UNLOCKING THE PROMISE OF IMMUNO-ONCOLOGY AND COMBINATION THERAPIES

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2013: "This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumors are paying off—even if the future remains a question mark."

Jennifer Couzin-Frankel, *Science* 20 Dec 2013: Vol. 342, Issue 6165, pp. 1432-1433

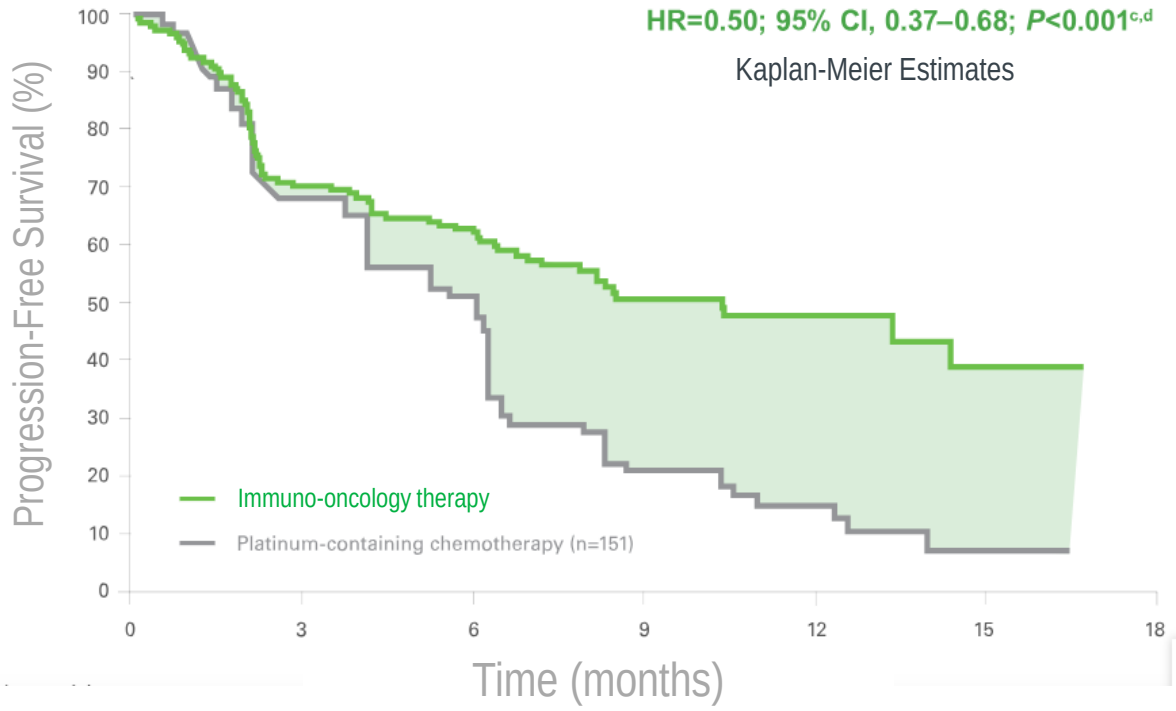
Immuno-oncology Therapy Can Offer Meaningful Benefit to Cancer Patients

Overall Response Rate: 24%; 12 month Overall Survival: 58%

Baseline 90 Days

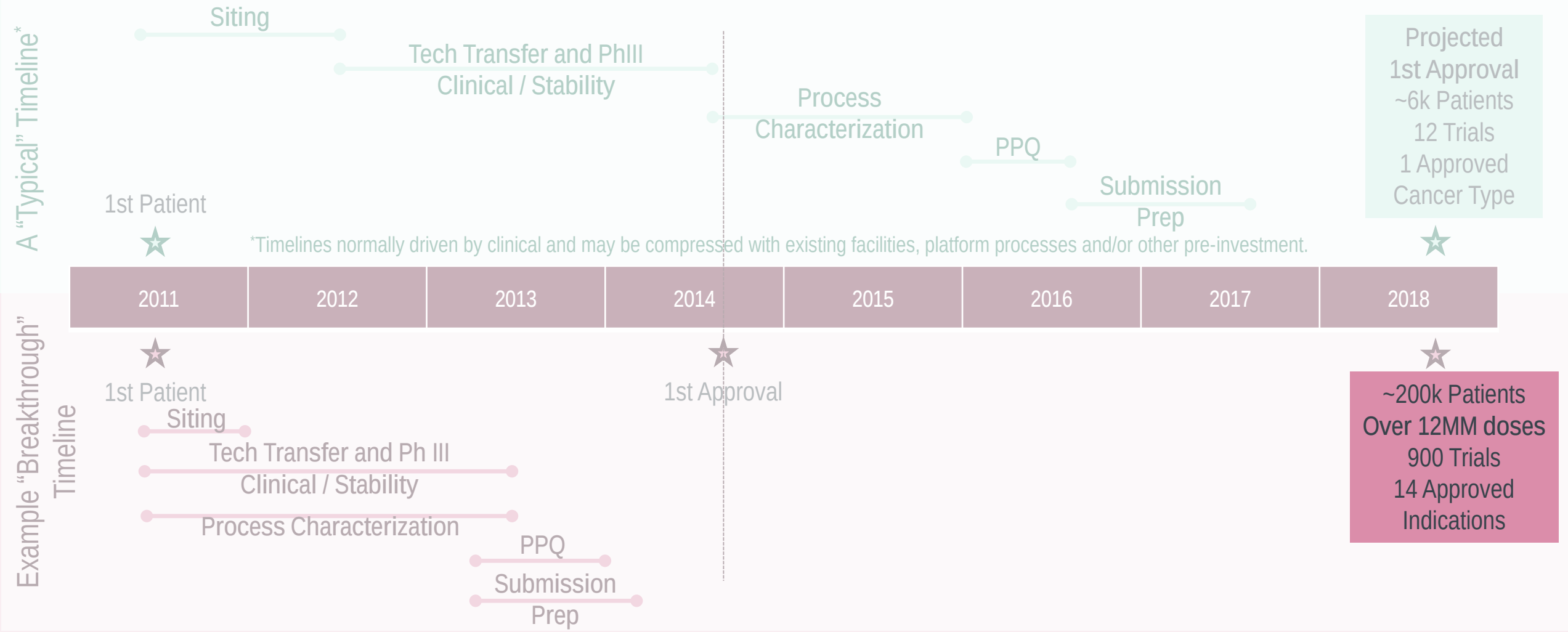
Pictures from Hamid, O et al. The New England Journal of Medicine 2013;369(2):142

