US CHINESE ANTI-CANCER ASSOCIATION
美中抗癌协会

东方临床肿瘤研究中心
East Clinical Center of Oncology

CSCO
Chinese Society of Clinical Oncology
Beijing Xisike Clinical Oncology Research Foundation

Early Clinical Development of Oncology Medicines - An Industry Perspective

Shanghai, China

Dec. 07, 2018

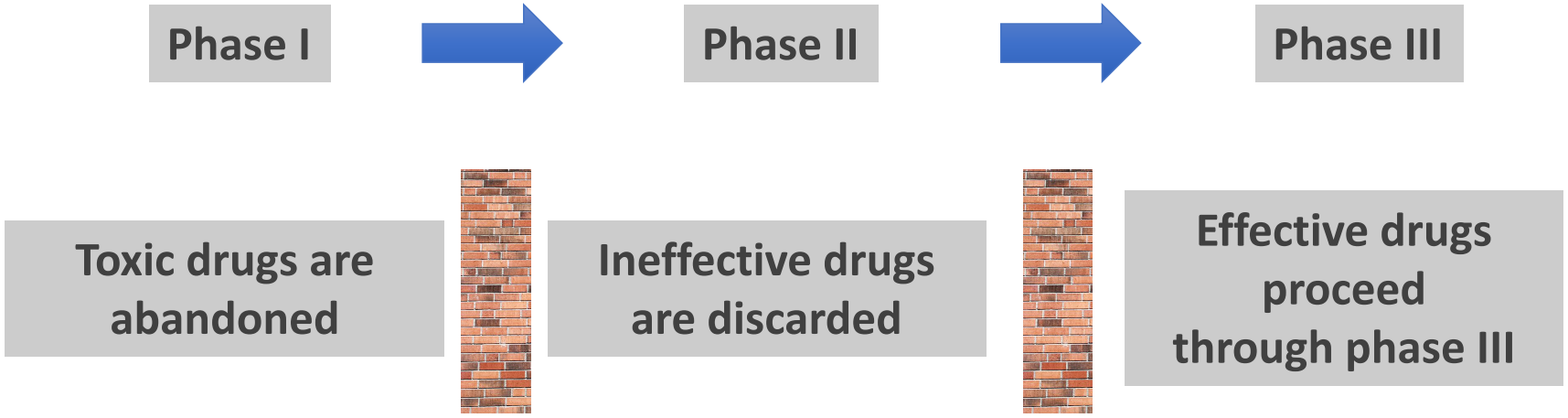
