Application of RNA technologies

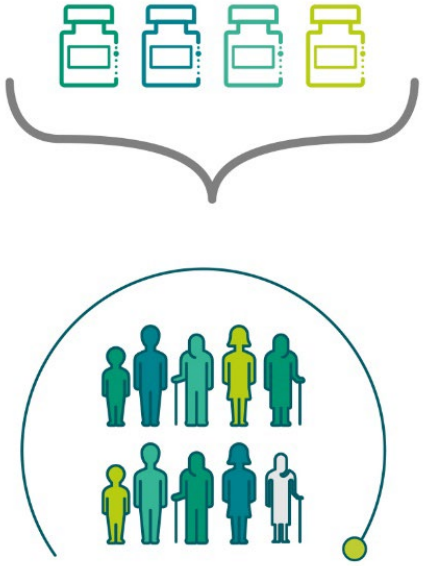
Clinical – An Industry Perspective

Michael Wenger, M.D.

BIONTECH

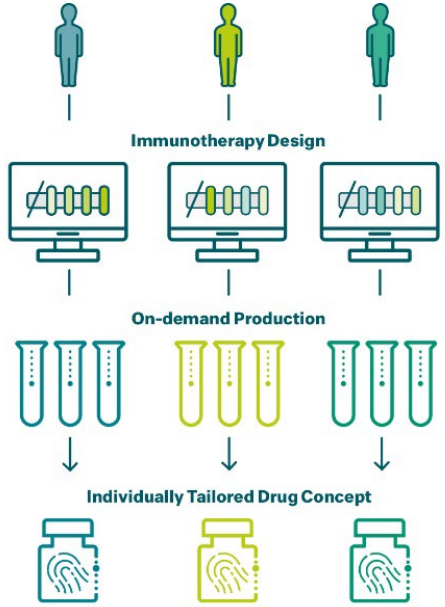
Cancer vaccine research – off-the-shelf and individualized approaches

Fixed Antigen Approach



- **Off-the-shelf <u>indication-specific</u> mRNA cancer vaccine approach (e.g., lung cancer, prostate cancer)**
- **Targeting a fixed combination of shared antigens[1,2]**
  - Non-mutated tumor antigens shared across patients
  - Applicable for almost all types of tumor antigens

Individualized Approach



- **<u>Individualized</u> mRNA cancer vaccine approach**
- **Targeting 20 neo-antigens unique to each patient[3,4]**
  - Majority of neo-antigens are unique to individual patients
  - Applicable across solid tumor types

1. Sahin, U. et al. Nature 585, 107–112 (2020); 2. Kranz, L.M. et al. Nature 534, 396–401 (2016), 3. Sahin, U. et al. Nature 547, 222–226 (2017). 4. Kreiter, S. et al. Nature 520, 692–696 (2015).

Challenges when developing mRNA-based medicines

- Concept of “platforms”
  - Assumption: the safety of mRNA-based vaccines is, at least in part, driven by the MoA and not by the encoded tumor-associated antigen
  - Clinical and pre-clinical safety data may be extrapolated across platform candidates
  - Across multiple oncology indications, or even beyond?
  - Established dose range for one platform compound may inform on dose range for other candidates

- Leveraging existing post-marketing experience for RNA-based vaccines
  - How can the global exposure to RNA-based infectious diseases vaccines inform on the use of RNA medicinal products based on the same platform in other therapeutic areas, e.g., oncology, auto-immune diseases?

- How does dose-finding work when there is
  - Little correlation between mass (per µg dose of mRNA) and translation?
  - Translation and immunogenicity?
  - Immunogenicity and tumor shrinkage?

Beyond vaccines: mRNA to produce cytokines *in vivo*

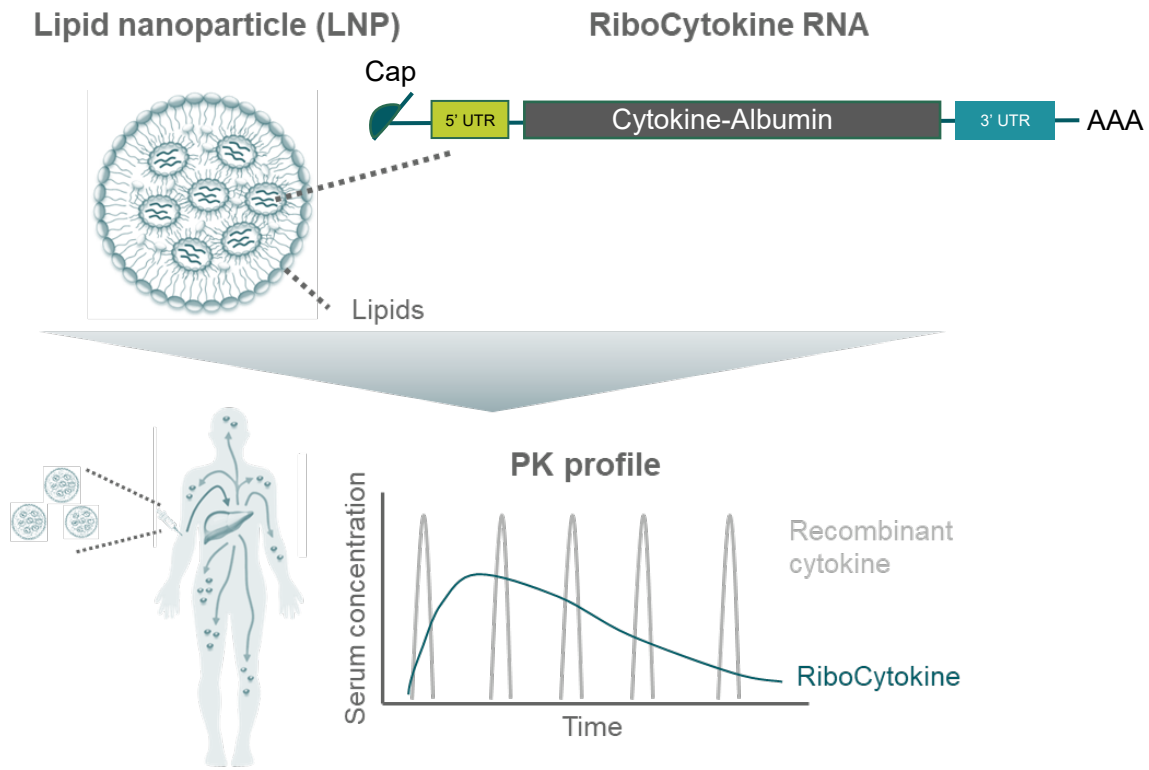
Cytokines encoded by mRNA: A novel therapeutic concept