Superior Progression-Free Survival with Immuno-oncology Therapy (NSCLC)



Data from Reck,, M et al. The New England Journal of Medicine 2016;375:1823-1833

Breakthrough Therapy Designation: An Opportunity for Accelerated Access



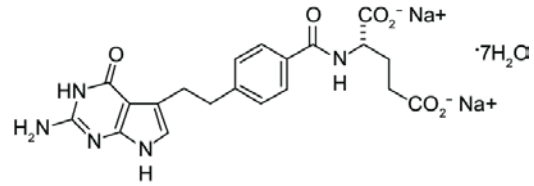
Impact

Patients Benefit!

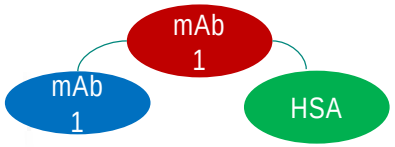
more trials, more indications, more patients

CMC is Crunched!

same activities, *but in less than half the time*



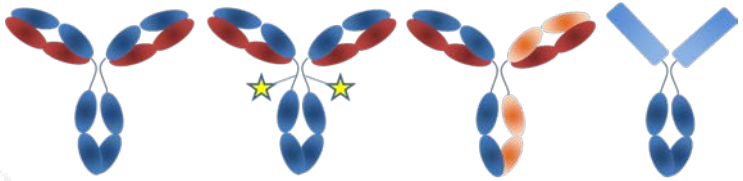
Small molecules



Nanobodies

Complex Biology
Complex Rx

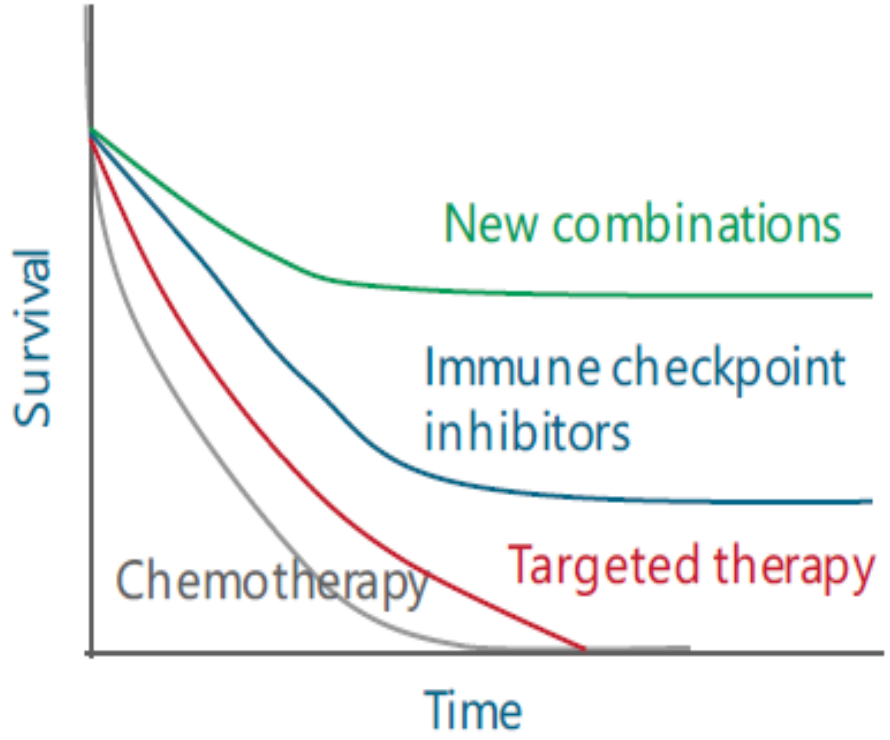
Viruses/Cells



mAb mAb-ADC mAb-Bsp Fc-Fusion

The Rise of Immuno-Oncology Combination Therapy

CHART 2: The focus in immuno-oncology is on "lifting the tail" of the survival curve

