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Noxxon Pharma

NOX-A12+Keytruda induisent une réponse immunitaire et apportent un bénéfice clinique dans les cancers avancés.

Les premiers résultats d'efficacité de l'étude OPERA (Nox-A12+Keytruda) montrent que cette association en mobilisant le système immunitaire peut induire une stabilisation de la maladie chez 25% des patients.

NOX-A12+Keytruda induce an immune response and provide a clinical benefit in advanced cancers

The first top line efficacy results from OPERA clinical trial (NOX-A12+Keytruda) show that the combo by mobilizing the immune system can induce a 25% stable disease.

Opinion	**1. Strong Buy**
Closing Price 19/12/2018	**1,07 €**
Target Price	**5,00 € (+317,5 %)**

Noxxon Pharma a publié des résultats particulièrement encourageants sur l'efficacité et la sécurité d'emploi de sa combinaison NOX-A12 +Keytruda.

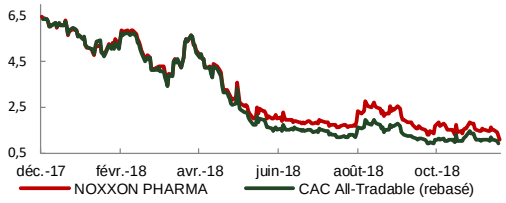
Dévoilés lors du congrès ESMO Immuno-Oncology par le Dr Niels Halama, Investigateur principal de l'étude NCT0368139 (NOX-A12 + anti-PD-1 pembrolizumab), les résultats montrent que le NOX-A12 avec le Keytruda induit une réponse immunitaire ainsi qu'un bénéfice clinique clair. De plus, dans des cancers difficiles à traiter (CRCm, CdPm) avec des patients ayant reçu plusieurs lignes de traitement, NOX-A12 + Keytruda ont eu une influence sur l'évolution de la maladie puisque 70% des patients étaient vivants à 24 semaines et 50% à 36 semaines. De plus, 25% des patients (5/20) ont vu leur maladie se stabiliser (selon les critères RECIST). Ces résultats confirment donc le potentiel thérapeutique de NOX-A12.

Noxxon Pharma has published encouraging efficacy and safety results on its NOX-A12 + Keytruda combination

Unveiled at the ESMO Immuno-Oncology congress by Dr. Niels Halama, lead investigator of the NCT0368139 study (NOX-A12 + anti-PD-1 pembrolizumab), the results show that NOX-A12 with Keytruda induces an immune response as well a clear clinical benefit. In addition, in hard-to-treat cancers (mCCR, mPC) with patients receiving multiple lines of treatment, NOX-A12 + Keytruda had an action since 70% of patients were still alive at 24 weeks and 50% at 36 weeks. In addition, 25% of patients (5/20) had their disease stabilized (according to RECIST criteria). These results confirm the therapeutic potential of NOX-A12.

Performances

Absolute perf.	1 month	6 months	12 months
	-13,9 %	-52 %	-63,7 %



Market data

Reuters / Bloomberg ticker	ALNOX.PA / ALNOX.FP
Market capitalisation (€m)	10,8 M€
Enterprise value (€m)	11,8 M€
Free Float	8,3 M€ (77 %)
Number of shares	9 319 205
Daily volume	166 074 €
Capital turnover rate (1 year)	253,5%
High (52 weeks)	6,35 €
Low (52 weeks)	1,07 €

Current shareholding structure

Free float : 7,20 % ; Kreos Capital 18,12 % ;TVM Capital : 13,25 %

Agenda

Q1 2019: Phase I/IIa initiation in newly diagnosed glioblastoma multiforme.
Q1 2019: extraordinary general meeting of shareholders

Key figures

	2016	2017	2018E	2019E	2020E
Revenues(M€)	0,1	0,0	0,0	0,0	26,0
Change (%)	-	-	-	-	-
EBITDA (M€)	-8,9	-4,8	-4,7	-4,7	21,3
EBIT (M€)	-8,9	-4,8	-4,7	-4,7	21,3
EBIT Margin (%)	*NS*	*NS*	*NS*	*NS*	*NS*
Net profit gp sh. (%	-11,0	-5,4	-4,7	-4,7	21,3
Net margin (%)	*NS*	*NS*	*NS*	*NS*	*NS*
EPS	-1,31	-0,49	-0,43	-0,43	1,94

Ratios

	2016	2017	2018E	2019E	2020E
VE / CA	NS	NS	NS	NS	NS
VE / EBIT	NS	NS	NS	NS	NS
VE / REX	NS	NS	NS	NS	NS
P / E	NS	NS	NS	NS	NS
Gearing (%)	NS	NS	NS	NS	NS
Net debt/ EBITDA	NS	NS	NS	NS	NS
RCE (%)	NS	NS	NS	NS	NS

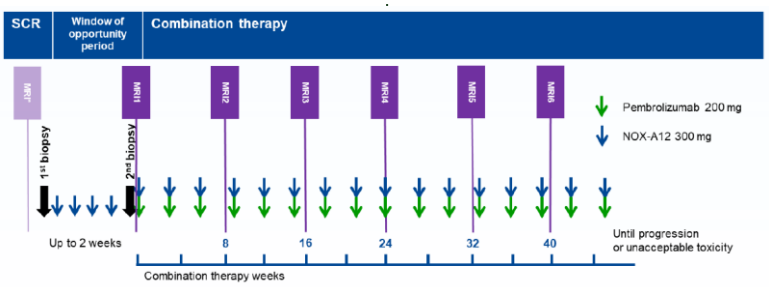
L'essai OPERA/KEYNOTE 559 : design et recrutement

20 patients ont été recrutés pour cet essai de phase I/II ouvert, qui évaluait dans un premier temps les effets pharmacodynamiques et la sécurité d'emploi de NOX-A12 en monothérapie, puis la tolérance et l'efficacité d'une combinaison NOX-A12 + pembrolizumab chez des patients présentant des cancers colorectaux (CCR) métastatiques à microsatellites stables et des cancers du pancréas (CdP) avec des métastases au foie.

The test OPERA / KEYNOTE 559: design and recruitment

20 patients were recruited for this open-label phase I / II trial, which first evaluated the pharmacodynamic and safety effects of NOX-A12 monotherapy and then the safety and efficacy of a combination of NOX-A12 + pembrolizumab in patients with metastatic colorectal cancers (CCR) with stable microsatellites and pancreatic cancer (COP) with liver metastases.

OPERA Study Design



Durant les deux premières semaines, les patients subissent une première biopsie à l'aiguille de leurs métastases hépatiques permettant de définir les valeurs initiales. Ensuite, ils reçoivent quatre injections de 300 mg de NOX-A12 aux jours J1, 4, 8 et 11 et une deuxième biopsie est réalisée, lorsqu'elle est médicalement faisable. Puis, durant 21 jours, ils reçoivent du NOX-A12 (300 mg) et du pembrolizumab (200 mg). A partir du jour 14, le sang périphérique a été prélevé aux mêmes moments. Les échantillons de tumeurs collectés ont été évalués pour une infiltration de cellules immunitaires par IHC et par signature de cytokine en utilisant une analyse protéinique multiplexée.

