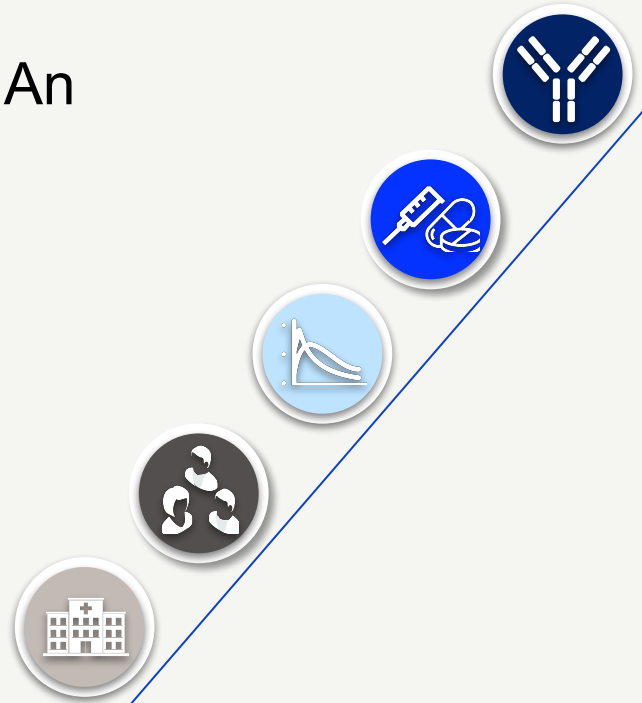
Subcutaneous Administration of High-Dose/High-volume Biotherapeutics – An Introduction

Dr. Beate Bittner, Global Head Product Optimization
F. Hoffmann—La Roche Ltd.

July, 2023

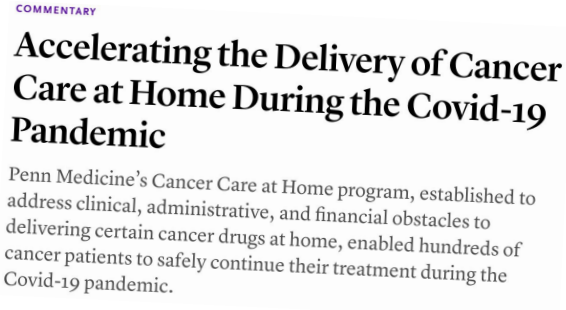


The increasing pressure on healthcare costs and resources and the COVID-19 pandemic demand simplified drug delivery to enable a flexible care setting

Flexible Care Setting

- People can choose the place of drug administration according to individual preferences and capabilities
- Including: clinic, physician's office, infusion centre, community centre, home- and self-administration

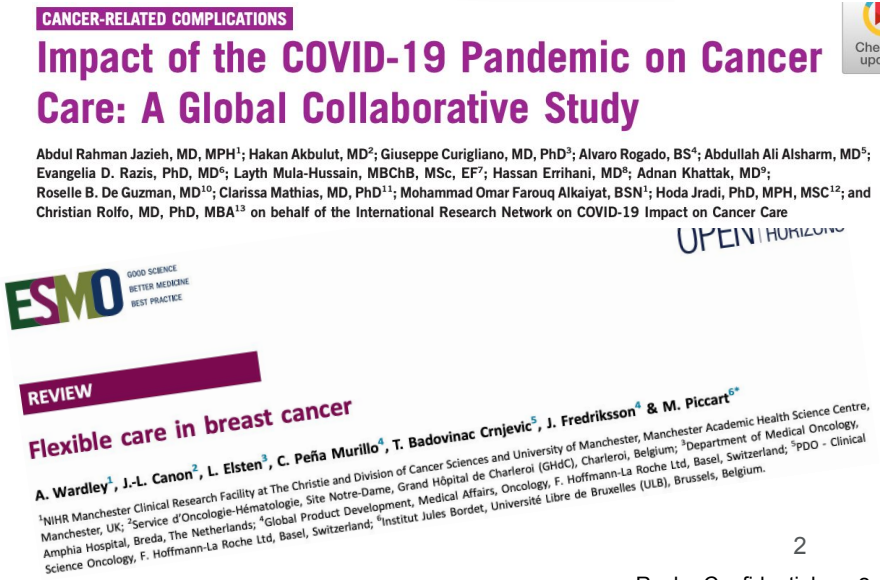
- Pre-requisite: Treatment has been shown to be safe and tolerated in general and by the individual patient



COMMENTARY

Accelerating the Delivery of Cancer Care at Home During the Covid-19 Pandemic

Penn Medicine's Cancer Care at Home program, established to address clinical, administrative, and financial obstacles to delivering certain cancer drugs at home, enabled hundreds of cancer patients to safely continue their treatment during the Covid-19 pandemic.



CANCER-RELATED COMPLICATIONS

Impact of the COVID-19 Pandemic on Cancer Care: A Global Collaborative Study

Abdul Rahman Jazieh, MD, MPH[1]; Hakan Akbulut, MD[2]; Giuseppe Curigliano, MD, PhD[3]; Alvaro Rogado, BS[4]; Abdullah Ali Alsharm, MD[5]; Evangelia D. Razis, PhD, MD[6]; Layth Mula-Hussain, MBChB, MSc, EF[7]; Hassan Errihani, MD[8]; Adnan Khattak, MD[9]; Roselle B. De Guzman, MD[10]; Clarissa Mathias, MD, PhD[11]; Mohammad Omar Farouq Alkaiyat, BSN[1]; Hoda Jradi, PhD, MPH, MSC[12]; and Christian Rolfo, MD, PhD, MBA[13] on behalf of the International Research Network on COVID-19 Impact on Cancer Care

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

REVIEW

Flexible care in breast cancer

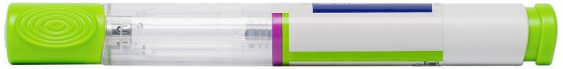
A. Wardley[1], J.-L. Canon[2], L. Elsten[3], C. Peña Murillo[4], T. Badovinac Crnjevic[5], J. Fredriksson[4] & M. Piccart[6*]

[1]NIHR Manchester Clinical Research Facility at The Christie and Division of Cancer Sciences and University of Manchester, Manchester Academic Health Science Centre, Manchester, UK; [2]Service d'Oncologie-Hématologie, Site Notre-Dame, Grand Hôpital de Charleroi (GHdC), Charleroi, Belgium; [3]Department of Medical Oncology, Amphia Hospital, Breda, The Netherlands; [4]Global Product Development, Medical Affairs, Oncology, F. Hoffmann-La Roche Ltd, Basel, Switzerland; [5]PDO - Clinical Science Oncology, F. Hoffmann-La Roche Ltd, Basel, Switzerland; [6]Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium.

The Subcutaneous Dosing Volume Makes the Difference

Volumes < approx. 2 mL:

Prefilled syringe (PFS)



Autoinjector (AI)

Established!

Volumes > approx. 2 mL:

Vial and handheld syringe (HHS)

Infusion set (IS)

Syringe pump

On-body delivery system (OBDS)

Emerging!

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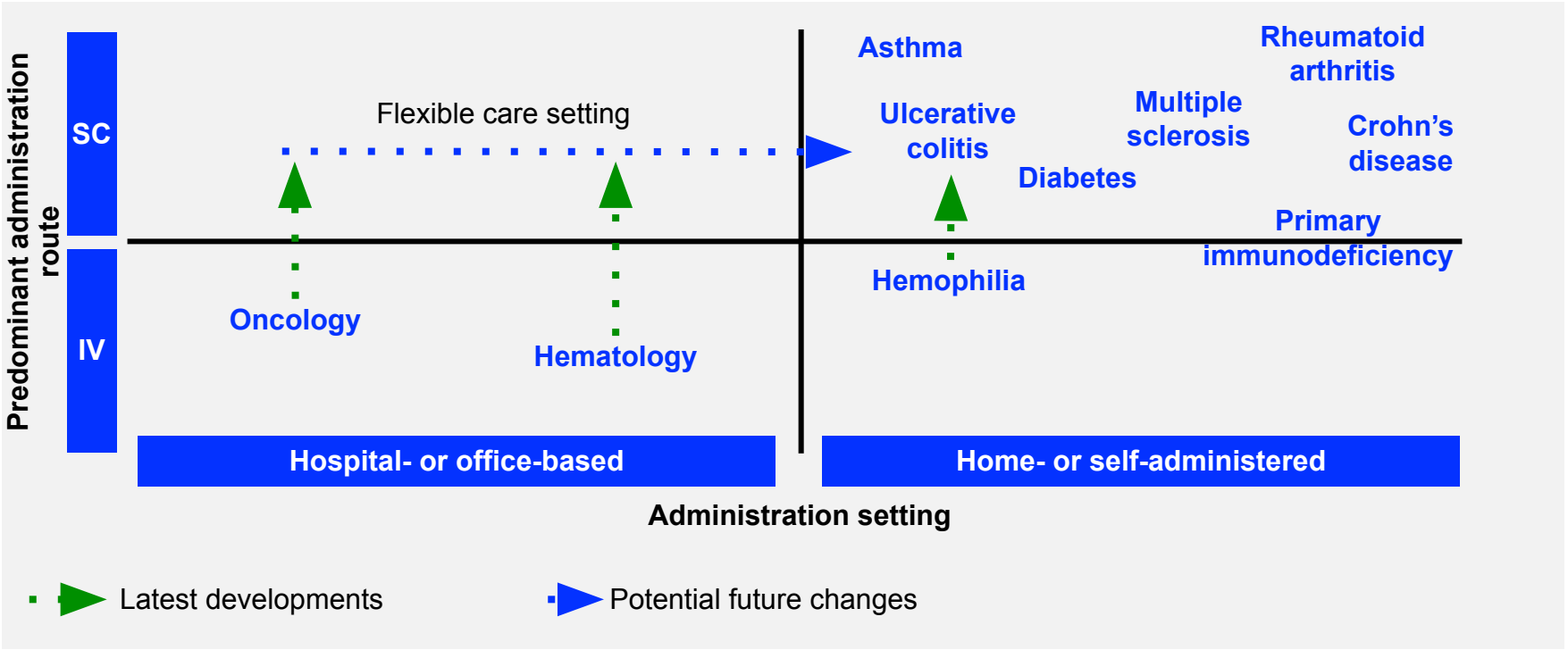
Role of Subcutaneous Dosing of Biologics by Indication



