Conflict of Interest

Joseph C. Cappelleri and Jinma Ren are employees and stockholders of Pfizer Inc.

This presentation reflects their personal views and not the views of Pfizer or any other organization.

Necessity of Approving Drugs Based on Single-Arm Trials

- to ensure timely access to highly specialized products

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Why to use a single-arm trial (SAT)?

- **RCT is not always available**
  - Feasibility
    - Small sample in rare disease
    - Faster recruitment
  - Ethical reasons
    - Parachute study
- **Although RCT is a gold standard, SAT might be sufficient sometimes**
  - Dramatic clinical benefit
    - Large magnitude of difference versus standard of care (e.g., any new drug for human rabies. Once a rabies infection is established, there's no effective treatment right now.)
  - Availability of robust data for historical comparison
    - Use of real-world data (e.g., historical cohort, registry data)


HULTON/GETTY

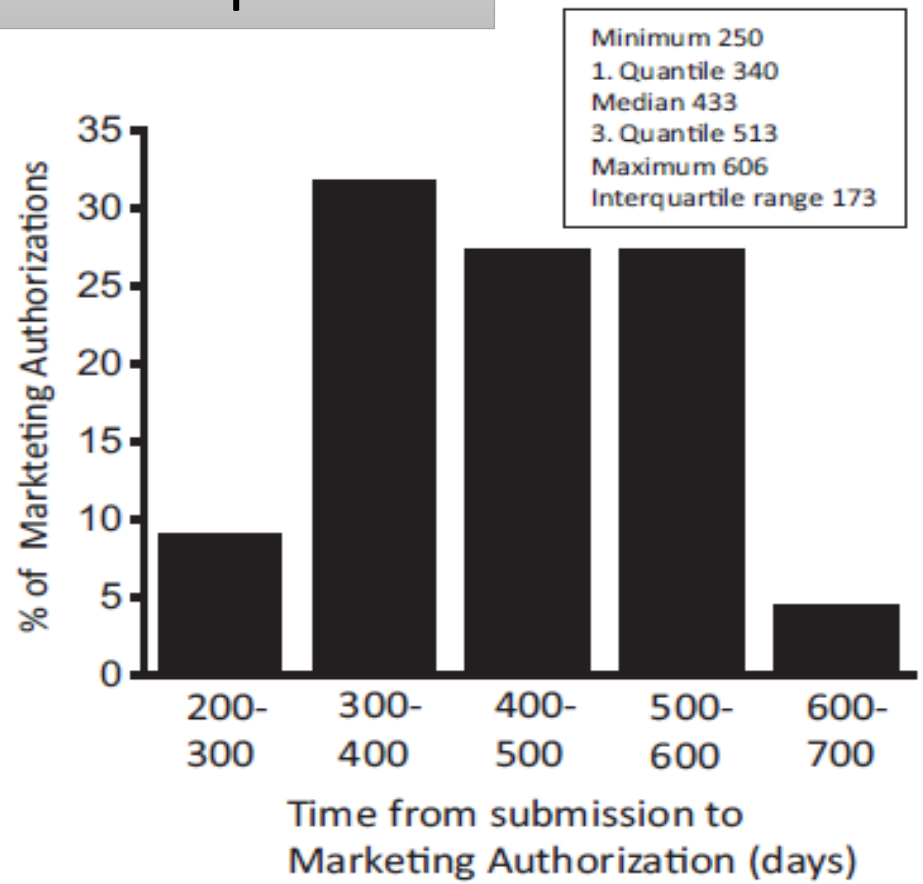
Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

Source: Smith and Pell 2003

Procedure for SAT approval needs to be improved

The current procedure time is a little longer than expected

- 22 European approvals of anticancer products based on SATs (2010-2019)
  - Median time of procedure time was **433 days** for SATs
- 96 applications for new anticancer drugs in Europe (2010-2019)
  - Average procedure time was 370 days, (200–215 days when accelerated assessment was granted)



