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Company Analysis
19 July 2022

Actinium Pharmaceuticals (ATNM)

General information

Actinium Pharmaceuticals, Inc.
https://www.actiniumpharma.com
275 Madison Avenue, 7th floor
New York, NY, 10016
USA

Twitter
LinkedIn

Founded:	**2000**	Employees:	**32**
Pipeline:		**External perception (July 19, 2022):**	
Lead product candidate:	**Iomab-B**	Tweets per day:	**2.60**
Lead indication:	**R/R AML**	Website traffic per month:	**1,696**
		Avg. Stocktwits Volume:	**120**
Clinical stage:	**Phase 3**	Estimation:	**Strong**
Stock information (July 19, 2022):			
Ticker (Exchange):	**ATNM (NYSE)**	Enterprise value:	**$48.29M**
Market cap:	**$118.69M**	52 Week Range:	**$4.41 – $10.30**
Avg. Vol (3 month):	**247.39k**	Avg. Vol. (10 day):	**98.62k**
Shares outstanding:	**23.78M**	Short Interest Ratio:	**2.75**
Insider Ownership:	**2.12 %**	Institutional Ownership:	**13.36 %**

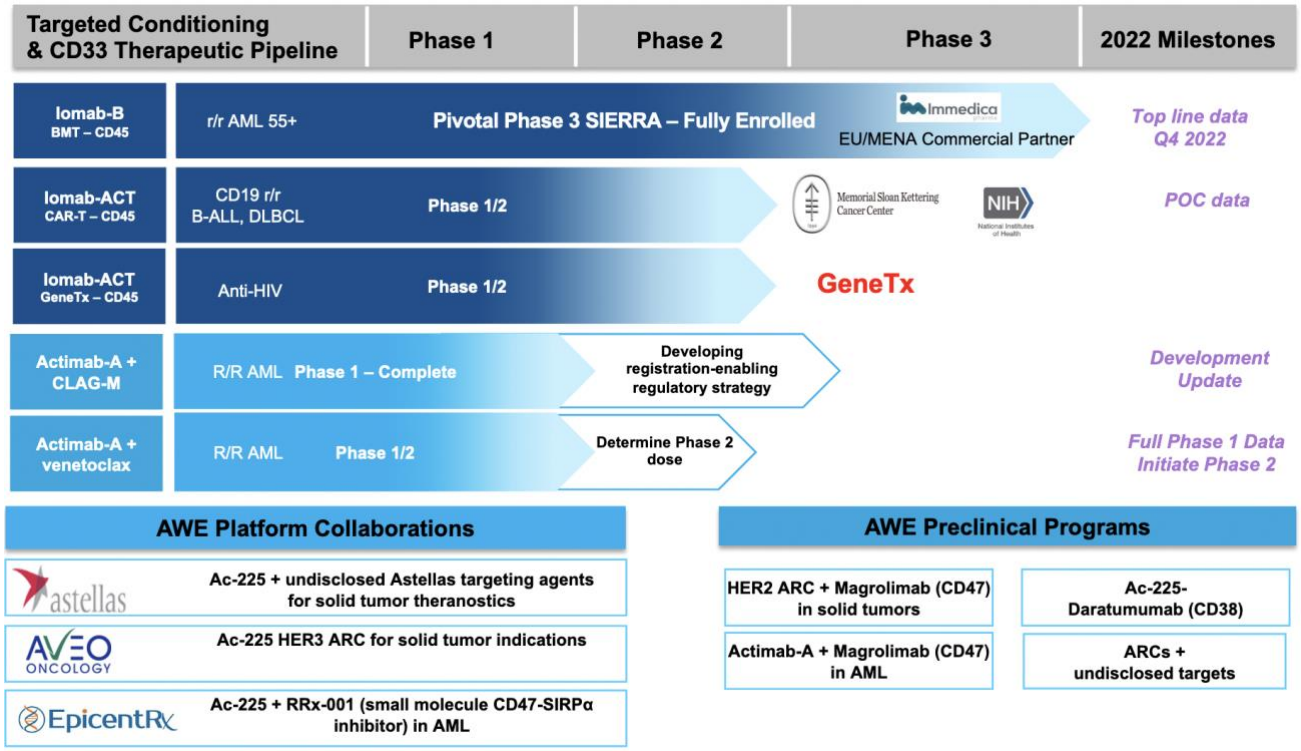
Short summary

ATNM is a clinical-stage biopharmaceutical company focusing on the development and commercialization of antibody radionuclide conjugates (ARCs) as conditioning therapies for bone marrow transplant (BMT) and for adoptive cell therapies. Lead product candidate is Iomab-B (I-131 apamistamab) that is investigated in a pivotal Phase 3 clinical trial for elderly relapsed or refractory acute myeloid leukemia patients for BMT conditioning. In two Phase 1/2 trials I-131 apamistamab is tested under the name Iomab-ACT for a CD19-targeted CAR T-cell therapy and an anti-HIV gene therapy. ATNM offers clinical and preclinical development programs that utilize multiple isotopes, including Actinium-225, Iodine-131, and Lutetium-177 directed at multiple validated cancer targets, including CD45, CD33, CD38, CD47, HER2, and HER3 for targeted conditioning prior to cell and gene therapies, such as bone marrow transplant and cancer therapeutics as single agents or in combination with other therapeutic modalities. It has collaboration with Astellas Pharma, Inc. to develop theranostics for solid tumor indications; EpicentRx, Inc that focuses on a novel CD47 immunotherapy targeted radiotherapy; and AVEO Oncology that focuses on developing a HER3 targeting ARC for solid tumors.