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Bittner B and Schmidt J. Academic press, Elsevier, 2022.

One size does not fit all - Disease Area Archetypes

Disease area	Treatment setting	Drug delivery profile	Market maturity (injectables)
1 RA/IBD			
2 MS			
3 ONC			

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Evolution of High-Dose Subcutaneous Drug Delivery

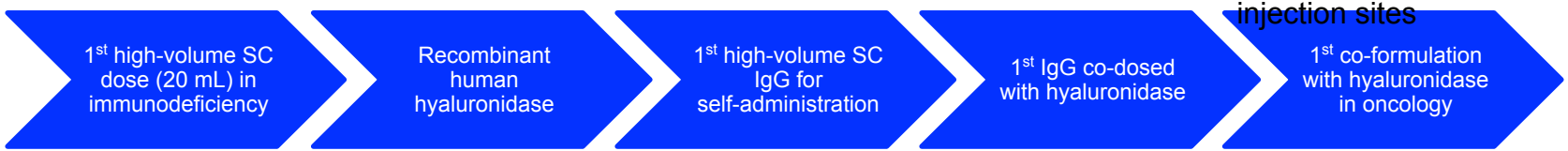
1952:
- 8-year-old boy dosed with immune human serum albumin

2005:
- Hylenex (SC dispersion enhancer) approved by FDA

2006:
- Vivaglobin approved for self-administration in the US
- Since then many more similar products have been (15 to 50 mL)
- Infusion pump into abdomen

2013 & 2014:
- Hyqvia approved by EMA & FDA
- Up to 600 mL per injection site
- Decreased dosing frequency from q1w or q2w to q1m

2013 & 2014:
- Herceptin SC and MabThera SC approved by EMA
- Allow for future home-administration in all patients and at preferred injection sites



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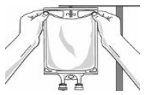
The Roadmap to More Convenient Administration for High-Dose Monoclonal Antibodies in Oncology

Roche

Enabling parenteral administration

- Liquid and lyophilized vial presentations
- Sufficient shelf-life
- Slow intravenous infusions
- Size-adjusted dosing
- Adaptive dosing regimens



Increasing patient convenience & healthcare capacity

- Fast intravenous infusions
- High-volume subcutaneous injections
- Fixed dosing
- Fixed-dose combinations
- Fast bolus injection

Enabling a flexible care setting

- Ready-to-use high-volume injection devices
- Home- and self-administration
- Patient & lay caregiver training and education
- Connected devices & health apps

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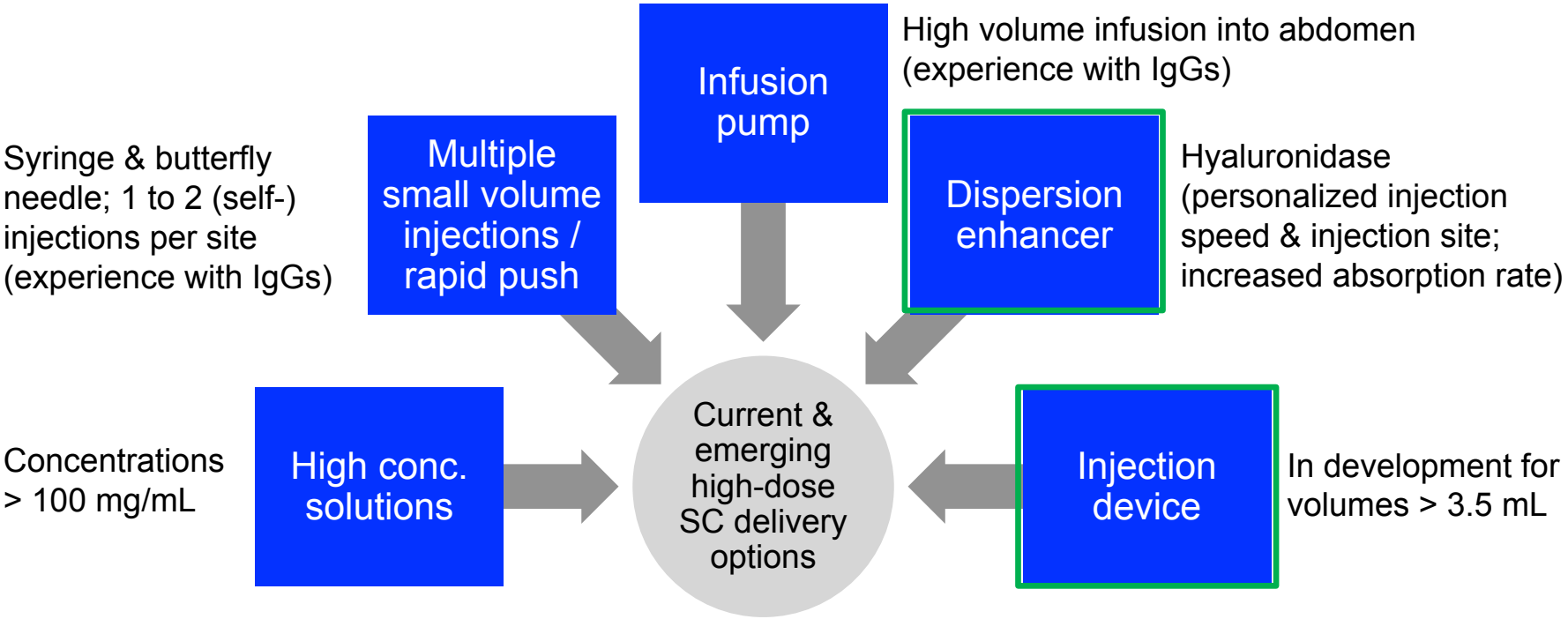
High-Dose Delivery of Biopharmaceutics

How to overcome drug administration challenges inherent to high doses of biologics?

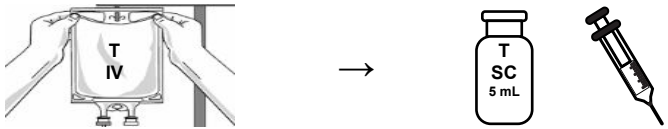


Bittner B *et al.*, BioDrugs 2018.

Marketed High-Dose/ High-Volume Monoclonal Antibodies with Intravenous & Subcutaneous Versions

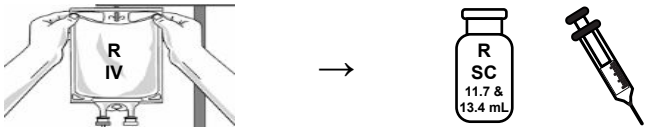
Trastuzumab SC

HER2+ breast cancer



Rituximab SC

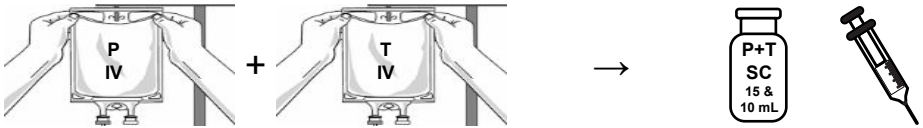
B-cell malignancies



1st dose IV

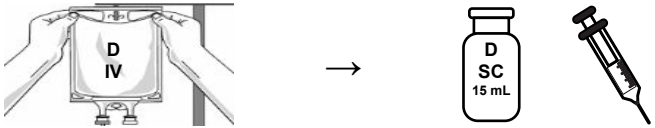
Pertuzumab+ Trastuzumab FDC SC

HER2+ breast cancer



Daratumumab SC

Multiple myeloma



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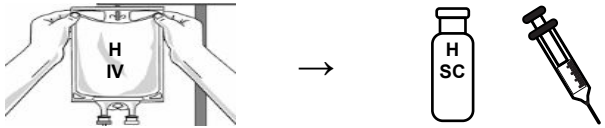
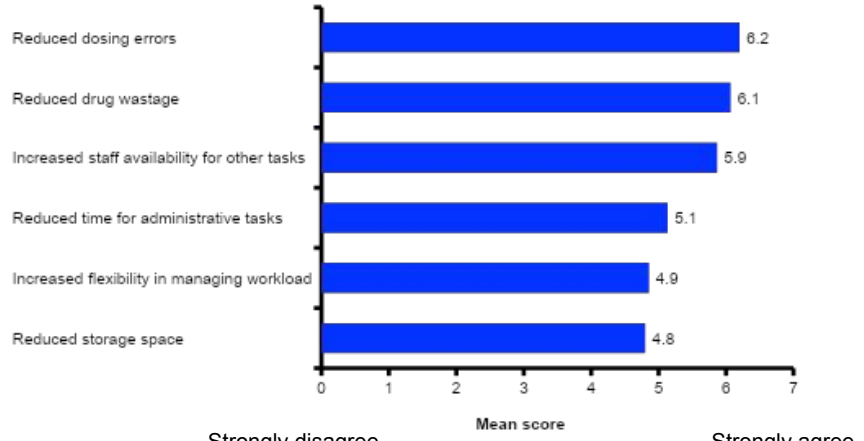
Bittner B and Schmidt J. Academic press, Elsevier, 2022.

