Lessons Learned from Oncology Dose Finding Workshops

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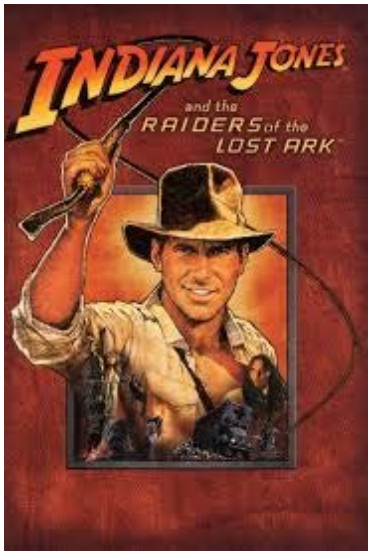
The Dose Optimization Issue

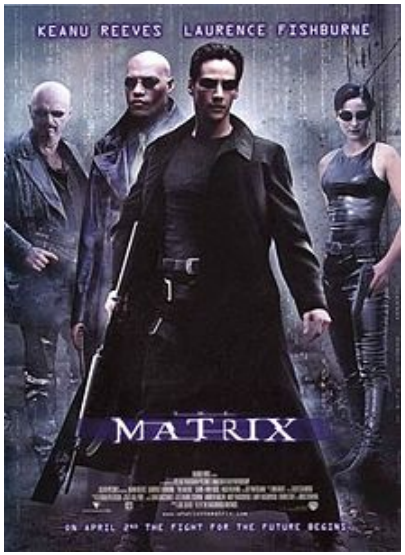
- High rate of dose reductions and discontinuations in clinical trials
- Adherence to therapy in the “real world”
- Redundant drug development process with inefficiencies
- More potential permutations of combinations than eligible patients
- Incomplete characterization of compounds and lack of full understanding of mechanisms of actions
- HIGHLY competitive and rapidly changing landscape

