Should dose finding be concluded pre or post approval?

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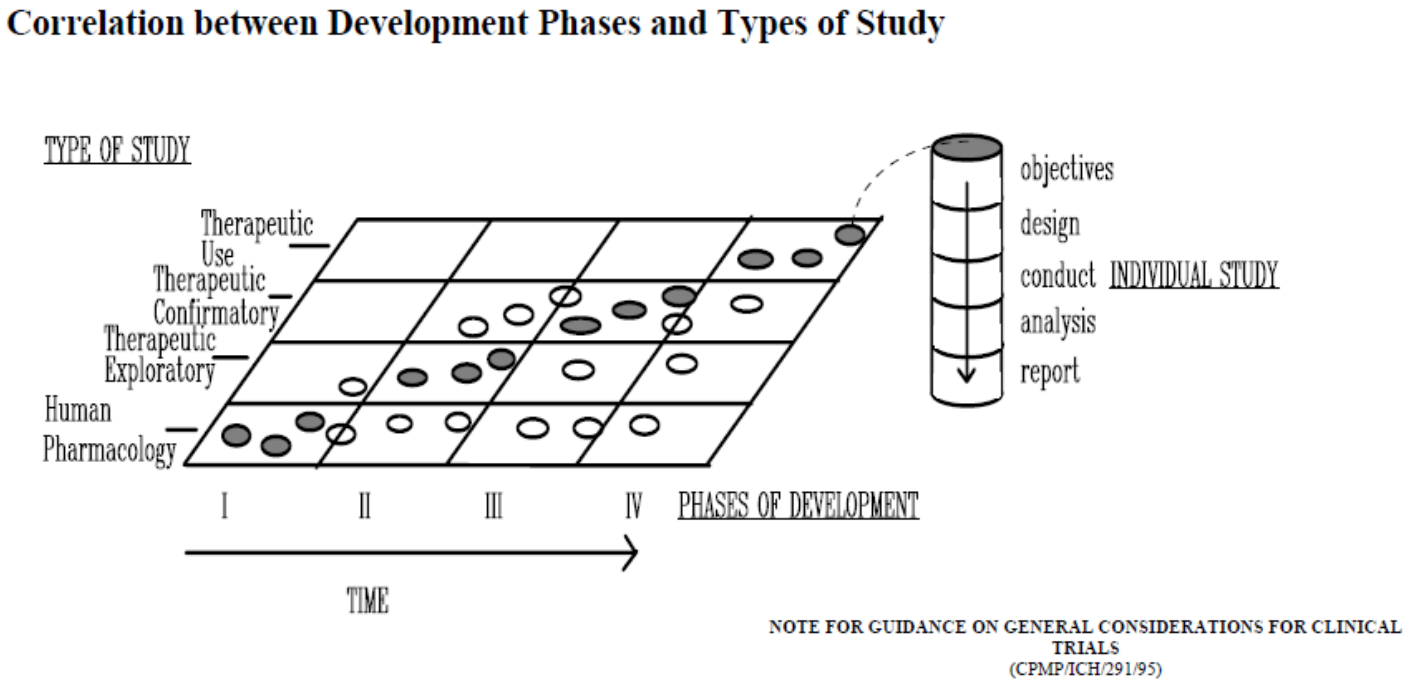
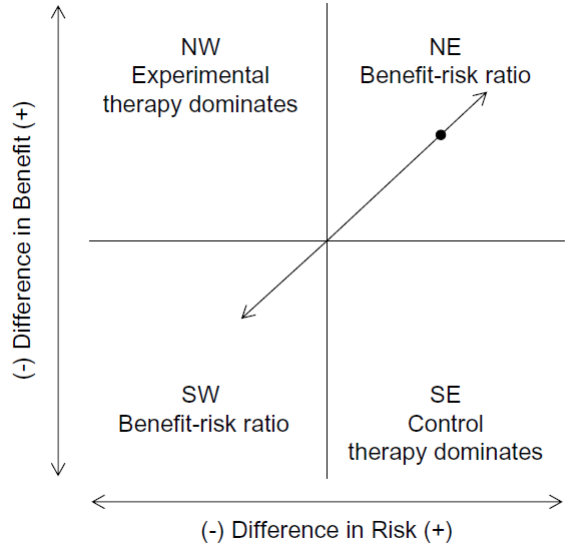
Disclosures

- Finnish Medicines Agency, Senior Medical Officer
- Oulu University Hospital, chief specialist
- European Medicines Agency, Scientific Advice Working Party, Member
- European Medicines Agency, Oncology Working Party, Vice-Chair
- National Committee on Medical Research Ethics, Finland, Member

