CDDF 10TH ALPINE CONFERENCE
CURRENT AND FUTURE CHALLENGES OF INNOVATIVE ONCOLOGY DRUG DEVELOPMENT
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Finding the Right Dose and Schedule of New Drugs

- Clinical Considerations –

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Disclaimer

- The views expressed in this presentation are those of the speaker and not necessarily those of Eli Lilly and Company.

Some Population Data (US)

2017:

- **1.6 mio new cancers diagnosed**
- **600 000 cancer-related deaths**
- **4.8 % of US population are cancer survivors**
- **87% of cancer diagnoses are made in individuals ≥ 50 y/o**

http://www.phrma.org/science/in-the-pipeline/medicines-in-development

Drug Development Response

2015:

- **800 drugs in development**
- **80% may be claimed to be First-In-Class**
- **≥ 70% expected to be „Personalized Medicines“**

2017:

- **> 1000 drugs in development**
  - **240 drugs in Immuno-Oncology**
  - **240 drugs against lymphomas/leukemias**

2018:

- **Number of FDA-approved anticancer drugs: > 230**

Adapted from: http://phrma-docs.phrma.org/sites/default/files/pdf/oncology-report-2015.pdf

Classes of Drugs

- Cytotoxic drugs
- Pathway-targeted small molecules
- Non-immuno-directed protein-engineered molecules
  - Fusion proteins
  - Peptides
  - Peptibodies
  - Non-immune-directed monoclonal antibodies
    - „simple“
    - ADC
    - Bispecific
- Immuno-directed protein-engineered molecules
  - Checkpoint inhibitors
  - Bispecific antibodies
- Cellular constructs
  - CART cells

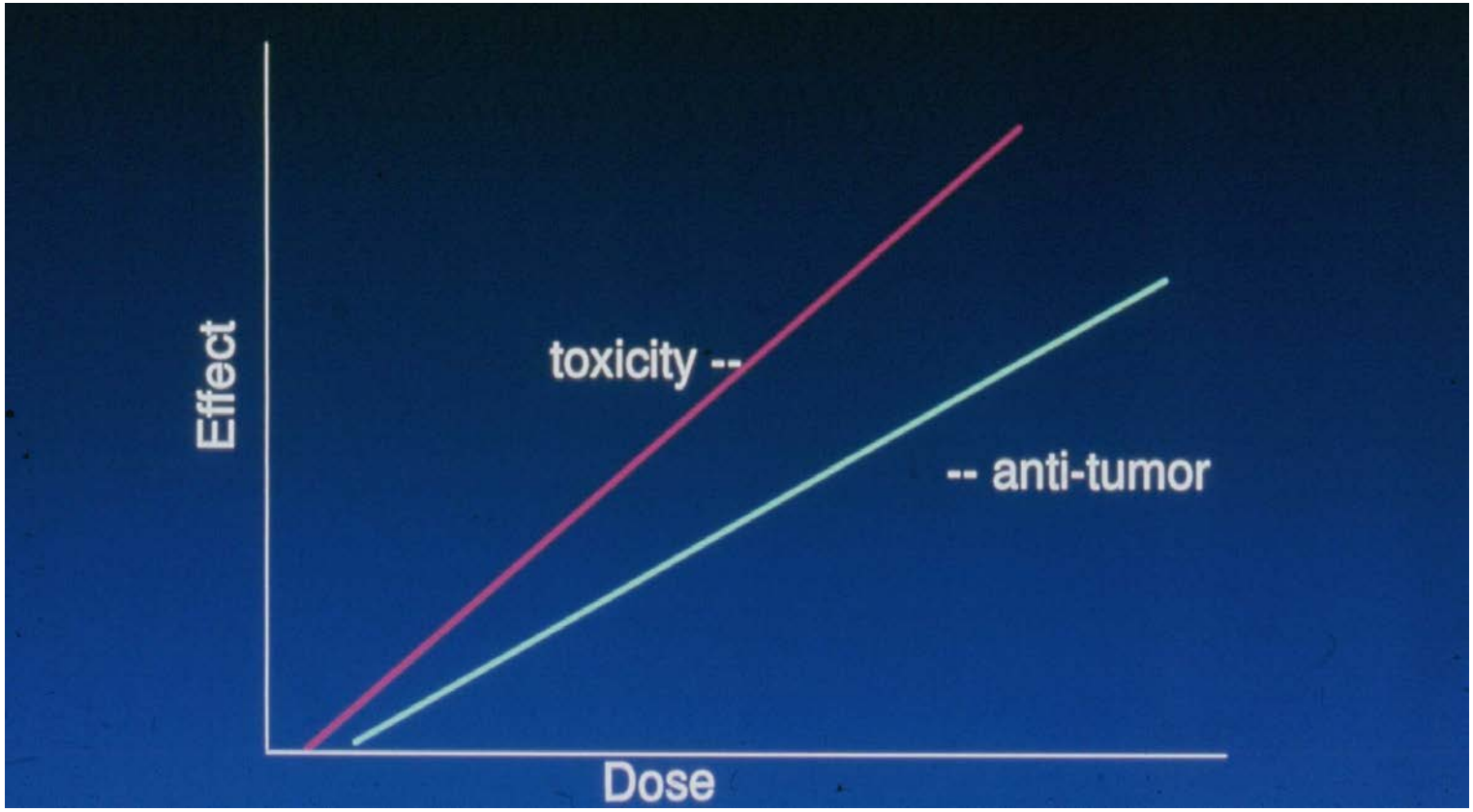
Bates Clin Cancer Res 21: 4257, 2015; http://phrma-docs.phrma.org/sites/default/files/pdf/oncology-report-2015.pdf