Subcutaneous Administration of Monoclonal Antibodies as Preferred and Cost-Efficient Dosing Alternative

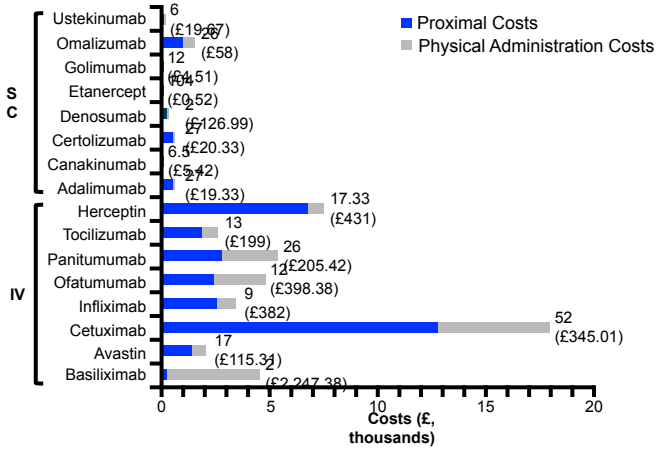


HCP perceptions on the value of in-clinic SC over IV administration – High-volume Herceptin SC



De Cock E *et al*. EBCC 2014.

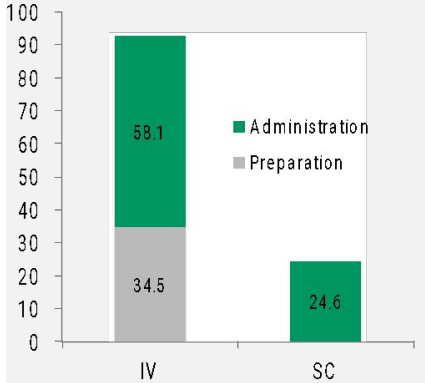
Overview administration costs of biologic drugs



Tetteh EK & Morris S. Health Econ Rev 2014.

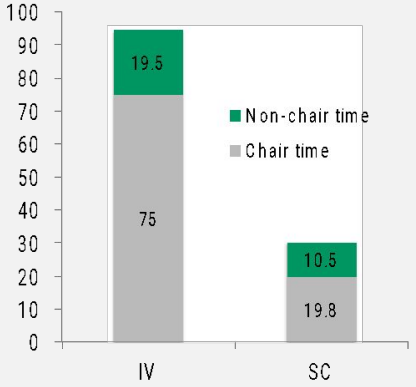
Trastuzumab IV vs. SC – A UK multi-centre prospective, observational Time and Motion study

Mean active HCP time (mins)



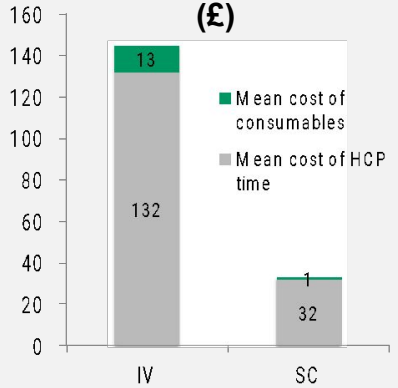
➡ Mean total HCP time saving of 68 mins

Mean patient time in unit (mins)



➡ Mean patient time saved over 18 cycles: 19 hours 16 mins

Mean costs (£)



➡ Mean cost saving per patient over 18 cycles: £2012

Assuming similar acquisition costs for the IV and SC formulations, conversion to trastuzumab SC could result in considerable savings to the NHS (over a full course treatment between £3m and £15m for a 20% and 100% conversion to SC, respectively)

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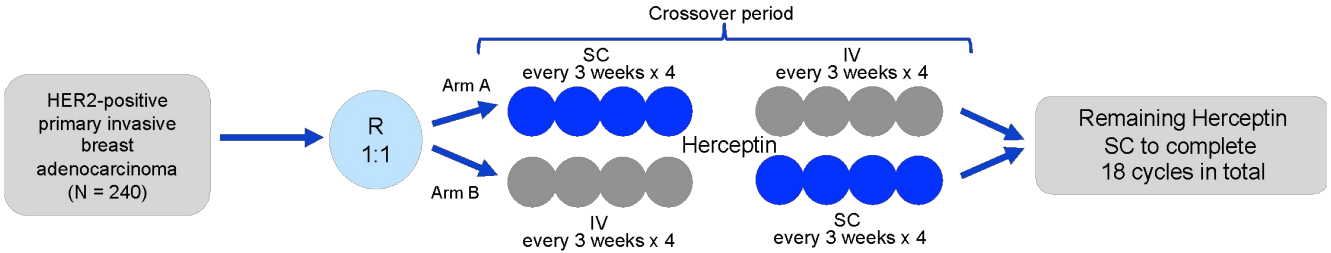
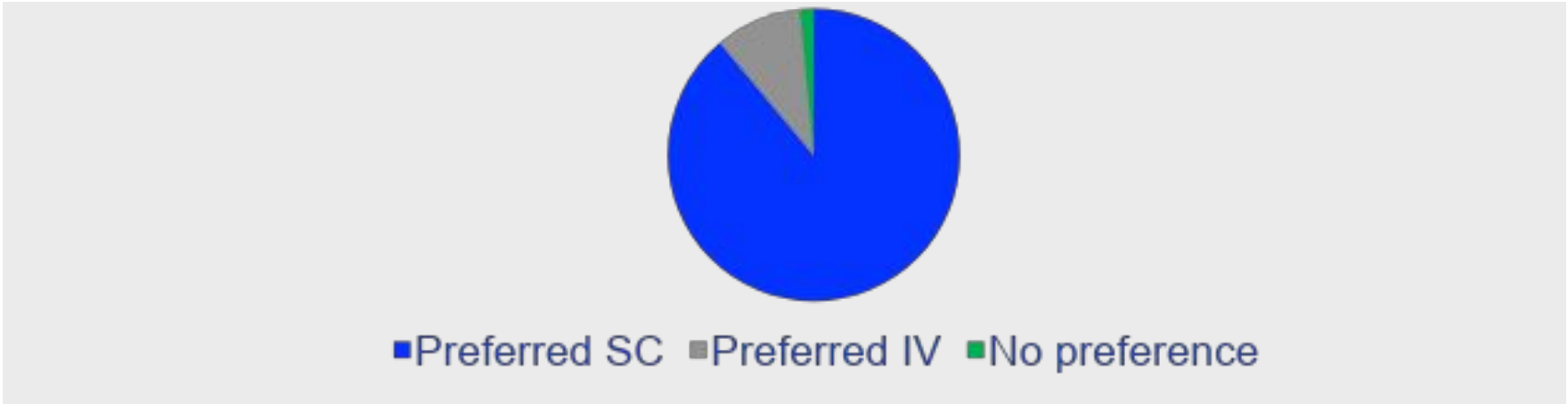
Burcombe R *et al*. Adv Breast Cancer Res

Global Preference Trial PrefHer - Participants





92%

of 236 eligible participants preferred Herceptin SC

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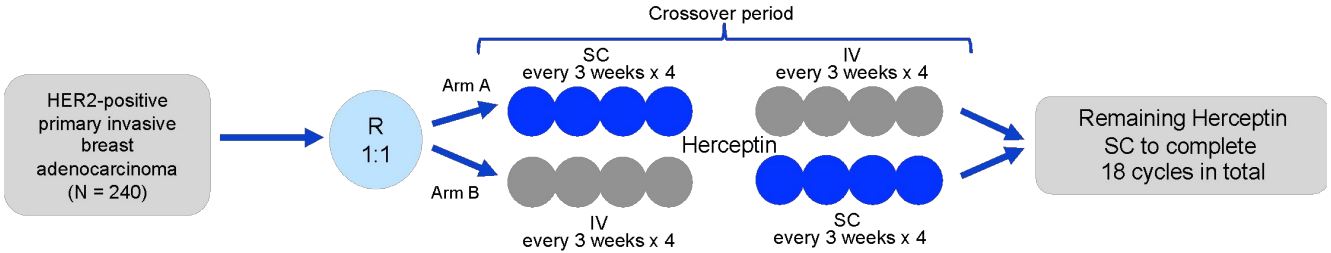
Pivot X *et al*. Lancet Oncol 2013.

