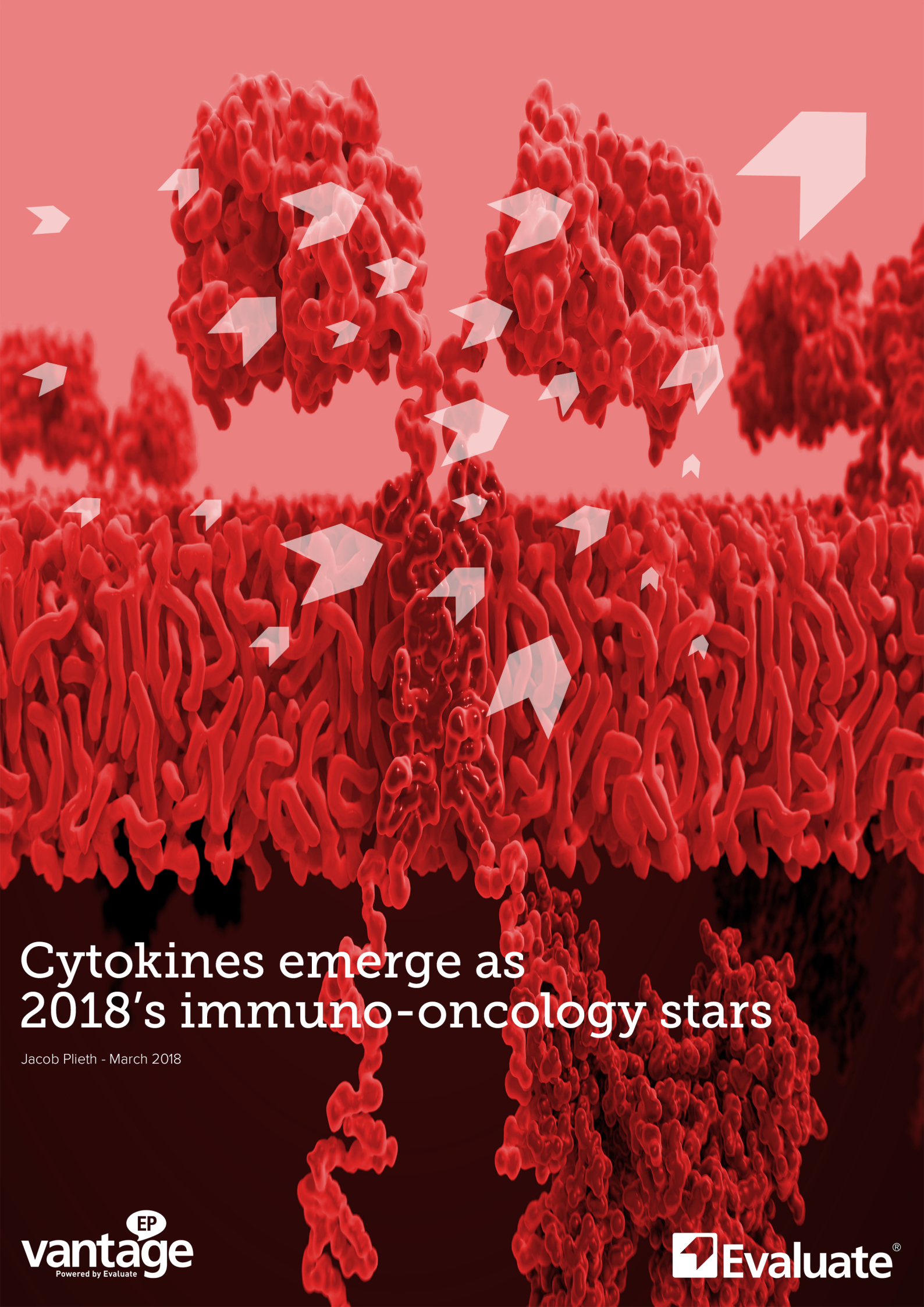


Cytokines emerge as 2018's immuno-oncology stars

Jacob Plieth - March 2018

EP vantage
Powered by Evaluate

Evaluate®

No sooner had cytokine therapies been labelled an area to watch in 2018 than Bristol-Myers Squibb paid a massive $1.85bn for rights to Nektar's NKTR-214, a project working specifically to stimulate signalling via the cytokine interleukin-2 and interest in IL-2 is not about to abate.

