Special Report

Pipeline Assessment –

Immuno-oncology and Gene Therapies

March 2021

aranca


Immuno-oncology

Global cancer immunotherapy market to reach ~USD137 billion by 2025; US NIH and 11 pharmaceutical companies enter partnership, focused on advancement of treatments

Therapy Overview: Immuno-oncology

1

Market Size:

- The global cancer immunotherapy market, valued at USD80.34 billion in 2019, is expected to reach USD136.9 billion by 2025, recording a CAGR of 9.86% over 2020–25 (forecast period).
- Increasing R&D activities as well as improving efficacy and accuracy of newer therapies are the key factors driving growth.

2

Partnership for Accelerating Cancer Therapies (PACT):

- The US National Institutes of Health (NIH) and 11 biopharmaceutical companies formed PACT in October 2017, a five-year public-private research collaboration worth USD215 million, as part of the Cancer Moonshot.
- It will focus on efforts to develop, identify, and validate potent biomarkers for the advancement of cancer immunotherapy.

3

Novel Mechanisms of Action:

- The earlier explored mechanisms largely involved targeting CTLA-4 or PD-1. However, the market potential has increased, with many different classes of immuno-oncology therapeutics such as chimeric antigen receptor T-cell (CAR-T) therapies and STING being explored.

4

Key Segments:

- The mAbs segment is expected to command a major share in the market, registering a CAGR of 5.47% over 2020–25.
- PD-1 and PD-L1 would continue to drive growth—annual sales of current products are projected to rise to USD41.3 billion by 2023, considering the approval of additional indications and new treatment combinations.

Source: *Industry Reports, Company websites, Aranca Analysis*

Roche's Tecentriq approved for multiple oncology indications; GSK expanding in oncology market with majority of pipeline drugs in early-stage development

Pipeline Analysis of Key Players in Immuno-oncology TA

	Roche		GSK	
Approved	**Tecentriq** (Metastatic NSCLC, RCC, bladder cancer)		**dostarlimab** (Endometrial cancer)	
Phase III	**RG 6058/ tiragolumab** (1L SCLC)		**GSK3359609** (Head and neck cancer)	
Phase II	**RG6180/ RO7198457** (Melanoma)		**GSK4045154/M7824** (Biliary cancer 2L)	**cobolimab** (Cancer)
Phase I	**RG7802/ cibisatamab** (Solid tumors)	**RG6026** (Non-Hodgkin lymphoma)	**GSK3174998** (Solid tumors and hematological malignancies)	**GSK3377794** (Cancer)
	RG6194 (Metastatic HER2-positive cancers)	**RG7828/ mosunetuzumab** (Hematologic tumors)	**GSK3745417** (Cancer)	**GSK4074386/TSR-033** (Cancer)
	RG7769 (Solid tumors)	**RG7827/ FAP 4-1BBL FP** (Solid tumors)		

