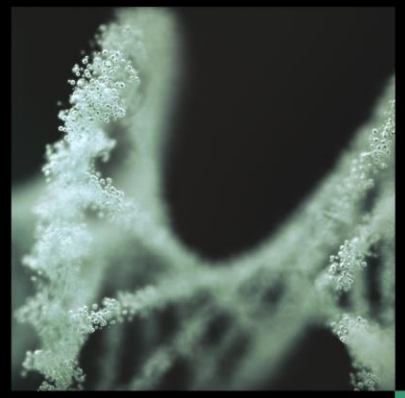
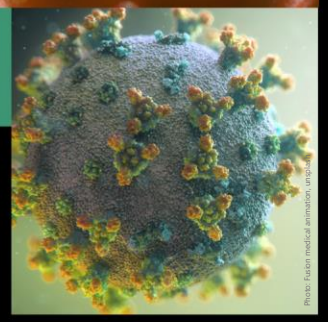
Innovation Series



June 29, 2022



BIONTECH

This slide presentation includes forward-looking statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning: the future commercial demand and medical need for initial or booster doses of a COVID-19 vaccine; competition from other COVID-19 vaccines or related to our other product candidates, including those with different mechanisms of action and different manufacturing and distribution constraints, on the basis of, among other things, efficacy, cost, convenience of storage and distribution, breadth of approved use, side-effect profile and durability of immune response; the rate and degree of market acceptance of our COVID-19 vaccine and, if approved, our investigational medicines; the initiation, timing, progress, and results of our research and development programs and our current and future preclinical studies and clinical trials, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work, the period during which the results of the trials will become available and our research and development programs; the timing of and our ability to obtain and maintain regulatory approval for our product candidates; our collaboration with Pfizer to develop and market a COVID-19 vaccine (including a potential booster dose of BNT162b2 and/or a potential booster dose of a variation of BNT162b2 having a modified mRNA sequence); the ability of BNT162b2 to prevent COVID-19 caused by emerging virus variants; our ability to identify research opportunities and discover and develop investigational medicines; the ability and willingness of our third-party collaborators to continue research and development activities relating to our development candidates and investigational medicines; the impact of the COVID-19 pandemic on our development programs, supply chain, collaborators and financial performance; unforeseen safety issues and claims for personal injury or death arising from the use of our COVID-19 vaccine and other products and product candidates developed or manufactured by us; our ability to progress our Malaria, Tuberculosis and HIV programs, including timing for selecting clinical candidates for these programs and the commencement of a clinical trial, as well as any data readouts; the nature and duration of support from the World Health Organization, the European Commission and other organizations with establishing infrastructure; the development of sustainable vaccine production and supply solutions on the African continent and the nature and feasibility of these solutions; our estimates of research and development revenues, commercial revenues, cost of sales, research and development expenses, sales and marketing expenses, general and administrative expenses, capital expenditures, income taxes, shares outstanding; our ability and that of our collaborators to commercialize and market our product candidates, if approved, including our COVID-19 vaccine; our ability to manage our development and expansion; regulatory developments in the United States and foreign countries; our ability to effectively scale our production capabilities and manufacture our products, including our target COVID-19 vaccine production levels, and our product candidates; and other factors not known to us at this time. In some cases, forward-looking statements can be identified by terminology such as “will,” “may,” “should,” “expects,” “intends,” “plans,” “aims,” “anticipates,” “believes,” “estimates,” “predicts,” “potential,” “continue,” or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this presentation are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond BioNTech’s control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. You should review the risks and uncertainties described under the heading “Risk Factors” in this presentation for the three months ended March 31, 2022 and in subsequent filings made by BioNTech with the SEC, which are available on the SEC’s website at https://www.sec.gov/. Except as required by law, BioNTech disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this presentation in the event of new information, future developments or otherwise. These forward-looking statements are based on BioNTech’s current expectations and speak only as of the date hereof.

Safety information

COMIRNATY® ▼(the Pfizer-BioNTech COVID-19 vaccine) has been granted conditional marketing authorization (CMA) by the European Commission to prevent coronavirus disease 2019 (COVID-19) in people from 5 years of age. The vaccine is administered as a 2-dose series, 3 weeks apart. In addition, the CMA has been expanded to include a booster dose (third dose) at least 6 months after the second dose in individuals 18 years of age and older. For immunocompromised individuals, the third dose may be given at least 28 days after the second dose. The European Medicines Agency's (EMA's) human medicines committee (CHMP) has completed its rigorous evaluation of COMIRNATY®, concluding by consensus that sufficiently robust data on the quality, safety and efficacy of the vaccine are now available.

IMPORTANT SAFETY INFORMATION:

- Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.
- Very rare cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.
- Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, tingling sensations and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.
- The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COMIRNATY® may be lower in immunosuppressed individuals.
- As with any vaccine, vaccination with COMIRNATY® may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their second dose of vaccine.
- In clinical studies, adverse reactions in participants 16 years of age and older were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.
- The overall safety profile of COMIRNATY® in participants 5 to 15 years of age was similar to that seen in participants 16 years of age and older.
- The most frequent adverse reactions in children 5 to 11 years of age were injection site pain (>80%), fatigue (>50%), headache (>30%), injection site redness and swelling (>20%), myalgia and chills (>10%).
- The most frequent adverse reactions in clinical trial participants 12 to 15 years of age were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%).
- There is limited experience with use of COMIRNATY® in pregnant women. Administration of COMIRNATY® in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.
- It is unknown whether COMIRNATY® is excreted in human milk.
- Interactions with other medicinal products or concomitant administration of COMIRNATY® with other vaccines has not been studied.
- For complete information on the safety of COMIRNATY® always make reference to the approved Summary of Product Characteristics and Package Leaflet available in all the languages of the European Union on the EMA website.

The black equilateral triangle ▼ denotes that additional monitoring is required to capture any adverse reactions. This will allow quick identification of new safety information. Individuals can help by reporting any side effects they may get. Side effects can be reported to EudraVigilance or directly to BioNTech using email medinfo@biontech.de, telephone +49 6131 9084 0, or via the website www.biontech.de

Safety information

AUTHORIZED USE IN THE U.S.

- COMIRNATY® (COVID-19 Vaccine, mRNA) is an FDA-approved COVID-19 vaccine for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. It is also authorized under EUA to provide a 3-dose primary series to individuals 6 months through 4 years of age, 2-dose primary series to individuals 5 years of age and older, a third primary series dose to individuals 5 years of age and older who have been determined to have certain kinds of immunocompromise, a single booster dose to individuals 12 years of age and older who have completed a primary series with Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY®, a single booster dose to individuals 18 years of age and older who have completed primary vaccination with a different authorized COVID-19 vaccine, a second booster dose to individuals 50 years of age and older who have received a first booster dose of any authorized COVID-19 vaccine; and a second booster dose to individuals 12 years of age and older who have been determined to have certain kinds of immunocompromise and who have received a first booster dose of any authorized COVID-19 vaccine.

The booster schedule is based on the labeling information of the vaccine used for the primary series.

IMPORTANT SAFETY INFORMATION

Individuals should not get the vaccine if they:

- had a severe allergic reaction after a previous dose of this vaccine
- had a severe allergic reaction to any ingredient of this vaccine

Individuals should tell the vaccination provider about all of their medical conditions, including if they:

- have any allergies
- have had myocarditis (inflammation of the heart muscle) or pericarditis (inflammation of the lining outside the heart)
- have a fever
- have a bleeding disorder or are on a blood thinner
- are immunocompromised or are on a medicine that affects the immune system
- are pregnant, plan to become pregnant, or are breastfeeding
- have received another COVID-19 vaccine
- have ever fainted in association with an injection

The vaccine may not protect everyone. Side effects reported with the vaccine include:

- There is a remote chance that the vaccine could cause a severe allergic reaction
  - A severe allergic reaction would usually occur within a few minutes to 1 hour after getting a dose of the vaccine. For this reason, vaccination providers may ask individuals to stay at the place where they received the vaccine for monitoring after vaccination
  - Signs of a severe allergic reaction can include difficulty breathing, swelling of the face and throat, a fast heartbeat, a bad rash all over the body, dizziness, and weakness
  - If an individual experiences a severe allergic reaction, they should call 9-1-1 or go to the nearest hospital
- Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have occurred in some people who have received the vaccine, more commonly in males under 40 years of age than among females and older males. In most of these people, symptoms began within a few days following receipt of the second dose of the vaccine. The chance of having this occur is very low. Individuals should seek medical attention right away if they have any of the following symptoms after receiving the vaccine:
  - chest pain
  - shortness of breath
  - feelings of having a fast-beating, fluttering, or pounding heart
- Additional side effects that have been reported with the vaccine include:
  - severe allergic reactions; non-severe allergic reactions such as injection site pain; tiredness; headache; muscle pain; chills; joint pain; fever; injection site swelling; injection site redness; nausea; feeling unwell; swollen lymph nodes (lymphadenopathy); decreased appetite; diarrhea; vomiting; arm pain; and fainting in association with injection of the vaccine
- These may not be all the possible side effects of the vaccine. Serious and unexpected side effects may occur. The possible side effects of the vaccine are still being studied in clinical trials. Call the vaccination provider or healthcare provider about bothersome side effects or side effects that do not go away

Data on administration of this vaccine at the same time as other vaccines have not yet been submitted to FDA. Individuals considering receiving this vaccine with other vaccines should discuss their options with their healthcare provider. Patients should always ask their healthcare providers for medical advice about adverse events. Individuals are encouraged to report negative side effects of vaccines to the US Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). Visit https://www.vaers.hhs.gov or call 1-800- 822-7967. In addition, side effects can be reported to Pfizer Inc. at www.pfizersafetyreporting.
com or by calling 1-800-438-1985.

Agenda

Ugur’s welcome

The BioNTech approach to innovation
- Target discovery and characterization
- Multi-platform innovation engine
- Digital & AI/ML
- Manufacturing and automation

New frontiers in infectious diseases

Q&A

Coffee break

An introduction to the oncology pipeline

mRNA cancer vaccines

Protein therapeutics

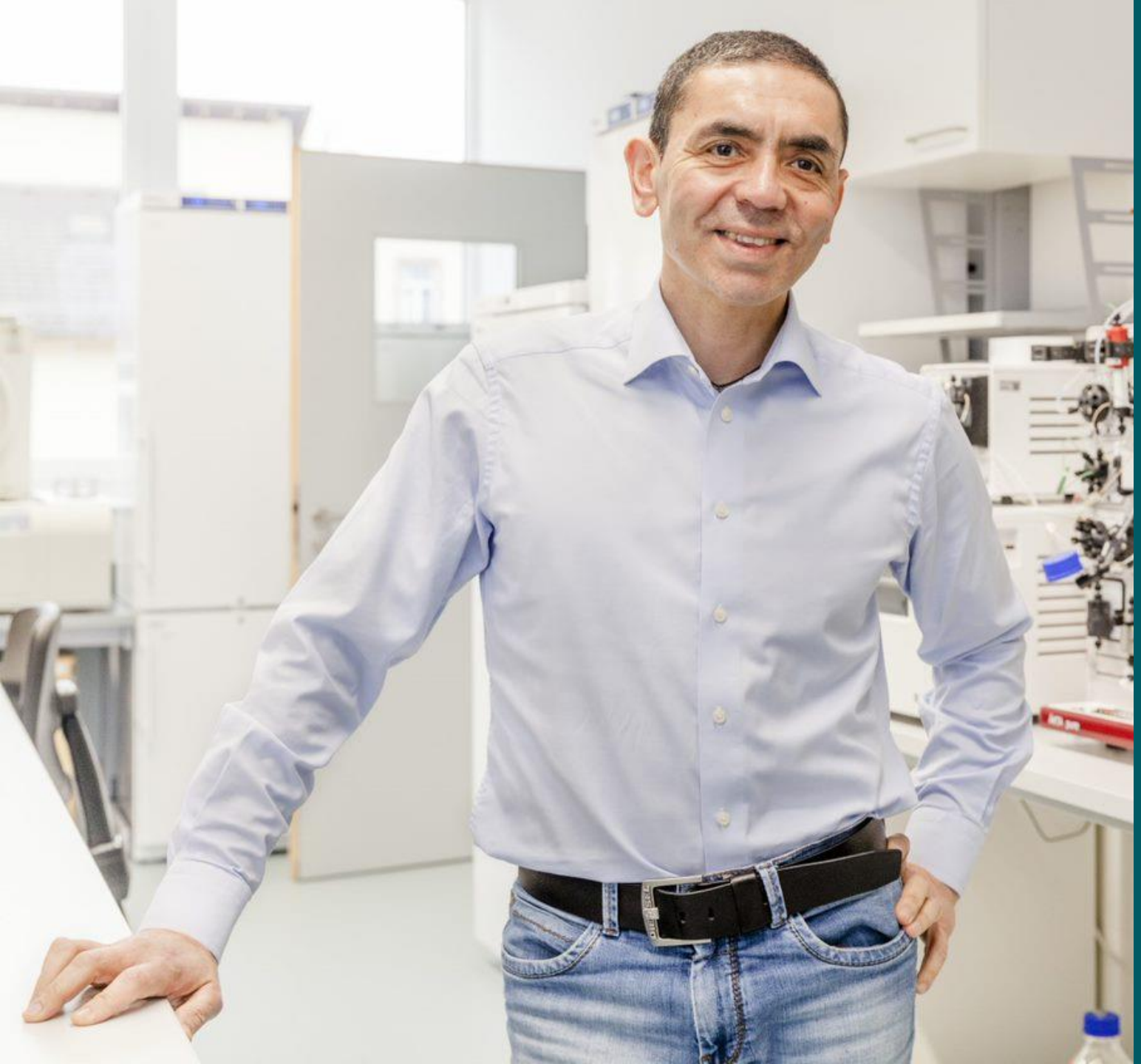
Extending cell therapy to solid tumors

RiboCytokines

Closing remarks

Q&A

Meeting close



Ugur’s welcome

The human immune system plays a central role in >80% of human diseases

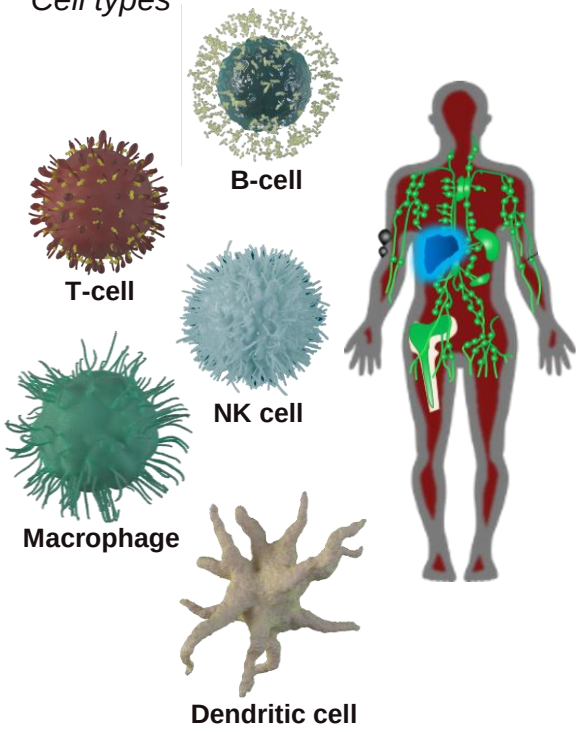
Hundreds of billion cells

Impacts the function of every organ system in the body

Ability to kill targeted cells or pathogens with high precision

Potential for long-term memory

Cell types



Function

Cell migration

Removal of diseased cells

Healing

Cell-cell communication

Diseases

Cancer

Infectious diseases

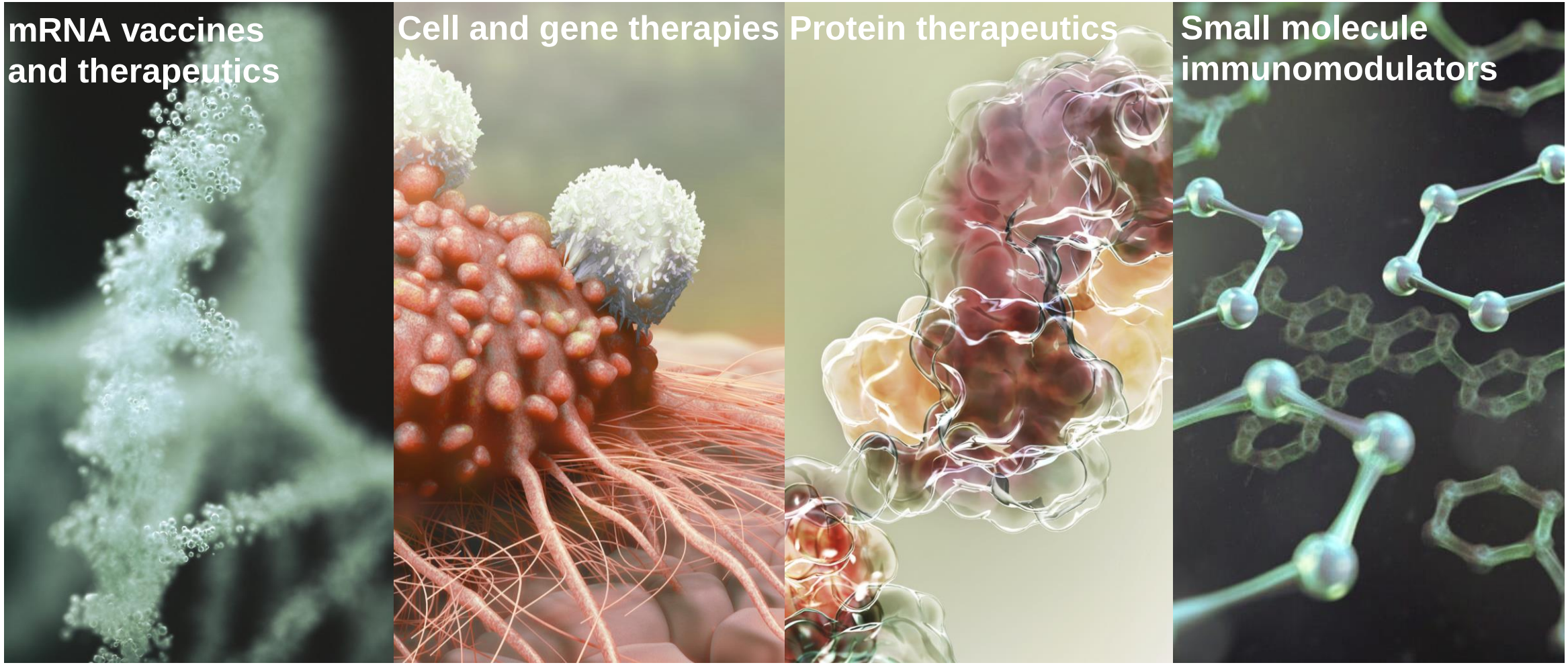
Autoimmune diseases

Cardiovascular disease

Neurodegenerative diseases

Inflammatory diseases

The tools we have developed for cancer will enable us to treat many diseases



Taking mRNA from vision to reality

First ever approved mRNA therapy[1]

Fastest pharma product development and launch

~ 3.4 bn doses administered[2]

~ 2 bn to low- and middle-income countries[3]

> 1 bn individuals vaccinated[2]

> 175 countries / regions reached

Millions of cases of severe illness or death likely averted[4]

Trillions of dollars of global economic impact[5]

[1] Authorized or approved for emergency use or temporary use or granted marketing authorization in over 100 countries and regions worldwide, April 2022;
[2] As of end April 2022; [3] By end of 2022; [4] Eric C. Schneider et al., The U.S. COVID-19 Vaccination Program at One Year: How Many Deaths and Hospitalizations Were Averted? (Commonwealth Fund, December 2021). European Centre for Disease Prevention and Control; 5. https://www.statista.com/topics/6139/covid-19-impact-on-the-global-economy/

Strong momentum built on two decades of innovation

Mid 1990s

Start of mRNA vaccine research by founders

2005

First mRNA patents

Published 2006 in *Blood*

2008

BioNTech founding

By Ugur Sahin, Özlem Türeci, and Christoph Huber in Mainz, Germany

2013

Off-the-shelf mRNA vaccine first-in-human trial

Published 2017 in *Nature*

2014

Individualized mRNA cancer vaccine first-in-human trial

2015

Nanoparticle mRNA vaccine first-in-human trial

Published 2016 in *Nature*

2016

Pre-clinical proof-of-concept of RNA-lipoplex treatment

2017

Individualized mRNA vaccine reduces metastatic relapse rate in melanoma patients published in Nature[1]

IVAC trial with extension of relapse free survival

2019

NASDAQ Initial Public Offering

Bispecifics first-in-human trial[3]

7 clinical programs

2020

***Project Lightspeed* initiated**

Small molecule immuno-modulator first-in-human trial

CARVac pre-clinical proof-of-concept published in *Science*

2021

COVID-19 vaccine full FDA approval[2]

RiboCytokine first-in-human trial

MS vaccine pre-clinical proof-of-concept published in *Science*

RiboMab first-in-human trial

Cell therapy first-in-human trial

2022

Improved COVID-19 vaccine formulation launch

Variant-adapted COVID-19 vaccine submission

PRIME designation for BNT211

Adjuvant pancreatic data presented at ASCO annual meeting

17 clinical programs

MS, multiple sclerosis.

[1] iNeST collaboration with Genentech; [2] Global co-development co-commercial agreement with Pfizer; [3] GEN1046 collaboration with Genmab.

BioNTech today

Discovery powerhouse

>1,000 research and development professionals

IP portfolio with >200 patent families

>300 publications including >100 in leading peer reviewed journals

Global organization on 3 continents

>3,300 employees

>60 nationalities

Presence in Europe, United States and Asia

Diversified pipeline across 4 drug classes

21 clinical trials

17 product candidates in clinical development

Diversified GMP manufacturing infrastructure

2 state-of-the-art cGMP cell therapy sites

Global commercial scale mRNA production

Initial commercial team in Germany

World-class partners

Pfizer, Genentech, Genmab, Regeneron, Fosun, Sanofi, Crescendo, Medigene, InstaDeep, TRON, BMGF, UPenn and multiple not-for-profit organizations

Strong shareholder base, fortress balance sheet

>€18bn in cash equivalents and trade receivables as end of Q1 22

Advancing toward our long-term vision

Driving transformation today

1 marketed vaccine
Market leader in COVID-19 vaccines

16 programs in 21 clinical trials

5 randomized Phase 2 trials

Oncology

1 Phase 1 program

10+ preclinical programs

Infectious diseases

Mid-term goals

Next-gen or variant adapted COVID-19 vaccines

Multiple product launches in next 3–5 years

5–10 IND submissions per year

Long-term vision

Maintain and deepen COVID-19 vaccine leadership

Approved products across various disease areas

By 2030, we aim to be a multi-product global biotechnology leader, aspiring to address the world's most pressing health challenges with pioneering, disruptive technologies delivered at scale

The BioNTech approach to innovation

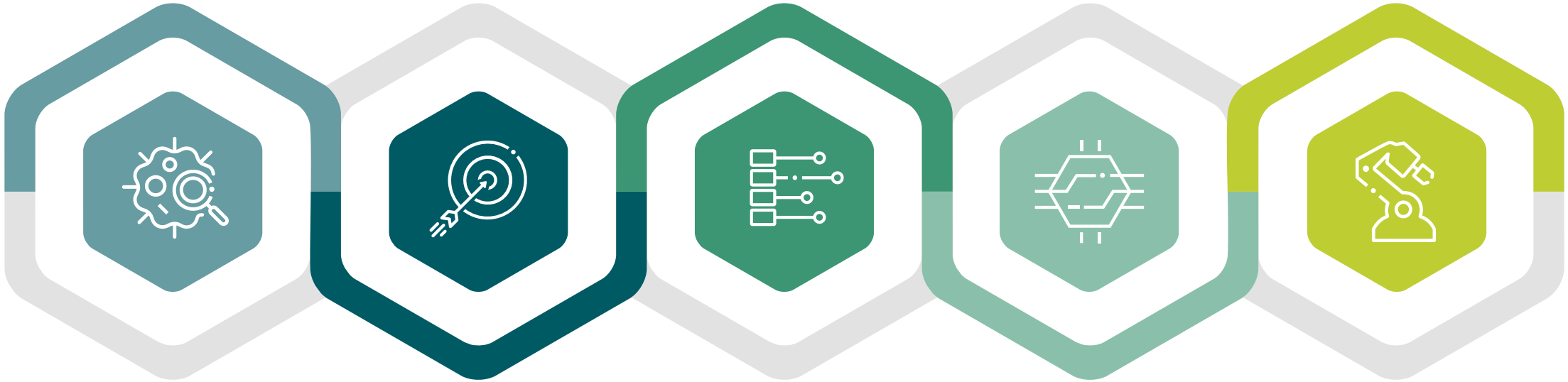
{Photo: V2osk, unsplash

Focused on five innovation pillars

Deep understanding of the immune system

Multi-platform innovation engine

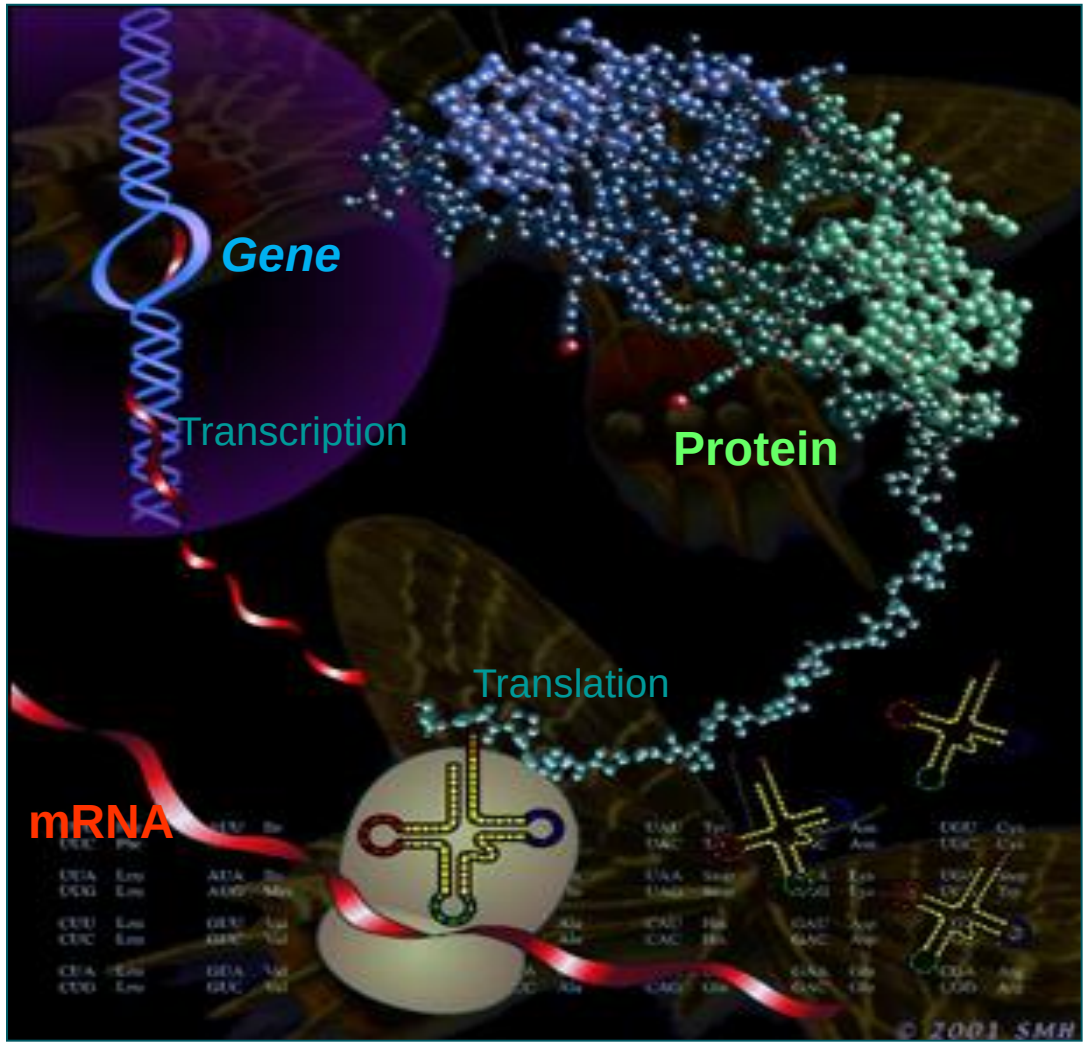
Manufacturing and automation



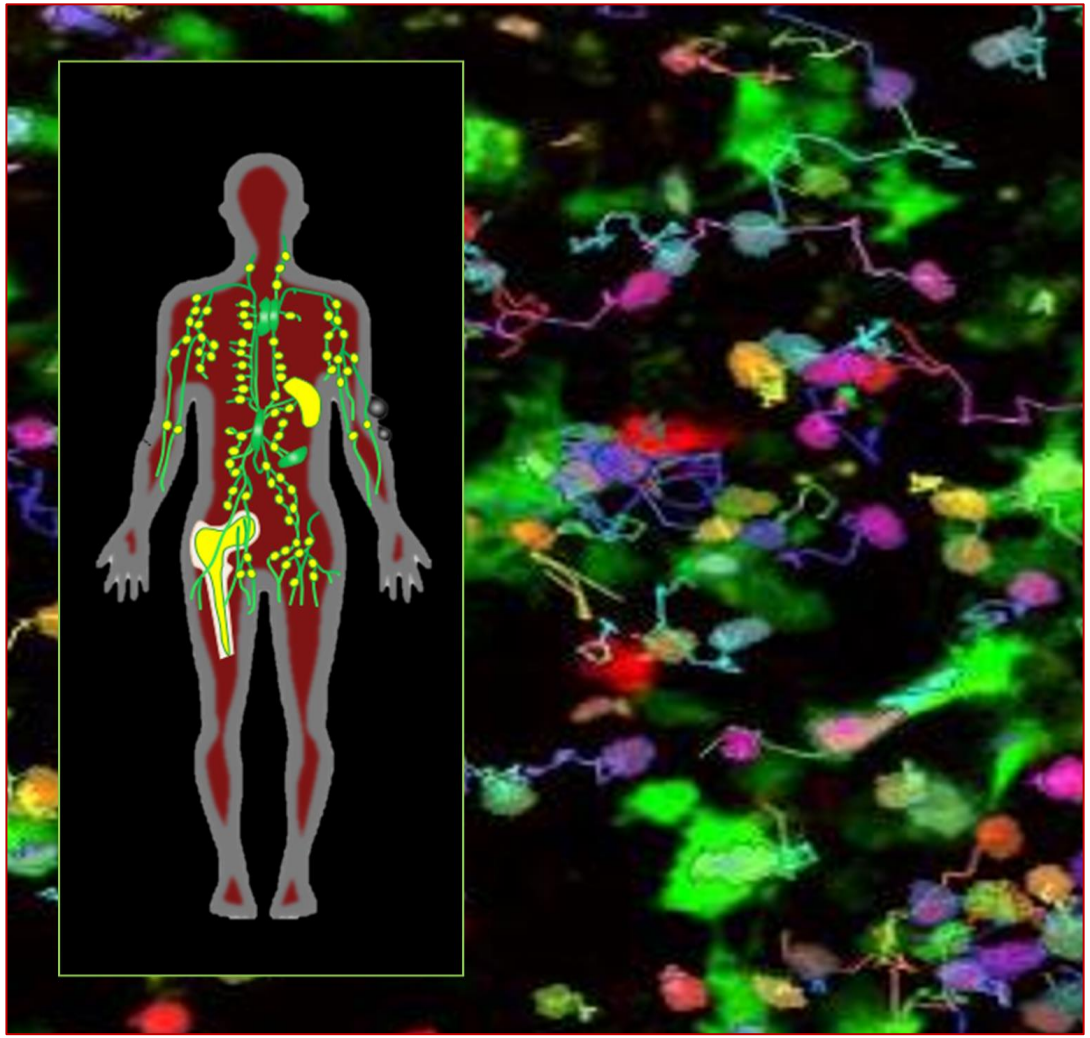
Target discovery and characterization

Digital & AI/ML

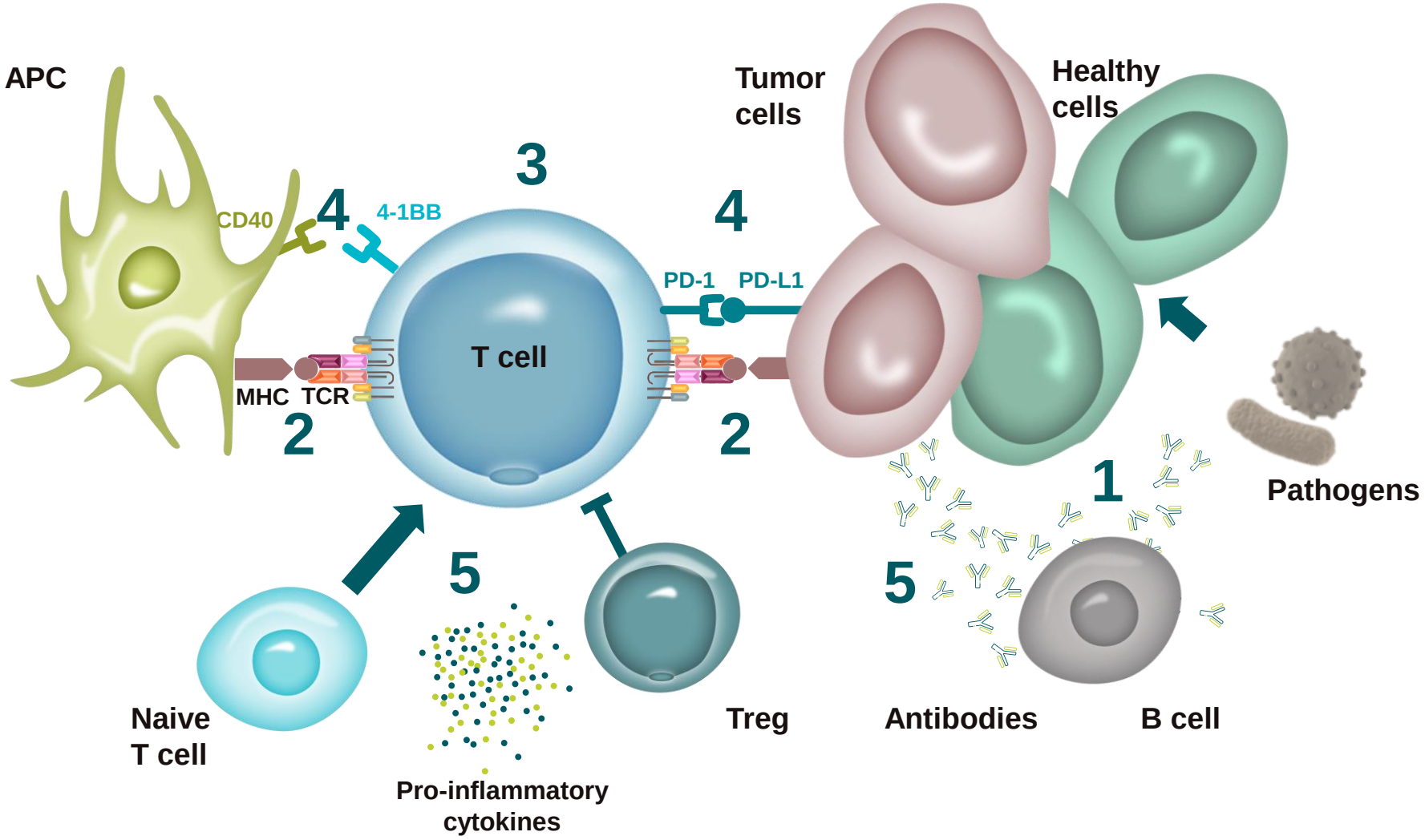
mRNA – involved essentially in all biological processes



The immune system – body-wide control of physiological and pathological mechanisms



Understanding and exploiting immunological mechanisms



1 mRNA-encoded infectious disease vaccines

2 mRNA-encoded cancer vaccines

Shared antigens
Individualized antigens

3 CAR-, TCR-, and non-engineered cell therapies

Shared antigens
Individualized antigens

4 Next-generation immunomodulators

Dual agonist
CPI + agonist

5 mRNA-encoded effector molecules

Antibodies
Cytokines

Focused on five innovation pillars

Deep understanding of the immune system

Multi-platform innovation engine

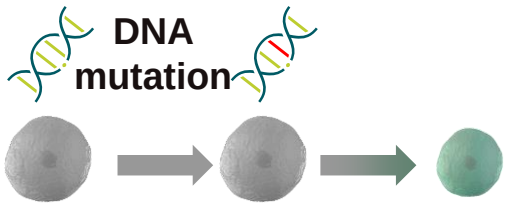
Manufacturing and automation

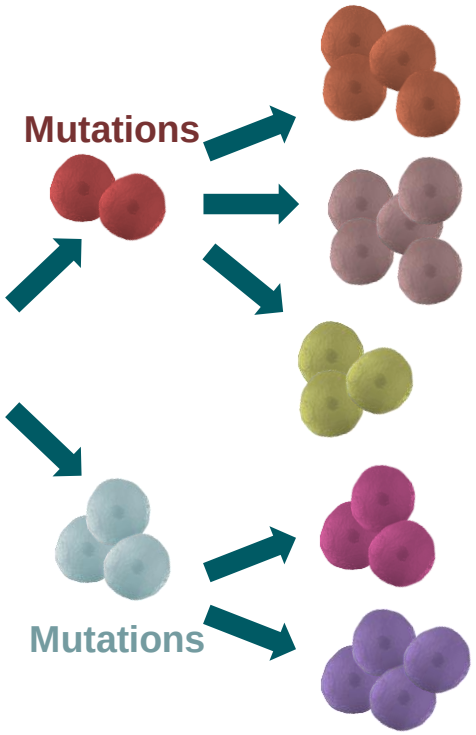
Target discovery and characterization

Digital & AI/ML

Mutation-based cancer heterogeneity: The root cause of cancer therapy failure

Individual patients





5–20 years

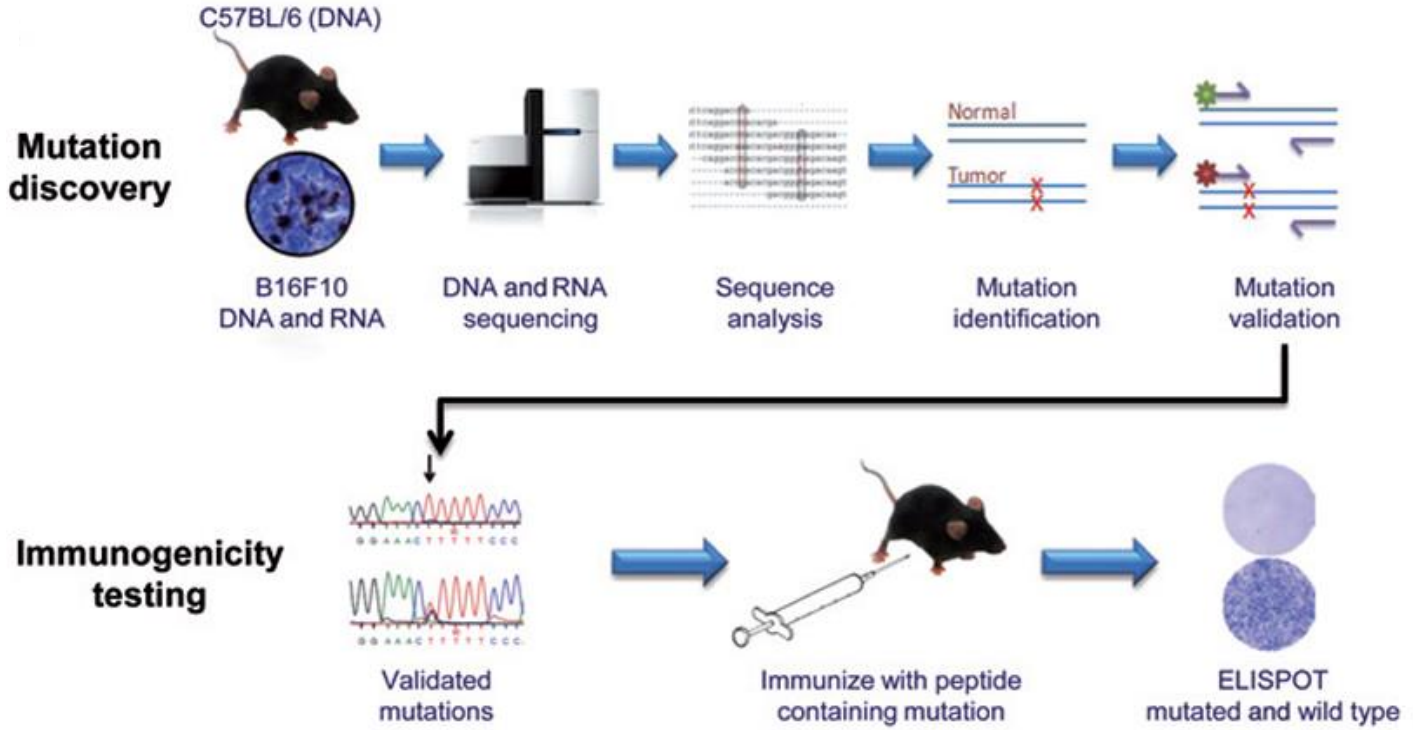
Up to 10,000 mutations

Mutations from cancer tissues are druggable and 15–20% of mutations are immunogenic when exploited as vaccine targets

Exploiting the Mutanome for Tumor Vaccination

Cancer Research

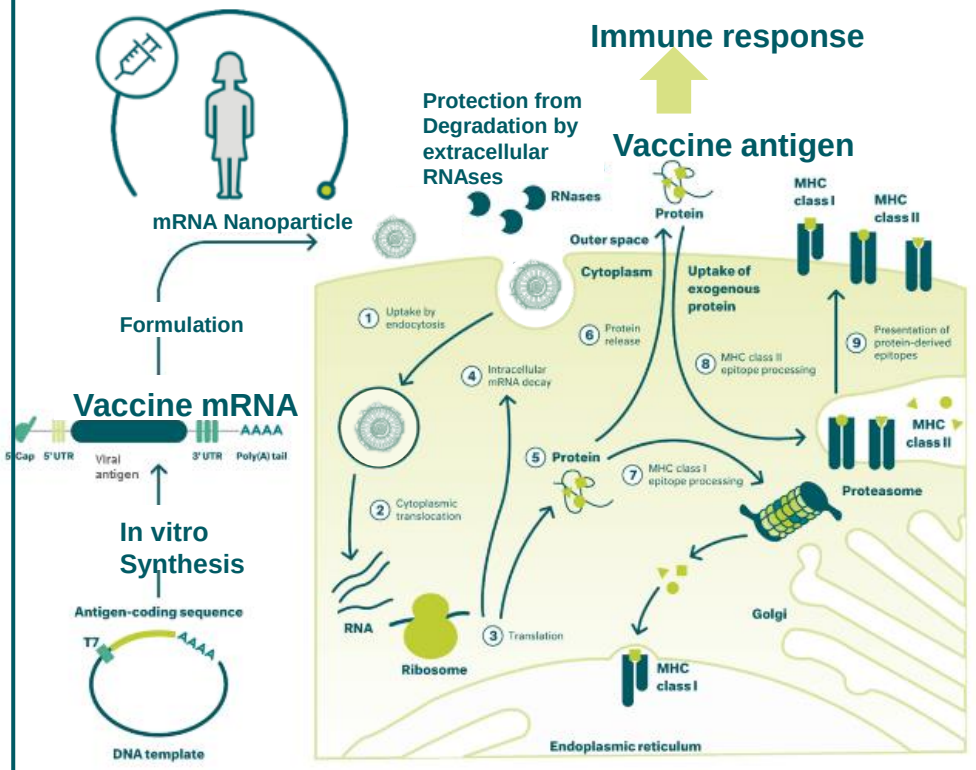
John C. Castle[1], Sebastian Kreiter[1], Jan Diekmann[1], Martin Löwer[1], Niels van de Roemer[1,2], Jos de Graaf[1], Abderraouf Selmi[1], Mustafa Diken[1], Sebastian Boegel[1,2], Claudia Paret[1], Michael Koslowski[1], Andreas N. Kuhn[1,3], Cedrik M. Britten[2,3], Christoph Huber[1,3], Özlem Türeci[4], and Ugur Sahin[1,2,3]



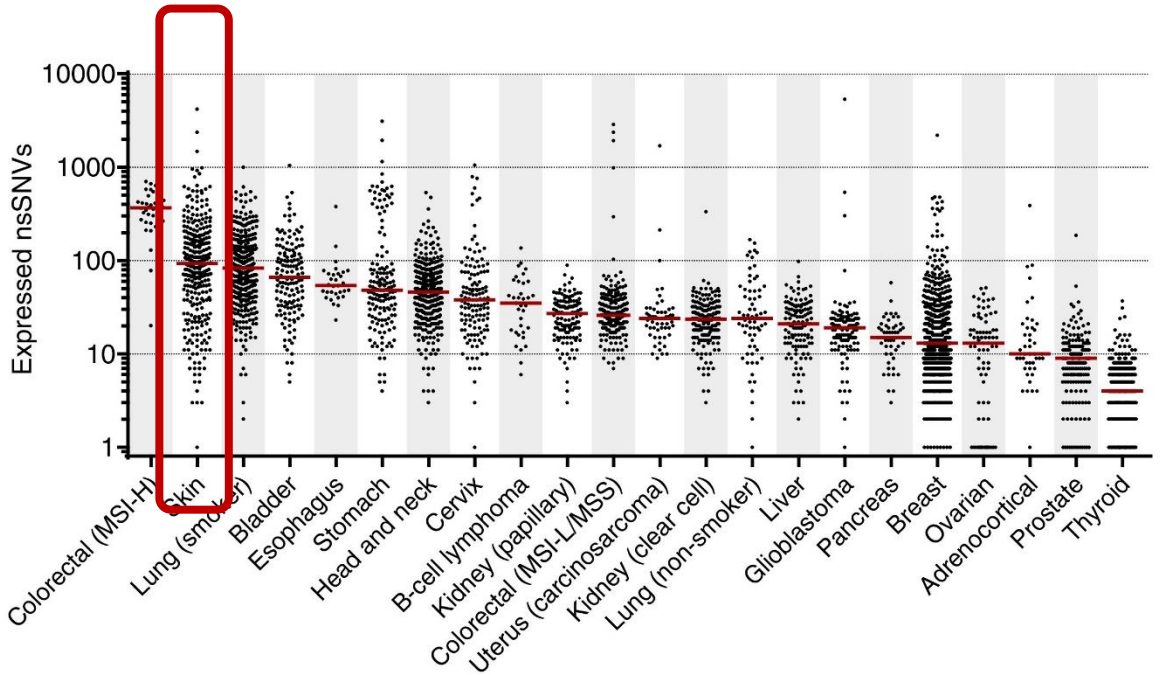
Castle JC, *et al. Cancer Res* 2012; 72:1081–1091.

