 in DLBCL

	2020	2021	2022	2023	2024	2025
DLBCL - Annual incidence	**73,272**	**74,005**	**74,745**	**75,492**	**76,247**	**77,010**
- USA	30,206	30,508	30,813	31,121	31,433	31,747
- Europe	22,046	22,266	22,489	22,714	22,941	23,171
- ROW	21,020	21,230	21,443	21,657	21,874	22,092
% CD19+	95%					
% Relapsing/Refractory patients	50%					
% PD-L1- patients	70%					
% GBC phenotype	55%					
Pricing per patient - US (USD)	110,000					
Pricing per patient - Europe & ROW (EUR)	80,000					
MOR208 - Market share - US (%)	5%	10%	20%	25%	35%	35%
MOR208 - Market share - Europe (%)	5%	10%	20%	25%	35%	35%
MOR208 - Market share - ROW (%)	5%	10%	20%	25%	35%	35%
MOR208 - Sales (EURm)	**61**	**123**	**249**	**315**	**445**	**449**
% var y-o-y		102%	102%	26%	41%	1%

Source: Company Data; Bryan, Garnier & Co ests.

5. A look at immuno-oncology

Immuno-oncology is currently one of the most dynamic segments and rightly so. Just a few years ago, advanced cancer patients only had a few months left to live, but this trend has gradually changed with the approval of new therapies such as ipilimumab (anti-CTLA4) and nivolumab (anti-PD-1). More and more patients with an extremely bleak prognostic, such as melanoma, can potentially benefit from long-term survival (Topalian *et al*, 2014, Schadendorf *et al,* 2015). However, despite this progress, the medical need remains more than significant and it is increasingly clear that monotherapies are not enough to face the heterogenic and adaptable nature of tumours and the complexity of the immune machine. For this reason, combination strategies or new approaches (CAR-T, anticorps bispécifiques, ADC, etc.) have emerged.

In this context, we have notably identified three candidates sufficiently well advanced or differentiated in Morphosys' pipeline: 1) an anti-CD137 developed in partnership with Pfizer, 2) MOR209, a bispecific jointly developed with Emergent Biosolutions in metastatic prostate cancer resistant to castration, and 3) anetumab ravtansine, an antibody-drug conjugate which could become one of the reference treatments for mesothelioma.

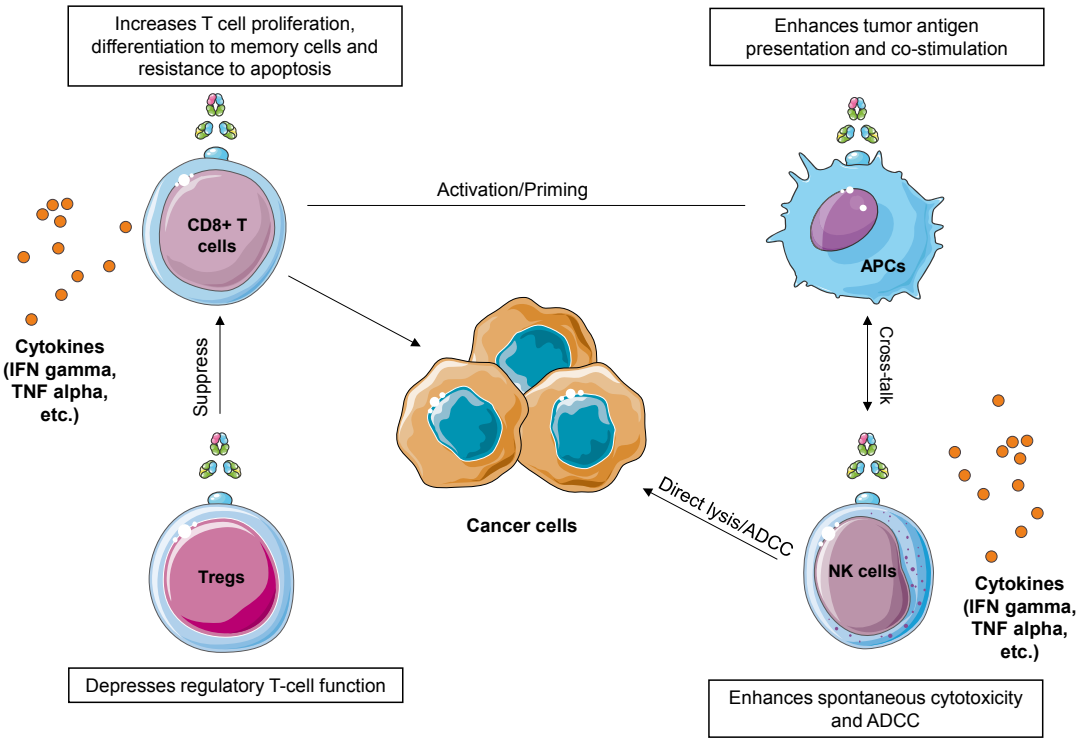
5.1. Anti-CD137: underestimated by the market?

Morphosys' immune-oncology portfolio is still fairly early-stage, but a number of projects have especially caught our attention and among these, the anti-4-1BB/CD137 currently developed by Pfizer (utomilumab). CD137/4-1BB is a receptor that among other factors takes part in 1/stimulating and proliferating soldiers such as NK, dendritic cells, macrophages and T CD8+ lymphocytes and 2/ downregulating regulating T cells that are expressed on their surface. The ability to stimulate thanks to an agnostic activator antibody like Morphosys' should therefore help trigger or amplify an anti-tumour immune response.

Other activating targets are currently of huge interest to major pharma labs with CD27, OX40, LAG-3 and GITR among those that have been cited the most often. However, if we extend our scope of analysis to other companies, we note that the segment leader, **BMS, is developing a similar approach known as urelumab (which was also presented as being one of its priority projects in the field – see Fig. 29).**

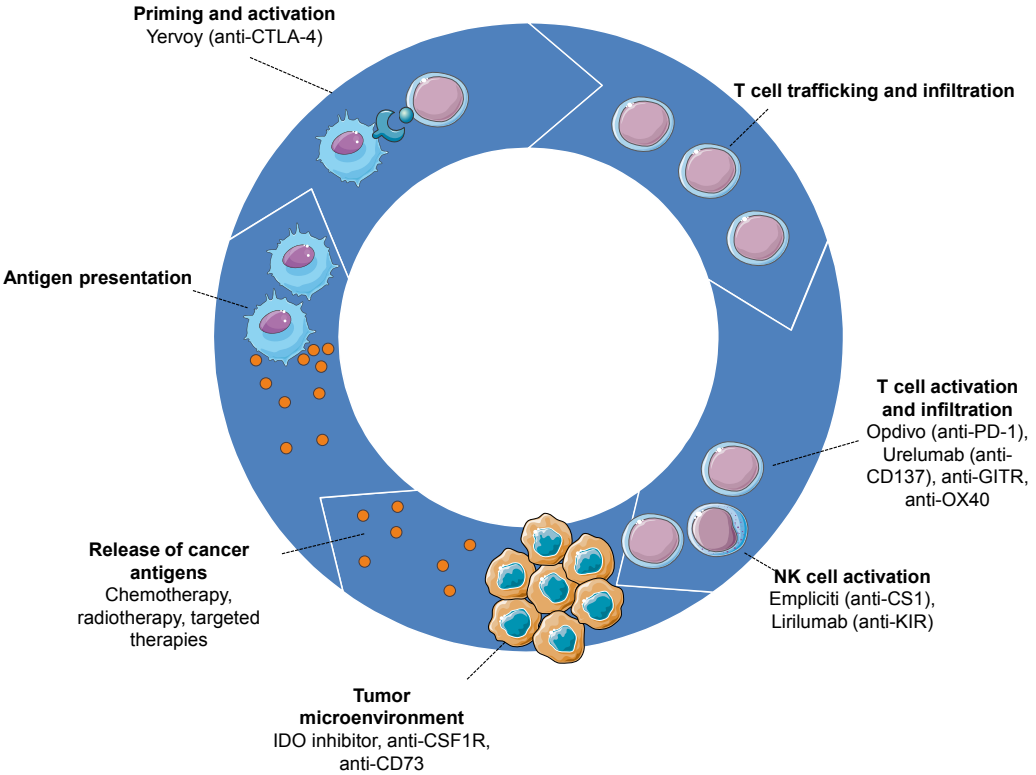
Very little clinical data is currently available that could help us to fully assess this project's potential, so we have chosen not to integrate the outlook for this project into our SOTP. That being said, further publications are expected in the coming months… it seems important to know what the minimum level to reach is in solid tumours such as melanoma and lung cancer (given that these are indications for which we have the most perspective in this field):

