TME PHARMA

BUY

TARGET PRICE : 4,21€ +310%

NEWSFLOW

MEDIAN SURVIVAL ABOVE 12 MONTHS... NEXT STOP - 15 MONTHS

Yesterday, TME Pharma reported overall survival rates after 12 months follow-up for patients suffering from glioblastoma and treated with its NOX-A12 combined with radiotherapy and bevacizumab. Five out of six patients monitored under the framework of the study are still alive after 12 months. This data should be compared with median overall survival rates for patients treated with the standard of care (radiotherapy and chemotherapy), which is "just" 10 months. This signifies that so far, the combo offers an improvement *a minima* in survival of more than two months, or an increase of at least 23% in the median overall survival rate vs. standard of care. In view of current data on both the reduction in size of the target tumour and overall survival, we reiterate our Buy rating and maintain our TP at €4.2.

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Reading after 12-month follow-up: five out of six patients still alive!

Slightly ahead of the expected schedule, TME Pharma announced yesterday that 83% of the patients in its cohort treated with RT/NOX-A12/beva (or five patients out of six) are still alive after 12 months of median follow-up. Note that this catalyst was initially expected for Q2 2023 and therefore comes slightly earlier than planned. Treatment of the RT/NOX-A12/beva arm is to continue over coming months to help obtain the median overall survival (mOS) rate once 50% of the cohort has died (i.e. three patients, bearing in mind that one patient out of six has already died), thereby allowing the company to define a median overall survival duration. This mOS parameter had therefore not been reached at 12 months, which is a very good sign since it indicates that patients are still responding to the treatment, that the disease is probably stabilised with tumours sizes stable and significantly reduced, and that mOS (duration at which 50% of patients monitored will still be alive) is above 12 months, compared with the median overall survival rate known from literature, which stands at 9.7 months for patients with an identical profile presenting non-methylated MGMT tumours with incomplete resection, but treated with the standard of care (study carried out on 20 patients treated with radiotherapy and chemotherapy). As such, the increase in mOS stands at two months, which is huge for these patient profiles, which after diagnosis and relapse, have very few solutions available and very low chances of survival at 12 months.

Improvement in median overall survival rate of more than 23% at present vs. SoC

This data is extremely encouraging since it suggests an improvement of at least 23% in the median overall survival rate vs. the standard of care at this stage of follow-up, thereby representing a two-month gain in additional median survival for these target patients. This arm of the Ph I/II GLORIA study showed outstanding clinical results in patients suffering from GBM with survival data at present confirming that 83% of patients are still alive after 12 months of treatment compared with standards of care, which offer an average of six months of progression-free survival and 9.7 months of overall survival in the precise indication targeted. Furthermore, note that 100% of targeted tumours treated with NOX-A12 decreased by more than 50%, and that 83% of patients obtained a partial response lasting more than six months (with two out of six patients seeing a reduction in the size of their target tumour of more than 99% (complete

Invest Securities and the issuer have signed an analyst coverage agreement

in € / share	2022e	2023e	2024e
Adjusted EPS	-21,88	-7,29	-9,09
chg.	*n.s.*	*n.s.*	*n.s.*
estimates chg.	*n.s.*	*n.s.*	*n.s.*

au 31/12	2022e	2023e	2024e
PE	n.s.	n.s.	n.s.
EV/Sales	6,3x	121,8x	279,5x
EV/Adjusted EBITD	n.s.	n.s.	n.s.
EV/Adjusted EBITA	n.s.	n.s.	n.s.
FCF yield*	n.s.	n.s.	n.s.
Div. yield (%)	n.s.	n.s.	n.s.