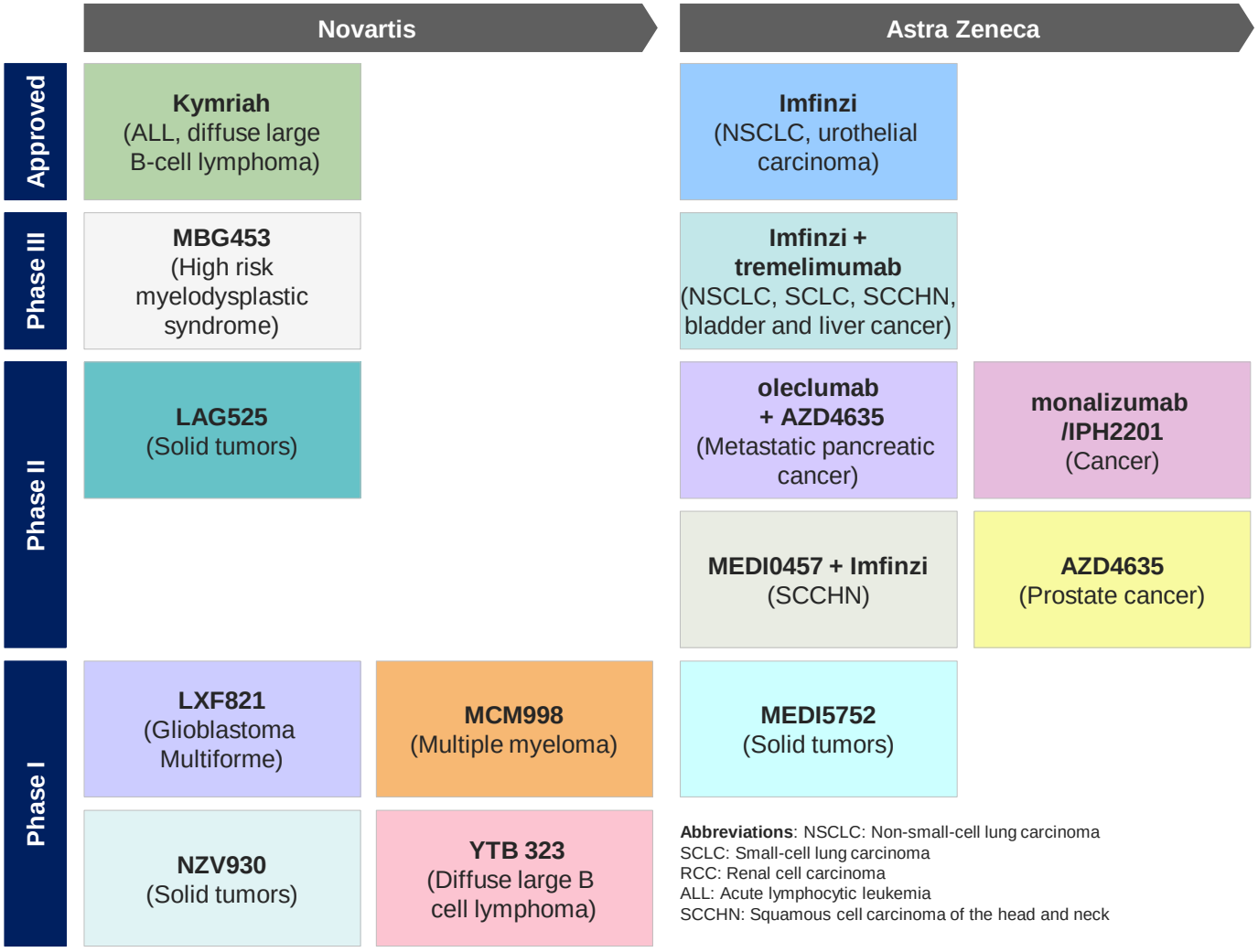
Abbreviations: NSCLC: Non-small-cell lung carcinoma
SCLC: Small-cell lung carcinoma
RCC: Renal cell carcinoma
ALL: Acute lymphocytic leukemia
SCCHN: Squamous cell carcinoma of the head and neck

Drug Mechanism of Action (MoA)

- Adoptive T-cell transfer
- Agonistic immune modulator and targeted T-cell costimulator
- Anti PD-L1 mAb
- Anti-CD20 and CD3 bispecific Ab
- Anti-TIM-3 Ab
- Anti-LAG-3 Ab
- Anti-PD-1
- Anti-TIGIT
- Carcinoembryonic antigen (CEA) and CD3 bispecific Ab
- HER2-positive and CD3 T-cell bispecific Ab
- ICOS receptor agonist
- Individualised neoantigen specific therapy (iNeST)
- PD-1 and TIM-3 bispecific Ab
- STING agonist
- Anti-OX40

Kymriah (Novartis) first CAR-T cell therapy to be approved by the US FDA; AZ's Imfinzi approved for multiple indications and undergoing trials for combination therapy

Pipeline Analysis of Key Players in Immuno-oncology TA



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Drug Mechanism of Action (MoA)

- A2aR inhibitor
- Anti-CD73
- Anti-CD73 mAb + A2aR inhibitor
- Anti-LAG-3 Ab
- Anti-PD-1
- Anti-PD-L1 mAb
- Anti-TIM-3 Ab
- BCMA CAR-T, CD19 CAR-T
- CAR T-cell therapy
- CD19 CAR T-cell immunotherapy
- DNA HPV vaccine + PD-L1 mAb
- EGFR CAR-T, PD-1 inhibitor
- Anti-NKG2A
- PD-1/CTLA-4 bispecific mAb
- PD-L1 mAb + Anti-CTLA-4 mAb

BMS has extensive immuno-oncology pipeline; Opdivo in combination with Cabometyx, recently approved for first line treatment of advanced renal cell carcinoma (RCC) patients