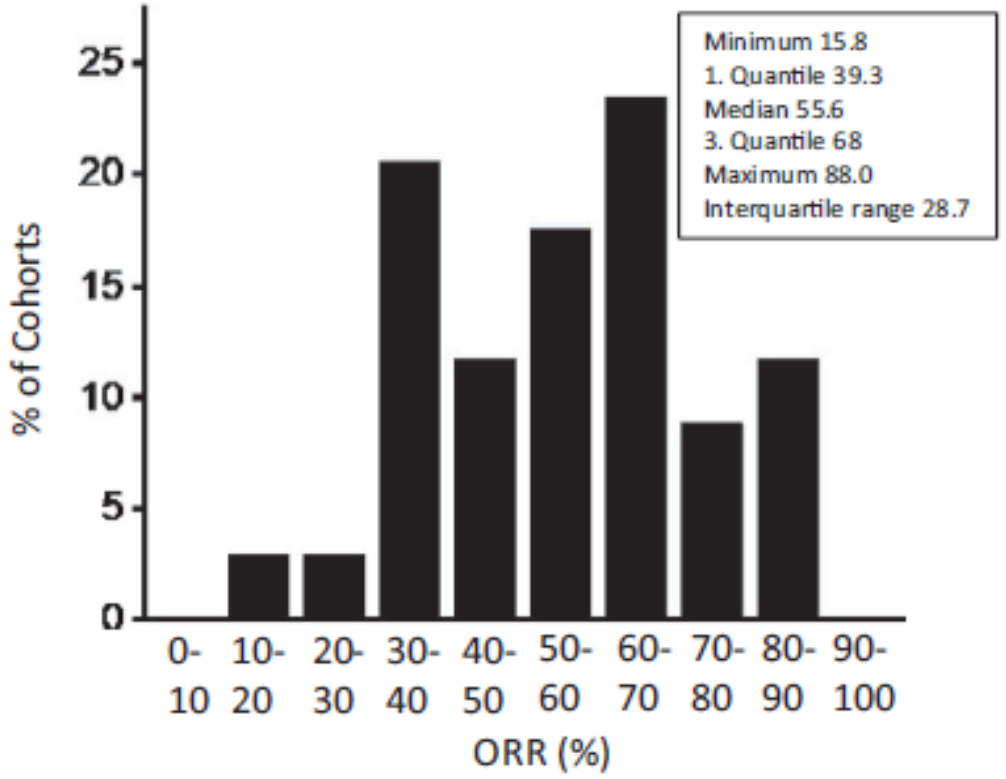
Source: Tenhunen et al. 2020; Garsen, Steenhof, and Zwiers 2021

SAT has usually a short follow-up time

Most of SATs use overall response rate (ORR) as primary endpoint because time-to-event endpoints require a longer follow-up time

22 European approvals of anticancer products based on SATs (2010-2019)

- 19 out of 22 studies defined ORR as the primary outcome
  - Median ORR = 55.6% (from 34 cohorts)
- Secondary efficacy end points
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - Overall survival (OS)



Source: Tenhunen et al. 2020

Acceptance of SAT with external control

A large increase in submissions to the EMA and FDA using external controls in recent years