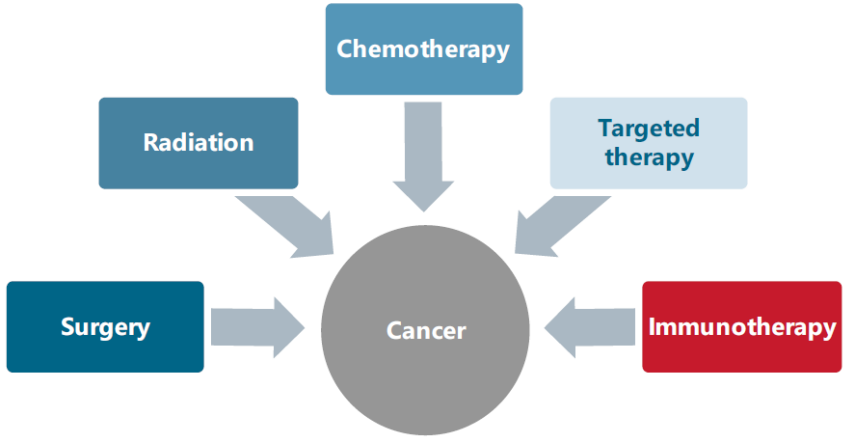


Source: goetzpartners Research

Partial Response Upon Combination Therapy for Head and Neck Squamous Cell Carcinoma