Pipeline Analysis of Key Players in Immuno-oncology TA

BMS

Approved	**Opdivo** (Malignant melanoma, NSCLC,RCC)	**Yervoy** (Metastatic melanoma)	**Breyanzi/ lisocabtagene maraleucel^** (R/R LBCL)	**idecabtagene vicleucel /bb2121** (Multiple myeloma)
Phase III	**Iinrodostat/BMS-986205** (Metastatic melanoma)	**relatlimab/BMS-986016** (Melanoma, gastric cancer, solid tumors)	**bempegaldesleukin/ NKTR-214** (Metastatic melanoma, RCC)	
Phase II	**Anti-CTLA-4 NF** (Solid tumors)	**Anti-CTLA-4 NF probody** (Solid tumors)	**BMS-986249** (Metastatic melanoma /Solid tumors)	
Phase I	**Anti-OX40** (Solid tumors)	**Anti-TIGIT** (Cancer)	**BET Inhibitor/ CC-90010** (Solid tumors)	**STING agonist** (Cancer)
	BMS-986179 (Cancer)	**BMS-986253** (Prostrate cancer)	**BMS-986258** (Advanced solid tumors)	**JCARH125** (Multiple myeloma)

Drug Mechanism of Action (MoA)

- Anti-BCMA CAR T-cell therapy
- Anti-CD73
- Immunologic cytotoxicity; T lymphocyte replacements
- Anti-CTLA-4 NF
- Anti-TIGIT
- Anti-TIM-3 Ab
- Anti-IL-8
- Anti-LAG-3 Ab
- Anti-OX40
- BET inhibitor
- CD122-biased agonist
- CTLA-4 inhibitor
- CTLA-4 NF probody
- IDO1 inhibitor
- IgG4 PD-1 immune checkpoint inhibitor
- STING agonist

Abbreviations: NSCLC: Non-small-cell lung carcinoma
SCLC: Small-cell lung carcinoma RCC: Renal cell carcinoma
ALL: Acute lymphocytic leukemia SCCHN: Squamous cell carcinoma of head and neck R/R LBCL: Relapsed or refractory large B-cell lymphoma
*Approval of Breyanzi is based on a BLA submitted by Juno Therapeutics

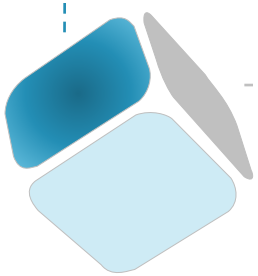
Source: *Industry Reports, Clinicaltrials.gov, Company websites, Aranca Analysis*

CRI's Clinical Accelerator collaboration aimed at developing promising therapies to fight cancer; significant growth in I-O pipeline despite COVID -19

Recent Developments in Immuno-oncology

1 Cancer Research Institute (CRI) Anna-Maria Kellen Clinical Accelerator

- It is an academia, nonprofit industry collaboration model serving as an incubator for delivering science-driven, multi-center clinical trials of promising cancer immunotherapy combinations. It has been involved in the PRINCE and PORTER clinical trials, which were co funded by the CRI and Parker Institute for Cancer Immunotherapy (PICI).
- PRINCE trial is a collaboration between CRI, PICI, and BMS, providing promising results for metastatic pancreatic cancer.



2 Significant growth in Immuno-Oncology (I-O) pipeline despite COVID-19 impact

- Immuno-oncology drugs in the development pipeline increased 22% from 2019 to 2020.
- Active clinical trials testing I-O agents increased 14% in 2020 compared to 2019.
- The trends are expected to continue, bringing hope for cancer patients globally.

3 Emerging role of checkpoint inhibitors for rare genitourinary cancers

- Combination immune checkpoint inhibition with nivolumab and ipilimumab is being widely applied in a variety of genitourinary cancers.
- A phase 2 study of Nivolumab and Ipilimumab showed objective responses in patients with rare genitourinary malignancies, especially with bladder and upper tract carcinoma of variant histology (BUTCVH).

Source: *Industry Reports, News Articles, Company websites, Aranca Analysis*

Gene Therapies

Global gene therapy market to reach ~USD16.3 billion by 2024; recombinant AAV products to continue dominating the pipeline

Therapy Overview: Gene Therapies

Market Size

- In 2018, the global gene therapy market was valued at USD3.23 billion. It is expected to reach USD16.368 billion by 2024, recording a CAGR of 28.32% during 2020–24.
- Technological advancements, increasing investment in R&D, and growing prevalence of target diseases like cancer, rheumatoid arthritis, diabetes and neurological ailments are driving the market.

