PANEL 1: CASE STUDIES: DATA COLLECTION AND APPLICATION OF RWE

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Meeting Goals

- Identify disease and drug candidates in oncology as potential case studies
- Develop strategies for optimal regulatory use of real-world evidence in oncology
- Outline potential pilots in oncology that could be used for clinical evidence generation to support regulatory decisions

Defining the Discussion

- **Real World Data (RWD)** - Data collected from sources outside of conventional randomized controlled trials
  - Electronic health records (EHRs), randomized trial supplements, pragmatic clinical trials, patient registries, administrative claims, surveys, and mobile health-generated data (e.g., smartphones, wearables, social media)

- **Real World Evidence (RWE)** - Evidence derived from RWD
  - Clinical research evidence summarizing the use, benefits and risks of medicines when prescribed in scenarios that fall outside the bounds of the classic clinical trial settings
  - Reflective of the heterogeneous patients seen in real world practice settings

Defining the Discussion

EXPLORE…

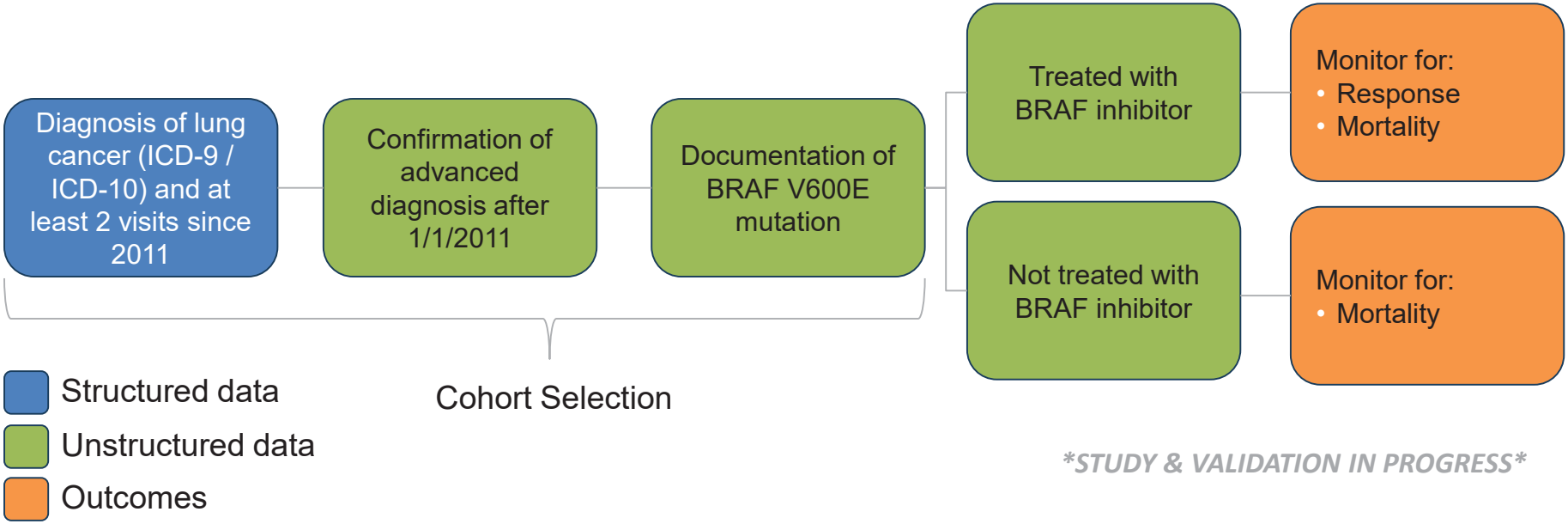
- **Value of incorporating RWE into drug development**
  - Supplementing post-market data collection
  - Decreasing costs and development timelines
  - Potential to reflect novel outcomes
  - Minimizing the number of patients exposed to a less efficacious therapy

- **Requirements and considerations for RWE in drug development**
  - Feasibility of data collection
  - Data quality concerns (e.g., missing information, non-systematic data collection)
  - Endpoints
  - Patient confidentiality and data security

Case Example: RWE for Label Expansion

Situation: *Positive preliminary results were reported last August in the New England Journal of Medicine for vemurafenib's efficacy in some non-melanoma cancers*

Objective: *Explore the utility of Flatiron real-world data to support understanding of role of vemurafenib in NSCLC patients with BRAF V600E mutations*