Sur les 20 patients inclus dans l'étude, 11 avaient un cancer colorectal métastatique et 9 un cancer du pancréas avec des métastases. Tous ces patients sont à un stade avancé de la pathologie (stade IV) lors de l'inclusion dans l'étude. Par ailleurs, les patients avaient reçu plusieurs lignes de traitement, en moyenne 5 pour les patients CCR et 3 pour les patients CdP. La grande majorité des patients (95%, 19/20) avait une maladie en progression, comme meilleure réponse à leur dernière thérapie anti-cancéreuse.

During the first two weeks, all patients, undergo a first needle biopsy of their liver metastasis to define the initial values. Then, they receive four injections of 300 mg of NOX-A12 on days 1, 4, 8 and 11 and a second biopsy is performed, when it is medically possible. Then, each 21 days, they receive NOX-A12 (300 mg) and pembrolizumab (200 mg). From day 14, the peripheral blood was taken at the same time. The tumor samples collected were evaluated for immune cell infiltration by IHC and by cytokine signature using multiplexed protein analysis.

Of the 20 patients included in the study, 11 had metastatic colorectal cancer and 9 had pancreatic cancer with metastases. All of these patients are at advanced stages of the pathology being stage IV at the time of trial entry. In addition, patients received several treatment lines, on average 5 for CCR patients and 3 for PC patients. The vast majority of patients (95%, 19/20) had a progressive disease (PD) as the best response to their last anti-cancer therapy.

La combinaison NOX-A12/Keytruda montre un bénéfice clinique

La combinaison (NOX-A12+pembrolizumab) induit une réponse immunitaire ainsi qu'un bénéfice clinique chez des patients ayant déjà reçu plusieurs lignes de traitements et dont la meilleure réponse à ces traitements était des maladies en progression. Des dix patients encore en vie après 3 mois (temps minimum défini par les protocoles de l'essai), 70% des patients étaient vivants à 24 semaines et 50% à 36 semain^^

The combo NOX-A12/Keytruda demonstrates a clinical benefit

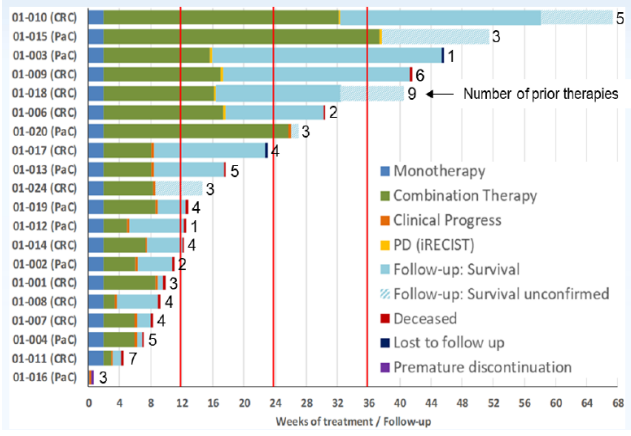
The combination (NOX-A12 + pembrolizumab) induces an immune response as well as a clinical benefit in patients who have already received several lines of treatment and whose best response to these treatments were progressive diseases. Among the ten patients still alive after 3 months (the minimum time defined by the trial protocols), 70% of patients were alive at 24 weeks and 50% at 36 weeks.

Trial demographics

	Colorectal Cancer	Pancreatic Cancer
N	11	9
Male/Female	7 / 4	8 / 1
Age, mean (range)	63 (55 – 73)	67 (48 - 82)
Stage at study entry	100% stage IV (metastatic)	
Microsatellite status at study entry	All patients MSS	
Prior lines of systemic treatment, mean (range)*	5 (2 – 9)	3 (1 – 5)
Patients with prior surgery (# of surgeries)	7 (1 – 4)	3 (1 – 2)
Best response last treatment	PD (10), SD (1)	PD (9)
Time since last systemic prior treatment (mean)	2.0 months	1.5 months

* excluding surgery

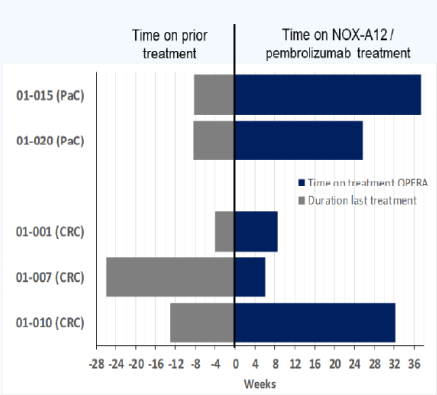
Large number of patients with longer time on study



Ces résultats indiquent que la combinaison NOX-A12+Keytruda induit un contrôle de la pathologie chez un certain nombre de patients atteints, soit d'un cancer du pancréas métastatique, soit d'un cancer colorectal métastatique à microsatellites stables. Par ailleurs, le nombre élevé de patients encore vivants à 9 mois (36 semaines) montrent aussi que la combinaison aurait un effet sur l'évolution tumorale et donc la survie des patients. D'ailleurs, 25% des patients traités lors de cet essai ont montré une stabilisation de leur maladie selon les critères RECIST (22% de CdP, 27% de CCR).

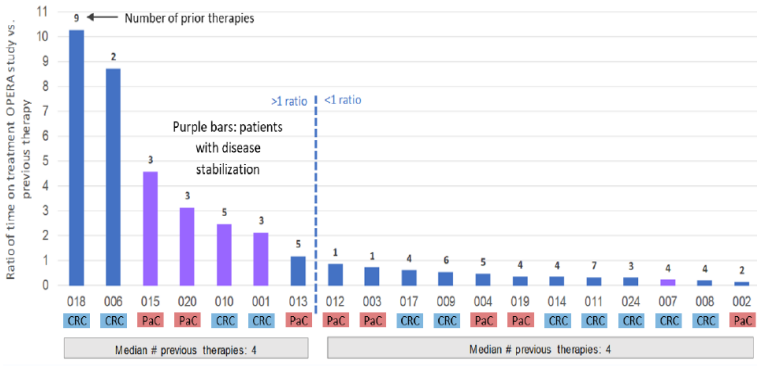
These results indicate that the combination of NOX-A12 + Keytruda induces pathology control in a number of patients with metastatic pancreatic cancer or metastatic colorectal cancer with stable microsatellites. In addition, the high number of patients still alive at 9 months (36 weeks) also shows that the combination would have an effect on tumor progression and therefore patient survival. In fact, 25% of the patients treated in this trial achieved a stabilization of their disease according to the RECIST criteria (22% with pancreatic cancer, 27% with colorectal cancer).