Exploiting the mutanome for personalized mRNA vaccination

mRNA delivers genetic information to APCs

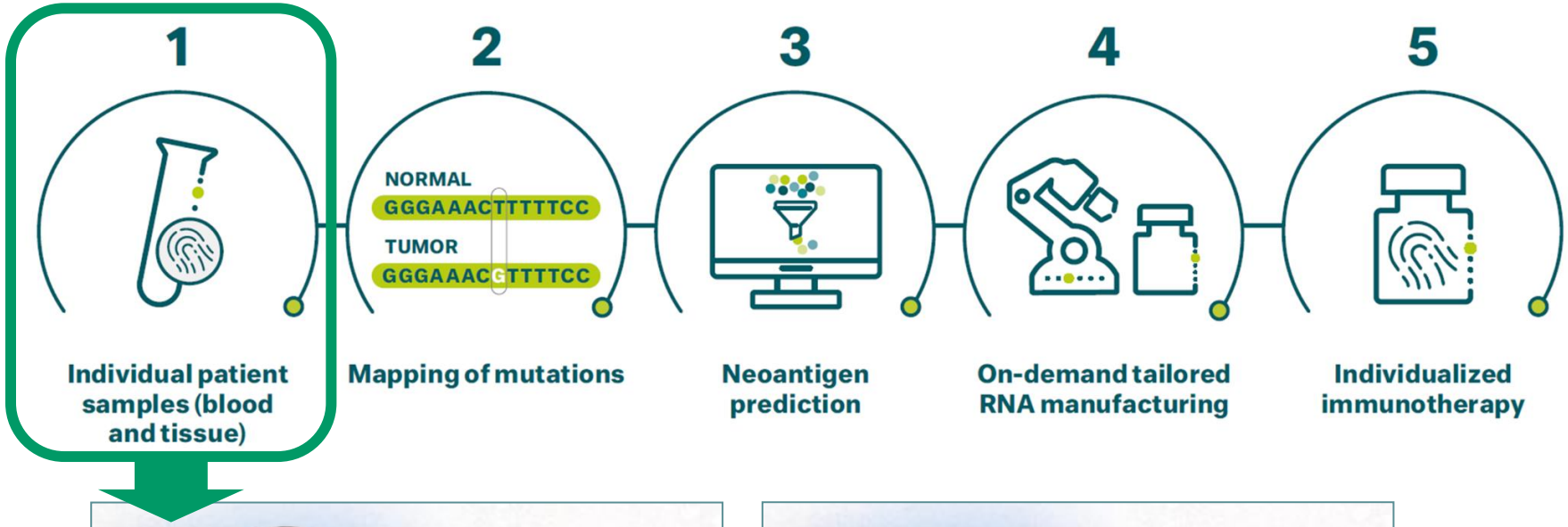


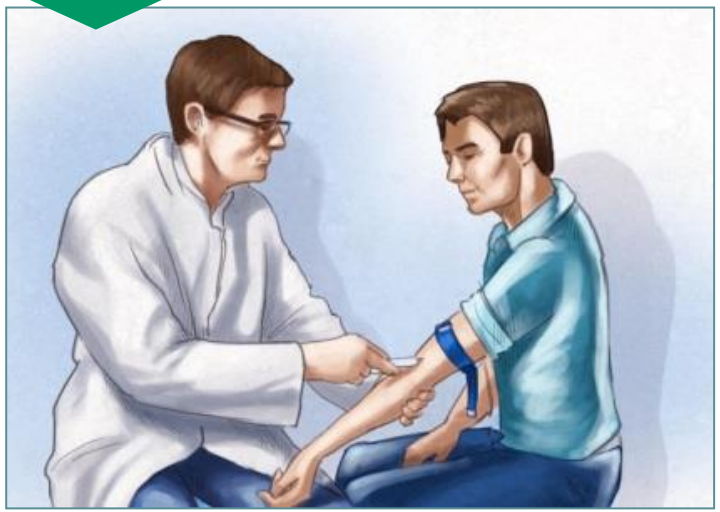
Mutations are prevalent across different cancer indications

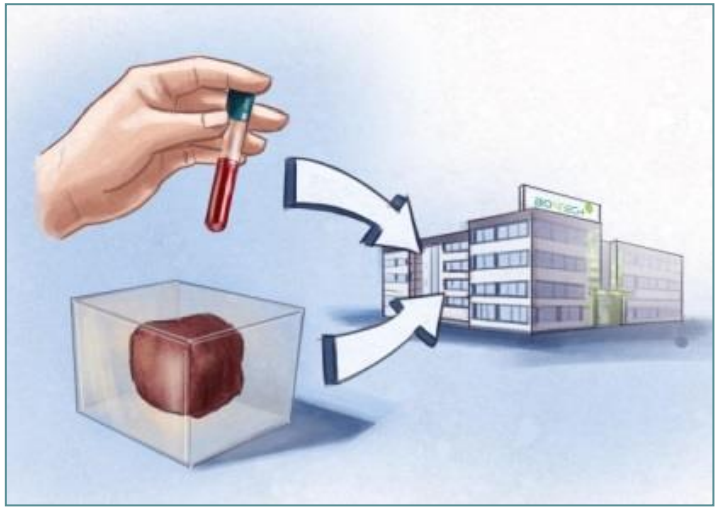


Vormehr *et al.*, Curr Opin Immunol 39:14-22 (2016).

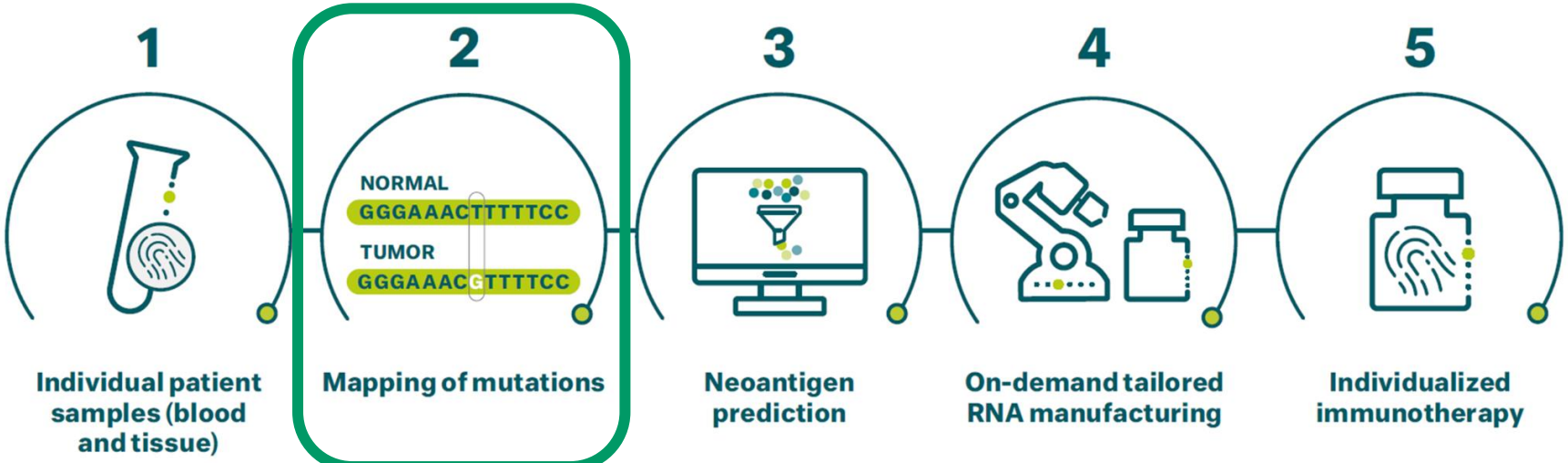
Acquisition of the patient´s tissue and blood samples

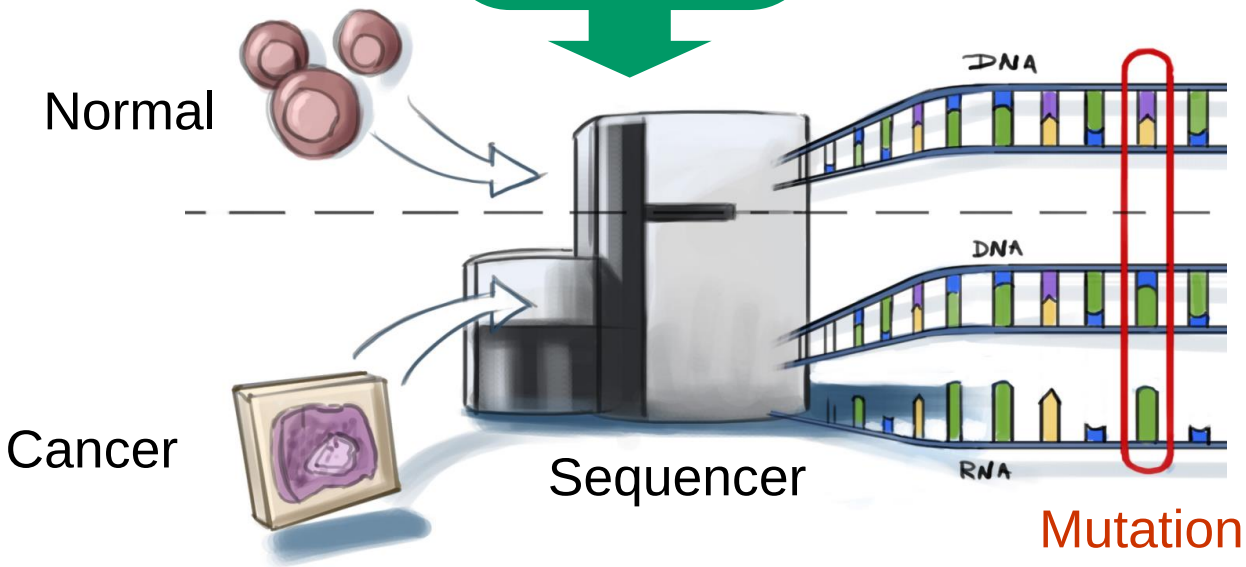






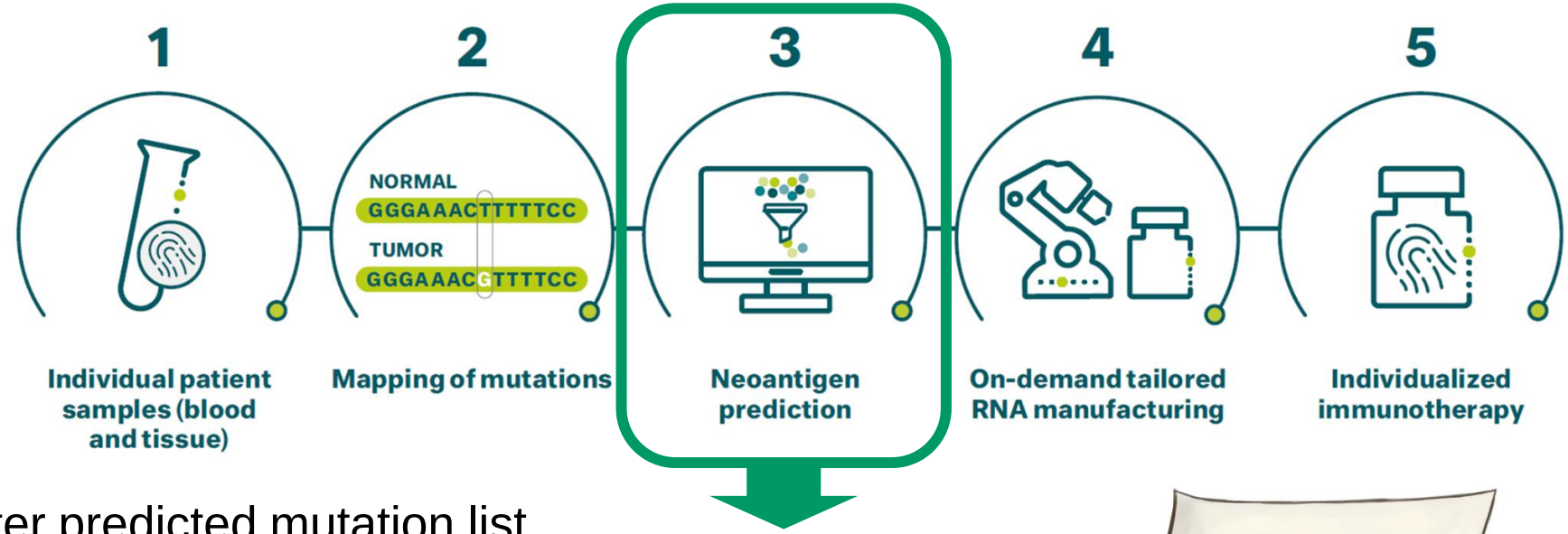
Identification of the patient´s cancer mutations





Cancer mutanome

Computerized prediction of mutations



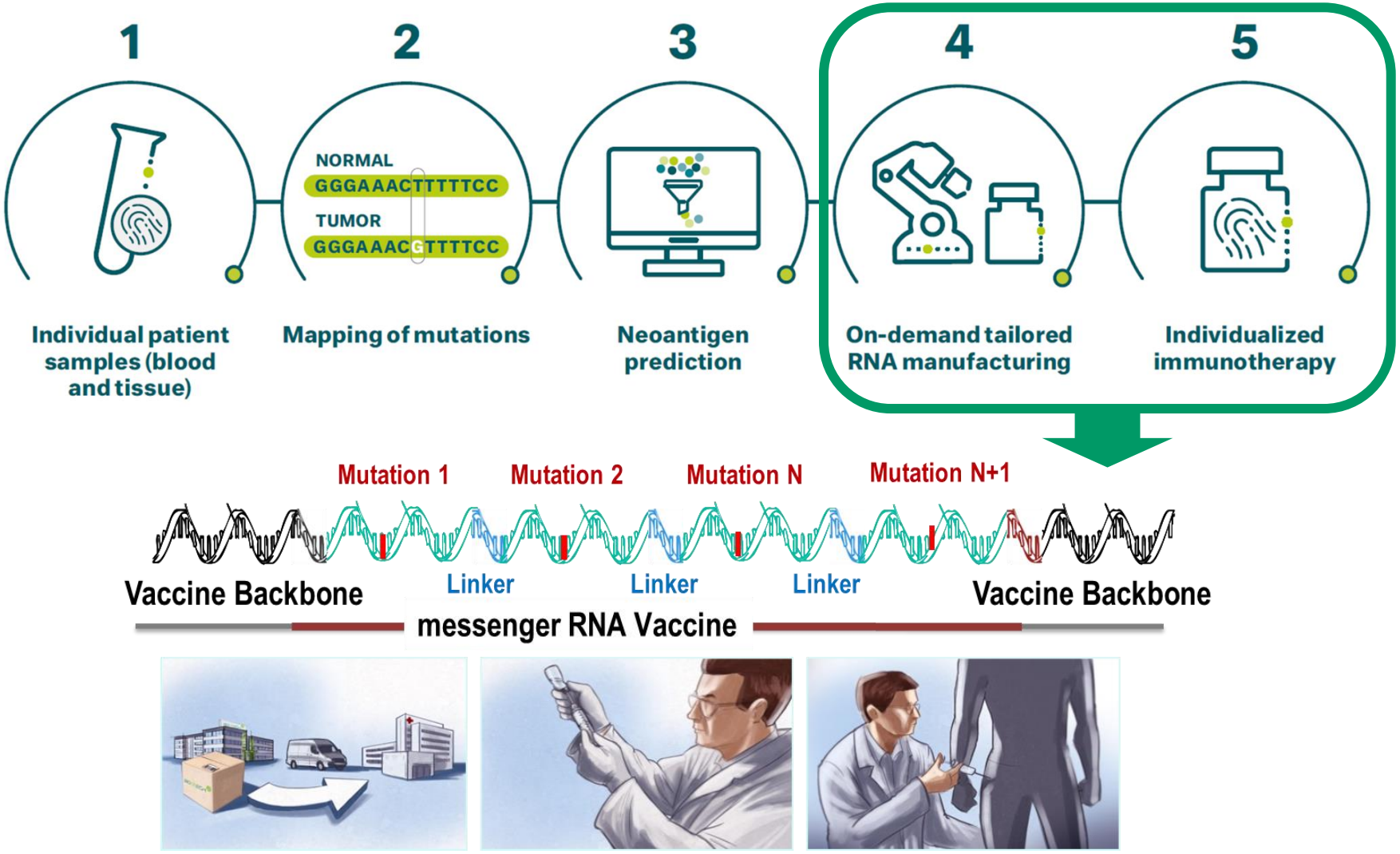
Computer predicted mutation list

Key	Gene	Mut	Chrom	Score
#001	PIK3CA	R115L	3	0,2
#002	IMPA2	R202P	18	0,3
#003	KRAS	G12D	12	0,45
#... …	…	…	…	
#267	KIF21B	P188S 1	3,45	

Verification by Expert Review

Kreiter et. al. Nature 2015

Individualized vaccine manufacturing



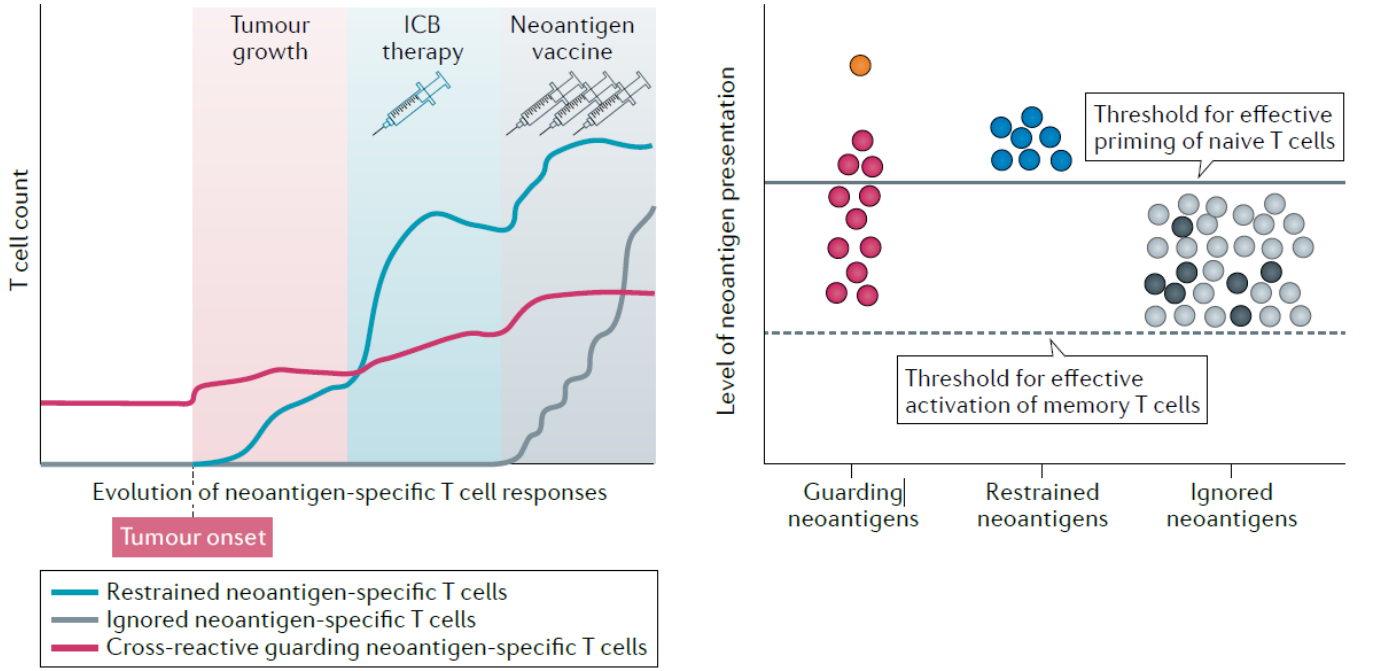
Kreiter, Vormehr et al, Nature 2015; Kranz, Diken et. al. Nature 2016.

How do different types of neoantigens induce T-cell responses and kill tumors?

NATURE REVIEWS | DRUG DISCOVERY

Identification of neoantigens for individualized therapeutic cancer vaccines

Franziska Lang[1], Barbara Schrörs[1], Martin Löwer[1], Özlem Türeci[2] and Ugur Sahin[2,3]

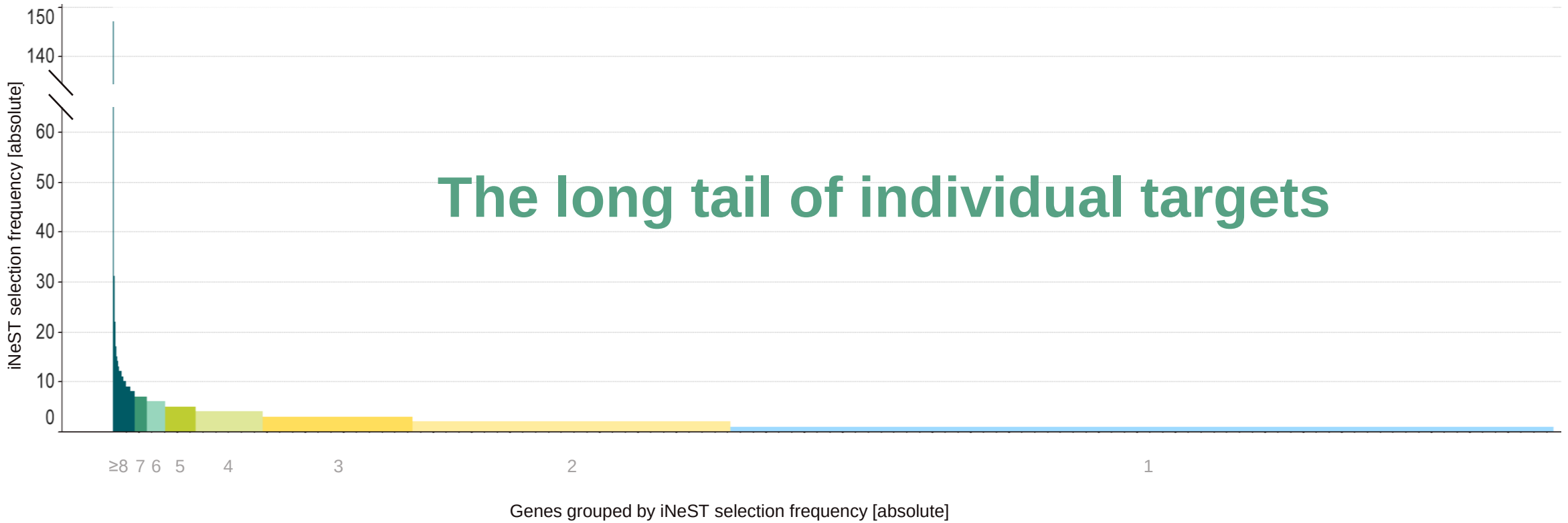


Characteristic feature	Estimated frequency
Guarding neoantigens	
Supreme neoantigens with strong antigenicity that drive early priming and rapid expansion of neoantigen-specific cytotoxic T cells	Extremely rare
Neoantigen cross-recognized by preformed memory T cells induced by heterologous immunity	<2% of all mutations
Restrained neoantigens	
Neoantigens that are immunogenic in the immunotherapy-naive host and induce PD1$^+$ memory T cells that proliferate and expand under ICB	<2% of all mutations
Ignored neoantigens	
Neoantigens that do not induce a relevant immune response in the tumor-bearing host but are able to drive tumor immunity once memory effector T cells are induced by vaccination	15–25% of all mutations

Lang F, *et al. Nature Rev Drug Discov* 2022; 21:261–282.

Absolute frequency of genes selected for iNeST[1] vaccination across BioNTech trials[2]

1,400+	28	~ 1,700	>12,500	~ 420+
patients screened	different cancer indications	tumor samples processed	neoantigens selected	patients treated



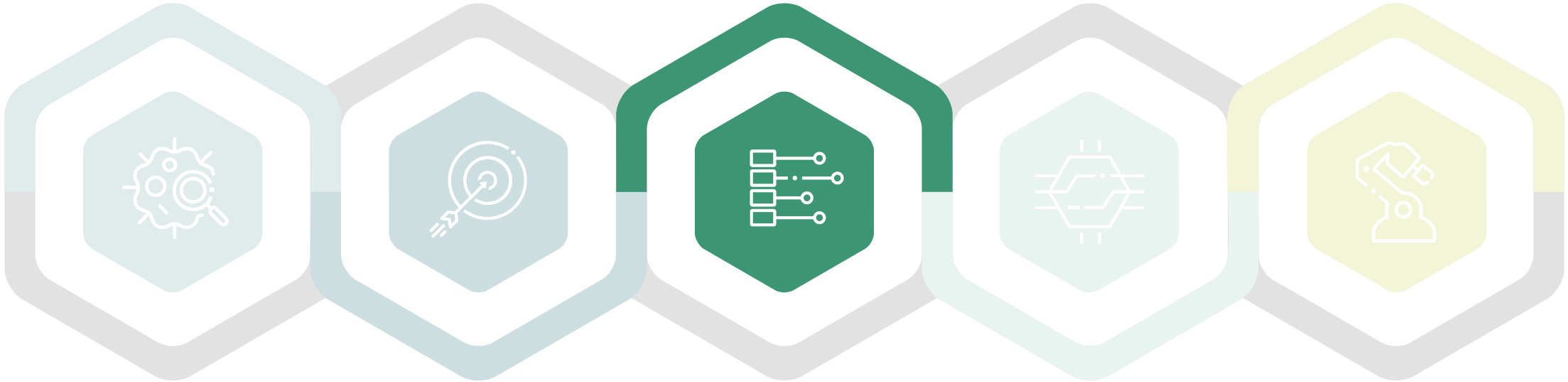
[1] Collaboration with Genentech
[2] GO39733, GO40558, BNT122-01, ML41081.

Focused on five innovation pillars

Deep understanding of the immune system

Multi-platform innovation engine

Manufacturing and automation



Target discovery and characterization

Digital & AI/ML

Multi-platform strategy
Technology-agnostic innovation engine

mRNA vaccines
- Individualized cancer vaccines (iNeST)
- Off-the-shelf cancer vaccines (FixVac)
- Antigen-specific tolerance vaccines
- Prophylactic infectious disease vaccines

Next-generation immunomodulators
- Targeting immune checkpoint molecules
- Engineered bispecific antibodies
- Engineered mechanisms of action

BIONTECH

- CAR T cells
- Individualized TCR therapies
- Polyspecific T-cell therapies
- *In vivo* engineered cell therapies

Cell & gene therapies

- Against highly selective cancer cell surface antigens for high precision

Targeted antibodies

- Selective TLR 7 antagonism

Small molecule immunomodulators

- mRNA-encoded cytokines (RiboCytokines)
- mRNA-encoded antibodies (RiboMabs)
- mRNA-encoded lysins (RiboLysins)

Ribologicals

Multiple product classes with unique combination potential

mRNA technology

Broad mRNA toolkit built out of deep immunological expertise

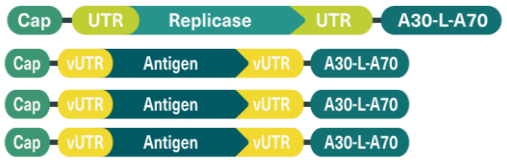
Multiple mRNA formats

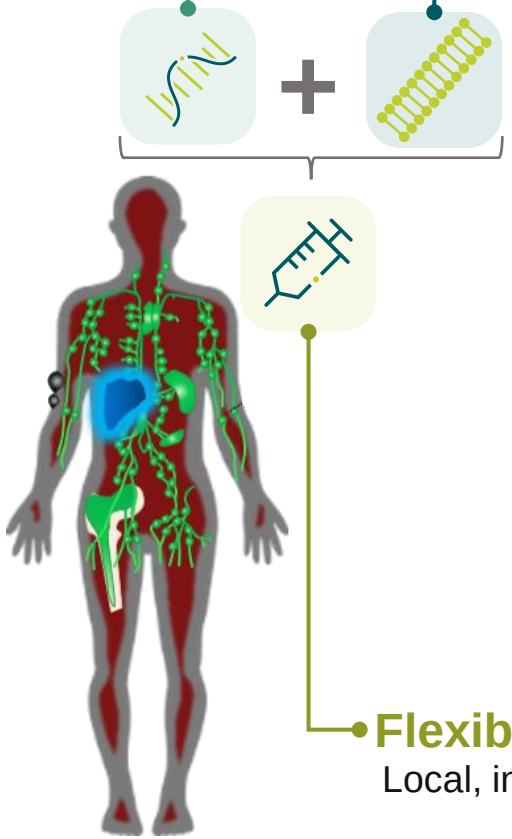
Backbone-optimized uridine mRNA (uRNA)

Backbone-optimized nucleoside-modified mRNA (modRNA)

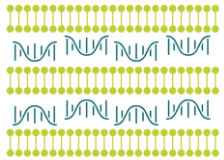
Self-amplifying mRNA (saRNA)

Trans-amplifying mRNA (taRNA)





Delivery formulations



Lipoplex (LPX)

Lipid nanoparticles (LNP)

Polyplexes

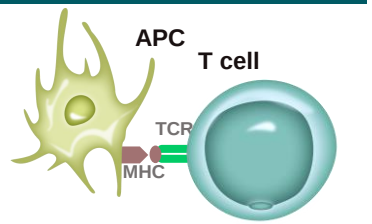
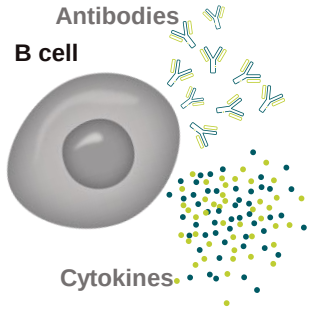
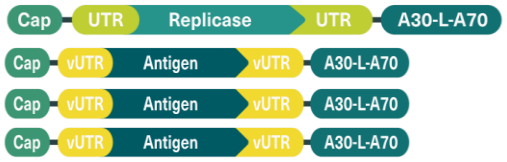
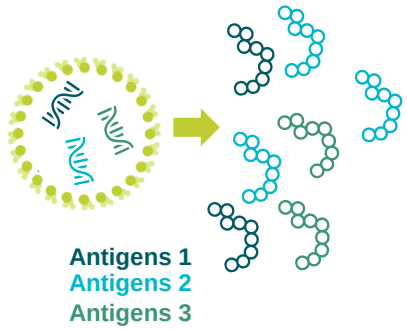
Flexible delivery routes

Local, intratumoral, tissue-specific, or systemic

More than a decade of mRNA research has led to potency increase of >10,000× and improved persistence

mRNA technology

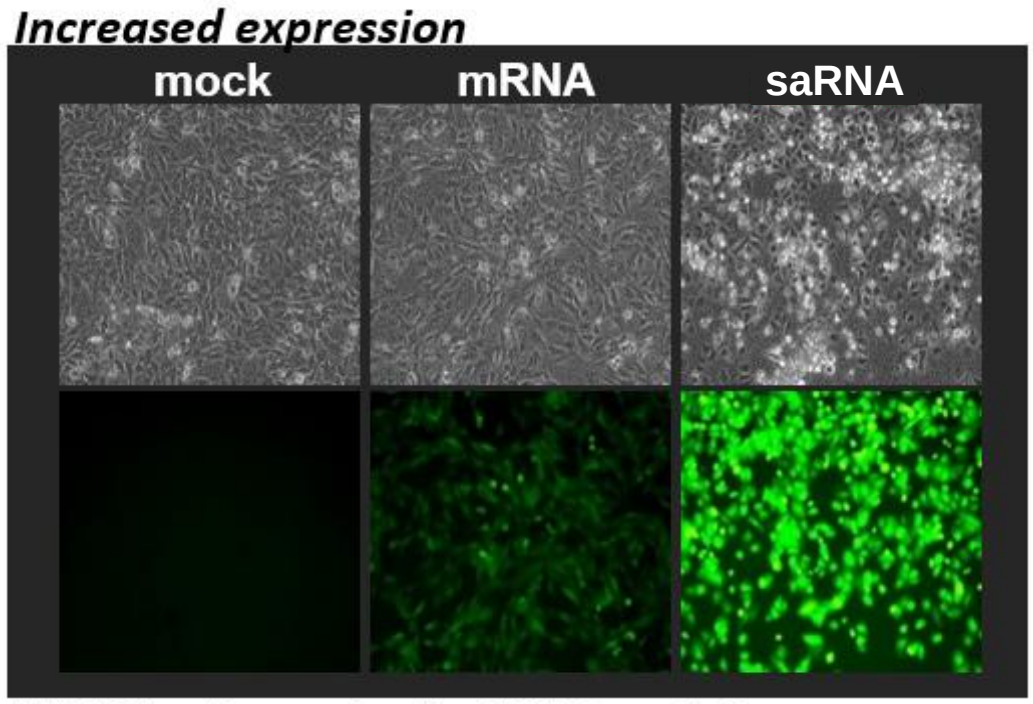
Each mRNA format is optimized for specific applications

Multiple mRNA formats	Targeted application	Platforms
Backbone-optimized uridine mRNA (uRNA) 	Potent T cell response Repeat administration 	Shared antigen mRNA vaccines Individualized neoantigen mRNA vaccines
Backbone-optimized nucleoside-modified mRNA (modRNA) 	Potent B cell response Non-immunogenic vector 	Infectious disease vaccines mRNA-encoded antibodies mRNA-encoded cytokines
Self-amplifying mRNA (saRNA)  Trans-amplifying mRNA (taRNA) 	Sustained expression High potency at low dose Sustained expression High potency at low dose Ability to co-develop multiple antigens 	Infectious disease vaccines

mRNA technology I saRNA could induce higher and extended *in vitro* and *in vivo* expression compared to mRNA

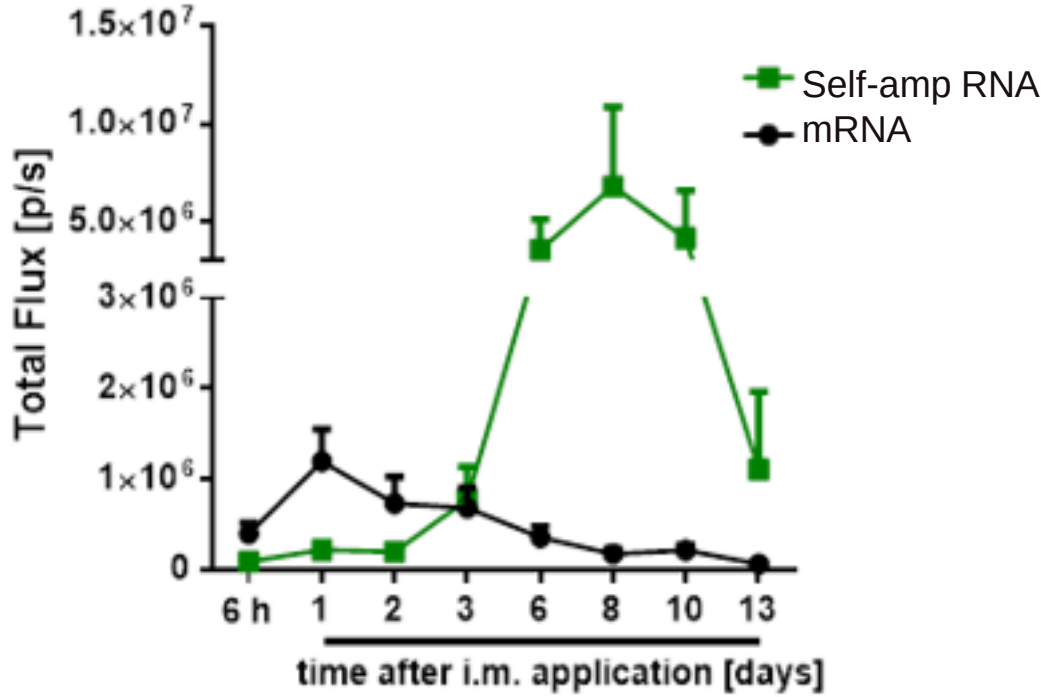
Backbone-optimized nucleoside-modified RNA (modRNA)

in vitro expression



(C2C12 cells, equimolar RNA transfer)

in vivo expression

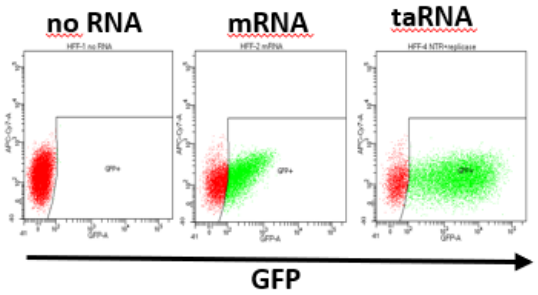


saRNA showed potential as a vaccine modality with much lower doses

Comparable immunogenicity with approximately 100-fold lower doses of saRNA compared to mRNA

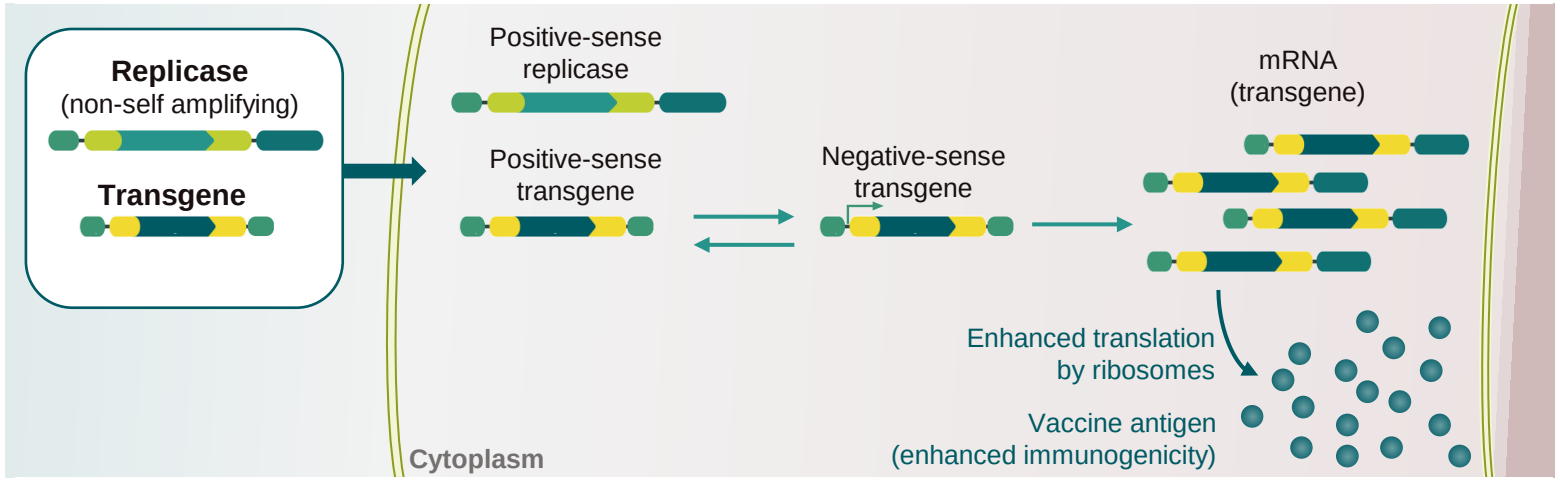
mRNA technology | Trans-amplifying RNA could potentially be a vaccine strategy to induce potent immunity

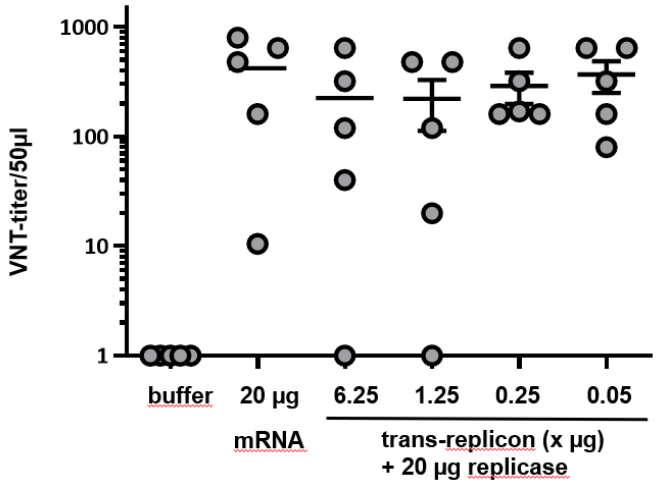
Trans-amplifying mRNA structure



Immunogenicity model

Trans-amplifying mRNA mechanism





Comparable immunogenicity with approximately 400-fold lower doses of taRNA compared to mRNA

mRNA technology

We are exploring taRNA and saRNA in multiple infectious disease programs

Disease type	mRNA modality			
SARS-COV-2	uRNA	modRNA	saRNA	
Influenza A virus	uRNA	modRNA	saRNA	taRNA
HIV			saRNA	
Ebola virus			saRNA	taRNA
Lassa virus			saRNA	taRNA
Marburg virus			saRNA	
CCHFV			saRNA	taRNA
Nipahvirus			saRNA	taRNA
MERS-CoV				taRNA

CCHFV, Crimean-Congo hemorrhagic fever orthonairovirus; MERS-CoV, Middle East Respiratory syndrome-related coronavirus; modRNA backbone-optimized nucleoside-modified RNA; saRNA, self-amplifying mRNA; taRNA, trans-amplifying mRNA; uRNA; backbone optimized uridine RNA.
Internal data.

Delivery formulations

A diversified and rationally designed delivery platform for mRNA medicine

Lipoplex (LPX): mRNA embedded between lipid bilayers to form a sandwich like complex

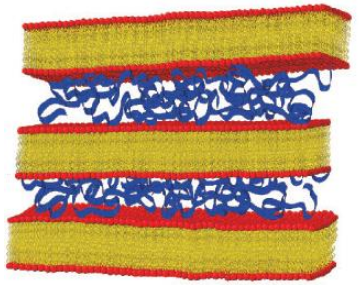
Target:

- Lymphoid-resident dendritic cells in lymphoid compartments body-wide (spleen, lymph nodes, bone marrow)

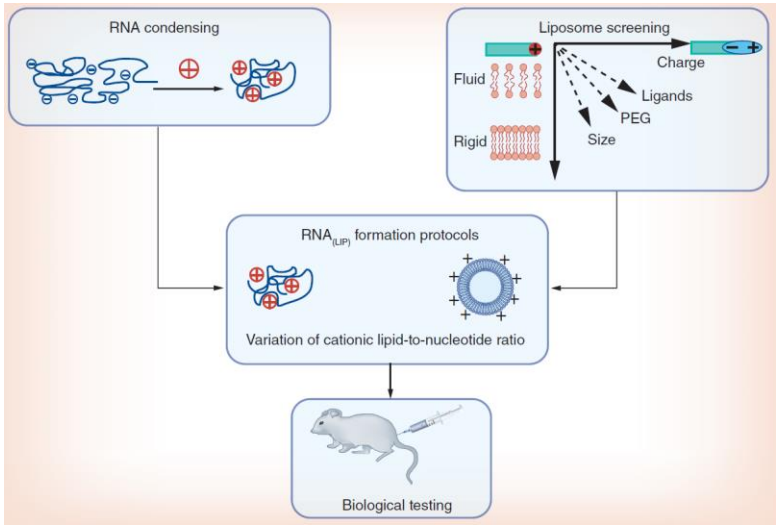
Therapeutic applications:

- Therapeutic cancer vaccines: FixVac, iNeST

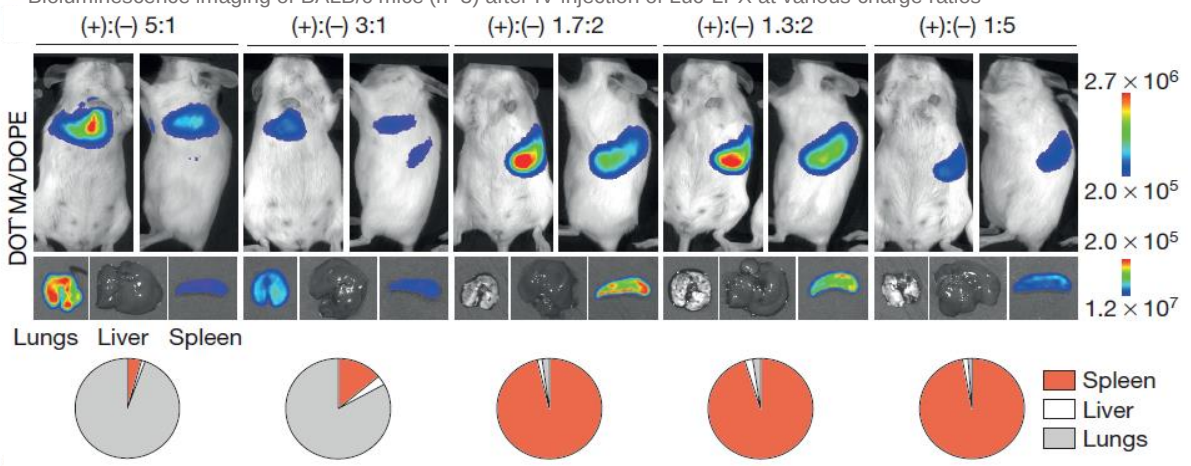
Schematic depiction of lipid bilayers[1]



Schematic depiction of RNA-lipoplex screening process[1]



Bioluminescence imaging of BALB/c mice (n=3) after IV injection of Luc-LPX at various charge ratios[2]



[1] Grabbe S, *et al. Nanomedicine* 2016; 11:2723–2734; [2] Kranz LM, *et al. Nature* 2016; 534:396–401.

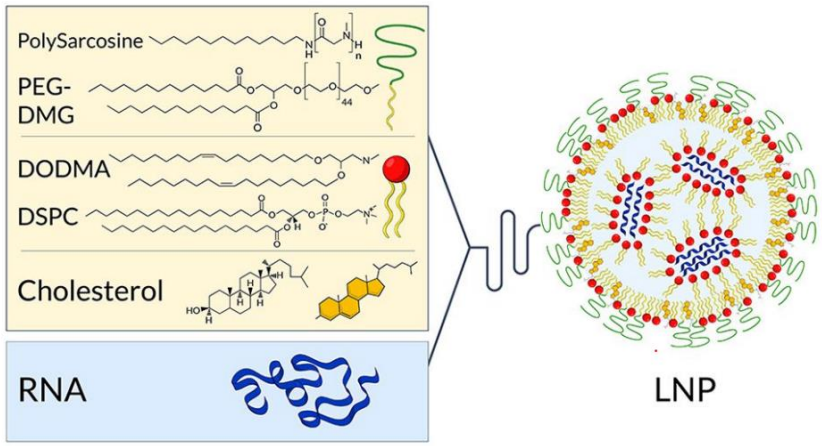
Delivery formulations

A diversified and rationally designed delivery platform for mRNA medicine

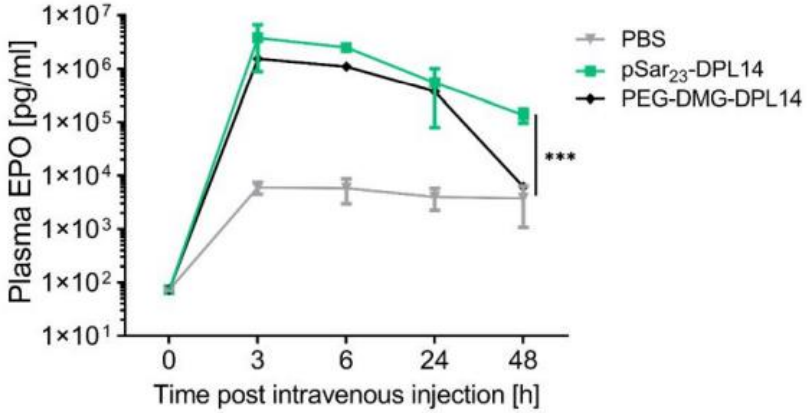
Exploring novel delivery formulation through a high-throughput screening platform to:

- Optimize stability
- Improve potency
- Maintain immune quiescence/reduce immunogenicity
- Seek PEG alternatives: reduce impact of anti-PEG antibodies to improve pharmacokinetics
- Seek alternative routes of administration

PSAR-LNP structure



Polysarcosine-functionalized LNPs exhibited comparable but more durable *in vivo* expression profile to pegylated LNPs



LNP, liquid nanoparticles; PEG, Polyethylene glycol.
Nogueira SS, *et al. ACS Appl Nano Mater* 2020; 3:10634–10645.

Focused on five innovation pillars

Deep understanding of the immune system

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Target discovery and characterization

Digital & AI/ML

BioNTech’s AI & ML applications

① Neoantigen prediction

② COVID-19 variants monitoring and prediction

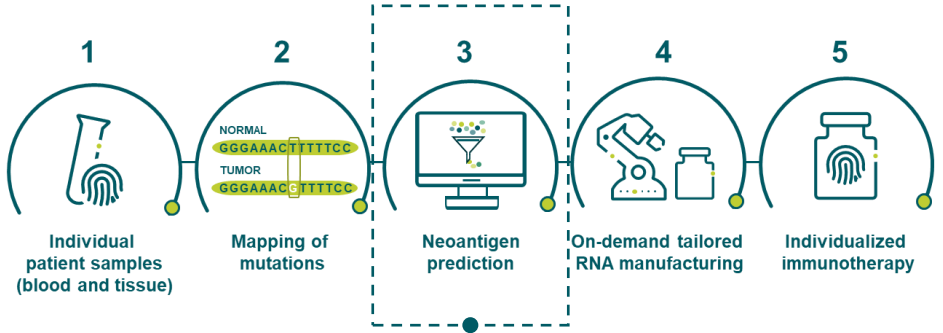
① Neoantigen prediction
AI & ML drive individualized cancer medicine

iNeST[1]
Individualized mRNA cancer vaccine
Neoantigens

NEO-STIM
Individualized T-cell therapy
Neoantigens

Individualized TCR T cells
Mix of shared and neoantigens

Powered by data and cutting-edge AI & ML technologies



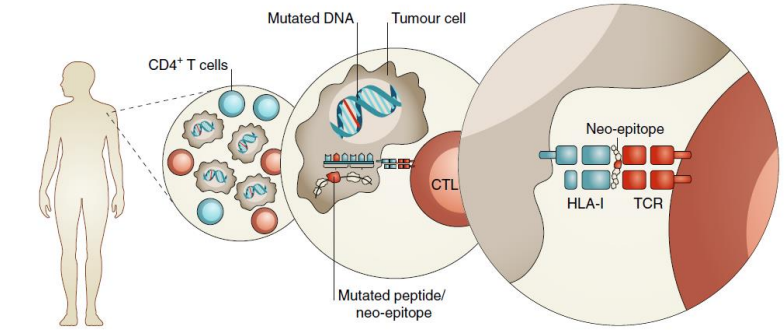
Target selection: AI and machine learning

Predicted MHC Class I or Class II binding

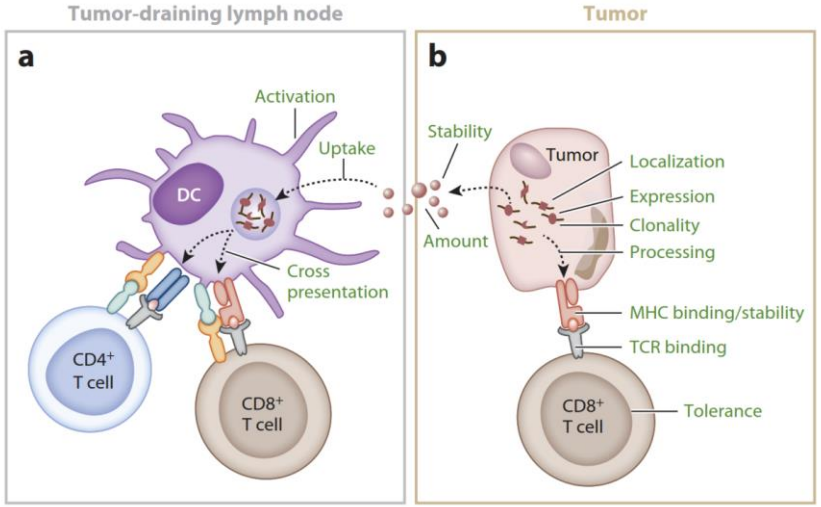
[1] Partnered with Genentech.