* After tax op. FCF before WCR

key points	
Closing share price 27/03/2023	1,03
Number of Shares (m)	2,3
Market cap. (€m)	2
Free float (€m)	2
ISIN	NL0015000YE1
Ticker	ALTME-FR
DJ Sector	Health Technology

	1m	3m	Ytd
Absolute perf.	-17,8%	-15,7%	-15,4%
Relative perf.	-12,5%	-18,4%	-18,3%

Source : Factset, Invest Securities estimates

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regression, which is difficult to quantify as such in GBM given the extent to which the disease is aggressive with a dire prognosis, and considered as being an incurable cancer (two-year survival rate of 18% and five-year rate of 4%). This is especially the case of the sub-type of GBM addressed by TME Pharma, since these patients are considered as being difficult to treat since they are chemotherapy-refractory and rarely respond to standards of care. As such, it is important to note that even if a patient suffering from GBM experiences a long period of progression-free survival (survival without relapse and/or with no increase in the size of the tumour treated post-treatment), the disease is still considered as incurable and there is a high probability of relapse. Consequently, constant monitoring and imaging follow-up studies are necessary to detect any sign of progress or relapse in the disease, in order to intervene as quickly as possible, in which case, the patient enters palliative care. Note that in the last communication provided at end-2022, all patients had shown a stabilisation and a lasting partial response with a median survival rate of 7.9 months.
As such, the results of the combo currently assessed by TME Pharma are very promising given the impact noted at this stage on mOS, although PFS data also remains a key parameter to assess. To date, the company has not provided PFS data, although a matched historical cohort treated with standard therapy showed a mean PFS of six months (vs. data not provided by TME Pharma) and mOS of 9.7 months (vs. more than 12 months at this stage for TME Pharma - final data pending), with only 25% of patients showing a reduction in tumour size with the standard treatment (vs. 100% for TME Pharma), while 10% of patients showed a 50% or greater reduction in tumour size when treated with the standard of care (vs. 100% for TME Pharma).

Next key milestone: median overall survival at 127 months - a new score to beat

At this stage, and taking into account the behaviour of the patients followed, the RT/NOX-A12/beva treatment combination should probably exceed the results obtained by TME Pharma with the simple RT/NOX-A12 combination but without beva, for which an mOS of 12.7 months was observed in the initial nine-patient Ph I/II study (with a response rate of nearly 90%). This mOS of 12.7 months already represents three additional months of survival vs. standard treatment, or an improvement of 31%. As such, we estimate that the follow-up milestone of 12.7 months should be watched carefully since it will help assess the interest of adding beva to the RT/NOX-A12 in survival parameters. Given the publication date for the 12-month follow-up results, we estimate that data at 12.7 months should be available in around mid-April. On that date, if the mOS is still not reached and more than three patients (cohort of six patients) are still alive, this would be a positive signal in terms of the benefit presented by treatment with the tri-combo vs. the bi-combo. In contrast, if the mOS is reached before the 12.7 month milestone or precisely at this milestone, which presumes a deterioration in the state of health and death of at least two patients within this period, this would imply that the tri-combo presents greater interest than the bi-combo in terms of:

- reduction in the size of the target tumour (maximum reductions noted without beva ranging from -2% to -71% according to the NOX-A12 [200, 400 and 600 mg/weeks] dose vs an average reduction of -74.9% [from -53.8% to -99.9%]),
- a partial radiographic response rate defined as being a reduction in the size of the tumour of more than 50% (40% without beva vs. 100% with beva),
- But not necessarily in terms of overall survival, which would be identical for the two protocols, if not slightly superior with beva (but potentially with a better PFS).

After this update with 12-month survival rates, the next date on the calendar is the company's participation in the ASCO congress in June 2023. This is where 15-month mOS data will be communicated, as well as the first results concerning sensitivity and specificity of the recently identified biomarker, the first data on the correlation between the biomarker and its predictive potential. PFS results are also key parameters that are useful to assess. The company provided no details as to when this parameter would be published.

