INTEGRATION OF PATIENT REPORTED OUTCOMES (PRO) IN PHASE I TRIALS

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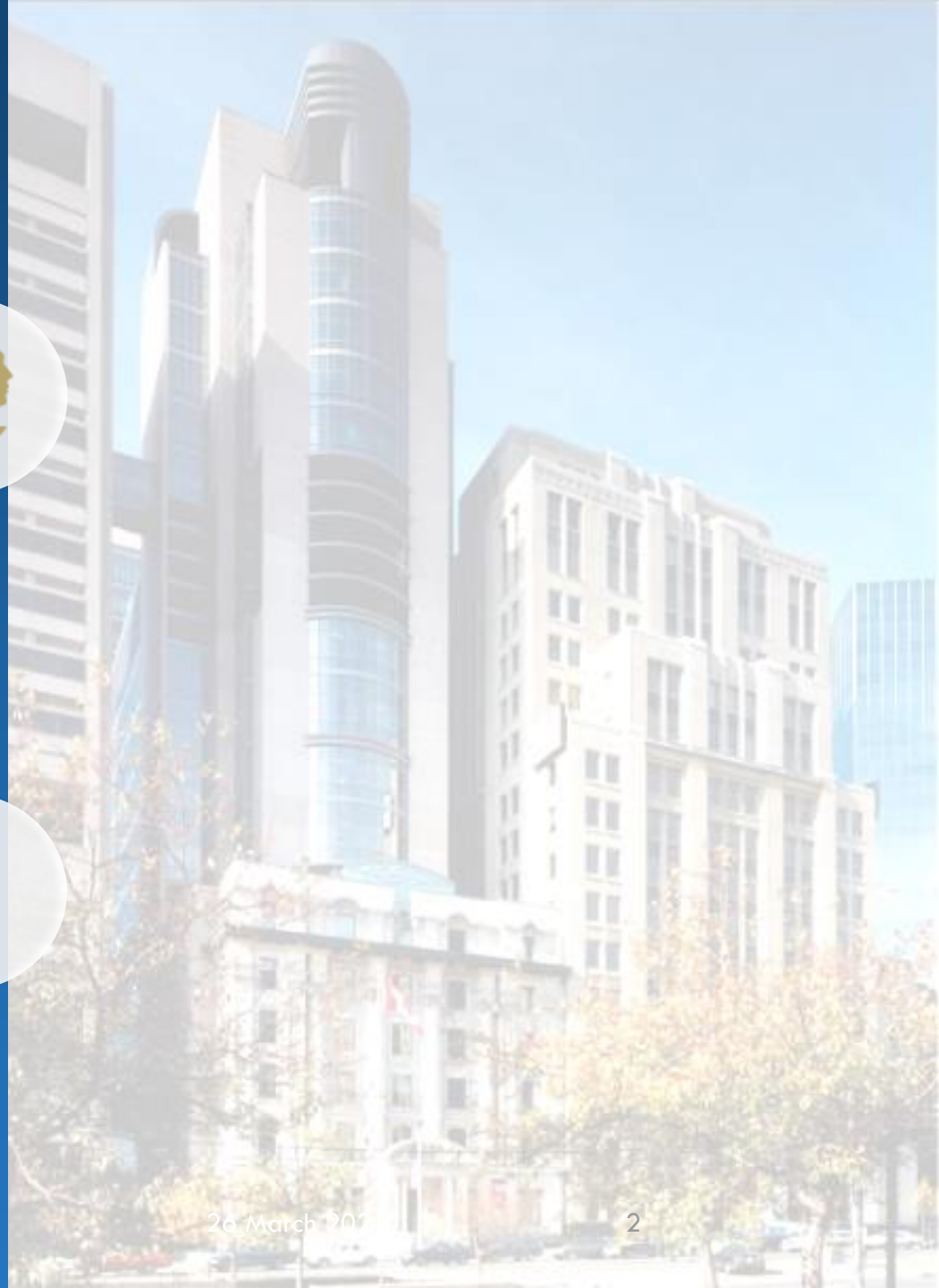