① Neoantigen prediction

How do we identify, predict, and characterize neoantigens?



Recognition of cancer-associated mutations by cytotoxic T cells[1]



Biology relevant for immunogenicity

Biology relevant for tumor cell recognition

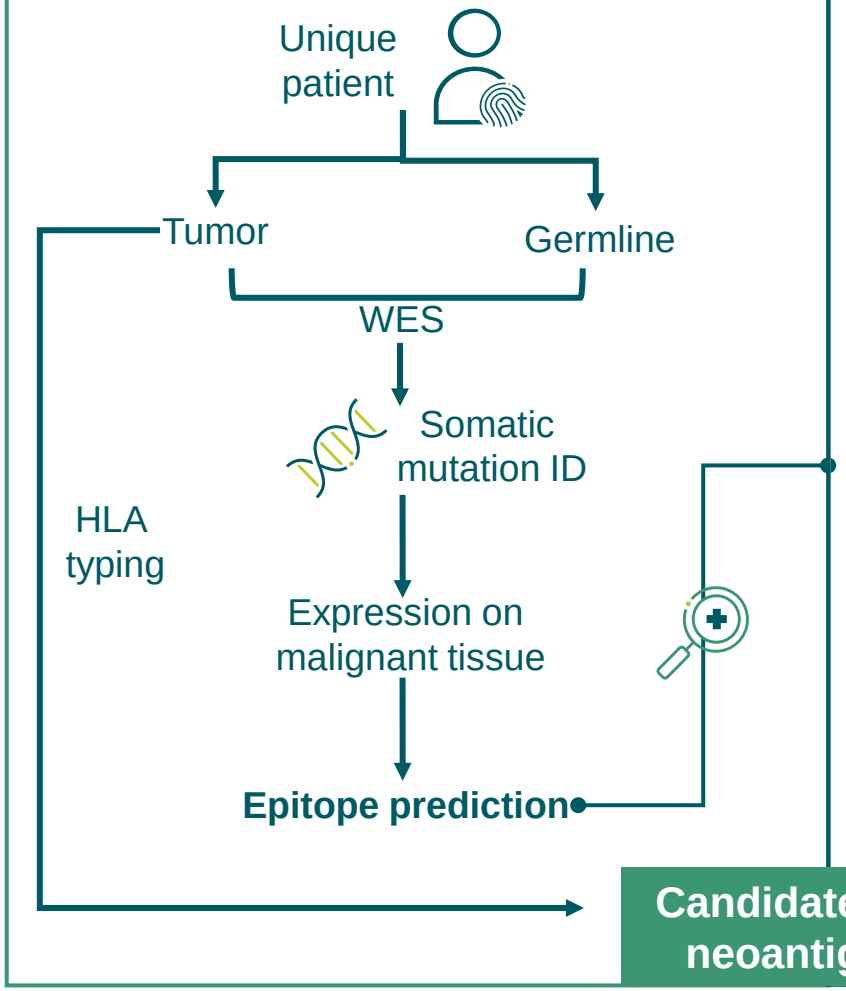
- Type of the mutation (SNV, INDEL, Fusion..)[2]
- Clonality of the mutation (clonal, subclonal)[3,4]
- Mutation position (anchor, non-anchor, TCR accessibility)[5–7]
- Mutated transcript expression level[8,9]
- Similarity to foreign antigens/lack of self-similarity[2]
- Peptide/HLA binding strength (affinity, off-rate)[2]

[1] Türeci Ö, *et al. Nat Biomed Eng* 2018; 2:566–569; [2] Sahin U. AACR Annual Meeting 2022; Oral presentation;
[3] McGranahan N, *et al. Science* 2016; 351:1463–1469; [4] Gejman RS, *et al. eLife* 2018; 7:e41090; [5] Duan F, *et al. J Exp Med* 2014; 211:2231–2248;
[6] Balachandran VP, *et al. Nature* 2017; 551:512–516; [7] Yadav M, *et al. Nature* 2014; 515:572–576; [8] Kreiter S, *et al. Nature* 2015; 520:692–696; [9] Abelin JG, *et al. Immunity* 2017; 46:315–326.

① Neoantigen prediction

Individualized targets: Not all neoantigens are created equal

Neoantigen selection process



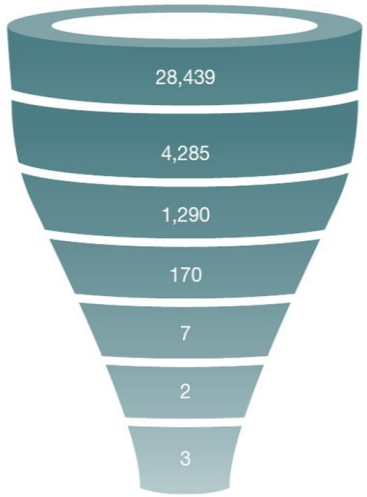
Quantifying mutant epitope characteristics to rank immunogenicity

Will the mutant peptide be presented on the antigen-presenting cell surface?

Is the mutation expressed in the tumor, but not in normal tissues?

Will T cells recognize the mutant peptide?

Is the mutation clonal?



Exome variations

Exome coding variations

Transcript coding variations

Predicted neo-epitopes

Spectra-identified neo-epitopes

Predicted immunogenic neo-epitopes

Validated immunogenic neo-epitopes

Target selection ranked list

Target rank #1
Target rank #2
…
Target rank #20

Yadav M, *et al. Nature* 2014; 515:572–576.

① Neoantigen prediction

Genomic and ligandomic expertise drive our individualized-target database

Neoantigen rank	Gene	Mutation	Length (aa)	Transcript VAF	MHC I score	MHC II score	Coverage in tumor	VAF in tumor	Coverage in normal tissue	VAF in normal tissue
1	SNF8	V183M	27	16.05	0.1	2.16	155	0.33	119	0.00
2	SEMA7A	G340S	27	1.44	0.04	8.6	113	0.44	120	0.01
3	DUS4L	S305P	26	2.07	0.28	8.54	213	0.48	150	0.00
↓										
20										

- Types of mutation and clonality of mutations
- Characterization of neoantigen peptide
- Mutated transcription expression level
- Peptide-MHC binding affinity/quality
- Similarity/richness across tumors
- Lack of expression in healthy tissues

① Neoantigen prediction

New AI-based immune response model may improve accuracy of prediction

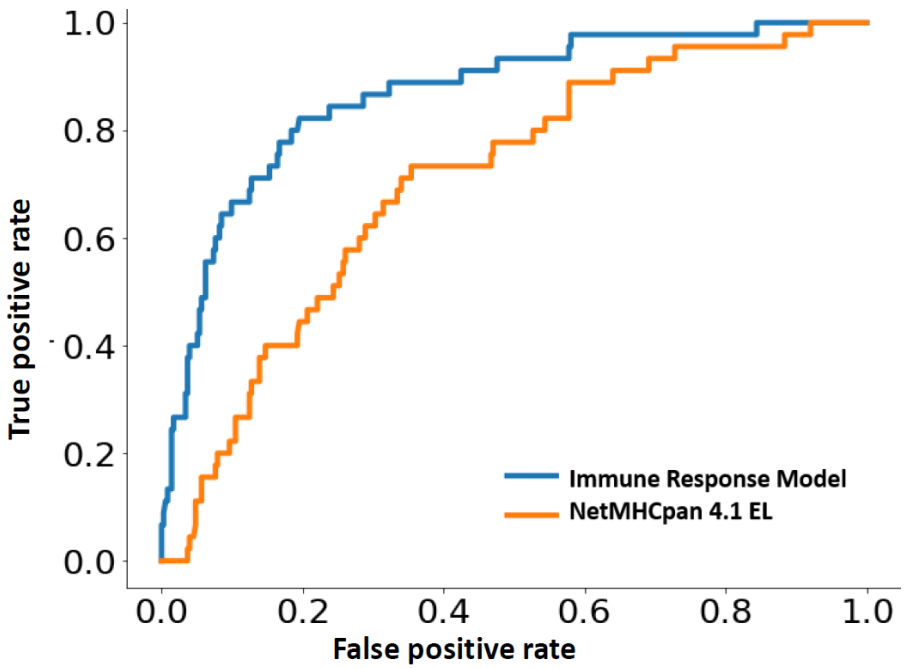
AI-based immune response model incorporates new features

Trained to enable an integrated view of immune response features i.e.

- Biochemical features
- Physical (structure-based) features
- Eluted ligand (also predicted by NetMHCpan)
- Transcript expression

Predicted immunogenicity of 3980 targets compared to NetMHCpan EL model

ROC curve for the AI-based immune response model and NetMHCpan 4.1 EL-based evaluation

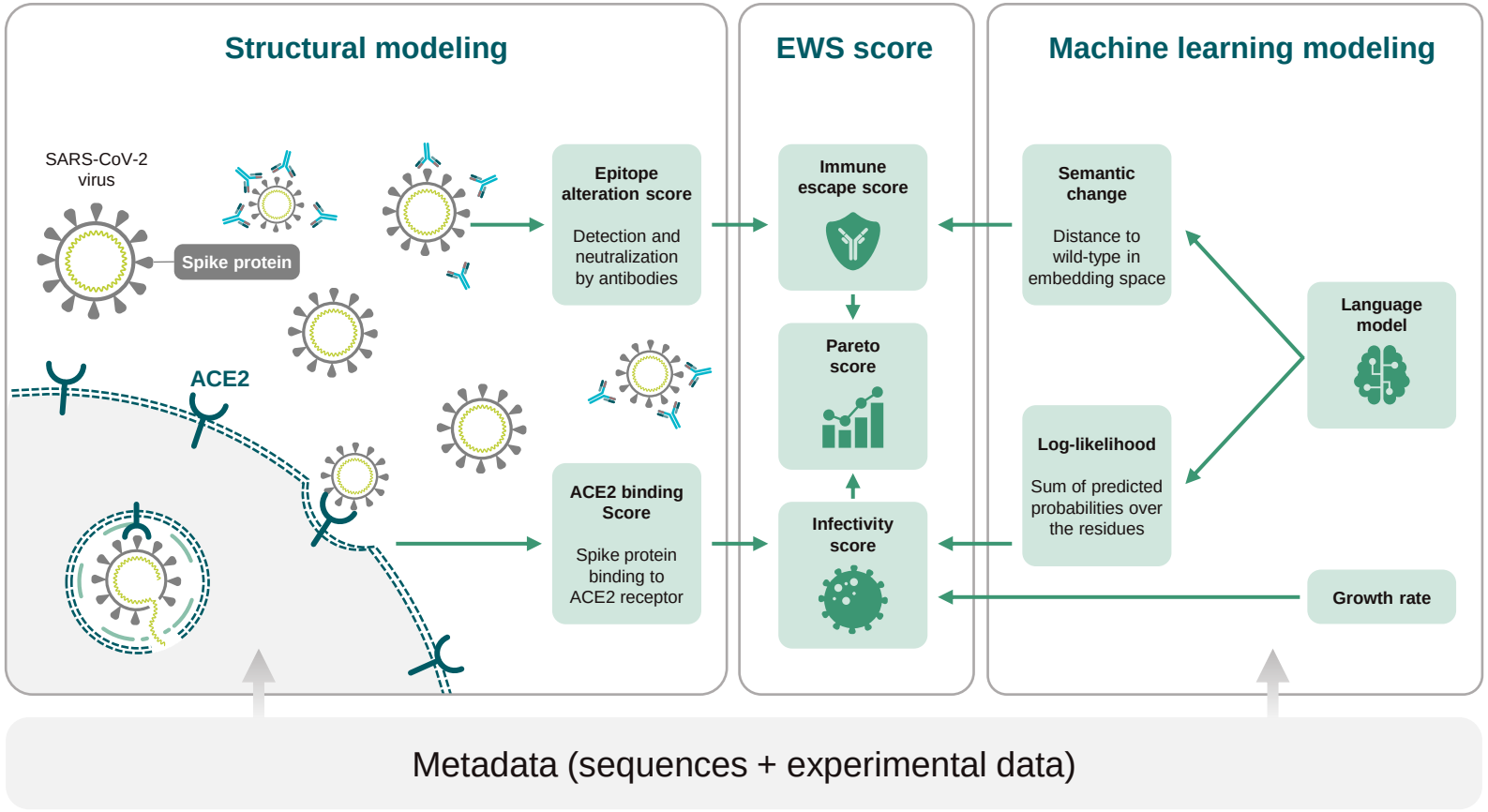


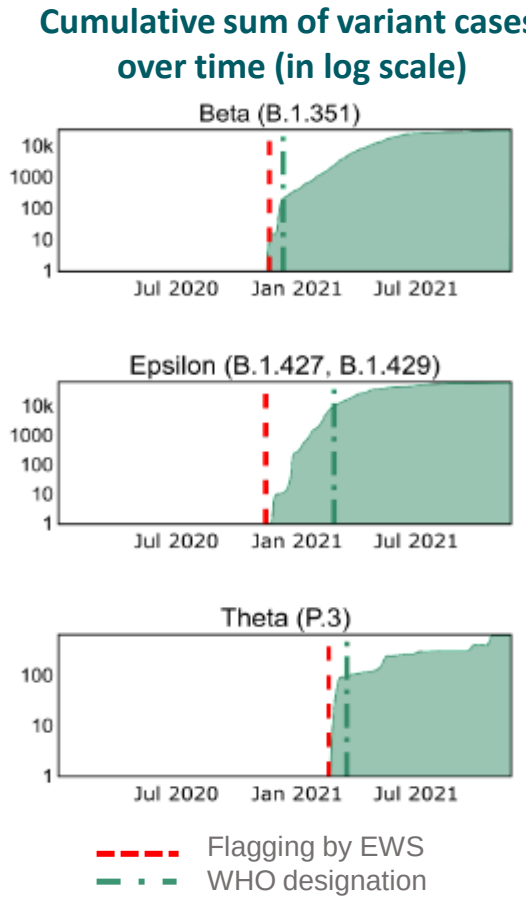
New features significantly improved immune response prediction across data from >100 publicly available resources vs NetMHCpan EL

EL, eluted ligand; ROC, receiver-operator-characteristics.
Lang M, *et al.* CIMT Annual Congress 2022; Poster presentation 21.

② COVID-19 variants monitoring and prediction

Reduction in time to detect new variants of concern by ~2 months





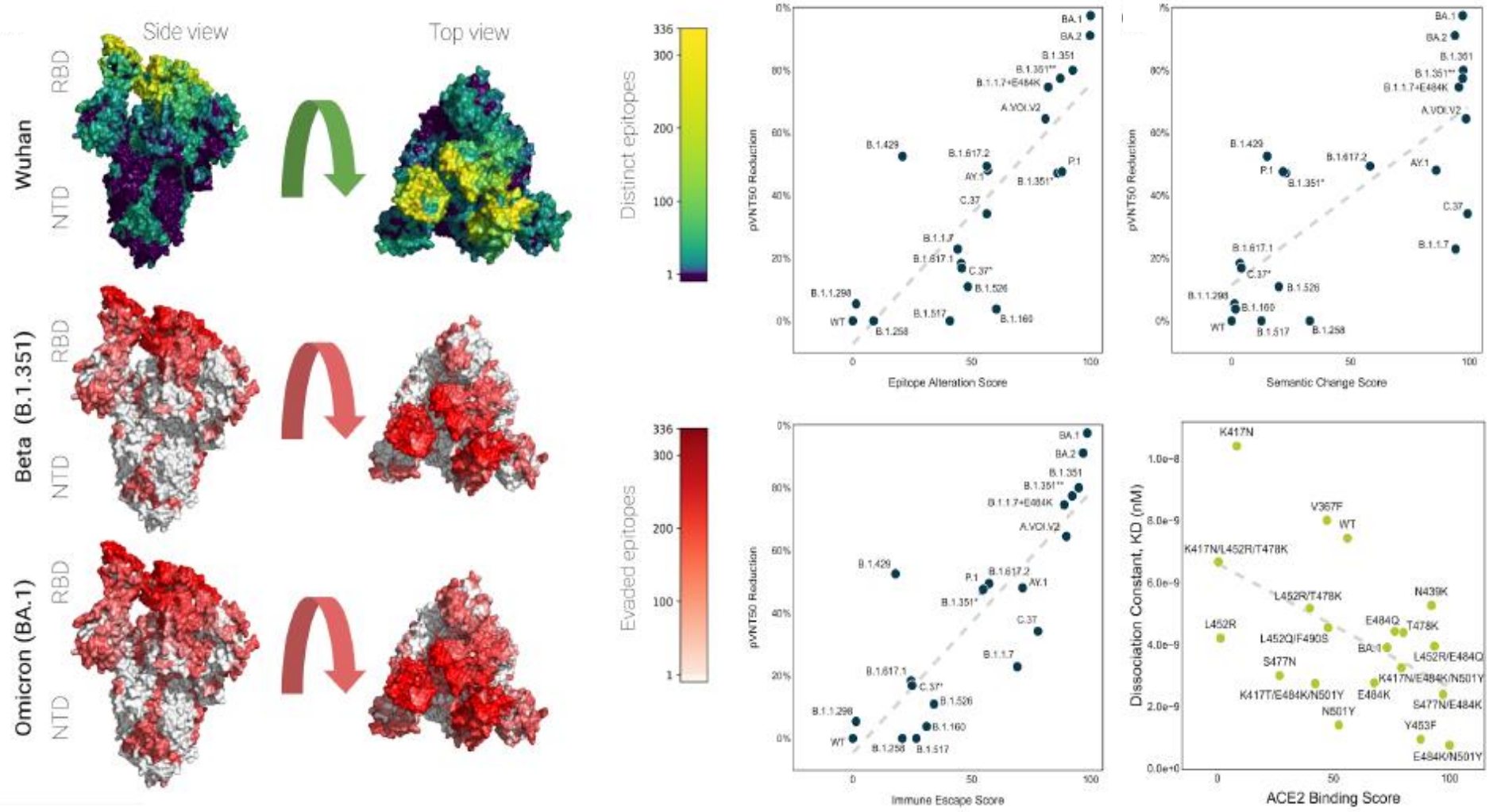
Early computational detection[1] of high-risk SARS-CoV-2 variants supports rapid COVID-19 vaccine adaptation to combat new threats, saving months in response time

[1] Artificial intelligence collaboration of BioNTech and InstaDeep. EWS, emergency warning system.
Beguir K, *et al*. bioRxiv 2021; doi: 10.1101/2021.12.24.474095.

InstaDeep™ BIONTECH

② COVID-19 variants monitoring and prediction

Predicted scores for immune escape and fitness prior correlate with *in vitro* data

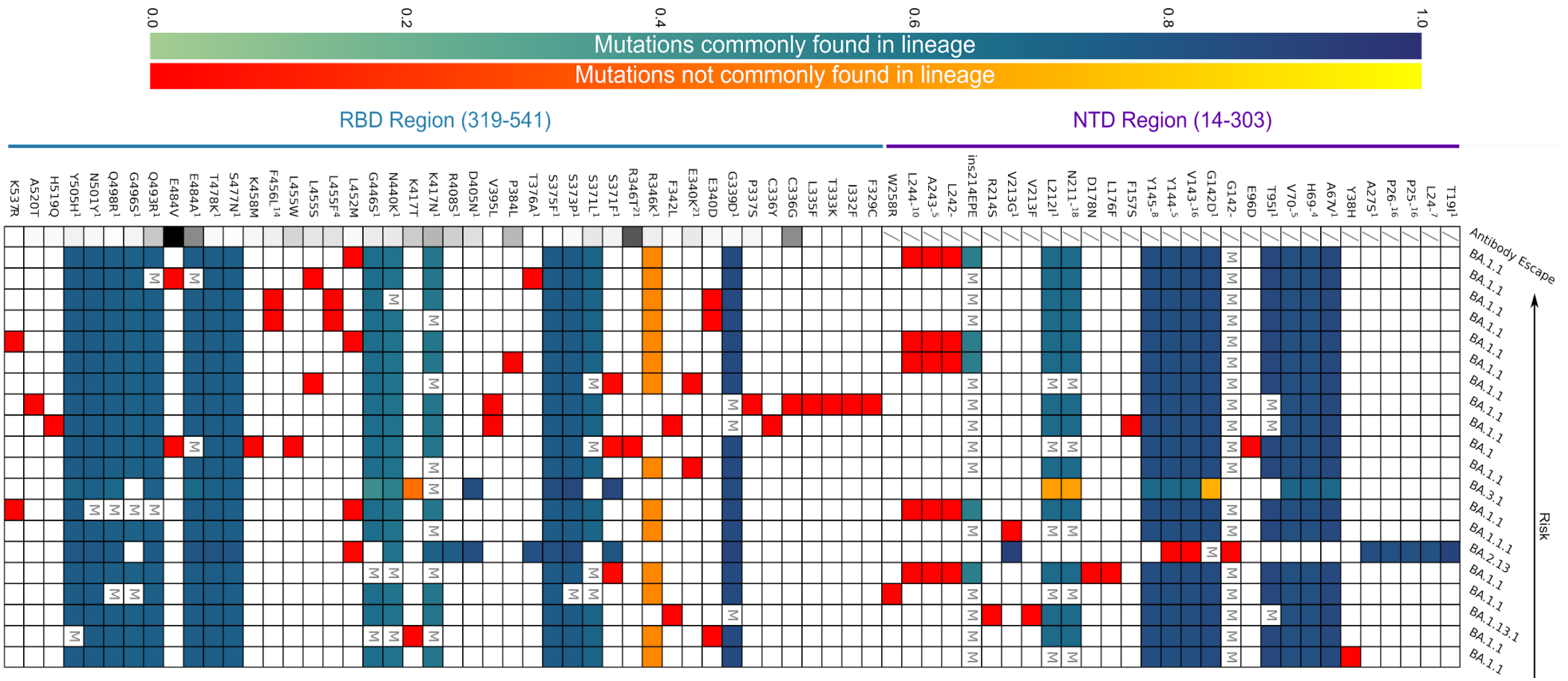


Beguir K, *et al*. bioRxiv 2021; doi: 10.1101/2021.12.24.474095.

InstaDeep™ BIONTECH

② COVID-19 variants monitoring and prediction

EWS report : June 24, 2022



Focused on five innovation pillars

Deep understanding of the immune system

Multi-platform innovation engine

Manufacturing and automation

Target discovery and characterization

Digital & AI/ML

Manufacturing and automation

Diversified manufacturing expertise across four distinct capabilities

Bulk mRNA

- End-to-end mRNA production capabilities
- Combined >100,000 square ft across 2 facilities
- Total capacity of >1 billion doses (COVID-19 vaccine)
- Flexibility to support broad range of mRNA therapies

Marburg, Germany
New site, Singapore (planned for 2023)

Individualized mRNA

- Semi-automated bespoke manufacturing capability to produce just-in-time mRNA vaccines
- >1,000 cGMP iNeST batches produced since 2018

Mainz, Germany *(clinical)*
New commercial site, Mainz (under construction)

BioNTech Manufacturing Infrastructure
>1,000 employees at 4 sites

Modular mRNA / BioNTainer

- End-to-end mRNA production units with capacity of up to >50 million doses/year
- To initially support sustainable production of COVID-19 vaccines and Pandemic Preparedness offerings

Rwanda *(under construction)*
New sites, Senegal, South Africa (planned)

Cell therapy

- Two clinical-scale facilities with combined ~80,000 sq. ft
- Deep expertise in gamma retroviral vectors and CAR-T and TCR cell therapies

IMFS, Idar-Oberstein, Germany | Gaithersburg, MD, USA

Expanding global manufacturing footprint

Construction and GMP licensure of new Mainz facility for iNeST

Marburg

Commercial-scale mRNA

~750 employees

>100,000 square ft

Mainz

Commercial-scale mRNA
Individualized mRNA

~200 employees

~5,500 square ft

Gaithersburg

Clinical-scale cell therapy

~50 employees

>45,000 square ft

Idar-Oberstein

Clinical-scale cell therapy

~220 employees

~30,000 square ft

Singapore

(planned for 2023)

Commercial-scale mRNA

Senegal, Rwanda, & South Africa

(planned for 2023)

Modular mRNA BioNTainer

As of June 2022.

Scaling up mRNA manufacturing

Annual clinical patient batch capacity

10 → **1,000** → **>10,000**

in 2011 | in 2022 | Planned capacity

Batch-size and capacity expansion through **digitalization and automation**

Marburg bulk mRNA batch size

1 g → **350 g** → **1.4 kg**

in early 2020 | in late 2020 | in 2022

Scaling up mRNA batch numbers: Marburg

Acquired from Novartis in 2020 for less than EUR 100M

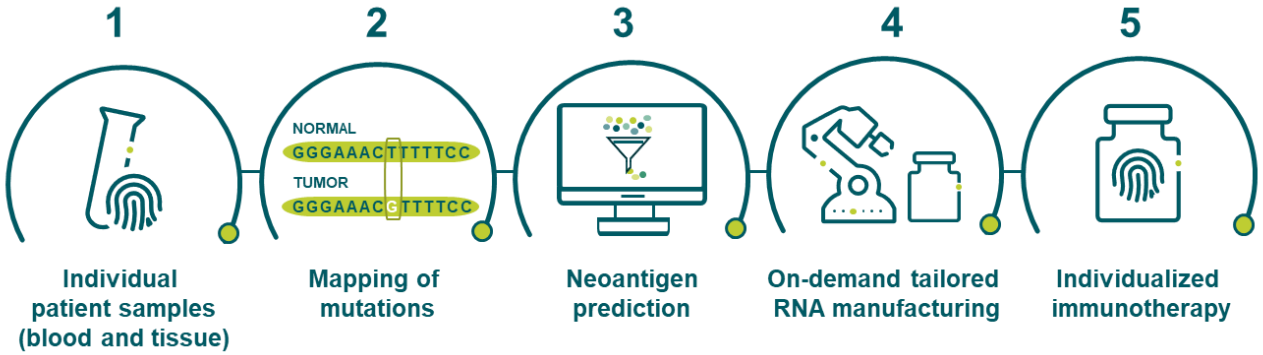
>100,000 square ft and 8 retrofitted production suites

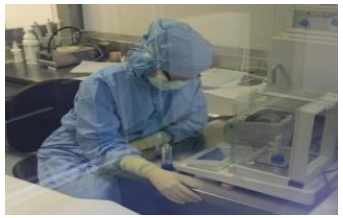
Retrofitted to produce mRNA vaccine within 6 months of acquisition

>1.5 billion doses of COVID-19 vaccine produced since Q2 2021

BioNTainer development hub

iNeST manufacturing innovation: Cycle-time reduction with automated process





Manual process *(until 2016)*

Weeks 1 2 3 4 5 6 7 8 9 10 11 12 13

Needle to needle: **>3 months**

Semi-automated process *(from 2017)*

Weeks 1 2 3 4 5 6 7 8 9 10 11 12 13

Targeting delivery: **<5 weeks**

We are investing in global cGMP cell therapy infrastructures

IMFS, Idar-Oberstein, Germany (fully owned)

BioNTech, Gaithersburg, MD, US (long-term lease)

Advantages of an automated approach

- 24/7 operational model
- Reduction of steps and time
- Reduction of complexity
- Increased efficiency
- Reproducibility of manufacturing process
- Unlocks capacity
- Faster turnaround time per patient
- Advanced planning algorithms

BioNTainer: A platform for localized and sustainable mRNA production

The challenge

Establishing GMP production of mRNA is complex and requires overcoming challenges at many levels

The solution

Turnkey package that includes modular production units, GMP-compliant setup and personnel training

BioNTainers: What is next in 2022

Finalize the planning and initial assets for the new facility in the African Union

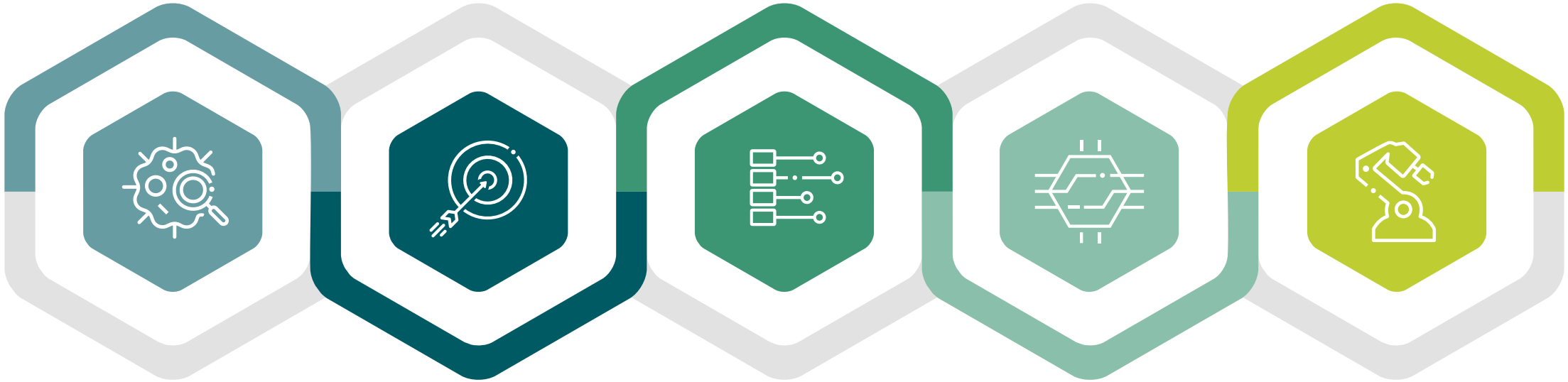
- Broke ground for first BioNTainer manufacturing facility in Rwanda
- First BioNTainer expected to be shipped (YE 2022)
- Regulatory framework in alignment with international and local standards
- Evaluation of additional use cases and products for BioNTainers worldwide

Focused on five innovation pillars to enable a new era of synthetic medicine

Deep understanding of the immune system

Multi-platform innovation engine

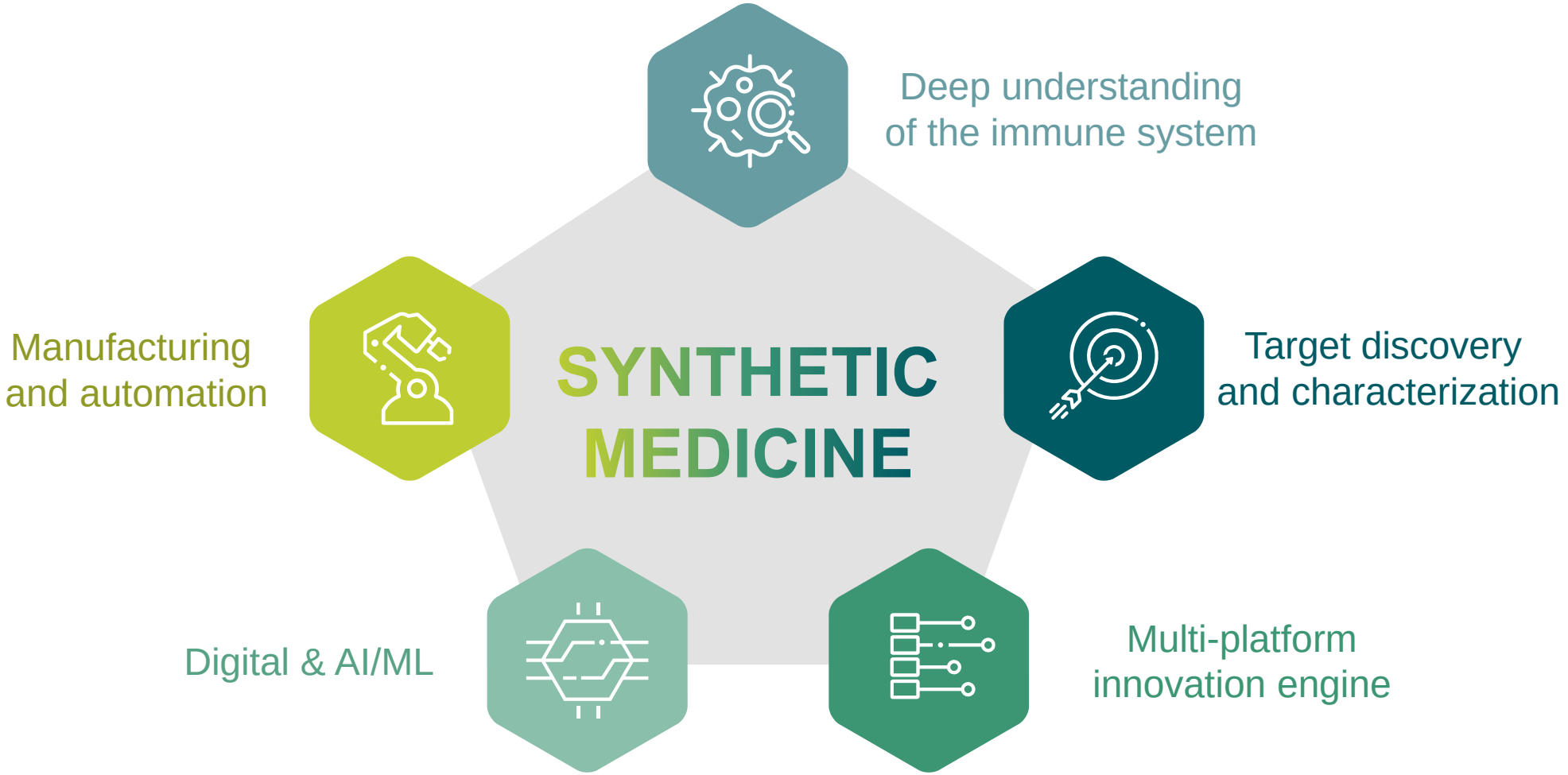
Manufacturing and automation



Target discovery and characterization

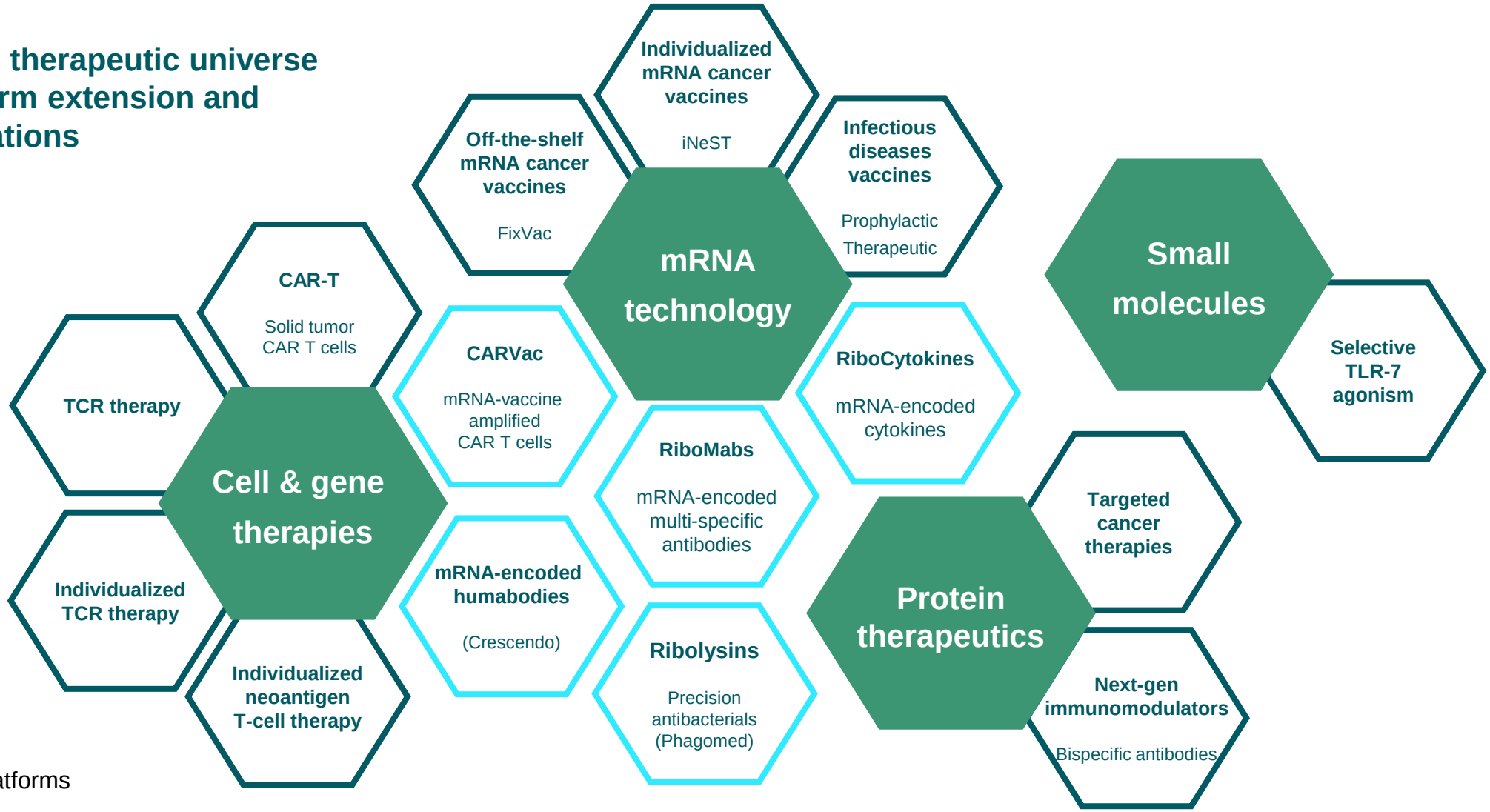
Digital & AI/ML

Focused on five innovation pillars to enable a new era of synthetic medicine



Multi-platform innovation engine

Expanding the therapeutic universe through platform extension and novel combinations



Four drug classes
Platforms
Combination of platforms

New frontiers in infectious diseases

Building on COVID-19 vaccine leadership to address global challenges

Advancing a broad toolkit of mRNA vaccines, Ribologicals, Ribolysins

Diverse pipeline of next-generation COVID-19 vaccines

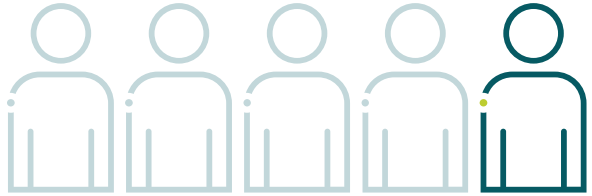
Delivering breakthroughs against infectious diseases with high need

Ability to precisely address diverse and difficult-to-target pathogens

New vaccine launches and clinical trial starts expected in 2H 2022

Medical burden from infectious diseases is a growing global challenge

Insufficient protection against wide variety of pathogens



~20%

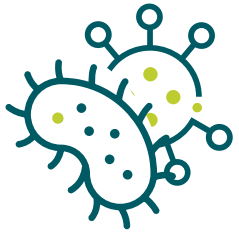
of **deaths worldwide** caused by infectious diseases with >10 million deaths in 2019[1]

Future pandemic threats

>600,000

undiscovered viruses thought to be transmissible from mammal/avian hosts to humans[2]

Antimicrobial resistance



Top 10

global public health threats include **antibacterial resistance** with >1 million deaths annually[3]

Our solutions

mRNA vaccines
RiboMabs

Rapid pandemic preparedness capability

RiboLysins

[1] World Health Organization; 2022. https://cdn.who.int/media/docs/default-source/gho-documents/world-health-statistic-reports/worldhealthstatistics_2022.pdf?sfvrsn=6fbb4d17_3 (accessed May 26, 2022);
[2] IPBES; 2020. https://ipbes.net/sites/default/files/2020-12/IPBES%20Workshop%20on%20Biodiversity%20and%20Pandemics%20Report_0.pdf (accessed June 08, 2022);
[3] World Health Organization; 2021. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (accessed June 08, 2022).

COVID-19 vaccine validates our mRNA technology and paves the way for future mRNA products

10 months development time

3.4 billion doses administered as of April 2022

1+ billion vaccinated persons safety database

BioNTech and Pfizer global mRNA collaboration programs in infectious diseases

COVID-19

COMIRNATY: globally leading franchise

Variant-adapted vaccine launch planned for 2H 2022

Shingles

Potential first-in-class mRNA-based shingles vaccine with blockbuster potential

FIH Phase 1 trial 2H 2022

BIONTECH + Pfizer

Influenza

Single-dose quadrivalent mRNA vaccine

Phase 1 data update expected in 2022

Building on a track record of rapid clinical development and successful global commercialization of infectious disease vaccines

FIH, first-in-human.

Well prepared for the next phase of COVID-19 pandemic

~3.4 billion doses delivered to >175 of countries and regions

Key drivers

1. **FDA EUA granted for pediatric use (6 months to <5 years old)**
2. **Prepared for launch of variant-adapted vaccine in 2H 2022**
3. **First pandemic response for governments contract signed**

As of March 2022

[1] Approved as a 2-dose series for prevention of COVID-19 in individuals 16 years of age and older; 2-dose series under Emergency Use Authorization for individuals 5–15 years old, and 3-dose series under Emergency Use Authorization for children 6 months through 4 years of age;

[2] The vaccine is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 5 years of age and older.

① FDA EUA granted for pediatric use
Low-dose vaccination safely confers high protection

Phase 2/3

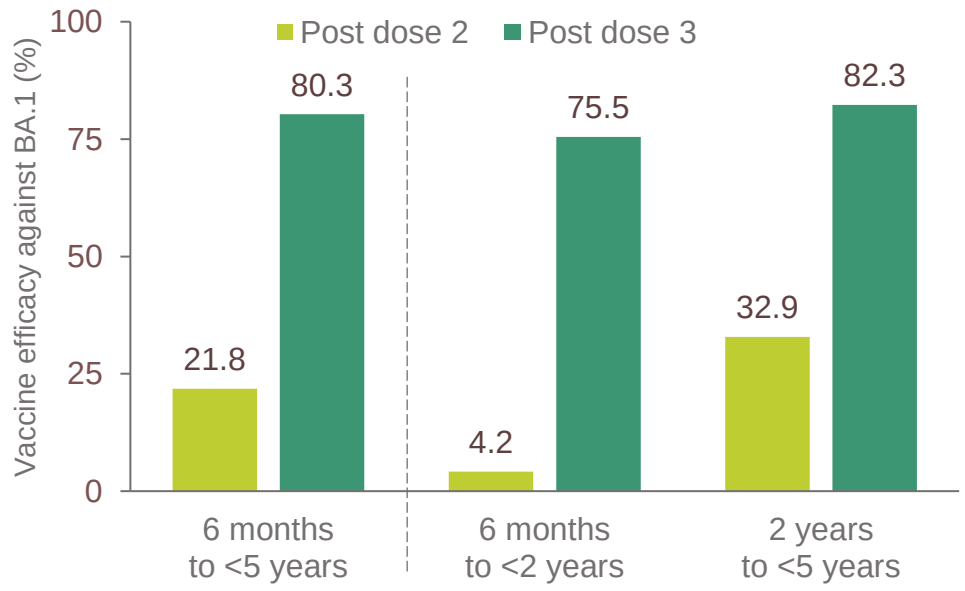
Children aged
6 months to <5 years

R
2:1

BNT162b2 – n=3,013
3 µg; 3 doses

Placebo – n=1,513

Three doses of BNT16b2 likely to confer high degree of protection against Omicron BA.1



Safety profile comparable to placebo

Reactogenicity mostly mild to moderate and short lived

- Systemic reactions comparable to placebo, after any dose
- AEs reflect reactogenicity/common childhood illnesses

Similar frequency of AESIs between BNT162b2 vs placebo

- FDA-defined AESI main categories: potential angioedema and hypersensitivity (mainly urticarias and rashes)
- CDC-defined AESIs: No vaccine-related anaphylaxis, myocarditis/pericarditis, Bell's palsy,[1] or MIS-C

[1] Or facial paralysis/paresis.
[2] Available at: https://www.census.gov/dataviz/visualizations/034/ and https://ec.europa.eu/eurostat/statistics-explained/index.php?title=File:Population_structure_by_five-year_age_groups_and_sex,_EU-27,_1_January_1999_and_2019_(%25_share_of_total_population)_BYIE20.png
AE, adverse event; AESI, AE of special interest; MIS-C, multisystem inflammatory syndrome in children.

② Variant-adapted vaccines

Next-generation vaccine approaches aim to provide durable variant protection

COMIRNATY

Variant adapted and next-generation vaccine approaches

Omicron-adapted

Mono-/Multi-valent

T-cell enhancing

Pan-coronavirus

Clinical data presented at VRBPAC meeting June 2022

Rolling submissions initiated in US and EU

Expected to enter the clinic in 2H 2022

② Variant-adapted vaccines I Omicron BA.1 GMR consistent with simple superiority criterion for Omicron-modified vaccines (>55y participants)

Participants WITHOUT evidence of infection up to 1 month after the study vaccination

Assay	Vaccine groups	n	GMT (95% CI) 1M post-dose	Vaccine group / BNT162b2 30 µg	
				GMR (95% CI)	Met superiority (Y/N)[1]
SARS-CoV-2 neutralization assay – Omicron BA.1 - NT50 (titer)	BNT162b2 30 µg	163	455.8 (365.9, 567.6)		
	BNT162b2 OMI 30 µg	169	1014.5 (825.6, 1246.7)	2.23 (1.65, 3.00)	Y
	BNT162b2 OMI 60 µg	174	1435.2 (1208.1, 1704.8)	3.15 (2.38, 4.16)	Y
	Bivalent OMI 30 µg[1]	178	711.0 (588.3, 859.2)	1.56 (1.17, 2.08)	Y
	Bivalent OMI 60 µg[2]	175	900.1 (726.3, 1115.6)	1.97 (1.45, 2.68)	Y

GMR superiority criterion: the lower bound of 95% confidence interval for GMR is >1.0

[1] Multiple hypotheses are to be evaluated in sequential order for alpha control. Declaration of OMI 30 µg simple superiority pending outcome of additional hypotheses.
Note: Omicron BA.1 NT50 measured using validated 384-well assay.
Internal data.

② Variant-adapted vaccines | Omicron BA.1 GMR consistent with super superiority criterion for monovalent Omicron-modified vaccine (>55y participants)

Participants WITHOUT evidence of infection up to 1 month after the study vaccination

Assay	Vaccine groups	n	GMT (95% CI) 1M post-dose	Vaccine group / BNT162b2 30 µg	
				GMR (95% CI)	Met superiority (Y/N)[1]
SARS-CoV-2 neutralization assay – Omicron BA.1 - NT50 (titer)	BNT162b2 30 µg	163	455.8 (365.9, 567.6)		
	BNT162b2 OMI 30 µg	169	1014.5 (825.6, 1246.7)	2.23 (1.65, 3.00)	Y
	BNT162b2 OMI 60 µg	174	1435.2 (1208.1, 1704.8)	3.15 (2.38, 4.16)	Y
	Bivalent OMI 30 µg[1]	178	711.0 (588.3, 859.2)	1.56 (1.17, 2.08)	Y
	Bivalent OMI 60 µg[2]	175	900.1 (726.3, 1115.6)	1.97 (1.45, 2.68)	Y

GMR superiority criterion: the lower bound of 95% confidence interval for GMR is >1.5

[1] Multiple hypotheses are to be evaluated in sequential order for alpha control. Declaration of super superiority pending outcome of additional hypotheses.
Note: Omicron BA.1 NT50 measured using validated 384-well assay.
Internal data.