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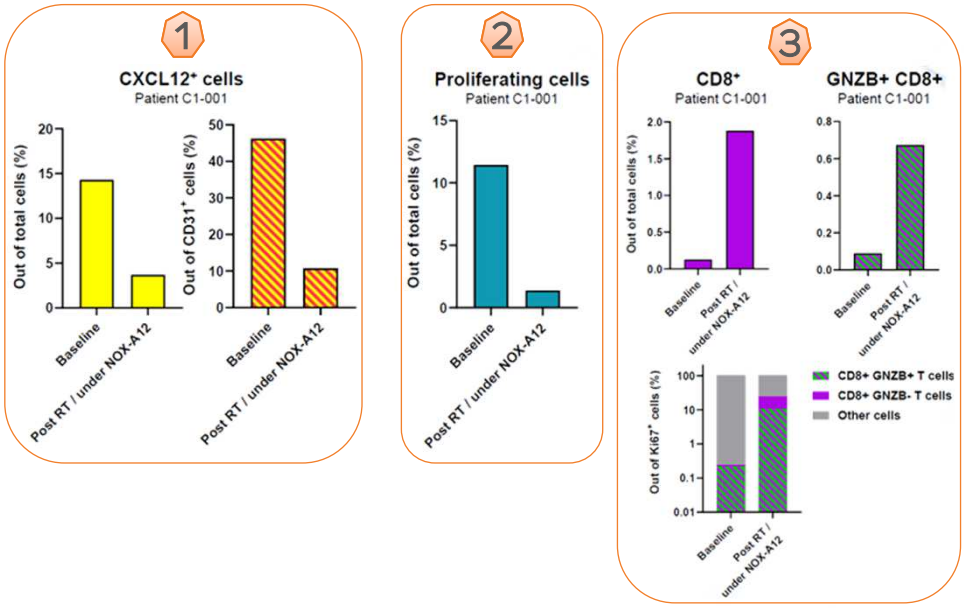
Identification of a predictive biomarker, an additional asset

At the same time as the extremely promising clinical data obtained so far, works undertaken on the biological front have helped identify a potential biomarker that could predict the clinical response of patients suffering from brain cancer to the NOX-A12 treatment. The presence of a specific biomarker is a huge asset in the patient care journey since it should enable prescribing doctors to better sort patients and select only those who present a responder profile and who would thus benefit the most from the treatment. This should theoretically avoid losing the probability of success and ultimately of survival for patients who only have little chances of responding favourably to the treatment. In addition, the presence of this predictive biomarker adds another advantage for TME Pharma since its existence should foster a positive assessment by reviewers and payers who ought to welcome the availability of an effective therapy with a sensitive companion test. This should increase the chances of regulatory approval and commercial success of NOX-A12 (better targeting of the market and therefore lower medico-economic costs associated with the management of GBM patients), while reducing the cost and duration of associated clinical trials through better stratification and selection of target patients.

Note that tissular analysis of a patient being treated with NOX-A12 in the first study carried out without beva showed a significant reduction in the NOX-A12 target CXCL12, in tumour blood vessels (chart 1), as well as a significant decline in proliferation of the tumour cells (chart 2) and increased tumour infiltration of effector immune cells activated (chart 3). These results were observed in all available tumour tissues analysed, suggesting that this is a general phenomenon and not just limited to small tumour sub-sections. Furthermore, in biological terms, a co-localisation of CXCL12 with endothelial cells was observed in the micro-vascular proliferation zone in two reference samples of a same patient. A comparative analysis before vs. during treatment with NOX-A12 in a matched sample of a patient, showed that the endothelial cells were positive for CXCL12 before treatment, but not during treatment with NOX-A12, with virtually all the cells extracted by biopsy of the cancer proving negative in the sample taken during treatment. This observation therefore suggests a reduction in the expression of CXCL12 after administration of NOX-A12 of around 70-80%.



Source: SNO 2021

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At this stage, apart from the information that a predictive biomarker has been identified, we have no further details on the nature of this biomarker, the target, or even the method of reading and monitoring it: indeed it could be a molecular biomarker measurable by blood test, or is it a radiographic, histological, or numerical test potentially assessable by imaging, or a physiological test measurable by monitoring constants? We expect more information and, potentially, data related to the biomarker to be disclosed at the company's presentation at ASCO in June 2023.