Patients with a long-time in study



Ratio	Prior lines of treatment	Best response last treatment
4.6	3	PD
3.1	3	PD
2.1	3	PD
0.2	4	SD
2.5	5	PD

Highly-pretreated patients evolving towards stabilization



Ainsi ce taux exceptionnel de malades ayant atteint une stade de stabilisation de leur maladie est particulièrement encourageant. En effet, les patients inclus dans cette étude présentaient de nombreuses lignes de traitements et étaient tous en situation de progression de leur maladie au moment de l'inclusion dans l'étude. Par ailleurs, 95% des patients recrutés n'avaient pas vu leur maladie se stabiliser avec leurs traitements précédents. Toutefois, en dépit de cette situation, la moitié des patients encore en vie 3 mois après l'initiation du traitement ont bénéficié de la combinaison NOX-A12+Keytruda, se traduisant par une amélioration de la survie, notamment en demeurant plus longtemps (x10) sous NOX-A12+Keytruda que sous leurs précédentes lignes de traitement. De plus, ce sont les patients ayant reçu le plus de ligne de traitement qui ont tiré le plus grand bénéfice de la combinaison jusqu'à une stabilisation de leur maladie.

Thus, this exceptional rate of patients having reached a stage of disease stabilization is particularly encouraging. Indeed, the patients included in this study presented many lines of treatment and were all in a situation of progression of their disease at the time of trial inclusion. In addition, the 95% patients recruited had not seen any disease stabilization with their most recent treatment. However, despite this situation, half of the patients still alive after 3 months benefited from the NOX-A12 + Keytruda combination, resulting in improved progression-free survival (PFS), including staying longer (x10) under NOX -A12 + Keytruda than with their previous treatment lines. In addition, it was the patients who received the most previous treatment line who benefited the most from the combination, including disease stabilization.

Ces résultats sont d'autant plus intéressants que les tumeurs considérées dans cet essai sont reconnues comme difficiles à traiter en immunothérapie, car elles sont généralement peu ou pas sensibles aux seuls inhibiteurs de point de contrôle immunitaire (IPCI). De plus, l'ensemble des patients recrutés dans l'étude présentait un phénotype « microsatellites stables (MSS) », un critère de non-réponse aux IPCI anti-PD1. Ainsi, dans un essai de phase II (Le et al, NEJM, 2015) évaluant le pembrolizumab dans trois différentes populations : des patients avec un CCR-chimio-réfractaires à microsatellites instables (N=10), des patients avec un CCR métastatique à microsatellites stables (N=18), et d'autres cancers à microsatellites instables (N=7), dans la sous-population MSS, seulement 11% des patients (2 patients/18) présentaient une maladie stable et 11/18, soit 61% étaient en situation de maladie en progression. Il n'y a pas à notre connaissance de cas de maladies stables chez des patients atteints d'un CdP avec MSS.

These results are even more interesting as these tumors are known to be difficult-to-treat, because they are generally little or no at all sensitive to immune checkpoint inhibitors (ICIs) alone. Furthermore, all patients recruited for the study presented a microsatellite stable phenotype (MSS), a criterium of non-responsiveness to ICIs (anti-PD-1 therapies). Thus, in a previous phase II trial (Le et al, NEJM, 2015) evaluating pembrolizumab in three different populations: patients with a CCR-chemo-refractory with unstable microsatellites (N = 10), patients with metastatic CCR with stable microsatellites (N = 18), and other unstable microsatellite cancers (N = 7), in the MSS subpopulation, only 11% of patients (2 patients / 18) had stable disease and 11/18, or 61% were in a state of progressive disease. To our knowledge there are no known examples of stable disease in Pc MSS patients.

Le NOX-A12 est particulièrement bien toléré

Les premiers résultats montrent que le NOX-A12 est très bien toléré et n'induit que des effets secondaires de faibles grades. En effet, sur les 141 événements indésirables liés au traitement (TEAE), 47% était de grade 1, 36% de grade 2, 16% de grade 3, aucun grade 4. L'unique cas de grade 5 (0,7%) était due à une reprise de la progression tumorale de l'un des patients, qui a conduit à une détérioration de son état physique général.

NOX-A12 is well tolerated

The first results show that NOX-A12 is very well tolerated and induces only low-grade side effects. Indeed, the total number of Treatment-Related Adverse Events (TEAEs) was 141. There were 47% Grade 1, 36% Grade 2, 16% Grade 3, no Grade 4. The only case of Grade 5 (0.7%) was due to a resumption of tumor progression in one of the patients, which led to a deterioration of his general physical condition.

Le profil des TEAE de l'essai OPERA est tout à fait similaire au profil d'innocuité du pembrolizumab ou typique des maladies sous-jacentes, le cancer colorectal et le cancer du pancréas. Ces résultats sont similaires à ceux obtenus lors du développement de NOX-A12 dans les leucémies, démontrant la bonne tolérance du NOX-A12 pour les différents types de cancer.

La neutralisation de CXCL12 lié à l'activation immunitaire et au bénéfice clinique

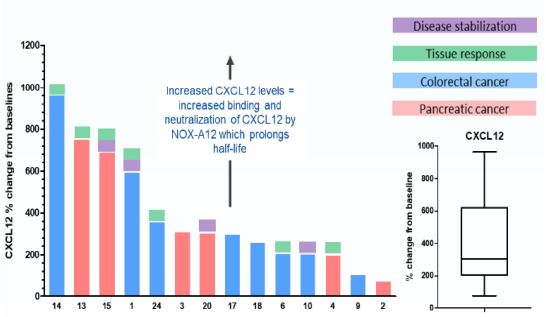
L'augmentation des taux de CXCL12 circulant est concomitante avec le traitement par NOX-A12, qui passe du microenvironnement à l'intérieur du tissu tumoral. Cette accroissement de la neutralisation (fixation du NOX-A12 sur le CXCL12) du CXCL12 est corrélé à la réponse Th1 observée dans les tissus ainsi qu'au bénéfice clinique.

The TEAE profile of the OPERA trial is quite similar to the safety profile of pembrolizumab or typical of the underlying diseases, colorectal cancer and pancreatic cancer. These results are similar to those obtained during the development of NOX-A12 in leukemias, showing the good safety profile of NOX-A12 throughout different types of cancers.

CXCL12 Neutralization Linked to Immune Activation and Clinical Benefit

The increase in circulating CXCL12 levels is concomitant with treatment with NOX-A12, which passes from the microenvironment inside the tumor tissue. This increase in CXCL12 neutralization (NOX-A12 binding to CXCL12) is correlated with Th1 response observed in tissues as well as clinical benefit.

Increased neutralization of CXCL12 by NOX-A12



La détermination du nombre de cellules T infiltrant la tumeur et de cellules T CD8 cytotoxiques pourrait compléter la compréhension du mécanisme d'action de NOX-A12 en association avec Keytruda. Toutefois, les données initiales de monothérapie (uniquement NOX-A12 publiés en juin dernier) montrent que NOX-A12 modifie le microenvironnement tumoral ainsi que le profil des cytokinique.