② Variant-adapted vaccines | Omicron BA.1 seroresponse rate exceeds noninferiority criterion for Omicron-containing vaccines (>55y participants)

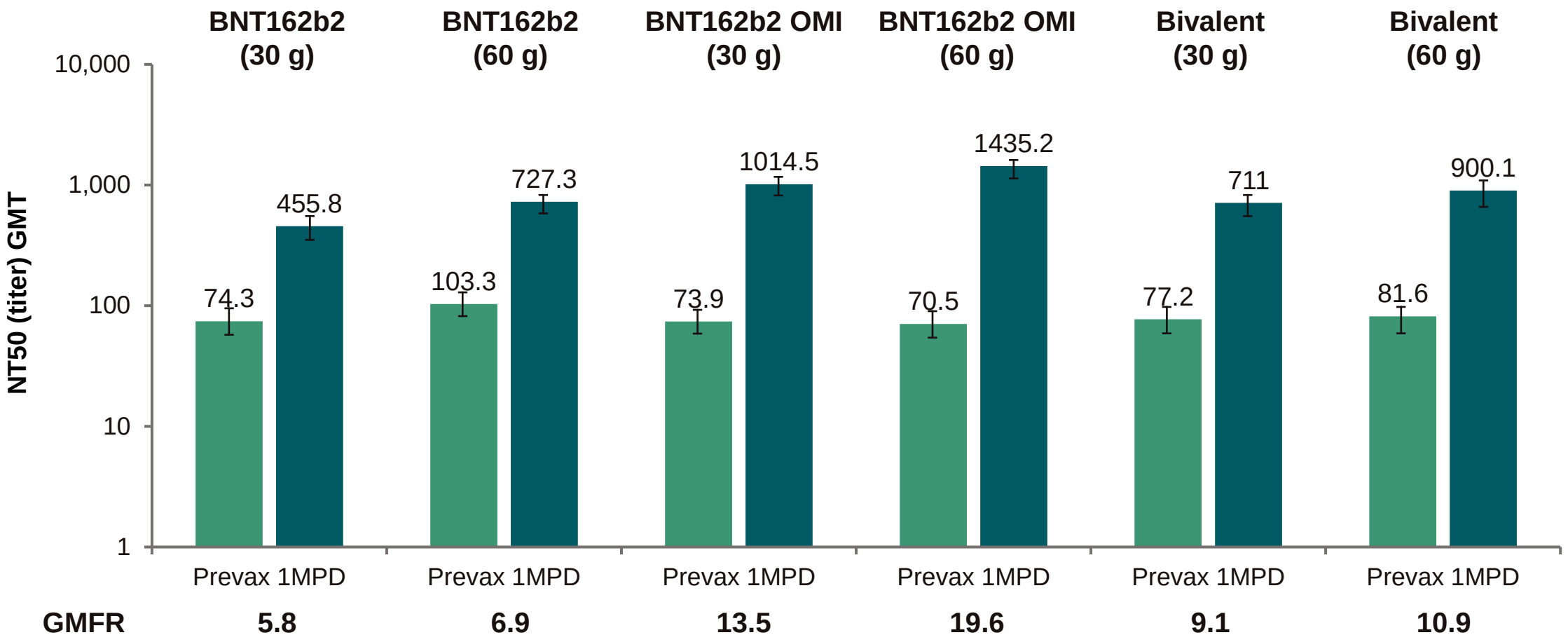
Participants WITHOUT evidence of infection up to 1 month after the study vaccination

Assay	Vaccine groups	N	n (%)	(95% CI) 1M post-dose	Seroresponse difference in % Vaccine group – BNT162b2 30 µg % (95% CI)	Met non-inferiority (Y/N)[1]
SARS-CoV-2 neutralization assay – Omicron BA.1 - NT50 (titer)	BNT162b2 30 µg	149	85 (57.0)	(48.7, 65.1)		
	BNT162b2 OMI 30 µg	163	125 (76.7)	(69.4, 82.9)	19.6 (9.3, 29.7)	Y
	BNT162b2 OMI 60 µg	166	143 (86.1)	(79.9, 91.0)	29.1 (19.4, 38.5)	Y
	Bivalent OMI 30 µg[1]	169	121 (71.6)	(64.2, 78.3)	14.6 (4.0, 24.9)	Y
	Bivalent OMI 60 µg[2]	162	110 (67.9)	(60.1, 75.0)	10.9 (0.1, 21.4)	Y

Non-inferiority criterion: the lower bound of 95% confidence interval for interval for the percentage difference is >-5

[1] Multiple hypotheses are to be evaluated in sequential order for alpha control. Declaration of OMI 30 µg noninferiority pending outcome of additional hypotheses.
Note: Omicron BA.1 NT50 measured using validated 384-well assay.
Internal data.

② Variant-adapted vaccines I GMTs in participants without evidence of infection up to 1 month after study vaccination: Immunogenicity subset



Internal data.

② Variant-adapted vaccines I Reactogenicity profile of variant vaccines overall similar to prototype BNT162b2 vaccine

Participants aged 18–55 years

- Monovalent Omicron-modified vaccine (30 µg) showed a similar local reaction and systemic event profile as the prototype vaccine (30 µg)

Participants aged >55 years

- Monovalent and bivalent Omicron-modified vaccines (30 µg) showed a similar local reaction and systemic event profile as the prototype vaccine
- 60 µg dose level: Mild to moderate injection site pain, fatigue and muscle pain were more common compared to 30 µg

Internal data.

② Variant-adapted vaccines

Omicron-containing modified-variant vaccine summary

Neutralizing responses for Omicron-containing vaccines are consistent with regulatory criteria:

- Simple superiority for GMR and non-inferiority for seroresponse (monovalent and bivalent vaccines)
- “Super” superiority for GMR (monovalent vaccines)

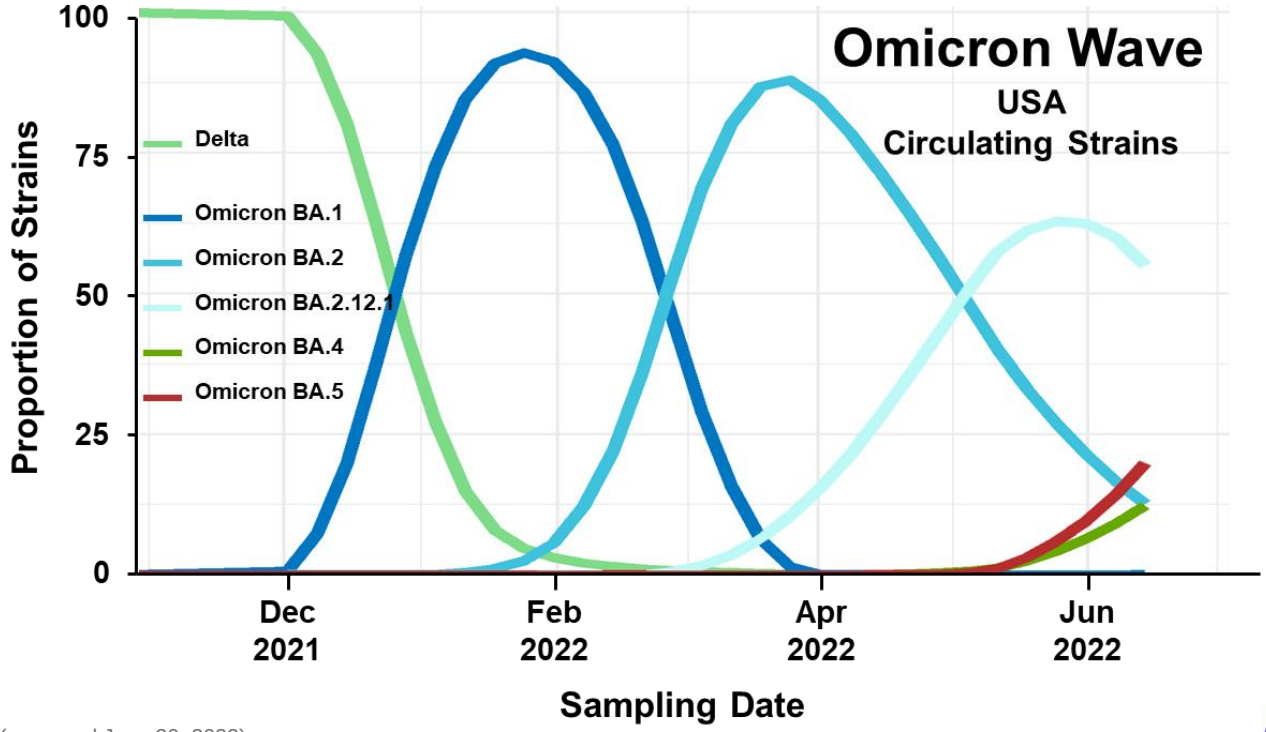
Reactogenicity profile of variant vaccines overall similar to prototype BNT162b2 vaccine

Internal data.

② Variant-adapted vaccines I SARS-CoV-2 epidemiology changes quickly: Vaccine updates need to adapt with the pace of the virus

Variant vaccine update pathway

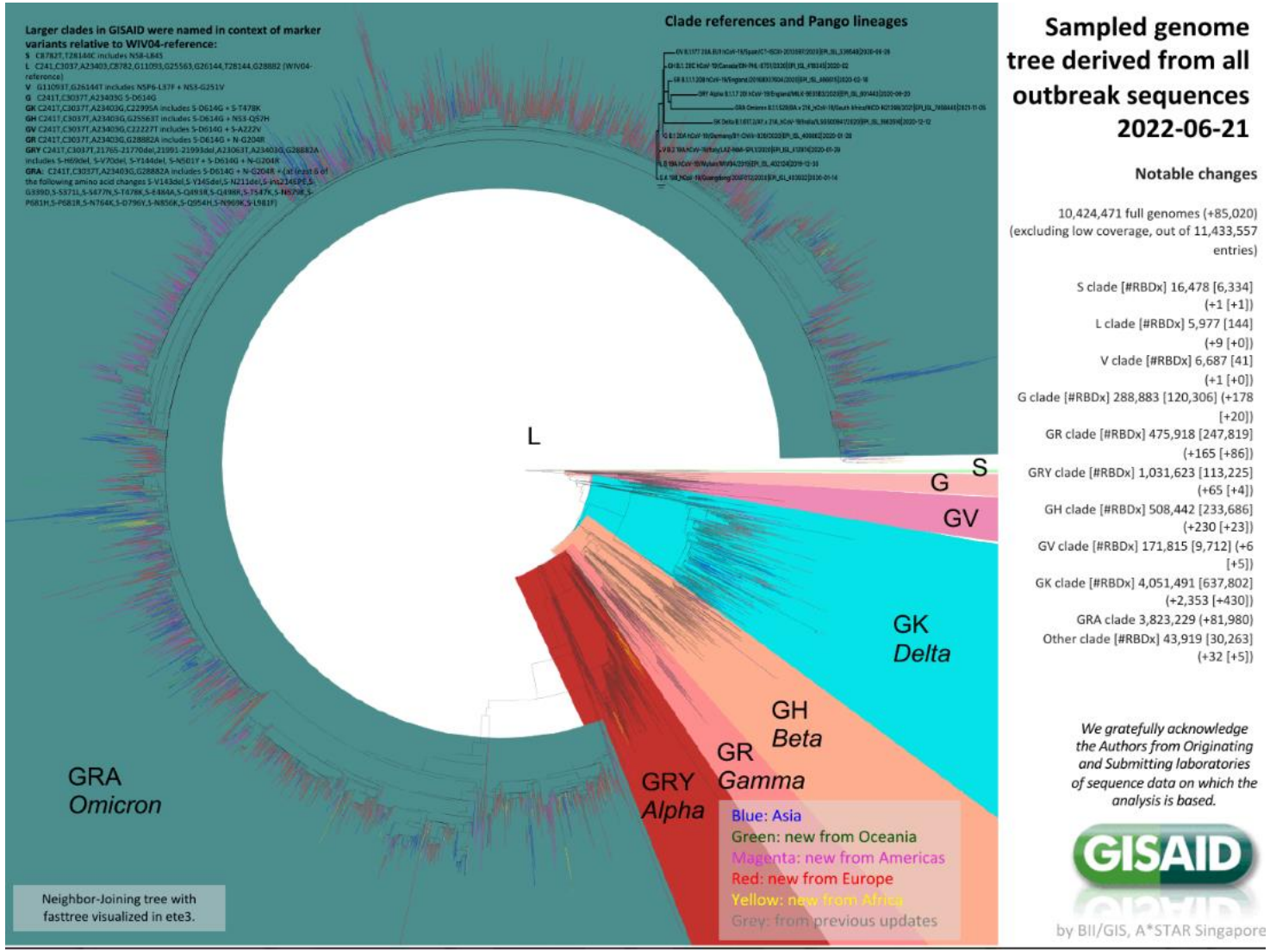
Clinical (current)	~8 months
Pre-clinical/CMC (proposed)	~3 months



GISAID Initiative database: https://www.gisaid.org/ (accessed June 20, 2022).

② Variant-adapted vaccines

Omicron has more sublineages than all other variants combined



Sampled genome tree derived from all outbreak sequences 2022-06-21

Notable changes

10,424,471 full genomes (+85,020) (excluding low coverage, out of 11,433,557 entries)

S clade [#RBDx] 16,478 [6,334] (+1 [+1])
L clade [#RBDx] 5,977 [144] (+9 [+0])
V clade [#RBDx] 6,687 [41] (+1 [+0])
G clade [#RBDx] 288,883 [120,306] (+178 [+20])
GR clade [#RBDx] 475,918 [247,819] (+165 [+86])
GRY clade [#RBDx] 1,031,623 [113,225] (+65 [+4])
GH clade [#RBDx] 508,442 [233,686] (+230 [+23])
GV clade [#RBDx] 171,815 [9,712] (+6 [+5])
GK clade [#RBDx] 4,051,491 [637,802] (+2,353 [+430])
GRA clade 3,823,229 (+81,980)
Other clade [#RBDx] 43,919 [30,263] (+32 [+5])

We gratefully acknowledge the Authors from Originating and Submitting laboratories of sequence data on which the analysis is based.

GISAID

by BII/GIS, A*STAR Singapore

Omicron mutanome continues to rapidly expand

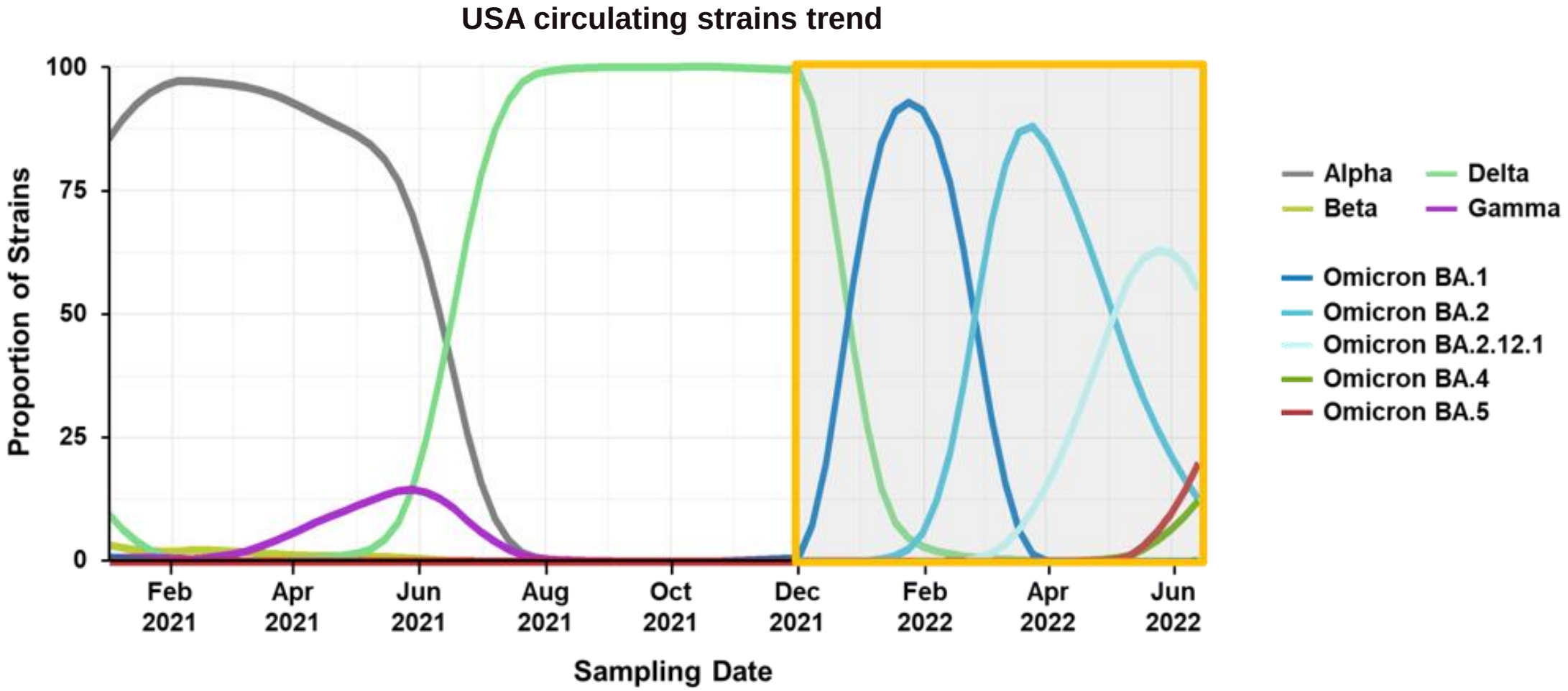
Omicron sublineages continue to show increased immune escape properties

Omicron sublineages have become mutationally distinct

GISAID Initiative database: https://www.gisaid.org/ (accessed June 22, 2022).

② Variant-adapted vaccines

BA.2.12.1 and BA.4/5 are now increasing in prevalence



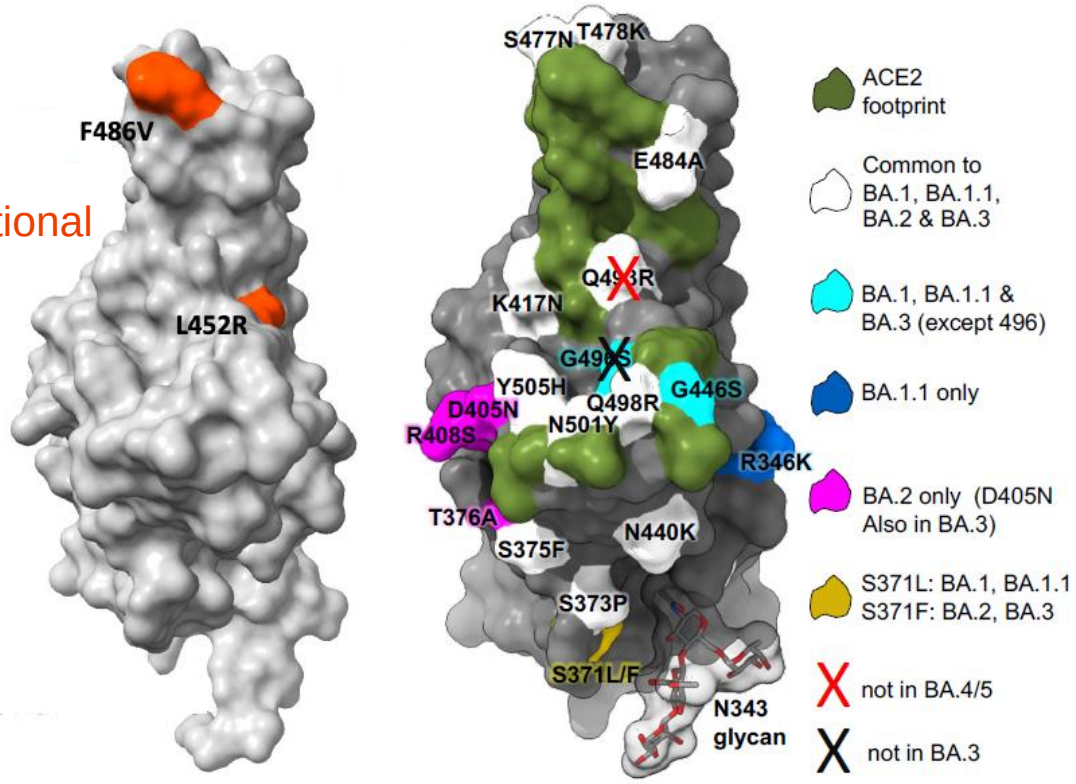
GISAID Initiative database: https://www.gisaid.org/ (accessed May 31, 2022).

② Variant-adapted vaccines

Omicron BA.4/5 RBD and NTD sequences are distinct from BA.1 and BA.2

RBD top view

BA.4/5 additional mutations



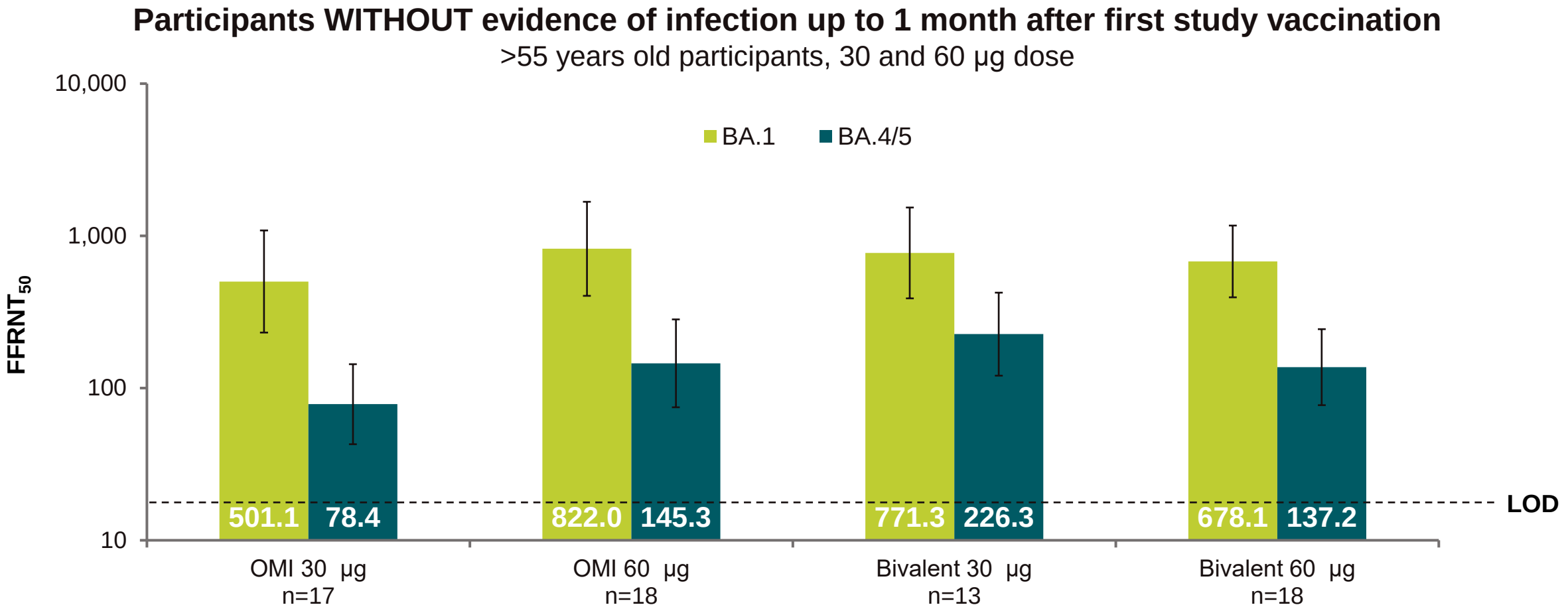
BA.1	A67V,Δ69-70,T95I,G142D,Δ143-145,N211I,Δ212, ins214EPE	NTD
BA.1.1	A67V,Δ69-70,T95I,G142D,Δ143-145,N211I,Δ212, ins214EPE	
BA.2	T19I,Δ24-26,A27S, G142D, V213G	
BA.3	A67V,Δ69-70,T95I,G142D, Δ143-145,N211I,Δ212	
BA.4/5	T19I,Δ24-26,A27S, Δ69-70, G142D, V213G	
BA.1	G339D, S371L,S373P,S375F, K417N,N440K,G446S	RBD
BA.1.1	G339D,R346K,S371L,S373P,S375F, K417N,N440K,G446S	
BA.2	G339D, S371F,S373P,S375F,T376A,D405N,R408S,K417N,N440K	
BA.3	G339D, S371F,S373P,S375F, D405N, K417N,N440K,G446S	
BA.4/5	G339D, S371F,S373P,S375F,T376A,D405N,R408S,K417N,N440K,	
BA.1	S477N,T478K,E484A, Q493R,G496S,Q498R,N501Y,Y505H	
BA.1.1	S477N,T478K,E484A, Q493R,G496S,Q498R,N501Y,Y505H	
BA.2	S477N,T478K,E484A, Q493R, Q498R,N501Y,Y505H	
BA.3	S477N,T478K,E484A, Q493R, Q498R,N501Y,Y505H	
BA.4/5	L452R,S477N,T478K,E484A,F486V, Q498R,N501Y,Y505H	

BA.1	T547K,D614G,H655Y,N679K,P681H,N764K,D796Y,N856K,Q954H,N969K,L981F
BA.1.1	T547K,D614G,H655Y,N679K,P681H,N764K,D796Y,N856K,Q954H,N969K,L981F
BA.2	D614G,H655Y,N679K,P681H,N764K,D796Y, Q954H,N969K
BA.3	D614G,H655Y,N679K,P681H,N746K,D796Y, Q954H,N969K
BA.4/5	D614G,H655Y,N679K,P681H,N764K, D796Y, Q954H,N969K

Omicron BA.4 and BA.5 contain additional mutations in the RBD, in particular the reversion mutation R493Q, together with mutations L452R and F486V

Tuekprakhon A, *et al. bioRxiv* 2022; doi.org/10.1101/2022.05.21.492554.

② Variant-adapted vaccines I Omicron-containing modified variant vaccines as 4th dose elicit improved Omicron neutralization response

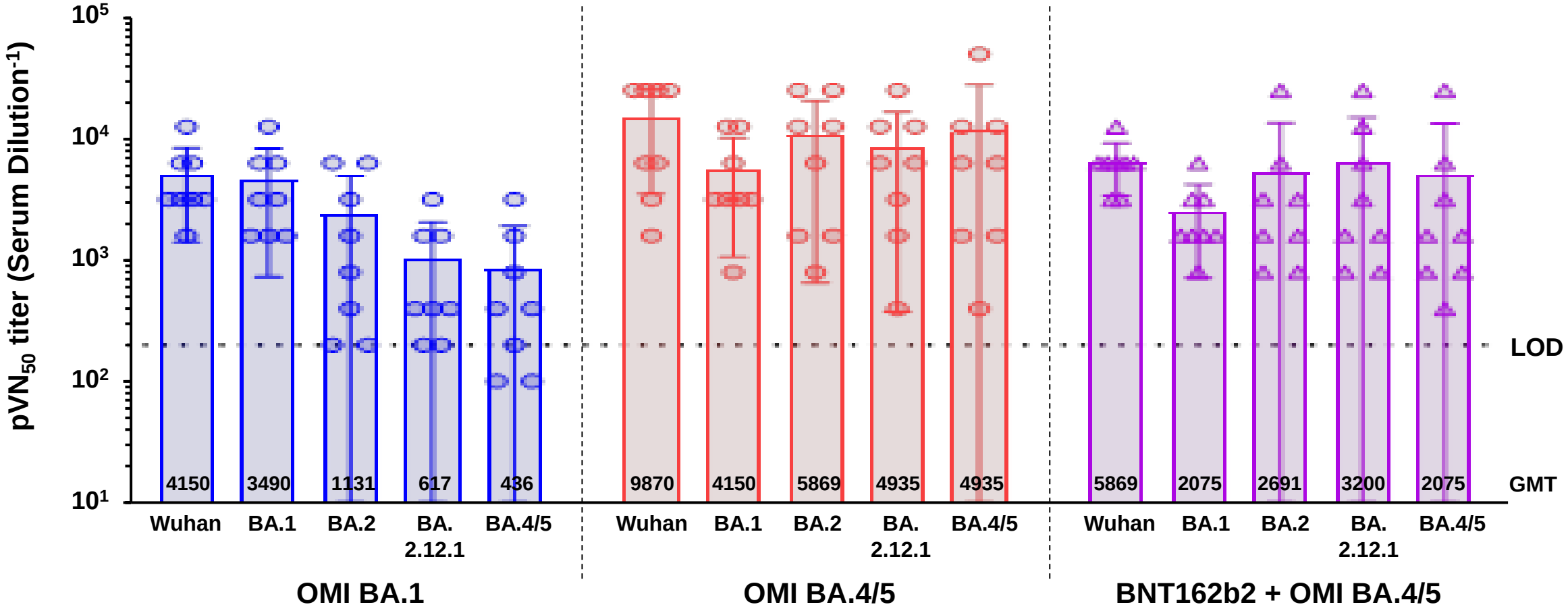


BA.4/BA.5 response lower than that of BA.1

FFRNT, fluorescent foci reduction neutralization test; LOD, limit of detection.
Internal data.

Omicron BA.4/5 Monovalent and Bivalent Boosters in Mice Substantially Increase Omicron Neutralization Responses to all Omicron Variants Including BA.4/5 and Reference Strain

Compared to Monovalent OMI BA.1, BA.4/5 neutralizing titers increase by ~11.3 fold [mono BA.4/5] or ~4.8 fold (bivalent BA.4/5)

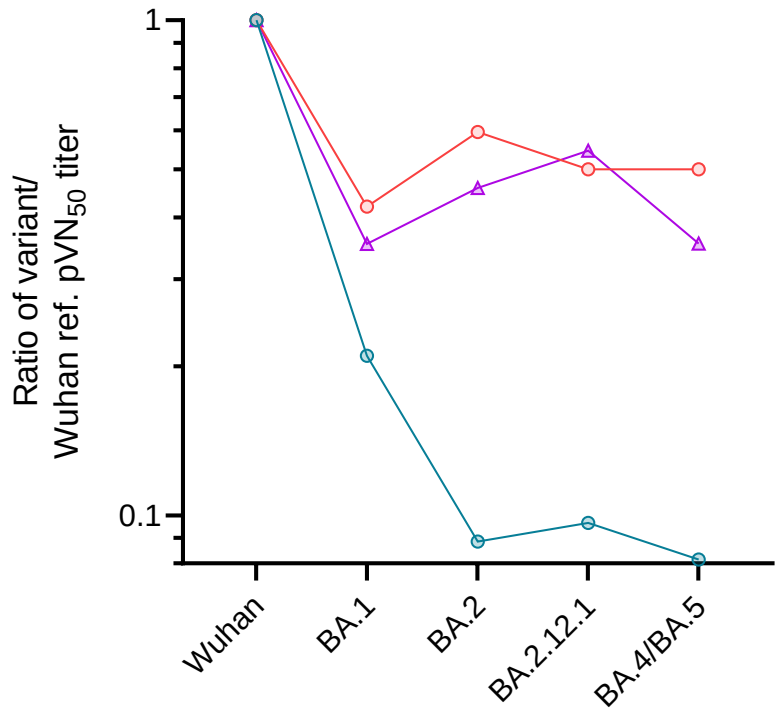


N=8 mice Balb/c mice. Mice preimmunized with 2 doses of BNT162b2; boosters given at day 104
Pseudovirus neutralization assay; LOD, Limit of Detection

BU-875

② Variant-adapted vaccines I Omicron BA.4/5 variant-adapted vaccines increase Omicron sub-lineages/Wuhan ref. pVN_{50} titer ratio in balb/c mice

Cross-neutralization analysis



Geometric mean ratio	Omi BA.1	Omi BA.2	Omi BA.2.12.1	Omi BA.4/BA.5
BNT162b2	0.21	0.09	0.10	0.08
Omi BA.4/5	0.42	0.59	0.50	0.50
b2 + Omi BA.4/5	0.35	0.46	0.55	0.35

- N=8 Balb/c mice per group
- Pre-immunized with 2-doses of 1µg BNT162b2 on day 0 and day 21
- Booster administered on day 104

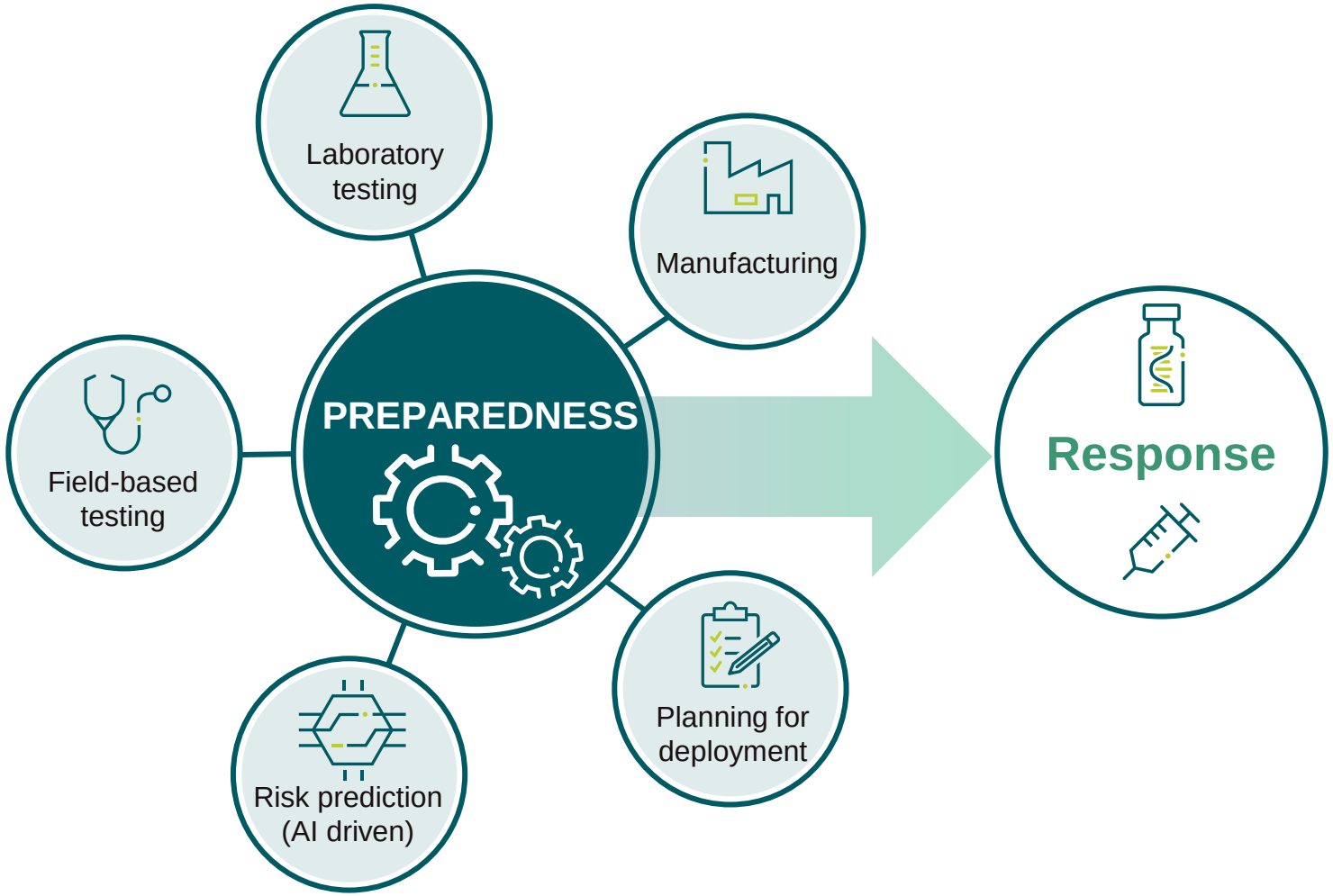
② Variant-adapted vaccines
A science-driven preparedness strategy

- Extensive **clinical experience with multiple other variant-adapted vaccines**
  - Consistent safety and immunogenicity profiles
- **Robust manufacturing process**
  - Requires minimal changes to introduce updated antigen sequence for new variant/sublineage
- As of today, **safety profile of COMIRNATY is well characterized**
  - Extensive post-marketing exposure and close monitoring
  - No identification of new important safety issues in pediatric populations as well as with booster schemes

Discussions with regulators are ongoing to define most appropriate pathways to leverage current experience and ensure that variant-adapted vaccines can be made available in the future to timely address newly emerging variants / sublineages

③ Pandemic preparedness

An integrated, multi-faceted model for future pandemic preparedness



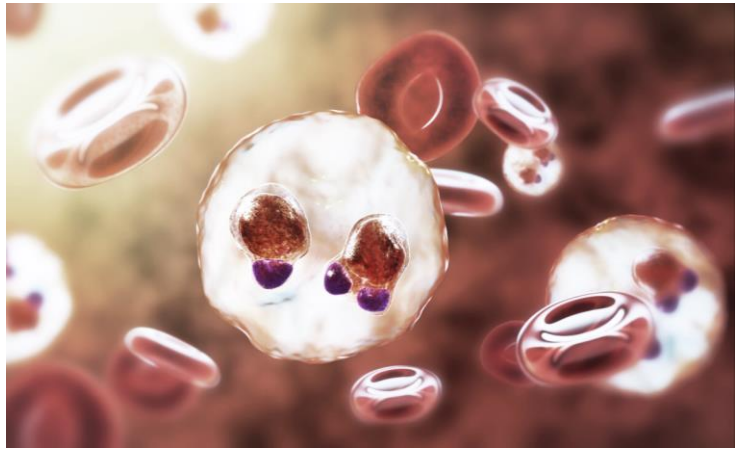
Our goal: Enable end-to-end manufacturing and delivery of our vaccines world-wide, whilst ensuring quality of production

Pandemic preparedness contract with German Federal Ministry of Health in April 2022

For the next five years: reserve and maintain manufacturing capabilities to produce at least 80 million mRNA-based vaccine doses per year

Malaria, tuberculosis, and HIV remain endemic

Malaria



~229 million cases
in 2020 across the WHO Africa Region

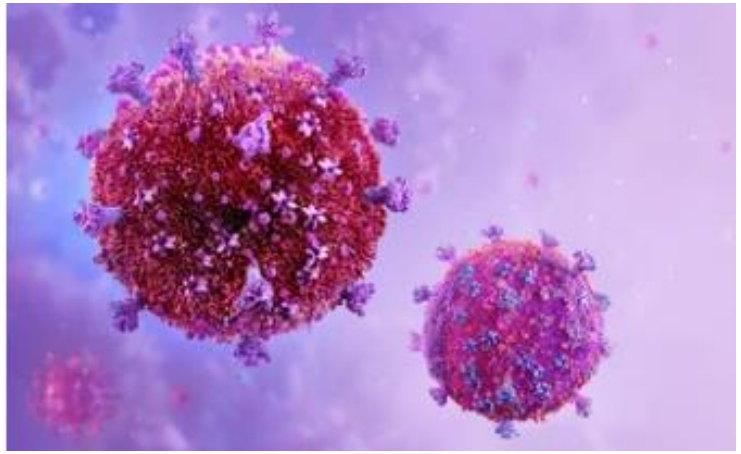
601,000 deaths
in 2020 in the WHO African Region
(**80% in children <5 years)**

Tuberculosis

10 million cases
globally in 2020

1.5 million deaths
globally in 2020

HIV

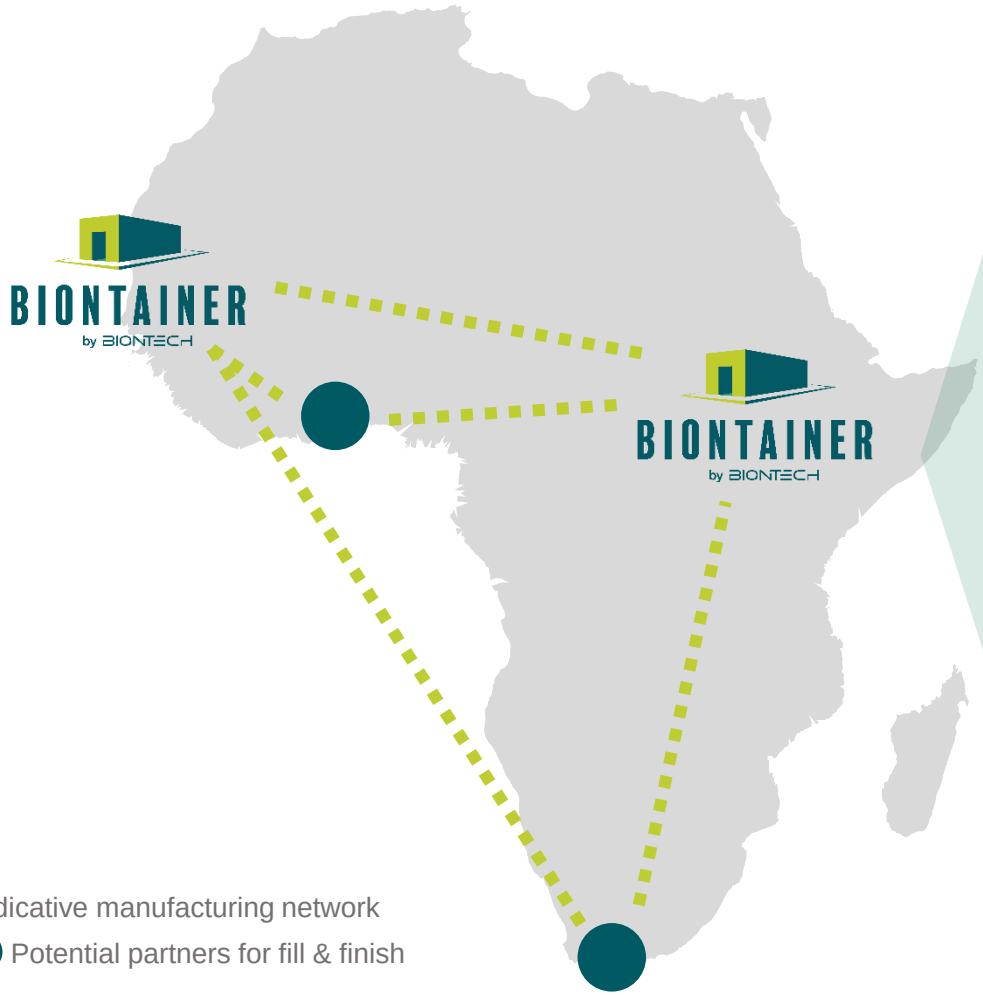


37.7 million living with HIV
(of whom 2/3 in the WHO Africa Region)

680,000 deaths
globally from HIV-related causes in 2020

HIV, human immunodeficiency virus; WHO, World Health Organization.
World Health Organization fact sheets. https://www.who.int/news-room/fact-sheets (accessed June 09, 2022).

BioNTainer: Building an mRNA manufacturing network to address infectious diseases in Africa and beyond



Indicative manufacturing network

Potential partners for fill & finish

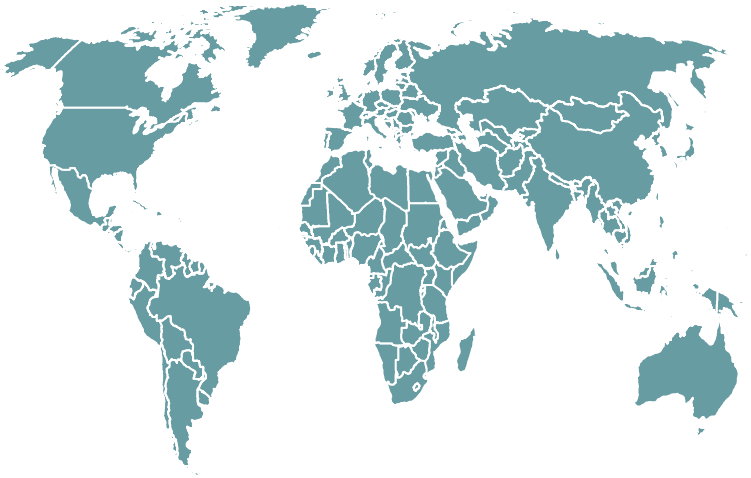
The BioNTainer solution aims to ensure:

- Acceleration of knowledge and technology transfer
- Rapid set-up of new mRNA manufacturing nodes for licensed mRNA vaccines
- Pandemic preparedness & other use cases
- Sustainability through maintenance and updating

Partner contribution:

- Utilities
- Access to talent
- Regulatory framework
- Operation permit
- Fill & finish capacity
- Logistics & supply

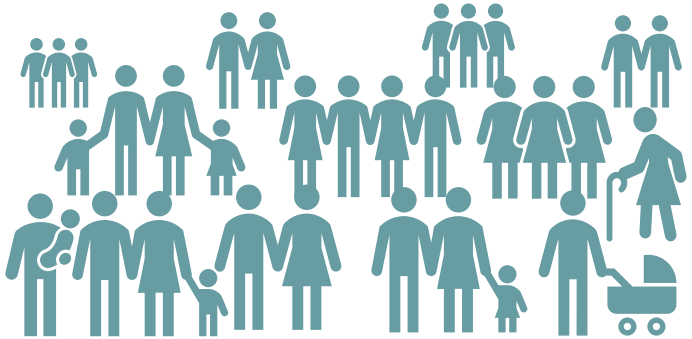
Urgent need for next-generation precision antibacterials



Prevent up to

10 million

deaths from antimicrobial resistance by 2050[1]



Improve standard-of-care for

>150 million

people suffering from chronic and severe bacterial infections[1]

Safeguard modern medicine via

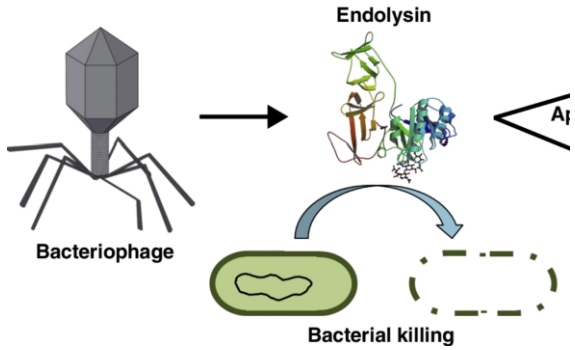
effective

antibacterials[1,2]

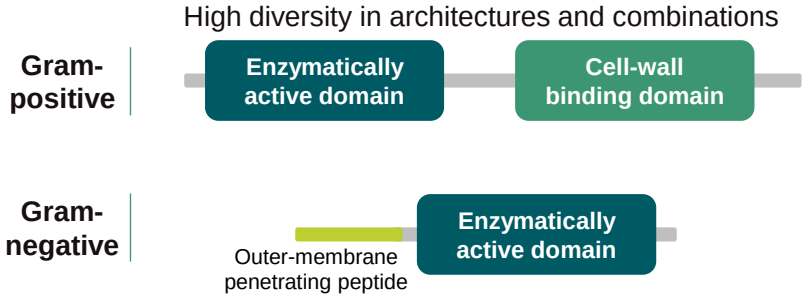
[1] Antimicrobial Resistance Collaborators. *Lancet* 2022; 399:629–655; [2] O'Neill J. Wellcome Collection. Attribution 2014; Available at: https://wellcomecollection.org/works/rdpck35v (accessed June 06, 2022).

Synthetic (endo)lysins – A potentially ideal class of precision antibacterials

Used by phages to degrade bacterial cell wall



Modular domain architecture

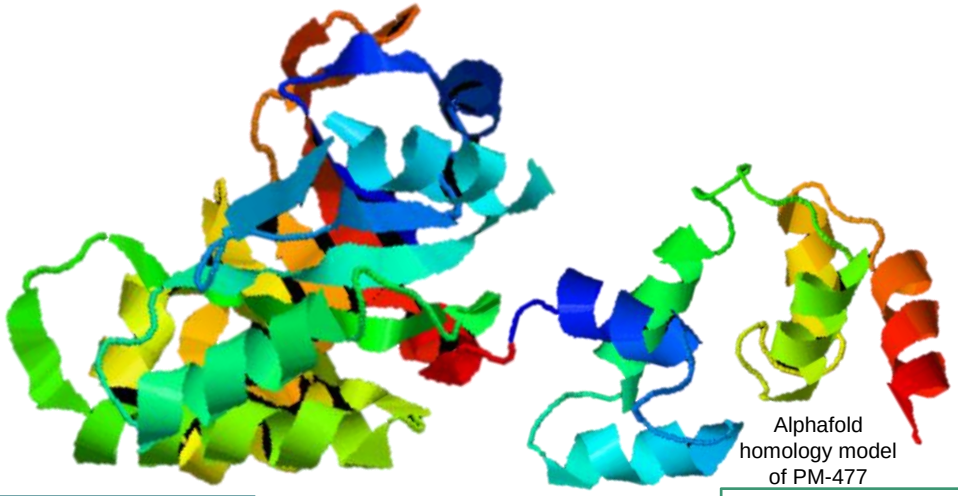


Highly potent	• Highly bactericidal • Minimum inhibitory concentration (MIC) often <1 µg/ml
No resistance	• Active on antibiotics-resistant bacteria • Resistance formation hardly possible
Biofilm active	• Lyse cell-wall irrespective of metabolic state • Penetrate biofilm matrix
Laser focus	• Do not harm beneficial bacteria • Suitable where microbiome has to be preserved
Safe	• Mammals have no peptidoglycan • Very safe, no off-target effects

(Endo)lysins could be developed against virtually any type of bacteria

[1] Fischetti VA. *Int J Med Microbiol* 2010; 300:357–362; [2] Vázquez R, *et al. J Virol* 2021; 95:e0032121; [3] Fowler VG, *et al. J Clin Invest* 2020; 130:3750–3760.