Next stages of development envisaged by the company

Based on the preclinical and clinical work to date, the safety and tolerability profile has been found to be satisfactory with no serious adverse events (beyond what is expected and commonly accepted in RT treatments with or without additional treatment). The data collected as of 15 October 2021 showed 80 adverse events related to treatment or the tumour, including 19 related to NOX-A12, among which just nine events were related to NOX-A12 alone. Among the adverse events only related to NOX-A12, most were not serious and only three cases were grades 2 and 3. As such, the data suggests good tolerance of NOX-A12, which causes few adverse events compared with the effects related to the tumour itself and radiotherapy (RT), and of limited seriousness. Different doses of NOX-A12 were evaluated in the first part of the Ph I/II trial (200, 400 and 600 mg/week). TME Pharma observed no difference between the 200 and 600 mg/week doses in terms of safety. Given the good safety profile, the highest dose was chosen for the second part of the Ph I/II. The company is now planning to rapidly initiate a Phase II trial to evaluate the 200 and 600 mg/week doses of NOX-A12 in combo with RT alone vs. RT + beva in a randomised, placebo controlled trial. We estimate that the cost of the future Ph II trial assessing the tri-combo of RT/NOX-A12/beva should stand at around €25-30m. Note that the company currently has financial visibility out to September 2023. Discussions are underway concerning partnerships and additional financing options, which have notably been strengthened in order to ensure the future clinical development of NOX-A12 without having to use convertible bond financing.

Glioblastomas can appear at any age and their development is often very fast over two/three months. In adults, GBM is the most frequent type of brain cancer with an incidence rate of around 1/33,330 per year, and prevalence estimated at 1/100,000. According to the literature, the prevalence of non methylated MGMT in GMB is around 30-40% in the US and Europe. Prevalence varies considerably depending on the study population and the methods used to detect MGMT methylation, but it is accepted that younger patients are more likely to have a non-methylated form. Treatment is firstly surgical with the widest possible resection bearing in mind that it is generally impossible to remove the entire tumour, which infiltrates the normal brain parenchyma. After surgery, when this is possible, the first line treatment consists of targeted radiotherapy in association with chemotherapy. The benefit of these two treatments in terms of survival nevertheless remains very modest, albeit proven. In the event of a relapse, second-line chemotherapy, or even a second round of surgery may be proposed. Indeed, the need for a new solution with a better therapeutic benefit is strongly expected to emerge in order to manage brain cancers more effectively.

Newsflow to watch in the short term

- Q2 2023: 12.7-month survival in RT/NOX-A12/beva arm in GBM – Ph I/II GLORIA.
- June 2023: participation in ASCO congress - 15m survival + biomarker data
- 2023: discussions with the FDA and EMA to validate the design of a Ph II randomised and controlled vs. SoC - for the RT/NOX-A12 with or without beva. Launch expected at end-2023.

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FINANCIAL DATA

Share information	2016	2017	2018	2019	2020	2021	2022e	2023e	2024e
Published EPS (€)	-6,71	-2,54	-2,70	-0,08	-0,32	-0,26	-21,88	-7,29	-9,09
Adjusted EPS (€)	**-6,71**	**-2,54**	**-2,70**	**-0,08**	**-0,32**	**-0,26**	**-21,88**	**-7,29**	**-9,09**
Diff. I.S. vs Consensus	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Dividend	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	1,00

Valuation ratios	2016	2017	2018	2019	2020	2021	2022e	2023e	2024e
P/E	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
EV/Sales	87,92x	144,40x	7,62x	9,36x	-49,68x	-29,41x	6,32x	121,77x	279,45x
EV/Adjusted EBITDA	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
EV/Adjusted EBITA	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Op. FCF bef. WCR yield	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Op. FCF yield	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Div. yield (%)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