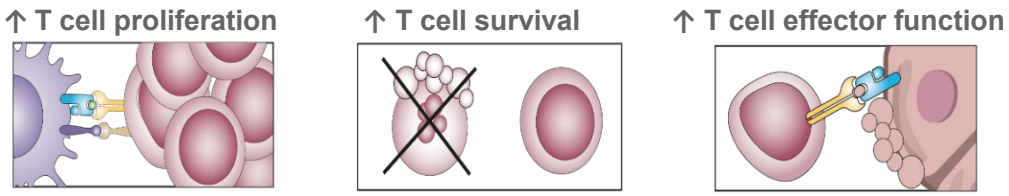
Systemic delivery with potentially minimal immunogenicity

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

Designed for optimized safety, tolerability and dosing

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





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

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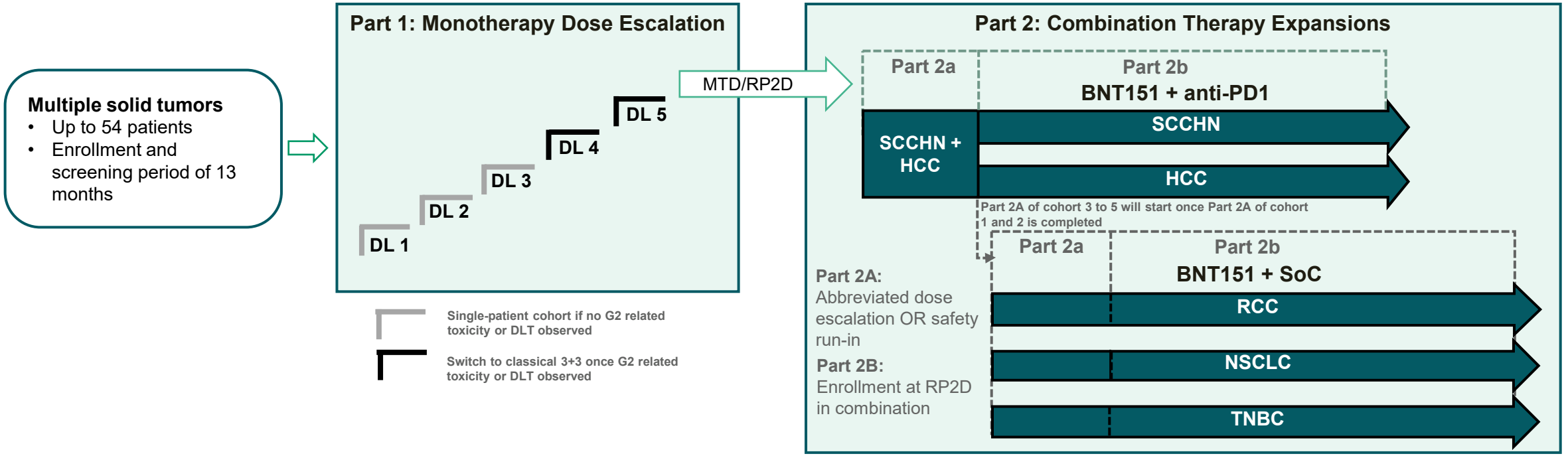
Example: BNT151-01 Open-label, multicenter Phase 1/2a, first-in-human trial

mRNA encodes for IL-2var



Evaluation of dose escalation, safety, pharmacokinetics and pharmacodynamics of BNT151 with expansion cohorts in multiple solid tumor indications

A relatively conventional Phase 1/1b design. Challenges lie in the details

NSCLC, Non-small Cell Lung Cancer; DL, dose level; MTD, maximum tolerated dose; RP2D, recommended Phase 2 dose; G2, grade 2; DLT, dose limiting toxicity; SoC, Standard of Care; SCCHN, Squamous cell carcinoma of the head and neck; HCC, Hepatocellular carcinoma; RCC, Renal cell carcinoma; TNBC, Triple-negative breast cancer; CPI; checkpoint inhibitor

Other challenges (and some opportunities)

- Lack of consistent understanding of genomic non-integration of RNA
  - Many queries and inconsistent interpretations on the need and duration of safety observation

- How can we deal with learning algorithms?
  - Screening for and detection of neoantigens for individualized vaccines requires tumor sampling
  - Sampling may lead to several thousands neoantigens available for mRNA production, but only few (up to ~20) comprise of a vaccine
  - Powerful algorithms select neoantigens with highest selectivity, binding affinity, and immunogenicity
  - Algorithms improve with the help of AI

- Immunotherapy due to its nature may work best in a low-tumor burden setting
  - Neoadjuvant, perioperative, and adjuvant concepts may be seen more frequently
  - These typically require very large trials, or novel endpoints (pCR), or both
  - Surrogate endpoints have not been consistently established, but are explored frequently (e.g., ctDNA)