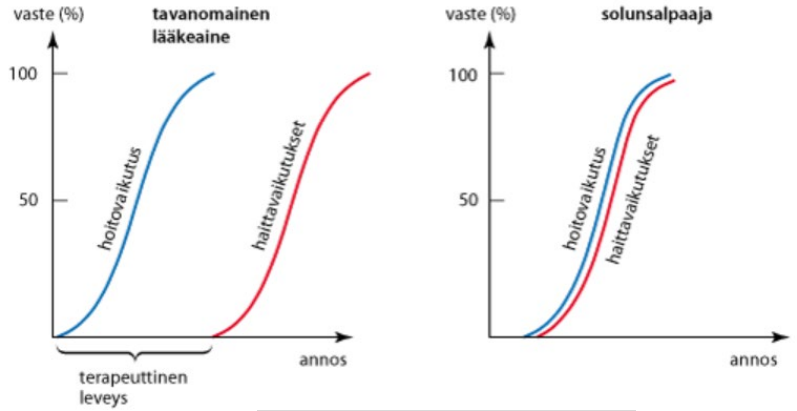
The views presented here are those of the presenter and should not be understood or quoted as those of the European Medicines Agency.

When it was easy...





Shaffer ML BMC Medical Research Methodology 2006 (1):48



Ruskoaho H, Hakkola J: Lääketieteellinen farmakolgoia ja toksikologia (2024)

- ”start with pharmacologically active but reasonably safe”
- MTD → RP2D → phase III dose → optimal dose in real life
- Dose escalation, 3+3 etc.

Or was it?

- Etoposide *(synthesised 1966)* dose range 40–200 mg/m2/d1- 3/5…
- Oxaliplatin *(authorised 1996)* - 85 mg/m2 q2w or 130 mg/m2 q3w – or for 6 months or 3 months…

Table 3 Sunitinib Dosing Patterns by First-Line Therapy Initiating Dose

Sunitinib Daily Dosing Patterns	Sunitinib Starting Dose			
	12.5 mg	25 mg	37.5 mg	50 mg
Unique Patient Count	4	20	33	178
% Patients Initiated With Sunitinib	1.7	8.5	14.0	75.7
No. Patients				
1 prescription	2	6	8	50
2 prescriptions	—	4	8	40
3 prescriptions	—	—	2	25
4 prescriptions	1	3	5	15
5+ prescriptions	1	7	10	48
Second Prescription Compared With First Prescription[a]				
% not fill second prescription (n)	50 (2)	30 (6)	24 (8)	28 (50)
% escalated (n)	—	10 (2)	3 (1)	
50 mg	—	100 (2)	100 (1)	
% maintained (n)	50 (2)	60 (12)	67 (22)	63 (112)
% reduced (n)		—	6 (2)	9 (16)
12.5 mg		—	50 (1)	6 (1)
25 mg			50 (1)	25 (4)
37.5 mg				69 (11)
Third Prescription Compared With First Prescription[a]				
% not fill third prescription (n)	50 (2)	50 (10)	49 (16)	51 (91)
% escalated (n)	25 (1)	5 (1)	9 (3)	
50 mg	100 (1)	100 (1)	100 (3)	
% maintained (n)	25 (1)	45 (9)	30 (10)	44 (78)
% reduced (n)		—	12 (4)	5 (10)
12.5 mg		—	50 (2)	10 (1)
25 mg			50 (2)	10 (1)
37.5 mg				80 (8)
Fourth or More Than Fourth Prescription Compared With First Prescription[a]				
% not fill fourth prescription (n)	50 (2)	50 (10)	55 (18)	65 (116)
% escalated (n)	50 (2)	20 (4)	9 (3)	
25 mg	50 (1)			
37.5 mg	50 (1)	75 (3)		
50 mg	—	25 (1)	100 (3)	
% maintained (n)	—	25 (5)	24 (8)	23 (41)
% reduced (n)		5 (1)	12 (4)	12 (21)
12.5 mg		100 (1)	25 (1)	—
25 mg			75 (3)	14 (3)
37.5 mg				86 (18)