NB : valuation based on annual average price for past exercise

Entreprise Value (€m)	2016	2017	2018	2019	2020	2021	2022e	2023e	2024e
Share price in €	*22,0*	*15,6*	*1,03*	*1,03*	*1,03*	*1,03*	*1,03*	*1,03*	*1,03*
Market cap.	45	36	2	2	2	2	2	2	2
Net Debt	*0,6*	*1,9*	*0,5*	*0,2*	*-9,7*	*-6,7*	*-1,5*	*15,5*	*36,7*
Minorities	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*1,0*
Provisions/ near-debt	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*
+/- Adjustments	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*1,0*
Entreprise Value (EV)	**46**	**38**	**3**	**3**	**-7**	**-4**	**1**	**18**	**41**

Income statement (€m)	2016	2017	2018	2019	2020	2021	2022e	2023e	2024e
Sales	1	0	0	0	0	0	0	0	0
chg.	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Adjusted EBITDA	-8	-5	-4	-4	-6	-14	-28	-12	-16
adjusted EBITA	**-9**	**-5**	**-4**	**-4**	**-6**	**-14**	**-28**	**-12**	**-16**
chg.	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***
EBIT	-9	-5	-4	-4	-6	-14	-28	-12	-16
Financial result	-2	-1	-6	3	-5	-5	-5	-5	-5
Corp. tax	0	0	0	0	0	0	0	0	0
Minorities+affiliates	0	0	0	0	0	0	0	0	1
Net attributable profit	-11	-5	-11	-1	-10	-19	-33	-17	-20
Adjusted net att. profit	**-11**	**-5**	**-11**	**-1**	**-10**	**-19**	**-33**	**-17**	**-20**
chg.	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***

Cash flow statement (€m)	2016	2017	2018	2019	2020	2021	2022e	2023e	2024e
EBITDA	-8	-5	-4	-4	-6	-14	-28	-12	-16
Theoretical Tax / EBITA	0	0	0	0	0	0	0	0	0
Capex	0	0	0	0	0	0	0	0	0
Operating FCF bef. WCR	**-8**	**-5**	**-4**	**-4**	**-6**	**-14**	**-28**	**-12**	**-16**
Change in WCR	1	0	0	0	0	0	0	0	0
Operating FCF	**-7**	**-5**	**-4**	**-3**	**-6**	**-14**	**-28**	**-12**	**-16**
Acquisitions/disposals	0	0	0	0	0	0	0	0	0
Capital increase/decrease	7	3	8	1	14	16	28	0	0
Dividends paid	0	0	0	0	0	0	0	0	0
Other adjustments	-2	-1	-6	3	-5	-5	-5	-5	-5
Published Cash-Flow	**-2**	**-3**	**-3**	**1**	**3**	**-3**	**-5**	**-17**	**-21**

Balance Sheet (€m)	2016	2017	2018	2019	2020	2021	2022e	2023e	2024e
Assets	0	0	0	0	0	0	0	0	0
Intangible assets/GW	0	0	0	0	0	0	0	0	0
WCR	-2	-2	-2	-2	-2	-2	-2	-2	-2
Group equity capital	-2	-4	-3	-2	8	-6	-11	-28	-50
Minority shareholders	0	0	0	0	0	0	0	0	1
Provisions	0	0	0	0	0	0	0	0	0
Net financial debt	**1**	**2**	**0**	**0**	**-10**	**-7**	**-1**	**15**	**37**

Financial ratios	2016	2017	2018	2019	2020	2021	2022e	2023e	2024e
EBITDA margin	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
EBITA margin	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Adjusted Net Profit/Sales	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
ROCE	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
ROE adjusted	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Gearing	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
ND/EBITDA (in x)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Source : company, Invest Securities Estimates ies Estimates ies Estimates

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INVESTMENT CASE

NOXXON is a biotech company with an oncology-focused portfolio. The two products it has developed to date—NOX-A12 (glioblastoma, as well as metastatic pancreatic and colorectal cancer) and NOX-E36 (solid cancers)—are designed to break the tumor protection barrier and block tumor repair by neutralizing chemokines in the tumor microenvironment (TME). Its clinical approach is unique and can be used in combination with other therapeutic approaches, notably radiotherapy and immunotherapy, to weaken tumor defenses against the immune system and enable greater therapeutic impact.

