The Question of Clinical Trials

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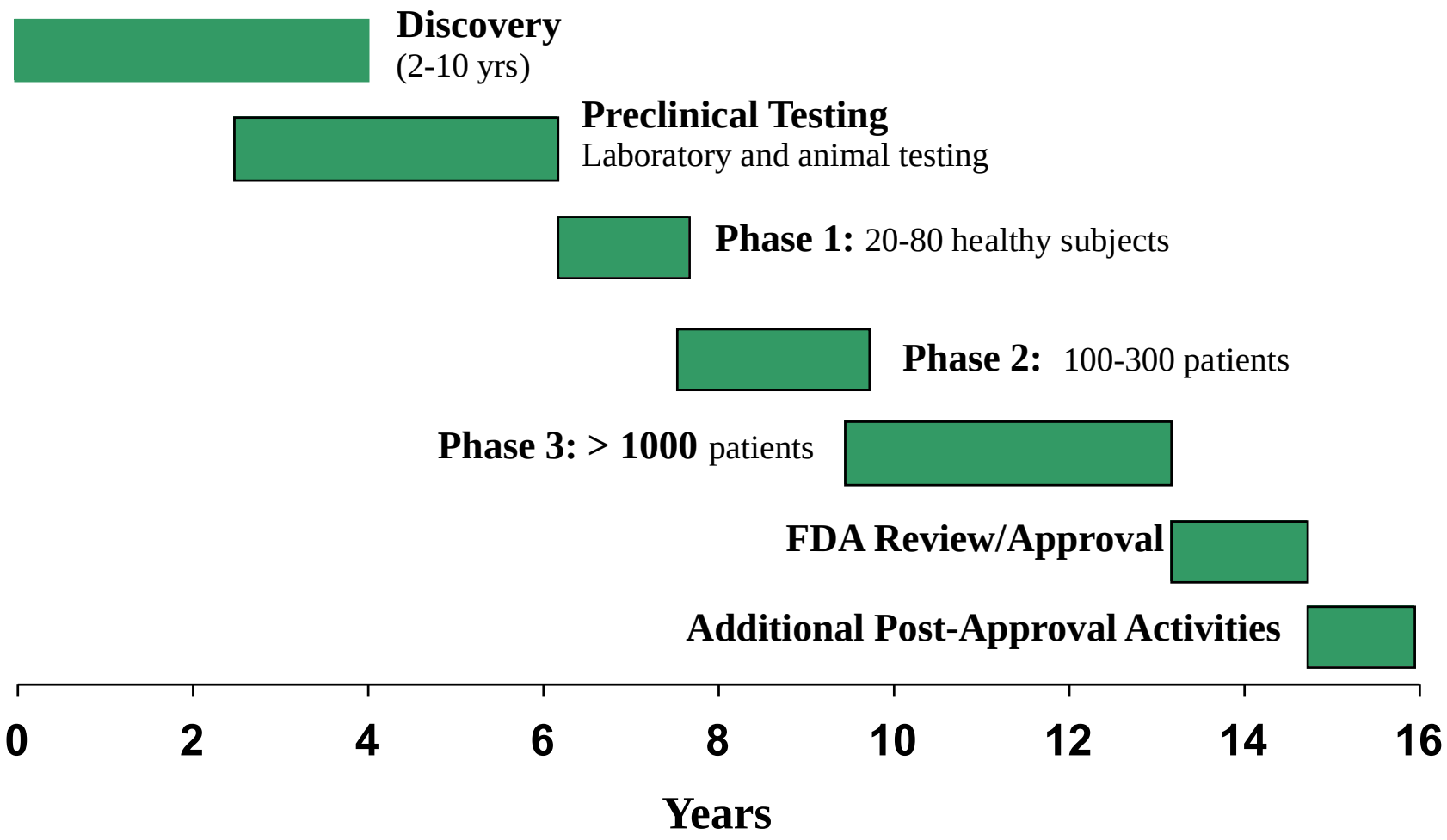
Case – Patient J