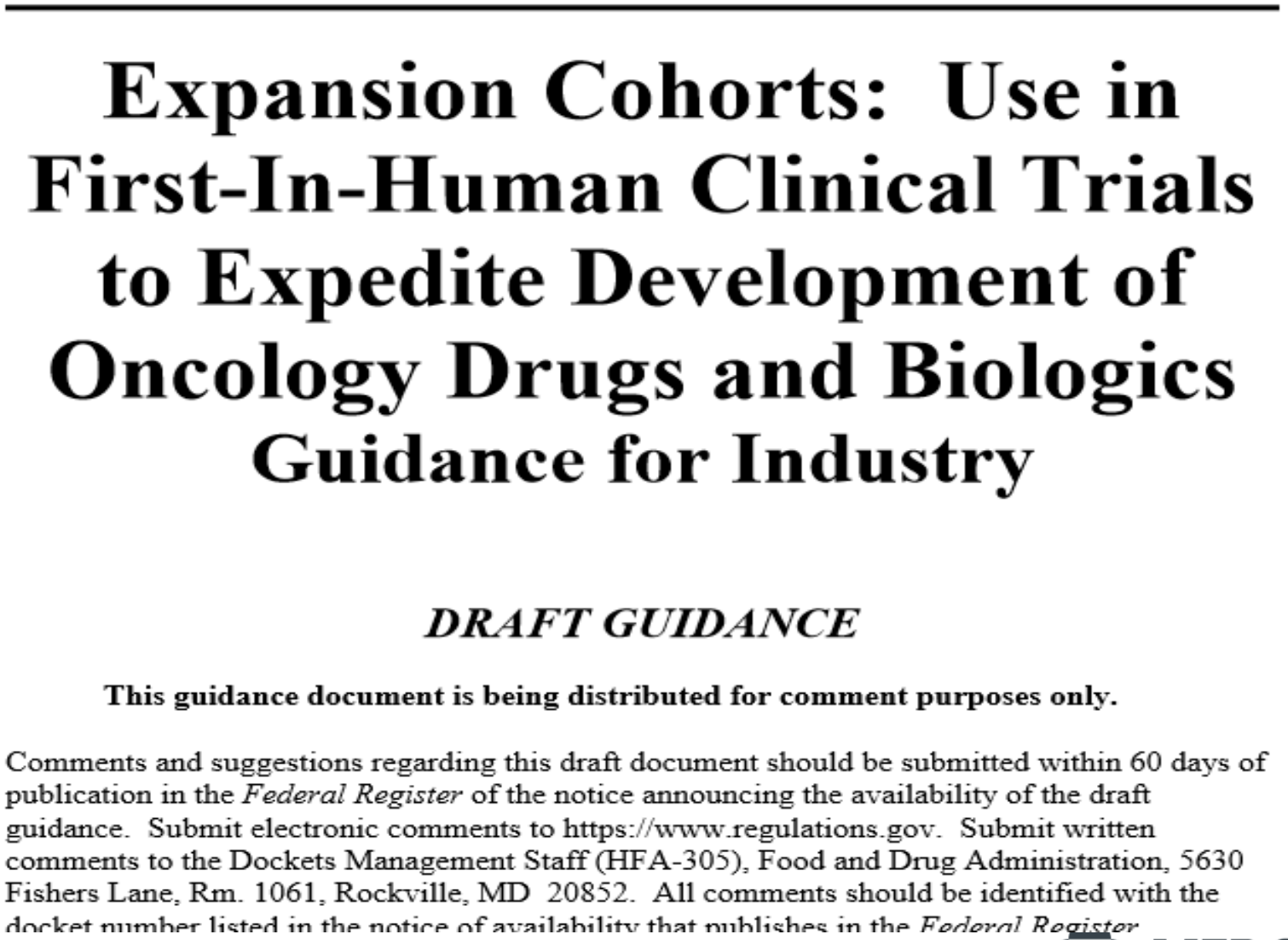
T= 0 | 6 weeks | 20 weeks

Pictures from Harrington et al.,Presented at ESMO 2018



Source: goetzpartners Research

Regulators Enabling “Hyper-Fast” Development Serving Patient Needs



Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*

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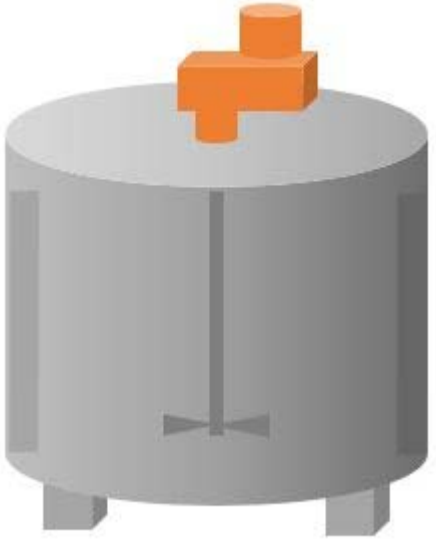