NOX-A12 en monothérapie modifie le microenvironnement tumoral en produisant une réponse immunitaire Th1

Les résultats de la première partie de l'essai OPERA ont été présentés lors du 4ème congrès du CRI-CIMT-EATI de l'American Association of Cancer Research en septembre dernier à New-York. Utilisé en monothérapie chez des patients atteints d'un cancer colorectal à microsatellites stables ou pancréatique métastatique, le NOX-A12 a montré :

- Qu'il pénétrait dans le microenvironnement tumoral et qu'il neutralise sa cible, le CXCL12, qui se traduisait par un accroissement du CXCL12 circulant.
- Qu'il modifiait le profil cytokinique et induisait une réponse immunitaire de type Th1 immunostimulatrice chez 50% des patients.
- Qu'il induisait l'émergence d'une sous-population cellulaire d'origine myéloïde porteuse des marqueurs de typeCD14 (caractéristiques des monocytes) et de type CD15 (caractéristique des granulocytes).
- Que son profil d'innocuité en association avec le pembrolizumab était conforme à celui du pembrolizumab en monothérapie.

Deux éléments méritent un peu plus d'attention. Tout d'abord, l'effet du NOX-A12 seul sur la tumeur et son microenvironnement.

Determination of the number of tumor infiltrating T cells and cytotoxic CD8 T cells may complement the understanding of the mechanism of action of NOX-A12 in combination with Keytruda. However, the initial monotherapy data (only NOX-A12 published last June) show that NOX-A12 modifies the tumor microenvironment and the cytokine production profile.

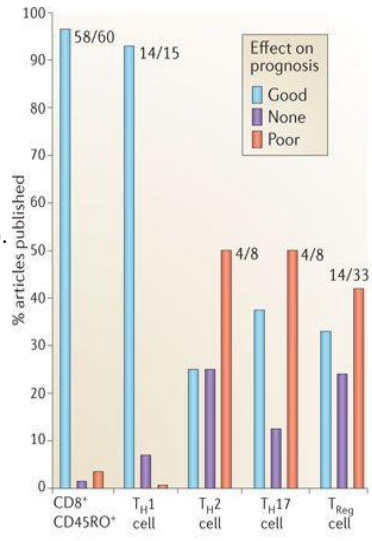
First encouraging results in monotherapy with NOX-A12 with a Th1 immune response

The results of the first part of the OPERA trial (NCT0368139) at the fourth CRI-CIMT-EATI conference of the American Association of Cancer Research last September in New York. Used in monotherapy in patients with metastatic colorectal with stable microsatellites or metastatic pancreatic cancer, the results showed that:

- NOX-A12 enters the tumor microenvironment and neutralizes its target CXCL12 since an increased circulating CXCL12 level.
- NOX-A12 modifies the cytokine profile and induces an immunostimulatory Th1 immune response in 50% of patients.
- The presence of one or more cell lines bearing markers of CD14 type (characteristics of monocytes) and of CD15 type (characteristic of granulocytes).
- The safety profile of NOX-A12 combined with pembrolizumab is consistent with that of pembrolizumab in advanced cancers patients.

Two elements deserve a bit more attention. First of all, the effect of NOX-A12 alone on the tumor and its microenvironment.

The association of immune cell infiltrates with prognosis in various types of cancer.



Fridman et al, 2012 Nature Reviews | Cancer

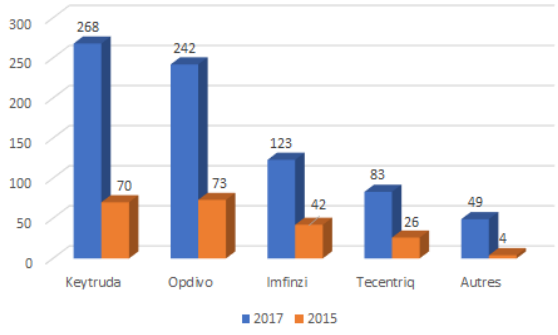
En effet, le NOX-A12 induit une modification des profils cytokiniques traduisant une orientation fonctionnelle de type Th1, une caractérisée par un accroissement des taux d'interféron gamma (IFN-γ), d'IL-2 et de TNF-béta (TNF-β) ainsi que des chimiokines (CXCL9, CXCL10).

L'IFN-γ est un activateur des réponses cellulaires : des lymphocytes T cytotoxiques, des cellules Natural Killer (NK). Ces résultats sont similaires aux précédents résultats précliniques. Ils sont aussi compatibles avec la mobilisation dans le microenvironnement tumoral de lymphocytes T CD4+ helper, qui vont contribuer à l'induction et au maintien d'une réponse immune adaptative effectrice. Par ailleurs, la production d'IL-2 pourrait aussi participer la prolifération des lymphocytes CD8 cytotoxiques ainsi qu'à leur maturation. De plus, la présence d'une réponse de type Th1 aurait aussi pour effet d'induire la production de lymphocytes T CD8+ mémoire : un ensemble de mécanismes renforçant la réaction immunitaire. En effet, une réponse polyfonctionnelle de type Th1 pourrait conduire à un meilleur pronostic (figure plus haut, Fridman et al Nature Reviews 2012). Ensuite, la présence dans le microenvironnement tumoral des chimiokines, CXCL9 et CXCL10, est un facteur supplémentaire pour le recrutement des lymphocytes T cytotoxiques (CD8). Mais aussi, d'autres cytokines comme l'Il-1a, IL-1b et l'IL-6 chez certains patients, caractéristiques des lignées myéloïdes. D'ailleurs, de plus en plus d'articles soulignent la nécessaire coopération des lignées lymphocytaires et myéloïdes au sein de la tumeur pour son éradication.

La révolution Immuno-oncologie a besoin de combinaison

Les inhibiteurs de point de contrôle immunitaires (IPCI) ont donné des résultats remarquables en termes de rémission ou de guérison totale dans plusieurs types de tumeurs, parfois même très avancées. Mais, les taux de réponse globaux aux thérapies à base d'anti-PD1/PD-L1 se situeraient généralement autour de 20%, ce qui laisse une très large proportion de la population en situation de non-réponse à ces traitements. Les raisons de ces non-réponses sont multiples, mais les principales ont souvent trait au statut mutationnel de la tumeur, ce qui conduit à distinguer les tumeurs dite « chaudes » (à fort pouvoir mutationnel) et les tumeurs dite « froides » ne mutant que très faiblement.

Number of association studies Anti-PD-1/anti-PD-L1 between 2015 & 2017



L'immuno-oncologie a transformé en profondeur la prise en charge de certains cancers (poumons, mélanome) en améliorant la survie des patients. Toutefois, la proportion de patients répondants à ces traitements immuno-oncologiques est encore faible de 15 à 30%. Plusieurs pistes sont aujourd'hui à l'étude afin d'accroître le nombre de patients traités par l'immunothérapie. L'une des premières est très certainement de mieux identifier les patients répondeurs aux anti-PD1 et d'améliorer la prédictivité des biomarqueurs utilisés (taux de PD1/PD-L1, charge mutationnelle de la tumeur). Une autre voie est l'amélioration de la réponse aux IPCI.