- Patient J was first diagnosed with metastatic NSCLC in Jan 2013
- Molecular testing demonstrated an ALK rearrangement
- He was started on first-line crizotinib and responded for about 5 months
- He developed worsening disease, and we recommended the phase 1 study of ceritinib
- He refused to participate in a phase 1 study
- He opted for standard platinum/pemetrexed chemotherapy, followed by pemetrexed

Case – Patient J

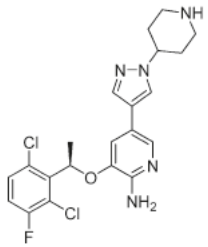
- He responded to chemotherapy for ~5 months
- When his disease progressed, we recommended the phase 1 study of alectinib
- He again refused to participate in a phase 1 study
- Instead he opted for a phase 3 study of ceritinib
- He was randomized to the control docetaxel arm
- He received 2 cycles of docetaxel and then discontinued due to toxicity
- When he progressed, he “crossed over” to the ceritinib arm
- He responded to ceritinib and has now been on for 3.5 years

Traditional Drug Discovery and Development

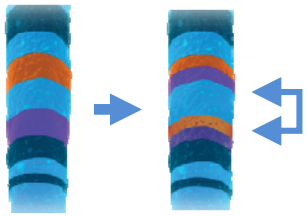


Source: Center for the Study of Drug Development, Tufts University, 1995

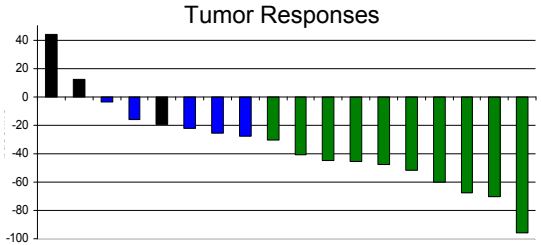
Crizotinib: From Target Discovery to FDA Approval in 4 Years



2004 Synthesis of crizotinib at Pfizer



8/2007 ALK reported in lung cancer



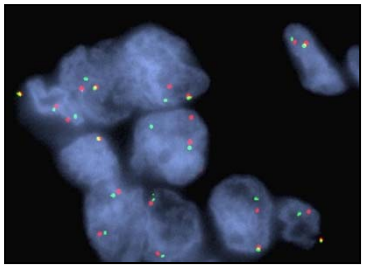
5/2009 First report of crizotinib activity

8/2011 FDA approval

2004 2007 2008 2009 2010 2011 2012

2006 Phase 1 trial initiated

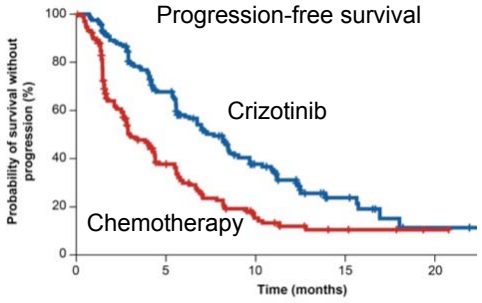
11/2007 Diagnostic test developed at MGH



12/2007 First ALK+ patient treated with crizotinib

2010 Phase 2 and Phase 3 trials initiated

9/2012 Phase 3 results



Clinical Trials

- **Definition: a prospectively planned experiment for the purpose of evaluating potentially beneficial therapies or treatments**
- **Clinical trials are conducted under *as many controlled conditions as possible* so that they provide definitive answers to pre-determined, well-defined questions**
- **Clinical trials are the most definitive method to establish the efficacy of a new treatment**
- **Clinical trials are also needed to determine the type/incidence of side effects and complications**

Adapted from P. LoRusso, 2017

Phase 1 Clinical Trials

- First-in-man studies
- Primary objective is typically to determine an acceptable range of dose(s) and schedule(s) for a new drug based on observed toxicities
- Secondary objectives usually include pharmacokinetics (what the body does to the drug), pharmacodynamics (what the drug does to the body), and antitumor activity
- Most phase 1 studies seek to establish the maximum tolerated dose and the recommended phase 2 dose