Objectives

AIM 1

PROBLEM

We don't define nor measure tolerability

AIM 2

PRO

Status and research of PROs in phase I trials

AIM 3

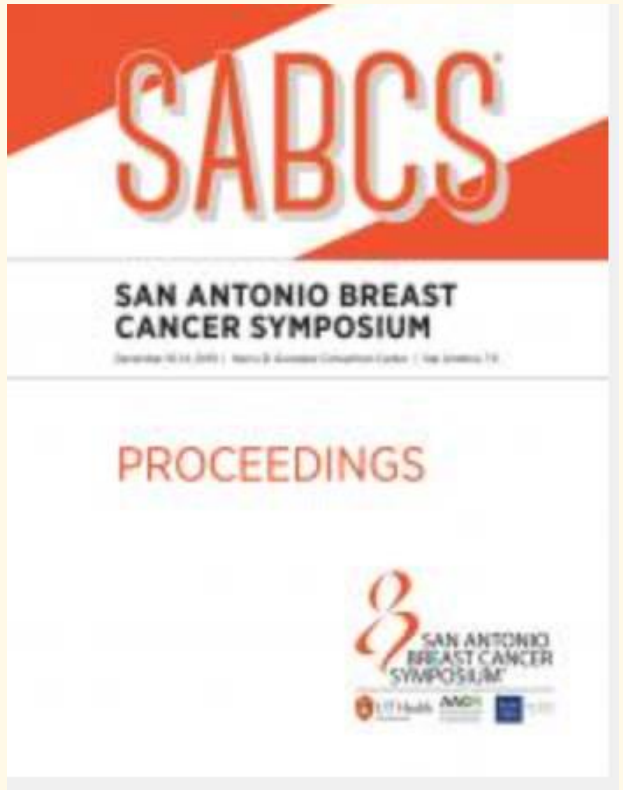
HOW?

Translating PROs into tolerability

Case Study: CX-5461 (G-quadraplex stabilizer)

- IND231 phase I clinical trial – 7 dose levels, IV D1 and 8, Q28 days
- Synthetic lethality in BRCA1/2 deficient cell lines
- Drug found to cause photosensitivity

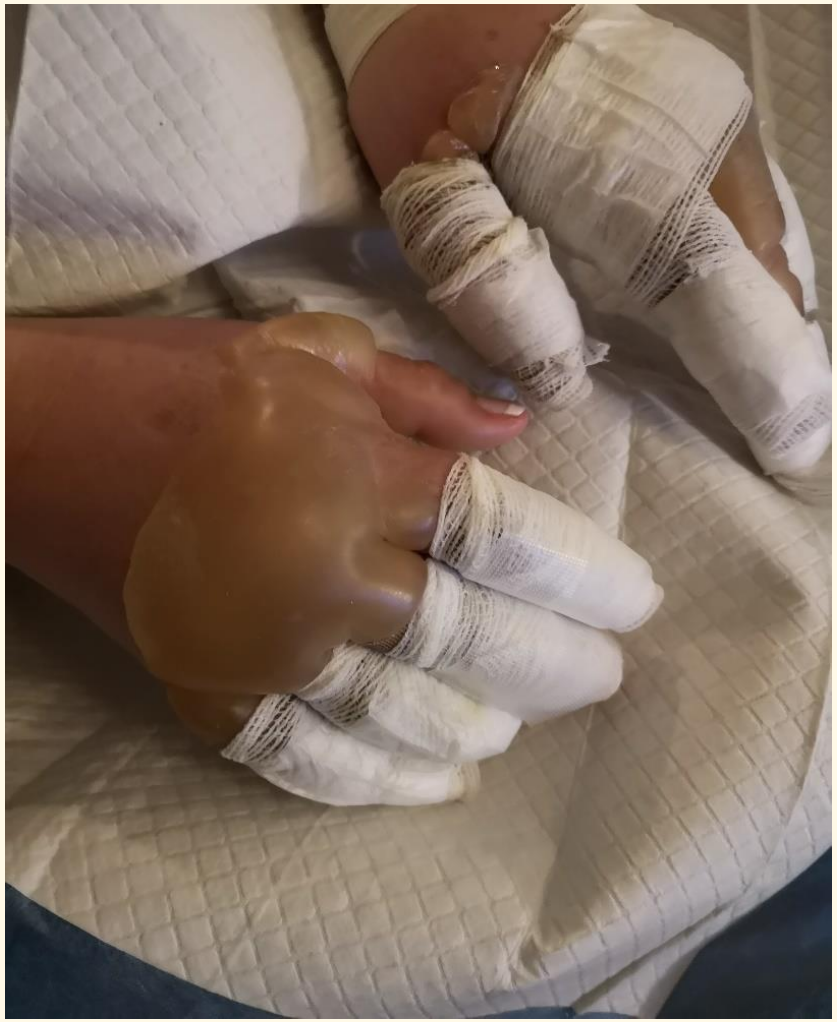
There were 5 treatment-related non-DLT grade 3 photosensitivity events (DL0, DL4, DL7, DL8, DL9) that were reversible and were secondary to lack of photo-protective measures. 3 SAEs were considered related to CX-5461 (photosensitivity of the skin (n=2); photosensitivity of the eyes (n=1). Treatment-related AEs ≥10% were photosensitivity of the skin (59%)