DFW:Part 1


STAR WARS


INDIANA JONES
and the
RAIDERS of the
LOST ARK

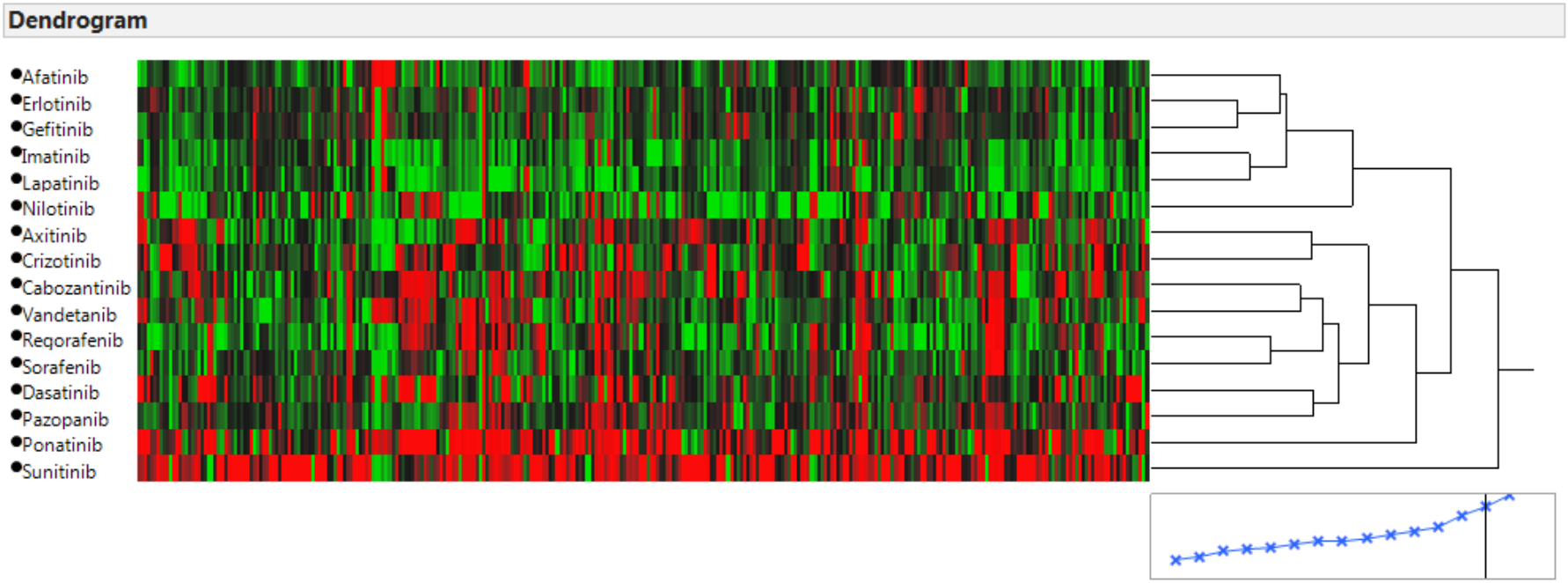

THE LORD OF THE RINGS
THE FELLOWSHIP OF THE RING


KEANU REEVES
LAURENCE FISHBURNE
MATRIX

Small Molecule Kinase Inhibitors

- Exposure response relationships are rarely defined nor interpatient variability adequately evaluated during early clinical development
  - Poor solubility and high variability of exposure
- AEs in Phase 2/3 clinical trials result in dose reductions, complicating study interpretation and determination of FDA-recommended dose
- Sponsor's have to conduct additional dose optimization studies as PMRs

Broad target selectivity for many FDA-approved kinase inhibitors



1 µM kinase inhibitor profiled against 300 kinases in a biochemical enzymatic assay

Uitdehaag et. al, PLOS one (2014)

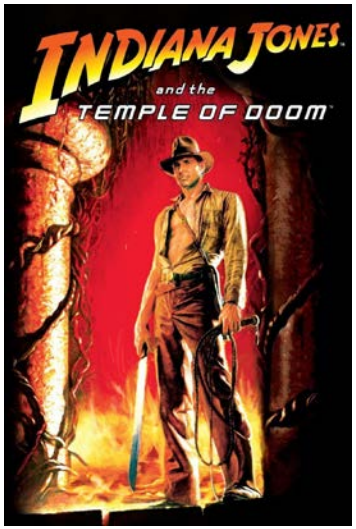
5

General Considerations

- Interdisciplinary Communication
- Revisit and retest when signals emerge
- Purposeful selection of trial designs