Diverse and modular domain architecture allows flexibility in engineering



Enzymatically active domain

EADs hydrolyze peptidoglycan

Different classes of EAD cleave 5 different chemical bonds in peptidoglycan

There are 28++ classes of EADs with low sequence similarity

Endolysins can have ≥1 EADs

Cell-wall binding domain

CBDs bind specific features on bacterial cell wall

CBDs mediate genus or species specificity (but EADs also contribute to specificity)

15+ different classes of CBDs known

Outer-membrane penetrating peptide (OMP)

Enzymatically active domain

To be active on Gram negative bacteria (outer-cell membrane), many but not all endolysins require **outer-membrane penetrating peptides**

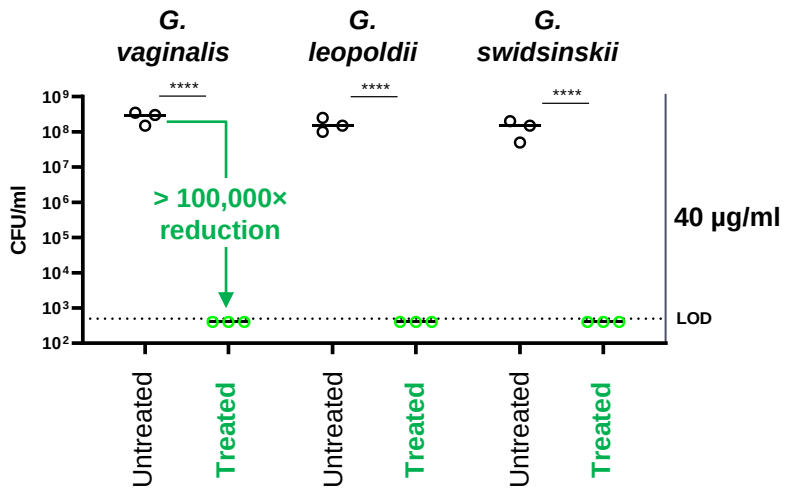
Engineered endolysins can combine modules of multiple classes
High sequence diversity and option space, even within one class

CBD, Cell-wall binding domain; EAD, enzymatically active domain.

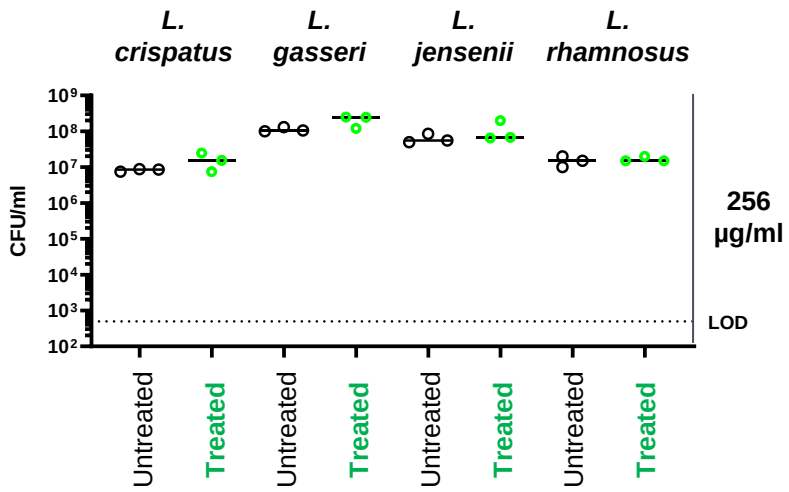
[1] Oliveira H, *et al. J Virol* 2013; 87:4558–4570; [2] Vázquez R, *et al. J Virol* 2021; 95:e0032121; [3] Gutiérrez D & Briers Y. *Curr Opin Biotechnol* 2021; 68:15–22.

Endolysins are highly potent and allow laser-focused microbiome modulation

Pathogenic bacteria[1]



Beneficial bacteria



Method: Bacteria grown *in vitro* and then treated with single dose of PM-477 for 5 hours. Suspension plated and CFU evaluated quantitatively on a $\log_{10}$ scale

MIC range (µg/ml) for *Gardnerella* (>20 strains tested)[2]

PM-477	Clindamycin	Metronidazole
0.03–1	<0.06–1	8 to **>128 (R)**

~60% of strains **resistant** to metronidazole (MDZ)

PM-477 with low MIC (0.1–1 µg/ml) for *Gardnerella*
Lactobacilli grow in the presence of high doses of PM-477 (MIC >256 µg/ml)

MIC, minimum inhibitory concentration
[1] Landlinger C, *et al. Pathogens* 2021; 10:54; [2] Landlinger C, *et al. Antimicrob Agents Chemother* 2022; 66:e0231921.

Expanding opportunities in infectious diseases: 4 first-in-human mRNA vaccine trial starts expected in 2022

Platform	Product candidate	Indication (targets)	Next milestone
mRNA vaccines	BNT162b2[1]	COVID-19	Data updates in 2022
	Omicron[1]	COVID-19	Data updates in 2022
	Omicron + BNT162b2[1]	COVID-19	Data updates in 2022
	BNT161[2]	Influenza	Data updates in 2022
	Preclinical unnamed program[2]	Shingles	First-in-human trial to start in 2H 2022
	BNT163 (prophylactic)[3]	HSV2	First-in-human trial to start in 2H 2022
	HeTVac (therapeutic)[3]	HSV2	
	BNT164[4]	Tuberculosis	First-in-human trial to start in 2H 2022
	BNT165	Malaria	First-in-human trial to start in 2H 2022
	Unnamed program[4]	HIV	
Ribolysins	Unnamed program	Precision antibacterials	

[1] Global co-development co-commercial agreement with Pfizer; [2] Global rights licensed to Pfizer; [3] University of Pennsylvania collaboration;
[4] Collaboration with Bill & Melinda Gates Foundation. BioNTech holds worldwide distribution rights except developing countries where BMGF holds distribution rights.

Q & A

BIONTECH

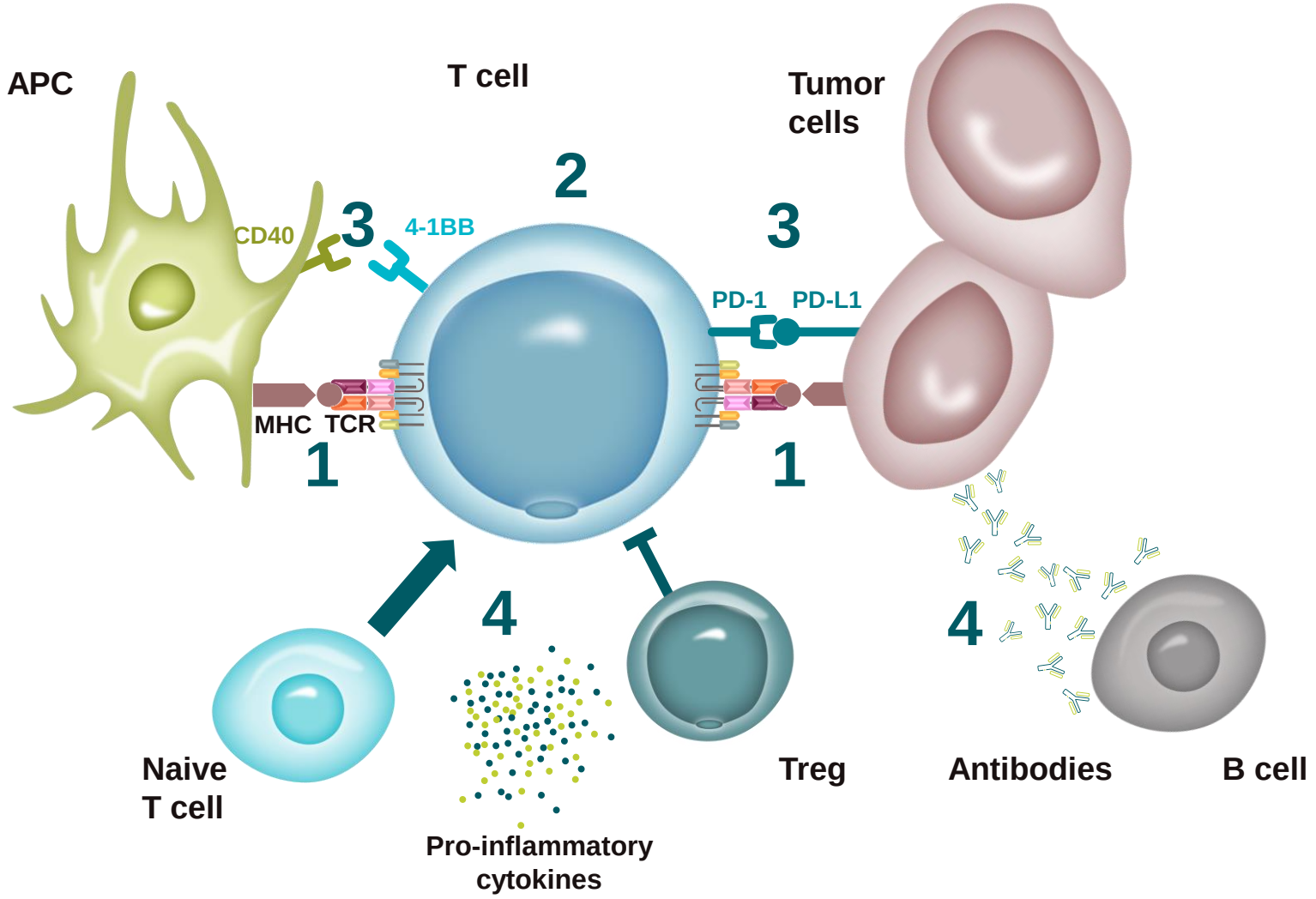
TIME FOR A

15-min BREAK!

BIONTECH

Oncology pipeline

Understanding and exploiting immunological mechanisms



1 mRNA-encoded cancer vaccines

Shared antigens
Individual antigens

2 CAR-, TCR-, and non-engineered cell therapies

Shared antigens
Individual antigens

3 Next-generation immunomodulators

Dual agonist
CPI + agonist

4 mRNA-encoded effector molecules

Antibodies
Cytokines

Oncology pipeline: Significant progress and expansion in 2022

Drug class	Platform	Product candidate	Indication (targets)	Pre-clinical	Phase 1	Phase 2	Phase 3	Milestones
mRNA	FixVac	BNT111	Advanced and R/R melanoma					FPD June 2021
		BNT112	Prostate cancer					
		BNT113	HPV16+ head and neck cancer					FPD, July 2021
		BNT115[1]	Ovarian cancer					
		BNT116	NSCLC					Start Phase 1/2
	iNeST	Autogene cevumeran (BNT122)[2]	1L melanoma					Data H2 2022
			Adjuvant colorectal cancer					FPD, Dec 2021
			Solid tumors					
			Adjuvant pancreatic ductal adenocarcinoma[1]					Follow-up trial
	Intratumoral immunotherapy	SAR441000 (BNT131)[3]	Solid tumors (IL-12sc, IL15-sushi, GM-CSF, IFNα)					
	RiboMabs	BNT141	Multiple solid tumors (CLDN18.2)					FPD Jan 2022
		BNT142	Multiple solid tumors (CD3×CLDN6)					Start Phase 1/2
	RiboCytokines	BNT151	Multiple solid tumors (optimized IL-2)					
		BNT152, BNT153	Multiple solid tumors (IL-7, IL-2)					
Cell therapies	CAR T cells + CARVac	BNT211	Multiple solid tumors (CLDN6)					Ph 2 planned 2023
		BNT212	Pancreatic, other cancers (CLDN18.2)					
	Neoantigen-based T cells	BNT221 (NEO-PTC-01)	Multiple solid tumors					
	TCR engineered T cells	To be selected	All tumors					
Antibodies	Next-gen checkpoint immunomodulators	GEN1046 (BNT311)[4]	Metastatic NSCLC (PD-L1×4-1BB)					FPD, Dec 2021
			Multiple solid tumors (PD-L1×4-1BB)					
		GEN1042 (BNT312)[4]	Multiple solid tumors (CD40×4-1BB)					
	Targeted cancer antibodies	BNT321 (MVT-5873)	Pancreatic cancer (sLea)					
SMIM	Toll-like receptor binding	BNT411	Solid tumors (TLR7)					

SMIM, small molecule immunomodulators.
[1] Investigator-initiated Phase 1 trial; [2] Collaboration with Genentech; [3] Collaboration with Sanofi; [4] Collaboration with Genmab.

Unique combination potential across platforms

Selected examples in the clinic

mRNA cancer vaccines

+

Approved anti-PD-1/PD-L1

Vaccine-induced T-cell response
+
expansion through PD1 blockade

Several Phase 1 and Phase 2 trials ongoing for both FixVac and iNeST platforms in combination with anti-PD1

mRNA cancer vaccines

+

mRNA-encoded cytokines

Vaccine-induced T-cell response
+
amplification through RiboCytokines

BNT151, BNT153: IL-2 RiboCytokines in preclinical studies

Engineered cell therapies

+

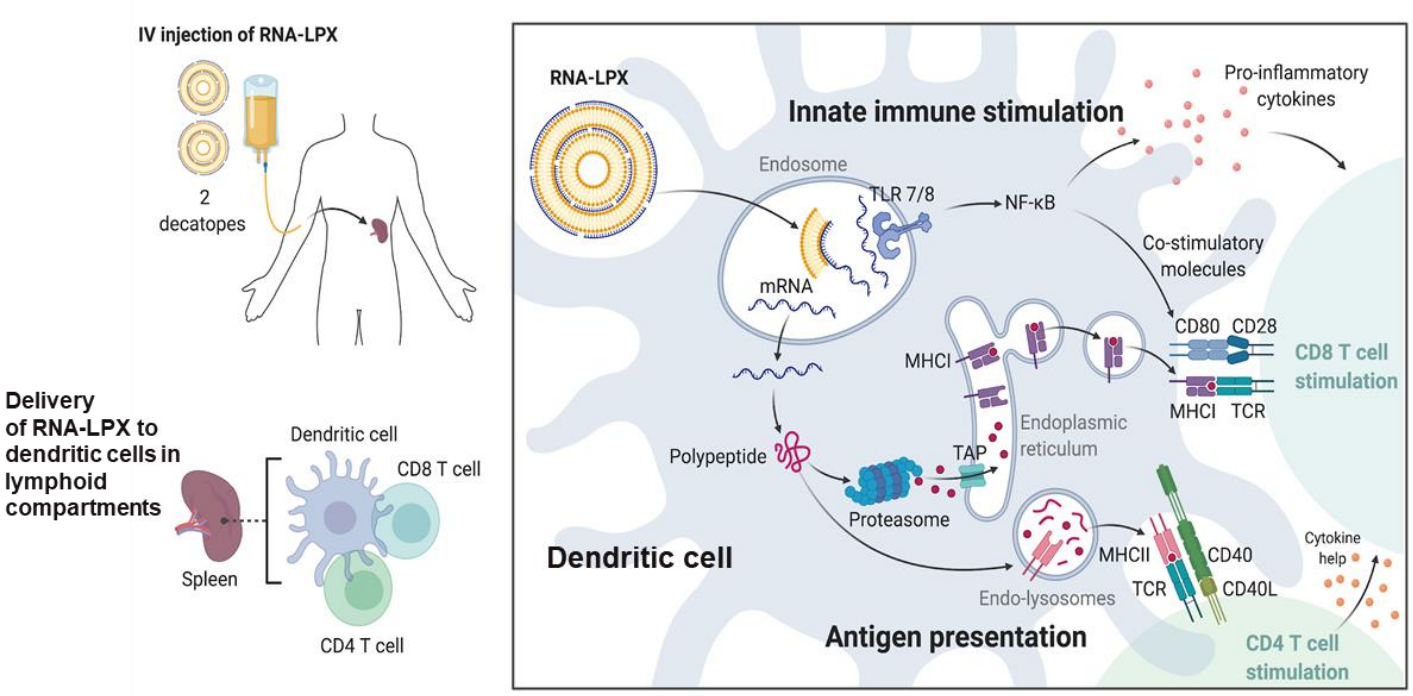
mRNA cancer vaccines

Autologous CAR T-cell therapy
+
vaccine-amplified T-cell response

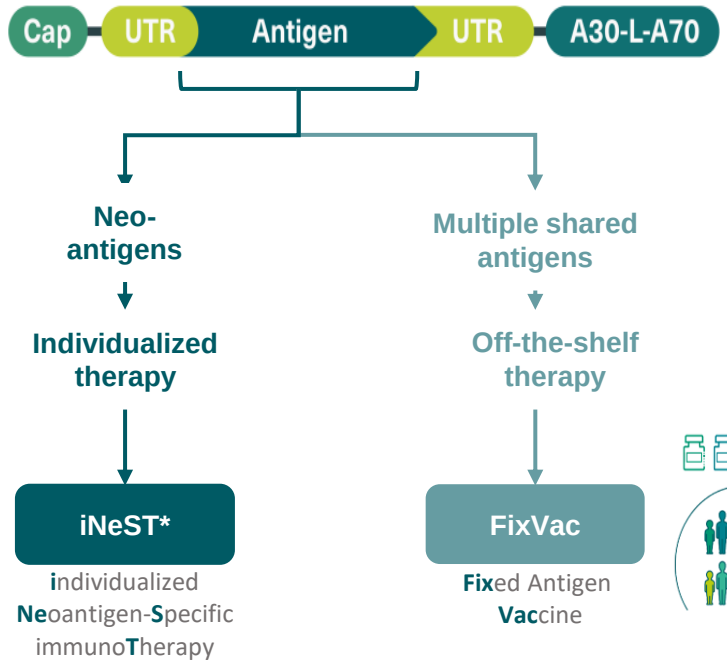
BNT211: Ongoing Phase 1 trial across multiple tumors


BIONTECH
mRNA
cancer vaccines

mRNA vaccines for enabling potent multi-targeting of cancers



Backbone optimized uridine mRNA (uRNA)



Kranz LM, et al. Nature 2016; 534:396–401; Lopez J, *et al.* AACR Annual Meeting 2020; Oral presentation CT301.
* Collaboration with Genentech.

iNeST | Autogene cevumeran (BNT122)

Driving continuous iNeST innovation with data

Driven by data

Constant improvement as more data are generated and analyzed

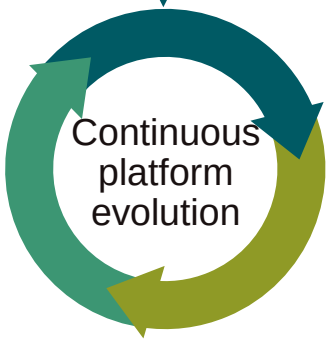
Selection algorithms

AI and ML optimization

Just-in-time manufacturing

Dedicated mRNA GMP production facilities

Targeting delivery of <5 weeks

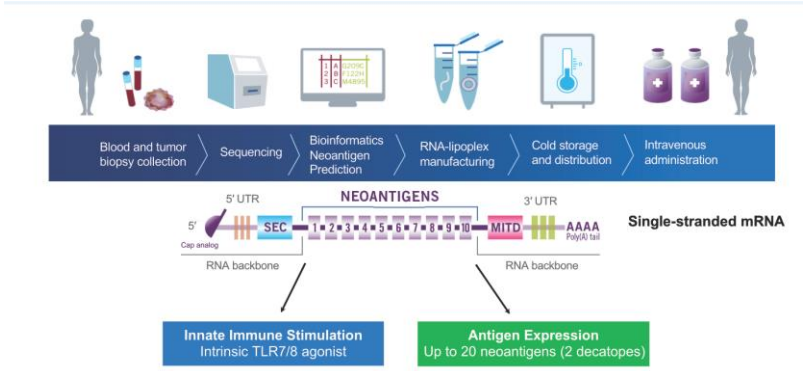


iNeST is being developed in collaboration with Genentech.

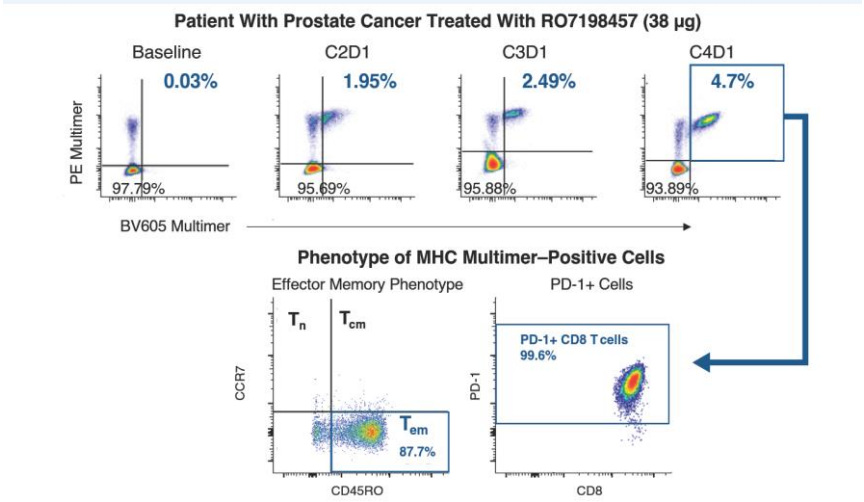
iNeST | Autogene cevumeran (BNT122)
Phase 1 as monotherapy and in combination with atezolizumab

- Data from Phase 1 trial in heavily pre-treated, PD-L1 low patients across multiple tumor types
- Demonstrated ability to elicit significant T cell responses of both effector and memory phenotype as monotherapy and in combination (multiple patients with > 5% T cell response per neoepitope)
- Treatment-related adverse events were primarily transient systemic reactions, manifesting as low-grade CRS, IRR or flu-like symptoms
- Initial signals of clinical activity observed as single agent and in combination with Atezo

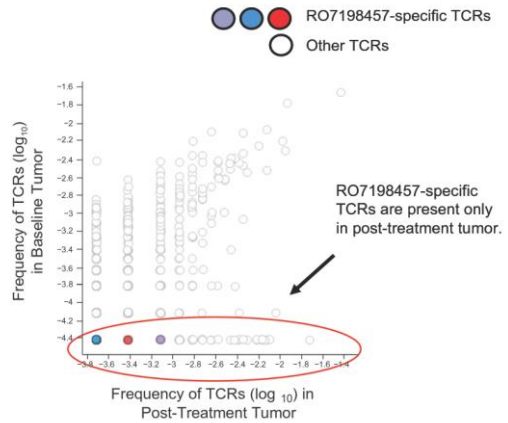
Evaluation of BNT122 safety & feasibility with/without Tecentriq in > 10 indications



BNT122 induces CD8+ T cells in CPI-sensitive and CPI-insensitive tumor types



BNT122 induces CD8+ T cell Infiltrates in tumors



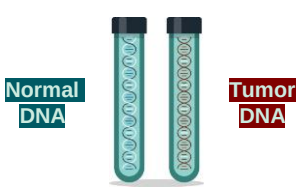
CPI, checkpoint inhibitor; PR, partial response; PD, progressive disease; SD, stable disease.

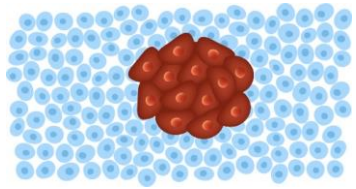
1. Sahin U, *et al. Nature* 2017; 547:222–226; BNT121 was a precursor to BNT122 and the iNeST collaboration with Genentech.
2. Lopez J, *et al.* AACR Annual Meeting 2020; Oral presentation CT301; 3. Braiteh F, *et al.* AACR Annual Meeting 2020; Poster presentation CT169; 4. Collaboration with Genentech.

iNeST | Autogene cevumeran (BNT122)

Neoantigen vaccines are well suited for the early-line setting

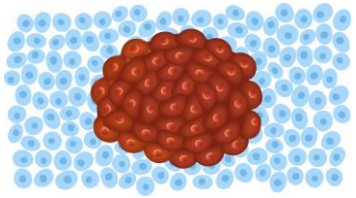
Adjuvant





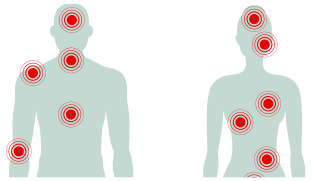
Residual cancer cells may remain – emphasis on recurrence free survival

1L metastatic



Rapidly growing but often still in early phase of metastases

Late-line metastatic



Bulky tumors with multiple organs involved

	Early line (adjuvant/first line)	Late line (refractory)
Tumor mass	Low tumor burden	Large bulky tumors
Tumor resistance mechanisms	Not fully established	Multiple resistance mechanisms
Immune system health	Functional T cell responses inducible	Higher rate of dysfunctional immune cells

Three trials ongoing in early lines:

- Advanced melanoma (Phase 2)
- Adjuvant colorectal cancer (Phase 2)
- Adjuvant pancreatic ductal adenocarcinoma (Phase 1)

iNeST is being developed in collaboration with Genentech.

iNeST | Autogene cevumeran (BNT122)
Phase 2 open-label, randomized trial in 1L advanced melanoma

- Advanced metastatic or unresectable melanoma
- Previously untreated

Safety run-in (n=6–12)

Pembrolizumab 1 cycle → **BNT122 + pembrolizumab**

R 1:2

Pembrolizumab 200 mg q3w, ≤24 months

Cross-over allowed after confirmed PD

Pembrolizumab (1 cycle) 200 mg q3w → **BNT122 + pembrolizumab** ≤24 months total

Key endpoints

- **Primary:** PFS
- Secondary: ORR
- Efficacy: OS, DoR, ORR post crossover
- Safety
- Quality of life

Status

- n=131 enrolled (active, not recruiting)
- Success may unlock 1L use of iNeST in CPI-sensitive advanced cancers for combination therapy
- Collaboration with Genentech

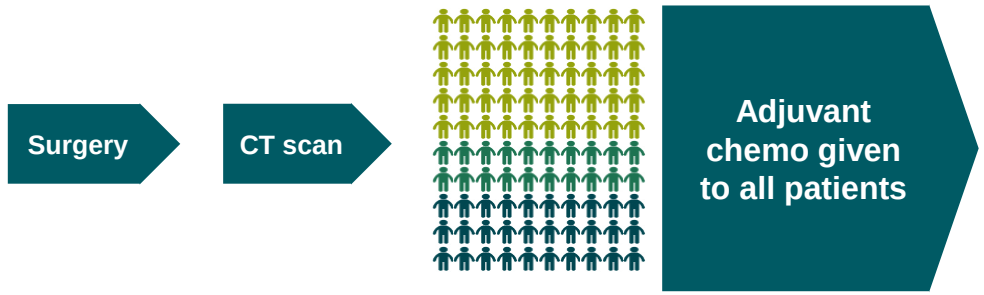
CPI, checkpoint inhibitor; DoR, duration of response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.
ClinicalTrials.gov: NCT03815058.

High medical need in the adjuvant treatment of Stage II (high risk)/Stage III colorectal cancer

High medical need in the adjuvant treatment of Stage II (high risk)/Stage III colorectal cancer

- Colorectal cancer is second deadliest cancer worldwide[1], 5-year OS in regional disease is 71%[2]
- SoC in Stage II (high risk) and Stage III CRC after removal of the primary tumor and adjuvant chemotherapy is watchful waiting
- ctDNA is a marker for minimal residual disease and thus can identify patients at high risk of disease recurrence[3,4]
- In ctDNA-positive, Stage 2 (high risk) and Stage 3 CRC post adjuvant chemotherapy, duration of disease-free survival is 6 months[5]

Stage II (high risk) and Stage III colorectal cancer

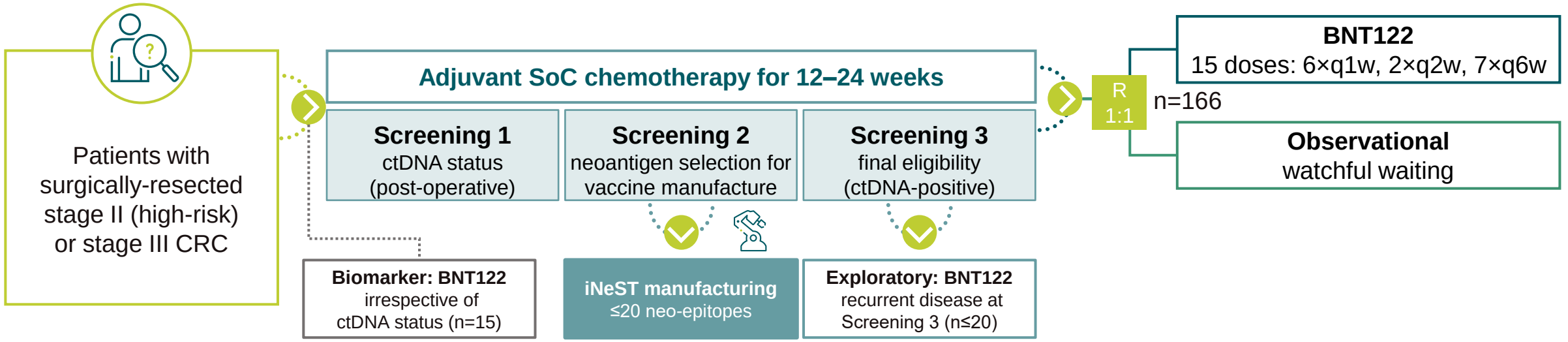


No residual disease	50%	Cured by surgery alone
Microscopic residual disease	20%	Cured by chemo on top of surgery
	30%	Recur despite surgery + chemo

CRC, colorectal cancer; ctDNA, circulating tumor DNA; ; OS, overall survival; SoC, standard of care.,
[1] WHO factsheet on cancer. 2018; [2] Seer database; [3] Fan G, *et al. PLoS One* 2017; 12: e0171991;
[4] Loupakis F, *et al. JCO Precis Oncol* 2021; 5:PO.21.00101; [5] Reinert T, *et al. JAMA Oncology*, 2019; 5:1124−1131.

iNeST | Autogene cevumeran (BNT122)

Phase 2 randomized trial vs watchful waiting in adjuvant colorectal cancer



Key endpoints

- **Primary:** Disease-free survival (DFS)
- Efficacy: RFS, TTR, TTF, OS
- Change in ctDNA status

Status

- First patient dosed (randomized cohort): December 2021
- Collaboration with Genentech

CRC, colorectal cancer; ctDNA, circulating tumor DNA; OS, overall survival; q1/2/6w, every 1/2/6 weeks; R, randomize; RFS, relapse-free survival; SoC, standard of care; TTF, time to treatment failure; TTR, time to response.
ClinicalTrials.gov: NCT04486378.

iNeST | Autogene cevumeran (BNT122)

Phase 1 trial of adjuvant BNT122 in pancreatic ductal adenocarcinoma

Surgically resectable PDAC

- No borderline resectable
- No locally advanced or metastatic
- No neoadjuvant therapy

Week 0	Week 6	Weeks 9–17	Weeks 21–43	Week 46	
Surgery	**Atezolizumab** 1 dose	**BNT122** 8 priming doses	**mFOLFIRINOX** 12 q2w cycles	**BNT122** 1 booster dose	Follow-up

Custom manufacture of BNT122;
up to 20 neo-antigenes from tumor sample

High unmet need in PDAC

PDAC: anticipated to be the 2nd leading cause of cancer-related death in the US by 2030

- Surgery offers the only chance of cure
- 5-year survival rates after resection alone: ~10%
- 69−75% relapse within 2 years after adjuvant therapy

Immunotherapy resistant:

- Low mutation burden presumed few mutation-derived neoantigens

Key endpoints

- **Primary:** Safety
- Immunogenicity
- Feasibility
- 18-month recurrence-free survival (RFS)

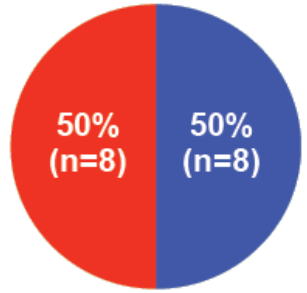
Status

- Target accrual n=20
- Investigator-initiated single-center study
- Collaboration with Genentech
- MSKCC-sponsored study

mFOLFIRINOX, modified FOLFIRINOX; PDAC, pancreatic ductal adenocarcinoma; q2w, every 2 weeks.
Balachandran VP, *et al.* ASCO Annual Meeting 2022; Poster presentation 2516; ClinicalTrials.gov: NCT04161755.

iNeST | Autogene cevumeran (BNT122): Substantial and durable T cell expansion observed in immune responders after BNT122 treatment

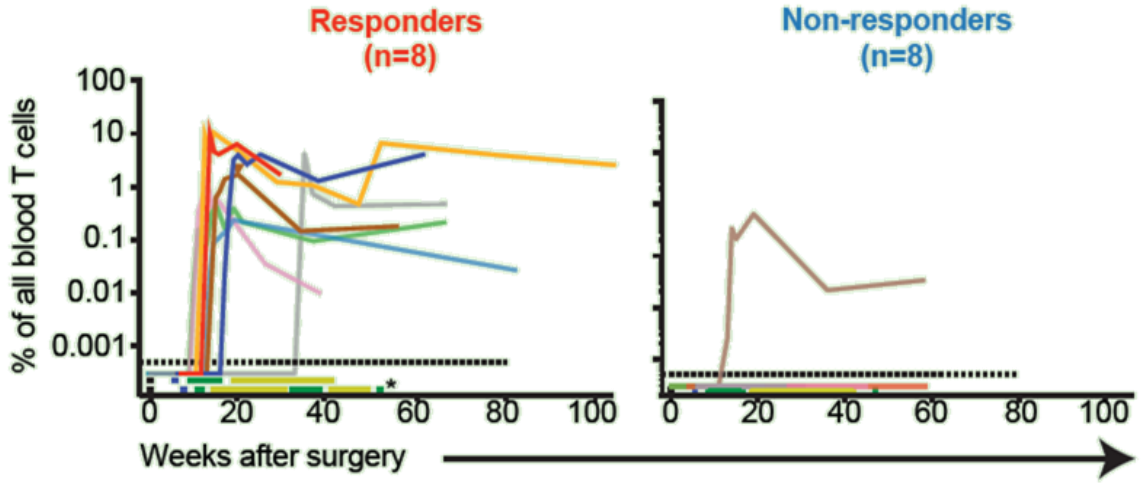
Immunogenicity



Immune responder
Immune non-responder

Responder = positive assay 1 and 2

Assay 1: T-cell clonal expansion by TCRVβ sequencing



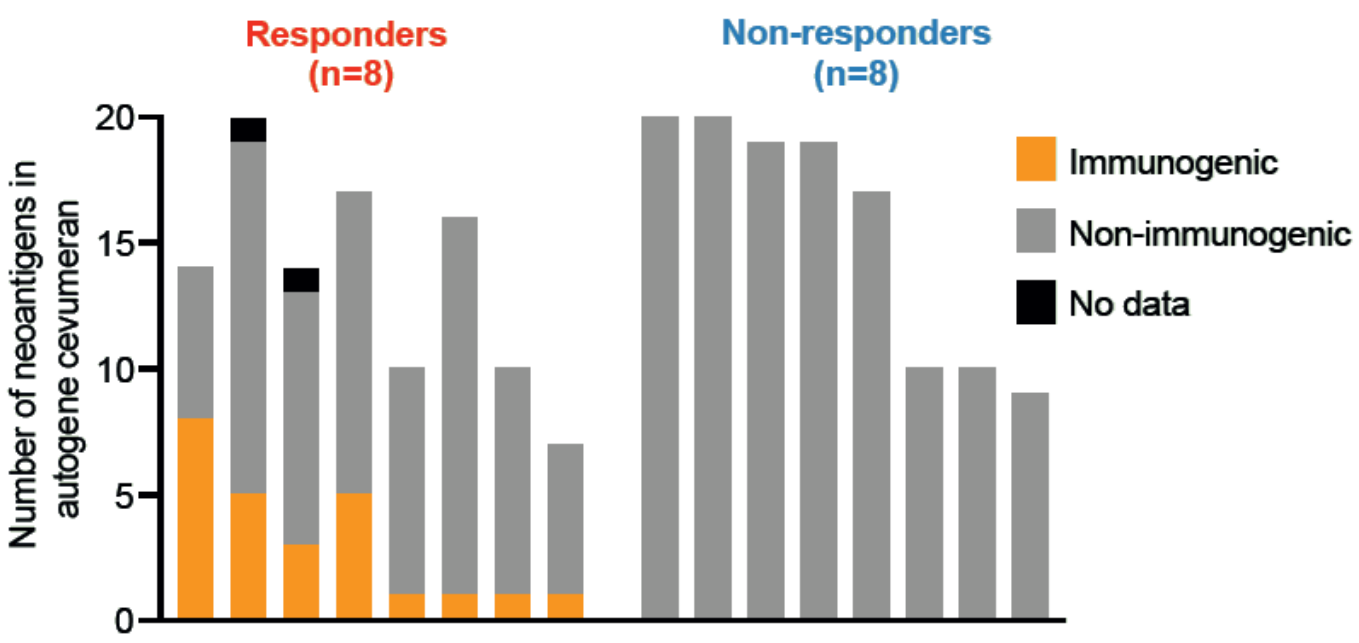
Median % of all blood T cells (95% CI)

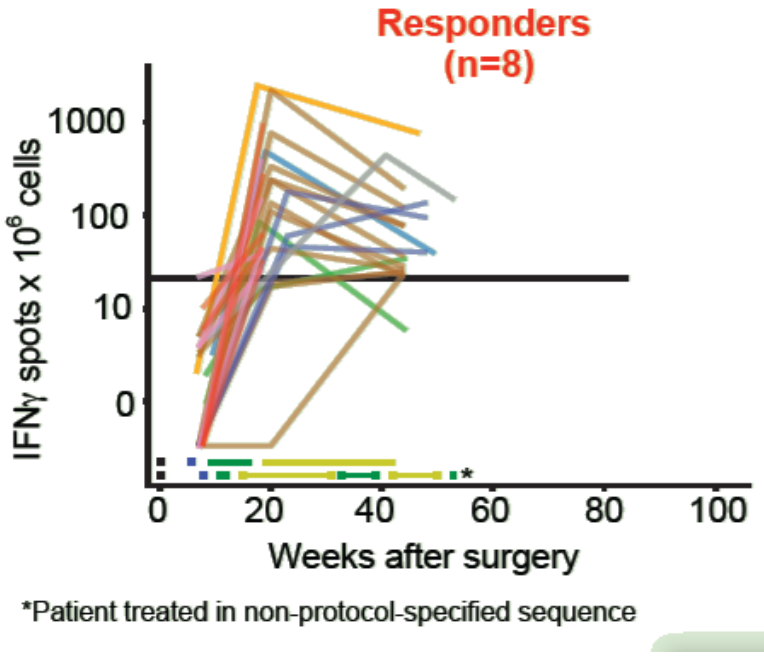
	Pre-vaccine	Post-vaccine	P value
Non-responders (n=8)	0 (0.0)	0 (0.0)	0.001
Responders (n=8)	0 (0.0)	2.9 (0.2−10.4)	

iNeST is being developed in collaboration with Genentech.
Balachandran VP, *et al.* ASCO Annual Meeting 2022; Poster presentation 2516.

iNeST | Autogene cevumeran (BNT122)
Functional T cells confirmed by ELISPOT in immune responders

Assay 2: T cell specificity to autogene cevumeran neoantigens by IFNγ ELISPOT





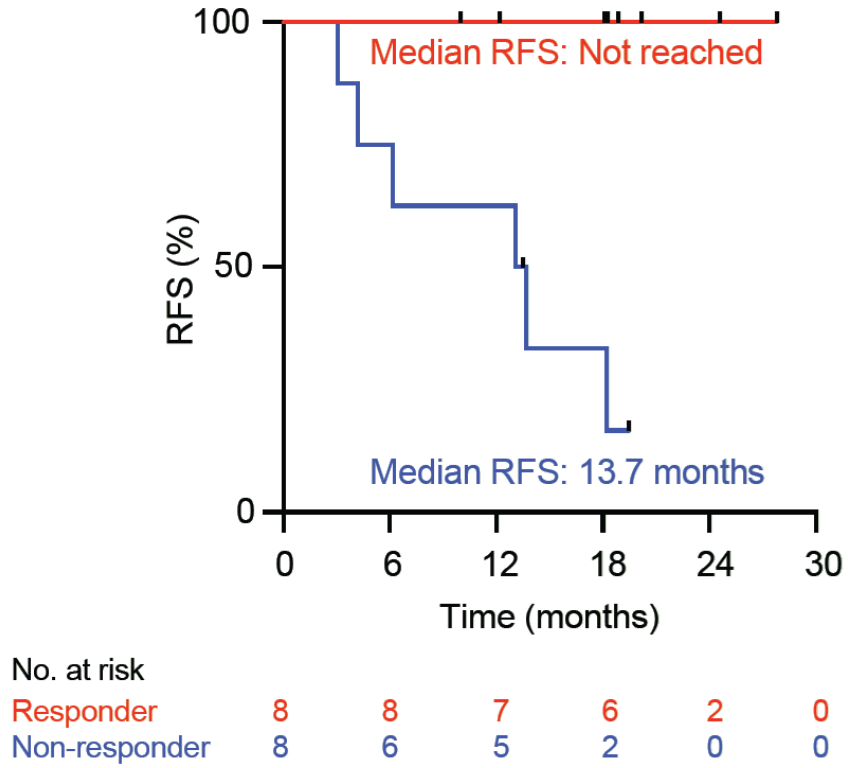
*Patient treated in non-protocol-specified sequence

iNeST is being developed in collaboration with Genentech.
Balachandran VP, *et al.* ASCO Annual Meeting 2022; Poster presentation 2516.

iNeST | Autogene cevumeran (BNT122)

Immune response correlates with delayed recurrence in adjuvant PDAC

RFS from resection (n=16)



- Responder = positive assay 1 and 2
- Median follow-up: 18 months
- HR=0.08 (95% CI 0.01–0.40); p=0.003

A follow-up randomization trial is being developed

iNeST is being developed in collaboration with Genentech.

Balachandran VP, *et al.* ASCO Annual Meeting 2022; Poster presentation 2516.

FixVac
Leveraging shared tumor-associated antigens for cancer treatment

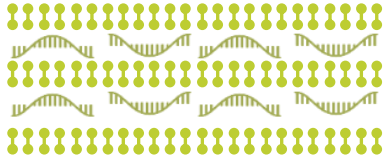
Vaccine backbone with shared antigens

Backbone-optimized uridine mRNA (uRNA)

Multi-antigen approach
tailored to each indication

+

Lipoplex



RNA-LPX formulation (IV)

=

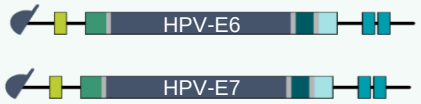
FixVac

Fixed vaccine combination against shared tumor-associated antigens

Melanoma

BNT111 encodes 4 tumor-associated antigens covering >90% of patients with cutaneous melanoma

HPV16+ HNSCC

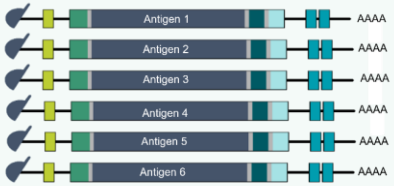


BNT113 encodes 2 oncoproteins exclusively expressed in pre-malignant and malignant tissue

Prostate cancer

BNT112 encodes 5 related antigens specific to prostate cancer

NSCLC



BNT116 encodes 6 different NSCLC tumor-associated antigens

HNSCC, head and neck squamous-cell carcinoma; HPV, human papilloma virus; NSCLC, non-small-cell lung cancer.

Treatment options needed to address CPI failure in advanced melanoma

Melanoma remains the deadliest skin cancer[1,2]

Incidence

↑ **50%**

Annual cases have increased by nearly 50% to over 287,000[1,2]

Deaths

↑ **20%**

WHO predicts by 2025, number of deaths will increase by 20%[3]

CPI R/R patients

~ 55%

patients refractory to or relapse on CPI treatment, leaving them with limited treatment options[4]

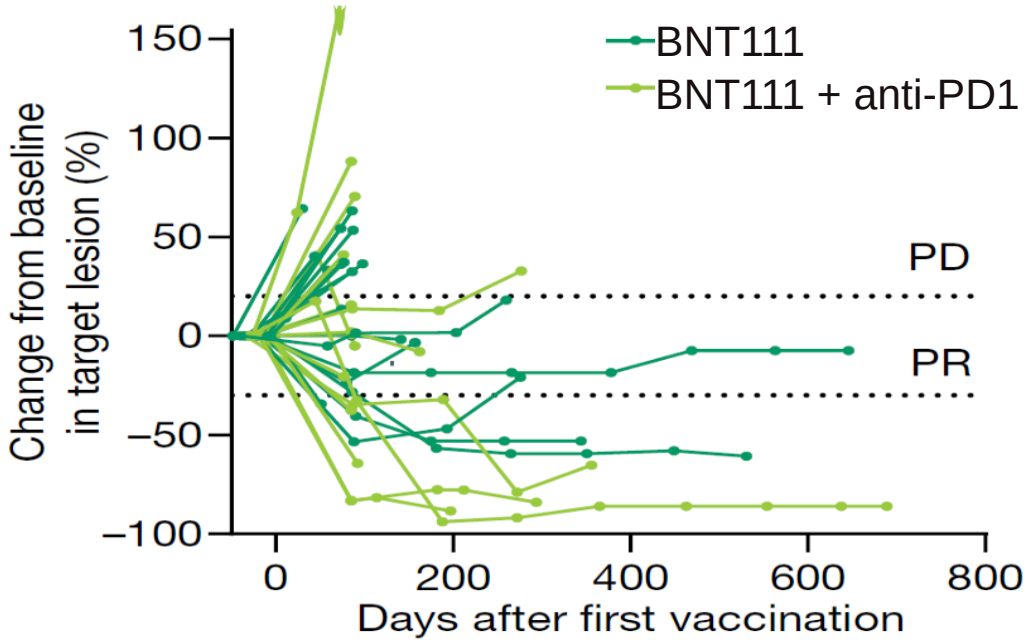
Significant opportunity to improve on standard of care

- 5-year survival for metastatic melanoma still only 29.8%[5]
- Frontline immunotherapy with CPI induces durable responses in max. 45−50% of patients but with relatively short PFS[4]
- CPI resistant/refractory patients that fail to respond to CPI or relapse after CPI have an especially poor prognosis with survival as short as 6 months depending on risk factors
- Advanced CPI R/R melanoma is a high medical need population with highly unfavorable prognosis

CPI, checkpoint inhibitor; DoR, duration of response; mPFS, median progression free survival; ORR, overall response rate; R/R, refractory/resistant; WHO, World Health Organization.
[1] Available at: https://www.melanomauk.org.uk/2020-melanoma-skin-cancer-report; [2] Global Cancer Observatory – 2018 data from 'Cancer Today'; [3] Global Cancer Observatory – projected 2025 data from 'Cancer Tomorrow'; [4] Larkin J. *et al. N Engl J Med* 2019; 381:1535−1546; [5] Available at: https://seer.cancer.gov/statfacts/html/melan.html (accessed August 06, 2021.