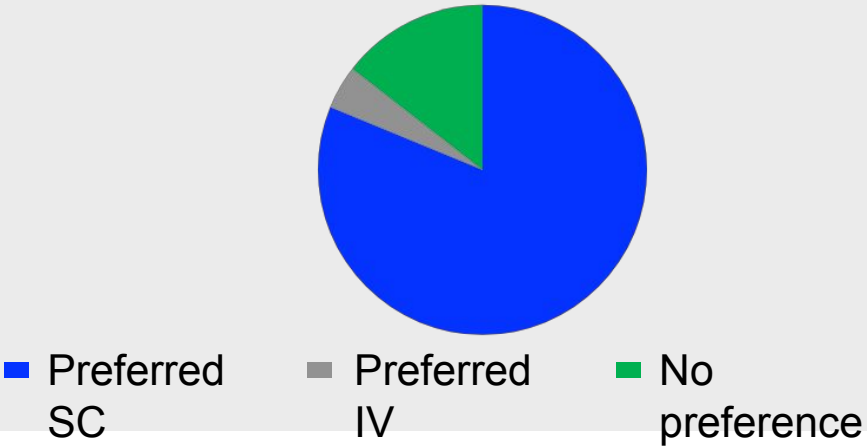
Global Preference Trial PrefHer - Time saving and less pain/discomfort/side effects were the main reasons for SC preference by participants

Category	n (%)†	Example
Time saving	179 (77.5)	“It does affect me being there so many hours. With this it was ‘Hello’ and ‘Bye’ without having to spend hours with patients”
Less pain/ discomfort/side effects	71 (30.7)	“The SC method was a lot less painful to me and my bruises faded faster than in the case of the intravenous method”
Problems with IV	26 (11.3)	“No veins to be found as my veins are collapsing”
Ease of administration	23 (10.0)	“Nurses can take care of many patients at the same time”
Convenience	21 (9.1)	“Busy mum with four young children – want to get on with life”
Less stress/anxiety	20 (8.7)	“IV reminds one of chemo and isn’t very pleasant for the head”
Other	14 (6.1)	“Safer – less risk of infections”‡

Pivot X *et al* SABCS 2013.

Global Preference Trial PrefHer - Providers





81%

of 117 providers preferred Herceptin SC

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Pivot X *et al*. Lancet Oncol 2013.

Healthcare Professional Reimbursement Model Drives Value of Reduced Dosing Complexity for Healthcare System

Model where incentives do <u>not</u> support complexity reduction	**Model where incentives do support complexity reduction**
Rewards volume & intensity of care	Rewards efficiency, cost-savings, performance
No incentive to implement cost-saving measures via reduced dosing complexity	Incentive to reduce dosing complexity and administration related costs & resources
↓	↓
i.e., fee-for-service	i.e., bundled payment, capitation, pay-for-performance, shared savings, global budget (value-based reimbursement)

- **Trend to shift from fee-for-service to value-based reimbursement models**

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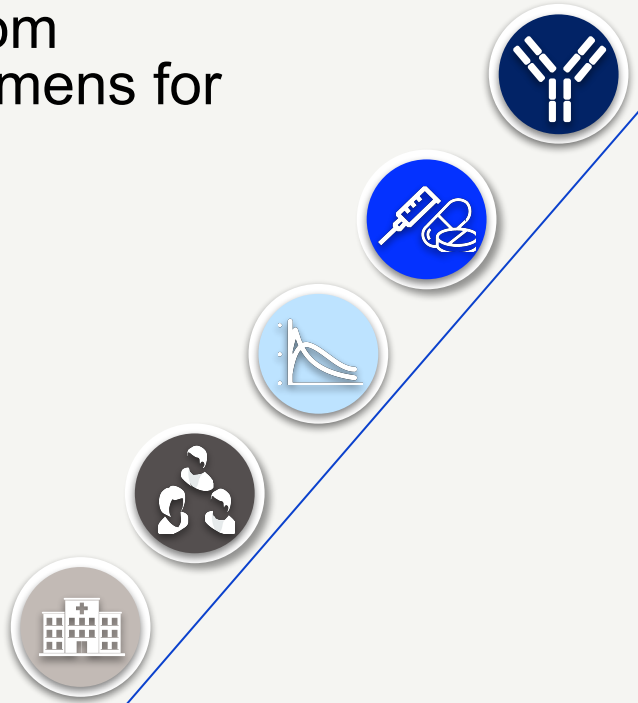
Doing now what patients need next

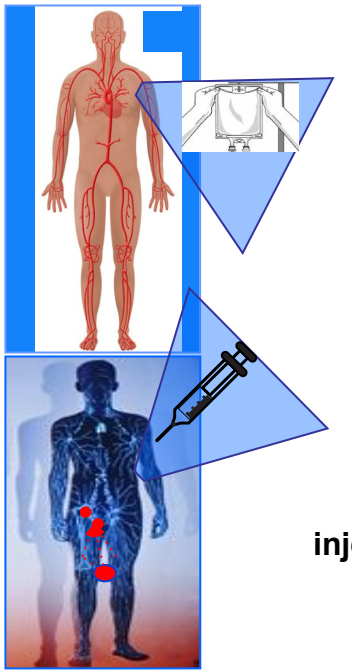
Leveraging Preclinical Data for Bridging from Intravenous to Subcutaneous Dosing Regimens for Monoclonal Antibodies

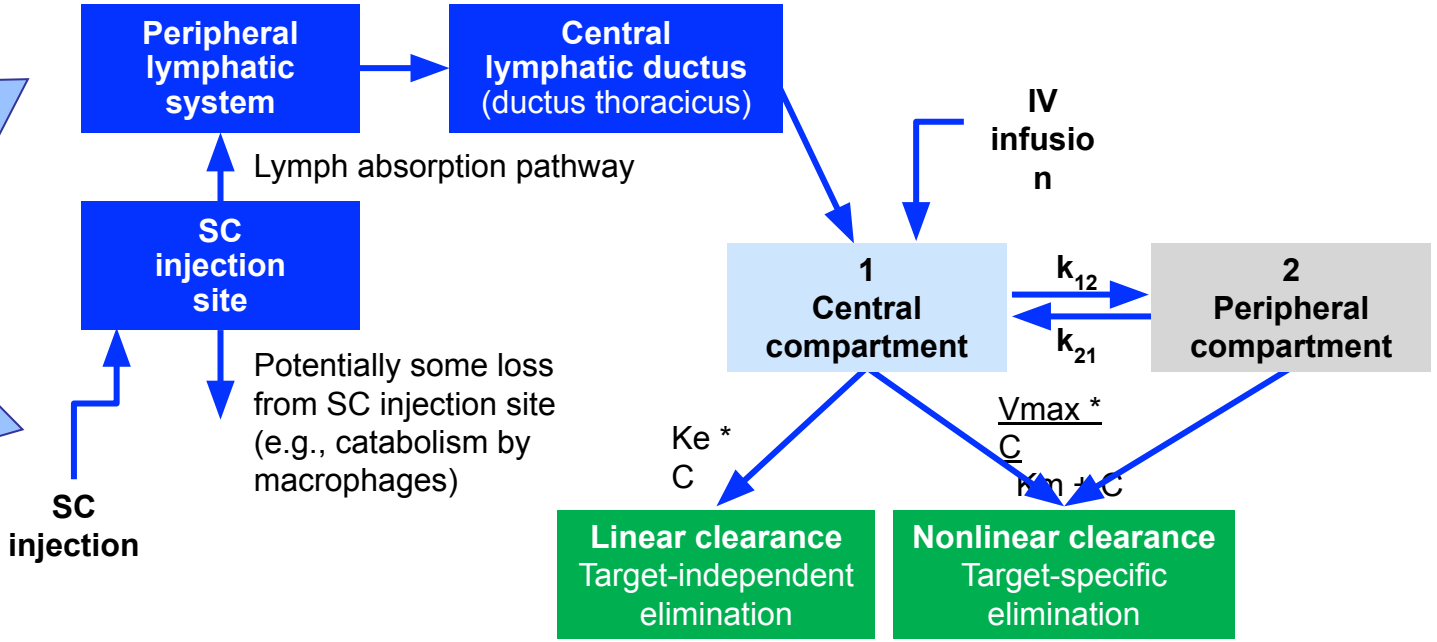
Dr. Beate Bittner, Global Head Product Optimization
F. Hoffmann—La Roche Ltd.