Next catalysts

Q4 2022	Phase 3 SIERRA trial topline data for Iomab-B in R/R AML patients
H2 2022	Phase 1 trial topline data for Iomab-ACT for targeted conditioning prior to CD19 CAR T-cell therapy
H1 2023	BLA filing for Iomab-B for the use in R/R AML patients

Pipeline



(Source: Corporate Presentation, May 2022, page 4)

ATNM develops antibody radionuclide conjugates (ARCs), which combine the targeting ability of antibodies with the cell killing ability of radiation. Lead application for ATNM's ARCs is targeted conditioning, which is intended to selectively kill patient's cancer cells and certain immune cells prior to a bone marrow transplant (BMT), CAR T and other cell therapies. ATNM's lead product candidate is Iomab-B, consisting of the monoclonal antibody BC8 that targets the antigen CD45 linked to the radioisotope Iodine-131 (I-131). Iomab-B is currently studied in a fully enrolled, multicenter, randomized, pivotal Phase 3 trial named SIERRA in elderly relapsed or refractory acute myeloid leukemia (R/R AML) patients. Iomab-B is intended to prepare and condition patients for a BMT, also referred to as a hematopoietic stem cell transplant, in a potentially safer and more efficacious manner than intensive chemotherapy conditioning that is the current standard of care in BMT conditioning. Topline data of the SIERRA trial are expected in early Q4 2022.
In addition to Iomab-B, ATNM develops a multi-disease, multi-target pipeline of clinical-stage ARCs targeting the antigens CD45 and CD33 for targeted conditioning and as a therapeutic either in combination with other therapeutic modalities or as a single agent for patients with a broad range of hematologic malignancies including AML, myelodysplastic syndrome (MDS), or multiple myeloma (MM). Special feature of ATNM's clinical programs is the proprietary Antibody Warhead Enabling (AWE) technology platform. With this platform, ATNM can construct and study novel ARCs and ARC combinations to strengthen its product pipeline.

Clinical product candidates				
Product candidate	**Antibody target**	**Radionuclide**	**Specific application**	**Broad application**
Iomab-B	CD45	Iodine-131	R/R AML	BMT conditioning
Iomab-ACT (CAR T)	CD45	Iodine-131	B-ALL, DLBCL	CAR T conditioning
Iomab-ACT (GeneTx)	CD45	Iodine-131	HIV	GeneTx conditioning
Actimab-A (CLAG-M)	CD33	Actinium-225	R/R AML	-
Actimab-A (venetoclax)	CD33	Actinium-225	R/R AML	-

In this report, we will focus primarily on the lead product candidate Iomab-B and the data and results published on it.

Iomab-B

Lead product candidate of ATNM is Iomab-B consisting of the monoclonal antibody BC8/Apamistamab (targeting the antigen CD45) linked to the radioisotope Iodine-131 (I-131). Iomab-B is used as a treatment to prepare and condition relapsed or refractory acute myeloid leukemia (R/R AML) patients older than 55 years for a bone marrow transplant. [1]
AML represents a challenging malignancy to treat, particularly in the situation of relapsed and refractory AML. Chemotherapeutic agents have shown the ability to simultaneously exert cytotoxic and cytostatic effects on leukemic cells and to suppress the patient's own immune system to reduce graft rejection. While increased doses of total body irradiation (TBI) reduce the risk of AML relapse, this also increases treatment-related mortality (TRM), often due to toxicity in the gastrointestinal system, the liver, and the lungs. Hence, BMT or hematopoietic stem cell transplantation (HSCT) is not an option for many older and medically infirm patients. Although high-intensity TBI doses reduce relapse rates, this is offset by increased conditioning regimen-related death. [2] Conversely, reducing the TBI allows for increased utilization of HSCT for patients with AML, however AML relapse rates increase. [3] Therefore, there is a dilemma to find an ideal regimen that allows for low toxicity yet potent myeloablation/myelosuppression before transplantation that improves patient survival. Targeted radiation could be an alternative. [4]
AML cells typically express antigens found on normal myeloid progenitor and differentiated cells, such as macrophages and monocytes, with aberrant expression of other lineage markers, e.g. CD45, CD33, CD13. CD11b. The most expressed antigens are CD45 (97.2%), CD33 (95.3%), and CD13 (94.3%) (according to a review of 106 AML cases). [5] These markers provide potential therapeutic targets to exploit. CD45 is a type 1 transmembrane glycoprotein present on all hematopoietic cells. [6] While CD45 is not an ideal target, as it is expressed on all hematopoietic cells, it can be used for myeloablative conditioning prior to HSCT. Monoclonal antibodies (mAbs) labeled with radionuclides provide continuous ionizing particle-based radiation exposure to cells expressing target antigens. Radioimmunotherapy for AML has been investigated for the past three decades, demonstrating its ability to kill leukemic cells and deliver radiation specifically to sites harboring AML disease. [7] Moreover, radiolabeled mAbs can deliver ionizing radiation to disease sites more specifically than traditional TBI.
A key property of radioimmunotherapy is the type of radionuclide that is attached to the mAb. Radioactively decay via α-particle or β-particle emission is different with the most relevant radionuclides for AML being the Ac-225 and At-211 emitting α-particles, whereas I-131 and Y-90 emit β-particles. α-particles have a range in tissue of 50–80 µm, which results in a linear energy transfer (LET) of 50–230 keV/µm. β-particles have a considerably reduced LET of 0.1–1 keV/µm as they have a range of 0.5–12 mm in tissue. I-131 and Y-90 have been employed in >95% of clinical radioimmunotherapy trials and represent the current standard to which all other radionuclides are compared. [8]
As Iomab-B uses the radionuclide I-131 there are some special properties of it that are notable. I-131 emits a second ionizing particle, the γ-ray and can thus be utilized for both imaging and therapy. I-131-mAbs degrade rapidly if the receptor internalizes upon mAb binding; this results in the release of I-131-tyrosine in the bloodstream. The γ-rays emitted by I-131 increase the absorbed radiation dose to tissues and pose a risk to family members and healthcare professionals and, hence, require patient isolation. These properties increase the absorbed radiation to healthy organs. [9]
The used mAb BC8/apamistamab targets the surface protein CD45. CD45 is expressed by most AML samples at relatively high levels (~200,000 receptors per cell) and is not internalized by the cell when bound to a mAb. Because CD45 is expressed on both normal and leukemic cells, it can be used to target the bone marrow. This allows the use of Iomab-B for myeloablation since the CD45 antigen is expressed on the surface of almost all hematopoietic cells, except mature red blood cells and platelets and is also present on AML blasts. [10]