Fig. 28: Action mechanism of anti-4-1BB/CD137



Source: Adapted from Yonezawa et al, 2015

Fig. 29: BMS – Focus areas in immuno-oncology

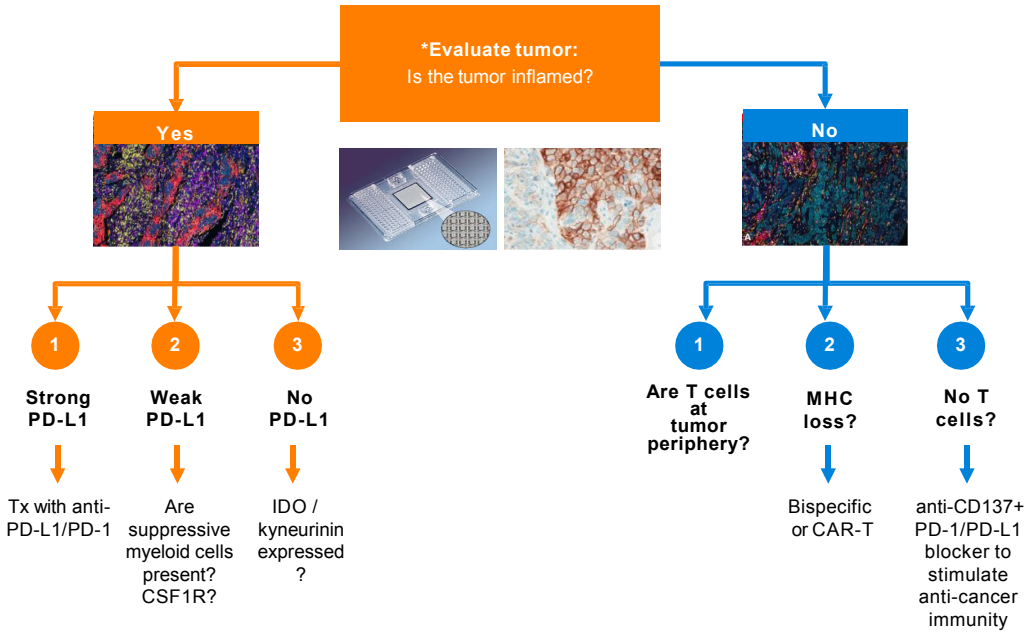


Source: Adapted from BMS, JPM Healthcare conference (Jan. 2016)

- **What positioning for a CD137?**

Like the large majority of immunotherapies being developed, this molecule's positioning above all needs to be assessed under the framework of a combination with a PD-1/PD-L1 inhibitor and depending on the characteristics of each patient. If we leave to one side the level of expression of the PD-L1 marker, we believe this combo should above all suit those presenting low inflammation at the tumour level and suffering from a reduced number of activated and infiltrated T lymphocytes (apart from stimulating the anti-tumour immune machine, we believe this selection could also mitigate risks associated with the release of pro-inflammatory messengers).

Fig. 30: Stratification of patients depending on tumour specifics



Source: Adapted from Roche, ASCO 2015 presentation

We also believe that a mAb of this type would be a very good candidate for a combination with cytotoxic antibodies developed or marketed for the treatment of haematological or solid cancers given its ability to activate and multiply natural killer cells (which are important mediators in the tumour destruction of antibodies such as rituximab and daratumumab). This is probably the reason why BMS is currently testing urelumab with 1/ elotuzumab (an anti-CS1) in multiple myeloma and 2/ cetuximab (anti-EGFR) for head and neck cancer.

Fig. 31: Clinical trials underway for urelumab and PFE-05082566

Candidate	Combo / Monotherapy	Indication	Stage
Urelumab	Rituximab (anti-CD20)	B-cell Non-Hodgkin Lymphomas	Phase I
	Rituximab (anti-CD20)	Chronic Lymphocytic Leukemia	Phase I
	Elotuzumab (anti-CS1)	Multiple Myeloma	Phase I
	Cetuximab (anti-EGFR)	Head and neck cancer	Phase I
	Nivolumab (anti-PD-1)	Solid tumours and B-cell NHL	Phase I/II
	Nivolumab (anti-PD-1)	Recurrent Glioblastoma	Phase I
	Monotherapy	Advanced solid tumours	Phase I
PF-05082566	Mogamulizumab (anti-CCR4)	Advanced solid tumours	Phase I
	Pembrolizumab (anti-PD-1)	Advanced solid tumours	Phase I
	Rituximab (anti-CD20)	Solid tumours and B-cell NHL	Phase I
	Avelumab (anti-PD-L1)	NSCLC, Melanoma, SCCHN	Phase I/II

Source: ClinicalTrial.gov

- **What is the threshold to reach?**

Fig. 32: Response rate of combinations in solid tumours (all comers)

Candidate 1	Candidate 2	Indication	ORR all comers
Pembrolizumab (anti-PD-1)	Epacadostat (IDOi)	Immunotherapy-naïve melanoma	53%
Pembrolizumab (anti-PD-1)	Epacadostat (IDOi)	Immunotherapy-naïve NSCLC	38%
Pembrolizumab (anti-PD-1)	Epacadostat (IDOi)	Immunotherapy-naïve RCC	25%
Pembrolizumab (anti-PD-1)	Ipilimumab (anti-CTLA-4)	2/3L NSCLC	33-50%
Pembrolizumab (anti-PD-1)	Pemetrexed + Carboplatin	1L NSCLC	58%
Nivolumab (anti-PD-1)	Ipilimumab (anti-CTLA-4)	1L NSCLC	13-39%
Nivolumab (anti-PD-1)	Paclitaxel + Carboplatin	1L NSCLC	47%
Nivolumab (anti-PD-1)	Ipilimumab (anti-CTLA-4)	1L Melanoma	58%
Nivolumab (anti-PD-1)	Ipilimumab (anti-CTLA-4)	1L RCC	38-40%
Atezolizumab (anti-PD-L1)	Vemurafenib (BRAFi)	1L BRAF+ Melanoma	76%
Atezolizumab (anti-PD-L1)	Bevacizumab (anti-VEGFR)	1L RCC	40%
Atezolizumab (anti-PD-L1)	Nab-paclitaxel	1L TNBC	67%
Atezolizumab (anti-PD-L1)	Nab-paclitaxel	2/3L TNBC	25-29%
Durvalumab (anti-PD-L1)	Tremelimumab (anti-CTLA-4)	Immunotherapy-naïve NSCLC	27%
Ipilimumab (anti-CTLA-4)	Talimogene laherparepvec (virus)	1L Melanoma	50%

Source: Company Data; Bryan, Garnier & Co ests.