DFW: Part 2


THE STAR WARS SAGA CONTINUES
THE EMPIRE STRIKES BACK


INDIANA JONES
and the
TEMPLE OF DOOM


THE LORD OF THE RINGS
THE TWO TOWERS
THE JOURNEY CONTINUES


MATRIX
RELOADED

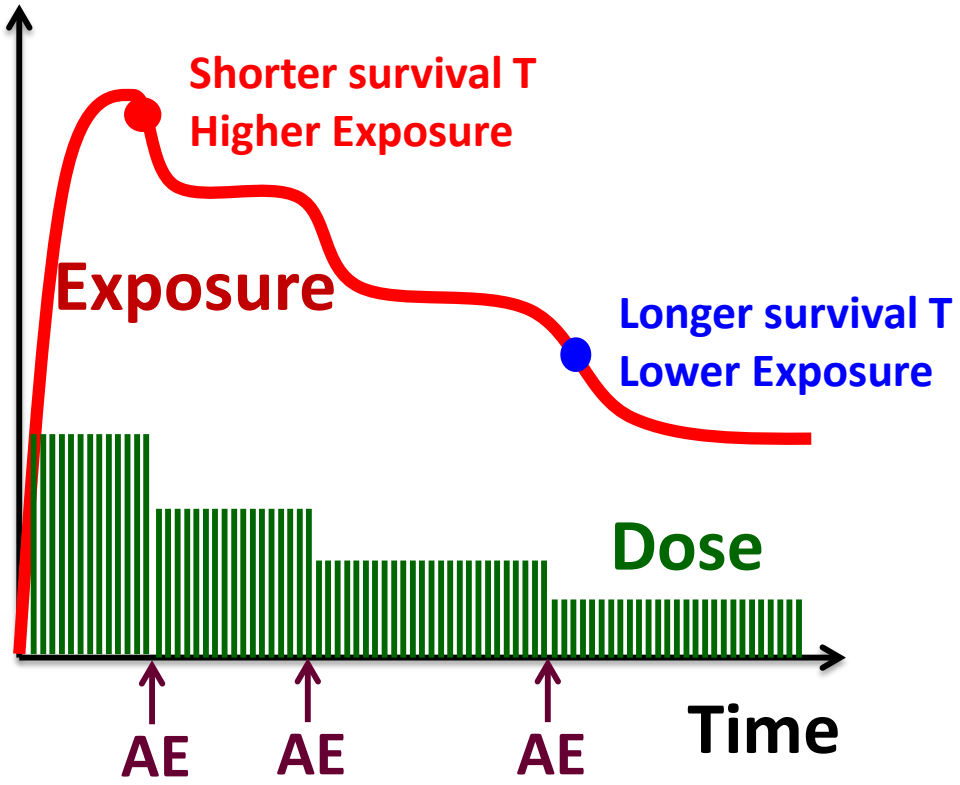
Large Molecules

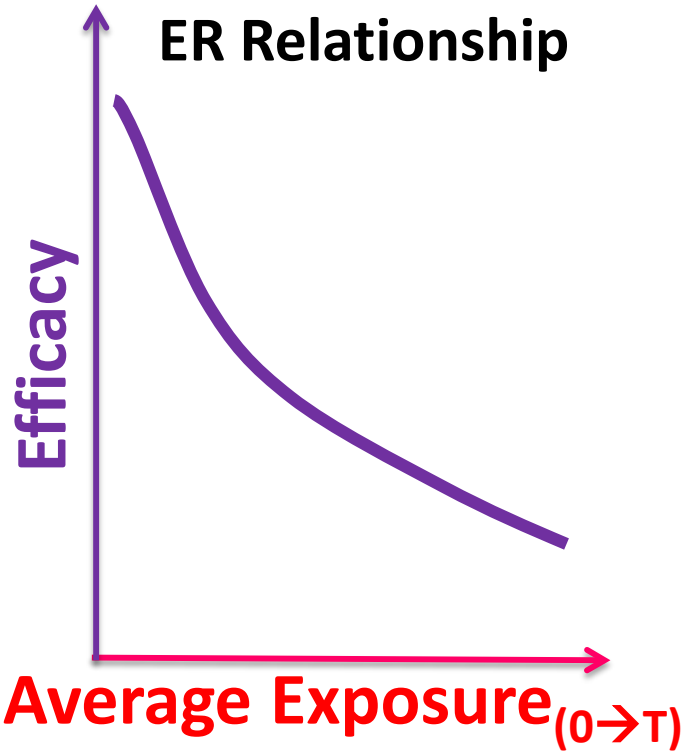
- FIH dose selection (Saber et al Regul Toxicol Pharmacol 2016)
  - MABEL approach: Minimally Anticipated Biological Effect Level
  - Use receptor occupancy or pharmacologic activity to start
  - Use strategies such as Intra-patient dose escalation and n=1 escalation cohorts to minimize patients exposed to dose levels not expected to have biologic effects

Large Molecules

- RO and saturation may inform safe start dose, but % saturation may not equate to optimal dose
  - May be thought of as lower bound?
- PK-PD models may be informative
- E-R relationships
  - Contribution of disease status

Dose Adjustment: Challenges for E-R Relationship Estimation





- Exposure not constant over time
- Biased ER relationship

E-R: Exposure-Response; AE: Adverse Event

Courtesy of Chao Liu FDA

All Products and Combinations

- Systems pharmacology approaches may be informative
- Integration of multiple sources
- Consider time as a key factor
  - Dose adjustment Integrated E-R analysis