[1] https://clinicaltrials.gov/ct2/show/NCT02665065
[2] https://pubmed.ncbi.nlm.nih.gov/9694737/
[3] https://pubmed.ncbi.nlm.nih.gov/27247754/
[4] https://pubmed.ncbi.nlm.nih.gov/31434267/
[5] https://pubmed.ncbi.nlm.nih.gov/9583894/
[6] https://pubmed.ncbi.nlm.nih.gov/29366662/
[7] https://pubmed.ncbi.nlm.nih.gov/31434267/
[8] https://pubmed.ncbi.nlm.nih.gov/25998714/
[9] https://pubmed.ncbi.nlm.nih.gov/31434267/
[10] https://pubmed.ncbi.nlm.nih.gov/9369421/

Clinical trials and clinical data

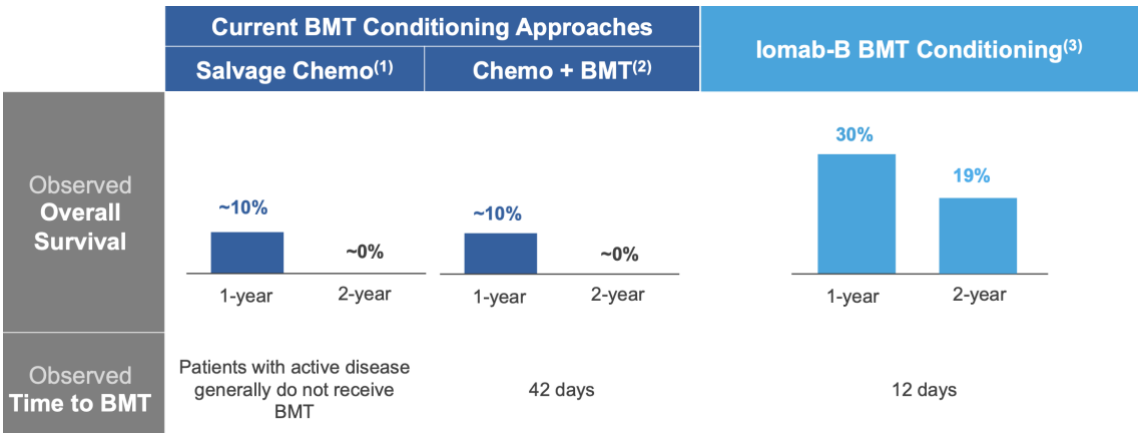
Iomab-B has been developed at the Fred Hutchinson Cancer Research Center and has been studied in several Phase 1 and Phase 2 trials in almost 300 patients in several blood cancer indications. [11] The Phase 3 SIERRA trial is the first and only trial with Iomab-B that is sponsored by ATNM.

Phase 1/2 trials

In 1999, results of a Phase 1 biodistribution trial with Iomab-B has been published in the scientific journal *Blood*. [12] 44 patients have been investigated in this study and received a biodistribution dose of trace I-131-labeled BC8 antibody. 31 patients had AML (9 remission and 22 relapse), 10 had acute lymphoblastic leukemia (ALL) (5 remission and 5 relapse), and 3 had myelodysplastic syndrome (MDS). 37 patients (84%) had favorable biodistribution of antibody, with a higher estimated radiation absorbed dose to marrow and spleen than to normal organs. 34 patients received a therapeutic dose of I-131-antibody labeled with 76 to 612 mCi I-131 to deliver estimated radiation absorbed doses to liver. Of 25 treated patients with AML/MDS, 7 survived disease-free 15 to 89 months (median, 65 months) posttransplant. Of 9 treated patients with ALL, 3 survived disease-free 19, 54, and 66 months posttransplant. The authors concluded that I-131-anti-CD45 antibody can safely deliver substantial supplemental doses of radiation to bone marrow (~24 Gy) and spleen (~50 Gy) when combined with conventional TBI.

In an article published 2005 in the journal *Blood*, targeted irradiation delivered by I-131-anti-CD45 antibody was combined with targeted busulfan (BU; 600-900 ng/mL) and cyclophosphamide (CY; 120 mg/kg) and investigated in a Phase 1/2 trial. [13] 52 (88%) of 59 patients receiving a trace I-131-labeled dose of 0.5 mg/kg anti-CD45 murine antibody had higher estimated absorbed radiation in bone marrow and spleen than in any other organ. 46 patients were treated with 102 to 298 mCi (3774-11 026 MBq) I-131, delivering an estimated 5.3 to 19 (mean, 11.3) Gy to marrow, 17-72 (mean, 29.7) Gy to spleen, and 3.5 Gy (n = 4) to 5.25 Gy (n = 42) to the liver. The estimated 3-year nonrelapse mortality and disease-free survival were 21% and 61%, respectively. The authors concluded that the addition of targeted hematopoietic irradiation to conventional BU/CY is feasible and well tolerated.