Li Yan, MD PhD

Brii Biosciences, Limited

US Chinese Anti-Cancer Association

Cancer Drug Development – The Old Paradigm

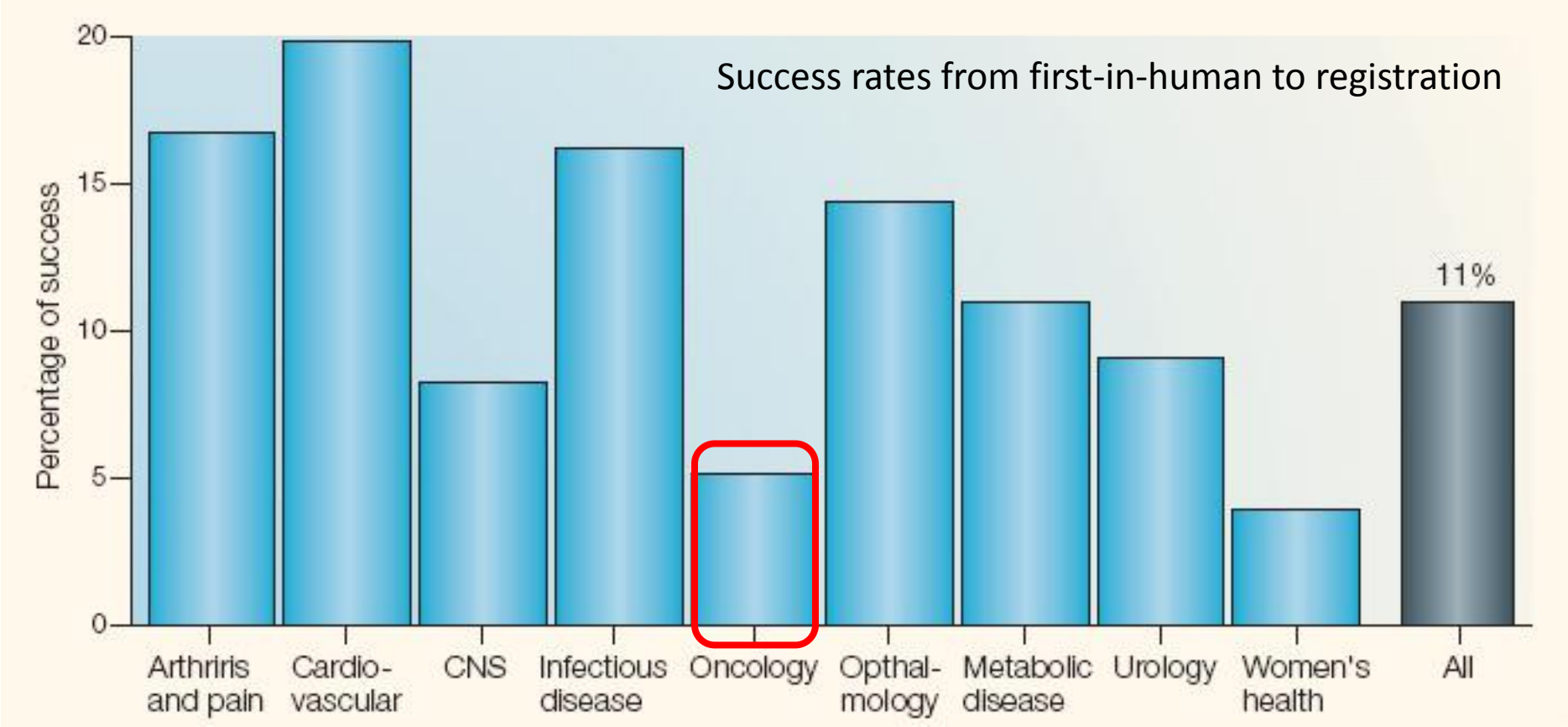
Linear, step-wise drug development



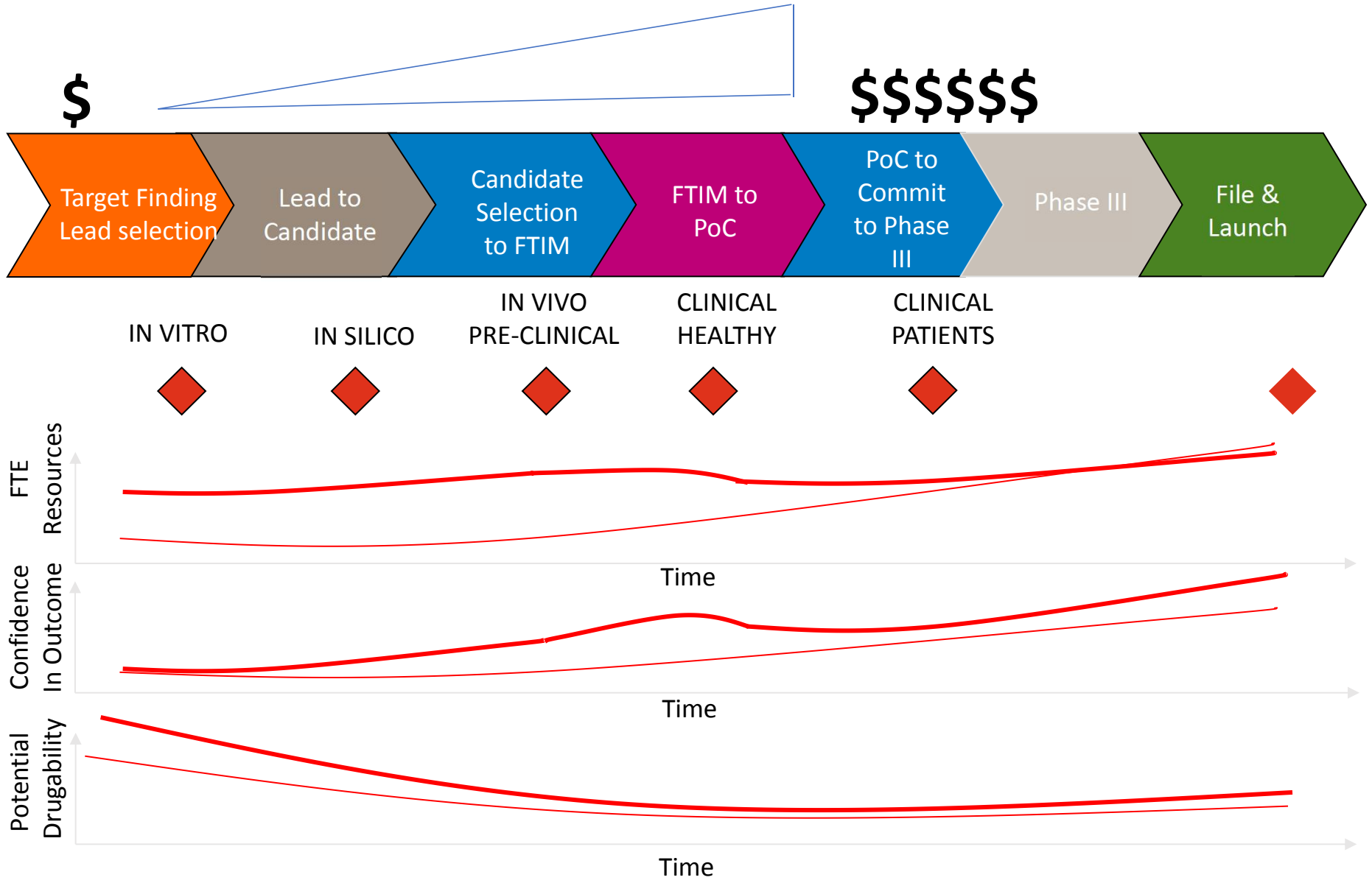
- Large and Costly phase III trials
- Ineffective drugs for patients
- Late phase drug attrition