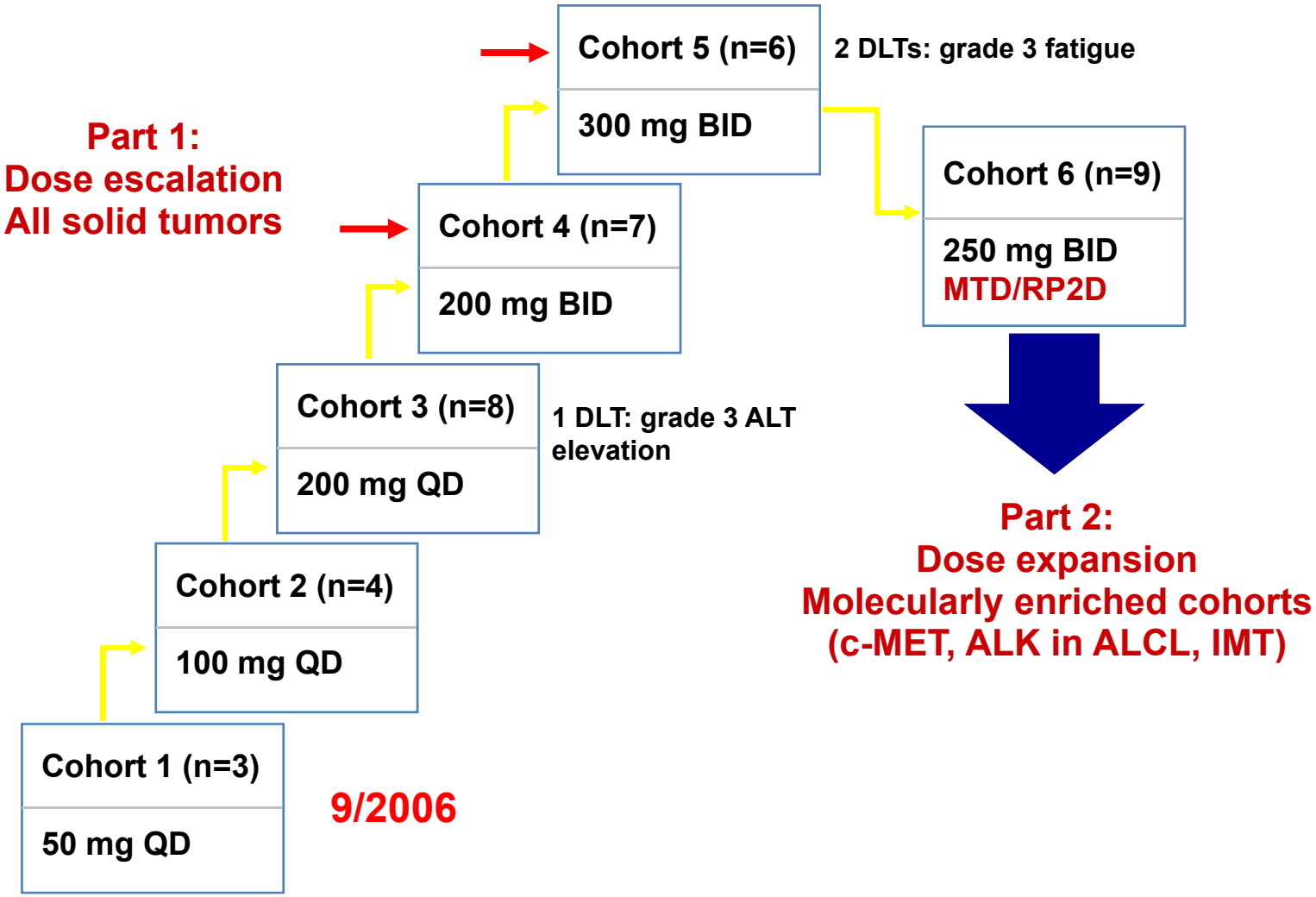
Adapted from P. LoRusso, 2017

Dose Escalation Schemes – One Example

1. Enter 3 patients at a given dose
2. If no toxicity, go to next dosage and repeat Step 1
3. a. If 1 patient has serious toxicity, add 3 more patients at that does (go to Step 4)
   b. If 1/6 have serious toxicity, consider MTD
4. a. If 2 or more of 6 patients have toxicity, drop down 1 dose to confirm safety
   b. If 1 of 6 has toxicity, increase dose and go back to step 1