AAV-based Products

- Recombinant adeno-associated virus (AAV)-based vectors are the most widely used gene therapy products and show the highest potential for delivery in gene therapy indications. Majority of AAV-based therapeutic products (~74%) are in the early to mid-phase of clinical development.
- Numerous encouraging clinical outputs have contributed to the growth of the pipeline of AAV-based products, such as Luxturna, where an AAV was used to deliver the gene in patients suffering from inherited eye disease.

Promotion of Gene Therapy

- Gene therapy is being promoted by various governments (such as the US, UK, Australia and Singapore). They are not just supporting clinical trials but also endorsing the integration of small gene therapy research centers and hospitals.
- Several government initiatives such as measures to increase awareness and streamline the regulatory environment (fast-tracking approval processes) are contributing to growth in the gene therapy market.

Source: *Industry Reports, News Articles, Company websites, Aranca Analysis*

Zolgensma (Novartis) first gene therapy for pediatric patients with spinal muscular atrophy (SMA); Bluebird's Zynteglo approved in Europe for beta-thalassemia

Pipeline Analysis of Key Players in Gene Therapy TA

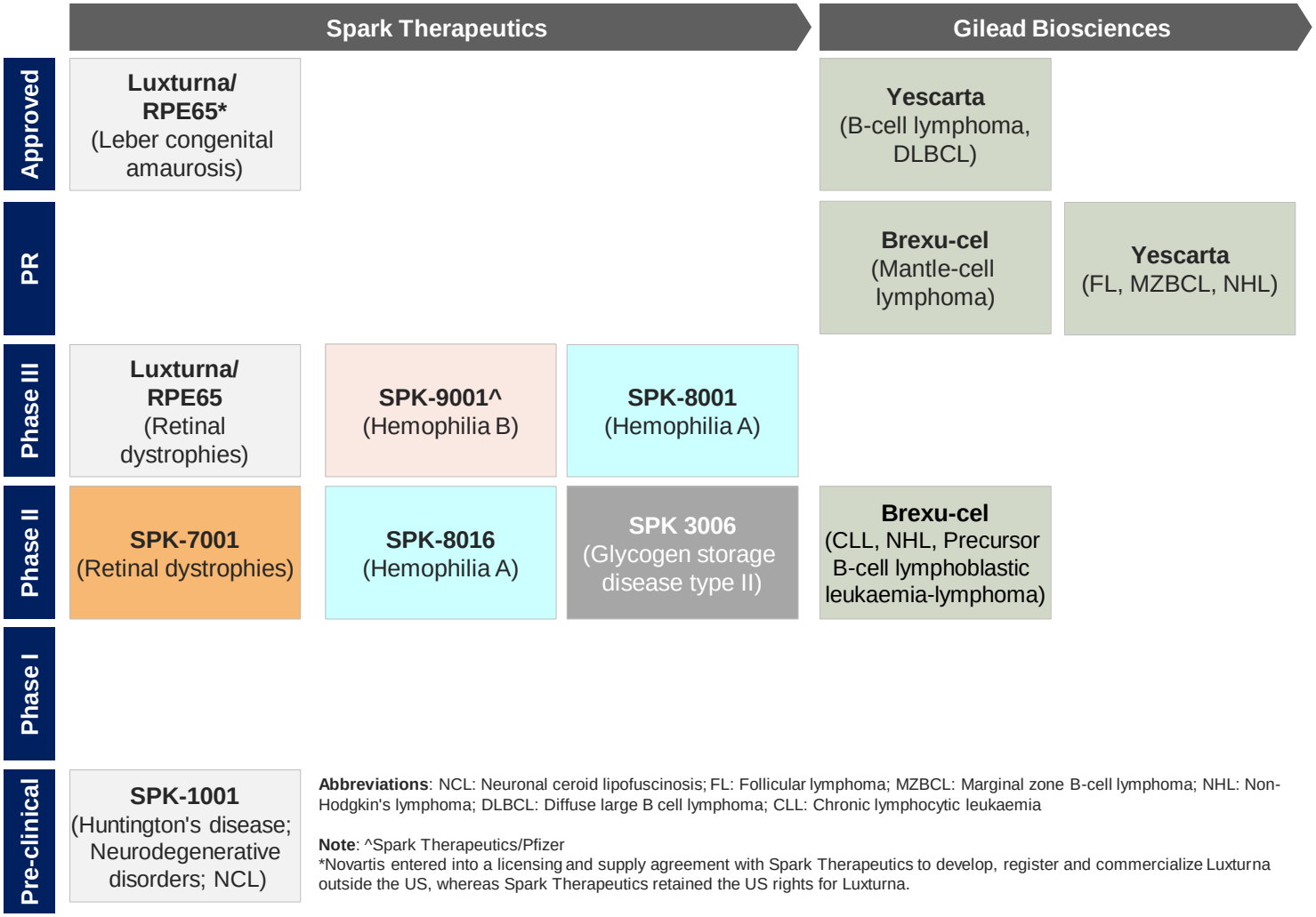
	Novartis	UniQure		Bluebird bio	
Approved	**OAV101 /AVXS-101/ Zolgensma** (Spinal muscular atrophy type 2/3)			**betibeglogene autotemcel/ Zynteglo** (Beta-thalassaemia)	
PR				**Lenti-D** (Adrenoleucodystrophy)	
Phase III		**AMT 061** (Haemophilia B)		**betibeglogene autotemcel/ bb1111** (Sickle cell anaemia)	**idecabtagene vicleucel** (Multiple myeloma)
Phase II	**OAV101 /AVXS-101** (Spinal muscular atrophy type 2/3)		**AMT 130** (Huntington's disease)		
Phase I	**OAV201/ AVXS-201** (Rett Syndrome)			**Bb21217** (Multiple myeloma)	
Pre-clinical	**AVXS-301** (Amyotrophic lateral sclerosis)	**AMT 190** (Fabry's disease)	**AMT 150** (Ataxia)		