Hess et al. Clin Genitourin Cancer 2013; 11:161-7

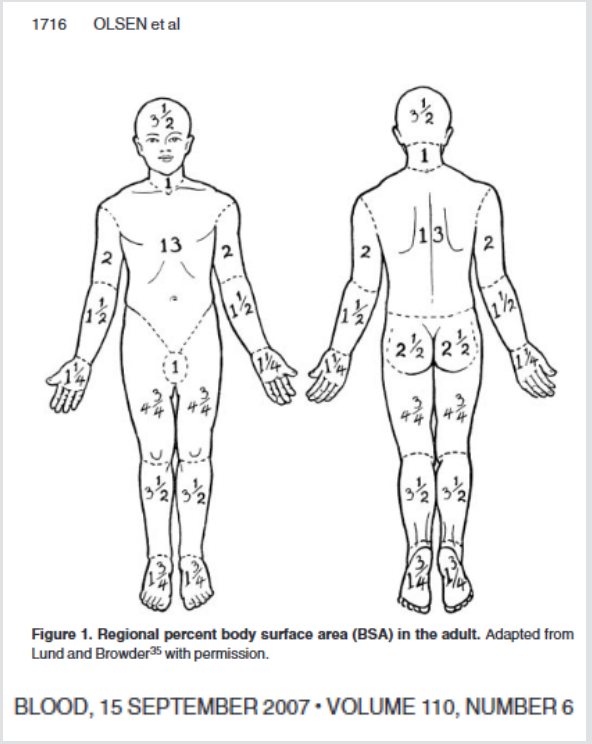


Figure 1. Regional percent body surface area (BSA) in the adult. Adapted from Lund and Browder[35] with permission.

$$\text{DuBois Formula: BSA } (m^2) = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3{,}600}}$$

https://link.springer.com/chapter/10.1007/978-3-030-10988-2_15

Legislation & dose & benefit/risk

Article 12

1. The marketing authorisation shall be refused if, after verification of the particulars and documents submitted in accordance with Article 6, it appears that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product.

Authorisation shall likewise be refused if particulars or documents provided by the applicant in accordance with Article 6 are incorrect or if the labelling and package leaflet proposed by the applicant are not in accordance with Title V of Directive 2001/83/EC.

2. The refusal of a Community marketing authorisation shall constitute a prohibition on the placing on the market of the medicinal product concerned throughout the Community.

3. Information about all refusals and the reasons for them shall be made publicly accessible.

Article 26

The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8 and 10(1), it proves that:

(a) the medicinal product is harmful in the normal conditions of use, or

(b) that its therapeutic efficacy is lacking or is insufficiently substantiated by the applicant, or

(c) that its qualitative and quantitative composition is not as declared.

https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32004R0726

- Dimensions: safety/tolerability, adherence, clinical benefit, subsequent treatments, QoL, OS

www.pharmaceuticalonline.com

Benefit–risk evaluations

Together with evaluation of the 'quality', 'safety' and 'efficacy' of a new drug, the evaluation of the benefit–risk balance is the cornerstone of the scientific opinions of regulatory agencies (including the EMA) when assessing new drug applications. This evaluation is based on the balance between the favourable effects (benefits) of a medicine against its unfavourable effects (harms, commonly referred to as 'risks'). Regulatory agencies can only recommend authorization of medicines with a positive benefit–risk balance. In conventional marketing authorizations, regulatory agencies do not evaluate the benefit–risk balance of medicines in the context of all approved drugs for the same indication, but instead base their assessments on the 'absolute' benefit–risk (exclusively the benefits versus the harms from the drug).

Pignatti et al. Nat Rev Clin Oncol 19: 207–215 (2022)

ICH E4

European Medicines Agency

November 1994
CPMP/ICH/378/95

ICH Topic E 4
Dose Response Information to Support Drug Registration

Step 5

NOTE FOR GUIDANCE ON DOSE RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION
(CPMP/ICH/378/95)

APPROVAL BY CPMP	May 1994
DATE FOR COMING INTO OPERATION	November 1994

2. OBTAINING DOSE-RESPONSE INFORMATION

Dose-Response Assessment Should Be an Integral Part of Drug Development

Assessment of dose-response should be an integral component of drug development with studies designed to assess dose-response an inherent part of establishing the safety and effectiveness of the drug. If development of dose-response information is built into the development process it can usually be accomplished with no loss of time and minimal extra effort compared to development plans that ignore dose-response.

Regulatory Considerations When Dose-Response Data Are Imperfect

Even well-laid plans are not invariably successful. An otherwise well-designed dose-response study may have utilized doses that were too high, or too close together, so that all appear equivalent (albeit superior to placebo). In that case, there is the possibility that the lowest dose studied is still greater than needed to exert the drugís maximum effect. Nonetheless, an acceptable balance of observed undesired effects and beneficial effects might make marketing at one of the doses studied reasonable. This decision would be easiest, of course, if the drug had special value, but even if it did not, in light of the studies that partly defined the proper dose range, further dose-finding might be pursued in the post-marketing period. Similarly, although seeking dose-response data should be a goal of every development program, approval based on data from studies using a fixed single dose or a defined dose range (but without valid dose-response information) might be appropriate where benefit from a new therapy in treating or preventing a serious disease is clear.

EMA regulatory guidance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 November 2023
EMA/CHMP/205/95 Rev.6
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the clinical evaluation of anticancer medicinal products

6.1 Cytotoxic compounds

6.1.1.3 Dose and schedules

Initial dosing may use flat doses or body surface area (BSA) scaled doses. The scientific support for the notion that BSA scaled dosing generally reduces inter-patient variability in exposure is weak and may lead to over and under-exposure in patients with a high and low BSA, respectively. It is expected that the importance of BSA or weight for variability in exposure is explored through modelling & simulation using actual pharmacokinetic data. The use of pharmacodynamic endpoints, where available, may also assist in dose selection.