The threshold for newly diagnosed or immuno-therapy naïve patients is probably set by nivolumab/ipilimumab. We deliberately leave aside cocktails based on PD-1/PD-L1 blockers with chemotherapy, targeted therapies or microenvironment modulators given that the populations addressed are unlikely to be the same (see our comment on the product's positioning).

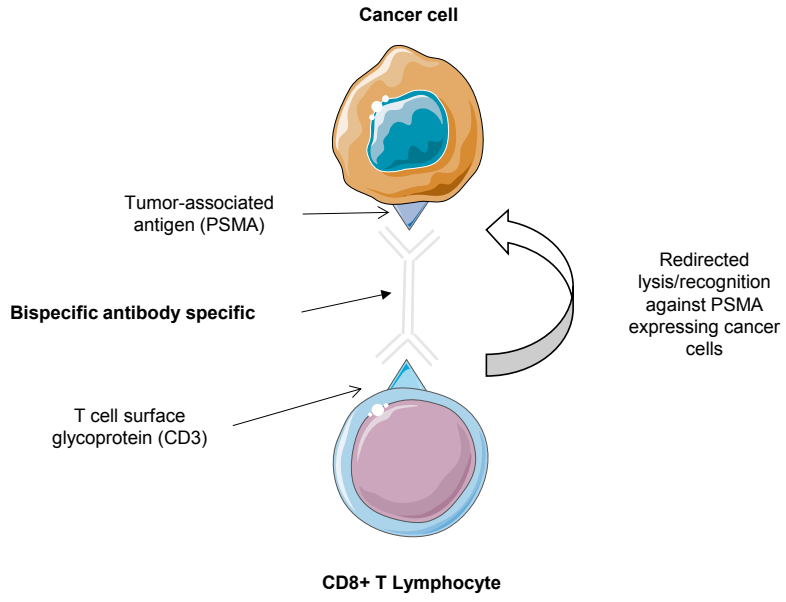
On this basis, we estimate that the response rate should be 50% higher in first-line patients, and this, independently of the PD-L1 status. And if we look at refractory or relapse patients, we would say that an ORR of between 30% and 50% is currently the threshold to reach (especially if the safety profile proves to be more favourable than that of nivo/ipi).

5.2. MOR209 in prostate cancer: reasons to believe

MOR209 is a bispecific linker targeting PSMA and CD3 proteins, the aim being to help lymphocyte populations carrying the CD3 marker to recognise tumour cells expressing PSMA. Although it is early-stage (Phase I), the project could rapidly become one of the group's standards in the oncology field given that 1/ we believe that its mechanism makes it very attractive in the treatment of metastatic prostate cancer, 2/ we have identified a single bispecific with a similar construction (BAY2010112 by Bayer), and which is also in Phase I, 3/ competition stems above all from antibodies combined with cytotoxic agents (PSMA ADC by Progenics, ATL101 by Atlab), whose toxicity profiles also seem far from satisfactory.

Note importantly that the project is part of a partnership with Emergent Biosolutions. Morphosys should shoulder 50-60%e of the R&D costs until its eventual approval, and once this hurdle is crossed, Emergent is to market the drug in the US and Canada (in exchange for which Morphosys will receive royalties of up to 20%), while Morphosys is to handle marketing in the rest of the world (we expect this to above all be the case for Europe with other zones to be covered by partnerships).

Fig. 33: MOR209 action mechanism (CD3xPSMA)



Source: Company data; Bryan, Garnier & Co. ests.

■ Rising interest in bispecifics

If we go deeper into the technical aspects, we would say that these approaches help stimulate the immune system slightly further. A classic monoclonal antibody can indeed create a contact between a target and the immunity soldiers expressing fragment constant (Fc) receptors (such as natural killer cells). The clinical and commercial success of drugs such as rituximab all prove the efficacy of these approaches, although we have to admit that by definition their construction means that their action cannot touch cells without Fc (such as T or B lymphocytes).

Aware of this, laboratories and university research departments have developed new approaches aimed at overriding or improving them. A first strategy consists of targeting two epitopes from two

different proteins or two epitopes from a same protein (dual targeting). However, in the case we're interested in, the aim is more to extend this action to cells that do not express the receptors we mentioned above (the best example being cytotoxic T lymphocytes or CD8+) and in this particular case, we would mention linkers such as Amgen's blinatumomab (a CD3xCD19).

Potential for these approaches is currently limited by their very low half-life (around two hours for blinatumomab compared with more than 20 days for IgG1). However, the majority of these new generation bispecifics seem to address this issue (the half life of MOR209 is actually thought to be three days).

- **Why target PSMA?**

PSMA is an antigen that is highly expressed by prostate cancer cells and especially in disseminated or metastatic cases or those resistant to hormonal castration (and its expression is positively correlated to the aggressiveness of the disease) and not very present on the surface of healthy prostatic cells.

In the past, numerous laboratories have tried to develop therapeutic vaccines or monoclonal antibodies focused on this protein. The clinical results have not really hit the spot. However, we believe that these failures stemmed a lot more from the inherent design of the vaccines rather than the target chosen (immunosuppressive microenvironment to overcome, loss of MHC molecules, innate immunity checkpoints to override etc.), and the fact that immune cells redirected by more classical mAbs lack power relative to this type of tumour.

Fig. 34: Comparison of PSMA and PSA antigens

PSA (Prostate specific antigen)	PSMA (Prostate-Specific Membrane Antigen)
Secretory protein	Integral membrane protein
Known function, liquefaction of semen	Several enzymatic functions
Measured in serum as a cancer marker	Upregulated with androgen deprivation
Decreased with androgen privation	Not verified as screening tool/marker
	Expression correlates with cancer aggressiveness
	and represents an independent indicator of poor prognosis

Source: Chang et al, 2004

- **What is the threshold to reach?**

From our viewpoint, the threshold is notably fixed by the performances of Xtandi (enzalutamide) in this setting. Apart from showing a substantial improvement in overall survival and in several other secondary criteria, the Astellas and Medivation product is far more restrictive than Dendreon's cell therapy (soft capsule taken orally) and is not administered in combination with corticosteroids such as prednisone (contrary to Zytiga).

Among the developments underway, we would say that ProstVAC (a therapeutic vaccine stimulating an immune response against PSA) from Bavarian Nordic is among the candidates that could potentially integrate the standard treatment. Assuming clearly that future trials confirm the OS data noted during the two previous trials (a Phase II trial indeed highlighted an improvement in the survival rate of +8.5 months relative to the placebo arm (HR: 0.56, p=0.0061), whereas a Phase Ib single-arm implying a combination with ipilimumab 10 mg/kg showed a median survival rate of 37.2 months).