Cancer Drug Development – The Old Paradigm

Oncology Drug Attrition Rate: **~95%** of drugs entered clinical trials ***FAIL***



Kola and Landis, Nat Reviews Drug Discovery 2004


$
$$$$$$
Target Finding Lead selection
Lead to Candidate
Candidate Selection to FTIM
FTIM to PoC
PoC to Commit to Phase III
Phase III
File & Launch
IN VITRO
IN SILICO
IN VIVO PRE-CLINICAL
CLINICAL HEALTHY
CLINICAL PATIENTS
FTE Resources
Time
Confidence In Outcome
Time
Potential Drugability
Time

Attrition: a multifactor reason for failure

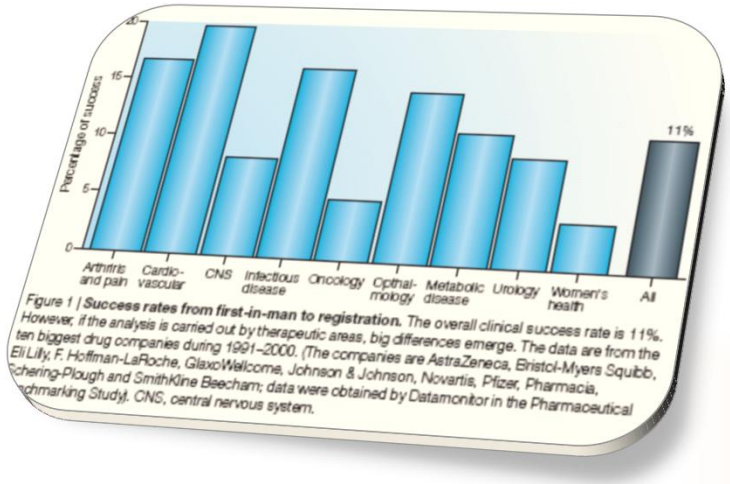
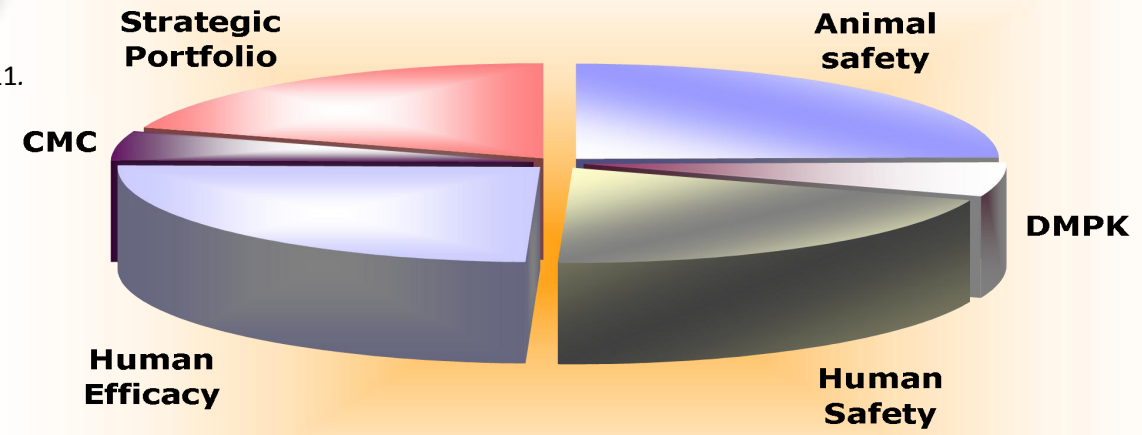