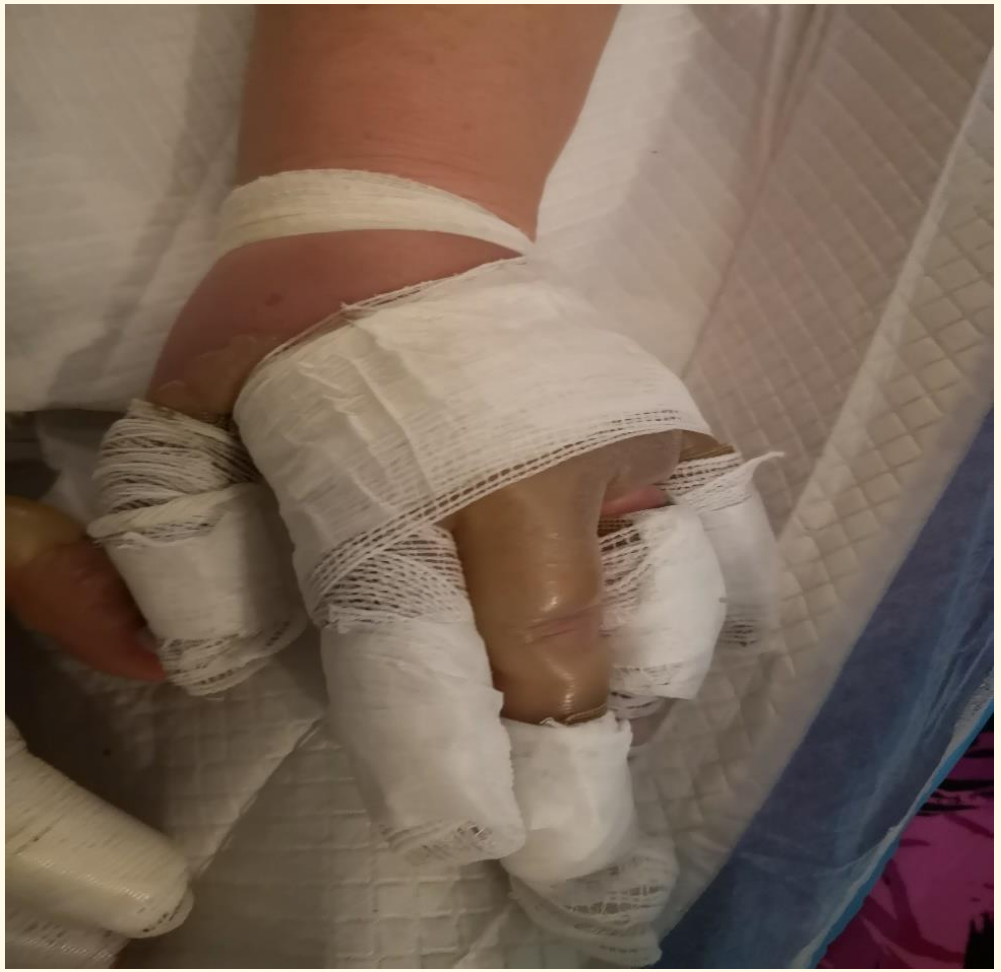


Hilton et al, SABCS 2020

Grade 3 photosensitivity

54 yo female, ovarian cancer (BRCA mutation VUS)