Successful Dose/Schedule-Finding Begins BEFORE Phase I

Review and consider during drug discovery:

- **Do we really want to pursue this target?**
- **Do we have a competitive drug to hit the target?**
- **How do we measure this?**
- **Do we have a viable biomarker hypothesis?**
- **Do we move into Phase I?**
- **What is the Phase I strategy?**
- **How should the label look like?**
- **What is the external environment doing?**

Phase I Paradigm for Cytotoxic Drugs



Goal: **Titration of DLTs to define Maximum <u>Tolerated</u> Dose**

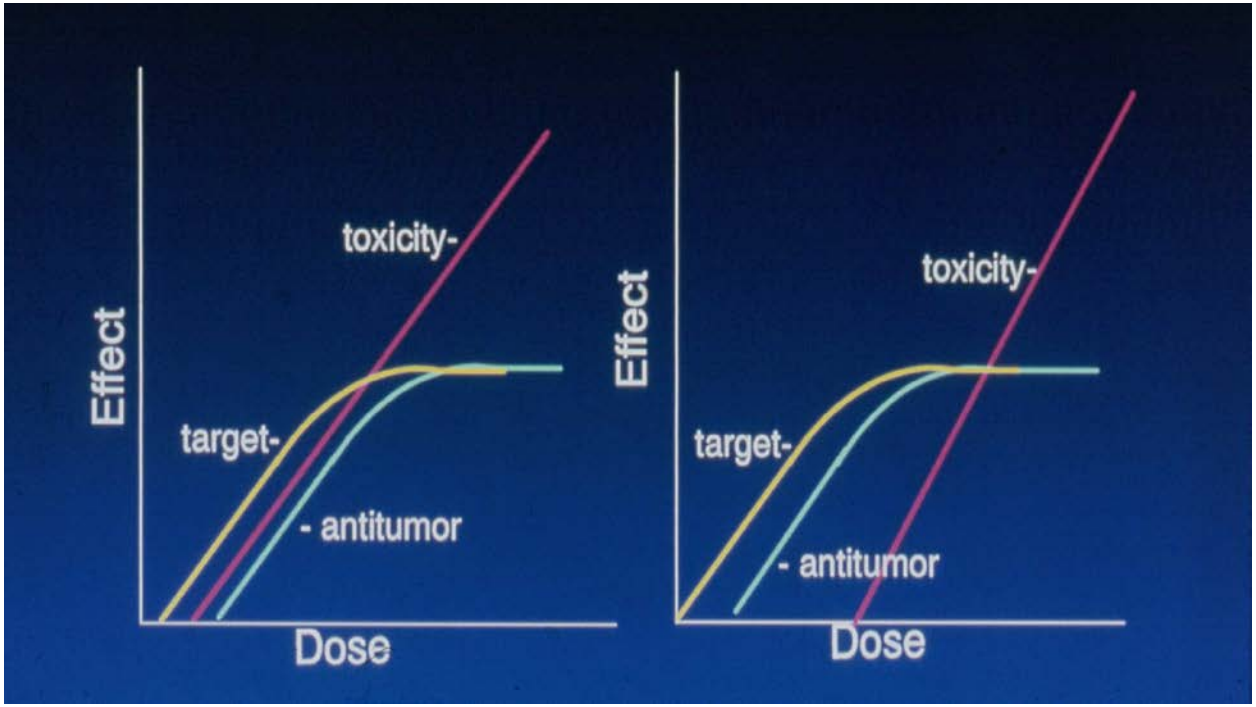
Assumption: **MTD identifies Maximum <u>Effective</u> Dose**
Toxicity is intrisically linked to antitumor activity