The choice of route and rate of administration of the first dose in man should be justified based on the non-clinical data. In most cases, intravenous administration, when feasible, is advisable for first use in man studies since it eliminates variability related to bioavailability.

For schedule finding, experience related to class of compounds is helpful. Non-clinical data with respect to cycle dependency and the ratio tumour / normal tissue cytotoxicity *ex vivo* may be of some interest.

In case of minimal toxicity, or occasionally in case of non-significant toxicity, within-patient dose escalation may be appropriate in order to reduce the number of patients exposed to non-active doses. This may be acceptable after the end of the period of DLT assessment, if non-clinical data provide evidence of no cumulative toxicity.

If toxicity is acceptable, the patient may be re-exposed upon resolution of toxicity and preferably should receive at least 2 cycles at the same dose level.

6.2 Non-cytotoxic compounds

In particular in the case of dose-finding for molecularly targeted agents (MTAs), the dose-finding strategy should not only focus on safety endpoints, but also on determining an optimal biologically active dose (alternatively termed "optimal biological dose" or "optimum biologic dose"). This refers to a dose at which optimal biological response according to a predefined effect marker is achieved (e.g. as determined in tumour tissue response) and giving a higher dose does not further improve outcomes (i.e. a dose somewhere at the beginning of the plateau of the dose–response curve). Examples include escalating doses until a target-mediated biologic pathway is optimally altered or escalating doses until a target becomes saturated with the drug, while minimizing the dose required to achieve this maximum pharmacodynamic effect (thereby aiming to minimise toxicity). Preferably a combination of pharmacokinetic/pharmacodynamic endpoints and clinical response endpoints (e.g. objective tumour response or progression-free survival), in addition to safety endpoints is used to determine the optimal biologically active dose.

FDA Guidance

Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2024
Clinical/Medical

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/optimizing-dosage-human-prescription-drugs-and-biological-products-treatment-oncologic-diseases)

B. Trial Designs to Compare Multiple Dosages

- Multiple dosages should be compared in a trial(s) that is designed to assess antitumor activity, safety, and tolerability to support the proposed recommended dosage(s) listed in a marketing application.
  - Data from products in similar classes or with the same mechanism of action can also be used, when appropriate, to support the dosages for further evaluation, if relevant.
  - Model-informed or model-based approaches can be helpful to identify and select the dosage(s) to be compared.
  - It may be useful to evaluate additional dose-level cohorts or add more patients to existing dose-level cohorts (i.e., backfill cohorts) in the dose-finding trial for dosages which are being considered for further development. This would provide additional clinical data to allow for further assessment of safety and activity prior to initiating a trial to compare multiple dosages.
- A recommended trial design to compare multiple dosages is a randomized, parallel dose-response trial.[22]
  - Randomization (rather than enrolling patients to non-randomized dosage cohorts) promotes comparability of patients receiving each dosage, minimizing bias in estimation of dose- and exposure-response relationships. Stratified randomization may be useful to improve comparability.
  - Blinding patients and investigators to dosage arm assignment may be considered as there could be bias that higher dosages are associated with greater activity.
  - The trial should be sized to allow for sufficient assessment of safety and antitumor activity for each dosage. The trial does not need to be powered to demonstrate statistical superiority of a dosage or statistical non-inferiority among the dosages using Type I error rates which would be used in registrational trials.
  - Relevant measures of activity may include tumor assessment-based endpoints (e.g., overall response rate: ORR, progression-free survival: PFS), and other tissue, blood, or imaging-based endpoints.
  - An adaptive design to stop enrollment of patients to one or more dosage arms of a clinical trial following an interim assessment of activity and/or safety could be considered.
  - If crossover is permitted, the analysis plan should pre-specify how safety and activity will be assessed to account for crossover.
- Multiple dosages may also be compared prior to a registration trial(s) or as part of a registration trial(s) by adding an additional dosage arm(s).
  - When a registration trial contains multiple dosages and a control arm and is designed to establish superior efficacy of one of the dosages compared to the control arm, the trial design should provide strong control of Type I error. The analysis plan should specify a multiple-testing procedure which accounts for testing multiple treatments versus a control as well as any interim assessments after which an inferior arm is dropped.
- If safety and efficacy data from multiple dosages will be used to support a marketing application, this approach should be discussed with FDA early in clinical development.