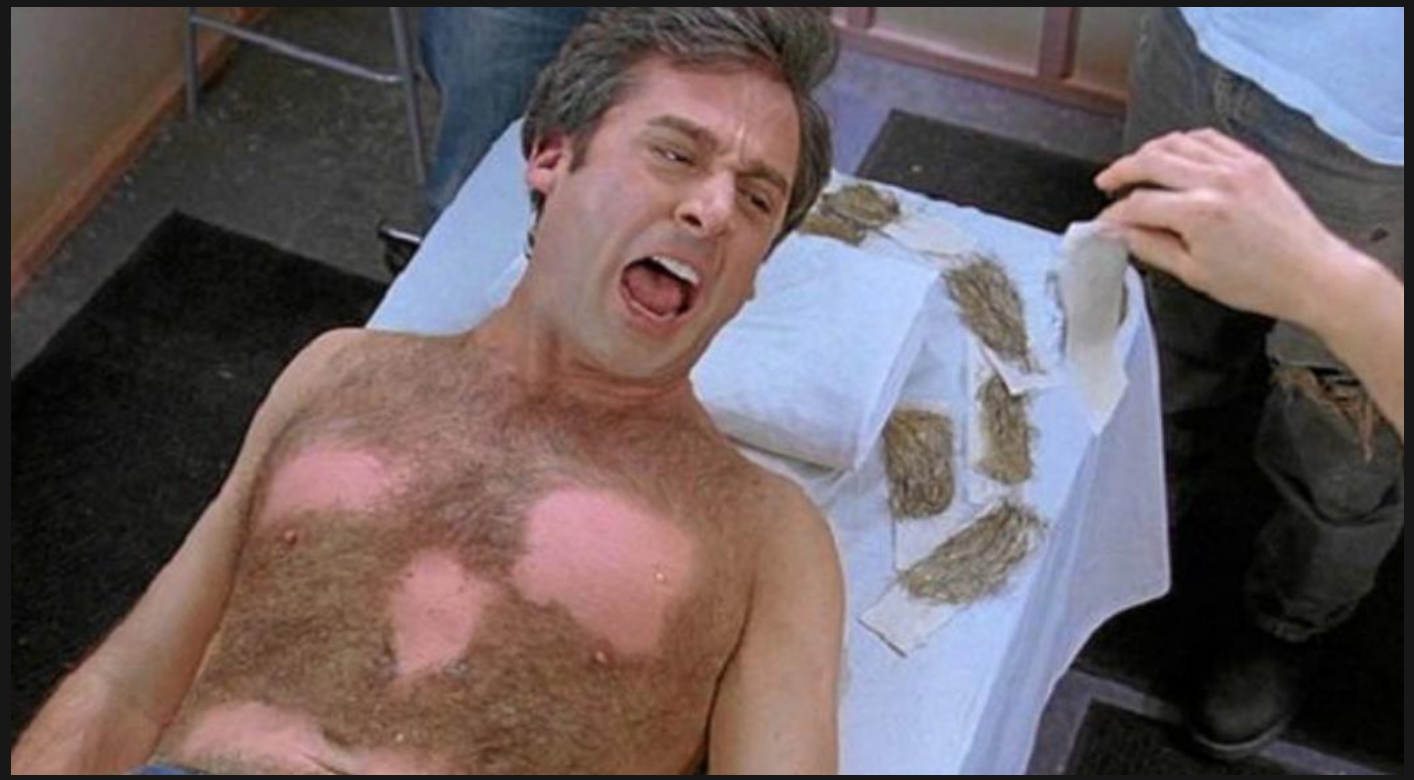
Clear tolerability issues with TKIs

- In 2016: 8 (26%) out of 31 TKIs needed post marketing studies to explore alternative doses and tolerability

Drug	Dose interruption	Dose reduction	Dose interruption or delay
Erlotinib	62%	19%	NA
Vandetanib	47%	49%	80%
Cabozantinib	NA	79%	86%
Ponatinib	66%	52%	74%
Ceritinib	69%	59%	71%
Idelalisib	NA	34%	53%
Lenvatinib	56%	68%	90%

Jänne et al, Clin Cancer Res; 2016

YES – WAXING HURTS!!



BUT DID YOU DIE?

What is tolerability?

Part A: [redacted] **Dose-Escalation as a Single Agent**

To describe the safety and tolerability profile of [redacted] as a single agent

To determine the MTD and/or the optimal biological dose (OBD) and/or the recommended dose for further development of [redacted]

- To investigate the single- and multiple-dose pharmacokinetics of [redacted] as a single agent