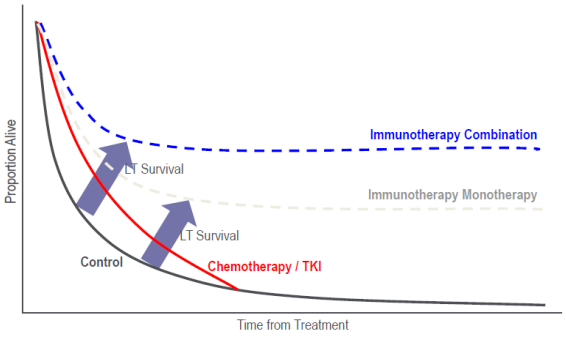
Indeed, NOX-A12 induces a modification of the cytokines' profiles translating a functional orientation of type Th1, one characterized by an increase in interferon gamma levels (IFN-γ), IL-2 and TNF-beta (TNF-β) as well as chemokines (CXCL9, CXCL10).

IFN-γ is an activator of cellular responses: cytotoxic T lymphocytes, Natural Killer (NK) cells. These results are similar to previous preclinical results. These results are apparently compatible with the mobilization in the tumor microenvironment of CD4 + helper T cells, which will contribute to the induction and maintenance of an effector adaptive immune response. In addition, the production of IL-2 could also participates in the proliferation of cytotoxic CD8 lymphocytes and their maturation. In addition, the presence of a Th1 type response would also have the effect of inducing the production of memory CD8 + T lymphocytes: a set of mechanisms reinforcing the immune reaction. Indeed, a polyfunctional response of Th1 type could lead to a better prognosis (figure above, Fridman et al., Nature Reviews, 2012).
Then, the presence in the tumor microenvironment of the chemokines, CXCL9 and CXCL10, is an additional factor for the recruitment of cytotoxic T lymphocytes (CD8). But the presence of cytokines such as IL-1a, IL-1b and IL-6, typical of myeloid cell lineage. Moreover, more and more articles underline the necessary cooperation of the lymphocyte and myeloid lineages within the tumor for its eradication.

The Immuno-Oncology Revolution needs combo

Immune Control Point Inhibitors (IPCI) have achieved remarkable results in terms of remission or total healing in several types of tumors, sometimes even very advanced. However, overall response rates to anti-PD1 / PD-L1 therapies would generally be around 20%, leaving a very large proportion of the population in non-response to these therapies. The reasons for these non-responses are many, but the main ones often relate to the mutational status of the tumor, which leads to distinguish so-called "hot" tumors (with high mutational power) and so-called "cold" mutant tumors very weakly.

Displacement of survival curves



Immuno-Oncology has profoundly modified the management of certain cancers (lungs, melanoma) by improving patient survival. However, the proportion of patients responding to these immuno-oncological treatments is still low from 15 to 30%. Several leads are currently under investigation to increase the number of patients treated with immunotherapy. One of the first once is certainly to better identify patients responding to anti-PD1 treatments and improve the predictivity of the biomarkers used (PD1 / PD-L1 rate, mutational load of the tumor). Another way is to improve the response to IPCIs.

Très souvent, la non-réponse observée est liée soit à un déficit d'induction du système immunitaire, soit à l'influence immunosuppressive du microenvironnement tumoral.
Le recours aux combinaisons entre des ICPI et différentes alternatives thérapeutiques devrait à terme permettre d'apporter une solution à ces problèmes. C'est pourquoi il est nécessaire de trouver des combinaisons associant les IPCI et d'autres molécules afin d'accroître le taux de réponse et réduire les taux de rechutes lors d'un traitement avec un anti-PD-1/PD-L1. Le nombre d'essais associant un IPCI et une autre molécule s'est accru fortement durant les dernières années. Toutefois, la toxicité de certaines de ces combinaisons peut poser un problème comme ont pu le montrer les études Checkmate-067 ou 069 dans le mélanome, où l'association d'un anti-PD-1 (Opdivo®) avec un anti-CTLA-4 (Yervoy®) améliorait l'ensemble de critères d'évaluation (survie globale, réponse complète ou partielle), mais au prix d'une toxicité importante.

Par ailleurs, l'industrie pharmaceutique est notablement prête à débourser des sommes importantes pour faire l'acquisition des molécules les plus prometteuses. Ainsi, en mai 2018, Roche rachetait l'IL-10 pégylée d'Armo Biosciences et le reste de ses actifs pour 1,6 milliards de dollars. J&J, par l'intermédiaire de Janssen, rachetait également en mai 2018 BeneVir Biopharm pour 1,040 milliards de dollars.

Kineta Immuno-Oncology, une filiale de Kineta Inc. a signé le 17 décembre 2018, un accord de collaboration de recherche et de licence avec Pfizer pour développer les immunothérapies à base de RIG-I (transformation de tumeurs « froides » en tumeurs « chaudes »). Kineta recevra 15 millions de dollars upfront et jusqu'à 505 millions de dollars en milestones et royalties.

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Very often, the nonresponse observed is related either to a lack of induction of the immune system or to the immunosuppressive influence of the tumoral microenvironment. The use of combinations between ICPIs and different therapeutic alternatives should eventually provide a solution to these problems.
Therefore, it is necessary to find combinations of IPCI and other molecules to increase the response rate and reduce relapse rates when treated with anti-PD-1 / PD-L1. The number of trials combining an IPCI with another molecule has increased significantly in recent years. However, the toxicity of some of these combinations may be a problem, as shown by the Checkmate-067 or 069 studies in melanoma, where the combination of an anti-PD-1 (Opdivo®) with an anti-CTLA -4 (Yervoy®) improved the set of evaluation criteria (overall survival, complete or partial response), but at the cost of significant toxicity.

In addition, the pharmaceutical industry is significantly prepared to invest large sums to acquire the most promising molecules. In May 2018, Roche bought the pegylated IL-10 from Armo Biosciences and the rest of these assets for $ 1.6 billion. J & J through Janssen also bought BeneVir Biopharm in May 2018 for $ 1.040 billion.

Kineta Immuno-Oncology, a subsidiary of Kineta Inc., signed on December 17, 2018, a research and license collaboration agreement with Pfizer to develop RIG-I-based immunotherapies (transformation of "cold" tumors into "hot" tumors). "). Kineta will receive $ 15 million upfront and up to $ 505 million in milestones and royalties.

Méthode de Valorisation

rNPV

Nous utilisons La méthode de la valeur actualisée nette ajustée en fonction du risque (rNPV), car elle nous semble être la plus appropriée pour une telle entreprise. Le facteur de risque a été calculé en fonction de la probabilité de réussite à chaque stade de développement clinique. Pour le NOX-A12, nous avons obtenu une valeur pour la société de 47,2M€, soit 5,00€/action. Cette évaluation met l'accent sur le fort potentiel du marché pour le NOX-A12 qui cible trois indications majeures, le cancer colorectal, le cancer du pancréas et le cancer du cerveau avec des besoins médicaux importants. Il prend également en compte le risque associé à un médicament candidat. À notre avis, l'un des éléments essentiels pour la société sera sa capacité à nouer un partenariat sous licence afin de poursuivre le développement du NOX-A12 au-delà de la phase II.

Après actualisation du free cashflow ajusté au risque à un WACC de 16,21 %, nous obtenons une valeur de 5.00 € par action.