Pre authorisation – pros and cons

- Applicability of MTD and DLT on a conceptual level
- MTD does not reflect low grade toxicities, duration, dosage modification, PK/PD
- Dose optimisation does not preclude expediting clinical development or e.g. seamless designs
- Dimensions: safety/tolerability, adherence, clinical benefit, subsequent treatments, QoL, OS
- Dose-optimisation trials are more complex than conventional MTD-finding trials
- Multidimensiality of dose-optimisation trials: safety and efficacy data, pharmacokinetics, pharmacodynamics, and biomarker data vs. simple decision rules in a MTD trial
- Clinical management of AEs, dose reduction instructions etc. needed for clinical practice

Post authorisation – pros and cons

Dosage optimization in drug development: An FDA Project Optimus analysis of postmarketing requirements issued to repair the cracks.

Authors: Brian Heiss, Lili Pan, Alemayehu Akalu, Jonathon Vallejo, Joyce Cheng, Pamela Balcazar, Nam Atiqur Rahman, Stacy Shifflett Shord, Mirat Shah, Richard Pazdur, and Marc Theoret | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 41, Number 16_suppl • https://doi.org/10.1200/JCO.2023.41.16_suppl.1598

PMRs) was 6 years (range: 0.7 to 8.3). **Conclusions:** A high proportion (15%) of new drugs required a PMR, which generally involved conducting a randomized trial with a substantial patient enrollment to evaluate an alternative dosage(s). This process was slow with a median of 6 years to fulfill a PMR. DO in the premarket setting has the potential to rapidly maximize BR, avoiding both patient exposure to unnecessary toxicity and large, resource-intensive, multi-year postmarketing trials. Project Optimus is working with stakeholders to advance a DO paradigm that occurs early and throughout premarket development to ensure an optimized recommended dosage at the time of approval.

Post authorisation – pros and cons

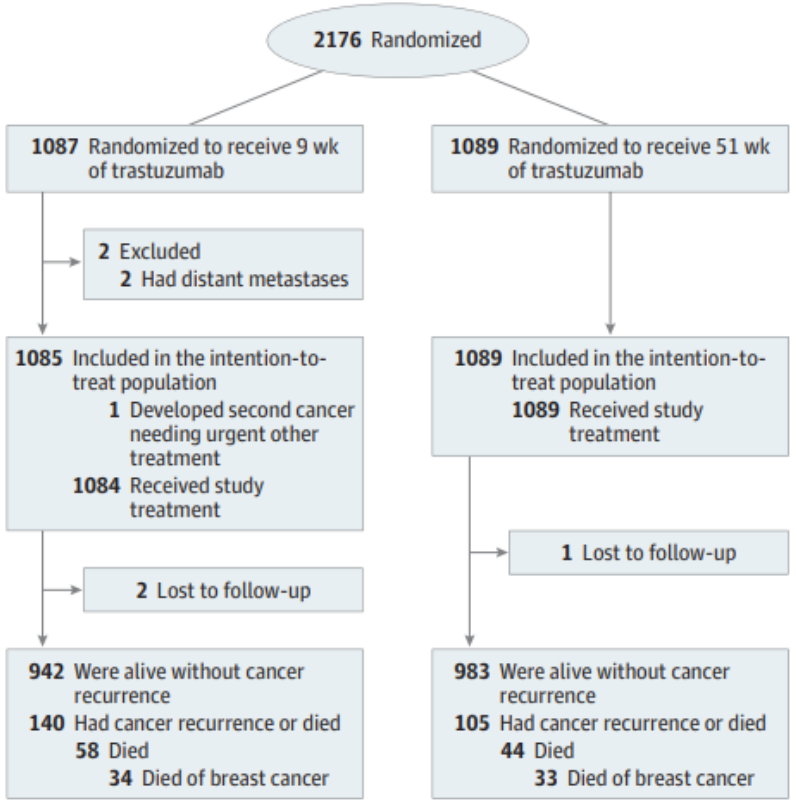
- Subgroups
- Older adults, frail patients
- Learning curve?
- Obvious challenges of de-escalation/optimisation trials: recruitment, funding, (lack of) incentives
- Better drugs vs. me too –drugs vs. optimised drug therapy?

JAMA Oncology | Original Investigation

Effect of Adjuvant Trastuzumab for a Duration of 9 Weeks vs 1 Year With Concomitant Chemotherapy for Early Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer
The SOLD Randomized Clinical Trial

Heikki Joensuu, MD; Judith Fraser, MD; Hans Wildiers, MD; Riikka Huovinen, MD; Päivi Auvinen, MD; Meri Utriainen, MD; Paul Nyandoto, MD; Kenneth K. Villman, MD; Päivi Halonen, MD; Helena Granstam-Björneklett, MD; Lotta Lundgren, MD; Liisa Sailas, MD; Taina Turpeenniemi-Hujanen, MD; Minna Tanner, MD; Jeffrey Yachnin, MD; Diana Ritchie, MD; Oskar Johansson, MD; Teppo Huttunen, MSci; Patrick Neven, MD; Peter Canney, MD; Vernon J. Harvey, MD; Pirkko-Liisa Kellokumpu-Lehtinen, MD; Henrik Lindman, MD