This might seem ironic, since IL-2 is already an established though now infrequently used melanoma therapy, sold since the 1990s; but it comes with serious side effects, which have driven the industry's efforts to develop a new wave of IL-2-based therapeutics. However, as recent volatility in Alkermes's share price shows, there are fears that not all these therapies hold equal promise.

Much of Alkermes's fall in late February had to do with a downgrade from Jefferies, which reckons that the company's ALKS 4230 might have weaker efficacy than NKTR-214. "A closer look at IL-2 science suggests not all IL-2s are the same," the analysts said.

Complex interactions

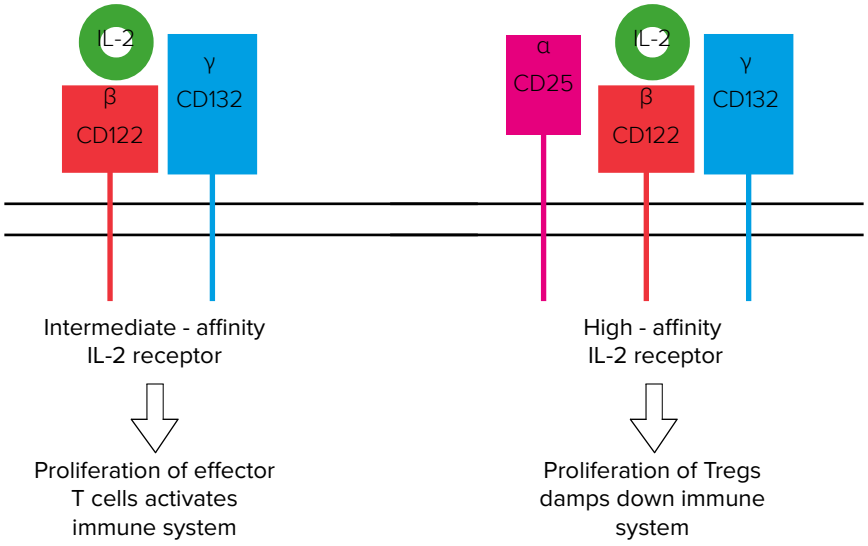
At play is a highly complex series of interactions that are only just starting to be understood. Cytokines are potent signalling proteins that, broadly speaking, stimulate cells in the immune system.

But there are problems. General IL-2 stimulation can cause severe vascular toxicity. Nevertheless, the 1998 launch of Novartis's Proleukin, a recombinant IL-2, following years of work by the NCI's Dr Steven Rosenberg, arguably represented the industry's first cancer immunotherapy, and Evercore ISI's Umer Raffat calls IL-2 a "good old immune therapy with safety baggage".

The promise of IL-2-based therapeutics lies partly in combination with checkpoint blockade, due to the potential of highly specific stimulation to turn cold tumours, those that do not attract T-cell infiltration, immunogenic – the approach that scored Nektar its $1.85bn up-front payment (Nektar delivers the sweetest deal, February 14, 2018).

Nektar's NKTR-214 is an agonist of the IL-2 receptor's β chain. This mechanism highlights the complexity of IL-2's interaction with its receptor, and the fact that the receptor can have either a heterodimeric or heterotrimeric form, depending on its composition of the chains α (CD25), β (CD122) and/or γ (CD132).

IL-2 receptor structures



CD122-biased activation causes proliferation of effector T cells rather than immune system-suppressing T regulatory cells, whereas CD25 bias triggers the opposite effect. Another possible benefit of avoiding CD25-mediated stimulation is that this has been suggested as the reason behind IL-2's vascular leak toxicity.

In a similar vein Roche is pursuing development of two assets, RG7461 and cergutuzumab amunaleukin, which are both fusion proteins that include an IL-2 variant meant to reduce binding to CD25 to avoid stimulating Tregs. And Medicena's MDNA109 is designed to bind 200 times more effectively to CD122 than to CD25.