Based on the data from these various therapies, we would say that MOR209 is only likely to be competitive if the RECIST response rates are close to 35-40% in post-chemotherapy patients and if the percentage of patients having benefited from a reduction in their PSA level of at least 50% works out to 60-65% (bearing in mind that the responses generated by immunotherapies tend to be far more lasting), and if the median survival rate exceeds 20-25 months.

Fig. 35: Efficacy results of drugs approved for mCRPC

Product	Company	PSA reduction (≥ 50%)	Median Overall Survival (OS)
Xtandi (enzalutamide)	Astellas/Medivation	54%	18.4 vs 13.6 months (HR: 0.63, p<0.001)
Zytiga (abiraterone acetate)	AZN/Cougar biotech/BTG	38%	15.8 vs 11.2 months (HR: 0.74, p<0.001)
Provenge (sipuleucel-T)	Dendreon	29%	14.8 vs 10.9 months (HR: 0.78, p<0.001)
ProstVAC	BMS/Bavarian Nordic	1%	25.5 vs 16.6 months (HR: 0.56, p=0.0061)
ProstVAC + Ipilimumab 10 mg/kg	BMS/Bavarian Nordic	Nd	37.2 months

Source: Companies Data; Bryan, Garnier & Co. ests.

- **Potential sales of EUR800m from a cautious perspective.**

Fig. 36: Sales estimates for MOR209 in prostate cancer

	2021	2022	2023	2024	2025	2026	2027	2028
Prostate cancer incidence	**717,840**	**725,018**	**732,268**	**739,591**	**746,987**	**754,457**	**762,001**	**769,621**
- US	244,885	247,334	249,808	252,306	254,829	257,377	259,951	262,550
- Europe	315,303	318,456	321,641	324,857	328,106	331,387	334,701	338,048
- ROW	157,652	159,228	160,820	162,429	164,053	165,693	167,350	169,024
% Advanced / Metastatic	20%							
% Castration-resistant	50%							
% Previously treated with docetaxel	60%							
Pricing per patient - US (USD)	85,000							
Pricing per patient - Europe & ROW (EUR)	65,000							
MOR209 - Market share - US (%)	5%	10%	15%	20%	25%	25%	25%	25%
MOR209 - Market share - Europe (%)	5%	10%	15%	20%	25%	25%	25%	25%
MOR209 - Market share - ROW (%)	1%	5%	10%	15%	20%	25%	25%	25%
MOR209 - Sales (EURm)	**124**	**270**	**425**	**582**	**743**	**783**	**791**	**799**
% var y-o-y		117%	57%	37%	28%	5%	1%	1%

Source: Bryan, Garnier & Co ests.

We believe that MOR209 could generate revenues close to EUR800m based on the principle that pricing per patient should be close to USD85,000 (or a monthly cost similar to that of Zytiga and Xtandi… which is fairly cautious in our view) and that the penetration rate could near 35% (although this figure could be adjusted once we have a bit more perspective on the potential improvement in survival enabled by the compound).

5.3. Anetumab ravtansine: a promising ADC in mesothelioma

Currently developed by Bayer, anetumab ravtansine is an ADC (anti-mesothelin attached to a DM4 tubulin inhibitor) evaluated as a treatment of malignant pleural mesothelioma (MPM), a fairly rare cancer which tends to develop from cells in the linings of the lungs and peritoneum of people exposed professionally to asbestos.

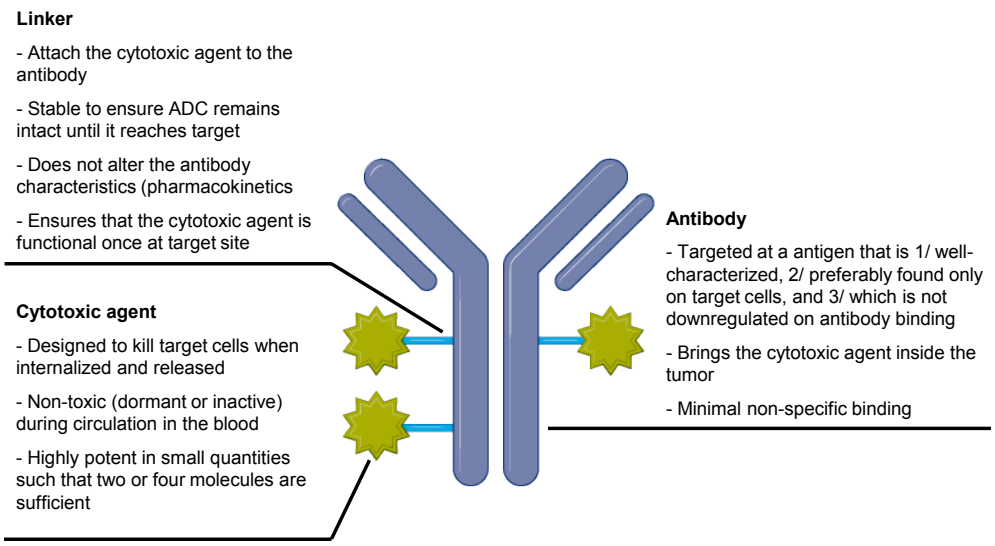
What is an ADC?

Chemotherapies are still the reference treatments for numerous cancers. Although they are very powerful, their use has been hugely limited by the side effects they cause and which are a source of early halts to treatment. For this reason, extensive research has been carried out to reduce the toxicity of these agents, while trying to maintain their efficacy profile. Various approaches have been developed, but in recent years, the focus has also turned to antibody drug conjugates (ADC).

But what is an ADC? An amalgamation would say that it is a type of remote-controlled missile combined with a C4 charge made up of three factors: 1/ a monoclonal antibody directed against a given antigen (preferably overexpressed in a differential manner by the cancers) and with its own anti-tumour activity (ADCC, blocking a certain signalling path etc.), 2/ a cytotoxic agent, and 3/ a linker attaching the first two factors and enabling the release of chemotherapy within the targeted cells.

Several years of research were needed before finding the ingredients and the mix enabling the most optimal risk-benefit, but the concept has become a reality with the approval of trastuzumab emtansine (anti-HER2/DM1) and brentuximab vendotin (anti-CD30/MMAE) at the start of the decade in indications with bleak outlooks such as HER2 breast cancer and Hodgkin's lymphoma.

Fig. 37: Structure and ideal features of an ADC



Source: Adapted from Zolot et al, 2013; Bryan, Garnier & Co. ests.

Fairly limited competition in mesothelioma

The competitive backdrop looks fairly beneficial when we analyse data for developments underway:

- So far, only the addition of Avastin (bevacizumab, an anti-VEGFR) to the current SOC has been able to improve survival in newly-diagnosed patients (+2.7 months vs pemetrexed/cisplatine, HR : 0.76, p=0.0127).

- A few checkpoint inhibitors have also been assessed in this indication, and for the moment, we would note that 1/ tremelimumab (anti-CTLA-4 by AstraZeneca) has unfortunately not managed to improve OS in monotherapy and in patients receiving a second/third-line treatment, 2/ pembrolizumab (anti-PD-1) nevertheless remains in the running with an ORR of 28% in patients overexpressing the PD-L1 market in a similar setting.