Figure 1 | **Success rates from first-in-man to registration.** The overall clinical success rate is 11%. However, if the analysis is carried out by therapeutic areas, big differences emerge. The data are from the ten biggest drug companies during 1991–2000. (The companies are AstraZeneca, Bristol-Myers Squibb, Eli Lilly, F. Hoffman-LaRoche, GlaxoWellcome, Johnson & Johnson, Novartis, Pfizer, Pharmacia, Schering-Plough and SmithKline Beecham; data were obtained by Datamonitor in the Pharmaceutical Benchmarking Study). CNS, central nervous system.

Nature Reviews Drug Discovery, Volume 3, August 2004, 711.

The R&D cost of developing a new medicine is

$2, 600,000,000



$$$$$$

$$

Cancer Drug Development – **New Paradigm**

Focused accelerated drug development

Phase I / II → **Phase III**

- Toxic AND ineffective drugs are abandoned in phase I/IIa
- Develop most efficient ways to identify the good drugs

Effective drugs proceed through phase III aided by BMx

- **Focused phase III trials**
- **Effective drugs in enriched patient population**
- **Avoid late phase drug attrition**

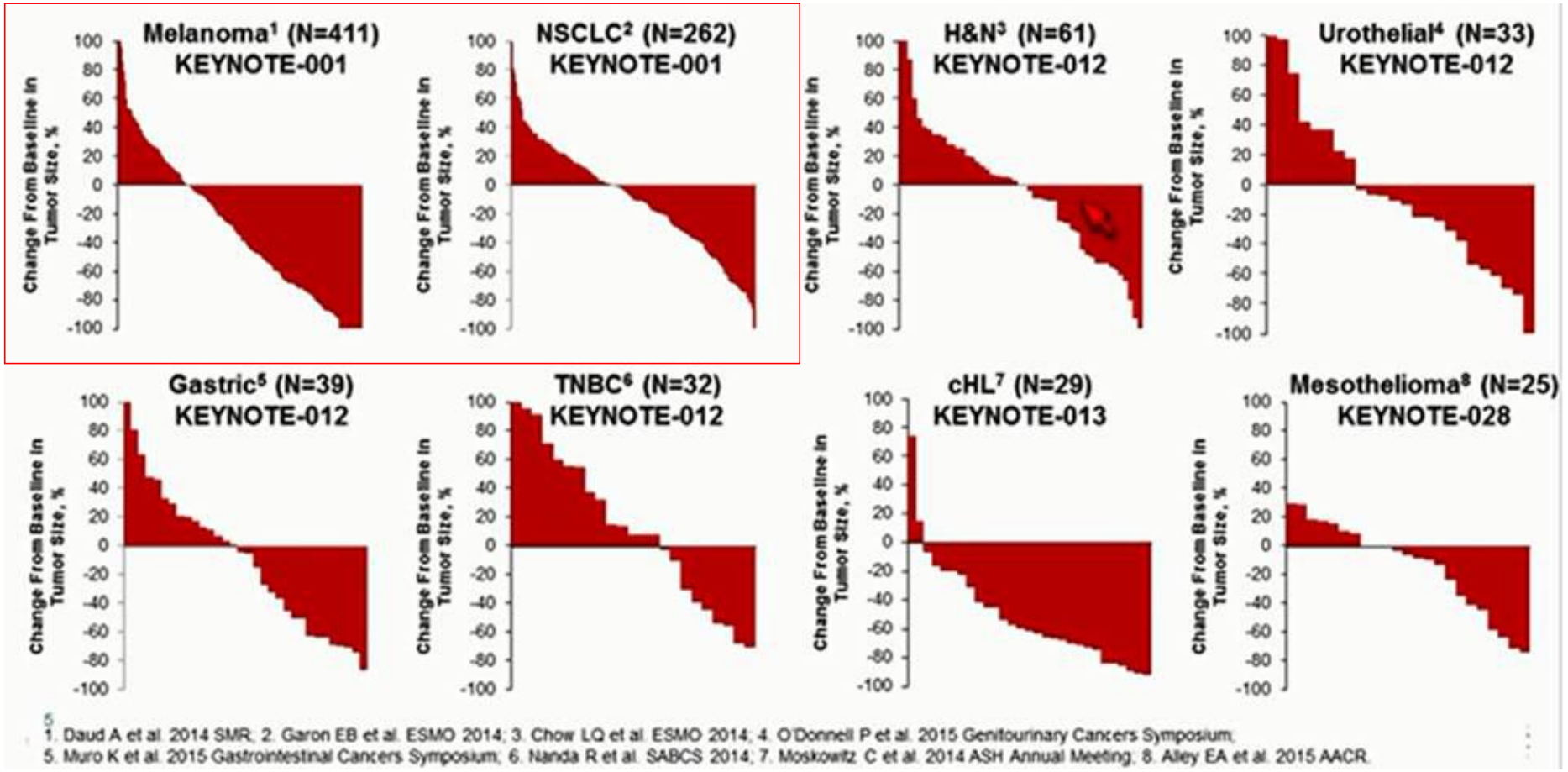
Timelines for Drug Development

- Traditional Approach
  - Phase I to determine recommended phase 2 dose (1.8 years), followed by Phase II to assess efficacy within an indication (2.5 years), followed by Phase III to demonstrate efficacy (2.4 years)
  - Average time from first in human to approval is 9.3 years
- 2 Ways to Accelerate Timelines
  - Utilize Accelerated Approval Registration Path
    - Keynote 001 (First in human) initiated April 2011
    - Keytruda first PD-1 approved in U.S. on Sept 2014 for patients with advanced or unresectable melanoma
  - Leapfrog Phase III Clinical Study Development
    - Checkmate 141: 2L Phase III in R/M HNSCC
    - Javelin 100: Phase III in Locally Advanced HNSCC

Progressive Regulatory Agencies – FDA & NMPA

- Breakthrough designation guidance
  - To qualify for the designation, a drug must
    - Treat a serious or life-threatening disease or condition and
    - Provide preliminary clinical evidence indicating a potential for substantial improvement over existing therapies on one or more clinically significant endpoints
- Breakthrough designation advantage
  - Provides timely advice and interactive communication regarding the development of the drug to ensure that the development program to gather the data necessary for approval is as efficient as practicable
  - Paves the way for accelerated approval application

Early Phase Cancer Drug Development – **Immunotherapy (Case Study of Pembrolizumab Keytruda®)**