DFW: Part 2.5


STAR WARS
I
THE PHANTOM MENACE


INDIANA JONES
KINGDOM OF THE CRYSTAL SKULL
MAY 22


THE HOBBIT
DECEMBER 14


FROM THE CREATORS OF THE MATRIX TRILOGY.
ANIMATRIX

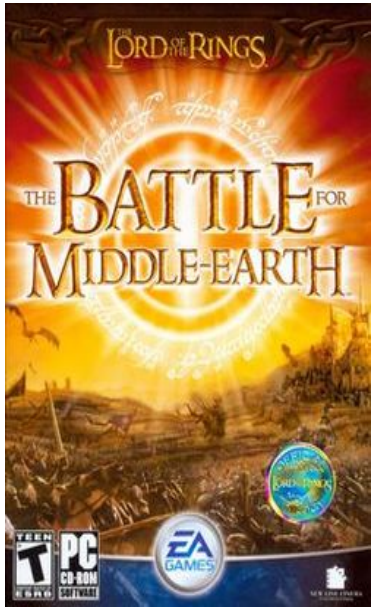
Dose-Finding: IO Agents and Combinations

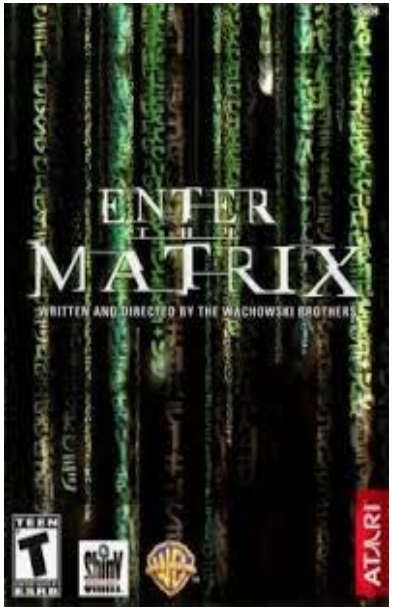
- Fixing dose and schedule of agents that are already approved or well characterized
- Safety attribution in combination studies
- Disease specificity for dose/schedule of combinations
- Benefits of larger sample sizes and randomized evaluation

DFW 2.75


STAR WARS
KNIGHTS
OF THE
OLD REPUBLIC
BIOWARE
CORP


LEGO
INDIANA JONES
THE VIDEO GAME


THE LORD OF THE RINGS
THE BATTLE FOR
MIDDLE-EARTH
PC
CD-ROM
EA
GAMES


ENTER
THE
MATRIX
ATARI

AACR 2017

- Biomarkers and IO combination
  - SITC working group
  - Industry perspective
  - Use of biomarkers in modeling and simulation approaches
- How can you find the right dose if you cannot find the right patient?
- Is survival the only endpoint?

DFW 3!!

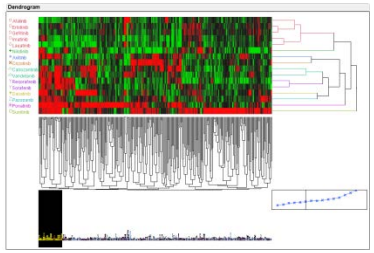

STAR WARS
RETURN OF THE JEDI

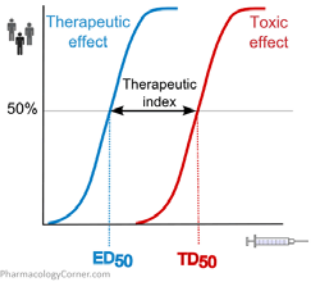

INDIANA JONES
and the
LAST CRUSADE

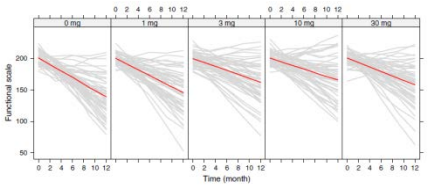

THE LORD OF THE RINGS
THE RETURN OF THE KING


TODO PRINCIPIO TIENE UN FINAL
MATRIX
REVOLUTIONS

In an Ideal (?) World







$$f(x,\theta) = \theta_0 + \theta_1 f^0\left(x,\theta^0\right)$$

$$\widehat{\Psi}(\theta) = (\bar{\mu} - f(x,\theta))' A_n (\bar{\mu} - f(x,\theta))$$

$$\sqrt{a_n}\left(\widehat{\theta} - \theta_0\right) \xrightarrow{d} N\left(0, B(\theta_0)' M(\theta_0) B(\theta_0)\right)$$