Oncology Phase I Clinical Trials: Historical Perspectives

Paradigm for Cytotoxic Drugs:

- Empirically-based process that evolved over decades
- Focused on the Maximum Tolerated Dose (MTD)
  - Standard formulas for starting dose from toxicology studies
  - Employed fixed-dose escalation scheme (ie, Fibonacci)
  - Dosing continued until unacceptable toxicity identified
  - Subsequent phase 2 dose set just below the MTD
- Pharmacokinetics were largely descriptive
- Biomarkers
  - Largely based on safety/tolerability as assessed by acute bone marrow toxicity, e.g. neutrophil counts

Phase I Paradigm for Pathway – Signaling Pathway Interfering Drugs



Goal: **Identify Maximum Effective Dose by other means than MTD**

Assumption: **MTD may not identify Maximum Effective Dose**
Extent and duration of target inhibition is linked to antitumor activity

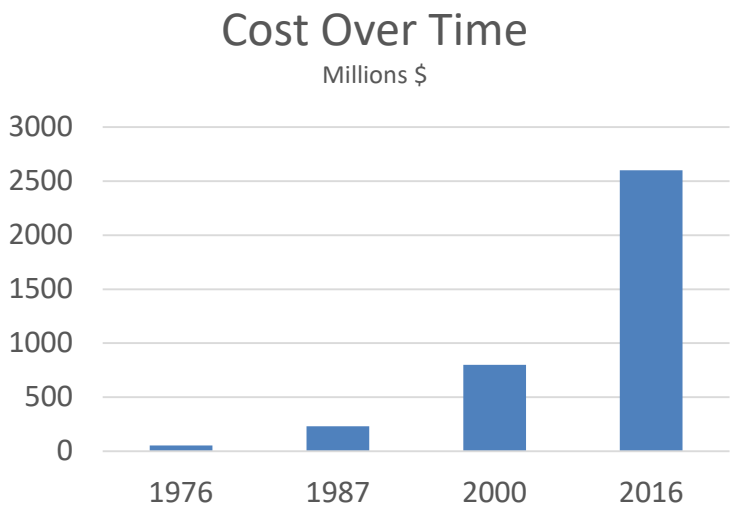
Protein-Engineered Compounds

- **DLTs may not be observed > MTD may not be reached**
- **Doses exceeding 30 mg/kg may raise concern of non-specific toxicities**
- **Acceleration thus often based on BED or BAD modelled from animal PK observations**
  - **BUT: animal models lack predictive accuracy for human outcomes**
- **> Significant risk that dose and schedule result in suboptimal efficacy and require refinement after Phase III trials have been completed**
- **Highest risk (even if compound has promising early activity): Acceleration into Phase III without DLTs or MTD – just based on a soft predictive biomarker and questionably validated modelling**
- **NEED to develop robust and predictive PK/PD modeling and use of reliable biomarker as early in the process of preclinical and clinical studies as possible**
- **Accepted approach: Bridging studies**