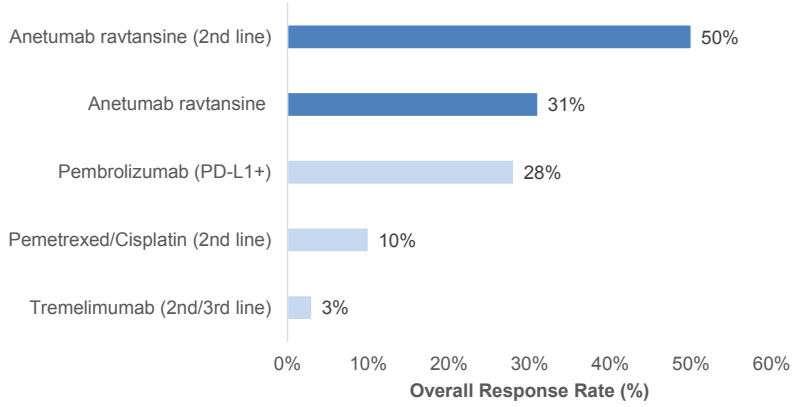
- An anti-mesothelin CAR-T is currently being developed by Novartis. However, we do not really see this approach as a genuine threat. Whether for mesothelioma or other solid tumours, we believe that the lack of tumour-specific antigens and the complex nature of the tumour micro-environment are all challenges that current constructions will find hard to overcome (whether allogenic or autologous). Nothing is set in stone, but we believe these various issues cannot be addressed before the next generation of CAR-Ts (see our report initiating coverage of Cellectis Super Mario CAR-T for further details).

■ **Very encouraging Phase I data**

A small Phase I study (n=16) notably showed an ORR of 31% for the entire population of patients. However, if we limit ourselves to 10 second-line patients, we note that the rate stood at 50% vs. 10% for chemotherapy based on historical controls) and that these responses tended to be lasting, with some having lasted for more than two years (whereas survival in this setting is generally lower than one year).

This data therefore has no reason to envy cisplatine/permetrexed or even pembrolizumab in fairly similar settings and makes us fairly optimistic for the future. However, we also note that improvement in overall survival (and eventually that of progression-free survival) is the only real judge.

Fig. 38: Candidate drugs – Comparison of ORRs obtained



Source: Bryan, Garnier & Co. ests.

■ **Sales potential of EUR600m in second-line treatment**

Mesothelioma is a fairly rare cancer, but the importance of the medical need and the virtual lack of competition mean that a penetration rate of almost 40%e looks quite feasible, especially if 1/ the therapeutic benefit that we see is confirmed and if 2/ a combo with an anti-PD-L1/PD-1 should emerge. In terms of pricing, we are assuming that the levels practiced are fairly similar to those for Kadcyla (whereas the latter is indicated for the treatment of a far more prevalent disease), or USD9,800, and the average duration of treatment is more than 12 months.

We are also assuming that the current Phase II is a pivotal study (like Bayer said during the latter ASCO meeting), meaning that the compound could reach the market by 2019…

Fig. 39: Anetumab ravtansine – Sales estimates (2019-2026)

	2019	2020	2021	2022	2023	2024	2025	2026
Mesothelioma incidence	**26,273**	**26,535**	**26,801**	**27,069**	**27,339**	**27,613**	**27,889**	**28,168**
- USA	8,758	8,845	8,934	9,023	9,113	9,204	9,296	9,389
- Europe	10,303	10,406	10,510	10,615	10,721	10,829	10,937	11,046
- ROW	7,212	7,284	7,357	7,431	7,505	7,580	7,656	7,732
% Refractory/Relapse	60%							
% Advanced or metastatic	85%							
Pricing per patient - US (USD)	120,000							
Pricing per patient - Europe & ROW (EUR)	90,000							
Market shares - US (%)	5%	15%	25%	35%	40%	40%	40%	40%
Market shares - Europe (%)	0%	5%	15%	25%	35%	40%	40%	40%
Market shares - ROW (%)	0%	2%	7%	15%	20%	35%	40%	40%
Anetumab Ravtansine - Sales (EURm)	**29**	**117**	**242**	**380**	**480**	**562**	**585**	**591**
% var y-o-y		310%	106%	57%	26%	17%	4%	1%

Source: Company Data; Bryan, Garnier & Co ests.

6. MOR202: the root of all evil

MOR202 is an anti-CD38 monoclonal antibody developed as a treatment for multiple myeloma. We already discussed the drug in our report initiating coverage of Genmab, but it is still useful to remember that 1) CD38 is a protein highly expressed by virtually all myeloma cells, 2) its expression is fairly limited on the surface of healthy cells. However, among these are highly immunosuppressive cells such as Tregs and MDSCs (such that its neutralisation has a very positive effect on pre-existing immune responses).

The fact that daratumumab by Genmab/JNJ was approved by the FDA for treatment of double refractory patients (to proteasome inhibitors and immunomodulators) clearly placed the spotlight on the anti-CD38 class, especially since the data used for compiling the regulatory file was far superior to that of other therapeutic modalities. However, can we really say that MOR202 really benefited? Nothing is less certain…

- **MOR202 less powerful than daratumumab?**

Let's take a look at the technical specifics of MOR202 and more particularly, those for which genuine differences with daratumumab exist. **The first distinctive point lies in the administration mode.** Admittedly, the two mAbs are currently being developed for intravenous administration, although we noted that JNJ and Genmab are now developing a subcutaneous form for dara. This point is far from meaningless since a subcutaneous administration method often helps significantly reduce the frequency of certain side effects (e.g. peripheral neuropathies for a proteasome inhibitor such as bortezomib).

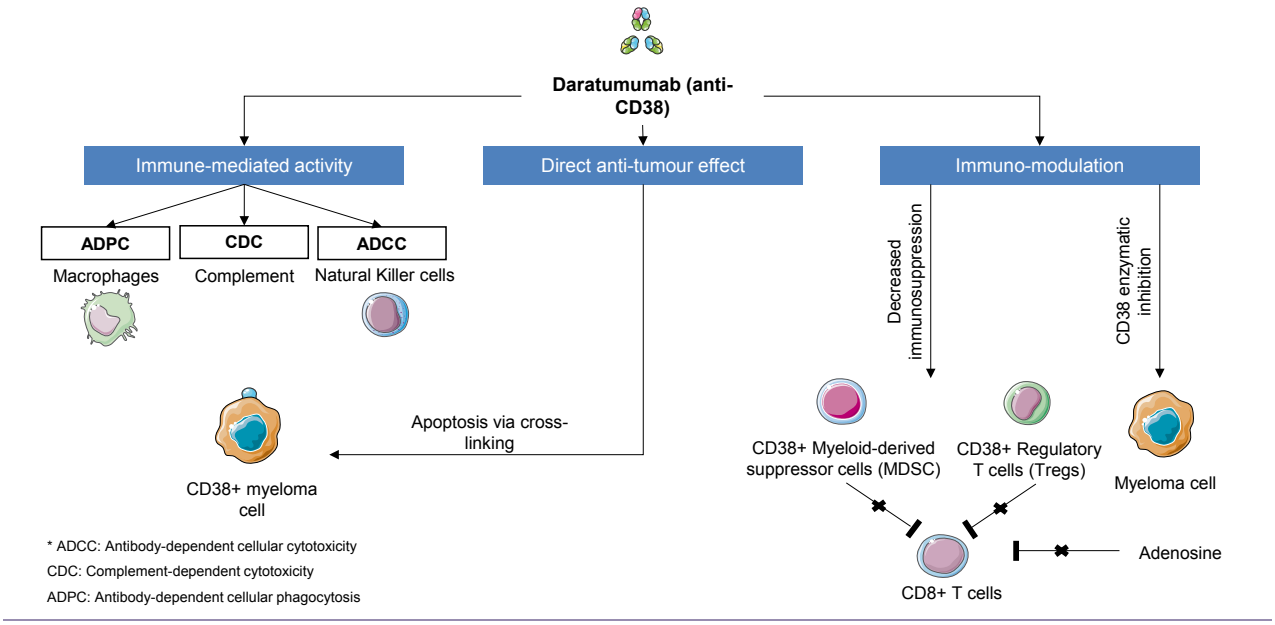
MOR202's anti-tumour activity, as well as its eventual ability to modulate immune response is probably inferior to that of daratumumab in that 1) the two drugs' ADCC abilities are theoretically similar, 2) the capacity to block certain enzymatic functions linked to CD38 can result in the production of immunosuppressive factors (such as adenosine), as well as the cytotoxicity mediated by the complement (CDC), could be less marked for MOR202.

