iNeSTs - individualisierte Therapien in der Krebsmedizin

Pharma Forum 2022

Dr. Carolin Steinl
Pipeline Product Strategy Lead
Roche Pharma AG Deutschland

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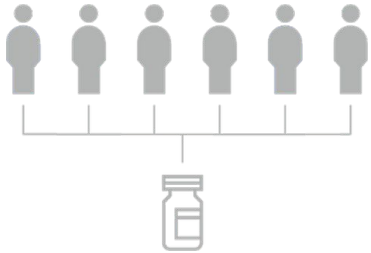
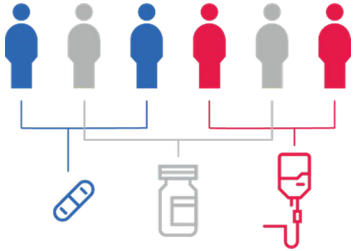
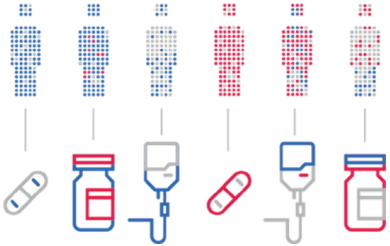
“The Future of Medicine Is in Your DNA”

Individualized Therapies

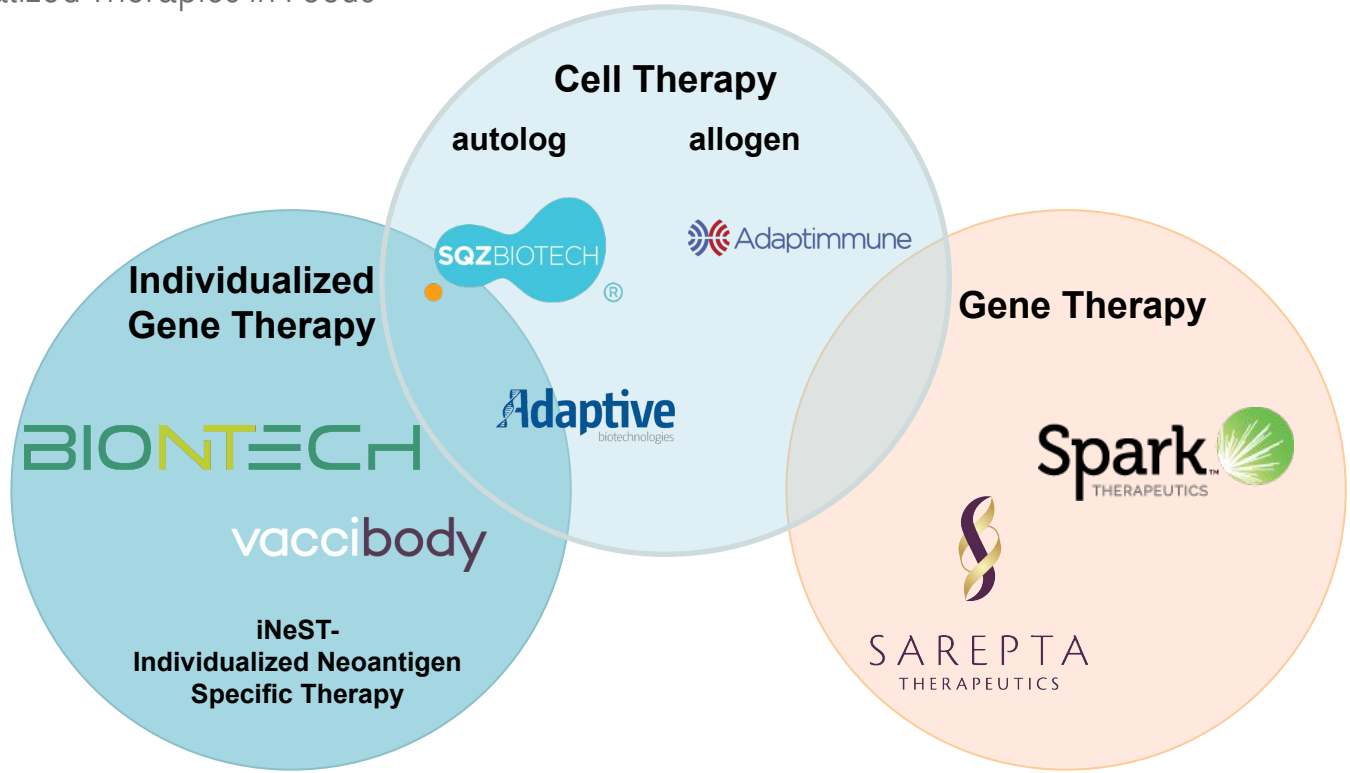
- Treatment of the Future

Past	Present	Future
		
Blockbuster drugs	**Targeted medicines**	**Individualised treatment**

"What does an individualized therapy mean for patients?