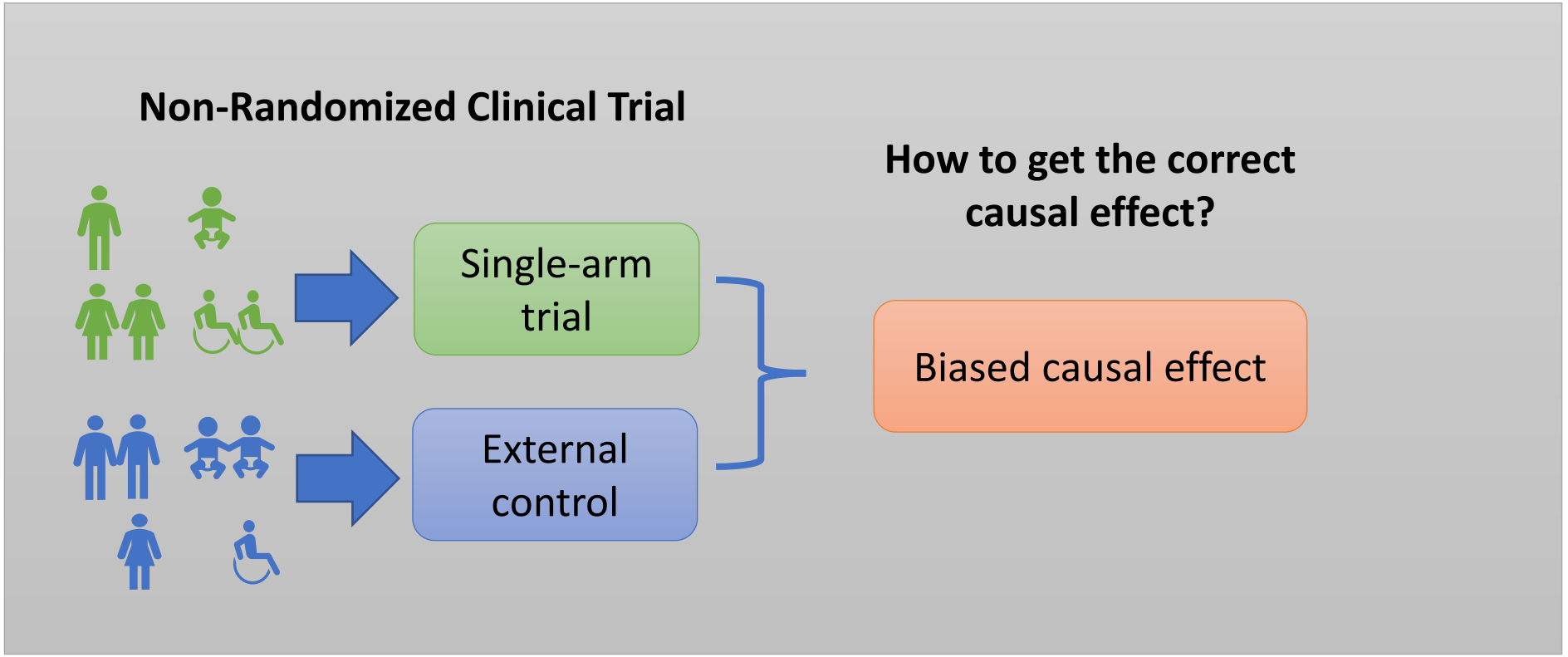
Item	Criterion for inclusion
Evidence base	Primary sources(s) of evidence came from uncontrolled trial(s), with or without an explicit comparison against external control(s).
Indication	The indication was within one of following broad therapeutic areas: • Stem cell transplants • Haematological cancers • Other haematological conditions • Rare metabolic diseases
Year	Submissions to FDA or EMA between 2005 to 2017

EMA, European Medicines Agency; FDA, Food and Drug Administration

	Single arm	Multi-arm uncontrolled	RCT	Other	Total (n)	Total (%)
Phase I	1	0	0	3	**4**	**4**
Phase I/II	3	2	0	2	**7**	**7**
Phase II	50	8	0	0	**58**	**60**
Phase II/III	1	2	0	0	**3**	**3**
Phase III	6	4	2	2	**14**	**15**
Other	3	0	0	7	**10**	**10**
N/R	0	0	0	0	**0**	**0**
Total (n)	**64**	**16**	**2**	**14**	**96**	**100**
Total (%)	**67**	**17**	**2**	**15**	**100**	

Source: Goring et al. 2019

Appropriate methods are needed to handle biases when using external control(s) for a SAT



Biases could be induced by:

- **Baseline characteristics** are unbalanced, such as age, gender
- Complex longitudinal data with **time-varying covariates**
  - Smoking is a confounder for the treatment effect, but participants might change their smoking behaviors during the follow-up time