Fig. 40: Technical comparison of various anti-CD38

	Daratumumab	MOR202	Isatuximab	AB79
Origin	Human	Human	Humanized	Human
Development phase	Marketed	Phase II	Phase II	Preclinical
Binding	+++	++	+++	+++
ADCC	++	++	++	++
CDC	+++	+	+	++
Phagocytosis	+++	++	nd	+++
Ecto-enzyme function	+	-	+++	+
Program cell death after cross-linking	+++	+++	+++	+++

Source: Company Data; Bryan, Garnier & Co ests.

Fig. 41: Daratumumab – Action mechanism



Source: Adapted from Genmab R&D day (Dec 2015); Bryan, Garnier & Co ests.

Does this necessarily imply a clinical underperformance of MOR202? Difficult to say for the moment due to the low number of patients, the lack of maturity in this data and the low doses used so far (4 mg/kg and 8 mg/kg vs 16 mg/kg for dara). However, the lack of a complete response is admittedly not very reassuring.

Fig. 42: Efficacy results for various agents in combination

Company	Drugs	Combo	R/R Setting	Efficacy data
Genmab	Daratumumab	Pomalidomide / Dexamethasone	Median prior lines: 4	ORR: 71%, sCR and CR: 12%, VGPR: 44%
Genmab	Daratumumab	Lenalidomide / Dexamethasone	Median prior lines: 2	ORR: 93%, sCR and CR: 43%, VGPR: 33%
Morphosys	MOR202	Lenalidomide / Dexamethasone	Median prior lines: 4	ORR: 60% (VGPR and PR)
Merck	Pembrolizumab	Lenalidomide / Dexamethasone	Median prior lines: 3	ORR: 76%, VGPR: 24%
Merck	Pembrolizumab	Pomalidomide / Dexamethasone	Median prior lines: 3	ORR: 60%
BMS	Elotuzumab	Lenalidomide / Dexamethasone	Median prior lines: 2	ORR: 79%, sCR and CR: 4%, VGPR: 28%
Amgen	Carfilzomib	Lenalidomide / Dexamethasone	Median prior lines: 2	ORR: 87%, sCR and CR: 32%, VGPR: 38%
Takeda	Ixazomib	Lenalidomide / Dexamethasone	Median prior lines: 2	ORR: 78%, CR: 12%, VGPR: 36%

Source: Company Data; Bryan, Garnier & Co ests.

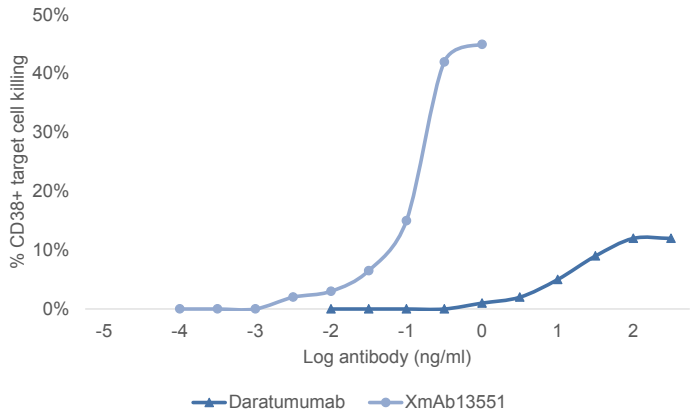
Is this really the end of the story? Morphosys' management nevertheless hopes to sign a new partnership agreement once clinical data has accumulated in combo with IMiDs + dexamethasone, and at the 16 mg/kg dose. Ideally, this would effectively help breathe some fresh optimism into the project which has had its share of highs and lows, although several context factors make us fairly sceptical on this prospect:

- Clinical data is more than likely to improve over time, but we already have doubts as to whether this can make up for the project's status of last entrant. On the other hand, we believe that Genmab/JNJ should rapidly sign other agreements with other pharma groups in order to widen the scope of possibilities for its anti-CD38 (eg. combo with ibrutinib in CLL,

or with another anti-PD-1 in non-Hodgkin's lymphomas – see our recent comments on the JNJ/Roche partnership here, for further details).

- New approaches aiming to redirect T cells towards the CD38 protein such as the bispecific linker by Xencor (XmAb13551) or UCART38 by Cellectis, should rapidly enter clinical trials in coming months. Admittedly, MOR202 still has a certain edge, but we ask ourselves whether big pharmas will favour these therapies with greater anti-tumour power and for which the development time is not as long as all that (if not why would Amgen have signed an agreement worth USD1.7bn with Xencor in order to get its hands on XmAb13551 and other projects?).

Fig. 43: *in vitro* results for XmAb13551 vs daratumumab (myeloma)



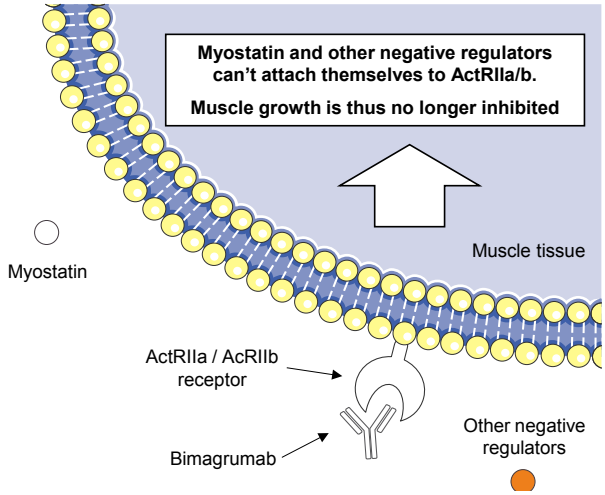
Source: Adapted from SY Chu et al, ASH 2014

For all of these reasons, we have chosen not to integrate the outlook for this project into our valuation. If we prove to be wrong on this subject, the result would simply be further upside for this case on which we have a positive opinion.