Results of a Phase 1/2 trial (NCT00008177) have been published in 2009 in the journal Blood. [14] 58 patients age ≥50 with advanced AML or high-risk MDS with a human leukocyte antigen (HLA)–matched related or unrelated donor were considered. Patients were treated with I-131-BC8 mAb and fludarabine plus 2 Gy total body irradiation. The maximum tolerated dose (MTD) of I-131-BC8 delivered to the liver was 24-Gy. At day 28 post-transplantation, all patients had a complete remission and donor-cell engraftment. Seven patients ultimately succumbed to TRM by day 100, while the one-year survival estimate was 41%. The overall survival rate of the 36 R/R AML patients was 30% at one year and 19% at two years. [15]

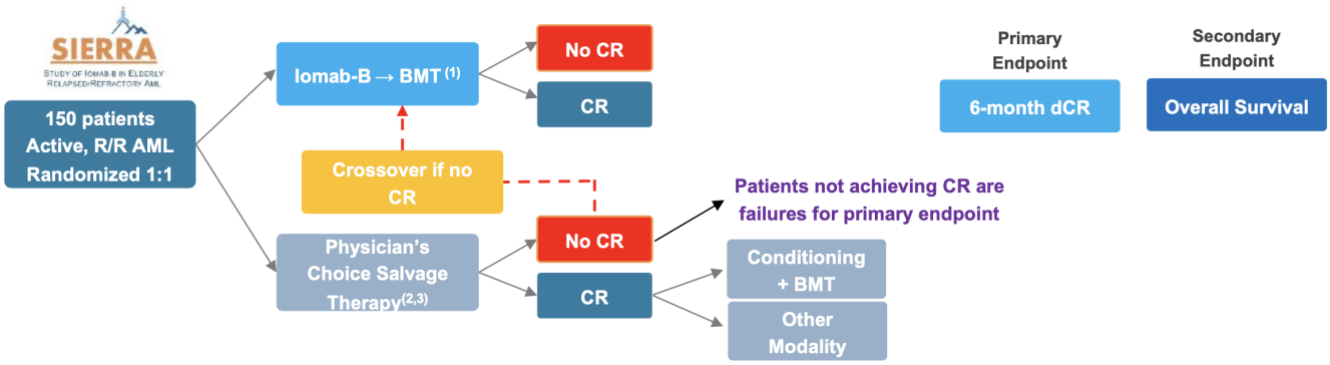


(Source: Corporate Presentation, May 2022, page 8)

[11] https://www.actiniumpharma.com/product-pipeline/iomab-b
[12] https://ashpublications.org/blood/article/94/4/1237/249681/Phase-I-Study-of-131I-Anti-CD45-Antibody-Plus
[13] https://pubmed.ncbi.nlm.nih.gov/16254140/
[14] https://pubmed.ncbi.nlm.nih.gov/19786617/
[15] https://www.actiniumpharma.com/product-pipeline/iomab-b

Phase 3 trial

The Phase 3 SIERRA (NCT02665065) trial compares conventional myeloablative conditioning regimen plus allogeneic HSCT versus I-131-BC8 (Iomab-B) plus HSCT. [16] The SIERRA trial is a randomized, open-label, multicenter trial, studying Iomab-B compared to physician's choice of salvage therapy in patients with active, R/R AML age 55 and above. Patients achieving a remission after therapy were offered a BMT. Patients not achieving remission after salvage therapy have the option to cross over to receive Iomab-B and subsequent BMT. The control arm of SIERRA included over 20 single agents or combination treatment options based on physician's choice which include salvage chemotherapy and recently approved targeted agents including Bcl-2 inhibitor (Venetoclax), FLT3 inhibitors and IDH 1/2 inhibitors as there is no standard of care for this patient population. The SIERRA trial was conducted at 24 sites in the United States and Canada. The trial was planned to enroll approximately 150 patients and on September 15, 2021, ATNM announced full enrollment of the trial with a total of 153 patients. [17] The primary endpoint of the trial is durable complete response (dCR) for 180 days and the secondary endpoint is 1-year overall survival (OS). [18, 19]



(Source: Corporate Presentation, May 2022, page 9)

ATNM conducted interim analyses and published several interim results of the SIERRA trial after 25%, 50%, 75%, and 100% enrollment: [20]

[…] This version of the analysis does not provide the full text.

Probability of positive Phase 3 topline data

The available data about the clinical trials investigating Iomab-B have been used to calculate the probability of positive Phase 3 SIERRA topline data using the BiotechProSchleuning algorithm for the evaluation of Phase 3 trial success.