Cost to Develop New Drugs

Estimated capitalized cost per approved drug in 2016 is $ 2.6 Billion

Pre-Clinical : $ 1.1 Billion / Clinical: $ 1.5 Billion



J.DiMasi, et al, J Health Econ (2016) 47:20-33

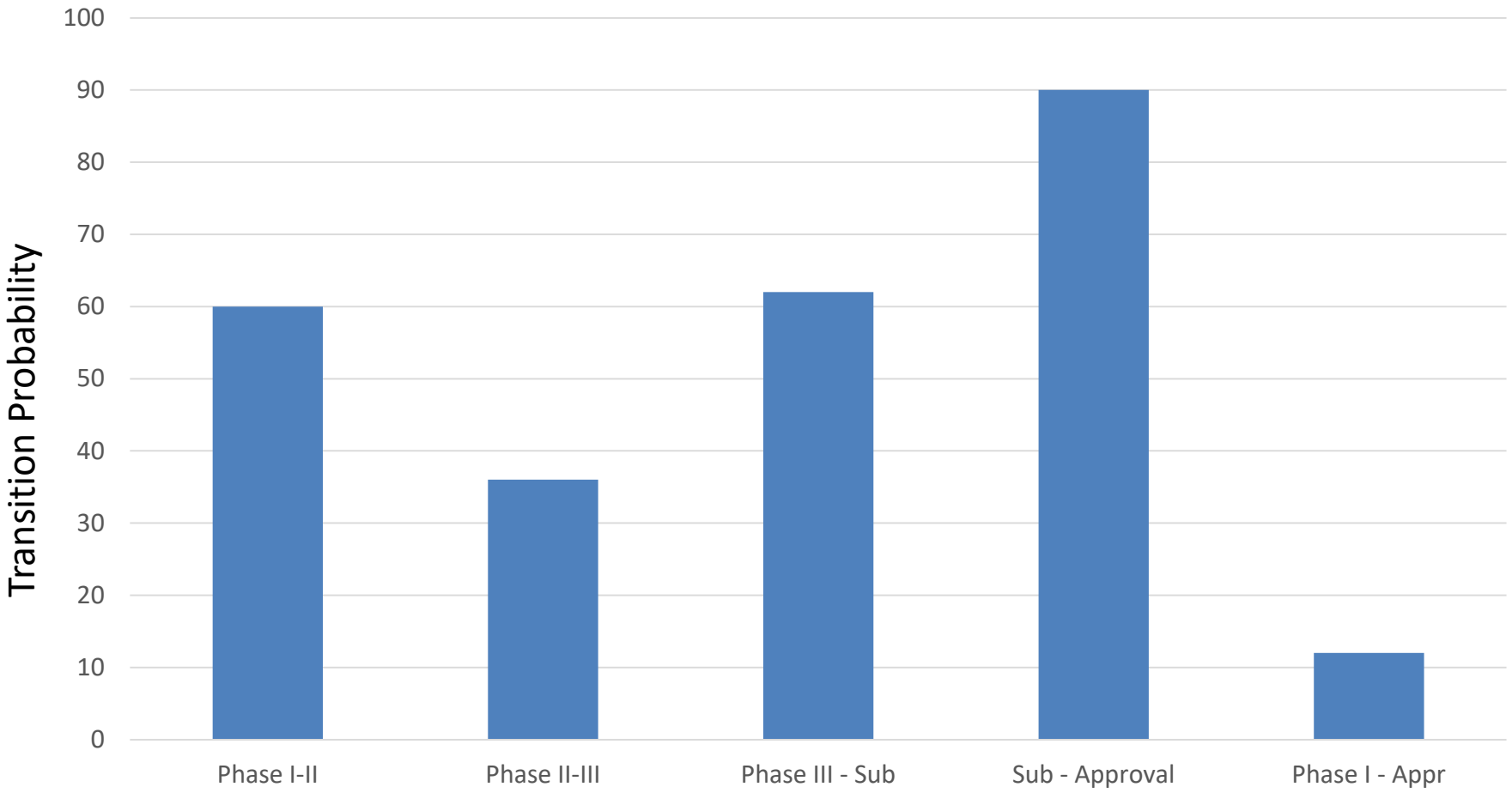
What is Driving Upward Spiraling Costs?

Estimated cost per phase, all therapeutic areas

Phase of Development	Median Cost (millions)	Mean Cycle Length (wks)
Phase I	$ 17	33
Phase II	$ 45	38
Phase III	$ 200	45

High rates of attrition

Estimated Attrition by Phases: All Therapeutic Classes



J DiMasi, et al, J Health Econ (2016) 47:20 - 33

Evolution of Phase I Trials

- More rapid dose escalations
  - Less dose levels tested
- Less schedules tested
- More intense PK/PD modeling
- Determination of BED in addition to MTD
- Additional endpoints
  - SD as valid sign of activity
  - Functional imaging
- Early integration of combinations
- Expansion cohorts in Phase I

Will Expansion Cohorts Help?

Lessons from Pembrolizumab – KN 001

- FIH study classic 3 +3 cohort design
  - 3 dose-levels, 2 schedules, 32 pts enrolled

- Multiple study amendments (parts B, C, D, E, F) examining multiple dose-schedules, effect of PDL-1 expression, and efficacy in melanoma and NSCLC
  - Opened March 2011, estimated closure July 2018
  - Total enrollment 1260 patients
  - Cohorts for melanoma and NSCLC served as a basis for accelerated approval in these indications

- Regulatory Backlash
  - FDA “never allow such a trial again..”
  - Expansion cohorts are now limited by FDA to 40 patients

Patnaik, et al, Clin Can cer Res, 21(19), 2015; Clin Trials Gov: NCT01295827

Feedback from EU Authorities on Cohort Expansion Designs

- **Safety Concerns**

  Complexity of the study might lead to a lack of oversight

  "…too many arms with different treatments administered…"