July 24, 2023



Impact of Subcutaneous vs. Intravenous Delivery on PK profile of Monoclonal Antibodies





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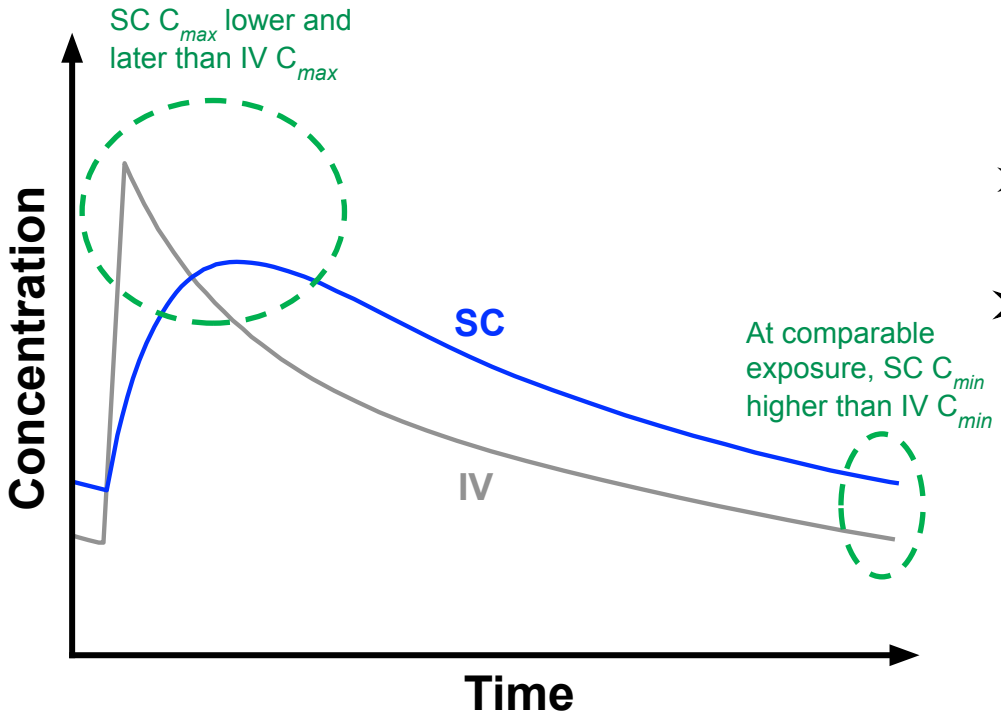
Adapted from McLennan DN *et al*. Drug Discovery Today 2005.

Impact of Subcutaneous vs. Intravenous Delivery on PK profile of Monoclonal Antibodies



- Impact of C_{max} and C_{min} on **efficacy & safety profile**
- **For high-dose mAbs: Technical feasibility** of high-concentration formulations and **high-volume injection**

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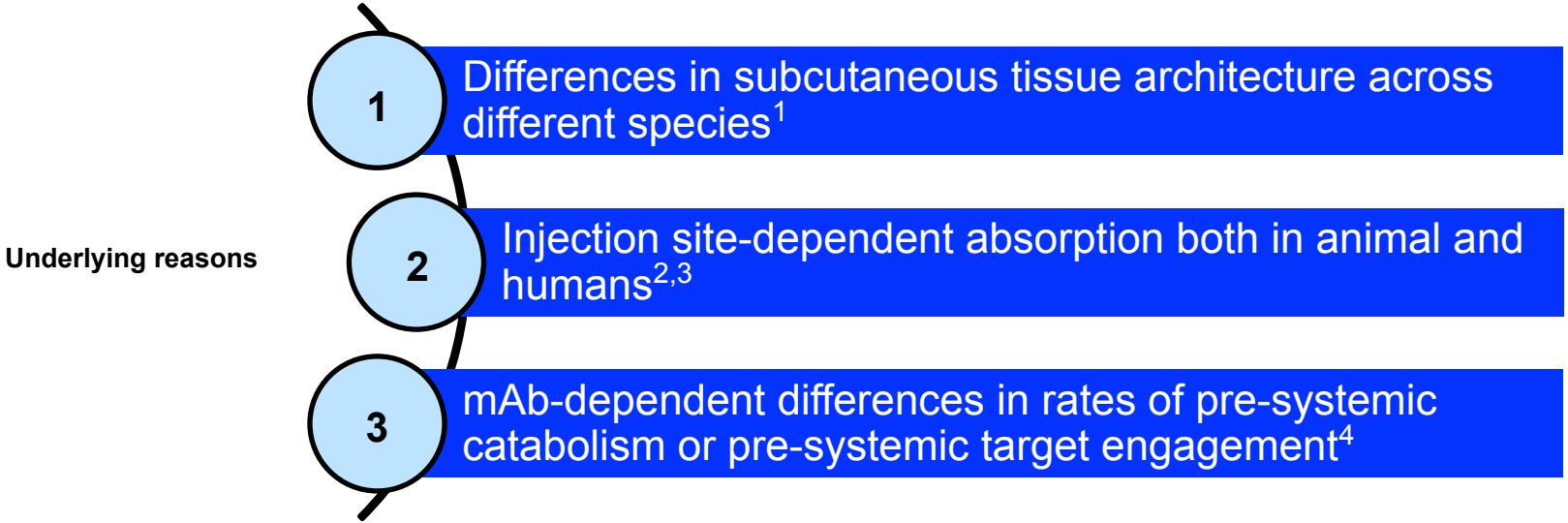
Problem Statement: Limited Predictability of the Human Subcutaneous Bioavailability for MAbs from Preclinical Models



- To what extent could data from different species still support subcutaneous development programs?

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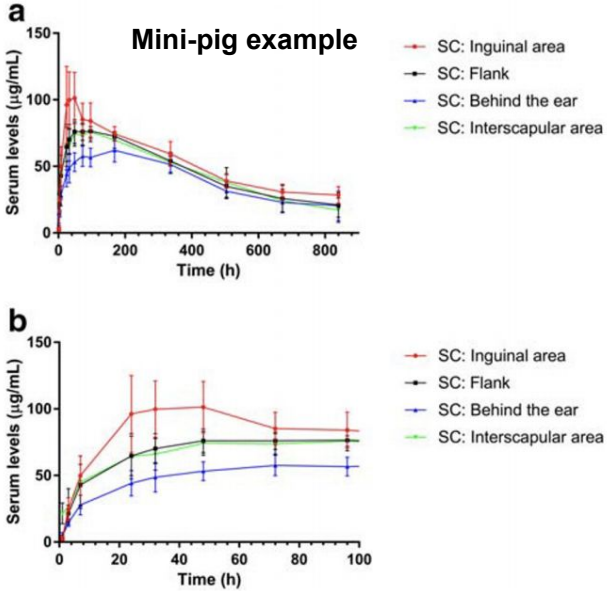
[1]Turner MR & Balu-Iyer V *J Pharm Sci* 2018

[2]Richter W *et al.* AAPS J. 2020

[3]Ubaldo M *et al.* J Asthma. 2019

[4]Thomas VA & Balthasar JP, Antibodies 2019.

Accurate Prediction of the Human Bioavailability from Subcutaneous Dosing in Animal Models Challenged by Differences in Tissue Architecture and Injection Site-Dependent Absorption



Tocilizumab: *Injection-site-dependent absorption rates*

a Complete concentration-time curves and **b** concentration-time curves in the initial absorption phase (first 96 h)

Richter W *et al.* AAPS J. 2020.

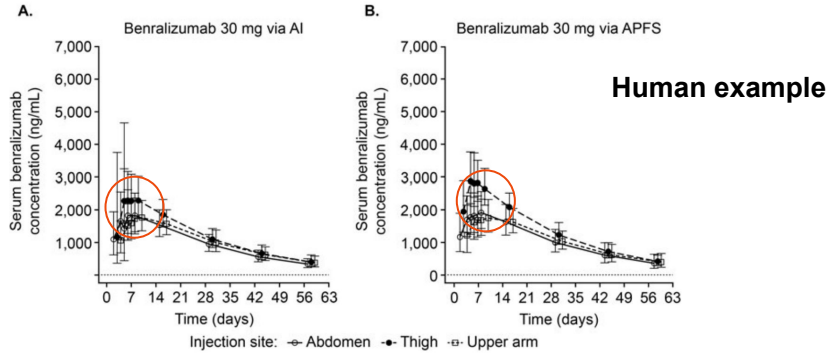


Figure 1. Geometric mean benralizumab serum concentration over time across injection sites and devices (PK analysis set). AI, autoinjector; APFS, accessorized prefilled syringe; PK, pharmacokinetic. Vertical lines represent ± standard deviation of the geometric mean. Dashed horizontal line represents the lower limit of quantification (3.86 ng/mL).

Benralizumab: *15 to 30% higher exposure with thigh administration compared to arm or abdomen*

Ubaldo M *et al.* J Asthma. 2019.