- ✓ Phase 1/2 trial has been successful and met endpoints
- ✓ Results of the Phase 1/2 trial have been published in a peer reviewed journal
- ✓ Iomab-B is very efficient as targeted conditioning therapy
- ✓ Interim results have been published and are positive
- ✓ The data safety monitoring committee (DSMC) recommended to continue the trial

- ✘ The safety profile of Iomab-B is moderate with some adverse events
- ✘ Phase 3 trial tests for different endpoints than Phase 1/2 trial
- ✘ Phase 3 trial has different inclusion and exclusion criteria than Phase 1/2 trial

Calculating the probability of positive Phase 3 topline data using the algorithm:

- The phase 1 study receives 65 out of a maximum of 70 points
  - The safety profile of Iomab-B is classified as moderate

[16] https://clinicaltrials.gov/ct2/show/NCT02665065?term=actinium+pharmaceuticals&draw=2&rank=4
[17] https://ir.actiniumpharma.com/press-releases/detail/401/actinium-completes-enrollment-in-the-pivotal-phase-3-sierra
[18] https://www.sierratrial.com
[19] https://www.sierratrial.com/wp-content/uploads/sites/2/2018/10/SIERRA_clinical_trial_patient_doctor_summary.pdf
[20] https://ir.actiniumpharma.com/press-releases/detail/412/actinium-pharmaceuticals-inc-announces-greater-difference

- The Phase 2 study receives 125 out of a maximum of 160 points
  - Points are lost because the trial was non-randomized, open-label and single-centered
- The Phase 3 study receives 175 out of a maximum of 240 points
  - Trial endpoints differ between Phase 1/2 and Phase 3 trial
  - Inclusion and exclusion criteria differ between Phase 1/2 and Phase 3 trial
  - Trial is open labeled

The probability for positive Phase 3 topline data is: **77.5%**

Based on these calculations, chances of positive topline data for the Phase 3 SIERRA trial are almost 80%.

Conclusion
There are already some promising data for Iomab-B as a therapy for targeted conditioning prior to BMT. ATNM has published some interim results and Iomab-B is not only safe to use in elderly patients with R/R AML, but also has a 100% success rate for engraftment compared to the much lower 18% in the control arm. After 100% enrollment there is an approximately 5-times difference for Iomab-B versus control arm in the number of patients potentially evaluable for the primary endpoint of the Phase 3 SIERRA trial. No results on the primary endpoint are available yet, but the algorithm calculates a probability of positive topline data of 77.5% based on published trial data.

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Competitive situation

Iomab-B is being investigated for targeted conditioning of R/R AML patients prior to BMT. Currently, the Phase 3 SIERRA trial is ongoing with topline data expected in Q4 2022. Crucial for the competitive situation around Iomab-B are not products directly targeting AML, but rather pharmaceuticals currently used for myeloablation prior to BMT.
Before healthy cells can be transplanted, almost all patient's hematopoietic cells are destroyed to eradicate the leukemia (myeloablative therapy). This leaves the patient with virtually no immune system or hematopoiesis of his own. This myeloablative therapy in preparation for stem cell transplantation is achieved with a combination of intensive chemotherapy (cytostatic administration) and radiotherapy (fractionated whole-body irradiation with approximately 10 Gy). By infusion of healthy hematopoietic stem cells, the patient's bone marrow is then colonized by the new stem cells. [21]
In addition to chemotherapy and radiotherapy, small molecules such as Venetocalx are also used for conditioning. In the SIERRA trial, Iomab-B is being used in conjunction with a Reduced Intensity Conditioning (RIC) regimen containing Fludarabine and low-dose Total Body Irradiation (TBI) prior to BMT. The comparator arm of the trial is treated with salvage chemotherapy with any combination of the following agents: Azacitidine, Carboplatin, Cladribine, Clofarabine, Cyclophosphamide, Cytarabine, Daunorubicin, Decitabine, Doxorubicin, Enasidenib, Etoposide, Fludarabine, Gemtuzumab ozogamicin, Idarubicin, Ivosidenib, L-Asparaginase, Midostaurin, Mitoxantrone, Sorafenib, Thioguanine, Topotecan, Venetoclax. [22]

[…] This version of the analysis does not provide the full text.

Market size

Lead product candidate of ATNM is Iomab-B consisting of the monoclonal antibody BC8/Apamistamab (targeting the antigen CD45) linked to the radioisotope Iodine-131. Iomab-B is used as a treatment to prepare and condition relapsed

[21] https://flexikon.doccheck.com/de/Stammzelltransplantation
[22] https://clinicaltrials.gov/ct2/show/NCT02665065

or refractory acute myeloid leukemia (R/R AML) patients older than 55 years for a bone marrow transplant [23], also referred to as a hematopoietic stem cell transplant. Therefore, Iomab-B is intended to be a targeted conditioning agent to enable potentially safer and more effective bone marrow transplants compared to current standard-of-care conditioning regimens. [24]

Initial market size for Iomab-B

Market size is estimated based on the number of total AML patients, the proportion of patients with R/R AML, and limiting factors from the Iomab-B Phase 3 SIERRA trial (NCT02665065), e.g., age restrictions, which will define the scope of Iomab-B.

Incidence:

Annual patients with acute myeloid leukemia (AML) in the USA: [25]		20,240 patients
Annual patients with AML in the USA, older than 55: [26]	76.4%	15,382 patients
Annual patients with relapsed/refractory AML (R/R AML) in the USA: [27, 28, 29, 30]	60.0%	**9,229 patients**

Based on the inclusion criteria of the Phase 3 SIERRA trial, Iomab-B could be used in nearly 10,000 patients per year after successful approval.
Of note, better first-line AML therapies would reduce the market size for Iomab-B. The use of Iomab-B could be extended to R/R AML patients under 55 years of age. In this additional 25%, or about 5000 patients, the chances of success of first-line chemotherapy are higher than in older patients. The market size for Iomab-B would thus possibly increase by 1000 patients to about 11,000 patients annually.