SWOT ANALYSIS

STRENGTHS

- An innovative approach within the IO space
- Partnership with Merck for brain cancer
- Drugs that target indications with little competition

WEAKNESSES

- Relatively early-stage pipeline
- Need for additional financing within a year

OPPORTUNITIES

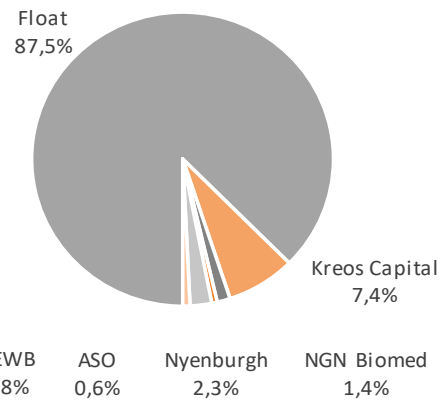
- Combination drug trials
- Possibility of new partnerships
- Significant M&A activity in the field

THREATS

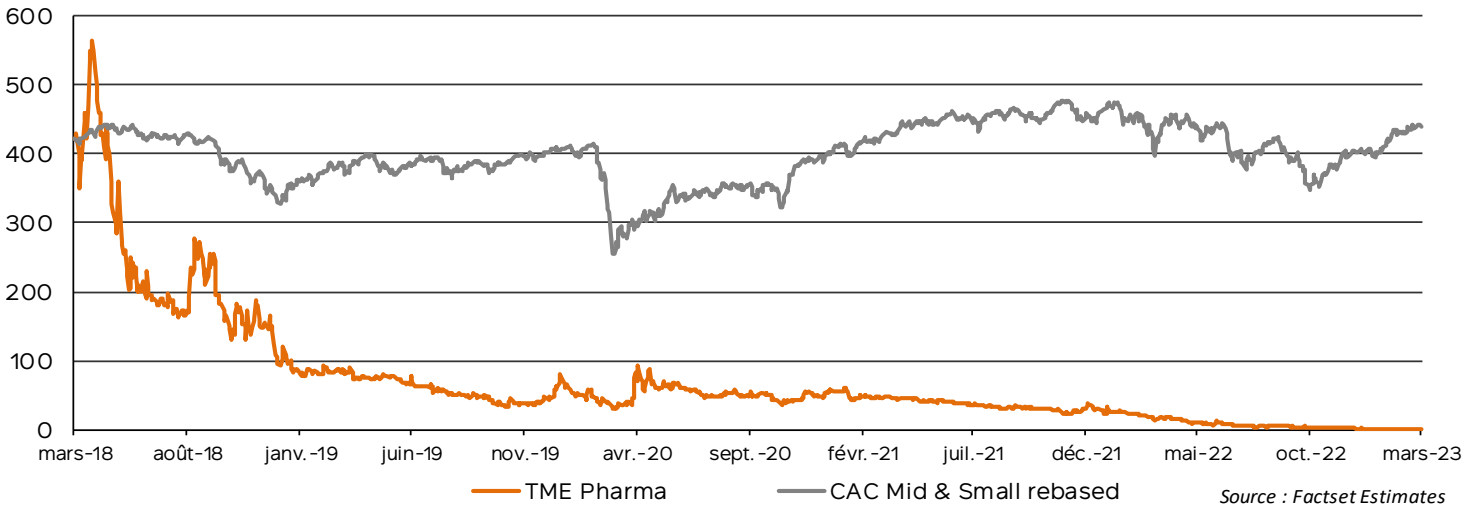
- Regulatory and clinical risks
- Legal risks
- Commercial risks