Different Modalities Present Unique CMC Challenges and Opportunities



Cell-Derived Modalities

Synthetic Modalities

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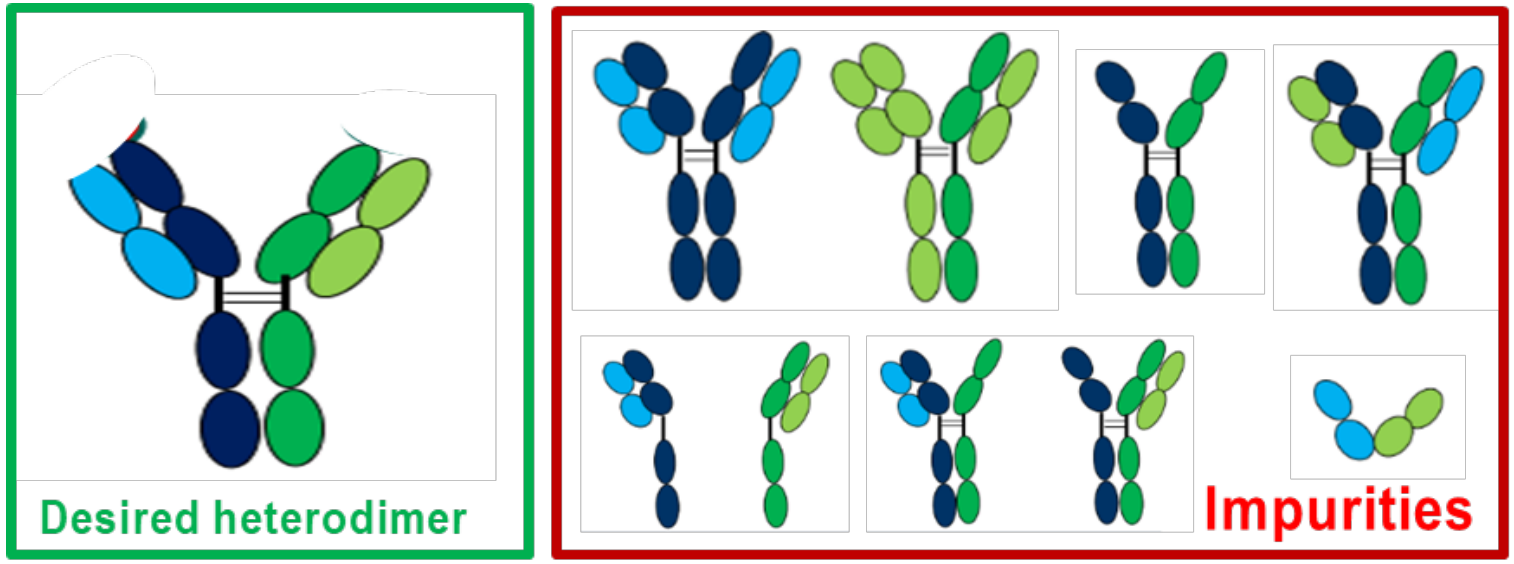
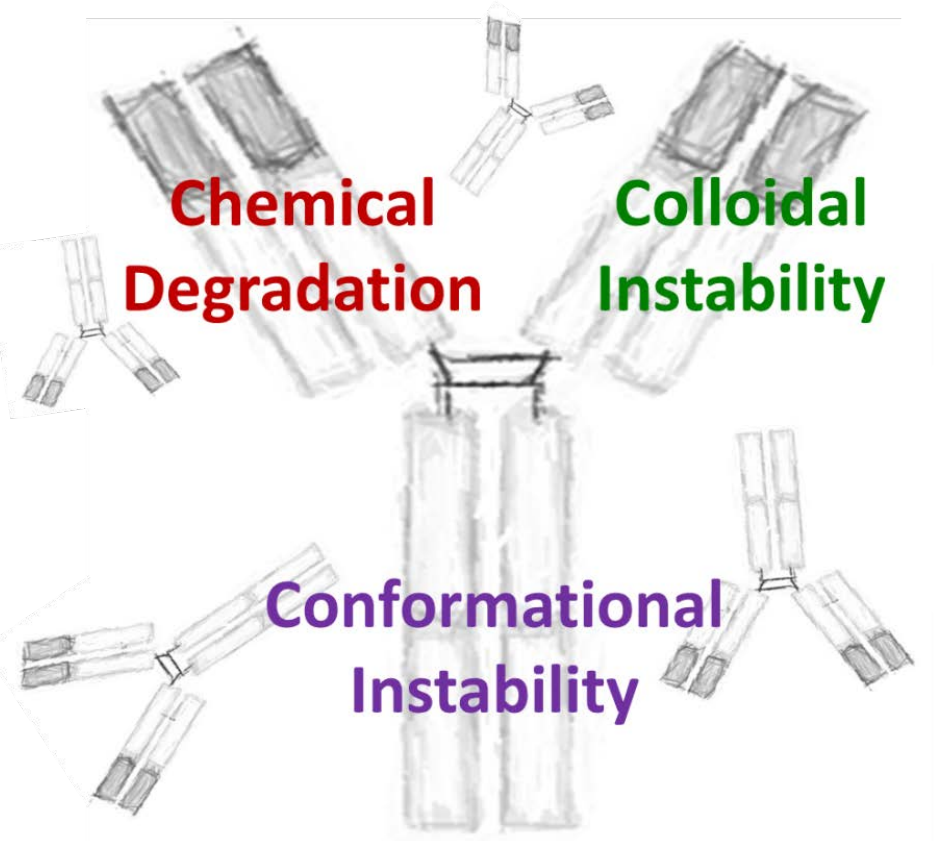
Novel Modalities and Associated Formulations Have Complex Characteristics