Opportunities to expand the market for Iomab-B

The opportunities to expand the market for Iomab-B lie firstly in the use of Iomab-B as first-line treatment against AML in place of chemotherapy. On the other hand, the use against other types of cancer or the use in other applications of targeted conditioning such as gene therapy or adoptive cell therapy in general would be possible.

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Summary

The initial potential market size for Iomab-B based on the criteria of the Phase 3 SIERRA trial is around 10,000 patients annually in the US. Off-label use, however, could increase this number depending on the indications Iomab-B is applied for: Use of Iomab-B for patients younger than 55 years would increase the annual patient population by approximately 1,000; use of Iomab-B as first-line therapy for AML would double the annual patient population to 20,000. If Iomab-B were to be used as first-line therapy against AML, further clinical trials would most likely be required by the FDA.

The use of Iomab-B in conditioning, i.e., in preparation for bone marrow transplantation, also allows its use in all hematological diseases, namely MDS, ALL and lymphoma in addition to AML. If Iomab-B were used here as first-line therapy, the total annual number of patients would be up to 126,000. For all uses of Iomab-B besides AML, however, further Phase 3 trials would most likely be necessary.

[23] https://clinicaltrials.gov/ct2/show/NCT02665065
[24] https://www.nature.com/articles/d43747-021-00111-0
[25] https://seer.cancer.gov/statfacts/html/amyl.html
[26] https://seer.cancer.gov/statfacts/html/amyl.html
[27] https://ashpublications.org/blood/article/126/3/319/34547/How-I-treat-refractory-and-early-relapsed-acute
[28] https://media.leukaemiacare.org.uk/wp-content/uploads/Relapse-in-Acute-Myeloid-Leukaemia-AML-Web-Version.pdf
[29] https://pubmed.ncbi.nlm.nih.gov/28286924/
[30] https://www.nature.com/articles/s41417-019-0119-5

With the investigation of Iomab-B for conditioning patients prior to adoptive cell therapies under the Iomab-ACT program, the potential number of patients increases further. The exact number is difficult to estimate at this early stage of the Iomab-ACT program and cell therapies. However, this market will grow strongly in the coming years. Here, it is necessary to wait for further clinical studies and their results before more precise statements can be made.

In summary, the initial market for Iomab-B is approximately 10,000 patients per year, which can be expanded to an expected 150,000 patients per year through further clinical trials and corresponding approvals.

The global AML therapeutics market is estimated at $976.2 million by 2026. As of 2022, this market is worth $587.6 million and thus is projected to grow at a CAGR of 12.6% over the 4 years. Overall, Iomab-B presents a potential paradigm shift in bone marrow transplant (BMT) conditioning. As of 2022, the global BMT market size was estimated at $10.357 billion. This value is projected to reach $12.856 billion by 2028 growing at a CAGR of 3.7%. [31]
The global Hematopoietic Stem Cell Transplantation (HSCT) market is projected to reach $5.665 billion by 2029 from a valuation of $2.337 billion as of 2021. During the forecast period, it is expected to grow at a CAGR of 11.70%.
As far as the Sierra trial and radio-immunotherapy are concerned, iomab-b in the future may also be used for cellular and gene therapies. The global cell therapy market is projected to reach $60.67 billion by 2030 growing at a CAGR of 21.72% from 2022-to 2030. [32]
In turn, the gene therapy market is estimated to reach $5.02 billion by 2028 growing at a CAGR of 17.0% in the forecast period. [33]

As of April 7, 2022, Actinium Pharmaceuticals announced that it had entered into a license and supply agreement with Immedica Pharma AB for Iomab-B (I-131 apamistamab). [34] In this deal, Immedica gets exclusive rights to Iomab-B in Europe, the Middle East, and North Africa. Actinium retains the drug's rights in the US and the rest of the world as well as the clinical, regulatory, and development activities. Actinium received $35 million as an upfront payment in May 2022 with a potential of up to $417 million in regulatory and commercial milestone payments. Royalties are in the mid-20% range on net sales.
An article on Seeking Alpha (with data from as early as 2015) stated that Actinium estimated the cost of Iomab-B treatment at $85,000. At the time, the number of elderly relapsed/ refractory AML cases was 7,000 bringing the total revenue to around $600 million (in sales). [35] However, as of 2021, the number of older patients (above 65 years old) with relapsed/ refractory AML had increased 71.43% to 12,000. [36]
Without factoring in the impact of inflation which stands at 8.5% as of March 2022 and we assume that the price of the Iomab-B treatment remains at $85,000, then Actinium stands to make at least $1.02 billion in sales (on the downside).

Manufacturing

ATNM depends on a single third-party manufacturer to produce its pre-clinical and clinical trial drug supplies. [37]
Iodine-131, the key component of ATNM's Iomab-B drug candidate, is currently sourced from three suppliers including two leading global manufacturers. ATNM states that there is sufficient supply of I-131 to advance its ongoing SIERRA clinical trial, support additional trials that may be undertaken utilizing I-131 and for commercialization of Iomab-B. ATNM states to continually evaluate I-131 manufacturers and suppliers and to intend to have multiple qualified suppliers prior to the commercial launch of Iomab-B. [38]