  "…heterogeneous patient population with different tumor types…"

  "…no guarantee of consistency of data obtained…"

  "….no Independent Data Monitoring Board in place…"

  "… how to manage communication between sites…"

- **Scientific Rationale**

  "…no scientific rationale to combine multiple expansions in one study…"

  "…each arm should be a separate study as there is no comparison between arms…"

  "…sample size too small to draw meaningful statistical conclusion…"

Expansion Cohorts

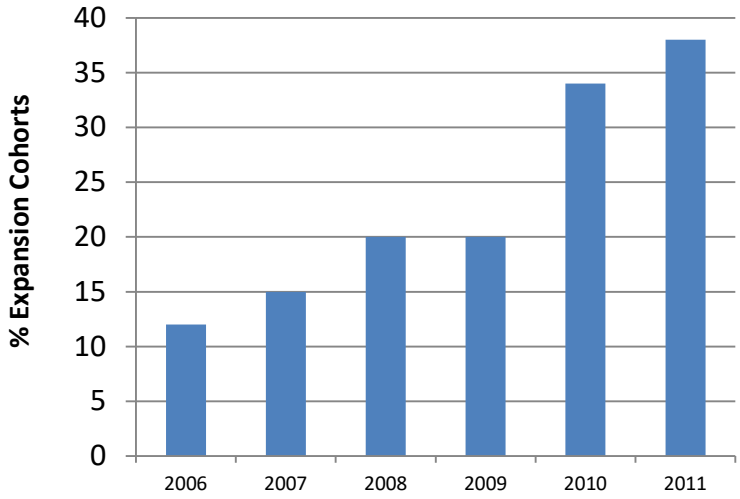
611 published unique phase I trials from 2006 through 2011

Overall 24% contained expansion cohorts but increasing by year

- **22 pts $_{(ave)}$ in dose-escalation**
- **17 pts $_{(ave)}$ in cohort expansion**

Objectives of cohorts

- **Safety (80%)**
  - **New toxicities identified (54%)**
  - **with changes to RP2D (13%)**
- **Efficacy (45%)**
- **Pharmacokinetics (28%)**
- **Pharmacodynamics (23%)**



Courtesy of Dr. C. Slapak; Manji, et al, JCO 31:4260 (2013)

Evolution of Phase II Trials

- **Innovative methodologies**
  - **Adative designs**
  - **Biomarker-directed designs**
- **Testing of multiple agents with shared control arm**
- **Translational studies included**
- **Exploration of molecular hypothesis in addition to clinical activity**
- **Evaluation of molecular endpoints**
- **Phase II is an important arena to study**
  - **Exposure/efficacy relationship**
  - **Comparison of doses and schedules**

Risks if Dose/Schedule is Suboptimal and this is Detected Late

- **<u>If registration trial has already started:</u>**
  - **Start over or increase sample size with subgroup comparisons**
- **<u>If registration trial is completed and negative but could be positive with improved dose/schedule:</u>**
  - **Ethical, operational, and management issues with encore trial**
- **<u>If registration trial is completed and shows small incremental improvement that could be larger with improved dose/schedule:</u>**
  - **Encore trial usually impossible**
  - **Sponsor likely has to live with smaller clinical benefit assigned by professional societies and lower market uptake**

Conclusions

- **The strategy to determine the best dose, schedule, formulation, exposure, route-of-administration (DSFER) needs to be tailored to the type of compound to be developed**
- **In the ideal situation DSFER optimization should occur in early phase**
- **Yet, early clinical studies may only result in a feasible and efficacious DSFER**
- **The risk of a suboptimal DSFER is mitigated by a holistic preclinical/clinical team approach**
  - **Goal is to develop a comprehensive understanding of DSFER as early as possible**
- **If DSFER adjustments are needed in later drug development (for efficacy or patient comfort reasons) bridging studies may provide a solution**

Points to Consider for Bridging Studies

- **What is the best trial design for a bridging study?**
- **What are adequate Primary and Secondary Endpoints of the bridging study?**
  - **If registration study was Phase III with OS as PEP:**
    - **Is a small study with RR or PFS as PEP acceptable?**
  - **If registration study was Phase III with PFS as PEP:**
    - **Is a smaller study with RR as PEP acceptable?**
  - **If registration study was less than a Phase III?**
- **Would the label need to recommend**
  - **both dose/schedules separately?**
  - **to replace the initial dose/schedule?**
- **What role do differences in safety play for the introduction of the dose-schedule with higher efficacy?**
- **Can we use the same approach**
  - **for immuno-oncologic agents?**
  - **for combinations?**