FixVac | BNT111
Durable responses in a Phase 1/2 trial in advanced CPI-experienced melanoma

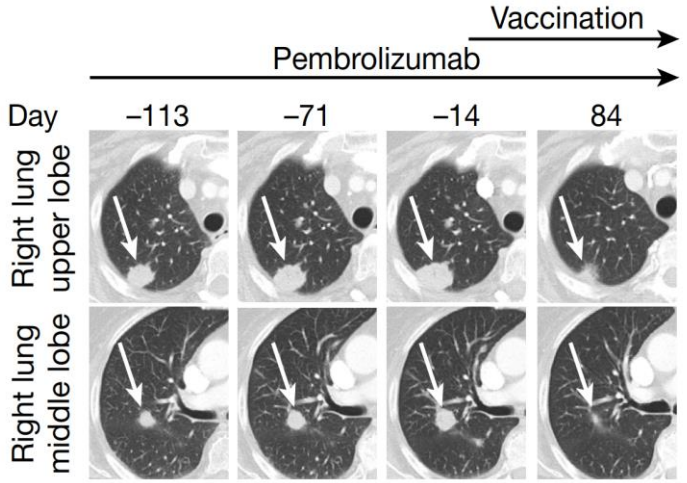
Article
nature
An RNA vaccine drives immunity in checkpoint-inhibitor-treated melanoma
https://doi.org/10.1038/s41586-020-2537-9
Ugur Sahin[1,2,3,4✉], Petra Oehm[1], Evelyna Derhovanessian[1], Robert A. Jabulowsky[1],



Lipo-MERIT trial

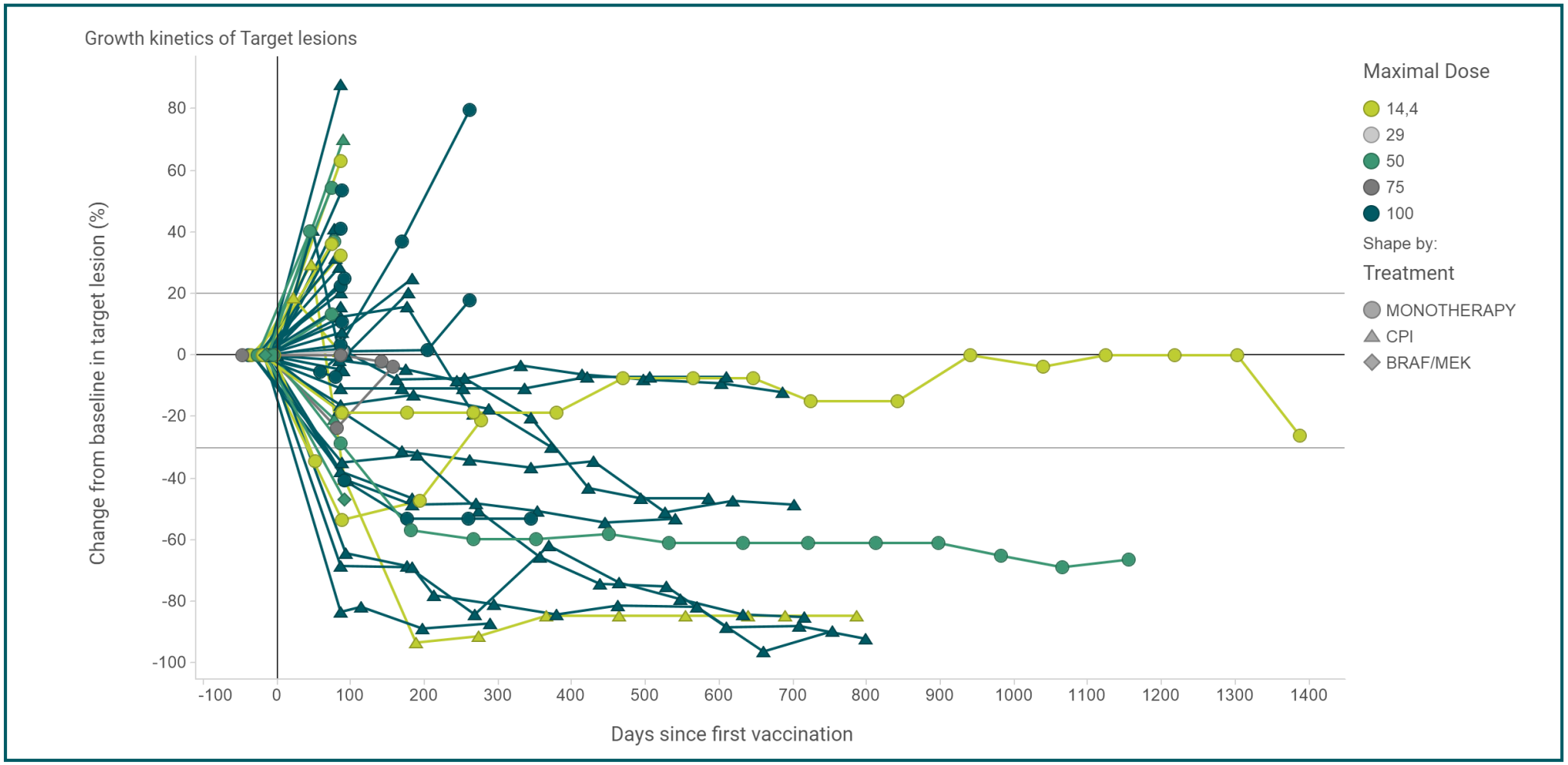
- Phase 1 trial data in CPI-experienced patients in monotherapy and in combination with anti-PD1

Analysis of patient subset with evaluable disease:
- All patients showed TAA-specific T-cell responses (post-IVS ELISpot)
- >75% of patients showed strong immune responses against ≥1 TAA (*ex vivo EliSpot)*
- **Durable ORR[1] in CPI-experienced patients**
  - BNT111 (n=25): **3 PRs** and **8 SDs[2]**
  - BNT111 + anti-PD1 (n=17): **6 PRs** and **2 SDs (ORR=35%)**
  - **Highest ORR=50%** in 5/10 patients treated with 100 µg of BNT111 + anti-PD1



Data cut-off: July 29, 2019.
[1] Patients evaluable for efficacy; [2] One patient had a metabolic complete response with SD as best response, according to irRECIST1.1.
CPI, checkpoint inhibitor; ORR, overall response rate; PR, partial response; SD, stable disease; TAA, tumor-associated antigen.
Sahin U, *et al. Nature* 2020; 585:107–112.

FixVac | BNT111 – Long duration of clinical responses observed for patients receiving BNT111 monotherapy and combination with CPIs[1]

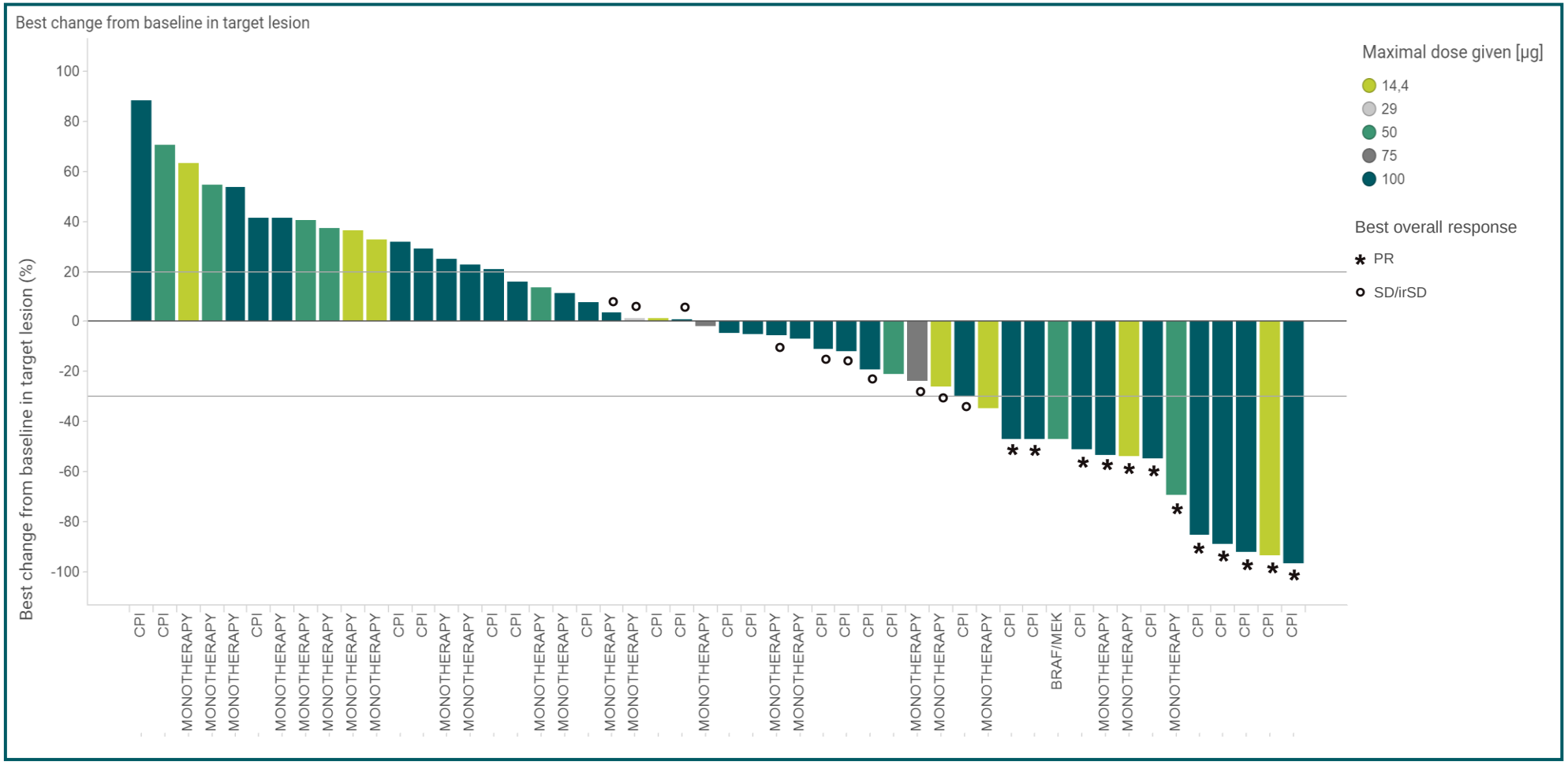


Data cut-off: May 24, 2021.

[1] One patient in the BNT111 monotherapy group who achieved a CR is not shown as only non-measurable target lesions were present (which later disappeared).

CPI, checkpoint inhibitor; CR, complete response

FixVac | BNT111 – Tumor shrinkage observed in patients receiving BNT111 monotherapy or combination with a PD-1 inhibitor [1,2]



Data cut-off: May 24, 2021.

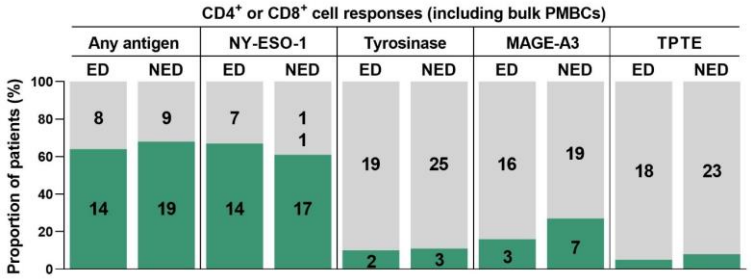
[1] One patient had an 83.2% decrease of target lesion from baseline but experienced a new target lesion and had SD as the best overall response. Patient B4-31 had several new lesions despite a reduction in the target lesions; [2] One patient in the BNT111 monotherapy group who achieved a CR is not shown as only non-measurable target lesions were present (which later disappeared).
CPI, checkpoint inhibitor; irRECIST, immune-related response evaluation criteria in solid tumors; SD, stable disease.

FixVac | BNT111

Strong immunogenicity and promising clinical activity in Phase 1 Lipo-MERIT

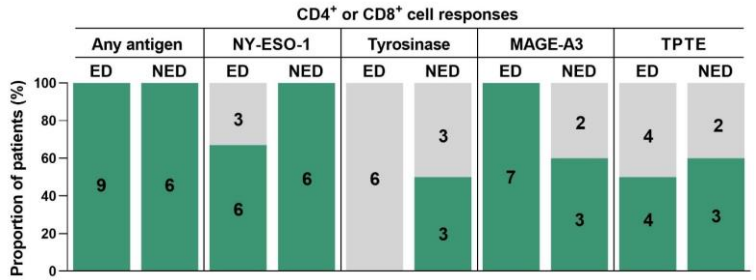
Comparable CD4+ and CD8+ T-cell responses was shown between ED and NED patients

Ex vivo ELISpot (ED, n=22; NED, n=28)



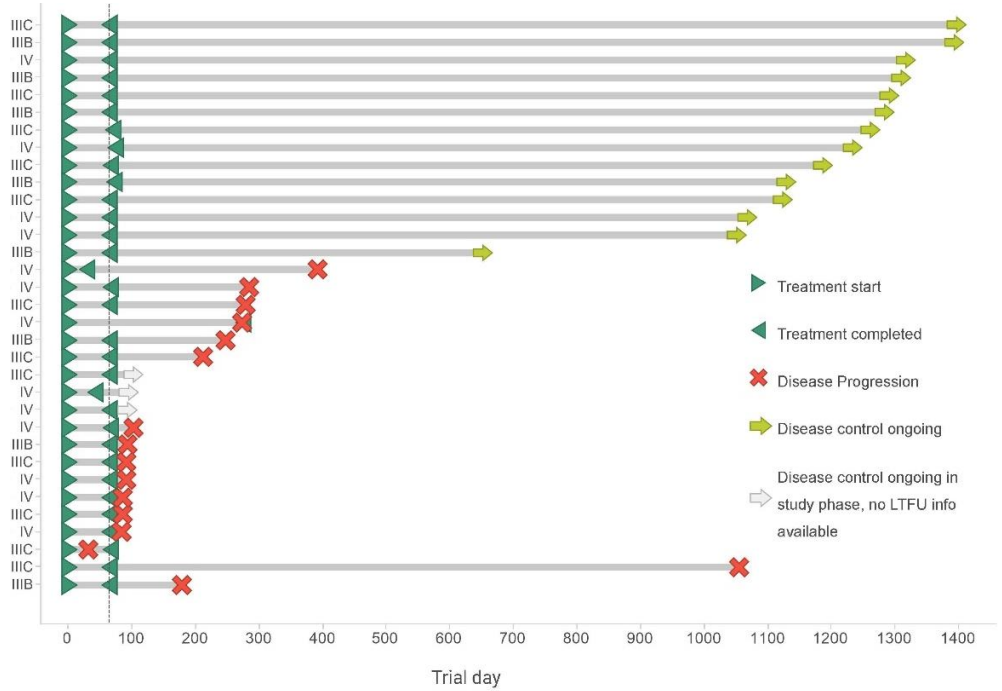
***Ex vivo* responses**
ED: 64% (n=14)
NED: 68% (n=19)

Post-IVS ELISpot (ED, n=9; NED, n=6)



T-cell response against ≥1 TAA observed in all patients

Preliminary disease-free survival in patients with no evidence of disease at trial inclusion



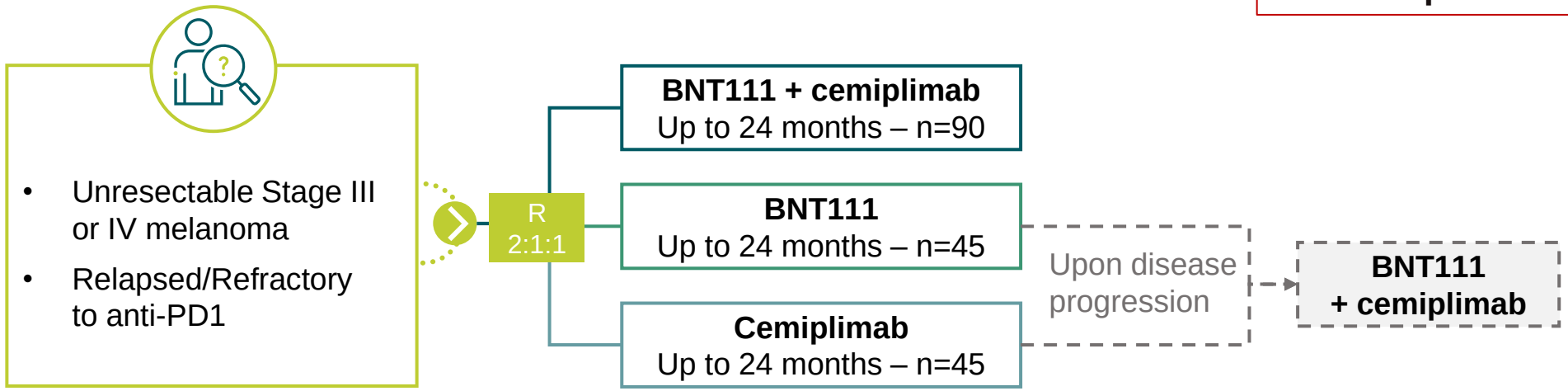
- In NED patients: 34.8 month median DFS (95% CI: 7.0–NR) after a median follow-up of 40.7 months (95% CI: 35.3–42.7)

Data cut-off: May 24, 2021.
ED, evidence of disease; IVS, *in vitro stimulation;* NED, no evidence of disease; NR, not reached; TAA; tumor associated antigen.
Loquai C, *et al.* SITC Annual Meeting 2021; Poster presentation 549.

FixVac | BNT111

Phase 2 randomized trial ± cemiplimab in patients with anti-PD1-R/R melanoma

US FDA Fast Track Designation and Orphan Drug Designation



Key endpoints

- **Primary:** Combination arm: ORR
- Efficacy: ORR, DoR, DCR, TTR, PFS, OS
- Safety, including immune-related AEs
- Quality of life

Status

- First patient dosed: June 2021
- n=180
- Global trial (Australia, Germany, Italy, Poland, Spain, UK, US)
- Collaboration with Regeneron

Success measures

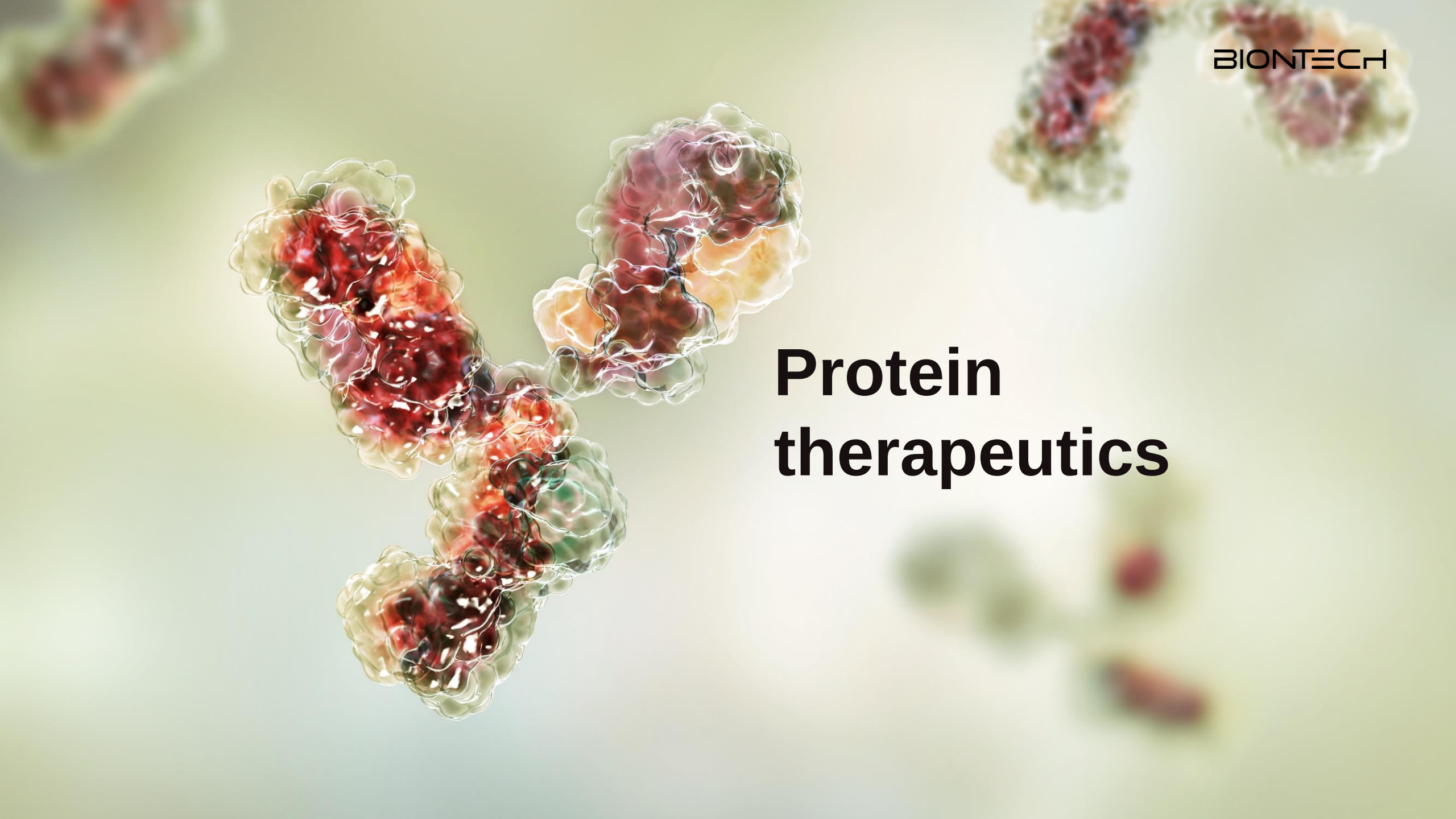
- ORR=30%

DCR, disease control rate; DoR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression free survival; R/R, relapsed/refractory; TTR, time to response.
ClinicalTrials.gov: NCT04526899.

mRNA cancer vaccines near-term milestones

Platform	Product candidate	Indication (targets)	Next milestone
iNeST Neoantigen mRNA vaccine	Autogene cevumeran (BNT122) + pembrolizumab[1]	1L melanoma	Phase 2 fully recruited; data update H2 2022
	Autogene cevumeran (BNT122)[1]	Adjuvant colorectal cancer	Phase 2 ongoing (FPD, December 2021)
	Autogene cevumeran (BNT122) ± atezolizumab[1]	Solid tumors	Phase 1 fully recruited
	Autogene cevumeran (BNT122) ± atezolizumab[1,2]	Adjuvant PDAC	Follow-up randomized trial being developed
FixVac Fixed-combination mRNA vaccine	BNT111 ± anti-PD1	Advanced melanoma	Phase 1 ongoing
	BNT111 ± cemiplimab	R/R melanoma	Phase 2 ongoing (FPD, June 2021) – **US FDA Fast Track Designation and Orphan Drug Designation**
	BNT112 ± cemiplimab	Prostate cancer	Enrolment ongoing for Part 2
	BNT113 + pembrolizumab	HPV16+ head and neck cancer	Phase 2 with registrational potential ongoing (FPD, July 2021)
	BNT115[2]	Ovarian cancer	Phase 1 ongoing

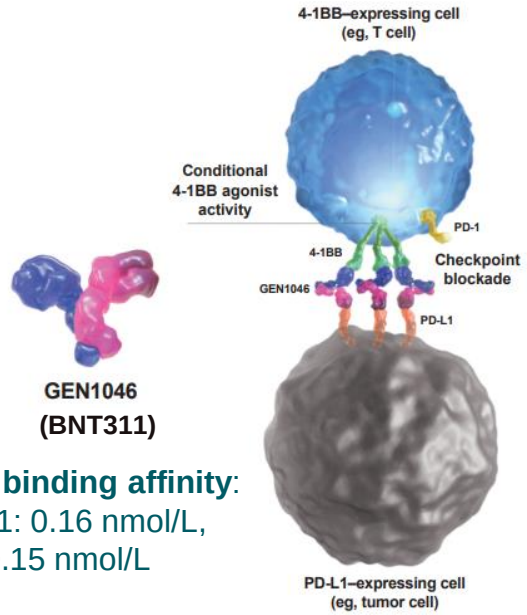
FPD, first patient dosed; HNSCC, head-and-neck squamous-cell carcinoma; NSCLC, non-small-cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; R/R, relapsed/refractory.
[1] BNT122, Collaboration with Genentech; [2] Investigator-initiated study.



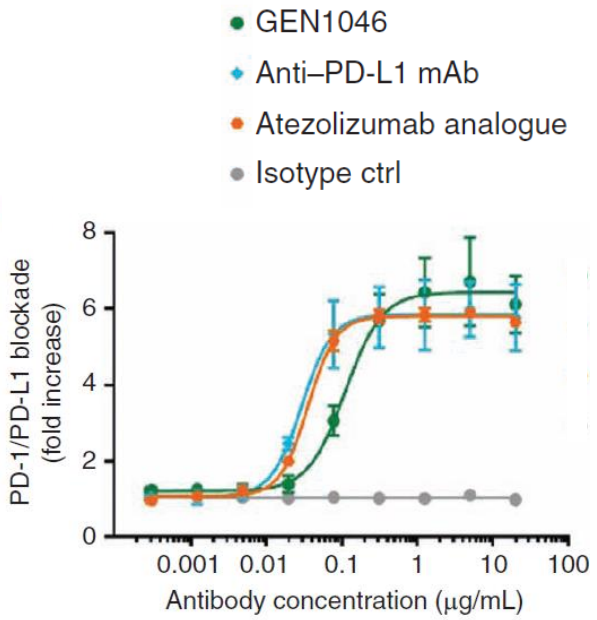
Protein therapeutics

BNT311
Combining checkpoint blockade and conditional T cell co-stimulation

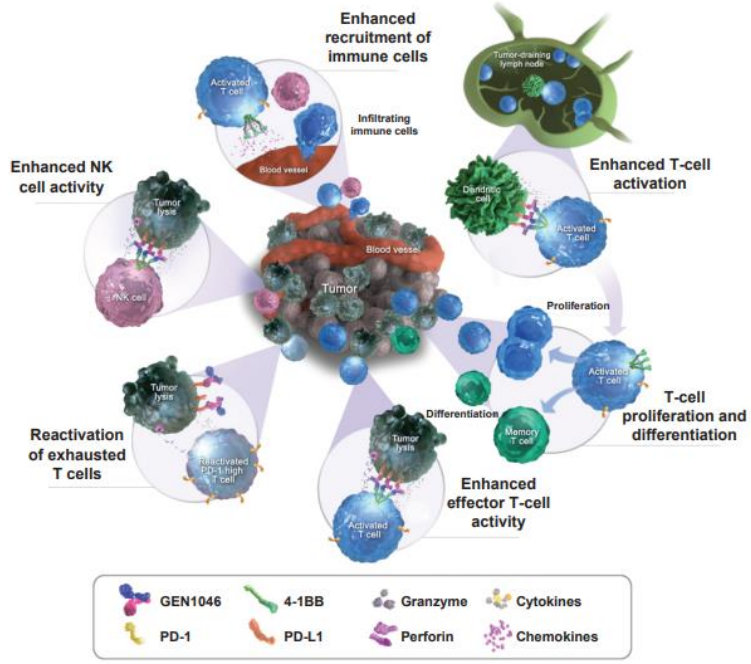
Dual targeted 4-1BB co-stimulation that is conditional on PD-L1 binding



BNT311 binding affinity:
K_D PD-L1: 0.16 nmol/L,
4-1BB: 0.15 nmol/L



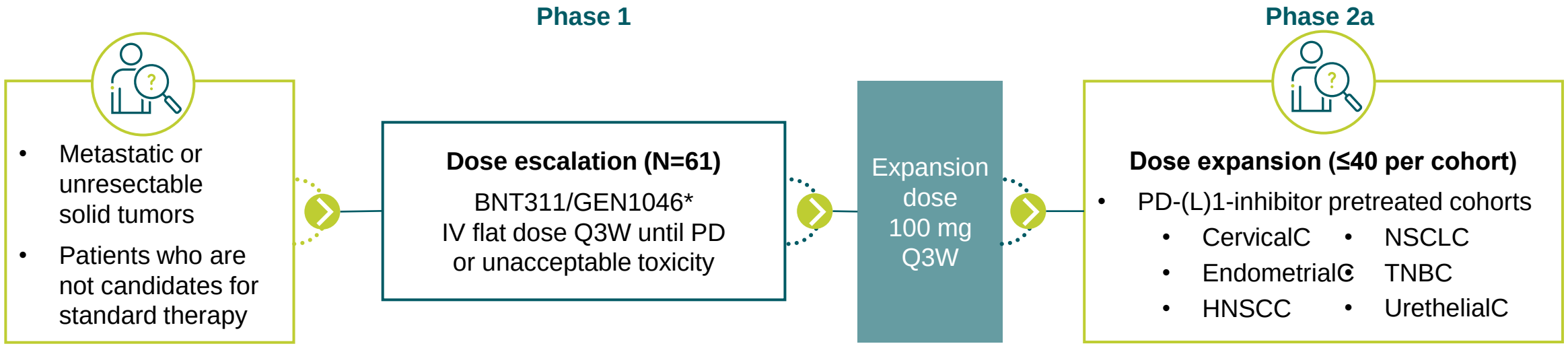
Novel mechanism that enhances T- and NK-cell function



- Conditional bi-specific molecule for two preclinically validated targets:
  - **PD-L1:** receptor-ligand expressed on tumor cells to inhibits the proliferation of PD1-positive cells, and participates in the immune evasion
  - **4-1BB:** costimulatory tumor necrosis factor expressed on T cells and NK-cells. Activating the 4-1BB pathway **enhances T cell proliferation, T cell effector functions, and prevents T cell death**

* BNT311 (Gen1046) is partnered with Genmab based on 50/50 sharing of costs and profits.
[1] Muik A, *et al. Cancer Discov* 2022; 12:1248−1345.

BNT311
First-in-human Phase 1/2 trial in heavily pretreated advanced solid tumors



Key endpoints

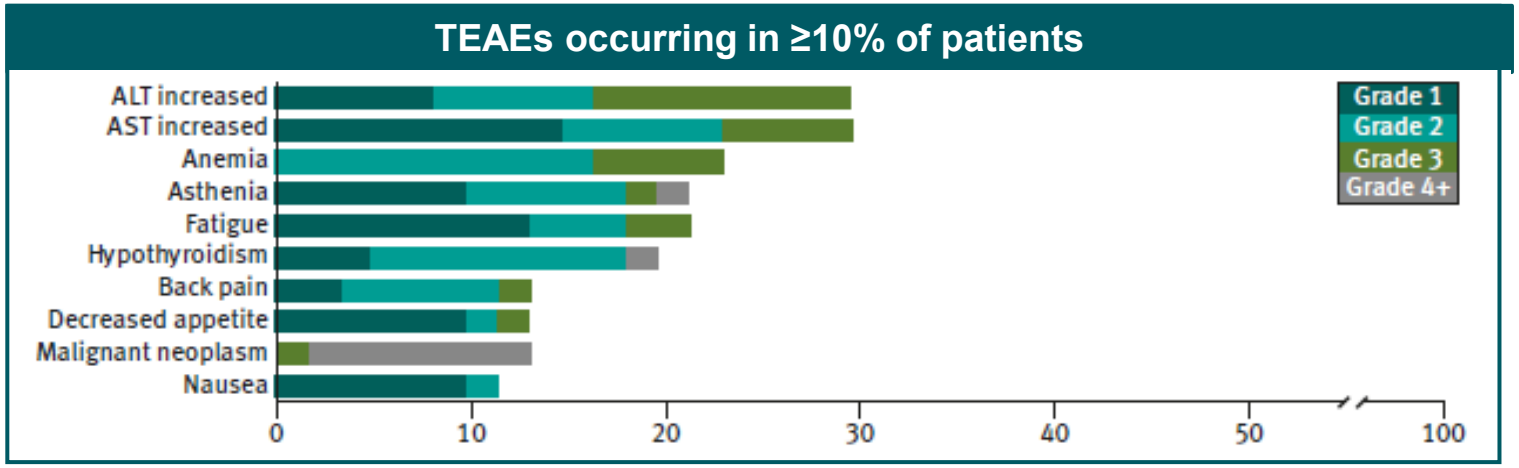
- **Primary**: MTD, RP2D
- Safety, pharmacokinetics, immunogenicity
- Pharmacodynamics and potential predictive biomarkers
- Antitumor activity (RECIST v1.1)

Status

- Recruiting
- 11 expansion cohorts
- Collaboration with Genmab

* BNT311 (Gen1046) is partnered with Genmab based on 50/50 sharing of costs and profits.
CC, cervical cancer; EC, endometrial cancer; HNSCC, head and neck squamous-cell cancer; MTD, maximum tolerated dose; NSCLC, non-small-cell lung cancer, PD, progressive disease; RP2D, recommended Phase 2 dose; TNBC, triple-negative breast cancer; UC, urothelial cancer.
NCT03917381.

BNT311: Initial results in dose escalation show a manageable safety profile with most AEs being Grade 1 or 2

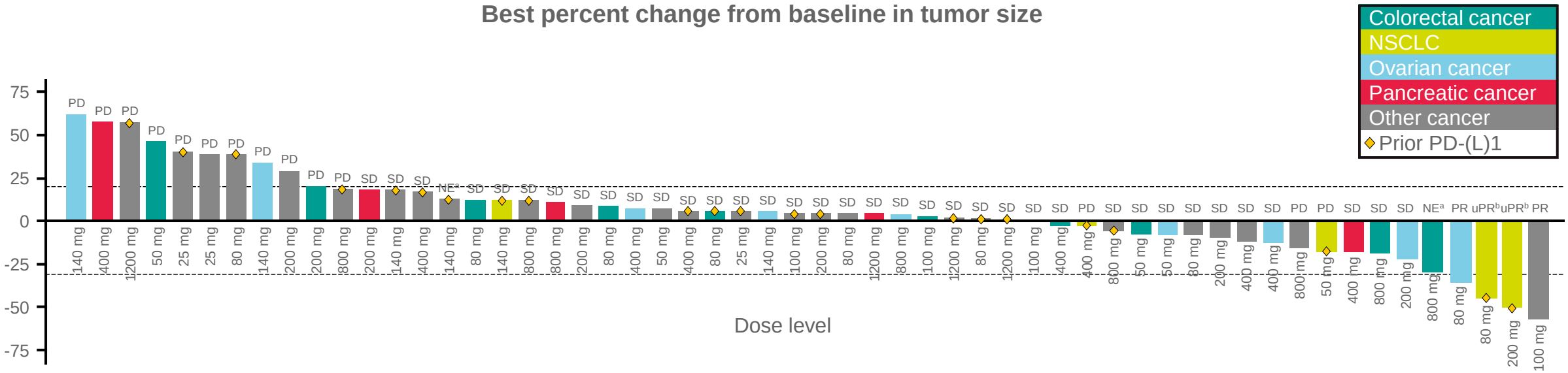


Dose escalation cohort TEAE's occuring in ≥10% of patients	All grades, n (%)	Grade ≥3, n (%)
Any TRAE	43 (70.5)	17 (27.9)
TRAEs in ≥10% patients, by preferred term		
ALT increased	14 (23.0)	5 (8.2)
AST increased	13 (21.3)	2 (3.3)
Hypothyroidism	11 (18.0)	1 (1.6)
Fatigue	8 (13.1)	1 (1.6)

- Treatment-related transaminase elevations occurred in 26.2% (Grade ≥3: 9.8%) and decreased with corticosteroid administration
- No treatment-related bilirubin increases or Grade 4 transaminase elevations
- 6 patients had DLTs:
  Grade 4 febrile neutropenia (n=2),
  Grade 3 nephritis (n=1),
  Grade 3 ALT increase (n=1),
  Grade 3 AST/ALT increase (n=1),
  Grade 3 transaminases increase (n=1)
- All six patients recovered without sequelae
- **MTD was not reached**

Data cut-off: August 31, 2020.
DLT, dose-limiting toxicity; MTD, maximum tolerated dose; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
Garralda E, *et al.* SITC Annual Meeting 2020; Poster presentation 412.

BNT311
Anti-tumor activity (Phase 1 dose escalation part)



- **Disease control achieved in 65.6% (40/61) of patients at a median of 3 months follow-up**
- **4 early partial responses in TNBC (1), ovarian cancer (1), and CPI pre-treated NSCLC (2) patients**

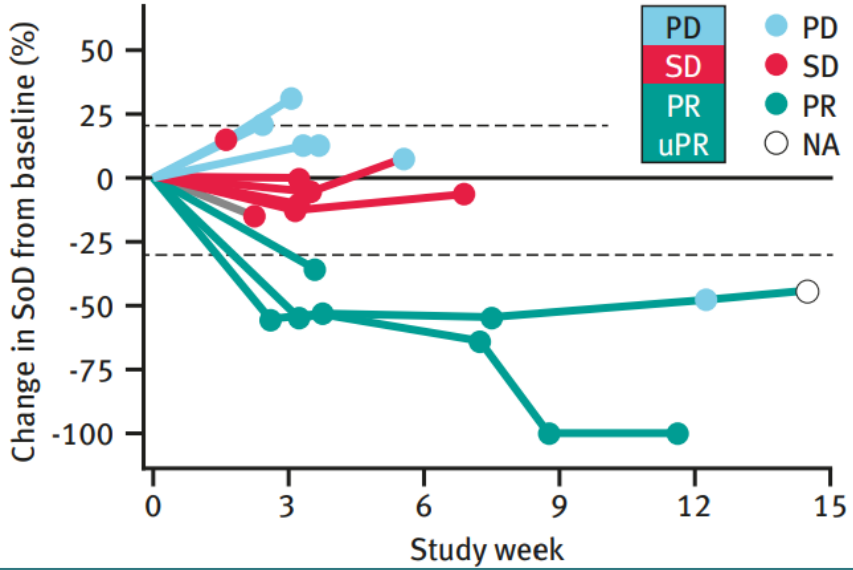
Data cut-off: September 29, 2020. Post-baseline scans were not conducted for five patients.
A Minimum duration of response (5 weeks) per RECIST v1.1 not reached.
B PR was not confirmed on a subsequent scan.
NE, non-evaluable; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-(L)1, programmed death (ligand) 1; PR, partial response; SD, stable disease; SoD, sum of diameters; uPR, unconfirmed partial response.
Garralda E, *et al.* SITC Annual Meeting 2020; Poster presentation 412.

BNT311
Clinical activity in patients with CPI-experienced relapsed/refractory NSCLC

- 12 evaluable patients in the NSCLC expansion cohort, of which **two experienced PR; one uPR; four SD**

Best change from baseline in tumor size in NSCLC with prior PD(L)-1 (n=12)

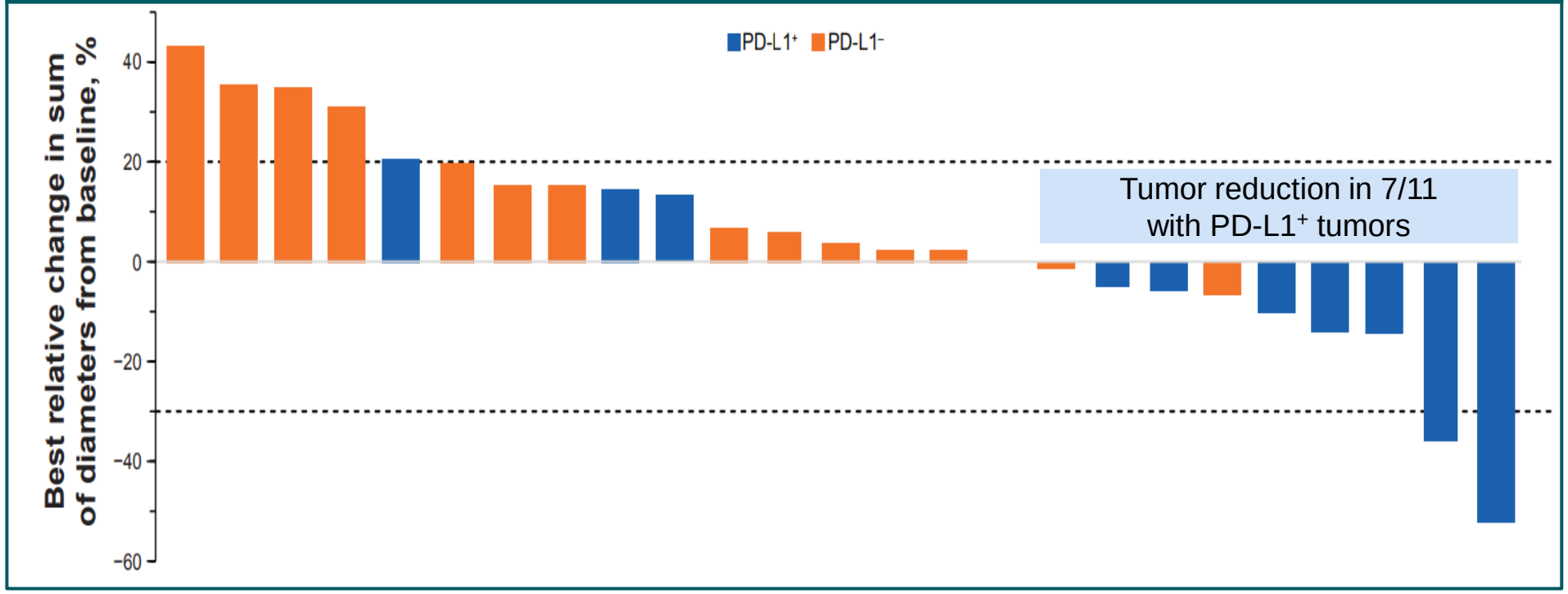
Target lesion SoD change from baseline in NSCLC with prior PD(L)-1 (n=12)



Data cut-off: October 12, 2020.
* PR was not confirmed by a subsequent scan.
Patients all had ≥1 post-baseline tumor assessment (scheduled every 6 weeks) and thus could be assessed for clinical benefit; 6 of 12 patients are still on treatment.
NA, not available, NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters; uPR, unconfirmed partial response.
Garralda E, *et al.* SITC Annual Meeting 2020; Poster presentation 412.

BNT311
Objective responses observed more frequently in PD-L1+ patients

Clinical activity by tumor PD-L1 status in CPI-experienced patients with NSCLC (n=25)[1]

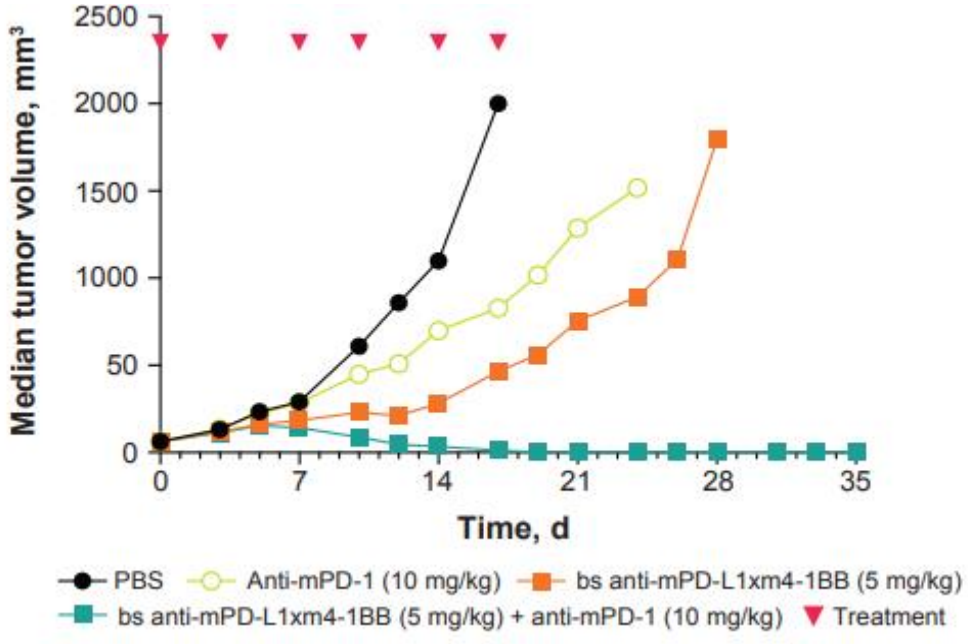


- Preliminary findings in CPI-experienced patients with advanced NSCLC support enrichment based on tumoral PD-L1 status (TPS ≥1%)
- A similar trend was observed in patients with UC, TNBC, and HNSCC

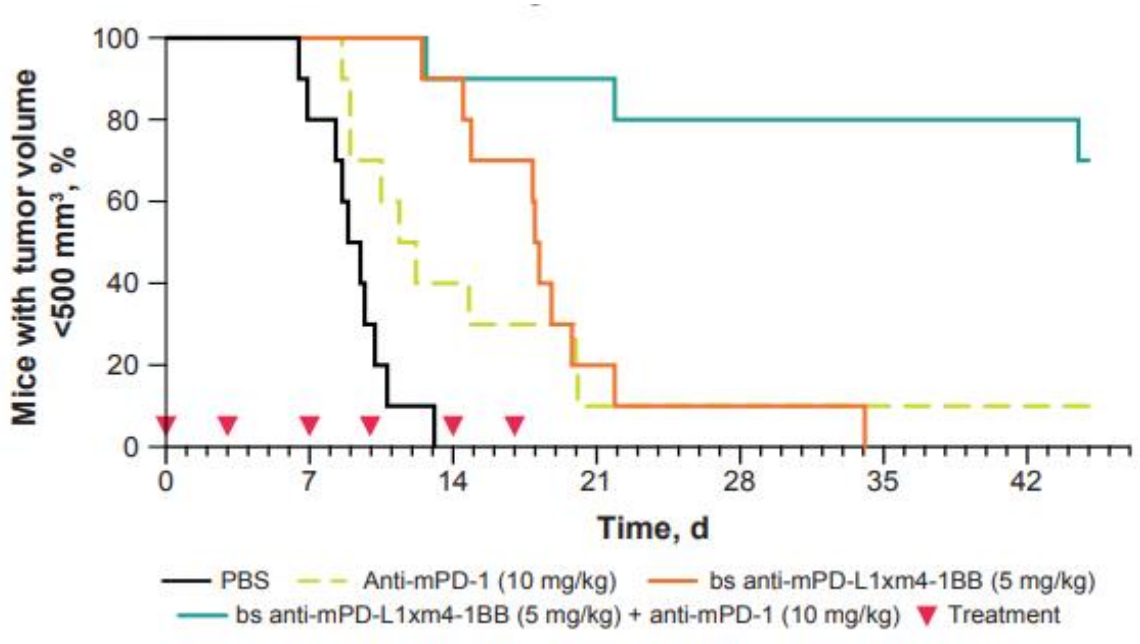
[1] Among patients with evaluable baseline tumors. Fisher exact test odds ration for PD-L1+ vs PD-L1- tumors OR=0.11.
Data cut-off: September 21, 2021.
Ponce Aix S, *et al.* SITC Annual Meeting 2021; Poster presentation 516.

Combination of PD-L1×4-1BB bispecific with PD-1 blockade improves activity in preclinical models

Median tumor volume per treatment group (n=10)[1]



Survival[2]



Complete tumor regression in 7/10 mice and significant enhancement of survival

[1] Growth curves were discontinued when <50% of the animals within a treatment group remained alive or at day 35; [2] Defined as the percentage of mice with tumor volumes <500 mm³.
Mantel–Cox analysis on day 45: PBS vs anti-mPD-1: p=0.012, PBS vs anti-mPD-L1×m4-1BB: p<0.001, PBS vs anti-mPD-L1×m4-1BB + anti-mPD-1: p<0.001, anti-mPD-1 vs anti-mPD-L1×m4-1BB: p=0.5; anti-mPD-1 vs anti-mPD-L1×m4-1BB + anti-mPD-1: p=0.001; anti-mPD-L1×m4-1BB vs anti-mPD-L1×m4-1BB + anti-mPD-1: p<0.001.
Ponce Aix S, *et al.* SITC Annual Meeting 2021; Poster presentation 516.

BNT311

Open-label, randomized Phase 2 trial in CPI-experienced PD-L1+ R/R NSCLC

- Stage IV metastatic R/R NSCLC (2L+)
- PD-L1 TPS ≥1%
- Prior treatment with an anti-PD-(L)1

1:1:1

R

N~130

- **A: BNT311 monotherapy**
- **B: BNT311 + pembrolizumab (every 21 days)[1]**
- **C: BNT311 + pembrolizumab (every 42 days)[1]**

Significant unmet need in R/R NSCLC

- ~1.8 million lung cancer deaths worldwide annually[2]
- NSCLC is most common type (~85%)[3]
- 5-year survival only 4% for advanced or metastatic NSCLC[4]
- CPI therapy fails in majority of NSCLC patients due to evolution of resistance
- Poor prognosis for CPI R/R NSCLC
  - Estimated PFS <6 months and OS <1 year
- New strategies needed to overcome resistance and maximize efficacy

Key endpoints[6]

- **Primary:** Overall response rate
- Efficacy: Duration of response, time to response, PFS, OS survival
- Safety and laboratory abnormalities

Status[6]

- Recruiting
- First patient dosed in December 2021
- Collaboration with Genmab

Partnered with Genmab; 50:50 profit/loss collaboration.

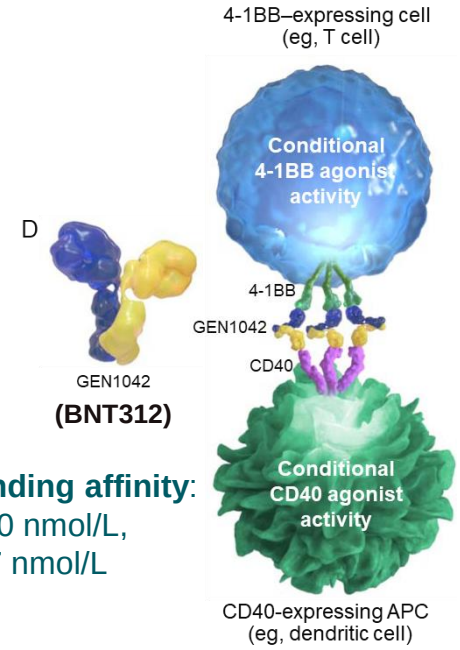
CPI, check point inhibitor; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; R/R, refractory/relapsed; TPS, tumor proportion score; SoC, standard of care.

[1] Following Safety run-in; [2] Bray F, *et al. CA Cancer J Clin* 2018; 68:394−424; [3] ASCO Cancer.Net® 2022. Available at: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics (accessed June 28, 2022); [4] Siegel RL, *et al. CA Cancer J Clin* 2018; 68:7−30; [5] Qu J, *et al.* 2021; 13; [6] ClinicalTrials.gov: NCT05117242.