tolerable *adjective*

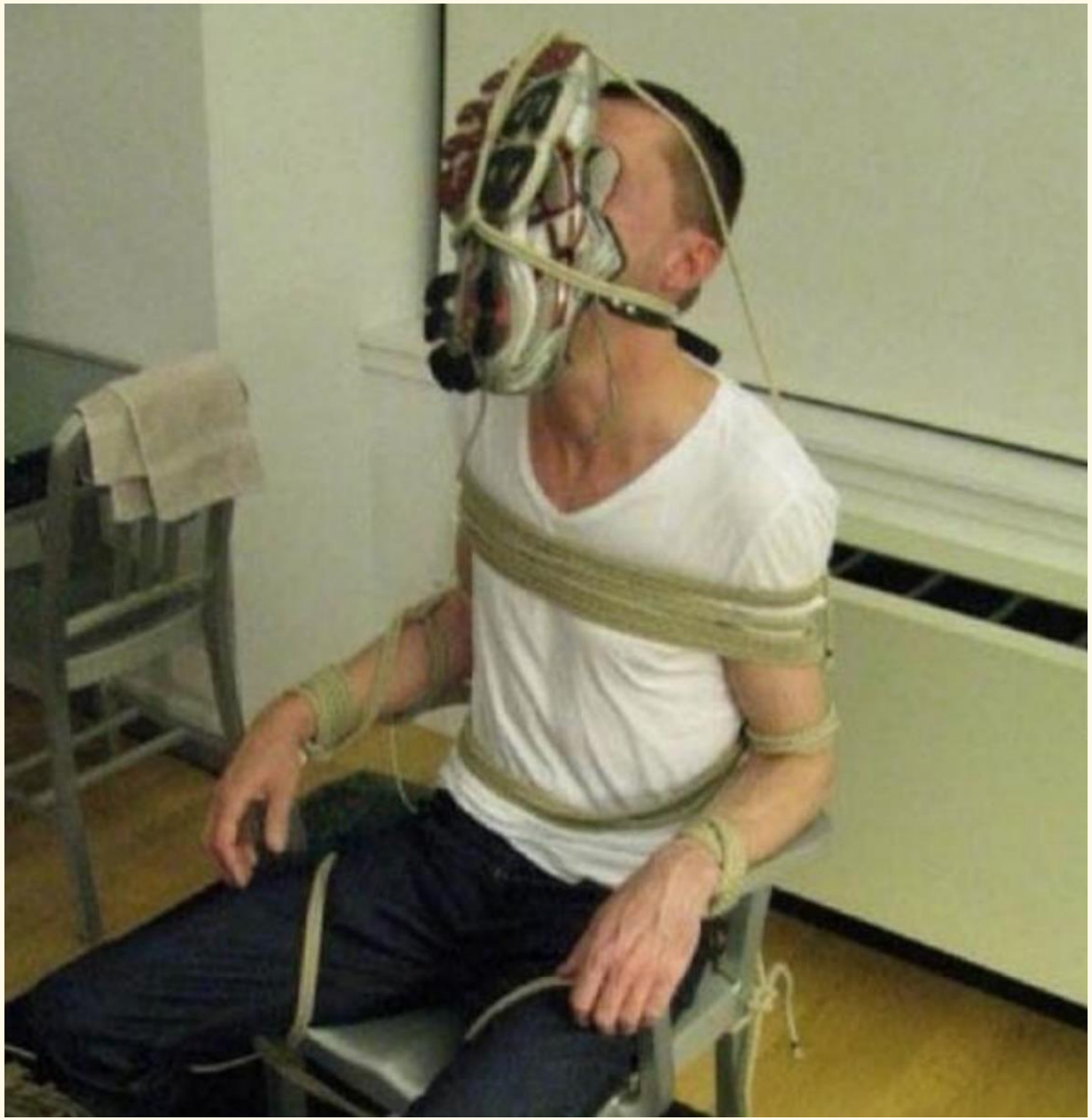
Save Word

tol·er·a·ble | \ ˈtä-lə-rə-bəl, ˈtäl-rə-; ˈtä-lər-bəl \

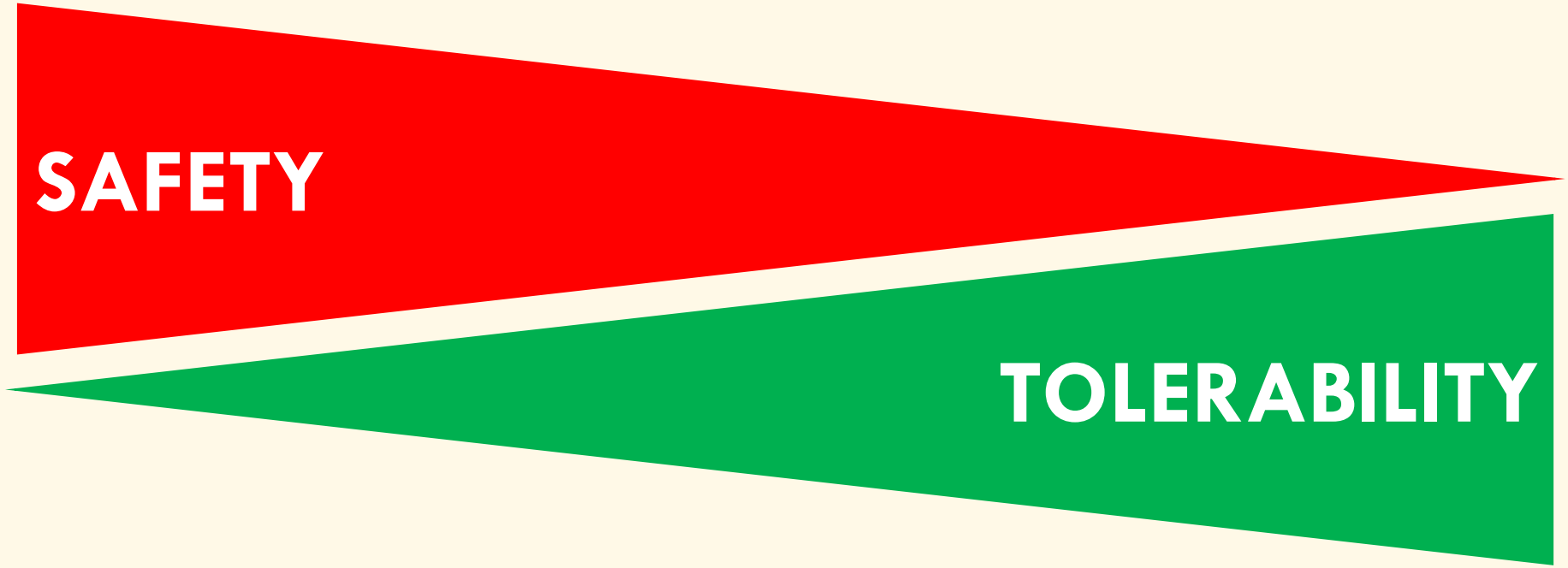
Definition of *tolerable*

1 : capable of being borne or endured

Safety and tolerability: The safety of a medical product concerns the medical risk to the subject, usually assessed in a clinical trial by laboratory tests (including clinical chemistry and hematology), vital signs, clinical adverse events (diseases, signs and symptoms), and other special safety tests (e.g., electrocardiograms, ophthalmology). The tolerability of the medical product represents the degree to which overt adverse effects can be tolerated by the subject.



Phase I Trial Transformation: Safety ➔ Tolerability



Chemotherapy Era (Past)

- Similar MOA
- Intermittent, limited cycles
- Short treatment duration (weeks to months)
- Similar AE profile: myelosuppression, neuropathy, N/V, mucositis etc…

Targeted and Immunotherapy Era (Present)

- Different MOAs
- Often continuous oral therapy
- Long treatment duration (months to years)
- AE dependent MOA and target

What are PROs (patient reported outcomes)?

- A PRO is information about patient's health condition directly from the patient without interpretation or amendment by the clinical team, family/partner or anyone!