Meanwhile, Alkermes's ALKS 4230 is a fusion protein comprising IL-2 and, paradoxically, CD25. This is also an attempt to reduce binding of IL-2 with CD25, via steric hindrance.

However, the jury is out as to which is the best approach. Jefferies analysts say that preclinically ALKS 4230 seems to generate a lower effector T cell/Treg ratio than NKTR-214. And safety is still unknown, so hard evidence will not come until clinical studies read out.

Selected oncology projects based on IL-2 signalling

Source: Clinicaltrials.gov and Evaluate

Project	Company	Status	Mechanism	Detail
Pulmoleukin	Immunservice	Phase III	Biomimetic inhaled IL-2	Inhaled therapy for lung metastases in renal cell carcinoma
NKTR-214	Nektar Therapeutics	Phase II	CD122 (IL-2Rβ)-biased pegylated IL-2	Keytruda and Opdivo combo trials under way
DI-Leu16-IL2	Alopexx/Provenance Biopharmaceuticals	Phase II	CD20 MAb/IL-2 fusion protein	Possible preference for CD20-expressing tumour cells
RG7461	Roche	Phase II	FAP/IL-2v fusion protein	Diminished CD25 (IL-2Rα) binding; two Tecentriq combo trials under way
Teleukin	Philogen	Phase II	F16 Ab/IL-2 fusion protein	F16 Ab is a targeting moiety
ALT-803	Altor Bioscience	Phase II	Mutant IL-15/IL-15Rα fusion protein	Stable heterodimer aiming to increase half life of IL-15
ALKS 4230	Alkermes	Phase I	IL-2/CD25 (IL-2Rα) fusion protein	Diminished CD25 (IL-2Rα) binding by virtue of steric hindrance
Cergutuzumab amunaleukin (RG7813)	Roche	Phase I	CEA MAb/IL-2v fusion protein	Diminished CD25 (IL-2Rα) binding; Tecentriq combo trial under way
Camidanlumab tesirine	ADC Therapeutics/ Genmab	Phase I	Anti-CD25 antibody-drug conjugate	Targets CD25-expressing laukaemia/lymphoma cells
NHS-IL2-LT/EMD 521873	Merck KGaA	Phase I	IL-2/Ab fusion protein	Ab portion meant to direct agent to regions of tumour necrosis and apoptosis
NIZ985	Novartis	Phase I	IL15/soluble IL-15Rα dimer	Through 2015 acquisition of Admune; PDR001 combo trial under way
MDNA109	Medicenna Therapeutics	Preclinical	Enhanced version of IL-2	PD-1 combo mouse data; clinical trial expected late 2018
Angeloxin	Angelica Therapeutics	Preclinical	Mutated diphtheria toxin/IL-2 fusion protein	Improved version of Ontak
PB101	Pivotal Biosciences	Preclinical	Low-toxicity IL-2 analogue	Aims to circumvent Proleukin's vascular leak syndrome toxicity
Anti-IL-2 Program	Xoma	Preclinical	IL-2/MAb complexes	MAb directs IL-2 to enhance effect; potential in PD-1 combo
NKTR-255	Nektar Therapeutics	Preclinical	IL-15Rα-specific agonist	Aims to engage IL-15Rα (CD215)/ IL-2Rγ (CD132) complex
CYP 0150	Cytunepharma	Preclinical	IL-15 linked to Sushi+ domain of IL-15Rα	Aims to circumvent IL-15Rα (CD215) cleavage from presenting cells
AM0015	Armo Biosciences	Preclinical	rhIL-15	Future development of AM0015 in combination with AM0010

Alkermes's phase I trial could yield some data around the mid-year, and Jefferies says vascular safety events were seen in one patient. Evercore's Mr Raffat additionally cites slow recruitment into Alkermes's study, something he puts down to five continuous days' IV infusion, which requires inpatient treatment.

The list above also includes projects targeting IL-15 because this cytokine is structurally similar to IL-2. In fact, its receptor's β and γ chains are identical to IL-2's. The leading project here appears to be Novartis's NIZ985, which works on the principle that combining IL-15 with its α chain can cause superagonist activity and spur proliferation of effector memory T cells.