Valorisation

En effet, consécutivement à la publication de résultats, qui confirment le mécanisme d'action et montrent le bénéfice ainsi que l'effet clinique, nous avons ajusté notre objectif de cours. Il passe de 4,80€ à 5,00€ due notamment à l'augmentation de nos probabilités de succès pour NOX-A12 dans le cancer colorectal. Nous avons aussi augmenté les probabilités de succès dans le cancer pancréatique ainsi que dans le cancer du cerveau (glioblastome), notamment sur la base des données de sécurité, qui montent que le NOX-A12 est particulièrement bien toléré. Toutefois, l'objectif de Noxxon est de nouer rapidement un partenariat pour accompagner le développement de NOX-A12 et de NOX-E36 qui représente aussi une potentialité importante.

News Flows

- T1 2019 : assemblée générale extraordinaire des actionnaires
- T2 2019 : initiation d'une phase I/IIa dans le glioblastome nouvellement diagnostiqué.

Valuation method

rNPV

The Risk-Adjusted Net Present Value (rNPV) method is used because we believe it is the most appropriate approach for such a company. The risk factor was calculated considering the probability for NOX-A12 to succeed in each clinical development stage. Considering NOX-A12, we obtained a value for the company of €47.2 M or 5.00€/share. This valuation highlights the market potential forNOX-A12 which targets three major indications with important unserved medical needs: colorectal cancer, pancreas cancer and brain cancer. It also considers the risk associated with a drug candidate which must demonstrate its efficacy in human subjects. The key trend, in our view, for the company will be its ability to sign an out-license partnership to pursue NOX-A12 development beyond phase II.

After discounting the risk adjusted free cashflow at a WACC of 16.21 %, we get to a rNPV valuation of € 5.00 per share.

Valuation

Indeed, following the publication of results, which confirm the mechanism of action and show the benefit as well as the clinical effect, we have adjusted our target price. It goes from 4.80 € to 5.00 € due to the increase of our probabilities of success for NOX-A12 in colorectal cancer. We have also increased the probabilities of success in pancreatic cancer as well as in brain cancer, particularly based on safety data, which states that NOX-A12 is particularly well tolerated. However, the goal of Noxxon is to quickly establish a partnership to accompany the development of NOX-A12 and NOX-E36 that also represents a significant potential.

News Flows

- Q1 2019: extraordinary general meeting of shareholders
- Q2 2019: Phase I/IIa initiation in newly diagnosed glioblastoma multiforme.

Valuation

rNPV

Discount rate calculation

The discount rate results from the weighted average rate between the capital cost and the cost of financial debt. The cost of capital is calculated based on the CAPM model to which is added a Small Cap risk premium according to the following formula:

Cost of capital = Rf +beta * (Rm-Rf) + Small Caps risk premium

Rf: risk free rate; (Rm-Rf): stock market risk premium

Depending on the company size, we add a Small Caps premium to the cost of capital. The Small Caps premium is calculated according to six criteria which are objectively evaluated. For each criterion, there are five increments from - - to + +. Each move upwards adds 20 basis points to the cost of capital.

Please find below the criteria table:

Criterium	Notation scale				
	++	+	=	-	--
Company governance [1]	4	3	2	1	0
Liquidity[2]	[66 %; 100 %]	[33 % ; 66 %[	[15 % ; 33 %[	[5 % ; 15 %[	[0 % ; 5 %[
Revenues size (€m)	[150; +∞ [	[100 ; 150[	[50 ; 100[	[25 ; 50[	[0 ; 25[
Operating profitability	[25 %; 100 %]	[15 % ; 25 %[	[8 % ; 15 %[	[3 % ; 8 %[	[0 % ; 3 %[
Gearing	]-∞ % ; -15 %]	]-15 % ; 15 %]	]15 % ; 50 %]	]50 % ; 80 %]	]80 % ; +∞[
Clients risks [3]	[0 % ; 10 %]	]10 % ; 20 %]	]20 % ; 30 %]	]30 % ; 40 %]	]40 % ; 100 %]

In the case of Noxxon Pharma, we obtain the following matrix:

	++	+	=	-	--	Prime Small Caps
Company Governance						1,00%
Liquidity						1,00%
Revenues size						1,00%
Operating profitability						1,00%
Gearing						1,00%
Client risk						1,00%
TOTAL						**6,00%**

Based on the prevalent risk free of 0.77%, a market risk premium of 7.03% (source: Fairness Finance, Market Risk Premia), a beta of 1.34, a Small Caps risk premium of 6.0%, we get to a discount rate of 16.21%.

Risk Free Rate	Risk premium	Beta	Small Caps risk premium	Cost of capital	Cost of debt	Financial leverage	Tax rate	WACC
0.77%	7.03%	1.34	6.0%	16.2%	N/A*	0.0%	25.0%	16.21%

* The cost of debt criterion is not applicable to Noxxon Pharma since they reported negative net debt.

Source: Agence France Trésor, Fairness Finance, Market Risk Premia, Damodaran, Genesta estimates

The Risk-Adjusted Net Present Value (rNPV) method, was used since we believe it is the most appropriate method for such a company. The risk factor was calculated considering the probability for NOX-A12 to succeed in each clinical development stage (see following table "Typical transition rate for drug development" updated from Keagan, Wiley Finance, 2008.

[1] Company's governance is evaluated through the 4 following criterions: separation of functions between president and top management or functioning as a supervisory board and a board of directors; presence of independent members in the board of trustees or in the supervisory board; presence of censors or control board; existence of specialized committees.

[2] Percentage of capital exchanged in the last 12 months

[3] Sales parts represented since by the 5 most important clients.

Typical transition rates for drug development

Phase	Transition Rate	Probability to reach the market
Phase IIa	70-80%	20-35%
Phase IIb	70-80%	30-45%
Overall Phase II	50-65%	20-45%
Phase III	50-65%	45-55%
Registration	90%	90%

Source: Karl Keegan, Wiley Finance (2008)

Enterprise value calculation

For valuation purpose, we assume that NOX-A12 will target the colorectal cancer (CRC) with microsatellite stable (MSS) activity, which represent around 80 to 90% of the CRC cases. We believe that Noxxon Pharma will finance the development of Phase IIb NOX-A12 until it reaches an agreement with a partner for the US and Europe. When NOX-A12 is licensed, there should be no additional costs as the partner is responsible for manufacturing and marketing. Based on several recent partnership agreements, we estimate that Noxxon could sign a partnership with a pharmaceutical company with an average value of 520 million euros, with an upfront representing 16% of this amount, 78 million euros as royalties. Furthermore, we believe that the agreement that could be signed by Noxxon Pharma could be on colorectal cancer. While the costs inherent in Phase III are difficult to estimate given the progress of NOX-A12, we can reasonably assume that Phase III clinical trials in colorectal cancer is estimated at between 10 and 15 million euros per indication. We estimate the probability of chance for NOX-A12 at 33% for colorectal cancer.
Noxxon Pharma intends to license the drug to a partner at the end of the phase 2b clinical trials, revenue forecast was calculated based on milestones and royalty payments. Our hypotheses consider a 12% royalty rate on total sales. The total milestones were estimated at €230m. Using our 16.21% discount rate, we obtain the following risk-adjusted cashflow statement for the period 2018E – 2027E and the current valuation for the CRC programme has a net value of € 23.30m and the pancreatic cancer has a net value of €8.15m.