STUDY & VALIDATION IN PROGRESS

Case Example: RWE for Label Expansion

Leveraging real-world data for potential label expansion requires alignment on variables and endpoints that go beyond what is typically found in real-world data

STUDY & VALIDATION IN PROGRESS

Approach to Real-World Endpoints for Discussion

Key Questions	Context and Approach
Real-World Tumor Response (rwTR)	Assessment of change in burden of disease over the course of treatment with BRAF inhibitor, including: ▪ Assessment of initial response, maximum response, and time to occurrence, provide insights into the depth, timing, and duration of response
Real-World Progression (rwP)	All distinct episodes in which the treating clinician concludes that there has been growth in the disease of interest ▪ Distinct episodes are disease-specific time intervals in which the patient is assessed for progression ▪ Source information considered includes radiology, laboratory evidence, pathology, clinical assessment

Case Example: RWE for Label Expansion

*The ability to **measure, track, and improve quality** is essential to leveraging real-world data to generate meaningful real world evidence. As RWE expands into new use cases, understanding the standards for quality and validating these methods will be critical.*

Example: Inter-rater agreement for NSCLC disease characteristics

Question	N	Question Type	Agreement
Does the patient have non-small cell lung cancer?	150	boolean	0.99
Does the patient have advanced lung cancer?	150	boolean	0.96
What is the date of initial diagnosis with NSCLC?	150	date	0.78
What is the date of diagnosis with advanced or metastatic NSCLC?	150	date	0.73
What was the patient's stage at initial diagnosis?	150	drop down	0.85
What is the patient's NSCLC histology?	150	drop down	0.95
What is the patient's smoking status?	150	drop down	0.93

Note:
Date matching agreement currently based on exact date (agreement goes up by ~0.02 when allowing for agreement within 2-week window and by ~0.04 when allowing for agreement within 1-month)

RWE Proposals – Vision for the Future

Utilizing RWE with the intent of answering specific clinical questions and, when appropriate, informing product labels, in the following areas:

1. Expanding the safety profiles of a therapeutic
2. Identifying populations with enhanced benefit/risk for an already approved therapy to inform clinical practice
3. Piloting studies to determine the potential correlation between feasible real world measures (such as time to treatment switching) and more traditional clinical trial endpoints (such as time to progression)
4. Building evidence for a supplemental package to expand the indication profile for a therapeutic
5. Supporting efficacy results observed in clinical trial setting, particularly in areas of unmet medical need, when a new drug shows substantial clinical benefit. Real world studies that are able to support the preliminary magnitude of effectiveness in a larger cohort may be sufficient to serve as post-market confirmation of clinical benefit

Meeting Goals (Reprise)

- Identify disease and drug candidates in oncology as potential case studies
- Develop strategies for optimal regulatory use of real-world evidence in oncology
- Outline potential pilots in oncology that could be used for clinical evidence generation to support regulatory decisions

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Why Is this Topic Important to Patients?

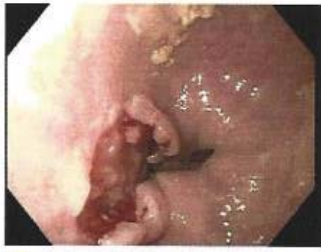
- Patients don't have the luxury of patience
- Patients in clinical trails are not representative of patients who are treated in all clinics
- Clinical trials have limitations (e.g., drug approval versus treatment optimization)
- Most patients would like to contribute to advancing medical knowledge even if they can't/don't participate in clinical trials

What are Patient Concerns?

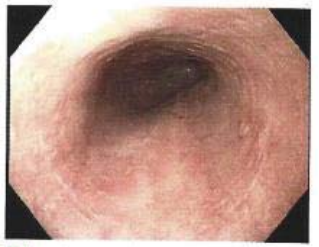
- Loss of privacy/security
- Consenting
- Hoarding of data

A **Lucky** Patient's Story

- **June:** Diagnosed with metastatic esophageal cancer
- **July:** Treated with two cycles of Oxiplatum and 5FU with no improvement; scheduled insertion of a feeding tube
- **August:** Approved to receive Ketruda through Merck's EAP; began treatment
- **September:** After two cycles of Ketruda began eating normally; had no side effects
- **March:** Had a repeat endoscopy



4 Lower Third of the Esophagus: Ulcer



2 Lower Third of the Esophagus: Pertinent

Many Patients are Not so Lucky

- One year survival of metastatic esophageal cancer is <25%; five year survival <5%
- There are other cancers for which these therapies are likely to be beneficial, but
- Many patients don't have access to off-label drugs
- Not all patients will respond; but many likely will

- If we continue to do thing as we always have, It will waste many years and patient lives

Proposal

- Rapidly approve new indications for already approved breakthrough therapies (i.e. PD-1 inhibitors)
- Site of origin and biomarker agnostic
- Supplement clinical trial data with high quality RWE
  - Multi-organ completed trials
  - Ongoing trials
  - N of one trials
  - TAPUR, etc.
  - Off-label use, especially EAPs

Help Patients NOW!