7. Bimagrumab: high risk, high reward

Bimagrumab is a monoclonal antibody that attaches itself with great affinity to the ActRIIb receptor in order to break the regulation ways widely implicated in muscle growth inhibition (Askanas *et al*, 2007, Lloyd *et al*, 2010). As it happens, the aim is therefore not to modulate the immune response, but rather to favour muscle growth and restore strength to patients suffering from the disease. And this is what makes the drug attractive in treatment of diseases characterised by muscular degeneration like sporadic inclusion body myositis (sIBM).

Fig. 44: Bimagrumab – Action mechanism



Source: Bryan, Garnier & Co. ests

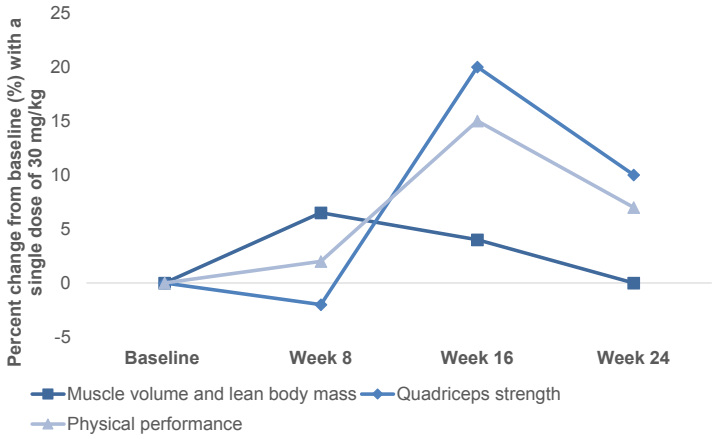
Sporadic inclusion body myositis is a degenerative inflammatory disease affecting skeletal muscles. The first signs of the disease are generally a weakness, or even atrophy of the quadriceps and flexor tendons in the fingers (such that the sufferer has a lot of difficulty in moving and using objects etc.). One of the major issues remains the general lack of knowledge on the causes of this particular form of myositis. Is it a primitive auto-immune disease (and if so, what is the trigger)? Or is it an initially degenerative disease in which the accumulation of degeneration proteins prompts a secondary immune response? For the moment, only one thing is sure: immunosuppressive or immunomodulating treatments struggle to generate constant and lasting efficacy (the failures of alemtuzumab and infliximab are just two examples among others).

Any clinical trial in this indication is therefore inherently risky. However, the therapeutic gap characterising the pathology and the lack of late-stage rivals mean that the project could rapidly prove to be lucrative in the event of a clinical success…

- **Very encouraging Phase II results…**

A small Phase II study helped validate the concept with a single dose of 30 mg/kg in 14 patients suffering from the disease: 1/ muscle growth in the thighs was statistically superior in the active group, eight weeks after administration (+6.5-7.6% vs placebo, $p<0.05$), and 2/ in the 16th week, the distance walked over a period of six minutes had improved by 14.6% relative to the baseline ($p=0.008$).

Fig. 45: Bimagrumab –Phase II results with a single injection (30 mg/kg)



Source: Adapted from Novartis, Meet the management Presentation (June 2015)

This data was extremely encouraging (without which the FDA would not have designated the drug a Breakthrough Therapy in 2013). However, we will not give in to all-out optimism as long as we have no convincing data for a larger number of patients, and over a longer observation period. As stated previously, sIBM is a little known disease for the scientific community and this is probably why a large number of developments have not succeeded.

For example, Shire and Acceleron Pharma have developed ACE-031, an ActRIIb decoy attaching to myostatin and other negative regulators (GDF-8, etc.). Efficacy looked good, but the development did not manage to go beyond the Phase I stage, following the emergence of side effects that were difficult to explain (nose bleeds, dilation of blood vessels etc.). That said, the read-across was not necessarily negative given that 1/ the action mechanisms are not the same, 2/ the Phase II trial for bimagrumab did not show major toxicity issues, 3/ contrary to the Shire study, the current Phase III by Novartis has gone ahead smoothly (no halt for futility or excessive toxicity)… In a word, we had reasons to believe in this project.

- **… Before a Phase III trial failure**

But the primary endpoint of the Phase III was not met…

But the verdict fell a few weeks ago: the primary endpoint of the Phase III study (improvement in the 6-minute walk distance test after 52 weeks of treatment) was not met. Admittedly, such a disappointment does not mean the drug candidate might fail in all the other indications given the differences in the aetiology and physiopathology of the patients… But we made the choice not to take into account this compound in our forecasts, at least until we get more promising data (perchance with the publication of the Phase II results in sarcopenia during the first semester of 2017; and knowing that a potential success might open the door to a EUR1.0Bn peak sales).

8. Gantenerumab: watch out for blind optimism

■ **Alzheimer's disease: an insanely large but challenging market**

Described in 1906 by the German doctor who lent his name to the disease, Alzheimer's is a degenerative disease affecting the way the brain works. The loss of neurones (ensuring the transmission of information within the nervous system) that the disease causes gradually affects various cognitive functions such as memory, language, orientation in time and space and reasoning. Memory problems, and especially short-term memory are the first to emerge since the disease initially affects the region where the hippocampus is located (a key structure for this function).

The potential addressable market is "insanely" large 1/ given that the prevalence of the disease with more than 30 million suffers in the world (including five million in the US) but also because 2/ the medical need remains considerable (all options currently available having only one aim, to treat symptoms of the disease). That said, we can easily affirm that any new disease-modifying option with a satisfactory toxicity and efficacy profile would rapidly become a blockbuster.

Clinical failures have nevertheless come in droves, and we believe this situation should last as long the pathogenesis is not better understood. The fact that so many molecules have failed in large Phase III trials is particularly symptomatic of this reality (one single candidate out of 244 was approved between 2002 and 2012), and it is probably for this reason that several big pharmas have decided to slow up on developments in order to better focus on fundamental research.

Fig. 46: Recent clinical failures in Alzheimer's disease

Compound	Company	Therapeutic class	Setting	Notes
Semagacestat	Eli Lilly	Gamma-secretase inhibitor	Mild to moderate	- Phase III failure in 2010 - ADAS-COG: 7.8 vs 6.4 points (placebo) - ADCS: 23 vs 9.0 points
Bapineuzumab	JnJ/Pfizer	Anti-beta-amyloid mAb	Mild to moderate	- Phase III failure in 2012 - Failed to meet the co-primary endpoint of change in cognitive or functional performance vs placebo
Solanezumab	Eli Lilly	Anti- beta-amyloid mAb	Mild to moderate	- Phase III failure in 2012 - Failed to meet the co-primary endpoint of change in cognitive or functional performance vs placebo