CRC	2017	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E
Total revenues	**0,0**	**0,0**	**0,0**	**26,0**	**0,0**	**26,0**	**0,0**	**51,0**	**92,7**	**96,6**	**180,2**
Clinical costs	0,0	0,0	5,0	5,0	3,5	4,0	2,5	1,5	0,0	0,0	0,0
Total Costs	**0,0**	**0,0**	**5,0**	**5,0**	**3,5**	**4,0**	**2,5**	**1,5**	**0,0**	**0,0**	**0,0**
EBITDA	**0,0**	**0,0**	**(5,0)**	**21,0**	**(3,5)**	**22,0**	**(2,5)**	**49,5**	**92,7**	**96,6**	**180,2**
Taxes	0,0	0,0	0,0	5,3	0,0	5,5	0,0	12,4	23,2	24,1	45,1
Cash Flows	0,0	0,0	(5,0)	15,8	(3,5)	16,5	(2,5)	37,1	69,6	72,4	135,2
Likelihood 2018	0,0%	100,0%	100,0%	100,0%	20,0%	20,0%	20,0%	20,0%	20,0%	20,0%	20,0%
Risk Adjusted CF	**0,0**	**0,0**	**(5,0)**	**15,8**	**(0,7)**	**3,3**	**(0,5)**	**7,4**	**13,9**	**14,5**	**27,0**

As previously mentioned, Noxxon should conduct a Phase I / II trial with NOX-A12 adjuvant therapy in glioblastoma for newly diagnosed patients. It is clear to us that Noxxon will have to identify its patients on the basis of methylation of the MGMT gene promoter, since non-methylation is correlated with poor prognosis and resistance to alkylating agents and more particularly to TMZ. This phase I / II confirmatory test of the efficacy of the molecule and its mechanism of action, would allow to position NOX-A12 in adjuvant post radiotherapy without TMZ, either a 1L treatment or 2L. So Noxxon Pharma should establish a licensing partnership to market NOX-A12 in glioblastoma. The partner must be present in the United States and in Europe. However, the value of the agreement and the number of milestones as well as the percentage of royalties will depend heavily on the benefit demonstrated in the Phase I / II trials and the scenario chosen for development. Based on several recent partnership agreements, we estimate that Noxxon could sign a partnership with a pharmaceutical company for 140 million euros with an upfront representing 28% of this amount, 40 million euros and royalties at the rate of 20%. This licensing agreement could take place as early as mid-2021 after the results of progression-free survival and first results on the overall survival of the phase I / II trial. Using our 16.21% discount rate, we obtain the following risk-adjusted cashflow statement for the period 2018E – 2027E and the current valuation for the CRC programme has a net value of € 23.30m and the pancreatic cancer has a net value of €8.15m.

GBM	2017	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E
Total revenues	**0,0**	**0,0**	**0,0**	**0,0**	**40,0**	**0,0**	**43,4**	**16,0**	**67,7**	**48,7**	**119,1**
Clinical costs	0,0	0,0	2,9	2,9	3,8	0,0	0,0	0,0	0,0	0,0	0,0
Total Costs	**0,0**	**0,0**	**2,9**	**2,9**	**3,8**	**1,5**	**0,0**	**0,0**	**0,0**	**0,0**	**0,0**
EBITDA	**0,0**	**0,0**	**(2,9)**	**(2,9)**	**36,2**	**(1,5)**	**43,4**	**16,0**	**67,7**	**48,7**	**119,1**
Taxes	0,0	0,0	0,0	0,0	9,0	0,0	10,9	4,0	16,9	12,2	29,8
Cash Flows	0,0	0,0	(2,9)	(2,9)	27,1	(1,5)	32,6	12,0	50,8	36,6	89,3
Likelihood 2018	100,0%	100,0%	100,0%	100,0%	9,0%	9,0%	9,0%	9,0%	9,0%	9,0%	9,0%
Risk Adjusted CF	**0,0**	**0,0**	**(2,9)**	**(2,9)**	**2,4**	**(0,1)**	**2,9**	**1,1**	**4,6**	**3,3**	**8,0**

Considering the mechanism of action of NOX-E36, which is targeting chemokines (CCL2, CCL8 and CCL13 involved in TAM-related microenvironment modifications), shows a significant improvement over CCR2 inhibitors or other molecules inhibiting only CCL2 and we estimate that NOX-E36 once approved, could reasonably position itself in 1L. NOX-E36 could be prescribed in combination with the current treatment standard (gemcitabine and nab-paclitaxel) or in combination with an ICI to approximately 30% of patients with metastatic pancreatic ductal adenocarcinoma. We believe that Noxxon Pharma will finance the development of Phase IIb NOX-E36 before entering into an agreement with a partner for the US and Europe. When NOX-E36 is licensed, there should be no additional costs as the partner is responsible for manufacturing and marketing. Based on several recent partnership agreements, we estimate that Noxxon could sign a partnership with a pharmaceutical company with an average value of 520 million euros, with an upfront representing 16% of this amount, 79 million euros. Noxxon is also expected to receive royalties on sales at the usual rate of 15%. While the costs inherent in Phase III are difficult to estimate given the current status of NOX-A12, we can reasonably assume that Phase III clinical trials in pancreatic cancer would be around 10 to 15 million euros. We estimate the probability of chance for NOX-E36 at 18% for pancreatic ductal adenocarcinoma.

PC	2017	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E
Total revenues	**0,00**	**0,00**	**0,00**	**0,00**	**26,00**	**0,00**	**26,00**	**38,00**	**114,62**	**80,31**	**112,80**
Clinical cost	1,50	1,50	6,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Total Cost	**2,75**	**2,75**	**7,25**	**1,25**	**1,25**	**1,25**	**1,25**	**1,25**	**1,25**	**1,25**	**1,25**
EBITDA	**(2,8)**	**(2,8)**	**(7,3)**	**(1,3)**	**24,8**	**(1,3)**	**24,8**	**36,8**	**113,4**	**79,1**	**111,6**
Taxes	0,00	0,00	0,00	0,00	6,19	0,00	6,19	9,19	28,34	19,76	27,89
Cash Flows	(2,8)	(2,8)	(7,3)	(1,3)	18,6	(1,3)	18,6	27,6	85,0	59,3	83,7
Likelihood 2018	0,0%	100,0%	100,0%	100,0%	15,0%	15,0%	15,0%	15,0%	15,0%	15,0%	15,0%
Risk Adjusted CF	**0,0**	**(2,8)**	**(7,3)**	**(1,3)**	**2,8**	**(0,2)**	**2,8**	**4,1**	**12,8**	**8,9**	**12,5**

For the period following the forecasts, we apply a terminal growth rate in two times, and obtain the following table (in €m):

	Value	%
1-10 year period		
Colorectal Cancer	23,9	50,5%
Pancreatic cancer	20,5	43,4%
Glioblastoma	2,9	6,1%
Total	**47,2**	100,0%

Source: Genesta estimates

Thus, Noxxon Pharma enterprise value stands at € 47.2million.