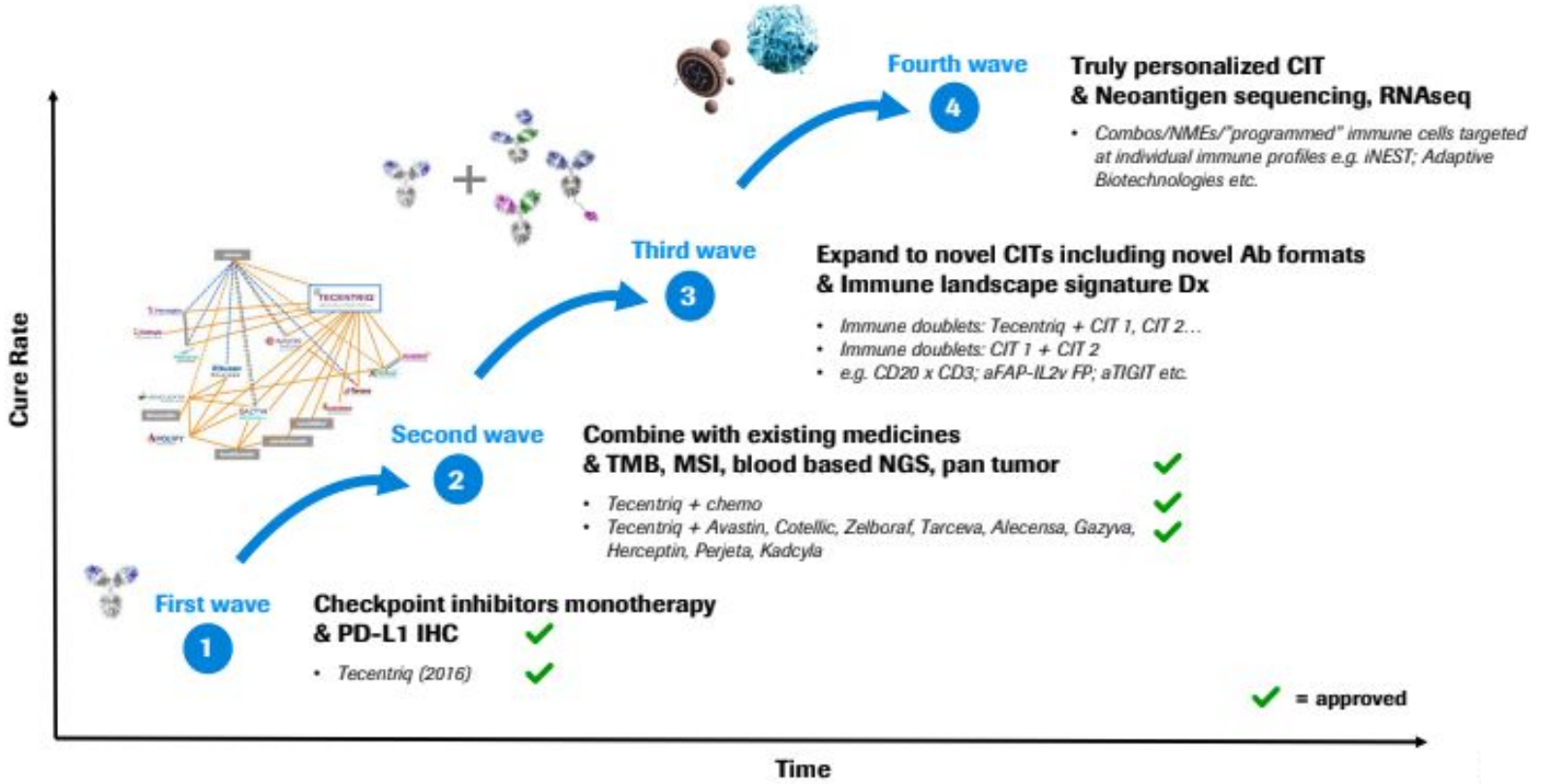
Cell and Gene Therapies are part of a broad technology platform