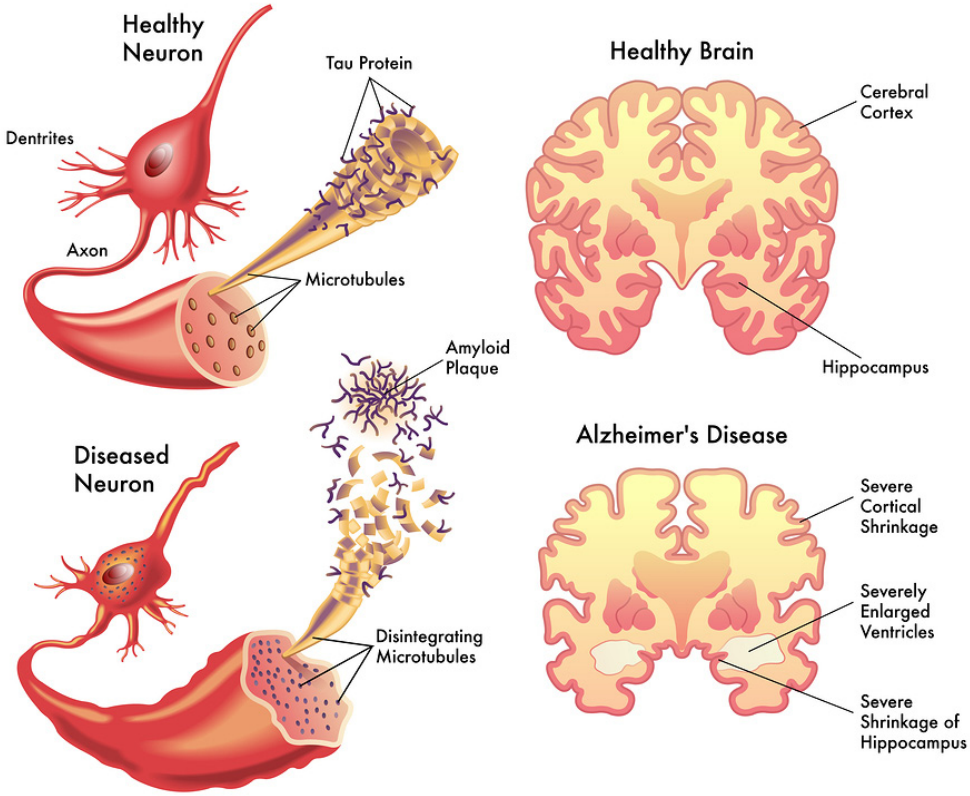
Source: Companies Data

■ **Can Gantenerumab change the landscape?**

Gantenerumab is a monoclonal antibody targeting beta-amyloid protein. A Phase III trial was initiated by Roche to assess the drug in patients suffering from prodromal Alzheimer's disease in 2010, before being halted for futility in December 2014. The story could have stopped there but Biogen recently published positive results for adacanumab (which is also an anti-beta-amyloid with a huge amount of similarities with Morphosys' product).

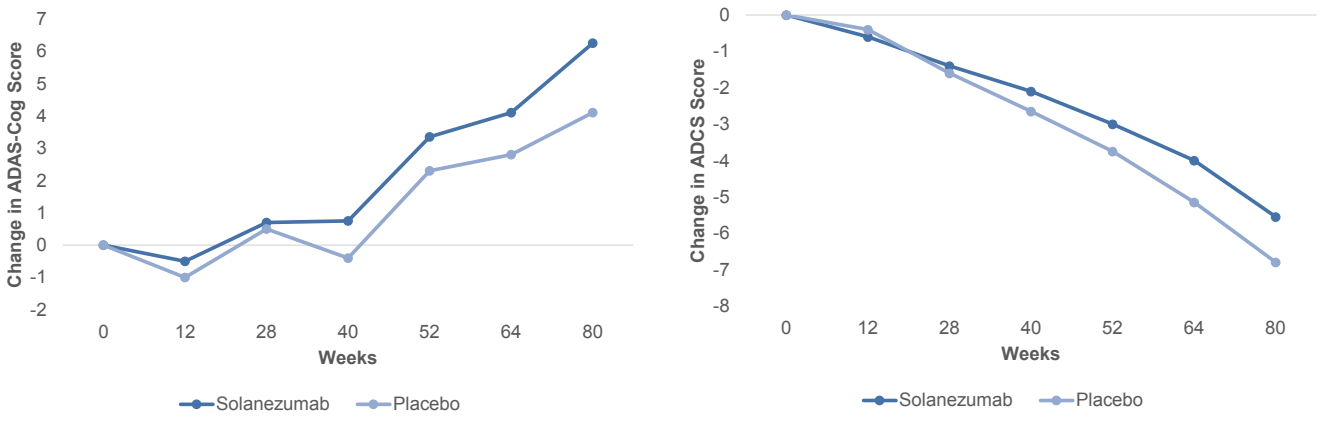
Before giving in to blind optimism, we believe that several questions should be asked: is the target chosen of interest? Are the results obtained with other antibodies of this type really convincing? What are the challenges? As the disease progresses, extracellular plaques made up of beta-amyloids (amyloid plaques), and intracellular tangles of Tau protein filaments accumulate in the brain. **The amyloid cascade theory (whereby the protein is toxic for nerve cells and prompts a greater phosphorylation of Tau protein) now seems to be returning to the limelight.** After becoming obsolete following numerous clinical failures, the theory has been resurrected following the publication of post-hoc clinical data concerning Lilly's solanezumab (anti-beta amyloid) and including patients with a light form of the disease.

Fig. 47: Alzheimer's disease – Tau proteins and beta amyloid



Source: Adapted from Morreale et al, 2012

Fig. 48: Solanezumab –Phase III results in light forms of AD



Source: Eli Lilly; Bryan, Garnier & Co. ests.

That said, note that retrospective analysis by sub-group often shows positive results, before finally resulting in a fresh failure (and examples are numerous: Stimuvax, Asentar, etc.). Analysis of this type clashes with numerous methodological difficulties that do not help draw any real conclusions: repetition of statistical tests, loss of power, inflation of beta risk or false negatives etc. In all, we only obtain new working assumptions which cannot be conclusive by definition We will see what results the future Lilly trials will bring, but we cannot help but remain cynical (especially since this compound has already failed twice).

A second important point: crossing the hemato-encephalic barrier remains a major challenge for a number of therapeutic approaches, and especially for monoclonal antibodies. Hence the need to develop administration methods enabling a play on mechanisms such as transcytosis (trans-cellular transport of macromolecules).

- **Caution is the mother of safety**

It is probably preferable to consider this asset as a free call option (especially since the costs are totally borne by Roche) as long as we lack prospective data from gantenerumab and its peers. That being said, let's note that 1/ the Phase III results of Lilly's solanezumab are expected during H2 16, and 2/ any positive read-across might lead us to change our stance. And if so, we believe a peak sales of USD2.2Bn would be largely achievable.

Fig. 49: Gantenerumab – Potential sales (2015-2025^{e})

	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Prodromal AD - Prevalence (in millions)	**7.8**	**7.9**	**8.0**	**8.0**	**8.1**	**8.2**	**8.3**	**8.4**	**8.4**	**8.5**	**8.6**
- US	3.8	3.8	3.9	3.9	4.0	4.0	4.0	4.1	4.1	4.2	4.2
% var yo-y		1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
- EU	4.0	4.0	4.1	4.1	4.2	4.2	4.2	4.3	4.3	4.4	4.4
% var yo-y		1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
% Diagnosed and treated	35%										
Pricing in the US (USD)	10,000										
Pricing in the US (EUR)	8,772										
Pricing in the EU (EUR)	6,140										
Gantenerumab - Market shares - US (%)	0%	0%	0%	0%	1%	3%	5%	7%	9%	10%	10%
Gantenerumab - Market shares - Europe (%)	0%	0%	0%	0%	0%	1%	3%	5%	7%	9%	10%
Gantenerumab - Sales	**0**	**0**	**0**	**0**	**121**	**458**	**893**	**1,336**	**1,789**	**2,122**	**2,238**

Source: Bryan, Garnier & Co ests.

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Stock rating

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