Price per share calculation

The table below details the final calculation of equity value per share.

rCF	47,2
+ Financial assets	0,0
+ Assets consolidted on an equity ba	0,0
- Provisions	0,0
- Net Financial debt	0,0
- Minorities	0,0
+ Discounted tax loss carry forward	(0,6)
= Equity value (in EUR million)	46,6
Number of shares (in million)	9,319
Share valuation (in EUR)	**5,00**

Source: Noxxon Pharma, Genesta estimates

Consequently, the use of the risk-adjusted Net Present Value method values Noxxon Pharma at €5.00 per share, representing an upside of +317 % compared to the last closing price of €1.07 on December 19th, 2018.

Summary of financial statements

Simplified Income Statement

31/12 (M€)	2015	2016	2017	2018e	2019e	2020e
Revenues	**0,0**	**0,1**	**0,0**	**0,0**	**0,0**	**26,0**
% change	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
Ebitda	**-15,0**	**-8,9**	**-4,8**	**-4,7**	**-4,7**	**21,3**
% change	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
% of revenues	*ns*	*ns*	*ns*	*ns*	*ns*	*0,8*
Ebit	**-15,0**	**-8,9**	**-4,8**	**-4,7**	**-4,7**	**21,3**
% change	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
% of revenues	*ns*	*ns*	*ns*	*ns*	*ns*	*81,8%*
Financial income and charges	**-1,3**	**-2,1**	**-0,7**	**0,0**	**0,0**	**0,0**
Earnings before tax	**-16,3**	**-11,0**	**-5,4**	**-4,7**	**-4,7**	**21,3**
Income tax	**0,0**	**0,0**	**0,0**	**0,0**	**0,0**	**0,0**
Tax rate %()	*4,4%*	*8,7%*	*21,2%*	*20,0%*	*20,0%*	*20,0%*
Net earnings	**-16,3**	**-11,0**	**-5,4**	**-4,7**	**-4,7**	**21,3**
% change	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
% of revenues	*ns*	*ns*	*ns*	*ns*	*ns*	*82%*

Balance Sheet – Main items

31/12 (M€)	2015	2016	2017	2018e	2019e	2020e
Goodwill	0,0	0,0	0,0	0,0	0,0	0,0
Intangible assets	0,0	0,0	0,0	0,1	0,1	0,1
Tangible assets	0,6	0,1	0,0	0,0	0,0	0,0
Financial fixed assets	0,0	0,0	0,0	0,0	0,0	0,0
Working Capital Requirements	**-4,2**	**-2,4**	**-2,2**	**0,0**	**0,0**	**8,0**
% of revenues	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
Gross financial debts	8,9	2,9	2,6	2,6	3,0	3,2
Cash and short term investments	4,1	2,2	2,6	-2,9	-5,3	9,1
Net financial position (net financial debt if a minus)	**4,8**	**0,7**	**0,0**	**5,5**	**8,3**	**-5,9**

Cash Flows Statement – Main items

31/12 (M€)	2015	2016	2017	2018e	2019e	2020e
Cashflow	**-16,1**	**-11,0**	**-5,4**	**-4,6**	**-4,6**	**21,4**
Capital expenditures	0,0	0,0	4,0	4,0	0,0	0,0
% of revenues	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
Impact of working capital requirements variation	23,3	1,8	0,2	2,2	0,0	8,0
Free cashflow	-39,4	-12,8	-9,6	-10,9	-4,6	13,3

Ratios

31/12 (M€)	2015	2016	2017	2018e	2019e	2020e
EPS (€)	**-2,4**	**-1,3**	**-0,5**	**-0,4**	**-0,4**	**1,9**
% change	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
Market capitalisation (€m)	**44,6**	**31,5**	**10,8**	**10,8**	**10,8**	**10,8**
Enterprise value	53,5	32,2	10,8	16,4	19,1	4,9
P/E	**-2,7**	**-2,9**	**-2,0**	**-2,3**	**-2,3**	**0,5**
Market to Book	90,5	15,4	4,7	4,7	4,7	4,7
EV/Sales	ns	ns	ns	ns	ns	0,2
EV/Ebitda	ns	ns	ns	ns	ns	0,2
EV/Ebit	ns	ns	ns	ns	ns	0,2
Ebitda/Sales	ns	ns	ns	ns	ns	0,8
Ebit/Sales	ns	ns	ns	ns	ns	0,8
Net earnings/Sales	ns	ns	ns	ns	ns	0,8
Gearing	9,7	0,4	0,0	2,4	3,6	-2,6

Important disclosures

Genesta Equity Research ratings and target prices definition

Genesta Equity Research stock market recommendations reflect the absolute change expected in the share price from a six to twelve month perspective (in local currencies).

1. Strong buy	The absolute share price performance is expected to be at least +25 %
2. Buy	The absolute share price performance is expected to be comprised between +10 % and +25 %
3. Neutral	The absolute share price performance is expected to be comprised between +10 % et -10 %
4. Sell	The absolute share price underperformance is expected to be comprised between -10 % et -25 %
5. Strong Sell	The absolute share price underperformance is expected to be at least -25 %

Details of valuation methods used by Genesta Equity Research in target price calculations are available at www.genesta-finance.com.

Detection of potential conflicts of interest

The analyst. Genesta or any of its employees is a shareholder of the issuer	The issuer subject of this report is a shareholder of Genesta	Other financial interest between Genesta and the issuer	Genesta is a market maker or liquidity provider in financial instruments issued by this issuer	Genesta has received compensation to produce this research report	Genesta has received compensation for another service than the production of this research report	This research report was sent to the issuer before its publication
No	No	No	No	Yes	No	No

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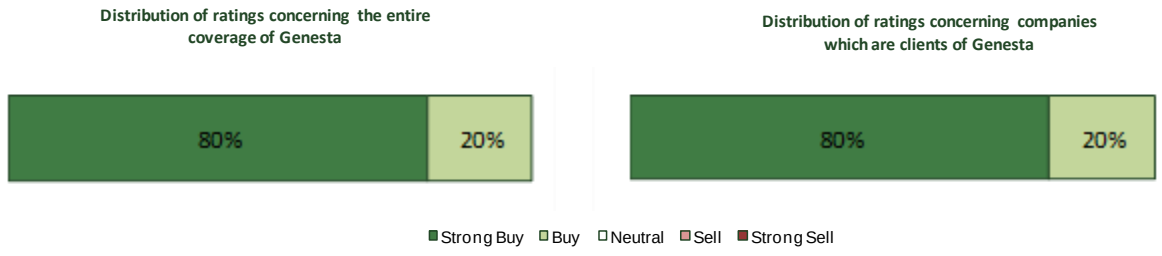
Rating and target price evolution throughout the last 12 months

Date of 1st publication	Rating	Target Price
20th December 2018	Equity Flash **Strong Buy**	**€ 5.00**
11th December 2018	Equity Flash **Strong Buy**	**€ 4,80**
3th March 2018	Initiation of coverage	**€ 17.9**

Ratings distribution



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