P. LoRusso, 2017

Study Design of Phase 1 Trial of Crizotinib



Kwak et al. NEJM 2010;363:1693-1703

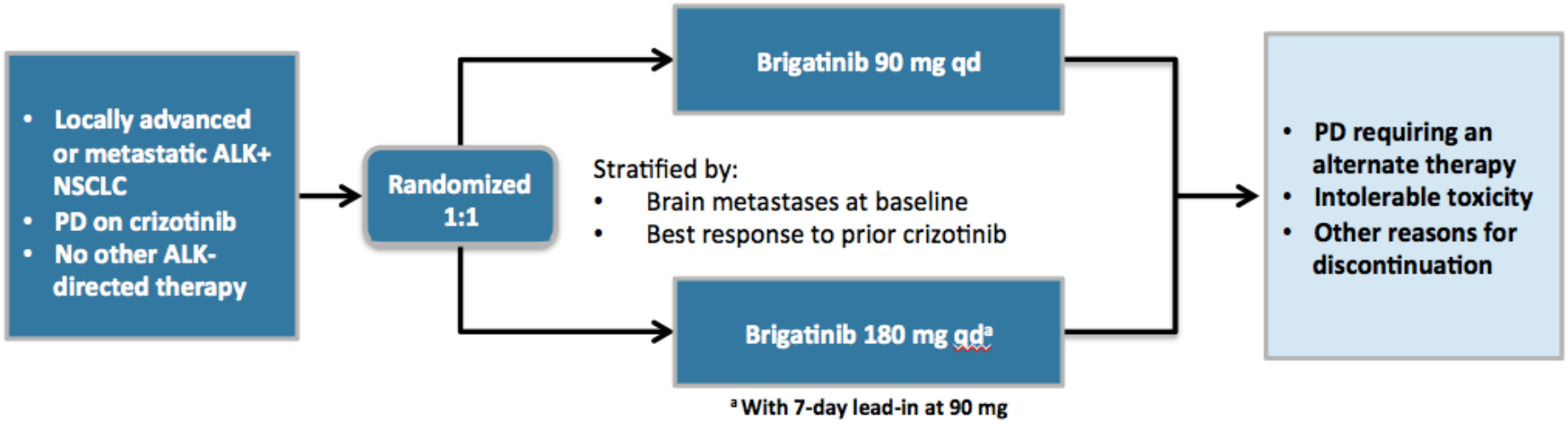
Phase 2 Clinical Trials

- Overall objective is to establish the clinical efficacy of a new drug
- Phase 2 studies are usually conducted in the patient population for whom the drug is most likely to be effective
- Phase 2 studies also provide more data on safety and tolerability
- Phase 2 studies are often single-arm (all patients receive the same dose of the same treatment), but can be randomized (for example to different doses or schedules of the same drug)

Adapted from P. LoRusso, 2017

Phase 2 Trial of Brigatinib (ALTA)

A phase 2, open-label, multicenter, international study (NCT02094573)