Roche's Individualized Therapies in Focus



The Next Step in Cancer Immune Therapies

Individual treatments for Cancer Patients



Every Tumor is Unique

Individualized Therapies Target Tumor Cells

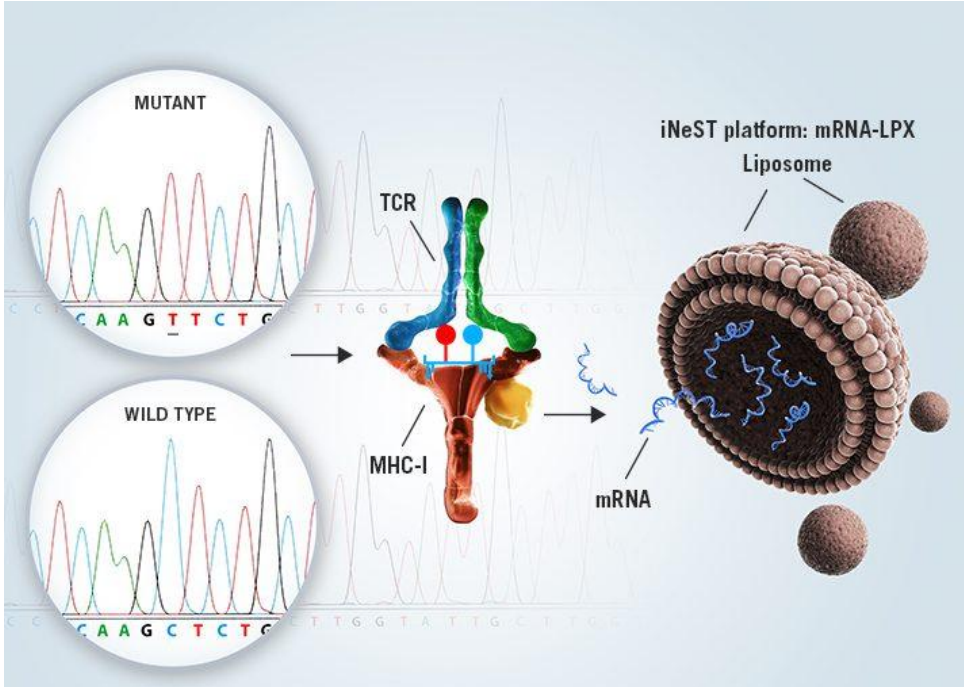
- Genetic mutations lead to the expression of unique tumor antigens called neoantigens
- For the identification of candidate neoantigens DNA is extracted from an individual patients tumor and sequenced
- By comparing the sequences of the patient's tumor mutations with germline DNA from normal cells, tumor mutations are identified
- With Individualized Neoantigen-Specific Immunotherapy (iNeST) the unique and individual mutations can be targeted

source: https://www.genentechoncology.com/development-platforms/individualized-neoantigen-specific-immunotherapy.html