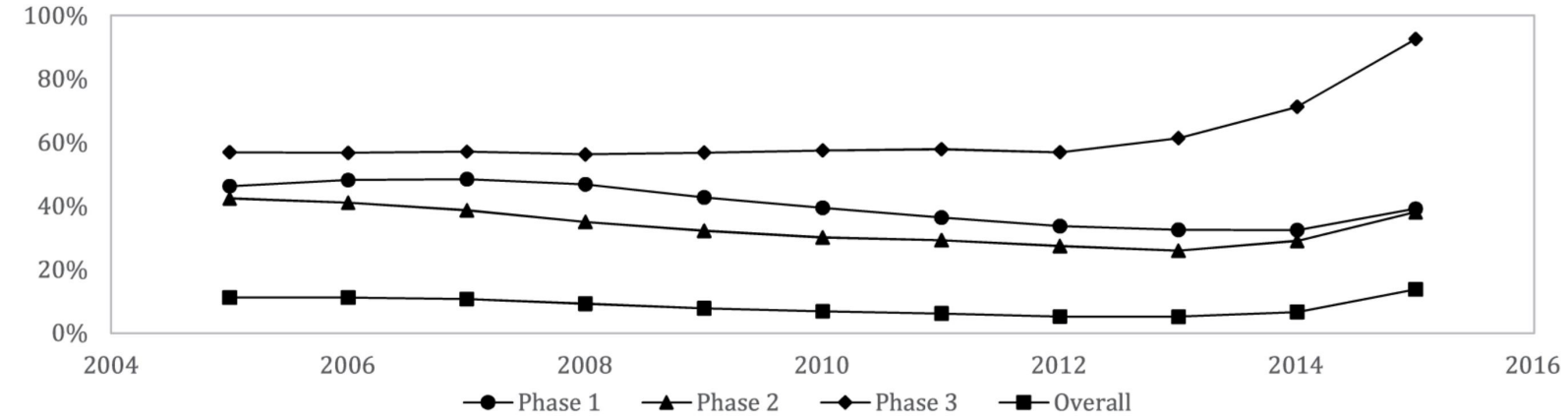


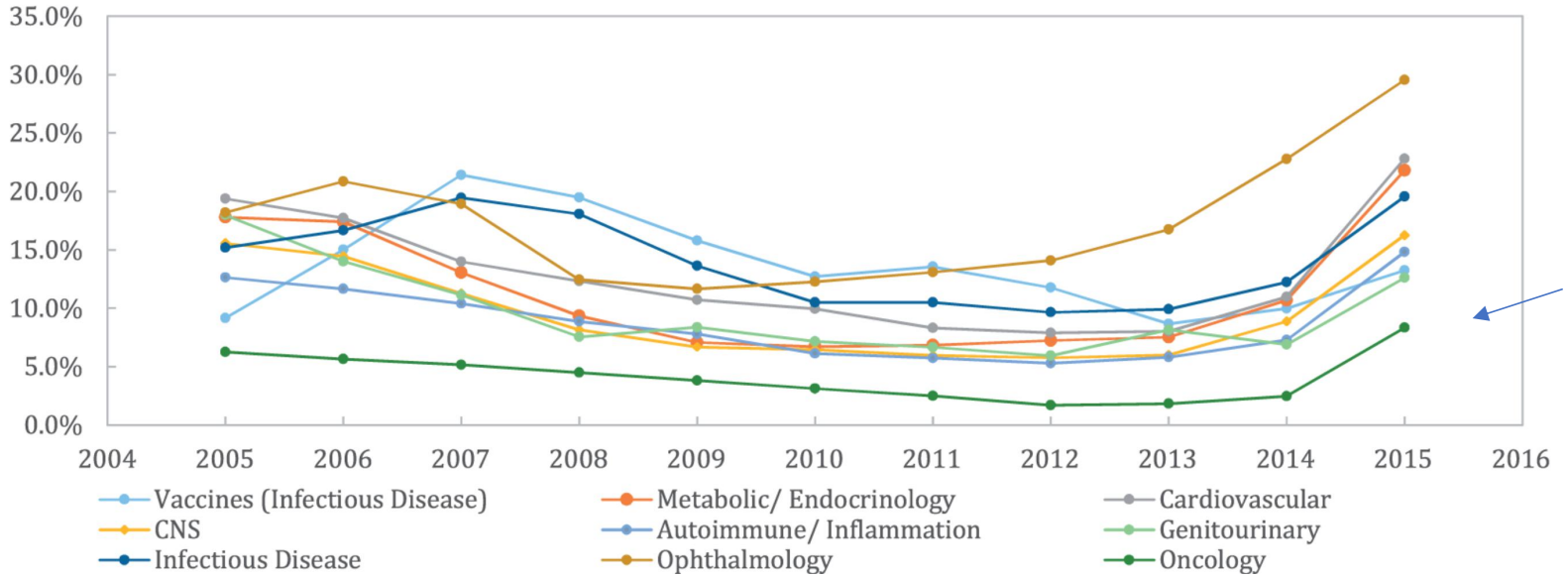
~1300 patients treated in a Phase 1 study with activity seen across an array of tumor types; Foundation for 2 indication approvals – melanoma and NSCLC

Accelerated Approval

- Accelerated Approval
  - Allows earlier approval of drugs and biologics based on a surrogate clinical endpoint for serious or life-threatening diseases that provide a meaningful therapeutic benefit over existing treatments
  - Clinical endpoint is often times superior ORR compared to historical control in an area of high unmet need
- Keytruda First to US Market
  - Keytruda received accelerated approved based on 173 patients in Keynote 001 in Sept 2014 (safety profile established in 411 patients)
  - Keytruda subsequently received accelerated approval in NSCLC, HNSCC, MSI High cancers, Gastric cancer…
  - Accelerated approval requires a confirmatory randomized study for full approval

There is still much to improve





Oncology

Estimation of clinical trial success rates and related parameters Chi Heem Wong Kien Wei Siah Andrew W Lo. *Biostatistics*, kxx069, https://doi.org/10.1093/biostatistics/kxx069 31 January 2018