This suggests a stark difference versus IL-2, with the IL-15 receptor's α chain stimulating rather than damping down effector T cells. Nektar's NKTR-255 and Cytunepharma's CYP 0150, both preclinical projects, also aim to make use of this finding.

Other approaches

Of course, there are other cytokine approaches that investors might watch out for too; in hot pursuit of IL-2 comes IL-12, a well-known target that has been dogged by similar complexities, which scientists are now trying to solve. And IL-10, where the recently floated Armo Biosciences claims the lead, offers more evidence that things in the cytokine world are anything but straightforward.

The strange thing about trying to use IL-10 in oncology, where the aim is to trigger an immune response, is that until recently this was thought of as a major immunosuppressive cytokine. Indeed, IL-10 and IL-12 – a typical pro-inflammatory cytokine – have been described as having antagonistically opposing functions.

However, Armo calls IL-10 a growth factor that is essential for the activation and expansion of cytotoxic T cells. Its lead asset, AM0010, is a pegylated form of IL-10 in a phase III study in pancreatic cancer; it showed a 16% remission rate in a 21-patient phase Ib trial.

Readout of AM0010's pivotal pancreatic cancer trial is not expected until 2019/20, but the study is due to undergo an interim analysis in the current quarter. This is believed by analysts to be a safety assessment only, but nevertheless it represents an important event in the cytokine space.

Paradox

The IL-10 paradox is perfectly illustrated by the fact that at one point IL-10 supplementation had been thought to have promise against Crohn's – an autoimmune disease – and that Merck & Co's anticancer project MK-1966 aims downregulate IL-10.

Much of AM0010's promise lies in combinations with either Opdivo or Keytruda. This is a common theme among cytokine-based approaches, and Nektar's 22% climb last week followed reports of two additional remissions in a trial of NKTR-214, which targets the IL-2 pathway, in combination with Opdivo.

Likewise, Oncosec hopes to broaden the scope of checkpoint blockade, attempting to make cold tumours immunogenic by priming them with IL-12. The T-cell activatory cytokine IL-12 has been described as an ideal therapeutic candidate, but – rather as is the case with IL-2 – data have so far been mixed.

Work has focused on reducing the toxicity inherent in broad immune system stimulation, for instance investigating the targeted delivery of IL-12 to make it a safer and more effective cancer therapeutic.

Oncosec's approach is to deliver IL-12 in a pulsed manner using electroporation, and early data from a Keytruda combo in melanoma were promising (SITC – Oncosec heats up tumours, and so might competition, November 15, 2017). But the group still has a micro-cap valuation, and subsequent efforts have focused on expanding into triple-negative breast cancer and raising cash.

In even worse shape is Celsion, a company valued at just $40m. Its GEN-1 delivers IL-12 via a plasmid vector formed into nanoparticles with a lipopolymeric delivery system. The group says avoiding the frequent, large bolus injections necessary when administering IL-12 as a recombinant protein could circumvent the serious toxicities and broaden this cytokine's use.

Selected oncology projects based on IL-10 & IL-12 signalling

Source: Clinicaltrials.gov and Evaluate

Project	Company	Status	Mechanism	Detail
AM0010 (pegilodecakin)	Armo Biosciences	Phase III	Pegylated rhIL-10	Armo claims that this stimulates expansion of CD8+ T cells
Ad-RTS-hIL-12	Ziopharm/Intrexon	Phase II	Intratumoural IL-12 gene therapy	Adenoviral vector controlled with Rheoswitch system by veledimex
GEN-1	Celsion	Phase II	IL-12 gene therapy	IL-12 DNA plasmid vector formed into nanoparticles with a lipopolymeric delivery system
HemaMax	Neumedicines	Phase II	rhIL-12	Studies in acute radiation syndrome as well as CTCL
LipoVIL12	Regulon	Phase II	IL-12 gene therapy	Uses liposome encapsulation; no longer listed in pipeline
Tavokinogene telsaplasmid	Oncosec Medical	Phase II	IL-12 gene therapy	Delivered by electroporation via Immunopulse device; Keytruda combo
EMD 521873/M9241	Merck KGaA	Phase I	IL-12/Ab fusion protein	Ab portion meant to direct agent to regions of tumour necrosis and apoptosis
AVR-ONC-01	Avrobio	Phase I	IL-12 gene therapy	Ex vivo, for AML; no longer listed in pipeline
MK-1966	Merck & Co	Phase I	IL-10 downregulator	Aims to counteract suppressive effects of IL-10, inhibiting Treg production
mRNA-2905	Moderna/Astrazeneca	Preclinical	mRNA encoding IL-12	Potential for combo with checkpoint inhibitor
AM0012	Armo Biosciences	Preclinical	rhIL-12	Potential for combo with AM0010