iNeST-RNA

Collaboration with BioNtech

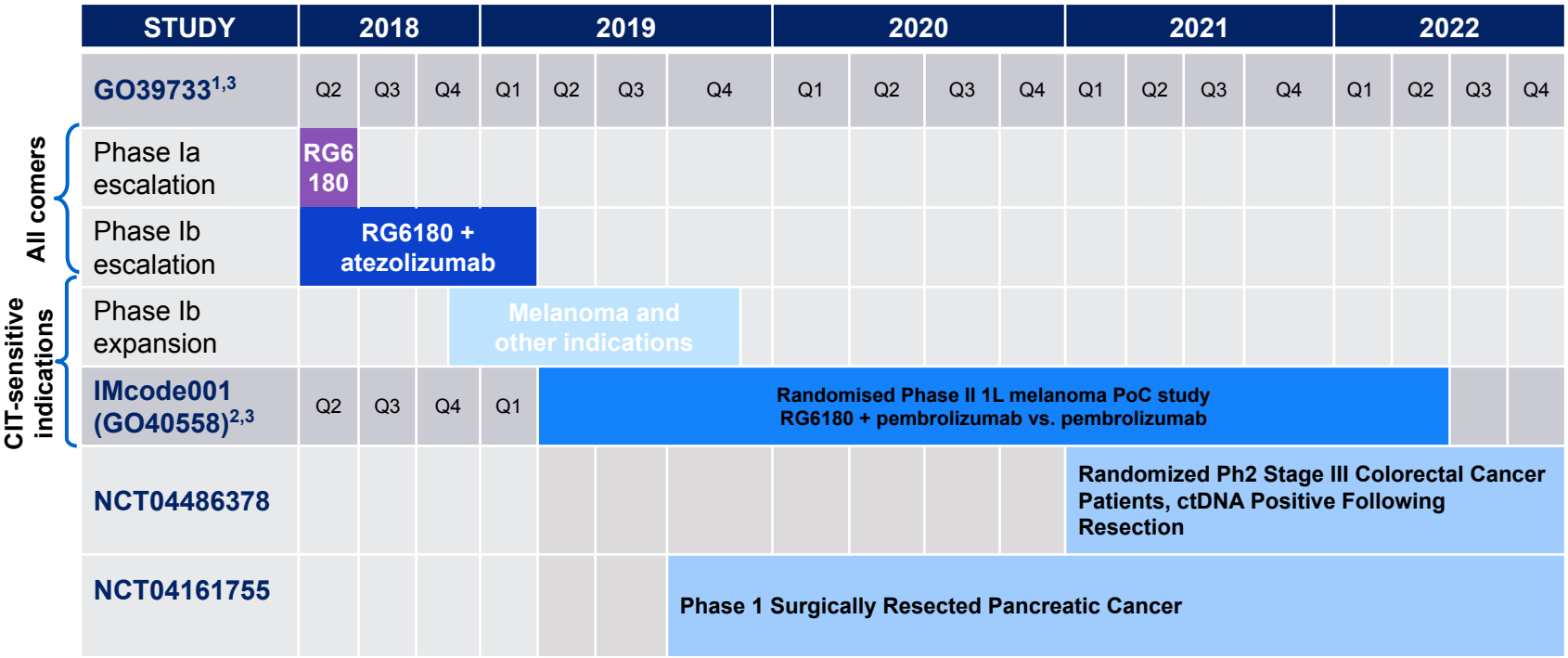
- iNeST mode of action uses neoantigens as targets to identify and eliminate cancer cells
- neoantigens are individual for every cancer patient
- A mRNA-lipoplex formulation can be delivered to the individual patient
- The mRNA-lipoplex localizes to the spleen, where it is taken up by dendritic cells
- mRNA translates into a polypeptide that is processed to neoantigens and presented to T-cells



source: https://www.genentechoncology.com/development-platforms/individualized-neoantigen-specific-immunotherapy.html

iNeST-RNA (RG6180) is currently in Phase I/II development

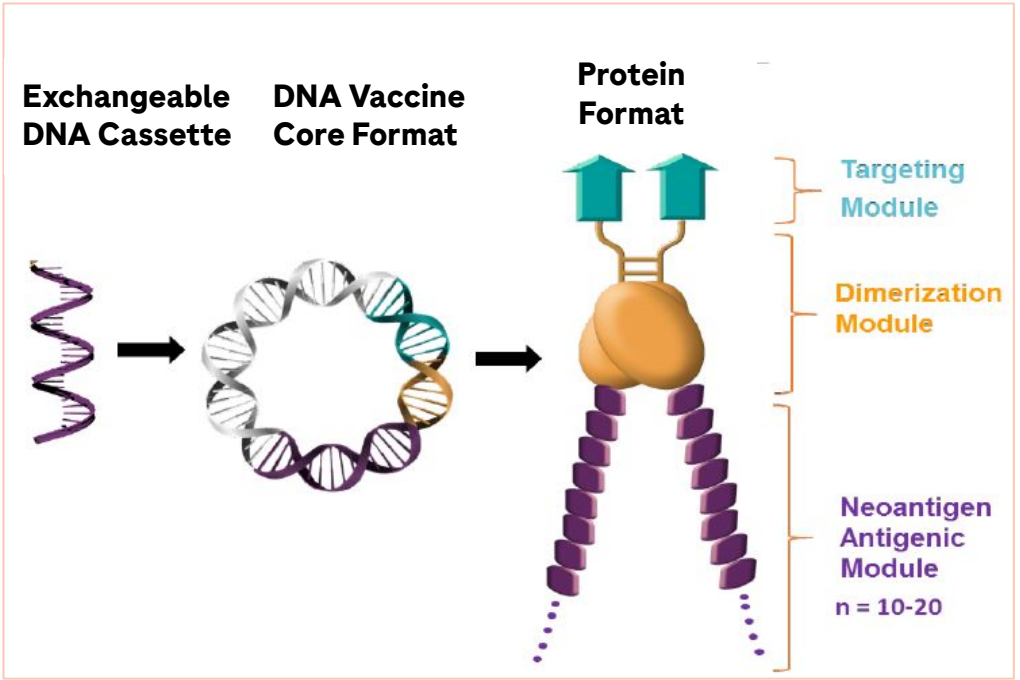
- in monotherapy or in combination with checkpoint inhibitors