[31] https://www.persistencemarketresearch.com/market-research/bone-marrow-transplantation- market.asp
[32] https://www.globenewswire.com/en/news-release/2022/05/12/2442322/0/en/Cell-Therapy- Market-Size-to-Surpass-US-60-67-Billion-by-2030.html
[33] https://www.prnewswire.com/news-releases/global-gene-therapy-market-size-expected-to-grow- to-usd-5-02-billion-by-2028--at-17-0-cagr-polaris-market-research-301516723.html
[34] https://www.nasdaq.com/articles/actinium-pharma-in-deal-with-immedica-for-iomab-b-sees-up-to-%24452-mln-milestone-payments
[35] https://seekingalpha.com/article/3198636-actinium-pharmaceuticals-bone-marrow-transplantation-drug-iomab-b-offers-goldmine-for-investors
[36] https://www.researchgate.net/publication/361050285_Older_Patients_with_Acute_Myeloid_Leukemia_Deserve_Individualized_Treatment
[37] https://ir.actiniumpharma.com/annual-reports/content/0001213900-22-015208/0001213900-22-015208.pdf, page 14
[38] https://ir.actiniumpharma.com/annual-reports/content/0001213900-22-015208/0001213900-22-015208.pdf, page 25

Management

ATNM's management team convinces through many years of experience and expertise in the respective field. Both the management and the directors include an exceptionally large number of members with a scientific background, especially with a biological focus. Thus, the team convinces through professional know-how. Many members have already been part of ATNM for several years. The only surprise was the sudden appointment of Avinash Desai as CMO, replacing Mark Berger. Since then, however, the enrollment of the Phase 3 SIERRA study has been accelerated significantly.

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Financial overview

According to the Quarterly Report from May 2022, ATNM had cash and cash equivalents of $72.0 million as of March 31, 2022, compared to $77.8 million as of December 31, 2021. [39] ATNM's debt is almost negligible at $0.2 million. Its working capital is approximately $66.3 million. Net loss was $24.6 in the 12 months leading to March 2022.

Cash Flow Statement								
	06/30/20	09/30/20	12/31/20	03/31/21	06/30/21	09/30/21	12/31/21	03/31/22
Net Income	-4.63	-5.54	-6.38	-5.32	-5.02	-6.42	-8.01	-5.13
Total Depreciation & Amortization	0.11	0.11	0.12	0.13	0.13	0.13	0.14	0.14
Cash from Operations	-4.51	-4.99	-6.26	-5.64	-4.58	-5.59	-5.05	-5.78
Cash from Investing		-0.01	-0.25	0	-0.06	-0.07		-0.01
Cash from Financing	52.04	-0.23	21.83	14.34	14.3	5.78	0.8	-0.02
Net Change in Cash	47.52	-5.23	15.33	8.69	9.66	0.12	-4.25	-5.81
Free Cash Flow		-5	-6.5	-5.65	-4.65	-5.66		-5.79

Based on the last eight quarters, ATNM has spent an average of $5.3 million per quarter. Here, expenditures are relatively stable over the eight quarters. In the 3 months ended on March 31, 2022, ATNM reported a 2.5% increase in the cash used in operations from $5.642 million in the 3 months ended in December 2022 to then $5.781 million. It shows the company used up approximately $2 million every month. The Phase 3 SIERRA trial is in the final analysis stage, so spending of around $6 million can be expected for the coming quarters until the end of 2022. In April 2022 ATNm entered a license agreement with Immedica Pharma AB and received an upfront payment of $35 million from Immedica, which was received in May 2022 (for details, see section "Commercialization").
Based on these assumptions and information, ATNM's existing cash for end of June 2022 can be calculated approximately as follows:

	$72.0 million	(March 31, 2022)
–	$6.0 million	(Cash burn Q2 2022)
+	$35.0 million	(Immedica agreement)
	$101.0 million	

With expenses otherwise unchanged, this funding should enable ATNM to get by until year end 2023. SIERRA topline data is expected to be announced in Q4 2022 and a BLA for Iomab-B is planned for H1 2023. Expenditures will increase for this, as well as for possible follow-up trials with Iomab-ACT and Actimab-A towards the end of 2023 and initial clinical trials with other as-yet preclinical product candidates. In addition, production of Iomab-B will be ramped up for its commercialization, resulting in further costs already in early 2023. ATNM will thus probably need to raise new money in late 2023.

[…] This version of the analysis does not provide the full text.

[39] https://ir.actiniumpharma.com/quarterly-reports/content/0001213900-22-026538/0001213900-22-026538.pdf, page 2

Intellectual property

In its 2021 Annual report, ATNM states that as of March 2022, its patent portfolio includes 39 patent families comprised of 174 issued patents and pending patent applications, of which 8 are issued and 30 are pending in the United States, and 135 are issued or pending internationally. Several non-provisional patent applications are expected to be filed in 2022 based on provisional patent applications filed in 2021. More than 90% of the patents are ATNM-owned and the remainder are in-licensed from third parties. These patents cover key areas of ATNM's business, including the use of Ac-225 and other alpha- or beta-emitting isotopes attached to cancer targeting carriers like monoclonal antibodies in the treatment of cancers and non-malignant medical disorders, methods for manufacturing key components of ATNM's product candidates including Ac-225, an alpha particle emitting radioisotope and carrier antibodies, or I-131, a beta particle emitting radioisotope, and methods for manufacturing finished product candidates for use in cancer treatment. [40]

[…] This version of the analysis does not provide the full text.