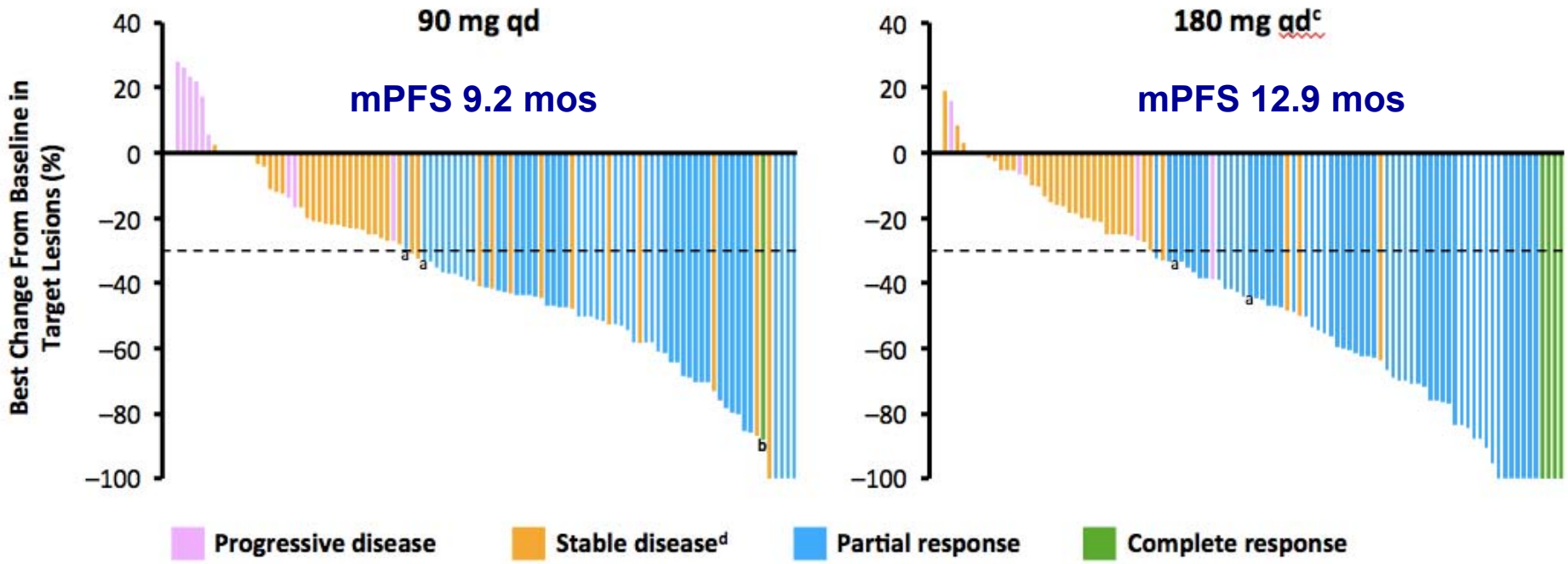


Primary Endpoint: Confirmed ORR per RECIST v1.1 (assessed by investigator)

Key Secondary Endpoints: Confirmed ORR (assessed by an IRC), CNS response (IRC-assessed intracranial ORR and PFS in patients with active brain metastases[b]), duration of response, PFS, OS, safety, and tolerability

Kim et al., JCO 35(22): 2490-98, 2017

Phase 2 Trial of Brigatinib (ALTA)



Dotted line at –30% indicates threshold for partial response per RECIST v1.1
[a] Single response awaiting confirmation
[b] Patient had a lymph node target lesion which resolved to <10 mm shortest diameter (CR per RECIST v1.1)
[c] 180 mg qd with 7-day lead-in at 90 mg
[d] Category includes single responses that were not confirmed