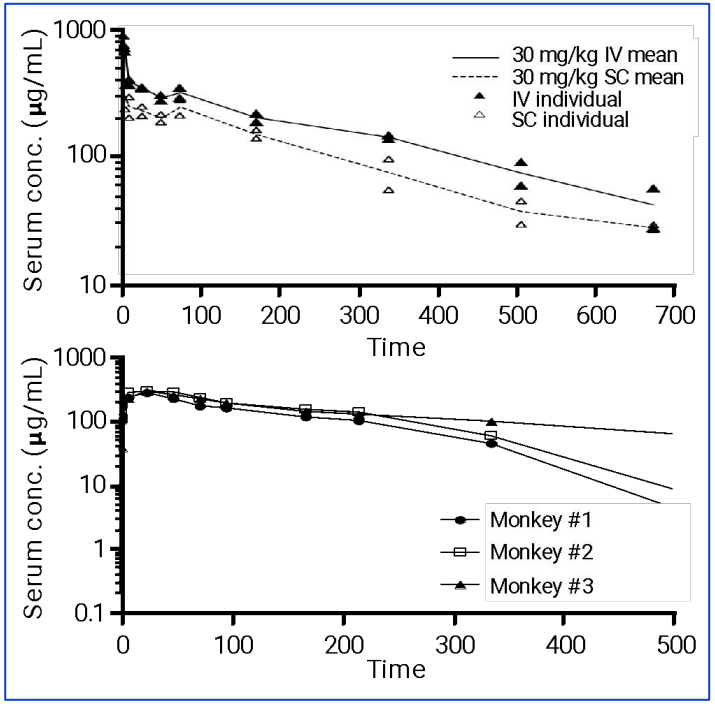
IV to SC Bridging: How to Leverage Preclinical Data During Development Pathway

Supporting preclinical data

- Assess impact of administration route on PD parameters, incl. relevance of C_{max}
- Demonstrate SC toxicology and local tolerability
- Assess the impact of different formulations on the PK profile

Bittner B *et al.* Drug Research 2012.

SC Bioavailability Varies Depending on the Preclinical Model, but PK Data Serve as a Basis for PK/PD Experiments that Inform Clinical Feasibility of SC Dosing – The Rituximab Example

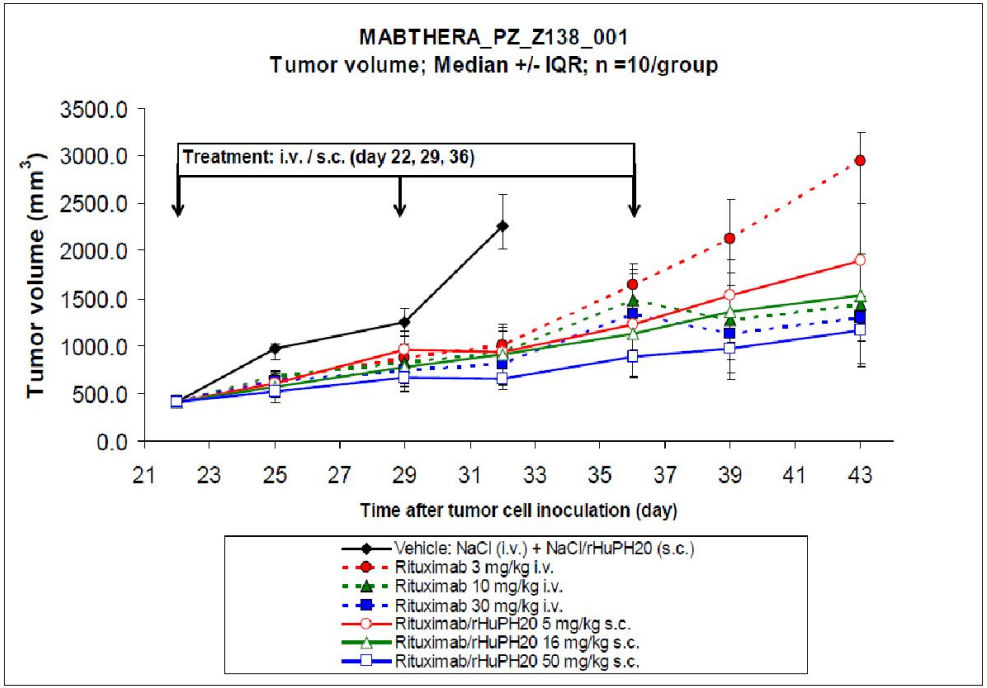


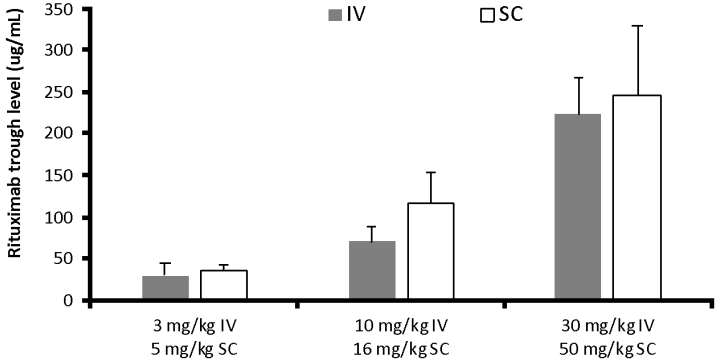
Bittner B *et al.* Drug Research 2012. Mao CP *et al.*, PlosOne 2013.

- IV/SC PK study in mice
  - Preparation for IV/SC PK/PD study in mouse xenograft model
  - Same dose SC or IV (30 mg/kg)
  - SC bioavailability 63%
- SC PK study in cynomolgus monkeys
  - Preparation for IV/SC PK/PD study in cynomolgus monkey B-cell depletion model and SC toxicology study
  - SC dose 20 mg/kg
  - ~ quantitative SC bioavailability

IV to SC PK/PD Bridging in Mouse Xenograft model – The Rituximab Example

Supporting evidence that the lower C_{max} following SC dosing would not impact PD effect



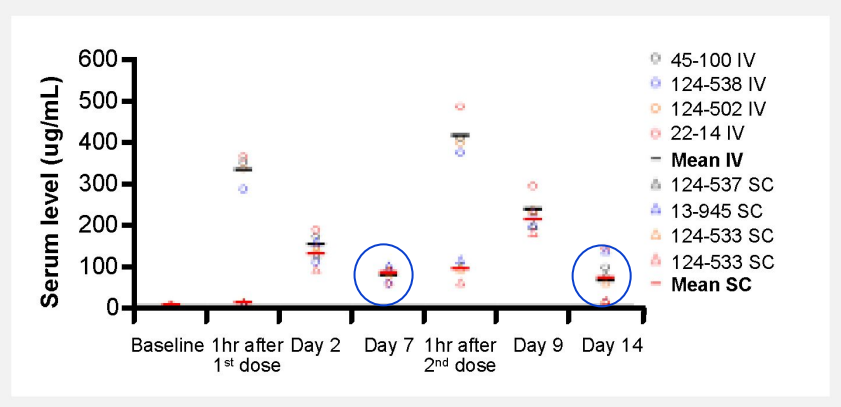


- Higher SC doses to compensate for incomplete SC bioavailability
- Similar IV and SC trough levels (depicted after third dose)
- **Similar tumour growth inhibition at matching IV and SC dose levels**

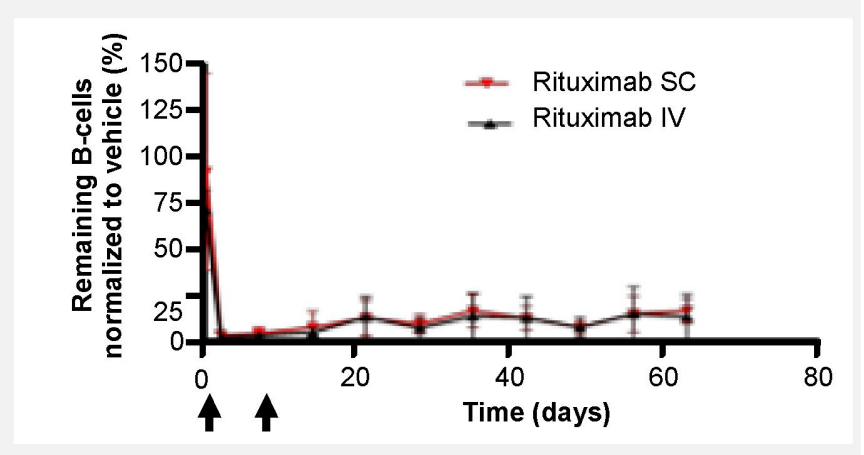
Bittner B *et al.* Drug Research 2012.

IV to SC PKPD bridging in B-cell depletion model – The Rituximab Example

Supporting evidence that the lower C_{max} following SC dosing would not impact PD effect



- Cynomolgus monkeys dosed twice (Day 0 and 7) with 10 mg/kg rituximab IV or SC
- Comparable trough levels due to virtually quantitative SC bioavailability in cynomolgus monkey

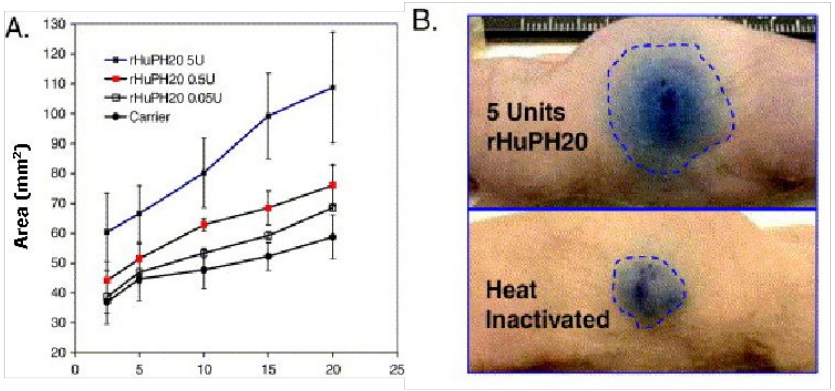


- Comparable B-cell depletion in circulation
- Comparable CD20 coverage in lymph nodes and circulation

Mao CP et al., PlosOne 2013.