iNeST-DNA

Collaboration with Nykode

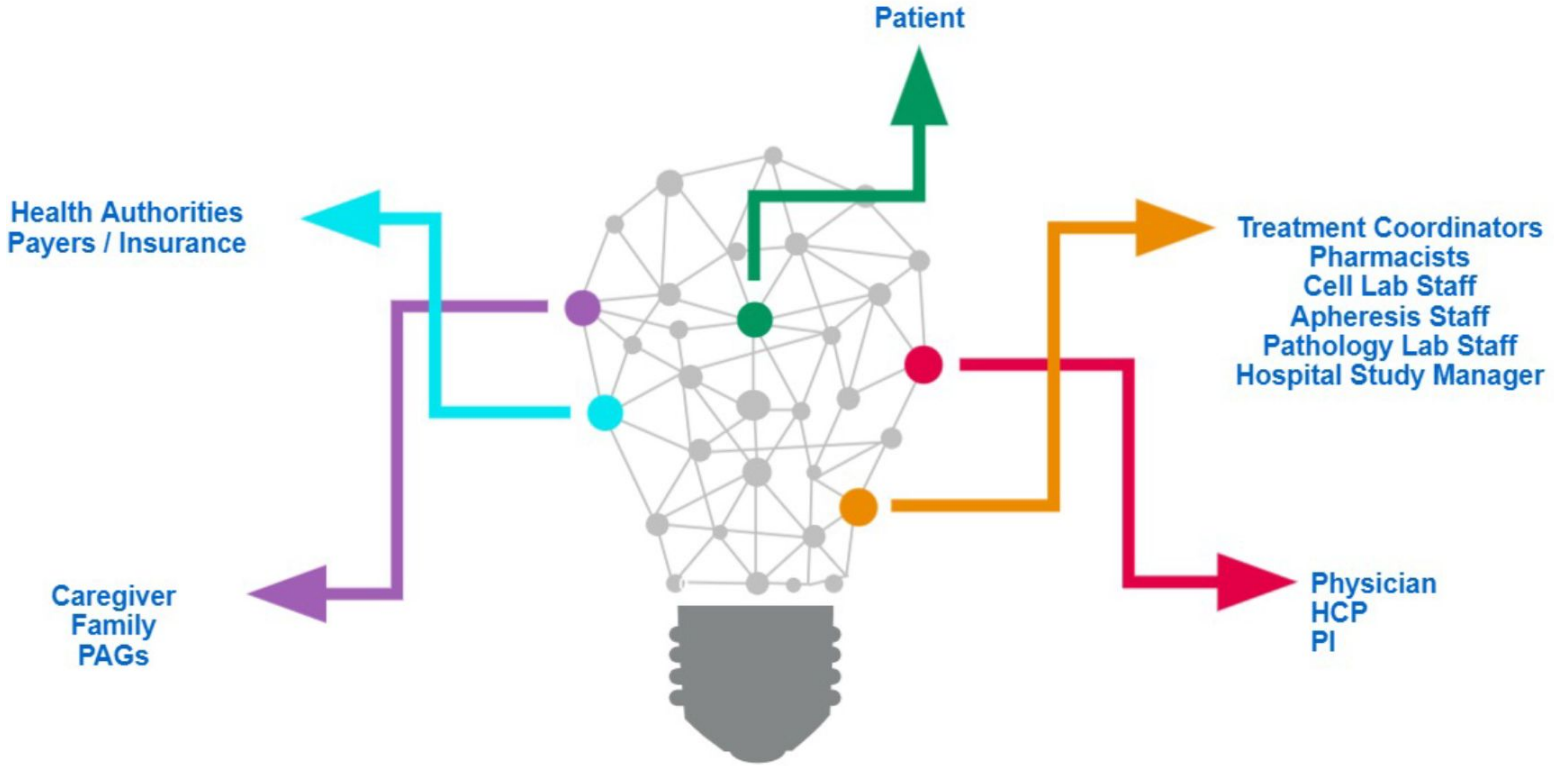
- Neoantigens incorporated in a DNA plasmid allows an intramuscular application
- DNA plasmid supports a stable expression of the protein
- Neoantigen modules are degraded and finally presented on Immune complexes
- Finally leading to the activation of T-cells and the targeting and elimination of cancer cells