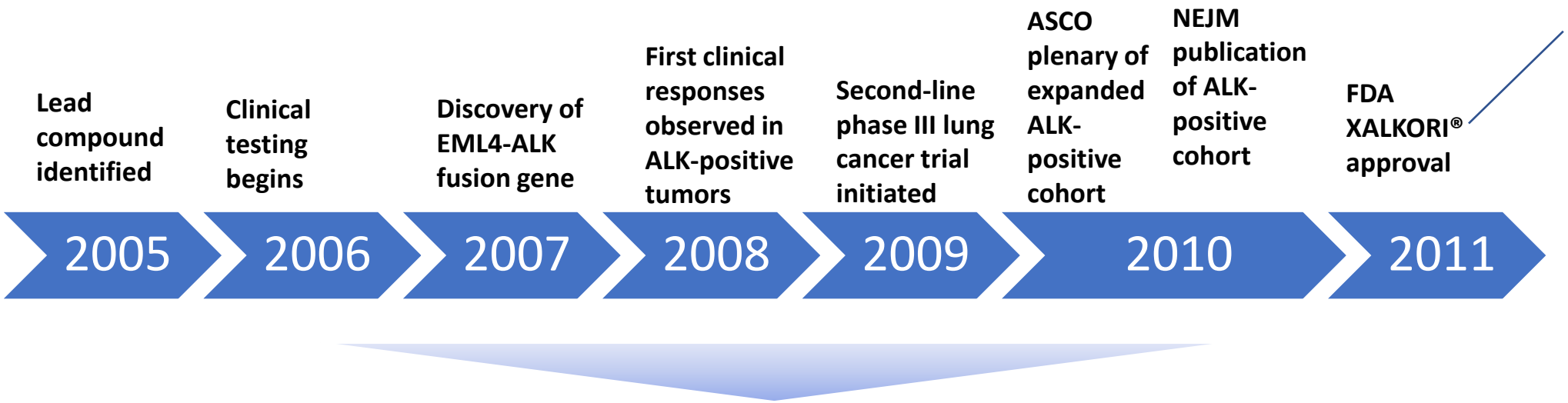
Common approaches for borrowing external controls

	Data type	Methods	
Frequentist	**Individual data**	**G-computation**	One of Robins' g methods
		Weighting (propensity score-based)	• Inverse probability of treatment weighting (IPTW) • Overlap weighting (OW) • Standardized mortality/morbidity ratio (SMR)
		Matching/stratification	• Variable matching • Propensity score matching • Propensity score stratification
	Summary data	Network meta-analysis (NMA), simulated treatment outcome (STC), or matching-adjusted indirect comparison (MAIC)	
Mostly Bayesian	**Individual/summary data**	NMA, Meta-analytic combined (MAC), meta-analytic predictive (MAP)	

Source: Naimi, Cole, and Kennedy 2017; Chatton et al. 2020; Ghadessi et al. 2020

Crizotinib case: timely market access

- Timeline from crizotinib compound identification and target discovery to clinical results and accelerated approval in the U.S.



Rapid timeline from compound identification, target discovery, and clinical results

FDA accelerated approval was primarily based on a single-arm Phase II trial (the first 136 patients enrolled as of Feb 2011)