Drug Mechanism of Action (MoA)

- Methyl-CpG binding protein 2 gene replacement therapy
- Survival motor neuron (SMN) gene replacement therapy
- Gene transference
- Factor IX stimulants; Gene transference
- Gene silencing
- ALDP replacements; Gene transference
- Immunologic cytotoxicity; T lymphocyte replacements
- CHM protein expression stimulants; Gene transference
- Factor VIII replacements; Gene transference
- Alpha glucosidase expression stimulants; Gene transference

Luxturna (Spark Therapeutics) first FDA-approved gene therapy for a genetic disease as well as first AAV vector gene therapy approved in the US

Pipeline Analysis of Key Players in Gene Therapy TA



Abbreviations: NCL: Neuronal ceroid lipofuscinosis; FL: Follicular lymphoma; MZBCL: Marginal zone B-cell lymphoma; NHL: Non-Hodgkin's lymphoma; DLBCL: Diffuse large B cell lymphoma; CLL: Chronic lymphocytic leukaemia

Note: ^Spark Therapeutics/Pfizer
*Novartis entered into a licensing and supply agreement with Spark Therapeutics to develop, register and commercialize Luxturna outside the US, whereas Spark Therapeutics retained the US rights for Luxturna.

Drug Mechanism of Action (MoA)

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- Gene transference
- Factor IX stimulants; Gene transference
- Gene silencing
- ALDP replacements; Gene transference
- Immunologic cytotoxicity; T lymphocyte replacements
- CHM protein expression stimulants; Gene transference
- Factor VIII replacements; Gene transference
- Alpha glucosidase expression stimulants; Gene transference

Key players strengthen position in gene therapy market through strategic acquisitions; CRISPR technology could alter conventional gene therapy approaches

Recent Developments in Gene Therapy

Strategic Acquisitions and Collaborations

- The recent acquisition of Asklepios Biopharmaceuticals (Askbio) by Bayer is expected to help Bayer cement its position in the gene therapy market. Asklepios will secure an upfront consideration of USD2 billion and potential success-based milestone payments of up to USD2 billion from Bayer.
- UCB strengthened its gene therapy portfolio through the acquisition of Handl Therapeutics BV and R&D collaboration with Lacerta Therapeutics.
- Eli Lilly recently announced plans to buy gene therapy developer Prevail Therapeutics for USD1 billion.

CRISPR Gene Editing Technology

- It involves altering the DNA to precisely disrupt, delete, or repair the original diseased gene. Some of the key players are Editas Medicine, Intellia Therapeutics, and CRISPR Therapeutics.
- CRISPR Therapeutics partnered with Vertex Pharmaceuticals and sponsored the first CRISPR trial in humans in 2018 for the treatment of beta-thalassemia and sickle cell disease.
- All key players have several CRISPR therapies for cancer and regenerative medicine in the pipeline.

Source: *Industry Reports, News Articles, Company websites, Aranca Analysis*

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