For e.g. Bispecific Antibodies



- Complex Impurity Profile : Homodimers, HC-HC only, HC-Flip, Half Abs, HC-HC only LAG3, ¾ Ab
- High resolution analytical methods required to quantify impurities
- Degradation pathway and stability may depend on type of impurity present

Formulation Challenges



Aggregation

Turbidity

Solubility/ Precipitation

Sub-Visible Particles

Liquid-Liquid Phase Separation

Protein Interactions

- Non-Covalent : charge , dipole, hydrophobic, specific
- Covalent : oxidation, deamidation isomerization

Formulation Factors

- pH
- Ionic Strength
- Buffer species
- Excipients

Process Parameters

- Stress: Heat, Light
- Shear- Filtration, Agitation, Pumping
- Interfaces- Freeze-thaw, Shaking
- Surfaces: Metal-ions, silicone oil

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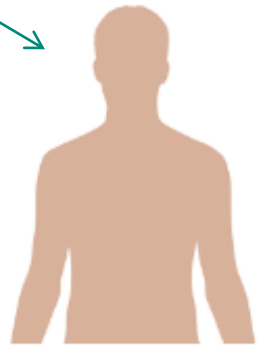
Emerging Strategies for Patient-Centered Product Design: Combinations

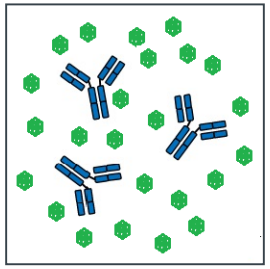
Individual products

Co-administration

Co-formulation

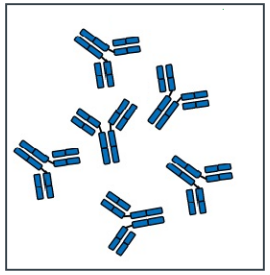


Antibody to Excipients



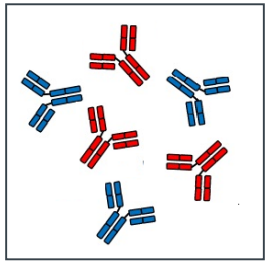
Low Concentration Formulations

Antibody to Antibody

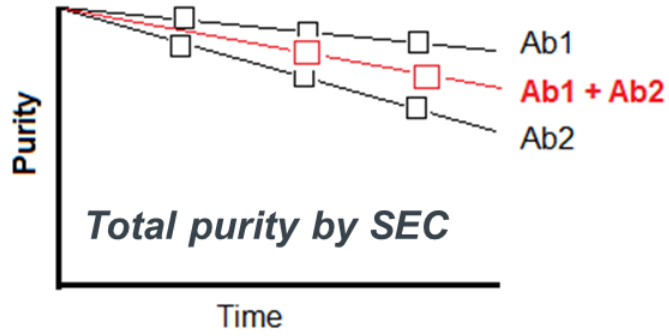


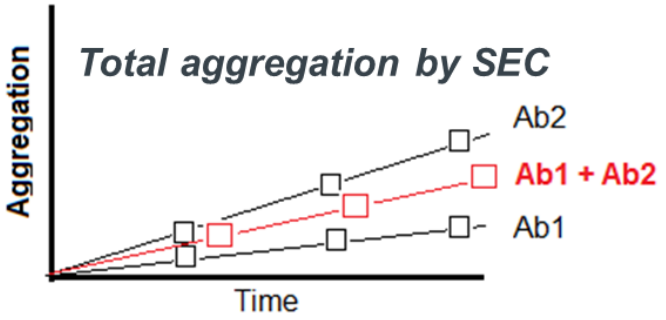
High Concentration Formulations

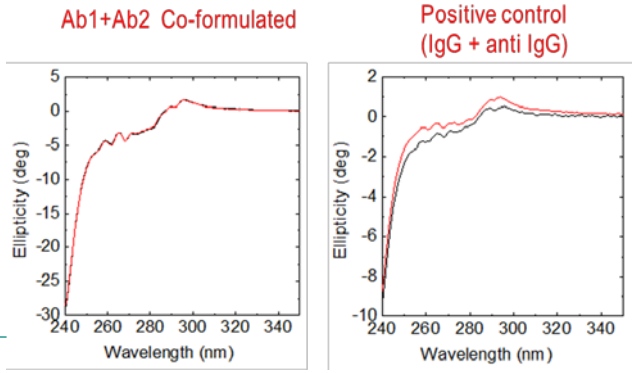
Antibody 1 to Antibody 2



Co-administration or Co-formulation







Public

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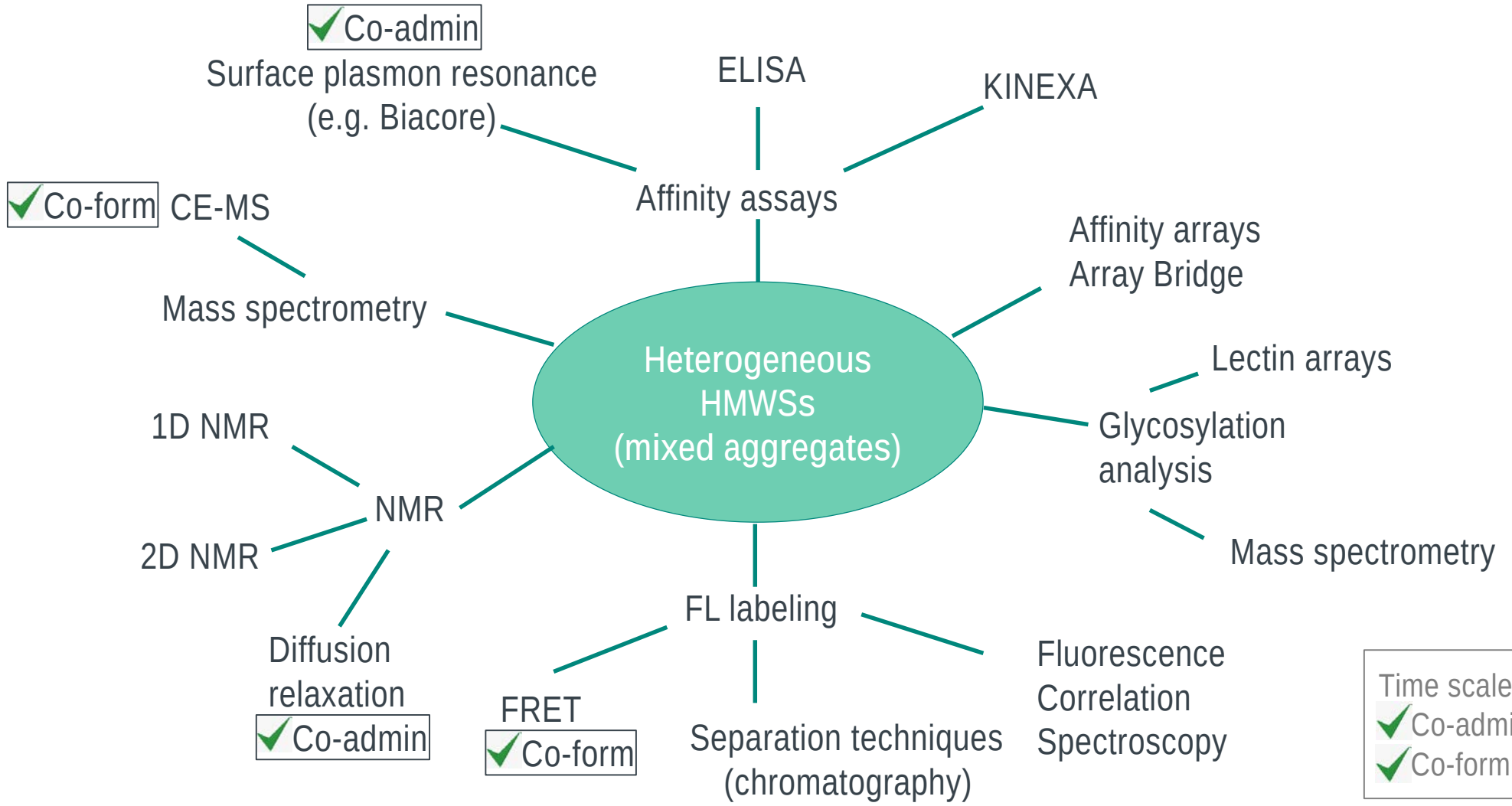
Advanced Analytical Tools Required for Characterization



Time scale:
- ✓Co-administration (< 2hours)
- ✓Co-formulation (1-2years)

Emerging Strategies for Patient-Centered Product Design: Subcutaneous Delivery

Patient

- Less Invasive
- Convenience

Provider

- Alleviates capacity constraints and increases throughput
- Facilitates long term IO maintenance therapy
- Better patient compliance