BNT312

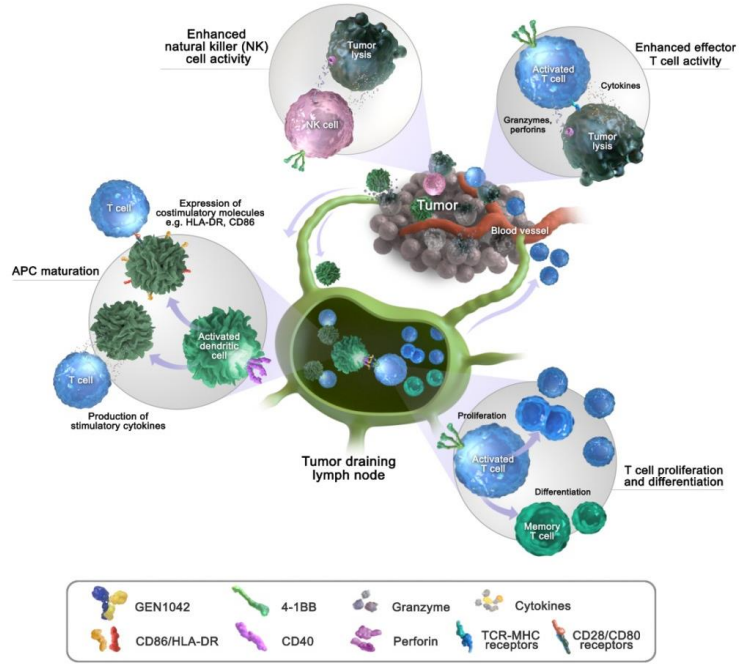
Bispecific antibody designed to strengthen T cell and APC synapse

Inert Fc, double conditional, dual CD40×4-1BB agonist



BNT311 binding affinity:
K_D CD40 1.0 nmol/L,
4-1BB: 0.17 nmol/L

Conditional CD40-stimulation of APC and conditional 4-1BB mediated stimulation of T cells



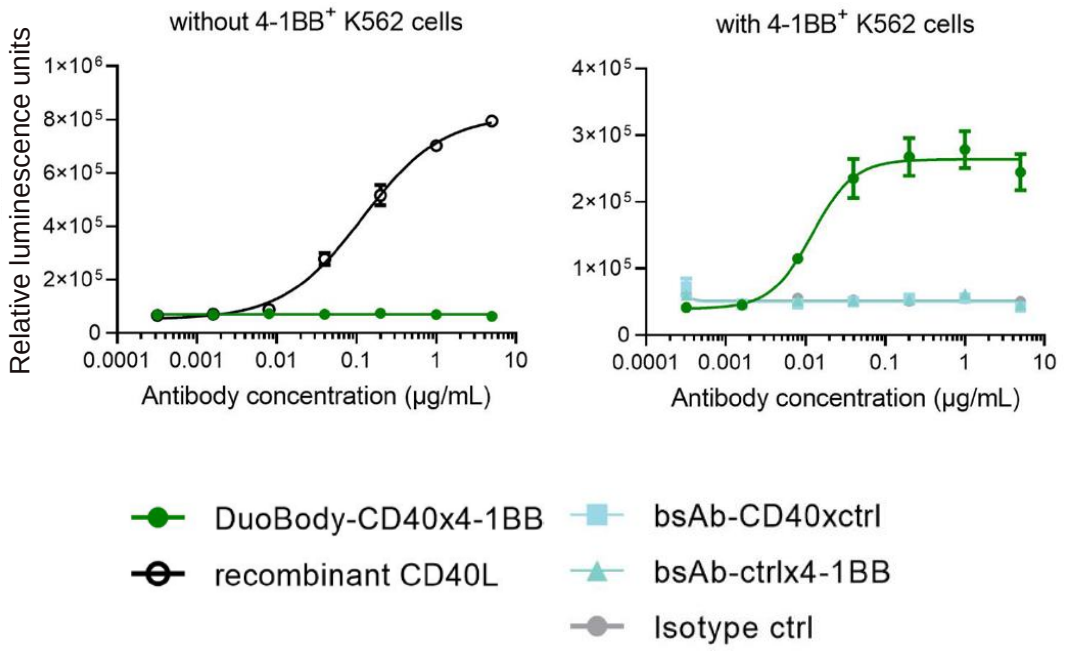
- "Double-conditional" "dual-agonist" molecule for two preclinically validated targets:
  - **CD40:** stimulatory receptor primarily expressed on APCs. Engagement of CD40 leads to **activation and maturation of APCs**
  - **4-1BB:** costimulatory tumor necrosis factor expressed on T-cells and NK-cells. Activating the 4-1BB pathway **enhances T cell proliferation, T cell effector functions, and prevents T cell death**
- **Inert Fc** to avoid unwanted immune cells crosslinking

BNT312 (Gen1042) is partnered with Genmab based on 50/50 sharing of costs and profits; [1] Muik A, *et al. J Immunother Cancer* 2022;0:e004322. doi:10.1136/jitc-2021-004322.

BNT312
Double-conditional dual-agonist molecule

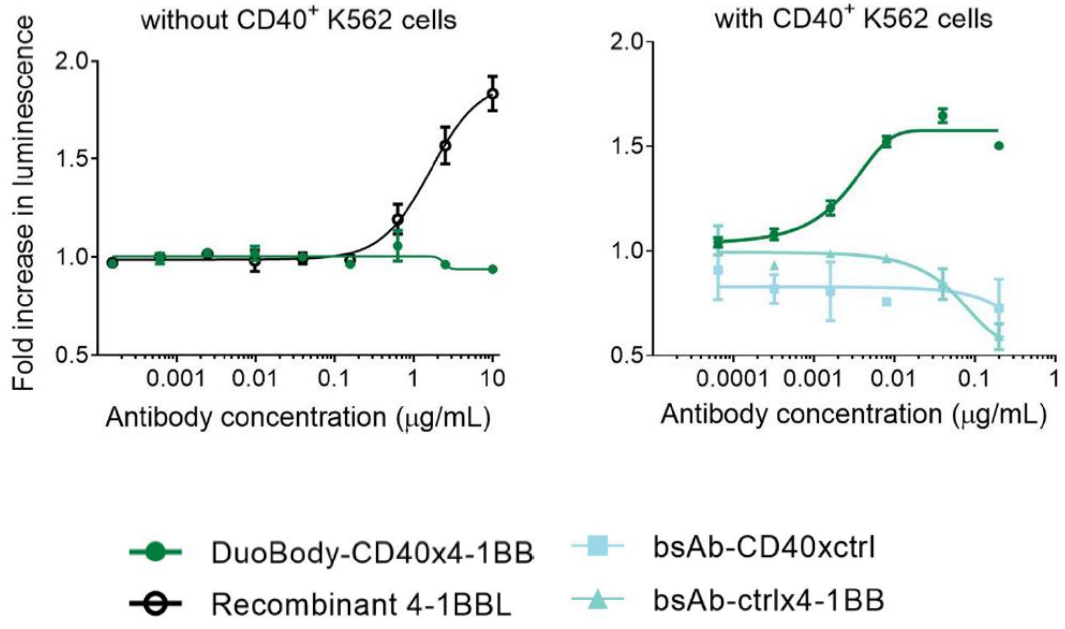
In the absence of CD40+ cells, BNT312 does not exhibit any 4-1BB activation

CD40 reporter assay



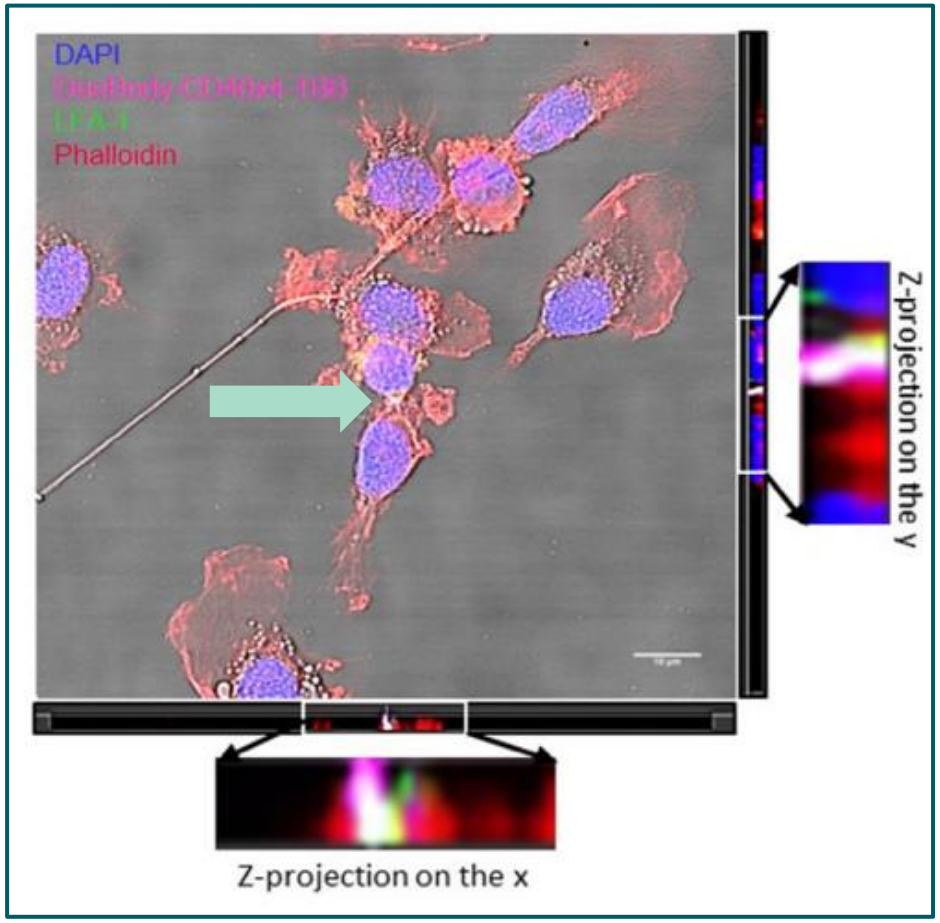
In the absence of 4-1BB+ cells, BNT312[1] does not exhibit any CD40 activation

4-1BB reporter assay



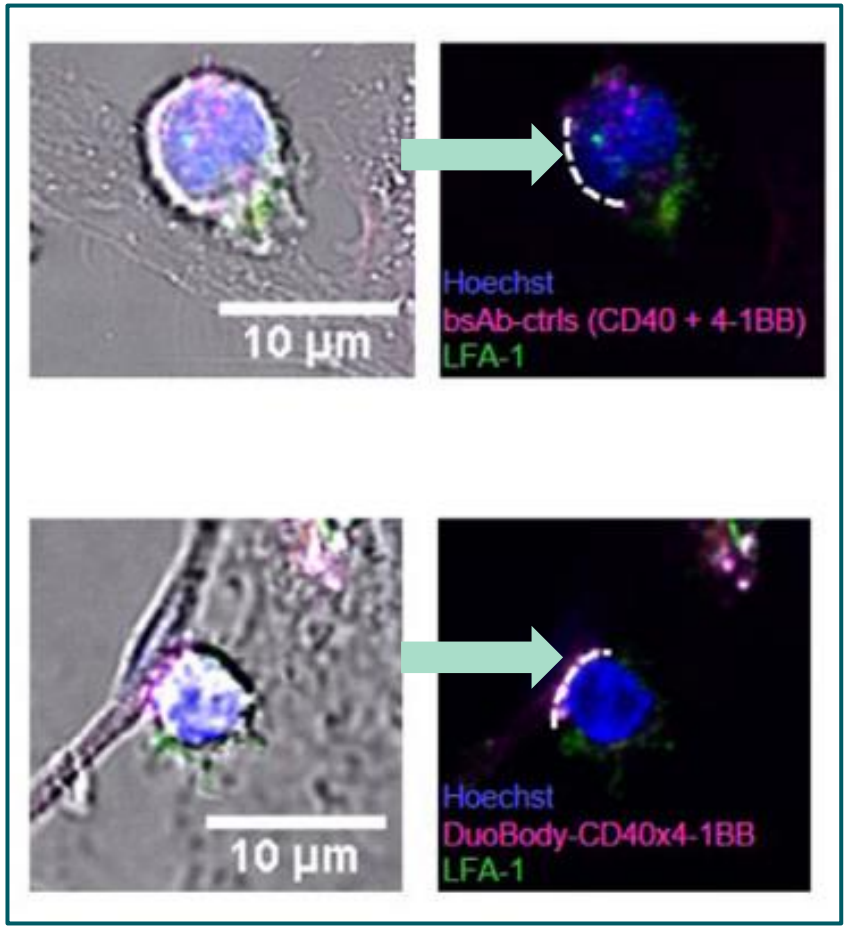
BNT312 (Gen1042) is partnered with Genmab based on 50/50 sharing of costs and profits.
Muik A, *et al. J Immuno Ther Cancer* 2022; 10:e004322.

BNT312 strengthens crosslinking between T cells and APCs



Single Z plane of iDC cocultured with preactivated CD8+ T cells in the presence of Alexa Fluor 647-conjugated DuoBody-CD40.4-1BB (magenta) and LFA-1 (green) antibodies, on the x and y axes the z-stack of the same picture with the relative zoom in. Nuclei were counterstained with Hoechst (blue)

Strengthened crosslinking

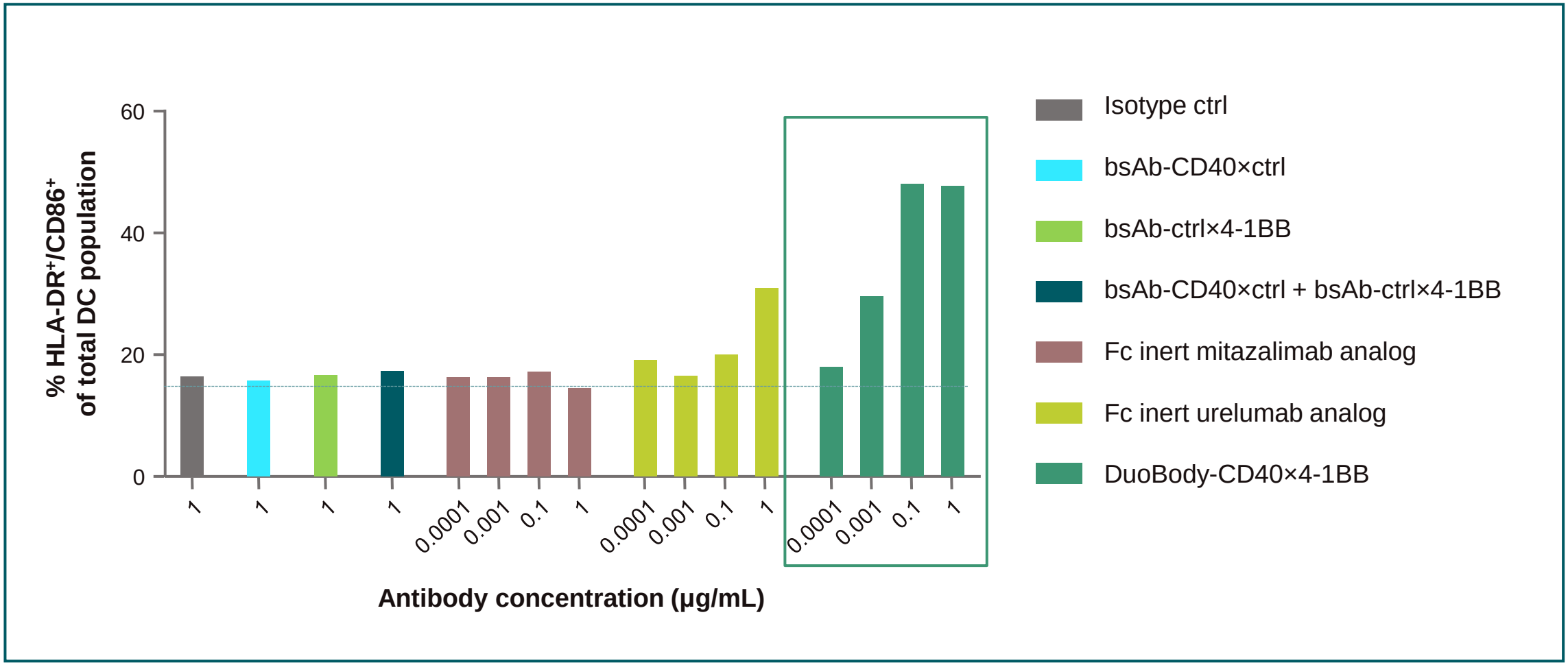


Representative fluorescent images of cocultures in the presence of DuoBody-CD40.4-1BB or control antibodies.
White dashed line = interface between DC and T cell

BNT312 (Gen1042) is partnered with Genmab based on 50/50 sharing of costs and profits.

Muik A, *et al. J Immuno Ther Cancer* 2022; 10:e004322.

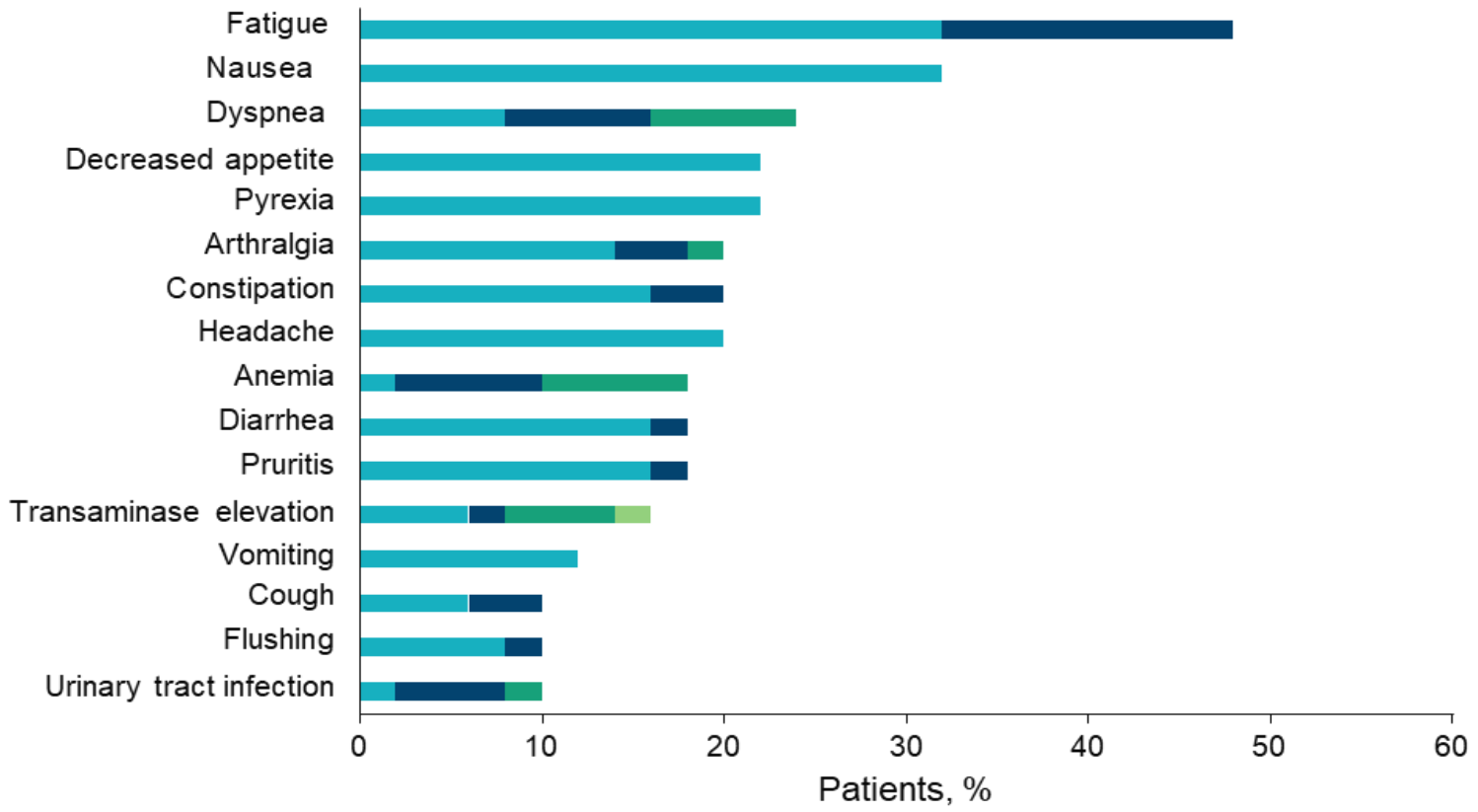
BNT312 showed higher ability to promote DC maturation vs either monoclonal antibody or their combination



BNT312 (Gen1042) is partnered with Genmab based on 50/50 sharing of costs and profits.
The dotted line shows the percentage of HLA-DR+ CD86+ DCs in DC-T- cell cultures in the absence of treatment.
Muik A, *et al. J Immuno Ther Cancer* 2022; 10:e004322.

BNT312: Favorable safety profile across a wide dose range; 100 mg selected for dose expansion phase

Treatment-emergent adverse events in ≥10% (N=50)

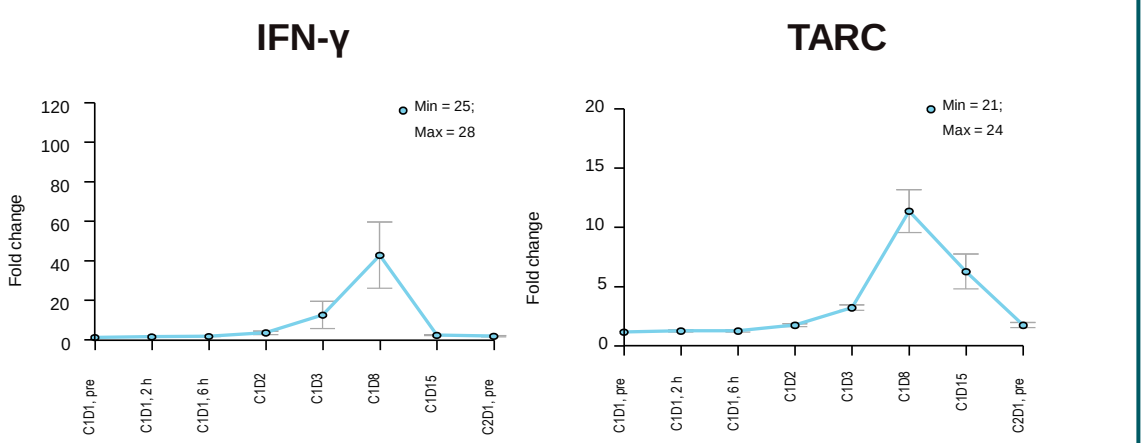


- MTD not reached
- 1 DLT (Grade 4 transaminase elevation at 200 mg) resolved with corticosteroids
- No drug-related Grade ≥3 thrombocytopenia or CRS
- No treatment-related deaths

Data cut-off: August 27, 2021.
Partnered with Genmab; 50:50 profit/loss collaboration.
CRS, cytokine release syndrome; DLT, dose-limiting toxicity; MTD, maximum tolerated dose.
Johnson M, *et al.* SITC Annual Meeting 2021; Oral presentation 493.

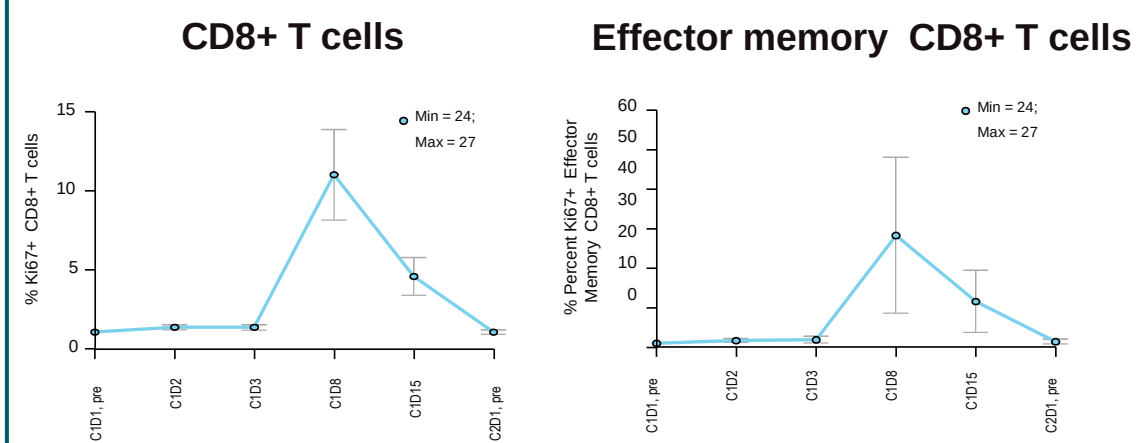
BNT312: Clinical modulation of peripheral biomarkers supports its function in a wide range of solid tumors

Doses ≥30 mg effectively induce proinflammatory cytokine release



- Higher doses more effectively induced IFN-γ and TARC, indicating T cell activation and DC/APC activation, respectively (≥30 mg dose vs <30 mg dose)

Doses ≥30 mg effectively induce cytotoxic T-cell proliferation



- Higher doses more effectively induced Ki67 (proliferation marker) in CD8+ T cells (≥30 mg dose vs <30 mg dose)

Data cut-off: August 27, 2021.
Partnered with Genmab; 50:50 profit/loss collaboration.
Mean fold changes of cytokine concentrations and % of CD8+ T cells ± standard error of the mean (SEM) are displayed for high- and low-dose cohorts during the first cycle.
Minimum and maximum numbers of patients with available data (n) at any given point are displayed.
APC, antigen-presenting cell; DC, dendritic cell; TARC, thymus- and activation-regulated chemokine.
Johnson M, *et al.* SITC Annual Meeting 2021; Oral presentation 493.

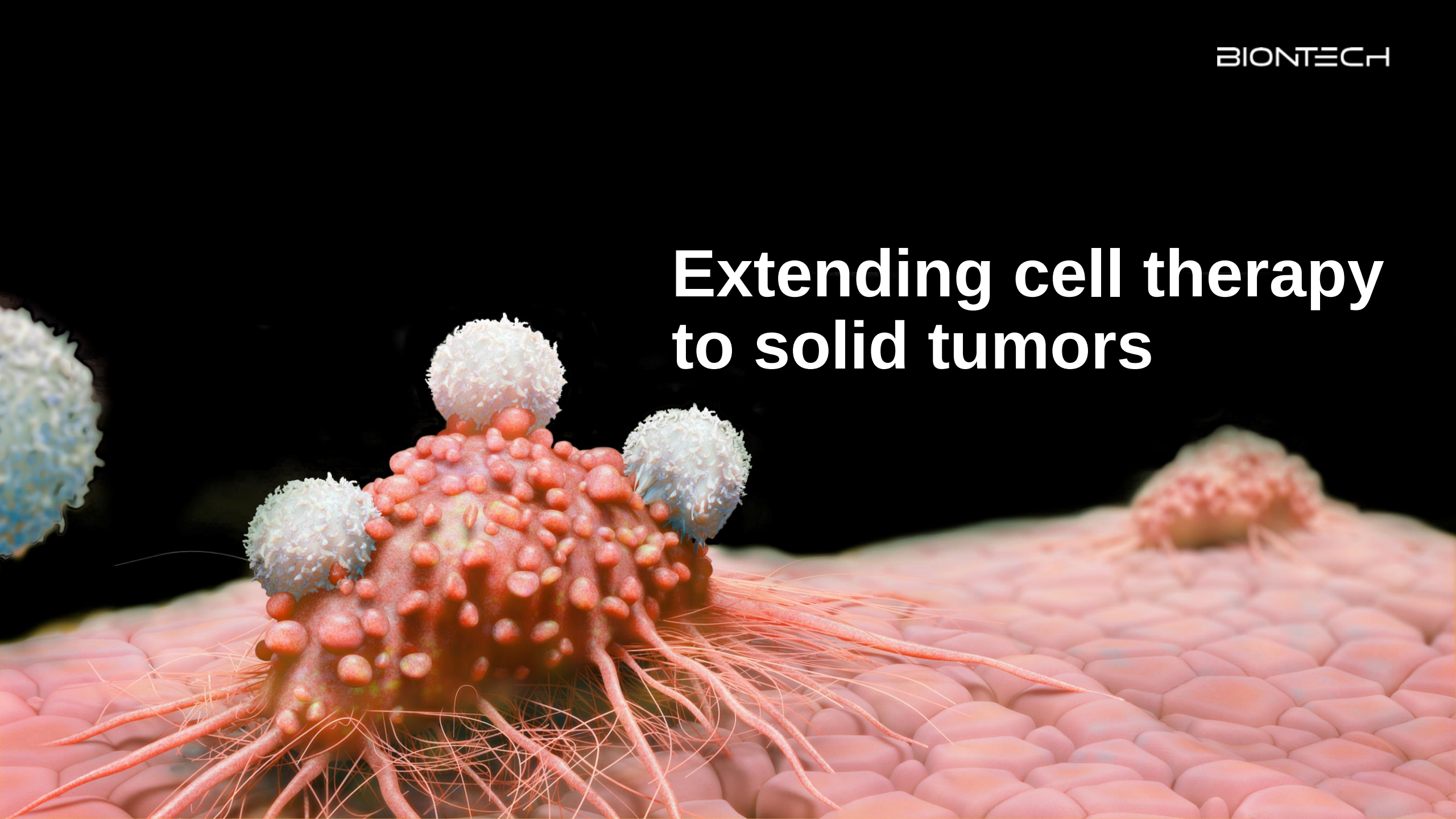
Near-term milestones for protein therapeutics

Platform	Product candidate	Indication	Next milestone
Next-gen immunomodulators	BNT311 (PD-L1×4-1BB)[1]	Multiple advanced solid tumors	Phase 1/2 trial: 8 expansion cohorts completed 2 cohorts enrolment ongoing, 1 cohort enrolment to be started
	BNT311 ± pembrolizumab[1]	PD1+ R/R NSCLC	Phase 2 ongoing (FPD, December 2021)
	BNT312 (CD40×4-1BB)[1] ± anti PD1 ± chemotherapy	Multiple advanced solid tumors	Phase 2b trial combination expansion cohorts enrolling

FPD, first patient dosed; NSCLC, non-small-cell lung cancer; R/R, relapsed/refractory.
[1] (GEN1046 and GEN10542), partnered with Genmab; 50:50 profit/loss collaboration..

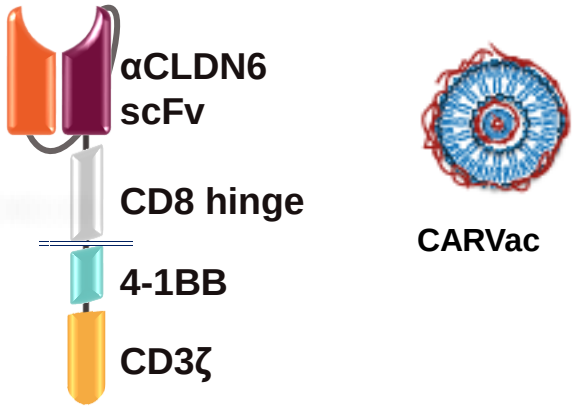
BIONTECH

Extending cell therapy to solid tumors



Developing 3 autologous cell therapy platforms and addressing novel targets

Chimeric antigen receptor (CAR)[1]

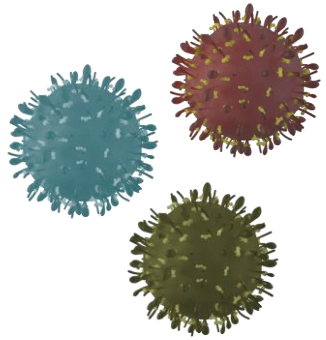


CARVac

- Autologous engineered cell therapy to address extra-cellular targets + RNA-LPX vaccine

Lead program:
BNT211 CARVac targeting CLDN6

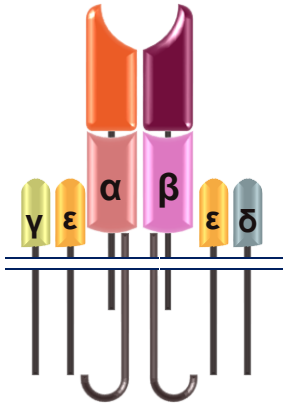
NEO-STIM

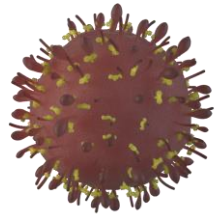


- Individualized e*x-vivo* T-cell therapy targeting neoantigens

Lead program:
BNT221 across multiple solid tumors

T-cell receptor (TCR)





- Engineered cell therapy to address both intra- and extra-cellular targets
- Individualized TCR-T in development

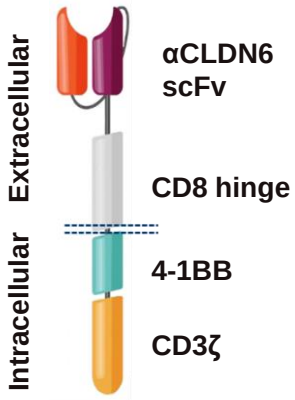
Programs:
KRAS, PRAME TCRs

Reinhard K, et al. Science 2020; 367:446–453

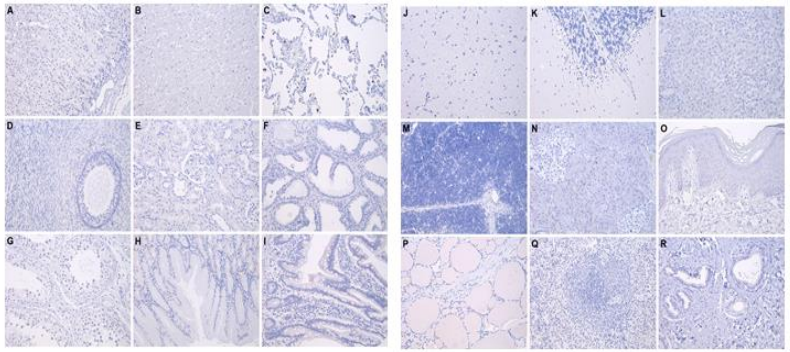
BNT211: Phase 1/2 trial evaluating next-generation CAR T targeting claudin-6 with CARVac in solid tumors

CAR T-cell therapy + CARVac RNA vaccine to amplify CAR T cells *in vivo*

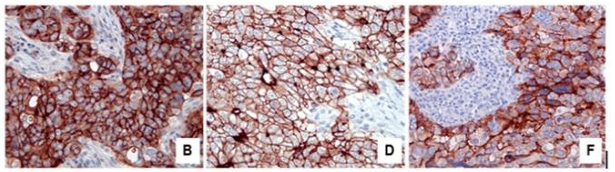
- 2nd generation CAR directed against CLDN6, a cancer specific carcino-embryonic antigen
- CLDN6 is expressed in multiple solid cancers with high medical need
- CARVac drives in vivo expansion, persistence and efficacy of CAR T



Claudin-6 not present in healthy tissues



Expressed in various cancers



Ovarian Testicular Lung

- Relapsed/Refractory advanced solid tumors
- CLDN6-positive: ≥50% of tumor cells CLDN6-high [II/III+]

Phase 1 – Dose escalation

Monotherapy
CLDN6 CAR T cells (3 DLs)

Combination
CLDN6 CAR T cells (3 DLs) + CLDN6-encoding CARVac

RP2D

Phase 2 – Dose expansion

- Testicular cancer
- Ovarian cancer
- Endometrial cancer
- Lung cancer
- Gastric cancer
- Tumors not otherwise specified

Phase 2 trial planned for 2023
EMA PRIME designation in testicular cancer

CLDN6, claudin 6; E15, embryonic day 15; EL, extracellular loop; P0, at birth.
Reinhard K, *et al. Science* 2020; 367:446–453.

BNT211

16 heavily pre-treated patients assessed in the trial

Patient characteristics	Monotherapy DL1 (n=3)	Combination DL1 (n=3)	Monotherapy DL2 (n=6)	Combination DL2 (n=4)	Total (n=16)
Median age, years (range)	33 (25–68)	41 (27–56)	56 (35–66)	44 (23–61)	**46 (23–68)**
Gender (male/female), n/n	2/1	3/0	3/3	2/2	**10/6**
Cancer type, n					
Testicular	1	3	2	2	**8**
Ovarian	1	0	1	2	**4**
Endometrial	0	0	1	0	**1**
Fallopian tube	0	0	1	0	**1**
Sarcoma	1	0	0	0	**1**
Gastric	0	0	1	0	**1**
Median CLDN6 II/III^{+} cells, % (range)	60 (60–80)	90 (90–95)	82.5 (50–90)	95 (75–100)	**85 (50–100)**
Median prior treatment lines (range)	4 (3–5)	4 (3–4)	5 (2–7)	5 (3–7)	**4 (2–7)**

Data cut-off: March 10, 2022.
CLDN6, claudin 6; DL, dose level.
Haanen J, *et al.* AACR Annual Meeting 2022; Oral presentation CT002.

BNT211 was well tolerated at the dose levels evaluated

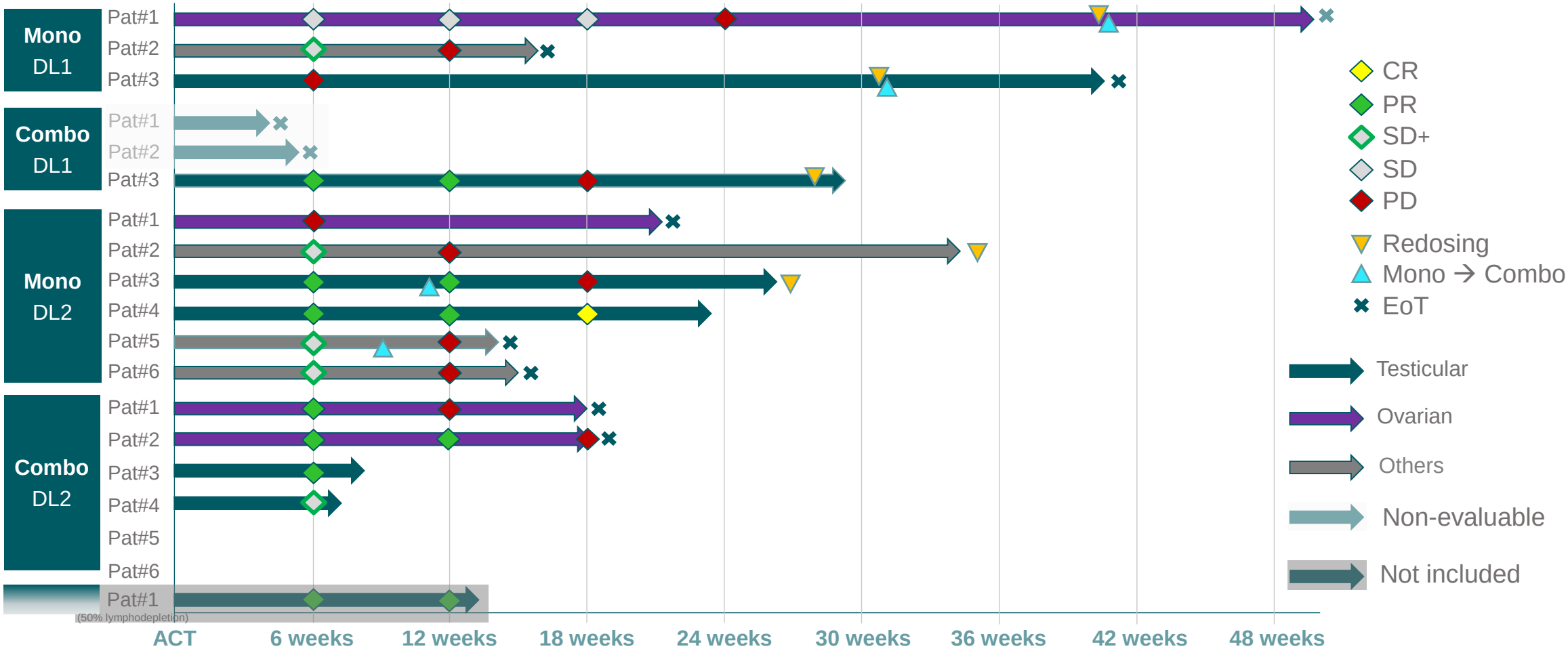
Treatment schedule	Monotherapy DL1 (n=3)	Combination DL1 (n=3)	Monotherapy DL2 (n=6)	Combination DL2 (n=4)	Total (n=16)
Median of follow-up, days (range)	284 (111–348)	38 (29–156)	157 (99–241)	93 (52–127)	**127 (2–348)**
Median CARVac injections, n (range)	N/A	2 (1–6)	N/A	4 (3–5)	**N/A**
Safety, n	**Monotherapy DL1 (n=3)**	**Combination DL1 (n=3)**	**Monotherapy DL2 (n=6)**	**Combination DL2 (n=4)**	**Total (n=16)**
DLTs	0	0	1	1	**2**
Patients with Grade ≥3 AEs	3	3	5	4	**15**
AEs Grade ≥3 suspected to be related to BNT211	4	8	11	22	**45**
Patients with CRS	0	1	4	3	**8**
Patients with ICANS	0	1	0	0	**1**
Deaths					
Disease progression	1	2	2	0	**5**
SAE	0	0	0	0	**0**

- **2 DLTs observed:** prolonged pancytopenia after lymphodepletion (monotherapy DL2) and HLH (combination DL2, before start of CARVac)
- **All CRS were Grade 1 or 2;** reported in 70% of patients at DL2 and manageable by administration of tocilizumab (if needed)

Data cut-off: March 10, 2022.
AE, adverse event; CAR, chimeric antigen receptor; CARVac, CAR T cell-amplifying RNA vaccine; CRS, cytokine release syndrome; DL, dose level; DLT, dose-limiting toxicity; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; SAE, serious AE.
Haanen J, *et al.* AACR Annual Meeting 2022; Oral presentation CT002.

BNT211

An ORR 43% and DCR of 86% (6 PR, 5 SD+, 1 SD) were achieved at 6 weeks

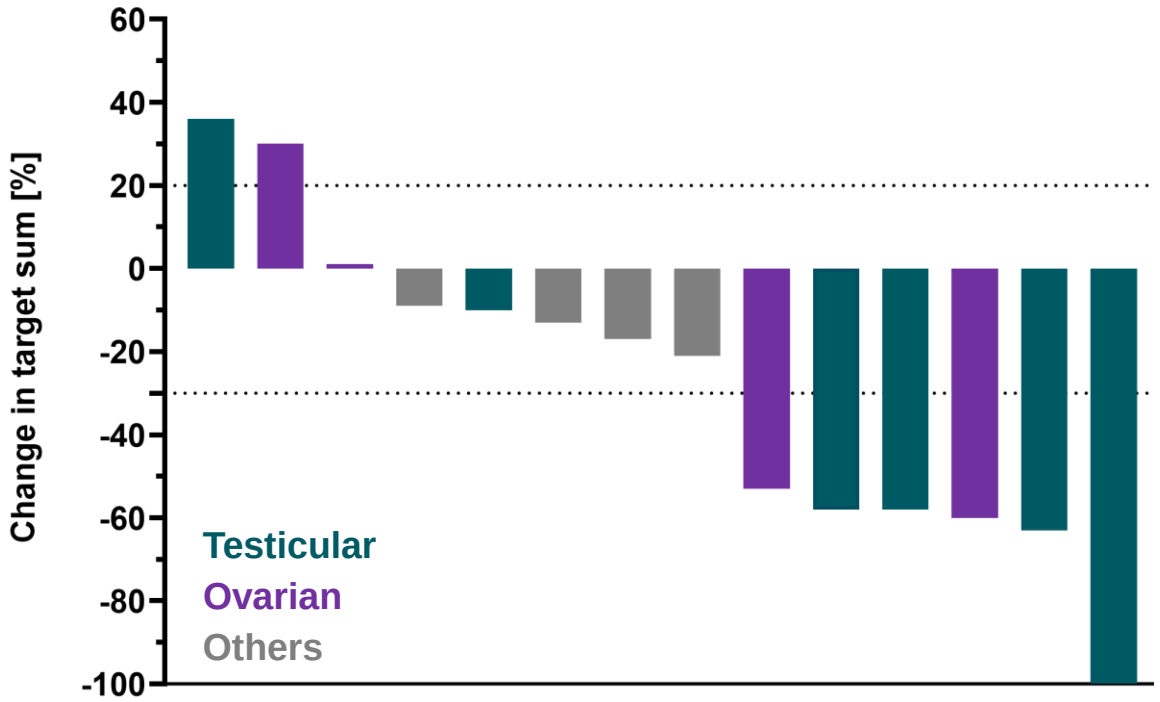


In testicular cancer at DL2 (n=5, incl. reduced LD): Best overall response rate–80%, DCR 100% (1 CR, 3 PR, 1 SD+)

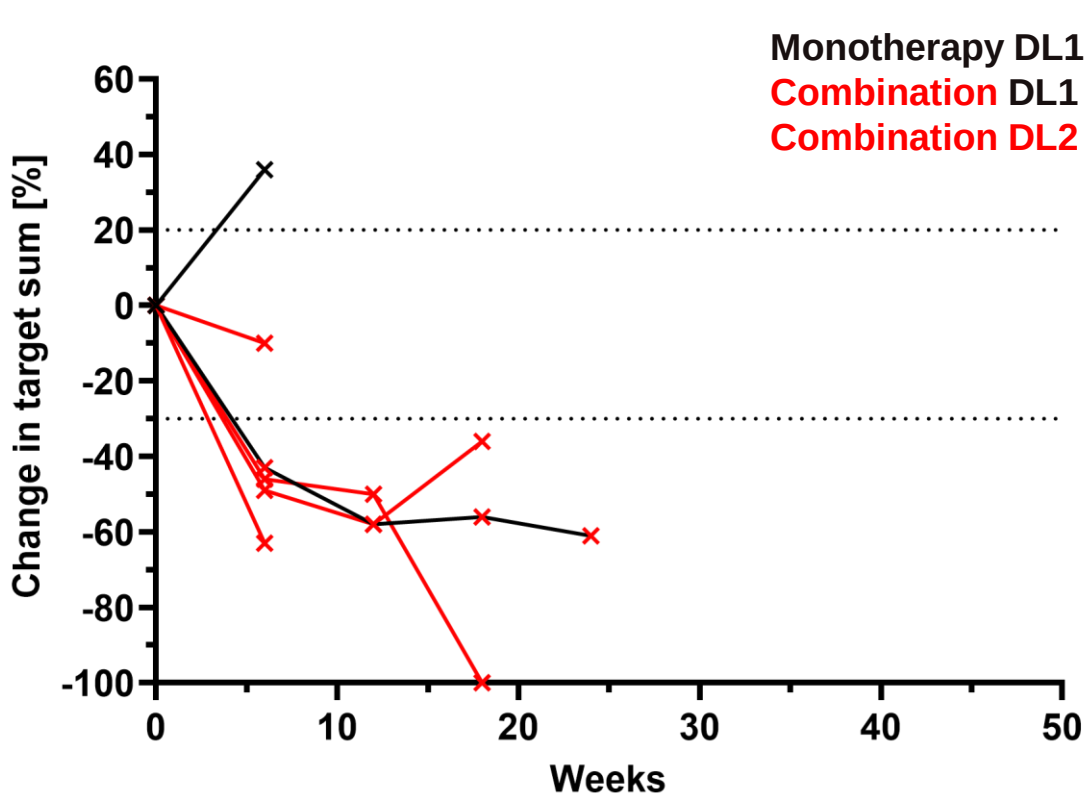
Data cut-off: March 10, 2022; first assessment, 6 weeks post infusion.
ACT, adoptive cell transfer; CR, complete response; DCR, disease control rate; EoT, end of trial (due to PD); PD, progressive disease; PR, partial response; SD(+), stable disease (with shrinkage of target lesions).
Haanen J, *et al.* AACR Annual Meeting 2022; Oral presentation CT002.