Figure 1. CONSORT Diagram



Cases - ADCs

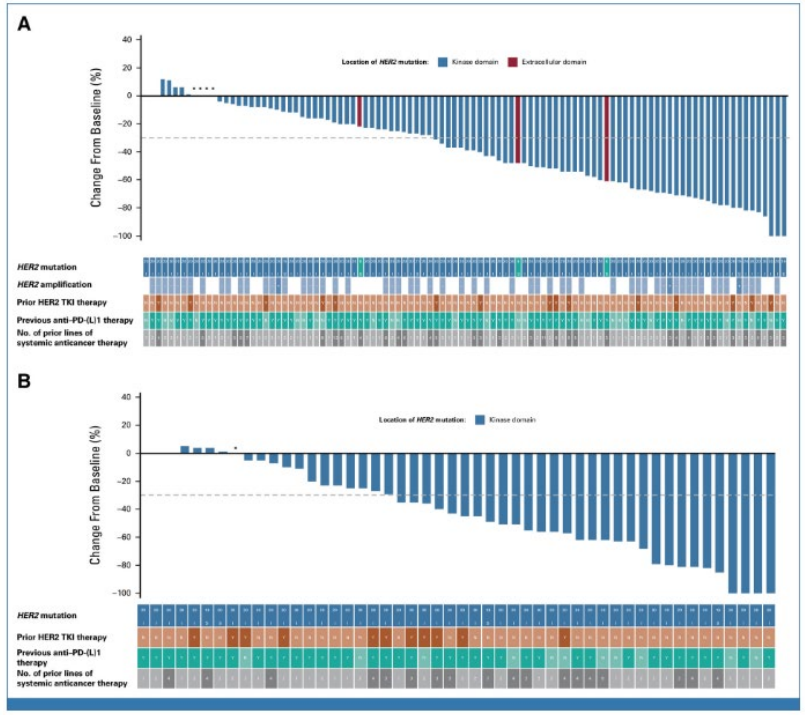


Fig 1. Antitumor activity of T-DXd in patients with *HER2*-mutant metastatic non–small-cell lung cancer by *HER2* mutation status and prior therapy. Best (minimum) percent change from baseline in the sum of diameters for all target lesions in (A) the T-DXd 5.4 mg/kg once every 3 weeks arm and (B) the T-DXd 6.4 mg/kg once every 3 weeks arm. The line at −30% indicates a partial response. Patients who had zero best percentage change from baseline in the sum of diameters for all target lesions are indicated with an asterisk (*). Numbers in the *HER2* mutation row indicate in which exon the mutation occurred (8, 19, or 20). *HER2* amplification was only assessed in patients who received T-DXd 5.4 mg/kg. HER2, human epidermal growth factor receptor 2; I, insertion; N, no; S, substitution; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; Y, yes.

Goto et al. J Clin Oncol 41, 4852-4863(2023)
Volume 41, Number 31
DOI: 10.1200/JCO.23.01361

TABLE 4. Overall Safety Summary and Adjudicated Drug-Related ILD

Type of AE	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 101),[a] No. (%)	T-DXd 6.4 mg/kg Once Every 3 Wee (n = 50),[a] No. (%)
Any-grade TEAEs	101 (100.0)	50 (100.0)
Drug-related	97 (96.0)	50 (100.0)
Grade ≥ 3 TEAEs	53 (52.5)	33 (66.0)
Drug-related	39 (38.6)	29 (58.0)
Serious TEAEs	37 (36.6)	20 (40.0)
Drug-related	14 (13.9)	12 (24.0)
TEAEs associated with drug discontinuation	15 (14.9)	13 (26.0)
Drug-related	14 (13.9)	10 (20.0)
TEAEs associated with dose reduction	18 (17.8)	16 (32.0)
Drug-related	17 (16.8)	16 (32.0)
TEAEs associated with drug interruption	45 (44.6)	31 (62.0)
Drug-related	27 (26.7)	24 (48.0)
TEAEs associated with an outcome of death	6 (5.9)[b]	2 (4.0)[c]
Drug-related	1 (1.0)	1 (2.0)
Adjudicated drug-related ILD[d]		
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)
Total (95% CI)	13 (12.9) (7.0 to 21.0)	14 (28.0) (16.2 to 42.5)

Adjudicated Drug-Related ILD in Patients With Prior Anti–PD-(L)1 Therapy	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 74), No. (%)	T-DXd 6.4 mg/kg Once Every 3 Wee (n = 39), No. (%)
Grade 1	4 (5.4)	2 (5.1)
Grade 2	5 (6.8)	9 (23.1)
Grade 3	1 (1.4)	0
Grade 4	0	0
Grade 5	1 (1.4)	0
Total	11 (14.9)	11 (28.2)