Payer

- Potential for better QOL outcomes

Pharma

- Differentiation in crowded space

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Design Considerations for SC: High concentration and Viscosity

Quality of candidates

- Hydrophobic and electrostatic effects
- mAbs and beyond mAbs

Crowding effect

- Concentration vs size of the molecule

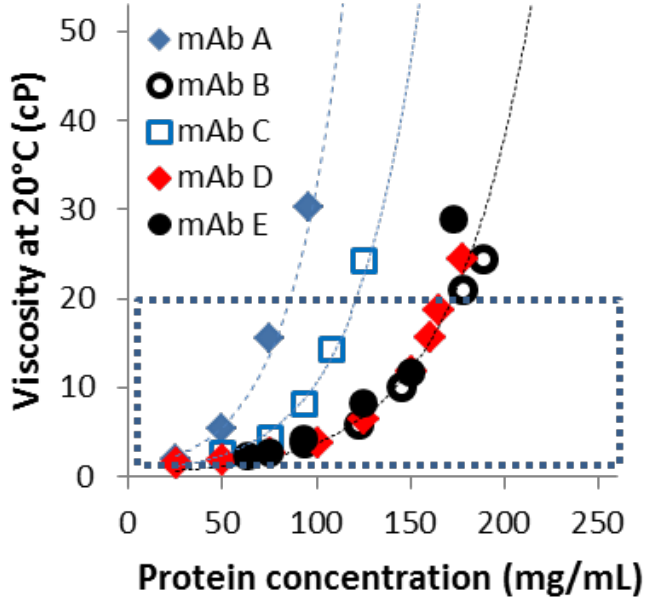
Excipients

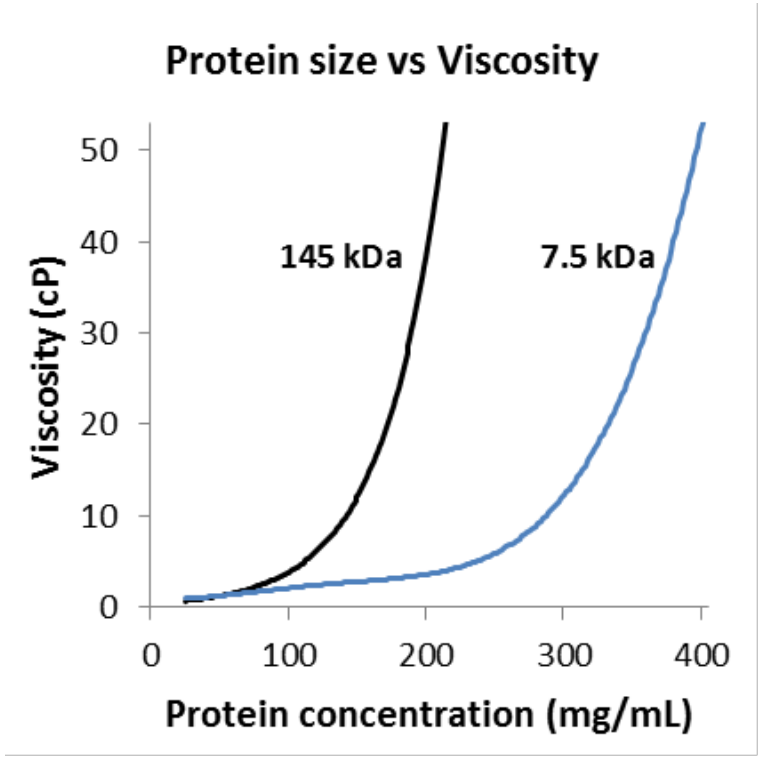
- Viscosity reduction vs stabilization

pH, ionic strength

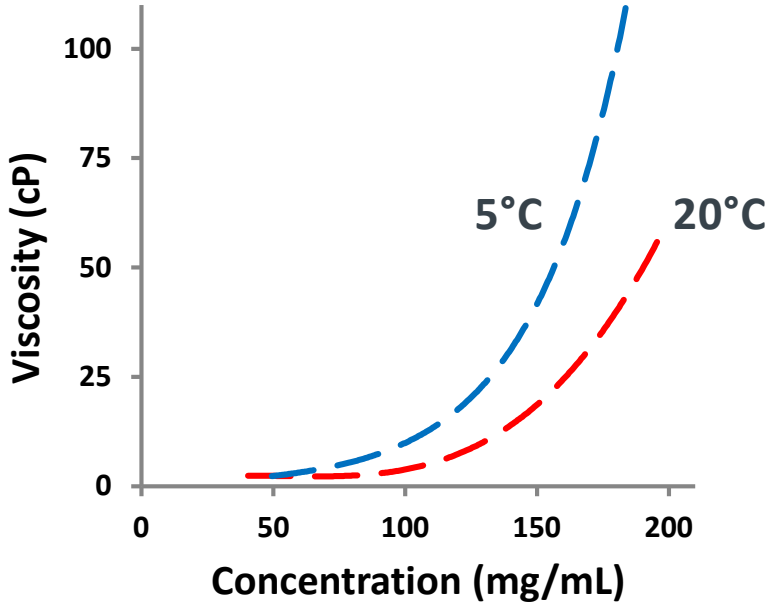
- Major formulation tools

Manufacturing process impact





V. Antochshuk 2015 Unpublished data



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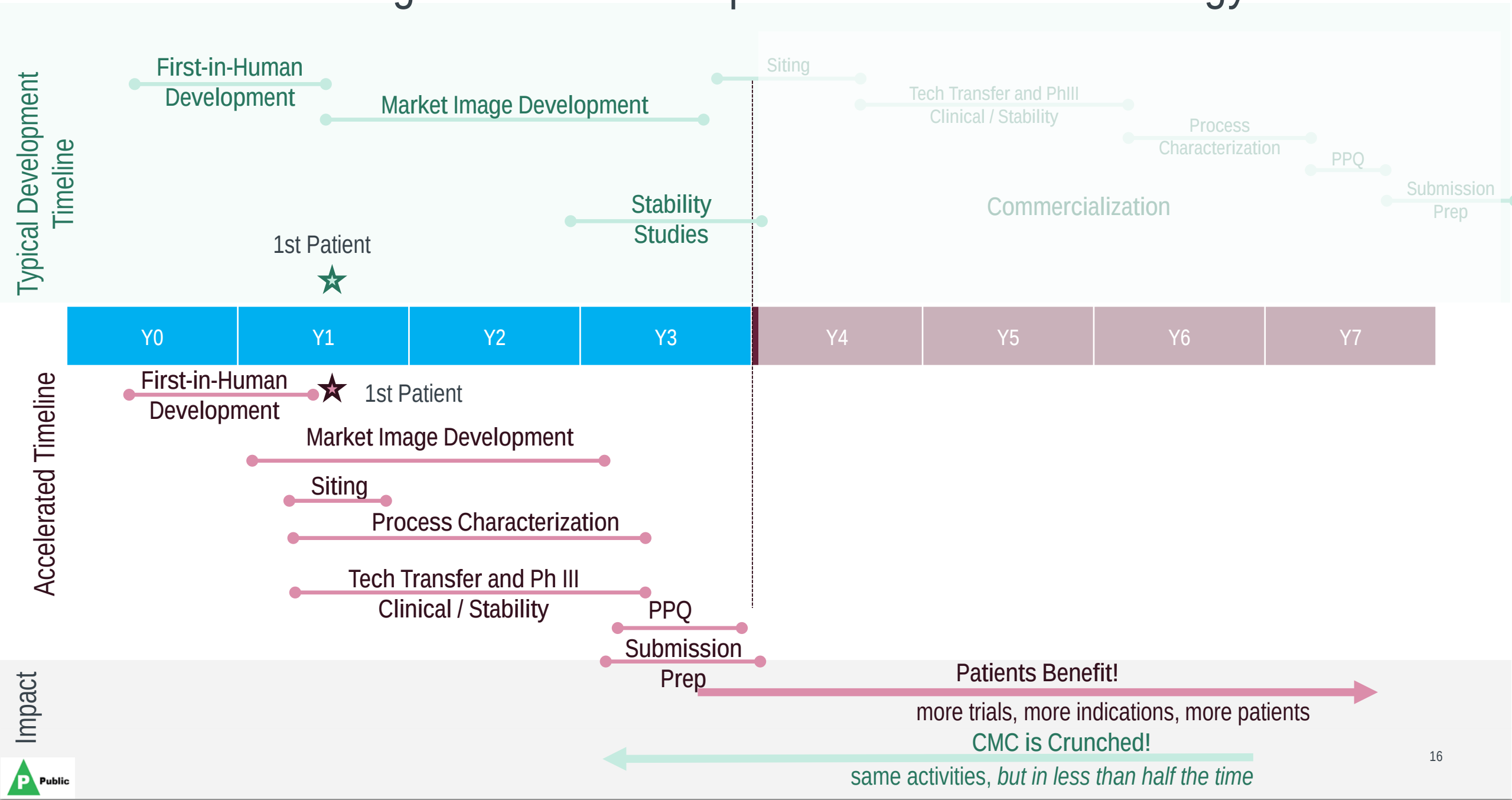
A Range of Analytical Techniques are Required for Characterization

Is it Time to Re-imagine CMC Development of Immuno-oncology Tx?



Our Work is Just Getting Started...

...we are investing in our patients

- New clinical trials and indications
- Patient-centered products

Analysts are projecting significant immuno-oncology growth, ~2.5x patients by 2023...

- "...a five-year compound annual growth rate of 14.4% is projected" BCC Research
- "...analysts forecast the global immune checkpoint inhibitors market to grow at a CAGR of more than 19% by 2023." Businesswire.com
- "...the global immune checkpoint inhibitors market...is projected to reach...a CAGR of 20.1% from 2018 to 2025." AMR
- "...global immune checkpoint inhibitors market...is projected to register a CAGR of 25.6% from 2018 to 2025." PR Newswire

...and We Can't Do it Alone.

These challenges are a shared burden between companies and health authorities...

We need proactive and ongoing dialogue with health authorities:

- New ways to generate relevant knowledge in less time
- Change categorization: simplify 'routine' changes
- Process optimization
- Specifications: balance of clinical relevance and stats

Enhanced partnership between health authorities.

- Further streamline global lifecycle management.
- Reduce redundant information requests.

Ultimately we are all working for the patients.

Acknowledgments

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Thank you !