BNT211
Clinical benefit seen in patients with testicular cancer receiving DL2

Best response



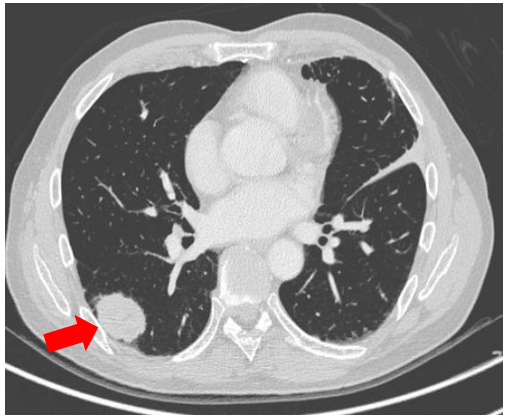
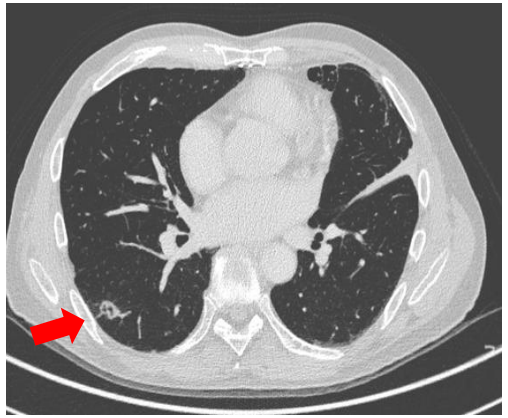
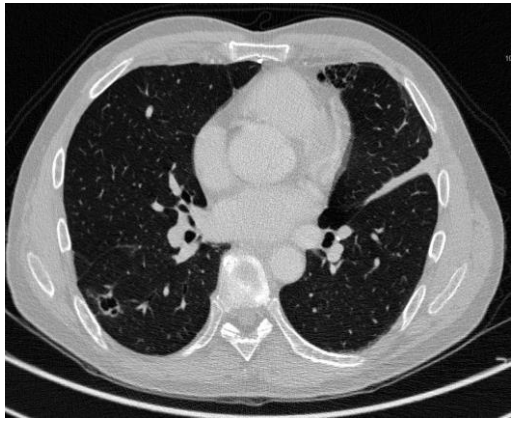
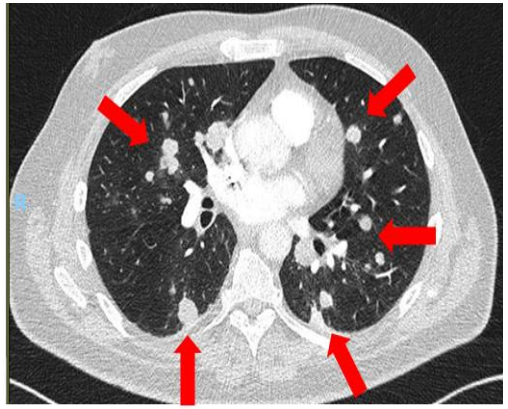
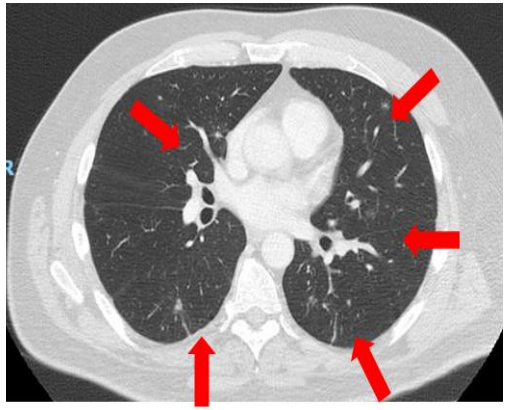
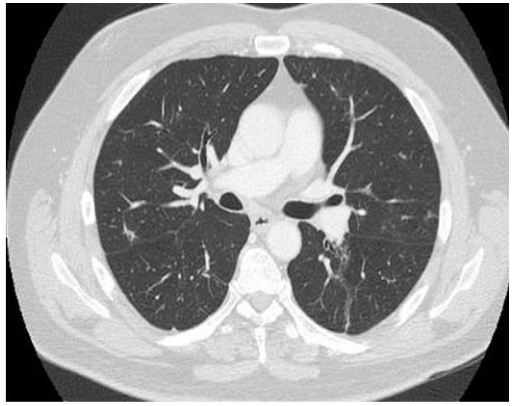
Durability of responses (testicular cancer)



One patient with initial PR showed deepening of responses over time, resulting in CR

Data cut-off: March 10, 2022. CR, complete response; DL, dose level; PR, partial response.
Haanen J, *et al.* AACR Annual Meeting 2022; Oral presentation CT002.

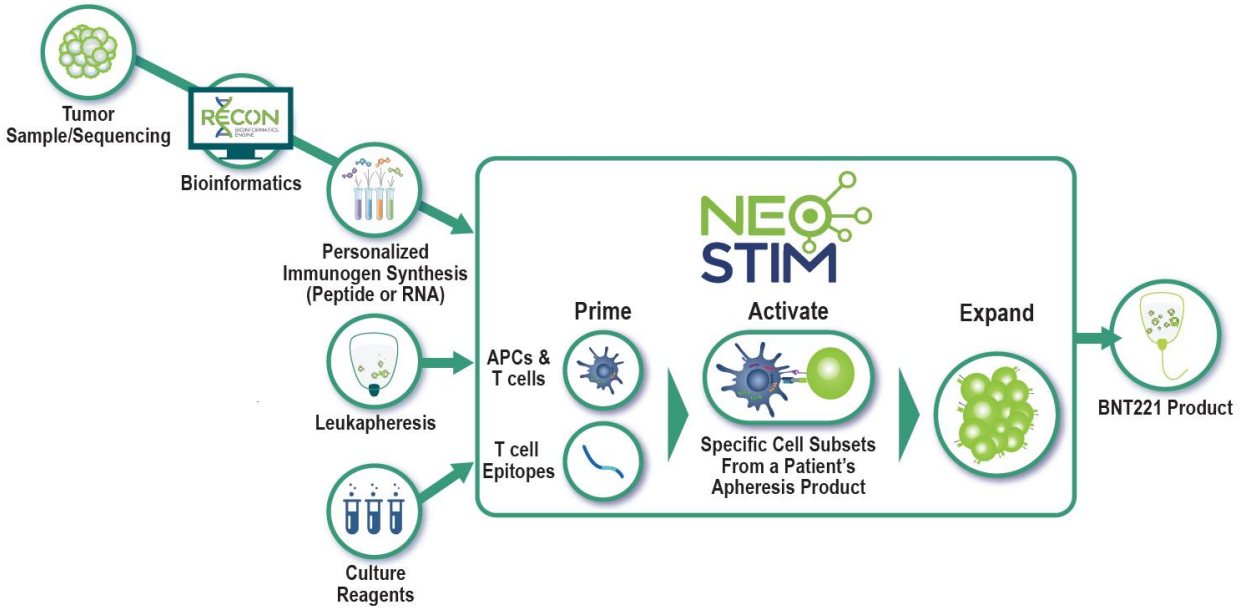
BNT211
Responses in two patients with testicular cancer

	Baseline	6 weeks post infusion	12 weeks post infusion	Post 12-week scan
Patient 1 61-year-old male Diagnosed 2008 (DL2: 1×10^8)				• No new lesions detected • Tumor marker (AFP) at normal level • Ongoing CR
Patient 2 56-year-old male Diagnosed 2020 (DL1: 1×10^7 + CARVac)				• After initial response, new lesions detected • On-treatment biopsy showed positivity for CLDN6 • Re-dosed on d197

Data cut-off: March 10, 2022.
AFP, alpha-fetoprotein; CAR, chimeric antigen receptor; CARVac, CAR T cell-amplifying RNA vaccine; CLDN6, claudin 6; CR, complete response; d, day; DL, dose level.
Haanen J, *et al.* AACR Annual Meeting 2022; Oral presentation CT002.

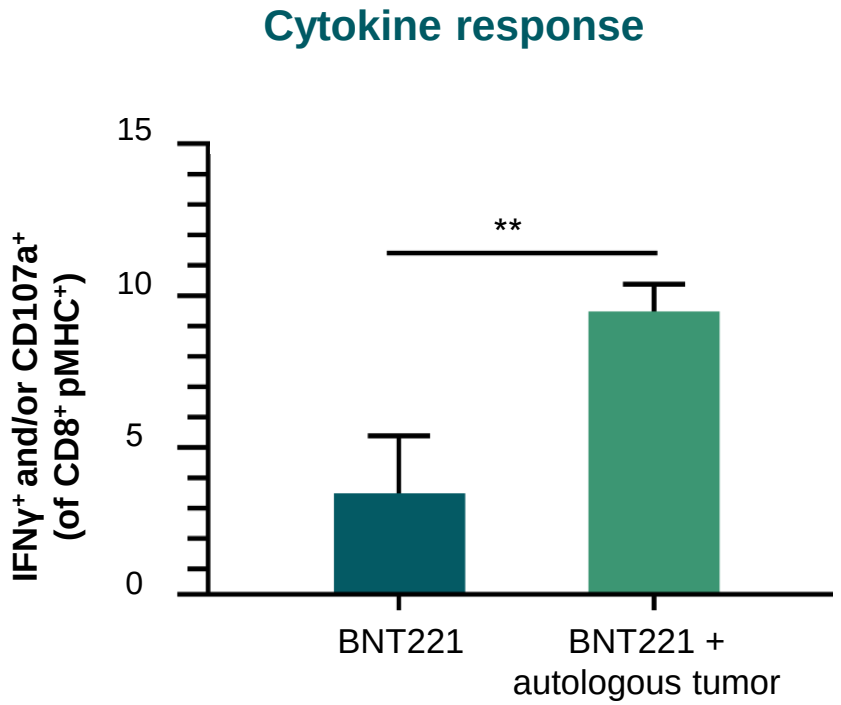
BNT221: NEO-STIM is an individualized neoantigen-targeted strategy that addresses the limitations of tumor-infiltrating lymphocyte therapies

Targets each patient's multiple tumor neoantigens[1]



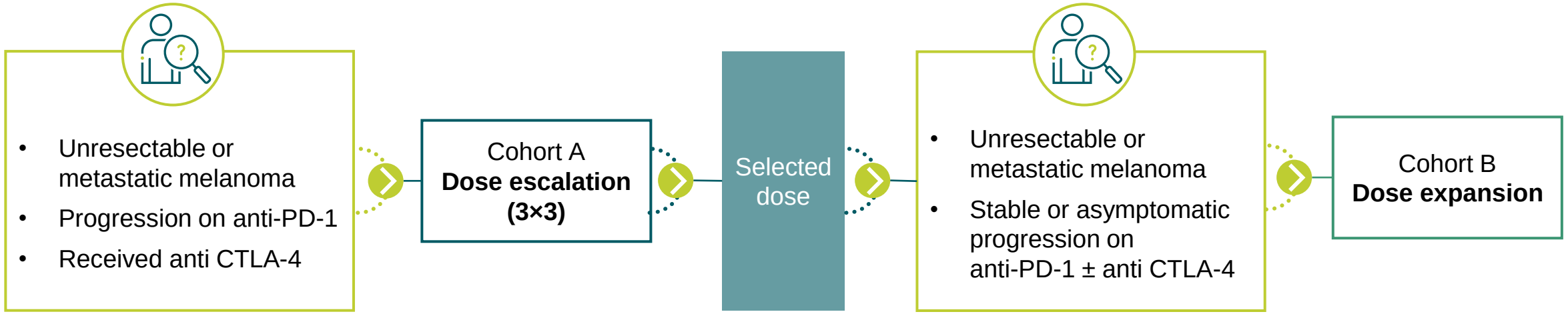
- Multi-target: reduced risk for antigen escape
- T cells are induced from peripheral blood with no gene engineering or viral vectors: reduced toxicity
- Broad clinical opportunity across solid tumors

BNT221 cells specifically recognize autologous tumor[2]



[1] Velez D, *et al.* SITC Annual Meeting 2021, Poster presentation 201; [2] Lenkala D, *et al.* SITC Annual Meeting 2020, Poster presentation 153.

BNT221
Phase 1 trial in patients with PD-1-refractory metastatic melanoma



Key endpoints

- Safety
- Clinical activity (ORR, response durability)
- Immune monitoring
- Cell viability

Status

- Recruiting
- Up to 20 patients will be treated in the dose-expansion Cohort B

Velez D, *et al.* SITC Annual Meeting 2021, Poster presentation 201; ClinicalTrials.gov: NCT04625205.

TCR discovery platform for tumor- and patient-specific therapies

Establish TCR platform in solid tumors

- **Technologic iterations**
- **Combination** with other assets (e.g. RiboCytokines)
- **Acquisitions**: PRAME-TCR and PD1-41BB switch (Medigene, Feb 2022)

Broad patient coverage

- **TCR warehouse**: multiple TCRs to target one or more antigens
- **Library-like approach** adding new targets and HLA alleles
- **Collaboration** with Medigene R&D

Individualized treatment

- **On-demand** identification of neoepitopes, timely manufacturing of customized T cells
- **Acquisition**: Neoantigen TCR platform (KITE, Jul 2021)

TCR, T-cell receptor.


BIONTECH
RiboCytokines

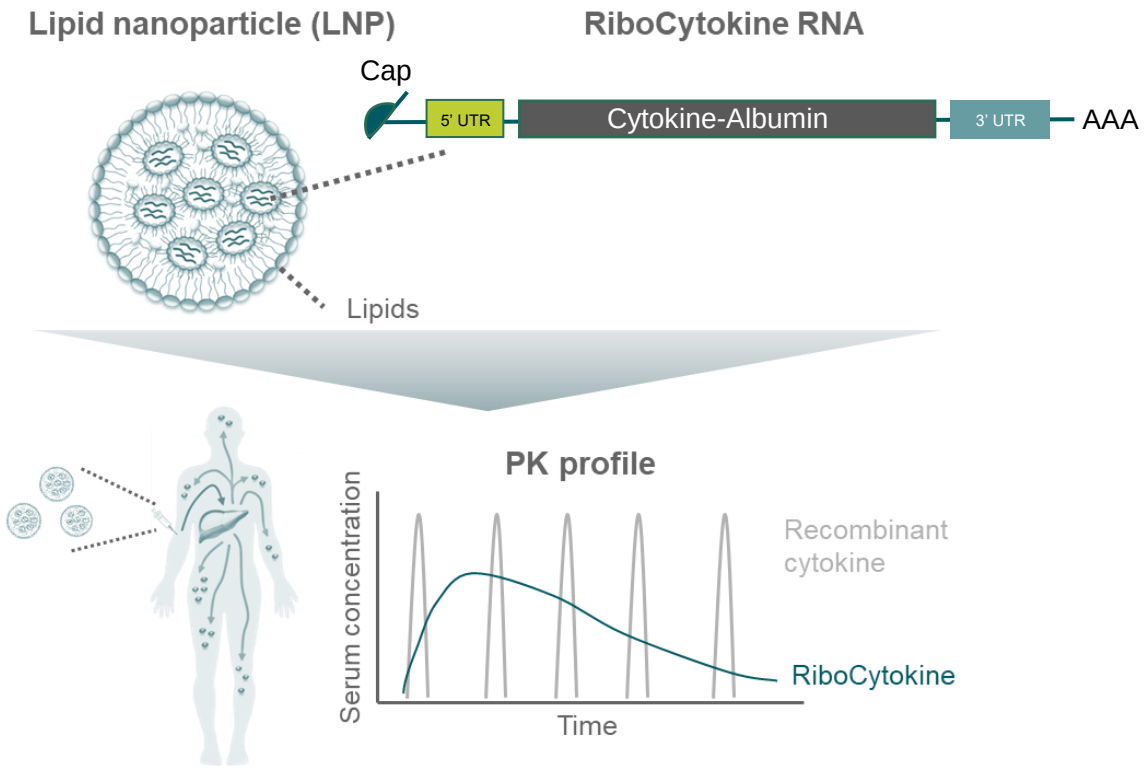
RiboCytokines
Designed to overcome limitations of recombinant cytokine therapy

Systemic delivery

- Backbone optimized and nucleoside-modified mRNA encoding cytokine fused to human albumin
- Liver-targeting LNP formulation with intravenous delivery
- Encoded cytokines translated in body cells and secreted

Designed for optimized safety, tolerability and dosing

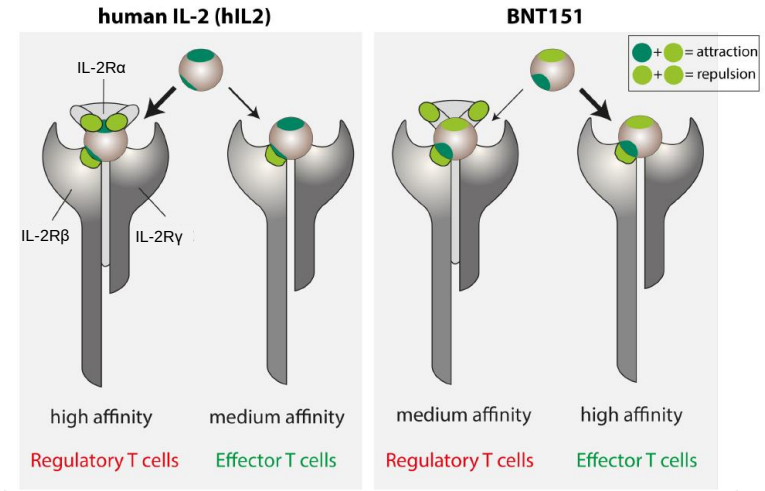
- Prolonged serum half-life
- High bioavailability
- Lower and less frequent dosing
- Lower toxicity



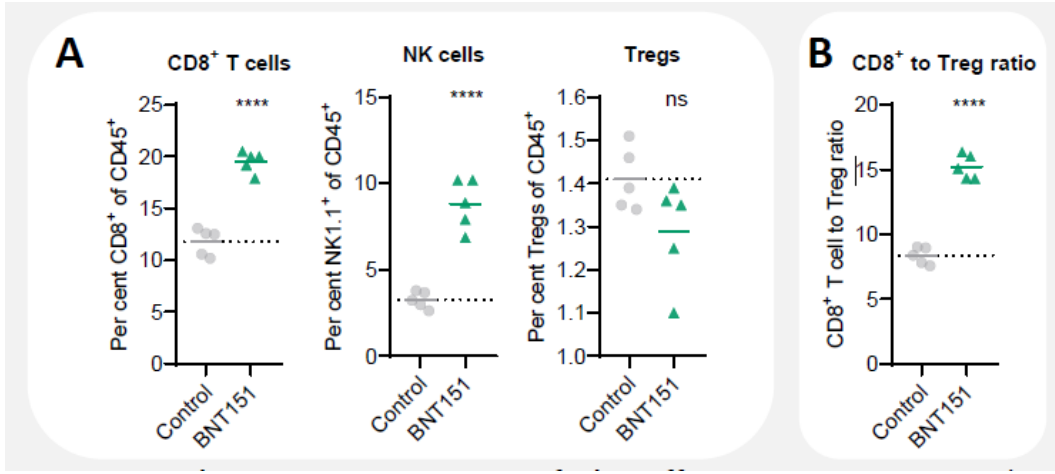
, lipid nanoparticle; PK, pharmacokinetic; IL-2, Interleukin-2; IL7, Interleukin-7; UTR, untranslated region

BNT151
Stimulates CD8+ and NK cells, without extensively triggering Treg cells

BNT151 design

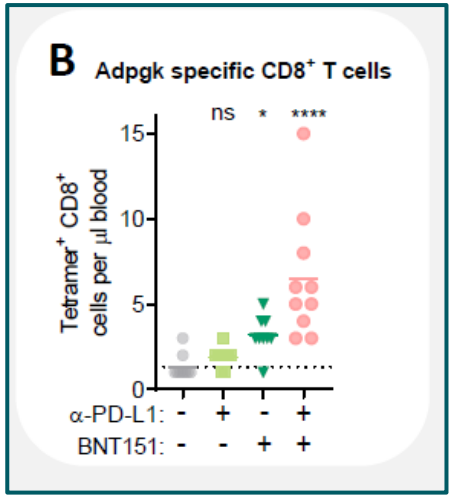


BNT151 mediates increase of effector CD8+ to Treg ratio



BNT151

- Weakened binding to IL-2Rα
- Designed to stimulate naïve and effector T cells with low to no expression of IL-2Rα ($CD25^{low/neg}$) without extensively triggering immunosuppressive regulatory T cells
- Increased binding to IL-2Rβ



Vormehr M, *et al.* SITC Annual Meeting 2019; Poster presentation 626.

BNT152 + BNT153
Increase CD8 proliferation and reduce Treg fraction

BNT152 (IL-7) is anticipated to potentiate the anti-tumor activity of **BNT153** (IL-2) by:

- Reduction/normalization of the BNT153-mediated increase in the Treg fraction among CD4+ T cells
- Support of T cell lymphopoiesis and survival of memory T cells

BNT152

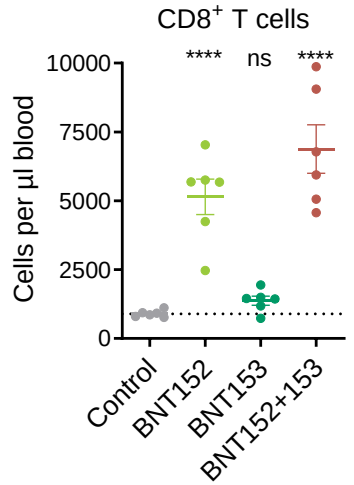
- Stimulates recently activated anti-tumor T cells and regulatory T cells

BNT153

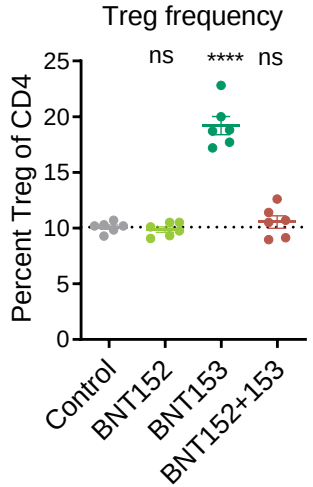
mRNA encoding IL-7

- Sensitizes T cells to IL2 & increases CD8+ and CD4+ T cell expansion and survival
- Controls fraction of immunsuppressive Treg among CD4+ T cells that are stimulated by IL-2

CD8+ T cell expansion of BNT152+153 mainly driven by BNT152

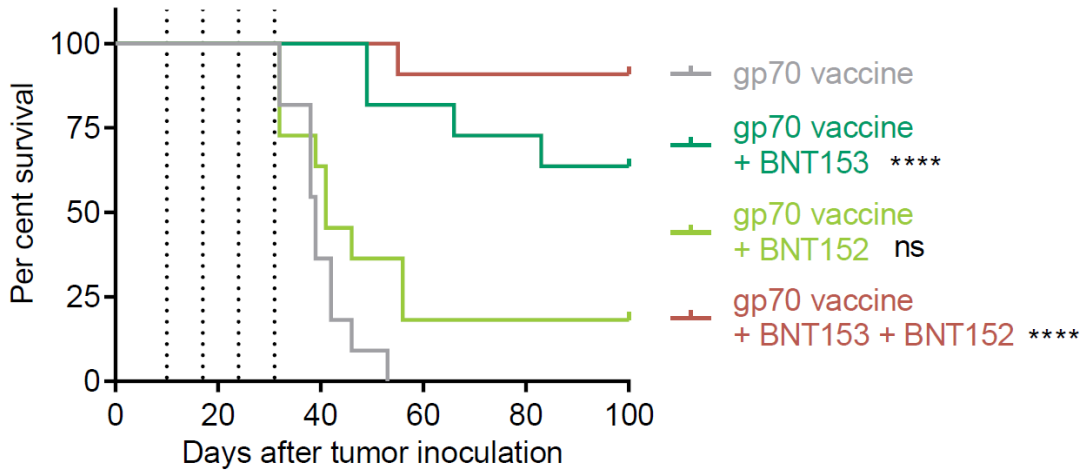


BNT152 normalizes the Treg fraction elevated by BNT153

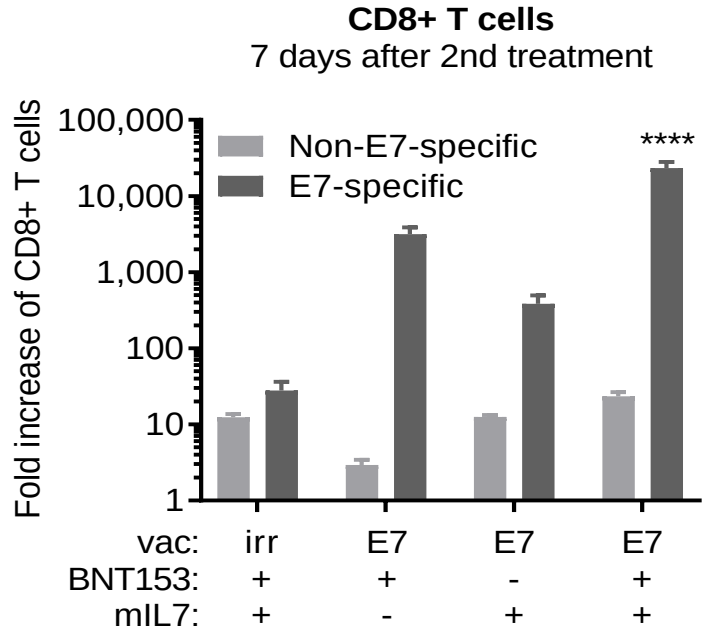


BNT152 + BNT153
Combining with mRNA vaccine

BNT152 boosts therapeutic anti-tumor activity of BNT153 in combination with an RNA vaccine in the CT26 model



BNT152 + BNT153 preferentially expands vaccine-induced CD8+ T cells

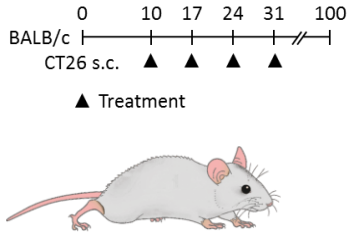


Kranz LM, *et al.* SITC Annual Meeting 2019; Poster presentation 620.

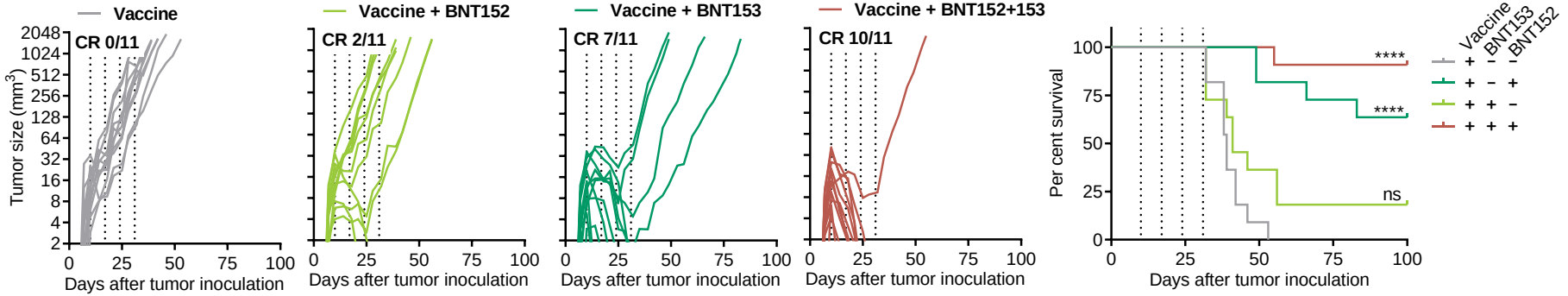
BNT152 + BNT153

Therapeutic efficacy of BNT152 + BNT153 in combination with RNA vaccination

Therapeutic efficacy of IL-2 and IL-7 RiboCytokines ± RNA vaccination in a "hot tumor" model[1]

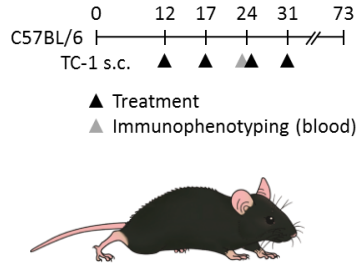


CT26: "hot tumor" model

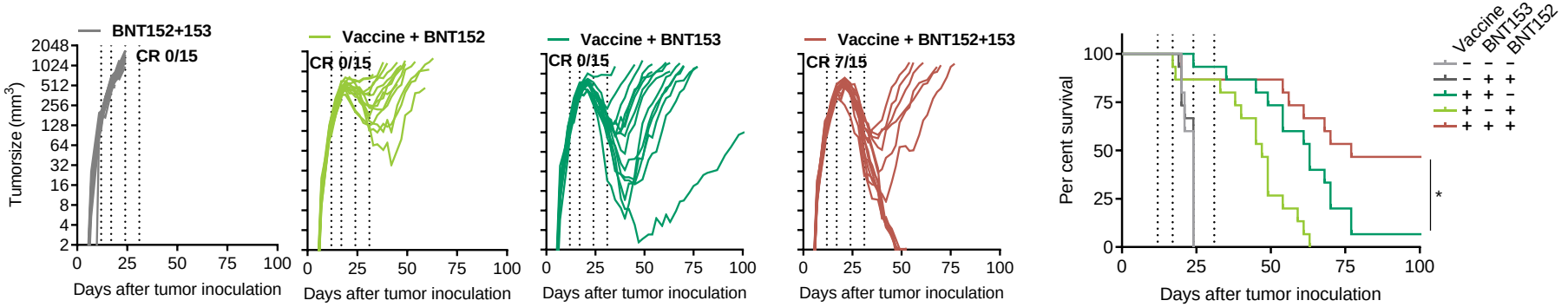


Vaccine antigen: gp70

Therapeutic efficacy of IL-2 + IL-7 depends on RNA vaccination in an advanced "cold tumor" model[2]



TC-1: "cold tumor" model



Vaccine antigen: E7

[1] Kranz LM, *et al.* SITC Annual Meeting 2019; Poster presentation 620; [2] Kranz LM, *et al.* CIMT Annual Meeting 2021; ePresentation.

BNT151

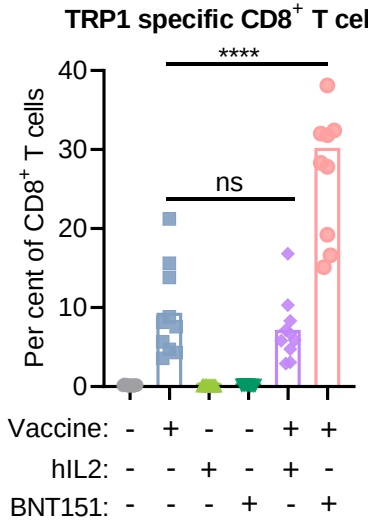
Therapeutic activity of BNT151 in combination with T cell vaccination

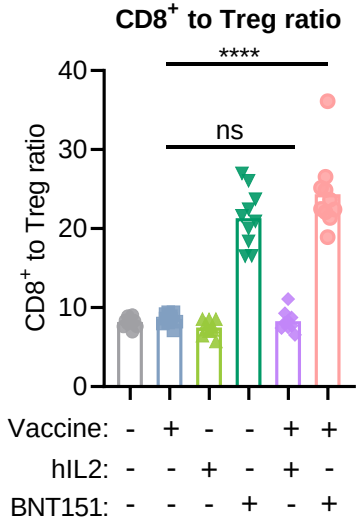
Substantial improvement of the therapeutic efficacy of RNA-LPX vaccination by BNT151

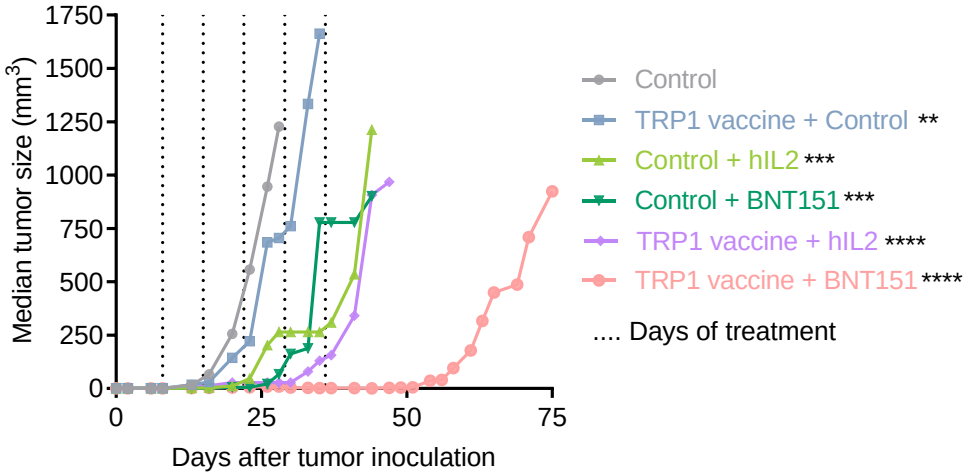
C57BL/6

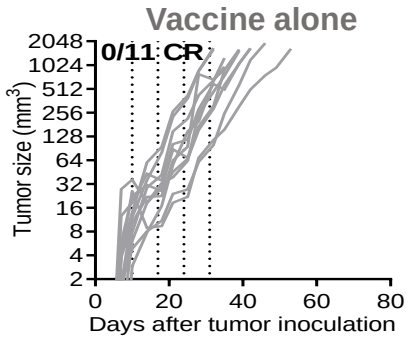
B16F10 s.c. tumor

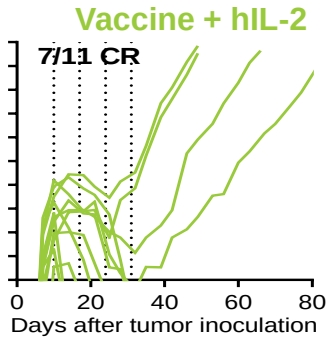
Vaccine target: TRP1
(differentiation antigen containing a CD8 T-cell epitope)

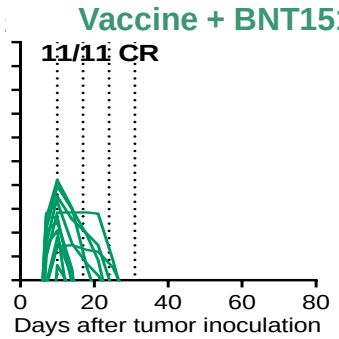








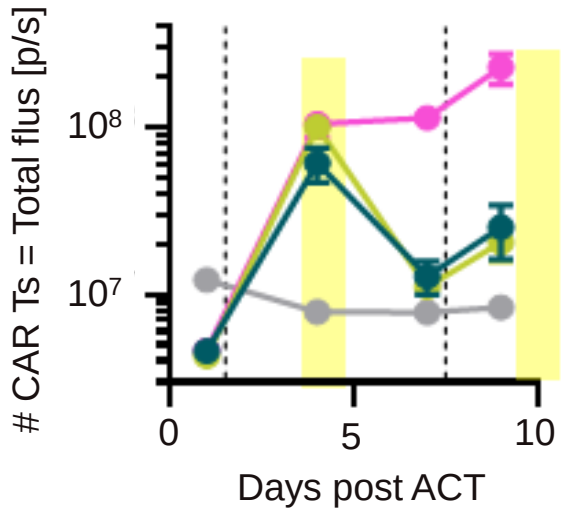




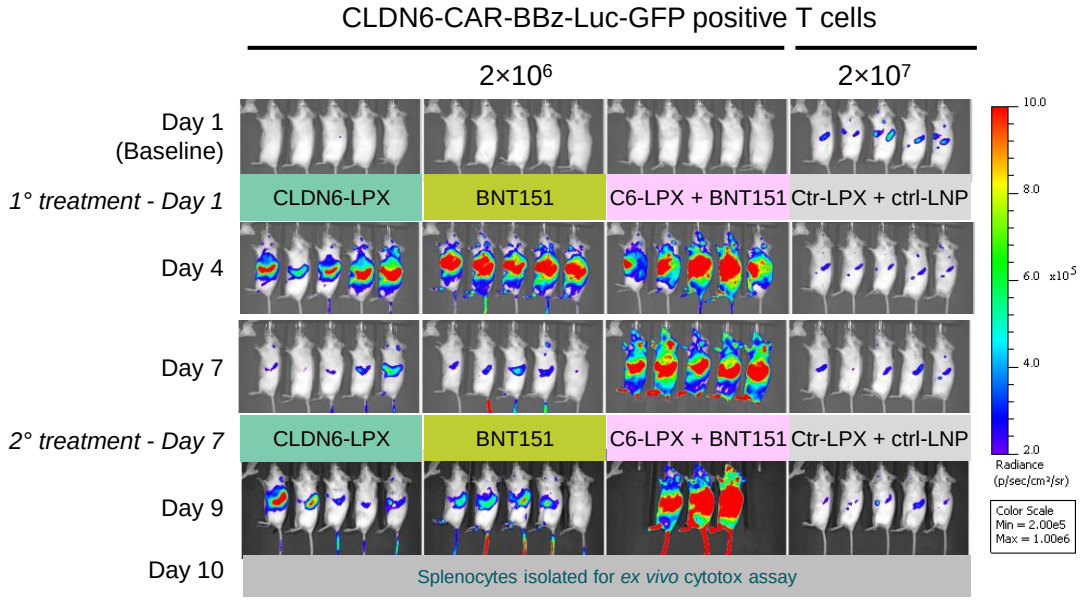
[1] Kranz LM, *et al.* SITC Annual Meeting 2019; Poster presentation 620; [2] Kranz LM, *et al.* CIMT Annual Meeting 2021; ePresentation. Vormehr M, *et al.* SITC Annual Meeting 2019; Poster presentation 626.

BNT151 mediates CAR T cell expansion in non-tumor bearing mice

Comparable *in vivo* expansion of CAR T cells in CLDN6-LPX or BNT151 treated mice



CAR T dose	Treatment
2×10^6	+ CLDN6-LPX
2×10^6	+ BNT151
2×10^6	+ CLDN6-LPX + BNT151
2×10^7	+ ctrl-LPX + crtl-LNP
·····	Treatment
	Time point of analysis



BNT151 treatment leads to initial similar CAR T cell expansion *in vivo* compared to CLDN6-LPX treatment

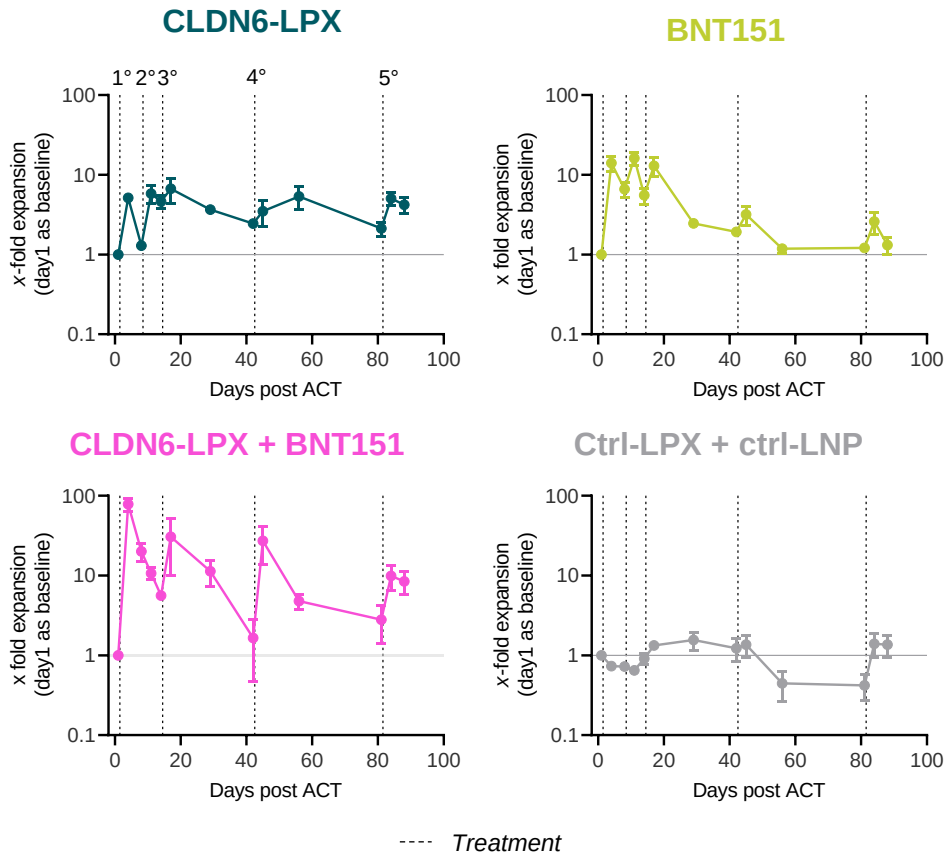
BNT151-mediated CAR T expansion peaks at day 3/4 after treatment, followed by contraction phase at day 7

CLDN6-LPX + BNT151 improves CAR T cell expansion

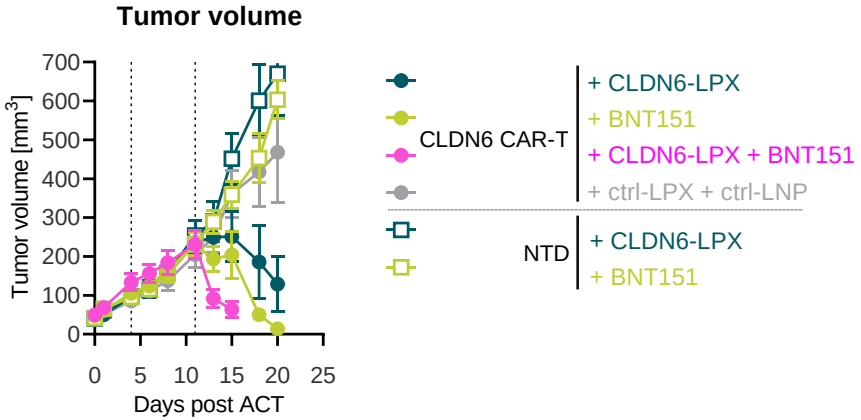
Data on file.

Long-term in vivo expansion and anti-tumor activity of CAR T cells in combination with vaccine and BNT151

CAR T-cell expansion and persistence in NSG mice after repetitive treatment cycles

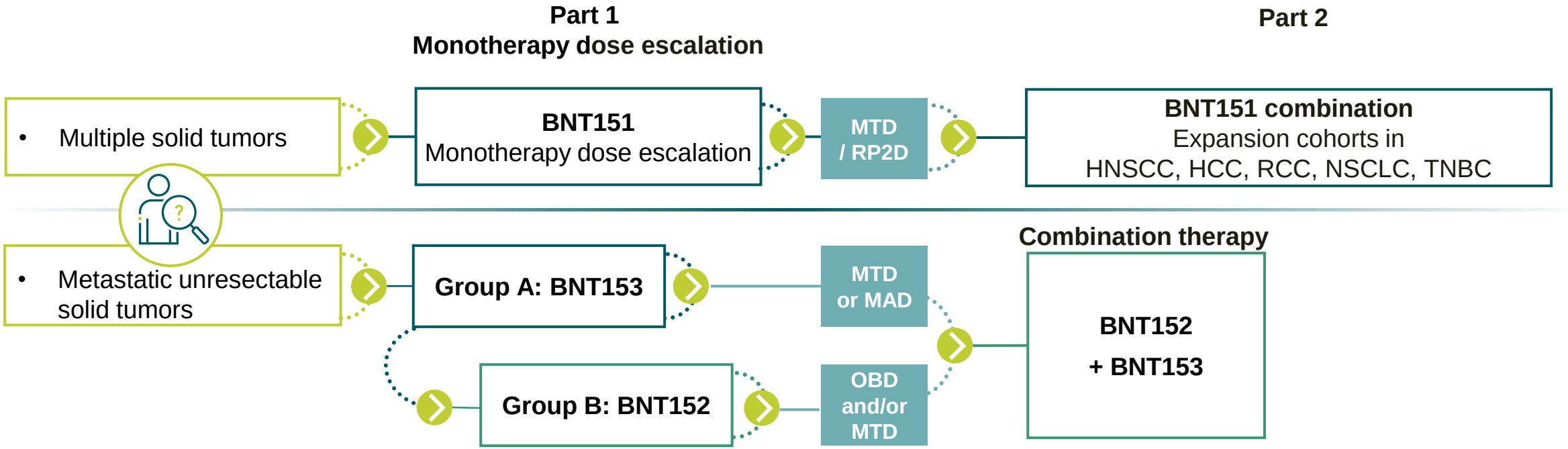


Anti-tumor activity of Prodigy-generated human CAR T cells in OV90 tumor-bearing NSG mice



- CAR-specific stimulation with CLDN6-LPX leads to persistence >90 days
- BNT151 stimulates repetitively (CAR) T cells. Combination of CLDN6-LPX and BNT151 superior in stimulating initial expansion and persistence
- CLDN6-LPX, BNT151 expand subtherapeutic CAR T cells in xenograft models and result in therapeutic activity

BNT151, BNT152 + BNT153
Two Phase 1/2 FIH trials of mRNA-encoded cytokines in solid tumors



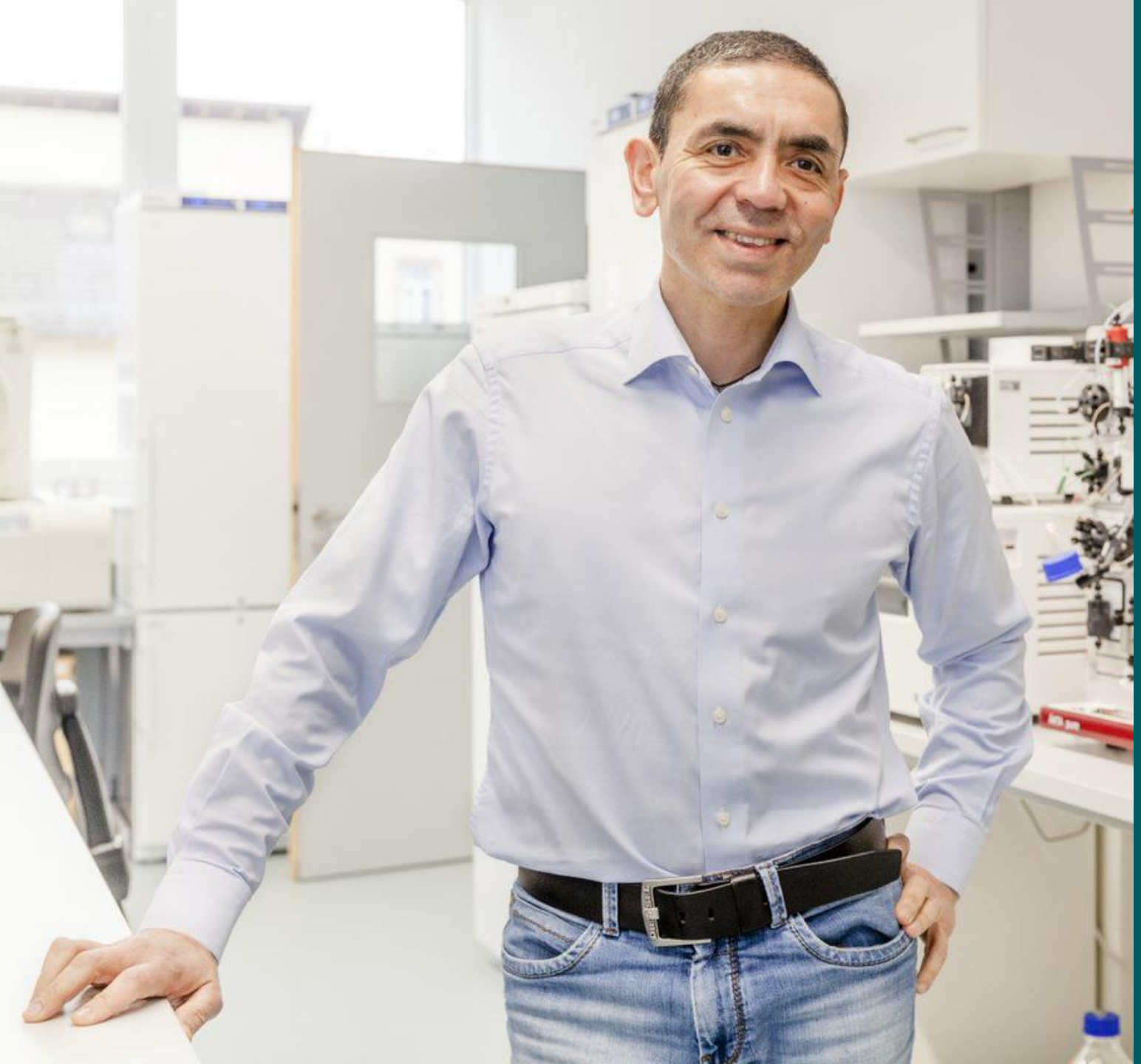
Key endpoints

- Safety and tolerability
- Antitumor activity
- Pharmacokinetics and pharmacodynamics

Status

- Dose-escalation ongoing
- Total number of patients dosed: 26

FIH, first-in-human, HCC, hepatocellular carcinoma; HNSCC, head and neck squamous-cell cancer; MAD, maximum-administered dose; MTD, maximum tolerated dose; NSCLC, non-small-cell lung cancer; OBD, optimal biological dose; RCC, renal cell carcinoma; RP2D, recommended Phase 2 dose; SoC, standard of care; TNBC, triple-negative breast cancer.
ClinicalTrials.gov: NCT04455620.



Closing remarks

Advancing toward our long-term vision

Driving transformation today

1 marketed vaccine
Market leader in COVID-19 vaccines

16 programs in 21 clinical trials

5 randomized Phase 2 trials

Oncology

1 Phase 1 program

10+ preclinical programs

Infectious diseases

Mid-term goals

Next-gen or variant adapted COVID-19 vaccines

Multiple product launches in next 3–5 years

5–10 IND submissions per year

Long-term vision

Maintain and deepen COVID-19 vaccine leadership

Approved products across various disease areas

By 2030, we aim to be a multi-product global biotechnology leader, aspiring to address the world's most pressing health challenges with pioneering, disruptive technologies delivered at scale

Q & A

BIONTECH

THANK YOU

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