source: Stubsrud, Elisabeth & Granum, Stine & Zell-Flagstad, Helene & Bersaas, Audun Trygge Haugen & Skullerud, Lise & Sekelja, Monika & Schjetne, Karoline & Fredriksen, Agnete. (2019). Abstract 5003: 5003-5003. 10.1158/1538-7445.SABCS18-5003.

iNeSTs require a closer collaboration

Is the German Health Care System ready for Individualized Therapies?



Doing now what patients need next

Appendix

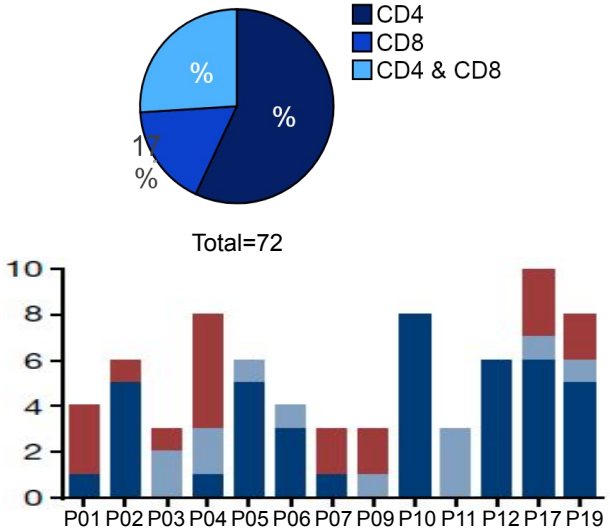
1.

Phase I immune monitoring data

Both CD4+ and CD8+ T-cell immune responses specific to predicted neoantigen were observed in patients that received IVAC® MUTANOME