Adjudicated Drug-Related ILD in Patients Without Prior Anti–PD-(L)1 Therapy	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 27), No. (%)	T-DXd 6.4 mg/kg Once Every 3 Wee (n = 11), No. (%)
Grade 1	0	2 (18.2)
Grade 2	2 (7.4)	0
Grade 3	0	0
Grade 4	0	0
Grade 5	0	1 (9.1)
Total	2 (7.4)	3 (27.3)

Abbreviations: AE, adverse event; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]The safety analysis set included all randomly assigned patients who received ≥1 dose of study drug.
[b]TEAEs associated with death were malignant lung neoplasm in two patients, malignant neoplasm progression in two patients, cerebrovascu incident in one patient, and pneumonitis in one patient.
[c]TEAEs associated with death were abnormal general physical condition in one patient and ILD in one patient.

- T-DxD 6.4 mg/kg vs. 5.4 mg/kg: gr3 AEs 58% vs. 38.6%; ILD 28% vs.12.9%

FREE ACCESS | EDITORIALS | September 11, 2023

Optimizing Dosing of Trastuzumab Deruxtecan in *HER2*-Mutant Non–Small-Cell Lung Cancer: A Reminder That More Is Not Always Better

Authors: Hui Jing Hoe, MBBS, and Benjamin J. Solomon, PhD, MBBS | AUTHORS INFO & AFFILIATIONS

J Clin Oncol 41, 4849-4851(2023) • Volume 41, Number 31 • DOI: 10.1200/JCO.23.01768

Cases – ICIs, CAR-Ts – spectrum of complexity

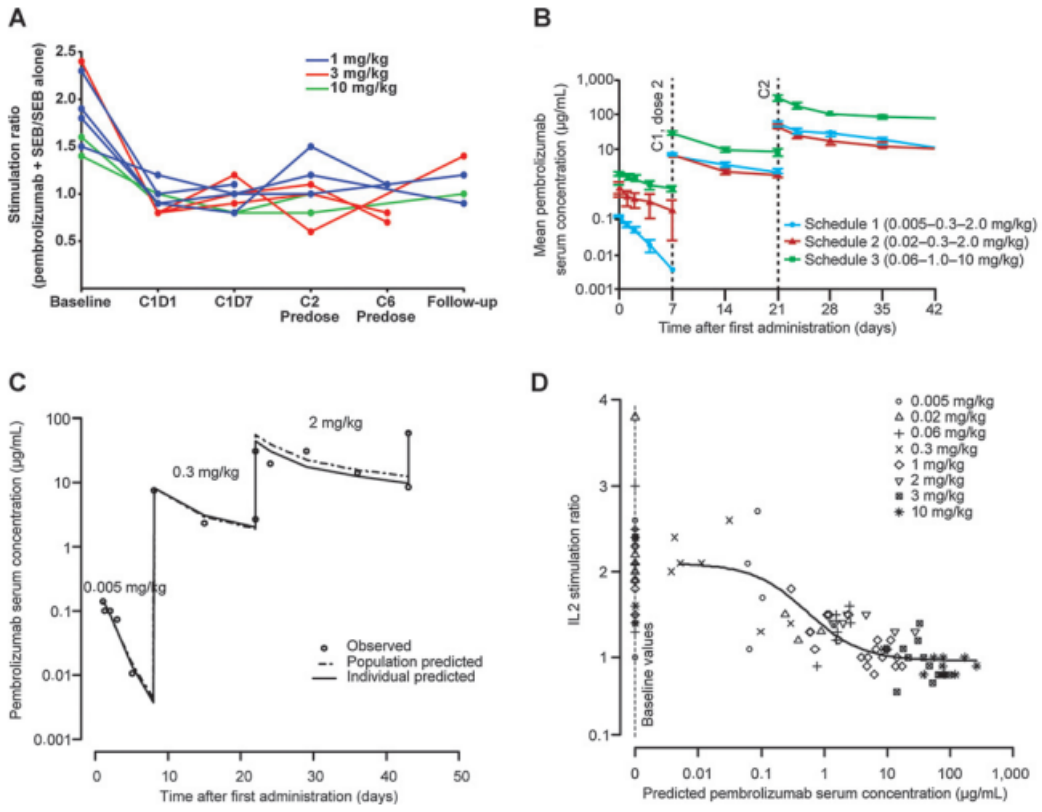


Figure 4.
Pharmacokinetic–pharmacodynamic profile. A, PD-1 receptor modulation assay for Parts A and A-1 demonstrates near-maximal activity of pembrolizumab at all doses and time points. B, serum concentration versus time profile by pembrolizumab dose for Part A-2. Data are presented on a linear-log scale as arithmetic mean (standard error). C, sample subject from cohort 1 with observed (circles), individually predicted (straight), and population-predicted (dashed) pharmacokinetics based on a population pharmacokinetics model. D, observed (symbols by dose) and population-predicted (straight line) PD-1 receptor modulation as a function of pembrolizumab exposure under the extended dose range, with dose- and concentration-dependent modulation lower than 1 mg/kg; model-predicted serum concentrations were used to allow inclusion of all pharmacodynamics observations through interpolation and extrapolation of exposure where no observed values were available. C, cycle; D, day.