Commercialization

On April 12, 2022, ATNM announced entering a license and supply agreement with Immedica Pharma AB for Iomab-B. [41] With this agreement Immedica obtains exclusive rights to Iomab-B in Europe, the Middle East, and North Africa including Algeria, Andorra, Bahrain, Cyprus, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya. Monaco, Morocco, Oman, Palestine, Qatar, San Marino, Saudi Arabia, Switzerland, Syria, Tunisia, Turkey, the United Arab Emirates, the United Kingdom, the Vatican City and Yemen. Under the terms of the agreement, ATNM received an upfront payment of $35 million, which was received in May 2022, and will be eligible to receive an additional $417 million in regulatory and commercial milestones as well as royalties in the mid-twenty percent range on net sales. Immedica receives commercialization rights in Europe and MENA countries. ATNM retains all rights related to Iomab-B in the United States and the rest of the world and will be responsible for certain clinical and regulatory activities and the manufacturing of Iomab-B. Shadow Lake Group (SLG) served as the advisor to Immedica.

Timeline

The Phase 3 SIERRA trial is fully enrolled [42] and the last patients received their BMT in Q4 2021. [43] According to the quarterly report published in May 2022 and the latest corporate presentation, ATNM expects topline data for the primary endpoint of dCR to be presented in Q4 2022 based on the status of the data collection and data query process with certain SIERRA trial sites. [44, 45]
ATNM believes that SIERRA trial topline data will support the submission of a Biologics License Application (BLA) with the FDA, which is expected to be filed in H1 2023.
In March 2016, the FDA granted orphan drug designation to Iomab-B, which provides a drug developer with certain benefits and incentives, including a period of marketing exclusivity if regulatory approval is ultimately received for the designated indication; potential tax credits on U.S. clinical trials; eligibility for orphan drug grants; and waiver of certain administrative fees. [46] However, ATNM has not yet received a designation from the FDA for Iomab-B that would allow for an accelerated priority review process of the BLA. Therefore, it can be assumed that an approval decision by the FDA after submission of the BLA will take a total of 12 months and will therefore not occur before H1 2024.

[40] https://ir.actiniumpharma.com/annual-reports/content/0001213900-22-015208/0001213900-22-015208.pdf, page 7
[41] https://ir.actiniumpharma.com/press-releases/detail/419/actinium-pharmaceuticals-inc-and-immedica-announce
[42] https://ir.actiniumpharma.com/press-releases/detail/401/actinium-completes-enrollment-in-the-pivotal-phase-3-sierra
[43] https://ir.actiniumpharma.com/quarterly-reports/content/0001213900-22-026538/0001213900-22-026538.pdf, page 15
[44] https://ir.actiniumpharma.com/quarterly-reports/content/0001213900-22-026538/0001213900-22-026538.pdf, page 16
[45] https://d1io3yog0oux5.cloudfront.net/_3a1b3d25ddb9cbb21be767c35a9d8846/actiniumpharma/db/206/944/pdf/Actinium_Investor+Presentation_May+13+2022.pdf
[46] https://ir.actiniumpharma.com/press-releases/detail/161

Timeframe by ATNM	Catalyst	Estimated timeframe
Q4 2022	Phase 3 SIERRA topline data	Late October 2022
H1 2023	BLA filing for Iomab-B	April 2023

ATNM has moved the timing of the Phase 3 SIERRA trial announcement back several times. Still at the beginning of the year and thus after full enrollment of the trial and completion of treatment of all patients, the topline data should be announced in Q3 2022.
It can be assumed that the analysis of the data has already started and in this context, it was determined that more time is needed for the entire analysis until publication. Therefore, if ATNM specifies Q4 2022 for the announcement of the Phase 3 topline data, it is highly likely that an early date in the quarter can be expected and thus most likely October 2022. ATNM should then need about half a year to prepare the BLA for Iomab-B, so the filing could occur in April 2023.

Summary

ATNM is a convincing company in several respects: the company's management excels with experience in the field of biology/biotechnology, most of them have already been with the company for many years, and it has already secured a promising partner in the form of the commercialization agreement with Immedica Pharma AB. Here, it remains to be seen whether additional experts in the field of regulatory affairs will be recruited for the upcoming BLA 2023 and whether additional agreements can be concluded with larger pharmaceutical companies. ATNM's pipeline makes a good impression and holds the potential for broad application. Lead product candidate Iomab-B is being investigated in a well-designed Phase 3 trial and, if successful and approved, serves a clear market with the opportunity for broad expansion of market size. Overall, however, the indications covered by the product pipeline could cover a broader spectrum. Iomab-B convinces with an excellent approach with broad application potential as well as very good results in Phase 1/2 trials and promising results from the conducted interim analyses. Based on the available data, there is a 77.5 % probability of positive topline data from the Phase 3 SIERRA trial according to the BiotechProfSchleuning algorithm. The competitive situation for Iomab-B looks good, as it is being compared against all current AML drugs in the SIERRA trial and can show its direct superiority if the results are good. Similar products in the field of ARCs are in development progress behind Iomab-B. Further progress will have to be monitored and the subsequent market entry and consequent reduction in the market dominance of Iomab-B will have to be anticipated.
Financially, ATNM is in very good position and has sufficient cash until at least the end of 2023. Even with an increase in expenses due to the planned BLA in H1 2023 and further clinical studies of the product candidates, ATNM should not need further financing before the end of 2023.
ATNM's timeline is clear: topline data from the Phase 3 SIERRA trial should come in Q4 2022. Despite repeated postponements of this catalyst to date, it is highly likely that topline data can be expected to be announced in October 2022. This will be followed by the submission of the BLA for Iomab-B in H1 2023, which is likely to happen in April 2023. The perception of ATNM by other investors and the activities in investor forums can be rated as "strong". Thus, positive catalysts should have a solid impact on the company's stock.

In summary, ATNM has a strong management team, an exceptionally promising lead product candidate, Iomab-B, with positive interim results, and an excellent financial situation with clear next catalysts.

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