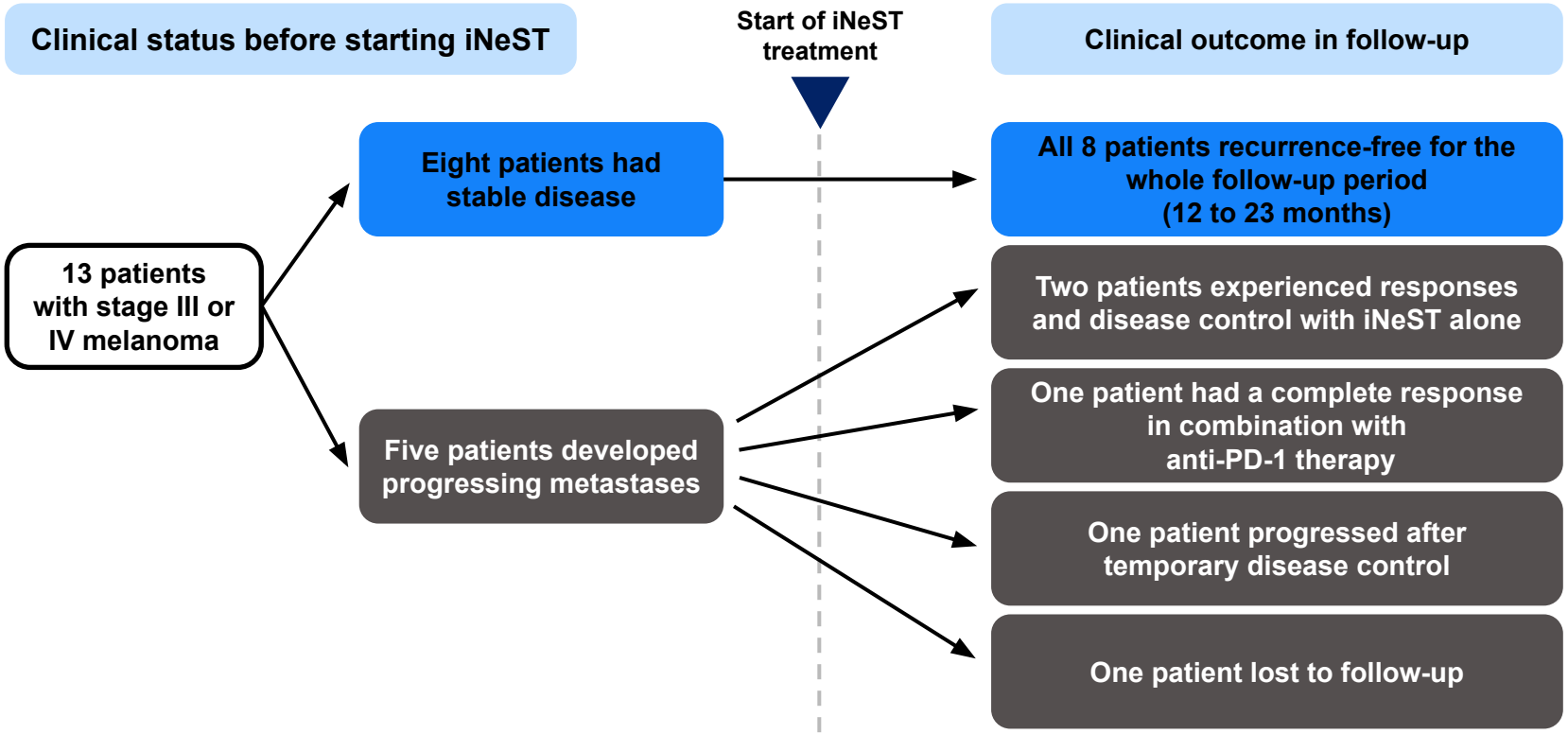
- The majority (57%) of the neoepitopes exclusively elicited CD4+ T-cell responses
- A smaller fraction of the neoepitopes (17%) produced only CD8+ cytotoxic T-cell responses
- Approximately one-quarter of the neoepitopes (26%) produced both CD4+ and CD8+ T-cell responses

T-cell responses against predicted neoantigens by cohort level or per individual patient[1]



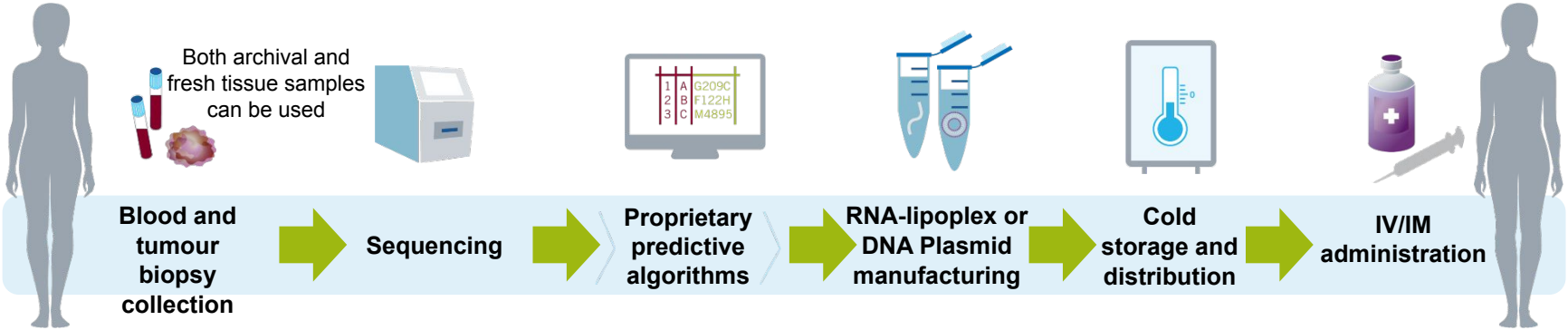
Sahin U. *Nature* 2017.