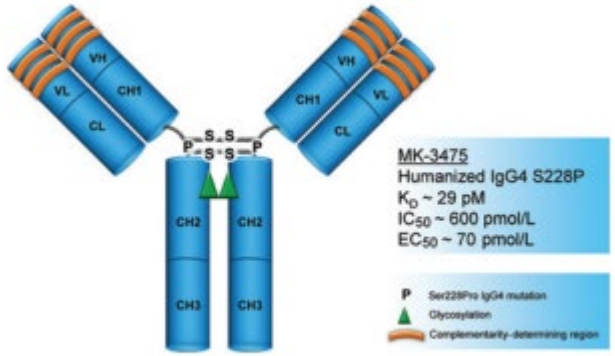


Figure 1.
Structure and key attributes of pembrolizumab.

Patnaik A et al. Clin. Cancer Res., 21 (2015), pp. 4286-4293, 10.1158/1078-0432.CCR-14-2607

- Dose range 0.005 mg/kg – 10 mg/kg; no dose-response with doses ≥ 1mg/kg

Cases - sotorasib

Table 1
FDA's justifications for requiring a randomized dose-ranging trial of sotorasib, CodeBreaK 100 part B [7].

Reason	Page numbers in FDA Multi-Discipline Review[7]
Saturable absorption with similar exposure at steady-state at doses from 180 −960 mg qd	88, 93 −94, 215 −216, 231 −246
No clear trend for dose-response	88, 94, 99 −100, 148, 155, 215 −216, 247 −250
Diarrhea and nausea may be alleviated by administering a lower dose	94, 100, 215 −216
Nonclinical data suggested that the minimal efficacious dose was 30 −240 mg qd	94, 155
The pill burden (i.e., eight 120 mg tablets) is reduced at a lower dose.	94, 215 −216

Moreover, our dosing concerns are exacerbated by the apparent lack of consideration in the prescribing information regarding management of chronic grade 1 and 2 gastrointestinal toxicity for a drug taken daily. Both the FDA label and EMA summary of product characteristics indicate that the dose should only be modified if the gastrointestinal toxicity (i.e., nausea, vomiting, or diarrhea) is (i) grade 3 or higher and (ii) persists despite supportive care. In other words, patients who experience grade 2 diarrhea (4–6 stools above baseline) every day are instructed to continue at a dose of 960 mg daily, without reliable evidence that the higher dose provides greater efficacy.

We also encourage European and other non-US regulatory agencies to conduct their own due diligence, rather than simply relying on statements by the sponsor, or even the implicit support of FDA, as evident from a lack of regulatory action despite the CodeBreaK 100 part B results. The burden of proof is on the sponsor (Amgen) to demonstrate by clear and convincing evidence that its drug is safe and effective at the labeled dose. While sotorasib 960 mg qd may be superior to docetaxel, it is not superior to sotorasib 240 mg qd. In fact, our review of the publicly available data suggests that sotorasib 960 mg is inferior to 240 mg, given the incremental gastrointestinal and hepatic toxicity without incremental benefit, thereby reducing the quality of any life years gained.

New legislation?

- Recital 48: “The opinion may recommend certain conditions that should be part of the marketing authorisation, for example on the safe and efficacious use of the medicinal product or on post-authorisation obligations that have to be complied with by the marketing authorisation holder. Those conditions may include the requirement to conduct post-authorisation safety or efficacy studies or other studies that are considered necessary to optimise the treatment, for example where the proposed dose scheme by the applicant, whilst acceptable and justifying a positive benefit-risk balance, could be further optimised post-authorisation.”
- Art 12h: “If an opinion is favourable to the granting of the relevant marketing authorisation, the following documents shall be annexed to the opinion: (h) where appropriate, details of any recommended obligation to conduct any other post-authorisation studies to improve the safe and effective use of the medicinal product”

https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52023PC0193

Conclusions

- No one-size fits all answer
- Identify dose-related uncertainties early in development
- Prospective planning of dose optimisation
- Keep pharmacology in mind
- Keep all clinical aspects in mind: safety/tolerability, adherence, clinical benefit, subsequent treatments, QoL, OS
- Keep obvious challenges of post authorisation dose finding/optimisation in mind, together with history

Thanks!