- Determine from FDA
  - What RWE will be acceptable for approval of new indications of breakthrough therapies (PD-1 inhibitors)
  - How much data will be required for a few of the most compelling cases
- Determine from sponsors what data are already available
- Report on progress at FOCR annual meeting in November

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Cyramza (Ramucirumab) Case Study

Allen Melemed, Eli Lilly and Company

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- Ramucirumab's approval was based on clinical trials conducted before immune □□e□□□□n□n□□□□□□□en□e□ed □□e m□□□e□n □ □□□□e□□□□□
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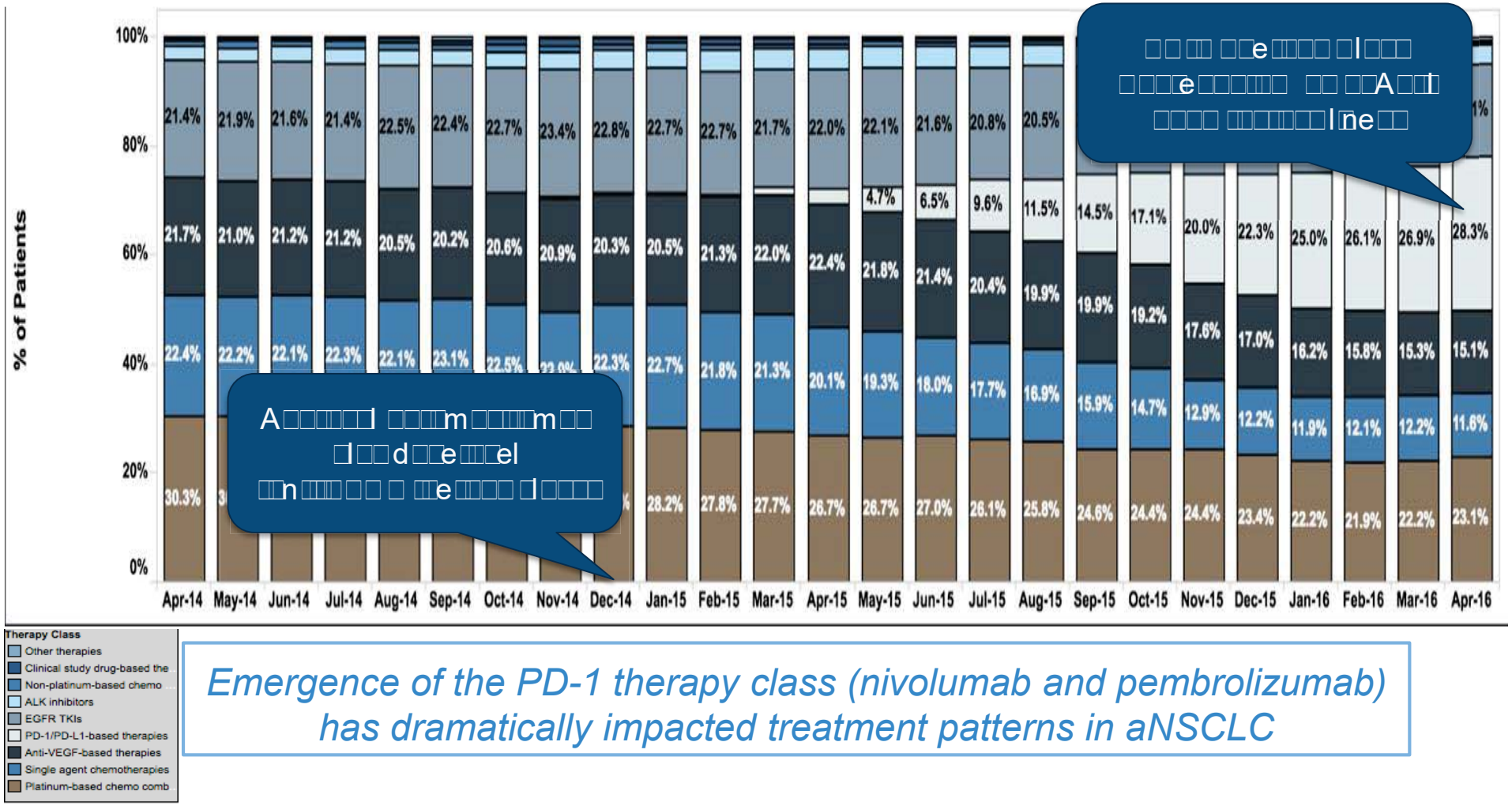
Patient Share by Therapy Class