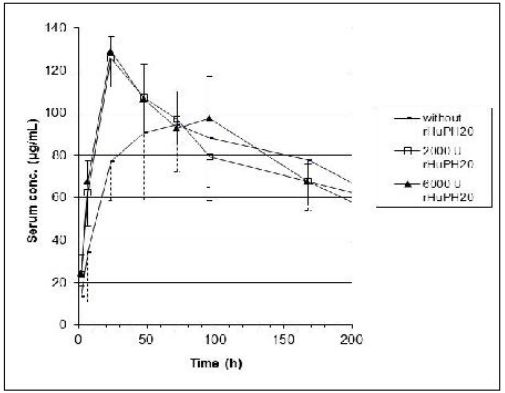
Preclinical PK Studies to Optimize Formulation Composition and Its Impact on the PK Profile – The Hyaluronidase Example

- Hyaluronan in SC extracellular matrix forms barrier to bulk fluid flow
- Local enzymatic hyaluronan cleavage by recombinant human hyaluronidase (rHuPH20) facilitates spreading of SC dosing solutions to allow administration of large volumes



A. rHuPH20 or carrier control was co-injected locally with trypan blue dye in mice (50 µl)
B. Heat inactivation of rHuPH20 (90°C, 10 min) stops dye spreading

Bookbinder LH *et al.* J Control Release 2006.



Trastuzumab absorption in minipigs more rapid with rHuPH20-containing formulations
N = 5 per dose group

Bittner B *et al.* Drug Research 2012.

IV to SC Bridging: How to Leverage Preclinical Data During Development Pathway

Supporting preclinical data

- Assess impact of administration route on PD parameters, incl. relevance of C_{max}
- Demonstrate SC toxicology and local tolerability
- Assess the impact of different formulations on the PK profile

Aims of the clinical development program

- Demonstrate PK non-inferiority between the IV and SC formulations to ensure comparable efficacy
- Show that the safety and immunogenicity profile of the SC formulation is consistent with that of the IV formulation
- Provide supportive efficacy data

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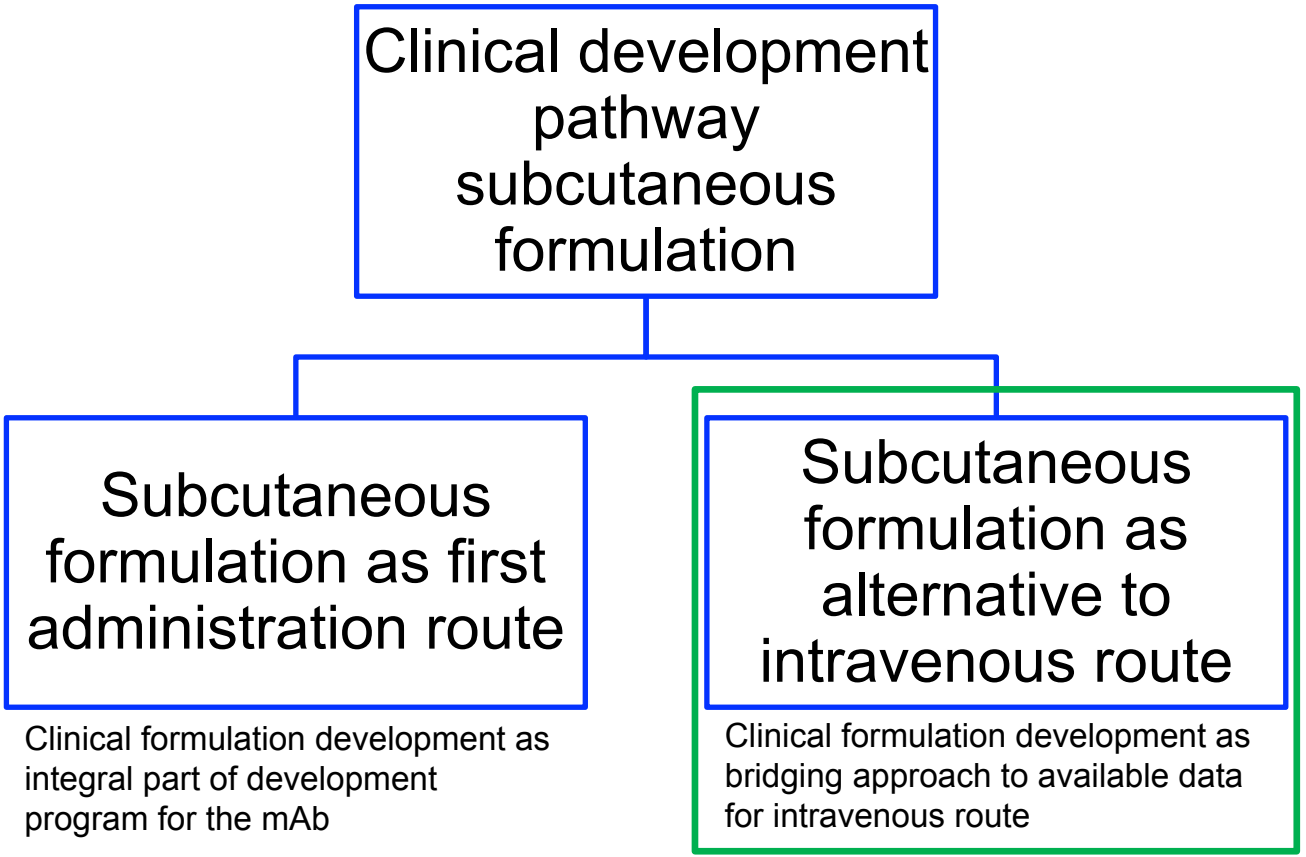
Bittner B *et al.* Drug Research 2012.

Subcutaneous Delivery of Monoclonal Antibodies

Development pathway depends on prior availability of an intravenous formulation



Comparison of Trastuzumab IV and SC

	Trastuzumab IV[1]	Trastuzumab SC[1]

eBC, early breast cancer; IV, intravenous; rHuPH20, recombinant human hyaluronidase;
SC, subcutaneous; SID, single-use injection device;
q1w, weekly dosing; q3w, 3-weekly dosing.

1. Herceptin® SC (Herceptin) Summary of Product Characteristics 2014
2. Jackisch C *et al*. Ann Oncol 2015
3. Goldhirsch A *et al*. Lancet 2013
4. Slamon D *et al*. N Engl J Med 2011
5. Perez EA *et al*. J Clin Oncol 2014
6. Perez EA *et al*. J Clin Oncol 2011.

The Lack of Predictive Animal Data on SC Bioavailability of MAbs is Overcome with an Adaptive Phase 1/1b Dose Finding Approach

Example: Selection of trastuzumab SC dose in healthy male and eBC participants

Concept: Leverage existing PK model built based on prior IV PK data in HER2+ BC

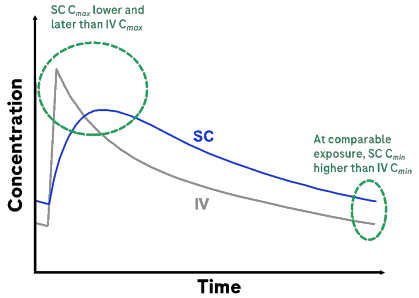
Part 1: Dose-finding

Dose-finding cohorts

Cohort 1*	Cohort 2*	Cohort 3	Cohort 4	Cohort 5
6 mg/kg IV HMPs n = 6	6 mg/kg IV eBC participants n = 6	6 mg/kg SC HMPs n = 6	10 mg/kg SC HMPs n = 6	8 mg/kg SC HMPs n = 6

Part 2: Dose confirmation

Cohort A‡	Cohort B§
8 mg/kg SC eBC participants n = 20	12 mg/kg SC eBC participants n = 20



*Receiving the approved IV infusion dose for Herceptin;

‡Dose level selected from part 1 that had resulted in exposure that is comparable with the approved IV infusion dose of 6 mg/kg;

§Dose level expected to achieve comparable exposure with the IV loading dose of 8 mg/kg;