GEN-1 is a gene therapy, an approach several groups had used to deliver IL-12. But at least two of these, Regulon's LipoVIL12 and Avrobio's AVR-ONC-01, appear to have been shelved, and the latter company is now focused on rare diseases.

A still prominent IL-12 gene therapy is Intrexon/Ziopharm's Ad-RTS-hIL-12, which additionally uses the groups' Rheoswitch, a technology aiming to switch transcriptional control on or off using the small molecule veledimex. However, frequent conference presentations notwithstanding, progress with this project has been painfully slow.

If gene therapies do not hold the key then investors might still look to Moderna/Astrazeneca's mRNA-2905 and Merck KGaA's M9241; the latter project, a fusion protein with an antibody-based targeting region, is in an open-label Bavencio combination trial that could generate results this year.

Meanwhile, mRNA-2905 is one the most technologically intriguing projects, comprising mRNA encoding IL-12, the aim being to express the cytokine locally in the tumour. This asset, which the companies also hope could be combined with checkpoint blockade, was highlighted when Moderna came out of stealth mode a year ago.

The start of mRNA-2905 clinical trials will be closely watched, though greater expectations likely rest with Armo, and of course any group that makes progress cracking the difficulties of IL-12 should expect its share of attention too.

In IL-2, despite the availability of Proleukin, next-generation agents are still in their infancy, so it might be hard for investors to look to specific data readout points. Still, Michael Gladstone, a partner at Atlas Venture, recently called 2018 the year of the cytokine, and the Nektar deal certainly suggests that this is how things are shaping up.

To contact the writer of this story email Jacob Plieth in London at jacobp@epvantage.com or follow @JacobPlieth on Twitter

Evaluate is the trusted provider of commercial intelligence including product sales and consensus forecasts to 2022 for commercial teams and their advisors within the global life science industry. We help our clients make high value decisions through superior quality, timely, must-have data and insights, combined with personalised, expert client support.

EvaluatePharma® delivers exclusive consensus sales forecasts and trusted commercial insight into biotech and pharmaceutical performance.
@EvaluatePharma

EvaluateMedTech® sets a new standard in commercial analysis and consensus forecasts of the global medical device and diagnostic industry.
@EvaluateMedTech

EvaluateClinical Trials® delivers unique clinical trial intelligence expertly curated to efficiently analyse the global clinical trial landscape.
@EPClinicalTrial

EP Vantage an award winning editorial team, provides daily commentary and analysis with fresh perspectives and insight into current and future industry trends.
@EPVantage

Evaluate Custom Services provides customised solutions to help you access, analyse and manage the information you need to support effective decision-making.

The Evaluate services enable the life science community to make sound business decisions about value and opportunity.

www.evaluate.com

Evaluate Headquarters
Evaluate Ltd.
11-29 Fashion Street
London E1 6PX
United Kingdom
T +44 (0)20 7377 0800
F +44 (0)20 7539 1801

Evaluate Americas
EvaluatePharma USA Inc.
60 State Street, Suite 1910
Boston, MA 02109
USA
T +1 617 573 9450
F +1 617 573 9542

Evaluate Asia Pacific
Evaluate Japan KK
Akasaka Garden City 4F
4-15-1 Akasaka, Minato-ku
Tokyo 107-0052
Japan
T +81 (0)80 1164 4754