ADDITIONAL INFORMATION

Shareholders



SHARE PRICE CHANGE FOR 5 YEARS



Source : Factset Estimates

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TARGET PRICE AND RECOMMENDATION

Our analyst ratings are dependent on the expected absolute performance of the stock on a 6- to 12-month horizon. They are based on the company’s risk profile and the target price set by the analyst, which takes into account exogenous factors related to the market environment that may vary considerably. The Invest Securities analysis office sets target prices based on a multi-criteria fundamental analysis, including, but not limited to, discounted cash flows, comparisons based on peer companies or transaction multiples, sum-of-the-parts value, restated net asset value, discounted dividends.

Ratings assigned by the Invest Securities analysis office are defined as follows:

- BUY: Upside potential of more than 10% (the minimum upside required may be revised upward depending on the company’s risk profile)
- NEUTRAL: Between -10% downside and +10% upside potential (the maximum required may be revised upward depending on the company’s risk profile)
- SELL: Downside potential of more than 10%
- TENDER or DO NOT TENDER: Recommendations used when a public offer has been made for the issuer (takeover bid, public exchange offer, squeeze-out, etc.)
- SUBSCRIBE or DO NOT SUBSCRIBE: Recommendations used when a company is raising capital
- UNDER REVIEW: Temporary recommendation used when an exceptional event that has a substantial impact on the company’s results or our target price makes it impossible to assign a BUY, NEUTRAL or SELL rating to a stock

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12-MONTH HISTORY OF OPINION

The table below reflects the history of price recommendation and target changes made by the financial analysis office of Invest Securities over the past 12 months.

Company Name	Main Author	Release Date	Rating	Target Price	Potential
TME PHARMA	Jamila El Bougrini	27-mars.-23	ACHAT	4,2	+310%
TME PHARMA	Jamila El Bougrini	11-nov.-22	ACHAT	16,1	+381%
TME PHARMA	Jamila El Bougrini	15-juil.-22	ACHAT	0,2	+220%

DETECTION OF CONFLICTS OF INTEREST

	TME PHARMA
Invest Securities was lead manager or co-lead manager in a public offer concerning the financial instruments of this issuer during the last twelve months.	No
Invest Securities has signed a liquidity contract with the issuer.	Yes
Invest Securities and the issuer have signed a research service agreement.	Yes
Invest Securities and the issuer have signed a Listing Sponsor agreement.	No
Invest Securities has been remunerated by this issuer in exchange for the provision of other investment services during the last twelve months (RTO, Execution on behalf of third parties, advice, placement, underwriting).	No
This document was sent to the issuer prior to its publication. This rereading did not lead the analyst to modify the valuation.	No
This document was sent to the issuer for review prior to its publication. This rereading led the analyst to modify the valuation.	No
The financial analyst has an interest in the capital of the issuer.	No
The financial analyst acquired equity securities of the issuer prior to the public offering transaction.	No
The financial analyst receives remuneration directly linked to the transaction or to an investment service provided by Invest Securities.	No
An executive officer of Invest Securities is in a conflict of interest with the issuer and was given access to this document prior to its completion.	No
Invest Securities or the All Invest group owns or controls 5% or more of the share capital issued by the issuer.	No
Invest Securities or the All Invest group holds, on a temporary basis, a net long position of more than 0.5% of the issuer's capital.	No
Invest Securities or the All Invest group holds, on a temporary basis, a net short position of more than 0.5% of the issuer's capital.	No
The issuer owns or controls 5% or more of the capital of Invest Securities or the All Invest group.	No

Invest Securities's conflict of interest management policy is available on the Invest Securities website in the Complicance section. A list of all recommendations released over 12 months as well as the quarterly publication of "BUY, SELL, NEUTRAL, OTHERS" over 12 months, are available on the Invest Securities research platform.

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