- It's important to capture these reports unchanged because multiple studies have demonstrated that clinicians report symptoms differently to patients.[1-3]

PROs cover:

- Measures of symptoms
- Measures of functioning
- HRQOL – combination of symptoms, function and QOL.
- Health status (Health Technology Assessment)
- Satisfaction etc.

[1] Fromme et al, JCO 2004
[2] Cirillo, Ann Onc 2009
[3] Di Maoi, JCO 2015

PROs in phase I trials

- PRO use in Phase I trials is limited, but increasing over time
- In a review of early phase trials between 2007 to 2019: PRO use tripled (9 to 29 studies) [average increase of 2.3/year].[1]
- PROs were typically used in academic-sponsored studies (135, 58.4%) and as a secondary endpoint (209, 89.7%).
- Most trials used 1 PRO measure (range 1-7).
- PROs were collected during dose escalation (114, 49.1%) or phase I/II (54, 23.3%).
- Most common PRO measures: EORTC QLQ C30 (81, 21.3%) and EQ-5D-5L (19, 5%).

[1]Lai-Kwon et al, Ann Oncol ESMO 2020

PRO-CTCAE

Oral	
Dry mouth	S
Difficulty swallowing	S
Mouth/throat sores	SI
Cracking at the corners of the mouth (cheilosis/cheilitis)	S
Voice quality changes	P
Hoarseness	S

Gastrointestinal	
Taste changes	S
Decreased appetite	SI
Nausea	FS
Vomiting	FS
Heartburn	FS
Gas	P
Bloating	FS
Hiccups	FS
Constipation	S
Diarrhea	F
Abdominal pain	FSI
Fecal incontinence	FI