Phase I trial data demonstrate favourable anti-cancer clinical responses induced by IVAC® MUTANOME



Sahin U. *Nature* 2017.

iNeST Logistics and Manufacturing

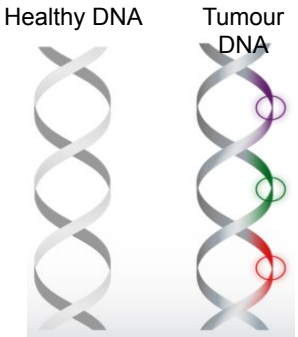


The logistics and manufacturing of individualized therapies like iNeSTs inherits several checkpoints that might influence timing and quality of the final product.

Prioritisation of neoantigens for each iNeST is critical as not all mutations in tumours generate immunogenic neoantigens

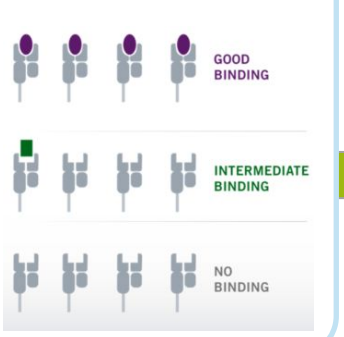
A proprietary predictive algorithm prioritises neoantigens based on multiple criteria, including predicted MHC Class I or Class II binding, gene expression and clonality[1–5]

Mutation calling and clonality



Levels of gene expression

MHC binding affinity



Target confirmation and selection

Top 20 neoantigen candidates are selected for incorporation into mRNA of the iNeST

- Multiple neoantigens are selected for each iNeST to increase the magnitude/chance of immune responses and minimise the chance for tumour escape by downregulation of a specific neoantigen
- The algorithm has been tested in clinical trials, and both CD4+ and CD8+ T-cell responses specific for predicted neoantigens have been observed[3]
- The algorithm offers the potential to learn and improve continually; data generated from patients or related research studies can be used for continuous improvement of the algorithm[2,3]

1. Kreiter S. *Oncoimmunology* 2012; 2. Castle JC. *Cancer Res* 2012; 3. Sahin U. *Nature* 2017;
4. Karasaki T. *Cancer Sci* 2017; 5. Roche/ BioNTech. Data on File.

Manufacturing individualized cell and gene & (incl. RNA) therapies

Existing drug modalities

One Batch – Many Patients
Pure "Make to Stock"
e.g. small molecules; antibodies

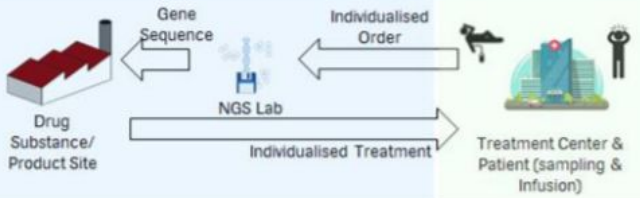
Highly individualized therapies

One Batch – One Patient
"Make to Order"
e.g. CARTs, RNA vaccines in oncology (iNEST)

Supply chain driven by new KPIs
Wait time, TAT, Zero Error SC.

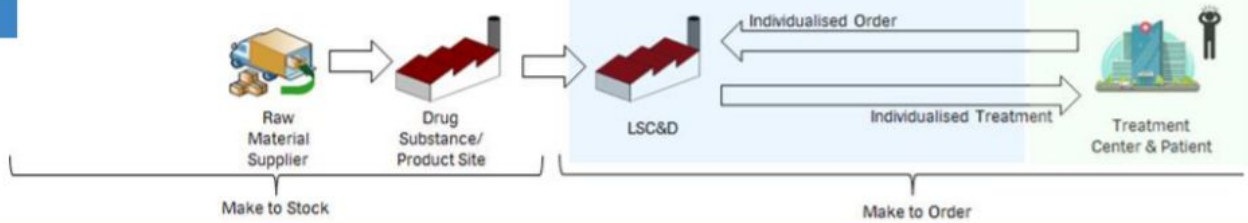
Unique requirements
Order Management, CoI/CoC, Protected health information, Make to Order scheduling, performance management & workflow management.

New orchestration and exception management



Individualized therapies

One Batch – Several Patients
"Make to Stock" with make to order kit"
e.g. off-the-shelf CARTs, gene therapies, RNA therapies



Ensuring the right patient is treated with the right product at the right time with zero error in the value chain

CoI/CoC=chain of custody/chain of identity; NGS=next generation sequencing; LSC&D=late stage customisation & distribution; CARTs=Chimeric antigen receptor T-cells; iNEST=Individualized NeoAntigen Specific Immunotherapy