Data as of February 29, 2016

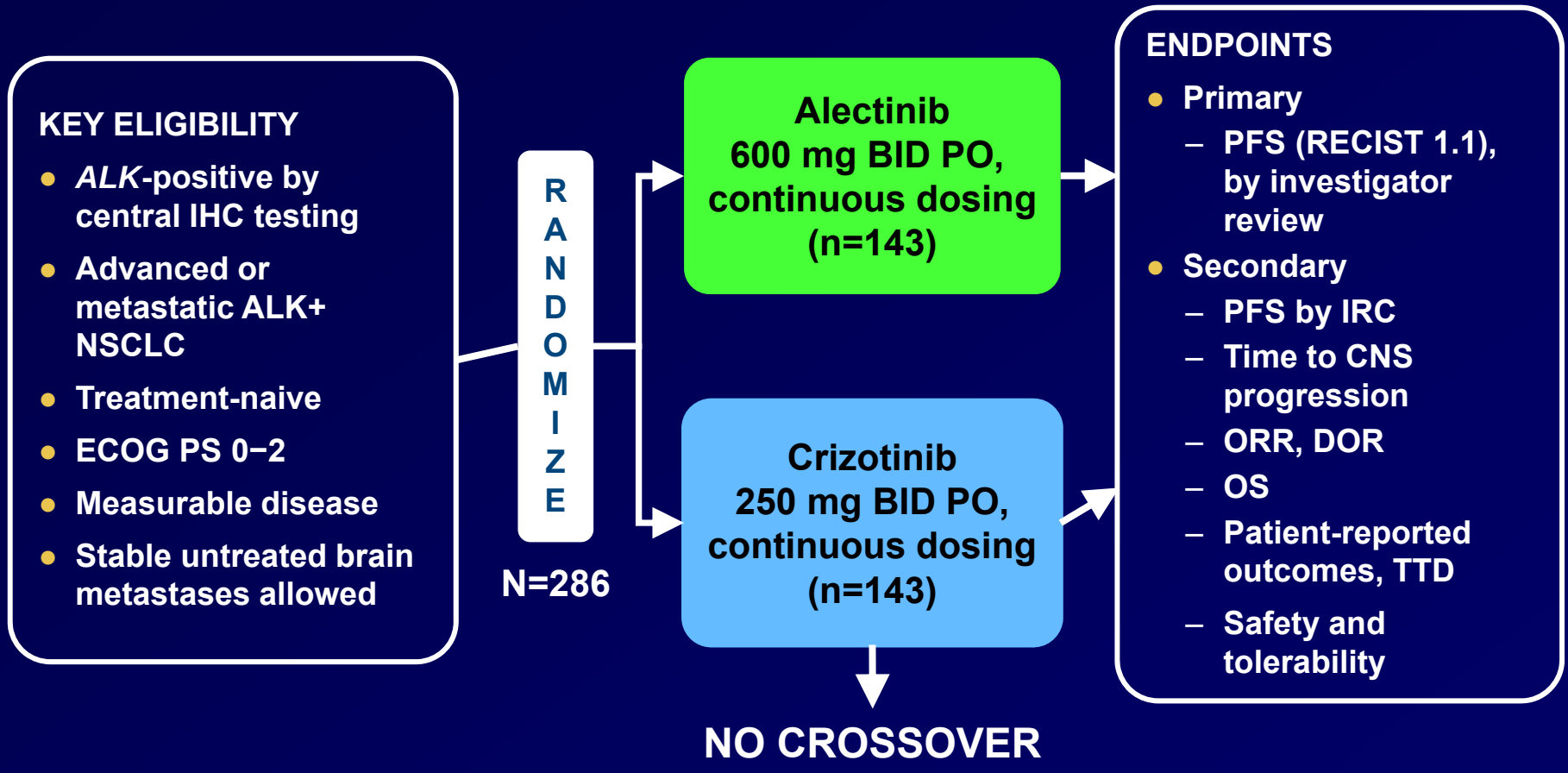
Kim et al., JCO 35(22): 2490-98, 2017

Phase 3 Clinical Trials

- Overall objective is to compare experimental therapies with standard of care therapy
- Phase 3 studies – typically *randomized control trials* – are usually required by the FDA for full approval
- The experimental and control groups should be alike in all important aspects and only differ in the treatments administered
- The control group usually receives standard of care treatment and not a "placebo"