Respiratory	
Shortness of breath	SI
Cough	SI
Wheezing	S

Cardio/Circulatory	
Swelling	FSI
Heart palpitations	FS

Cutaneous	
Rash	P
Skin dryness	S
Acne	S
Hair loss	P
Itching	S
Hives	P
Hand-foot syndrome	S
Nail loss	P
Nail ridging	P
Nail discoloration	P
Sensitivity to sunlight	P
Bed/pressure sores	P
Radiation skin reaction	S
Skin darkening	P
Stretch marks	P

Neurological	
Numbness & tingling	SI
Dizziness	SI

Visual/Perceptual	
Blurred vision	SI
Flashing lights	P
Visual floaters	P
Watery eyes	SI
Ringing in ears	S

Attention/Memory	
Concentration	SI
Memory	SI

Pain	
General pain	FSI
Headache	FSI
Muscle pain	FSI
Joint pain	FSI

Sleep/Wake	
Insomnia	SI
Fatigue	SI

Mood	
Anxious	FSI
Discouraged	FSI
Sad	FSI

Gynecologic/Urinary	
Irregular periods/vaginal bleeding	P
Missed expected menstrual period	P
Vaginal discharge	P
Vaginal dryness	S
Painful urination	S
Urinary urgency	FI
Urinary frequency	PI
Change in usual urine color	P
Urinary incontinence	FI

Sexual	
Achieve and maintain erection	S
Ejaculation	F
Decreased libido	S
Delayed orgasm	P
Unable to have orgasm	P
Pain w/sexual intercourse	S

Miscellaneous	
Breast swelling and tenderness	S
Bruising	P
Chills	FS
Increased sweating	FS
Decreased sweating	P
Hot flashes	FS
Nosebleed	FS
Pain and swelling at injection site	P
Body odor	S

Attributes	
F: Frequency	I: Interference
S: Severity	P: Presence/Absence /Amount

PRO-CTCAE vs CTCAE

CTCAE					
Adverse Event	Grade				
	1	2	3	4	5
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	-

PRO-CTCAE
Please think back over the past 7 days:
What was the severity of your MOUTH OR THROAT SORES at their WORST? None / Mild / Moderate / Severe / Very severe
How much did MOUTH OR THROAT SORES interfere with your usual or daily activities? Not at all / A little bit / Somewhat / Quite a bit / Very much

Basch et al, Conference Clinical Res 2015

Messages

- Under reporting of symptomatic AEs by clinicians in phase I trials
- High acceptance (>95%) and completion (~90%) rates of the full PRO-CTCAE survey establish the feasibility of integrating such a questionnaire in the phase I setting.
- We identified the top 50 PRO-CTCAE items occurring at a frequency ≥10%; and 19 clinician-reported CTCAE items occurring at a frequency of ≤1% despite higher patient reporting (≥10%), with generally low levels of agreement.
- Total number of clinician-reported AEs were associated with survival, but not the total patient-reported AEs.

Veitch, Hansen et al, JNCI 2021

PROs and tolerability

- Regulatory guidelines exist: FDA (2009) and EMA (2016)
- Several categories of PROs that can assess tolerability:

Patient-reported symptomatic adverse events
Patient-reported overall burden of adverse events
Patient-reported physical functioning
Other types of functional assessments

- Data must be collected from reliable, well-defined "fit-for-purpose" tools e.g. PROCTCAE for symptomatic AEs

Basch et al, Conference Clinical Res 2015

Translation of PROs into tolerability

- Proportion of patients experiencing the worst magnitude of each response level of each elicited symptomatic AE PRO item, by treatment, each time point of measurement, and for the total period of study participation
- Proportion of patients with each response level of an item eliciting overall perceived burden of adverse events
- Qualitative inquiry with patients on relevant PRO items contributing to tolerability (e.g., end of treatment questionnaire)
- Impact of frequent or high-grade symptomatic AEs on physical function, HRQOL and other functional measures
- Comprehensive description of global side effect impact

Basch et al, Conference Clinical Res 2015

How should we define tolerability?

- No intentions to state a drug or regimen is tolerable BUT rather provide a thorough description of patient experience

The tolerability of a medical product is the degree to which symptomatic and non-symptomatic adverse events associated with the product's administration affect the ability or desire of the patient to adhere to the dose or intensity of therapy. A complete understanding of tolerability should include direct measurement from the patient on how they are feeling and functioning while on treatment.

- Descriptive analysis (in table format) of key aspects from PRO components with impact noted.