FDA regular approval was based on a RCT Phase III trial in Nov 2013

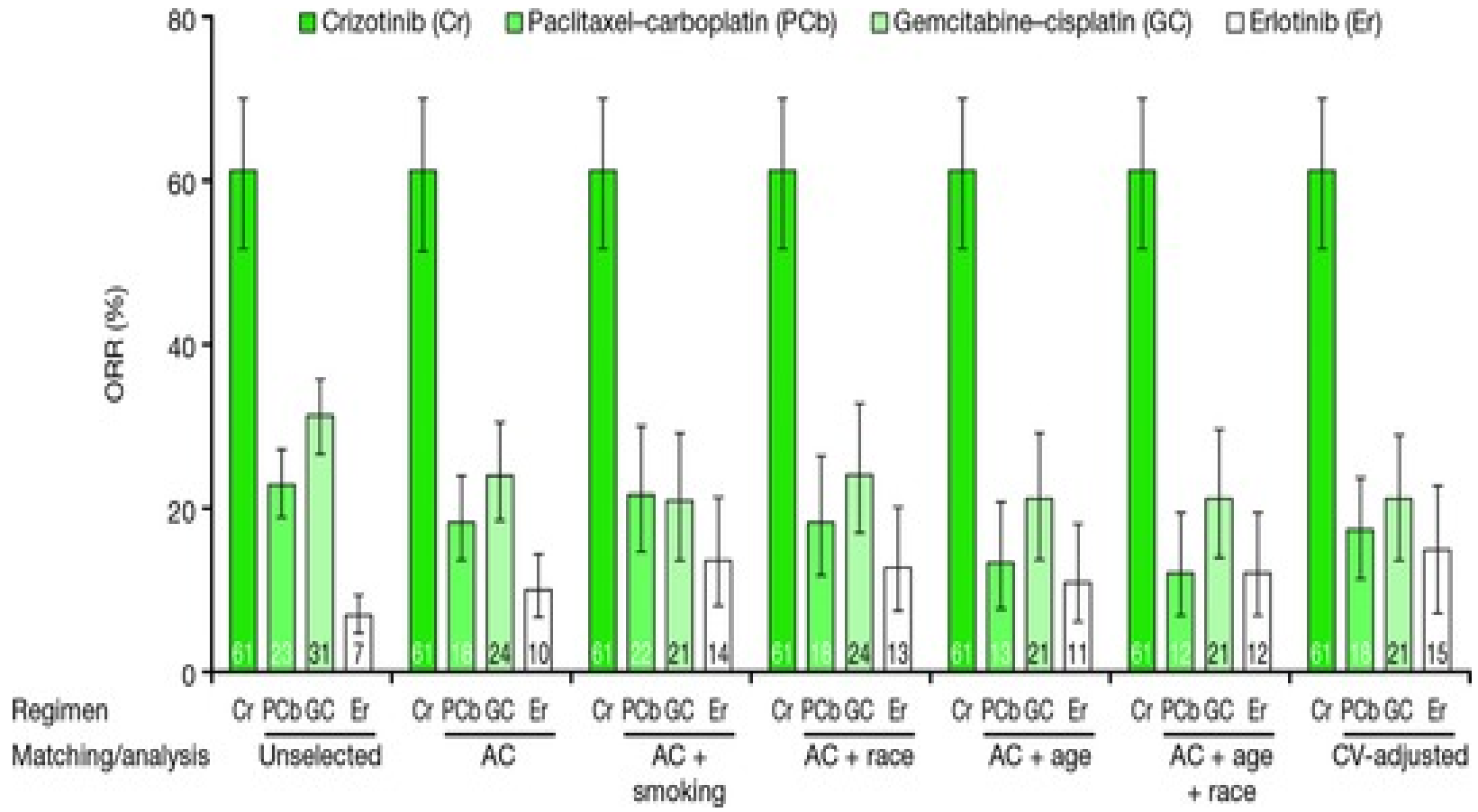
ALK, anaplastic lymphoma kinase; ASCO, American Society of Clinical Oncology; EML4, echinoderm microtubule-associated protein-like 4; FDA, Food and Drug Administration; NEJM, New England Journal of Medicine.

Source: Kwak et al. 2010; Bang et al. 2010; Kazandjian et al. 2014

Crizotinib case: ORR= 53-61%

- Single-arm trials of crizotinib
  - Phase I (study 1001): 149 pts
    - ORR = 61%
  - Phase II (study 1005): 261 pts
    - ORR = 53%

- Control arms
  - Three Pfizer-sponsored phase III studies in patients with non-small cell lung cancer (NSCLC)
  - Covariate-adjusted ORR
    - Study 1001: 15-21%
    - Study 1005: 14-21%