EBC, early breast cancer; HMVs, health male volunteers

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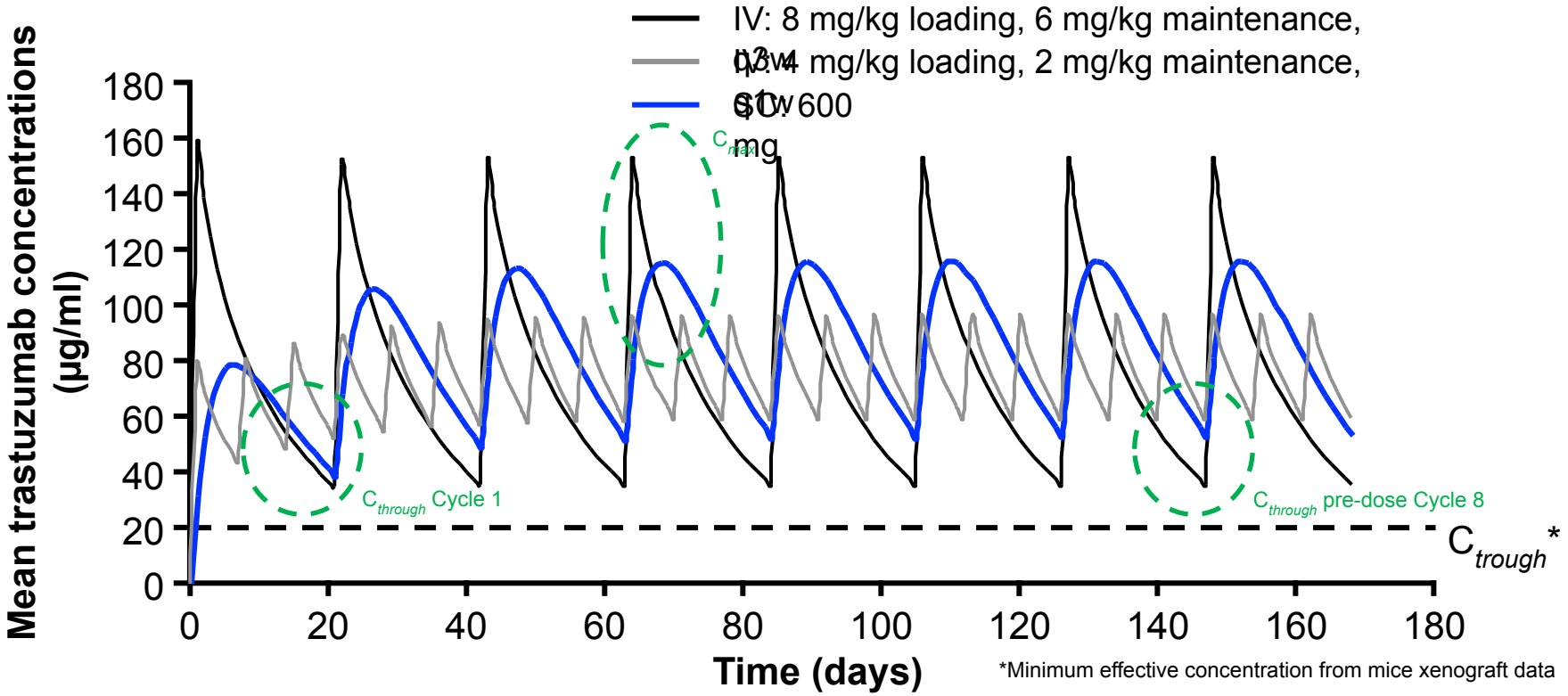
Wynne C *et al*. J Clin Pharmacol 2012.

PK-based Clinical Bridging Approach

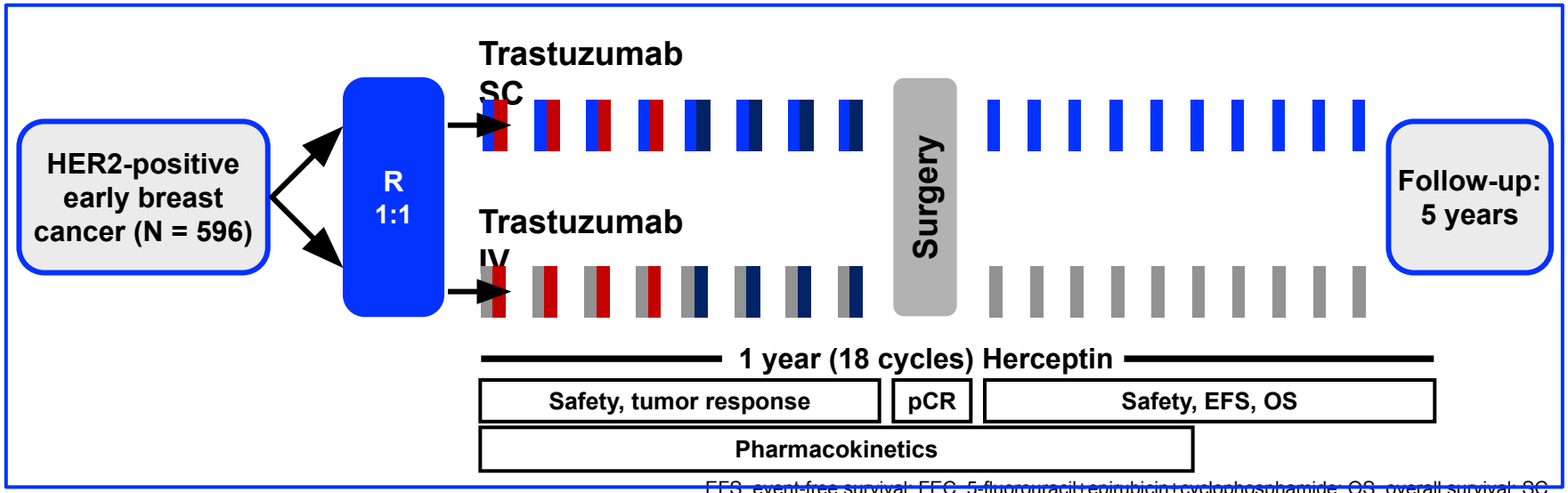
Hypothesis generation based on available trastuzumab PK data. The PK profile of the SC formulation was bridged by the q3w and q1w IV regimens.



Bittner B and Schmidt J. Academic press, Elsevier, 2022.

Phase 3 Study: HannaH

Randomized, open-label, Phase 3, non-inferiority study to compare the PK, efficacy and safety of trastuzumab SC and IV in HER2-positive EBC



EFS, event-free survival; FEC, 5-fluorouracil+epirubicin+cyclophosphamide; OS, overall survival; SC, subcutaneous.

Trastuzumab SC
Fixed dose of 600 mg (5 ml over 5 minutes)

Trastuzumab IV
8 mg/kg loading dose; 6 mg/kg maintenance dose

Docetaxel 75 mg/m^2

FEC 500/75/500

Co-primary endpoints

- Pharmacokinetics: observed trastuzumab C*trough* pre-dose Cycle 8 (pre-surgery)
- Efficacy: pCR in the breast

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Ismael G *et al*. Lancet Oncol

HannaH Phase 3 Non-inferiority Trial

Comparable drug exposure and efficacy can be achieved with trastuzumab SC and IV

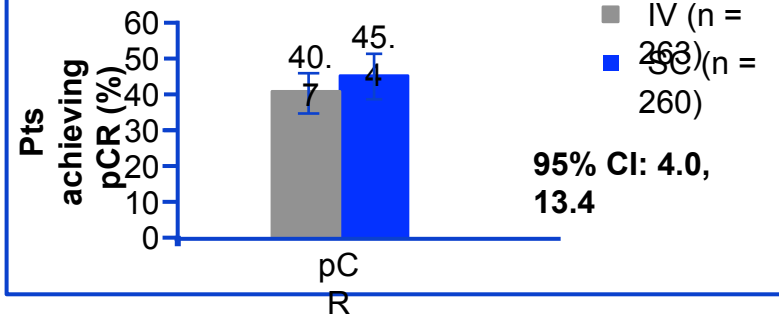
- HER2-positive eBC evaluating non-inferiority of 1 year (18 cycles) Herceptin SC vs. IV
- Co-primary endpoints:
  - Pharmacokinetics: observed trastuzumab C_{trough} pre-dose Cycle 8 (pre-surgery)
  - Efficacy: pCR in the breast

Pharmacokinetics: C_{trough} non-inferiority demonstrated

- Lower limit of 90% CI greater than pre-specified non-inferiority margin for geometric mean ratio SC vs. IV of 0.8
  - Geometric mean (µg/mL SC vs. IV): 69.0 vs. 51.8
  - Geometric mean ratio SC vs. IV: 1.33 (90% CI 1.24–1.44)

Efficacy: Non-inferiority demonstrated

- Lower limit of 95% CI greater than pre-specified margin for pCR rate difference in SC vs. IV of –12.5%



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Ismael G *et al*. Lancet Oncol

Summary & Conclusion

- Despite the lack of predictability of the subcutaneous bioavailability in humans from preclinical models, data have supported intravenous to subcutaneous bridging programs for several high-dose mAbs
- Supporting preclinical evidence included data on
  - the impact of administration route on PD parameters, incl. relevance of C_{max},
  - the SC toxicology and local tolerability profile, and
  - the impact of different formulations on the PK profile
- Clinical dose finding trials, allowing for interim PK analyses and subsequent dose adaption support subcutaneous dose finding in the absence of predictive preclinical data
- Relative changes in bioavailability with different SC formulations or injection devices expected more transferrable to humans

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