Basch et al, Conference Clinical Res 2015

Example - Sotorasib

Current

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 24, 2020 VOL. 383 NO. 13

KRAS^{G12C} Inhibition with Sotorasib in Advanced Solid Tumors

D.S. Hong, M.G. Fakih, J.H. Strickler, J. Desai, G.A. Durm, G.I. Shapiro, G.S. Falchook, T.J. Price, A. Sacher, C.S. Denlinger, Y.-J. Bang, G.K. Dy, J.C. Krauss, Y. Kuboki, J.C. Kuo, A.L. Coveler, K. Park, T.W. Kim, F. Barlesi, P.N. Munster, S.S. Ramalingam, T.F. Burns, F. Meric-Bernstam, H. Henary, J. Ngang, G. Ngarmchamnanrith, J. Kim, B.E. Houk, J. Canon, J.R. Lipford, G. Friberg, P. Lito, R. Govindan, and B.T. Li

RESULTS

A total of 129 patients (59 with NSCLC, 42 with colorectal cancer, and 28 with other tumors) were included in dose escalation and expansion cohorts. Patients had received a median of 3 (range, 0 to 11) previous lines of anticancer therapies for metastatic disease. No dose-limiting toxic effects or treatment-related deaths were observed. A total of 73 patients (56.6%) had treatment-related adverse events; 15 patients (11.6%) had grade 3 or 4 events. In the subgroup with NSCLC, 32.2%

Table 2. Adverse Events in All 129 Patients.

Events	Any Grade	Grade ≥3	Grade ≥4	Grade 5: Fatal
	number (percent)			
Adverse events of any cause that occurred during treatment				
Any	125 (96.9)	68 (52.7)	26 (20.2)	22 (17.1)
Serious	58 (45.0)	51 (39.5)	25 (19.4)	22 (17.1)
Resulting in discontinuation of treatment*	9 (7.0)	9 (7.0)	4 (3.1)	4 (3.1)
Adverse events of any cause that occurred during treatment in ≥10% of patients				
Diarrhea	38 (29.5)	5 (3.9)	0	0
Fatigue	30 (23.3)	3 (2.3)	0	0
Nausea	27 (20.9)	2 (1.6)	0	0
Vomiting	23 (17.8)	5 (3.9)	0	0
Abdominal pain	23 (17.8)	4 (3.1)	0	0
Dyspnea	21 (16.3)	3 (2.3)	1 (0.8)	1 (0.8)
Cough	20 (15.5)	0	0	0
Back pain	19 (14.7)	2 (1.6)	0	0
Decreased appetite	19 (14.7)	1 (0.8)	0	0
Headache	18 (14.0)	0	0	0
Aspartate aminotransferase increase	17 (13.2)	3 (2.3)	0	0
Anemia	17 (13.2)	6 (4.7)	0	0
Dizziness	17 (13.2)	0	0	0
Alanine aminotransferase increase	15 (11.6)	6 (4.7)	1 (0.8)	0
Constipation	15 (11.6)	0	0	0
Pyrexia	14 (10.9)	0	0	0
Insomnia	14 (10.9)	0	0	0
Myalgia	13 (10.1)	0	0	0
Peripheral edema	13 (10.1)	0	0	0
Arthralgia	13 (10.1)	2 (1.6)	0	0

Example – Sotorasib ("PROposed")

PRO (Severity)	Severe and Very Severe			
	180mg	360mg	720mg	960mg
Diarrhea				XX (AA%)
Fatigue				YY (BB%)
Nausea				ZZ (CC%)

PRO (Interference)	Quite a bit and Very Much			
	180mg	360mg	720mg	960mg
Diarrhea				PP (DD%)
Fatigue				QQ (EE%)
Nausea				RR (FF%)

PRO	Severity				Interference		
	Mild	Moderate	Severe	Very Severe	Somewhat	Quite a bit	Very much
Diarrhea							
Fatigue							
Nausea							

- *At the recommended dose of 960mg, the main symptomatic AE was diarrhea which was severe to very severe in AA% patients and was 'quite a bit' to 'very interfering' with ADLs for DD% patients.*
- *Overall fatigue was considered by most patients to be moderate and only somewhat interfering, but nausea was often severe or worse and they reported nausea very much interfered with their ADLs.*

Take aways

- Need to improve our understanding, measurement, analysis and reporting of tolerability of experimental regimens.
- Clear role for the incorporation of PRO instruments into phase I trials eg PROCTCAE.
- Symptomatic AEs are under reported by clinicians on phase I trials
- Further work is needed to understand the clinical actionability of PROCTCAE responses.
- Need to move away from a binary definition of tolerability and towards a descriptive analysis of the patient experience.
- Beyond tolerability, PROs could be used in Phase I trials to obtain preliminary data about HRQOL and inform PRO endpoints in future trials

Acknowledgments

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Questions