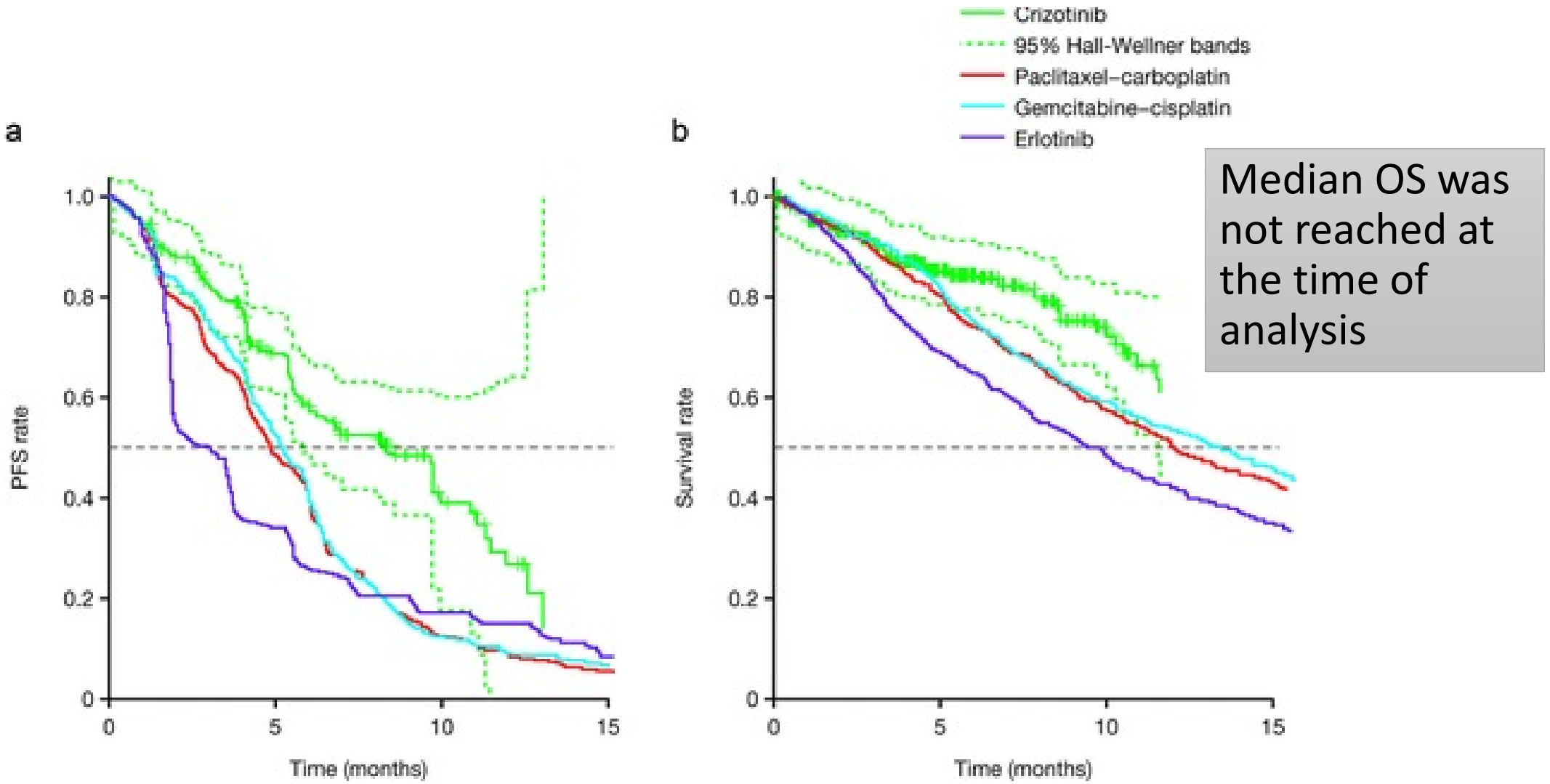


Note:

- Figure was based on Phase I (study 1001), with error bars as 95% confidence intervals
- unselected, patients with unselected NSCLC; AC, adenocarcinoma; CV-adjusted, covariate-adjusted analysis based on histology, race, smoking classification, age, gender, disease stage, Eastern Cooperative Oncology Group (ECOG) performance status, and weight

Source: Selaru et al. 2016

Crizotinib case: median PFS=10 months



Median OS was not reached at the time of analysis

Source: Selaru et al. 2016

Note: results on crizotinib were based on Phase II single-arm study 1005

Crizotinib case: summary of single-arm trials

- They were the **first studies** of any molecularly targeted agents in patients with NSCLC prospectively selected for *ALK* gene rearrangement.
- They were also notable because of the **large clinical benefits** observed, further supported by retrospective analyses.
- FDA **accelerated approval** was based on single-arm trials (Phase I & II), then regular approval was based on a Randomized Controlled Clinical Trial (Phase III).

Source: Selaru et al. 2016

Concerns and solutions for SAT

Concerns	Possible Solutions
Potential biases	• Build comparable external controls with appropriate statistical methods
Efficacy: not meet substantial clinical benefit thresholds	• Conduct a confirmatory post-marketing study
Validity of surrogates: not truly established (e.g., ORR vs PFS/OS)	• Add secondary efficacy endpoints • Conduct a confirmatory post-marketing study

Overall, it is necessary to approve drugs based on SATs in order to ensure timely access to highly specific treatments for patients with an unmet need

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