Adapted from P. LoRusso, 2017

ALEX: Global Phase 3 Randomized First-Line Study of Alectinib *vs* Crizotinib



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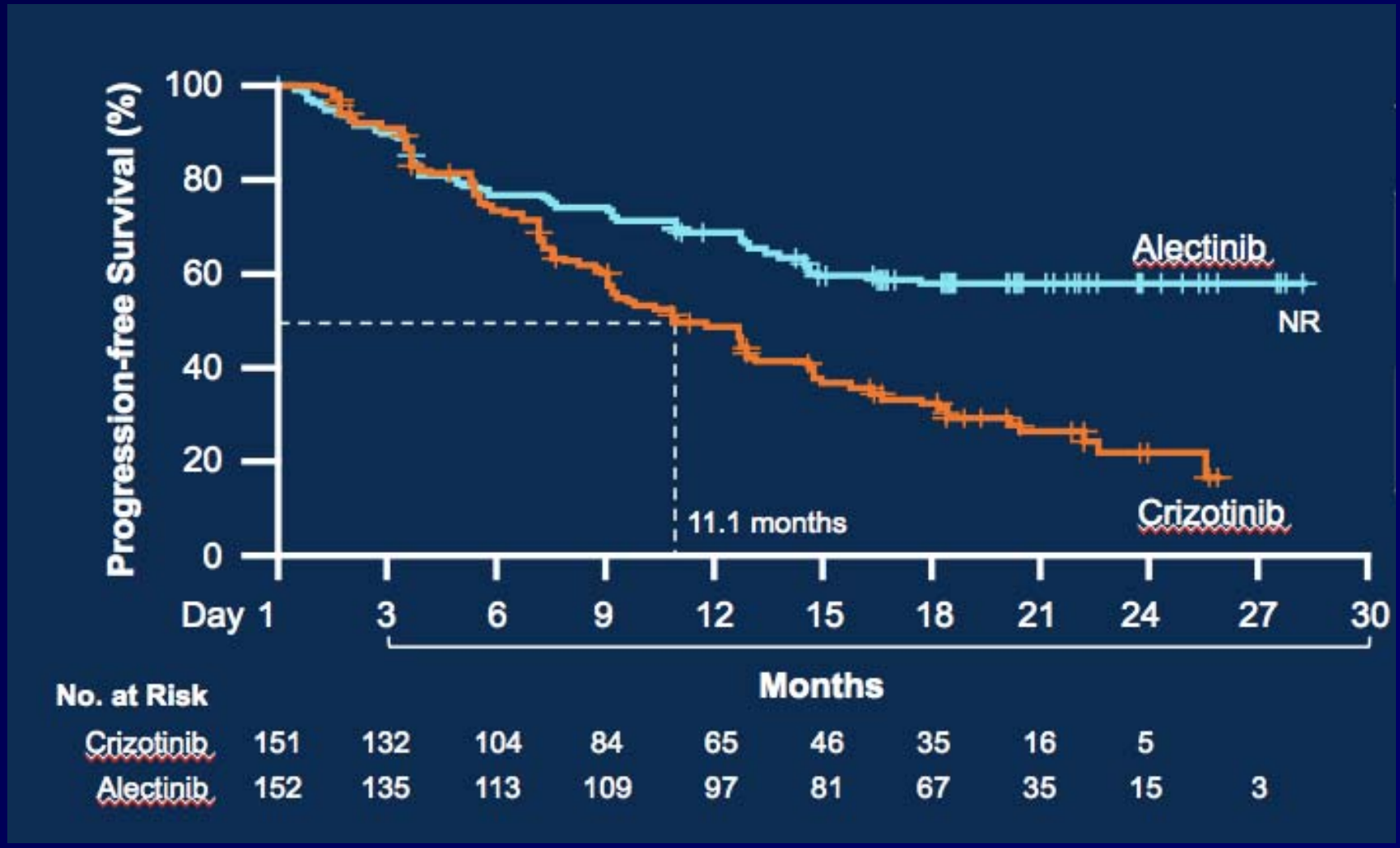

Shaw et al., ASCO 2017

Summary

- Clinical trials are essential to cancer drug development
- Phase 1 (first-in-man) studies: establish safety, dosing, pharmacokinetics, and preliminary antitumor activity
- Phase 2 studies: focus on efficacy, but also obtain additional safety data and correlative studies
- Phase 3 studies: establish benefit over standard of care treatment, compare safety profiles

Only 3% of patients with cancer participate in clinical trials