Emergence of the PD-1 therapy class (nivolumab and pembrolizumab) has dramatically impacted treatment patterns in aNSCLC

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Objectives:
To describe patient characteristics, safety, real-world progression, response, and mortality in patients with advanced NSCLC receiving treatment with ramucirumab plus docetaxel (R/D) either prior to or following treatment with a PD-1 inhibitor (PD-1).

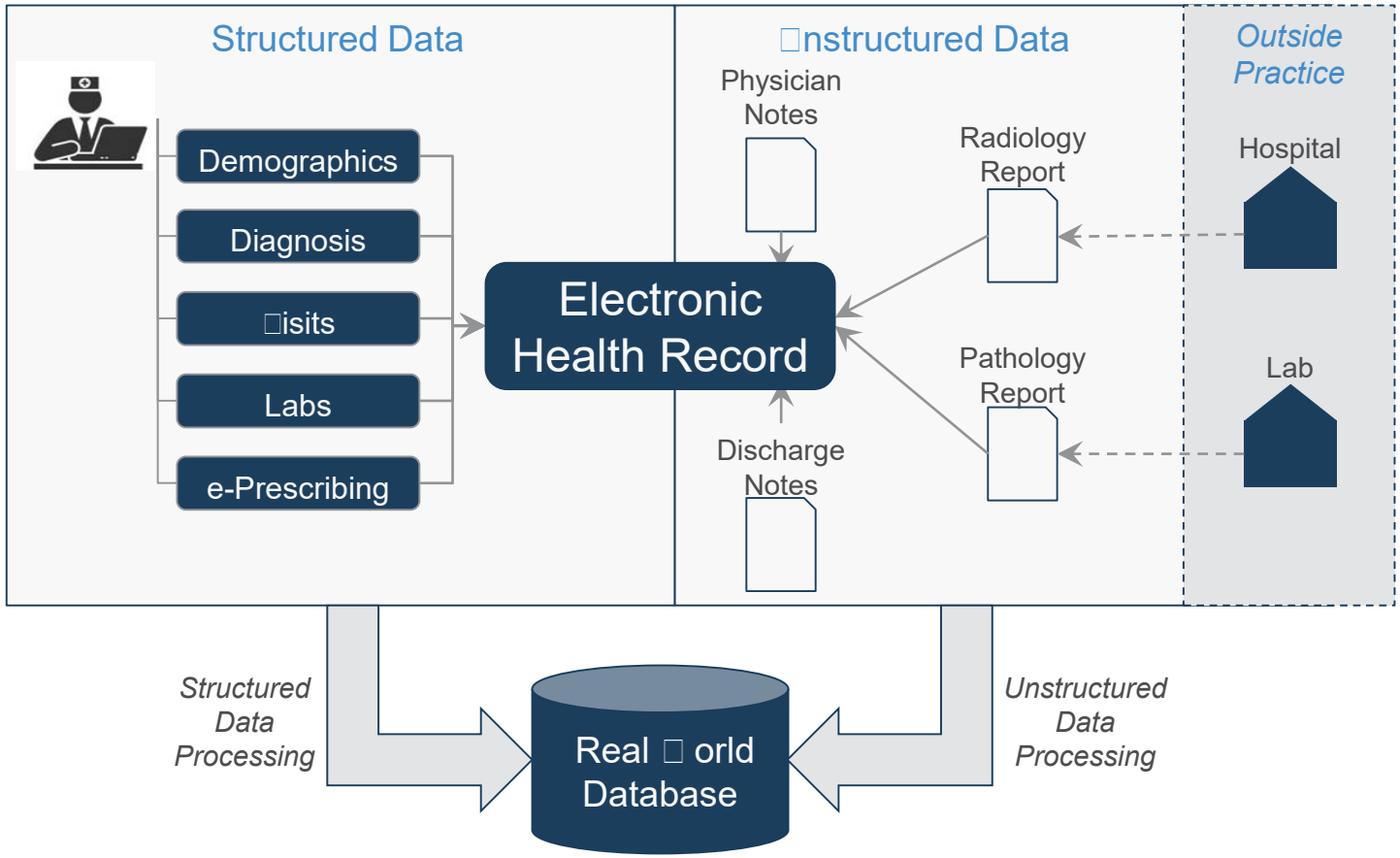
Specifically, this analysis will be designed to:

- Describe the demographics and clinical characteristics of patients in this cohort, including:
  - Stratification by patient subcohort of interest (e.g., histology, biomarker status, LOT)
- Describe the treatment sequencing of R/D, PD-1 and other therapies in this population
  - Lines of therapy
  - Treatments received before and after R/D among patients who received both R/D and PD-1

Source data
Continually aggregating real-world EHR dataset of 1.3M+ patients
Data will be extracted from structured data as well as unstructured (free-text) records to increase quality and completeness of key variables

Data cutoff date
March 31, 2016

Source: □latiron Real □ orld Data



By accessing and processing the complete electronic health record, the Flatiron real world database significantly improves completeness and accuracy of key data variables

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Study design: Ramucirumab / PD-1 treatment sequencing

Patients diagnosed with □dvanced NSCLC since 2011 (**N = 23,139**)
51% of these patients are active as of December 2014 (Cyramza plus docetaxel approval)

□sage of a PD-1 inhibitor: Order or administration of nivolumab or pembroli□umab
N = 1,845

Completeness of record**:** Less than a □0 day gap between advanced diagnosis date and structured first activity date
N = 1,578

Cyram□a and a PD-1 inhibitor order/administration in distinct lines of therapy
N = 62

Cyramza → PD-1
N = 40

PD-1 → Cyramza
N = 23

Note: One patient, who received a PD-1 inhibitor followed by Cyram□a followed by a different PD-1 inhibitor, was considered in both cohorts.

Data cutoff: March 31, 2016

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Baseline patient characteristics

Ramucirumab / PD-1 cohort

	All N=63	Cyramza ⟶ PD-1 N=40	PD-1 ⟶ Cyramza N=23
Gender:			
Female	26 (41.3%)	17 (42.5%)	9 (39.1%)
Male	37 (58.7%)	23 (57.5%)	14 (60.9%)
Group stage at diagnosis:			
Stage I-II	6 (9.52%)	4 (10.0%)	2 (8.70%)
Stage III	13 (20.6%)	10 (25.0%)	3 (13.0%)
Stage IV	43 (68.3%)	26 (65.0%)	17 (73.9%)
Group stage is not reported	1 (1.59%)	0 (0.00%)	1 (4.35%)
Histology:			
Non-squamous cell carcinoma	48 (76.2%)	33 (82.5%)	15 (65.2%)
Squamous cell carcinoma	15 (23.8%)	7 (17.5%)	8 (34.8%)
Smoking status:			
History of smoking	52 (82.5%)	34 (85.0%)	18 (78.3%)
No history of smoking	11 (17.5%)	6 (15.0%)	5 (21.7%)
Age at advanced diagnosis (years), Median [IQR]	62.0 [59.0;68.0]	62.0 [60.0;68.0]	61.0 [55.0;67.5]
Follow-up time from advanced diagnosis (months), Median [IQR]	20.0 [13.1;27.2]	21.5 [15.1;30.2]	16.4 [11.3;25.6]
Follow-up time from initiation of PD-1 (months), Median [IQR]	3.52 [1.91;6.13]	2.53 [1.41;3.74]	6.84 [5.18;8.48]
Follow-up time from initiation of Cyramza (months), Median [IQR]	6.97 [2.66;9.88]	8.58 [6.85;10.8]	1.84 [1.08;3.71]
% deceased	15 (23.8%)	12 (30.0%)	3 (13.0%)

Note: One patient, who received a PD-1 inhibitor followed by Cyramza followed by a different PD-1 inhibitor, was considered in both cohorts.

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Baseline patient characteristics

Ramucirumab / PD-1 cohort

	All N=63	Cyramza ⟶ PD-1 N=40	PD-1 ⟶ Cyramza N=23
% PD-L1 Tested:	9 (14.3%)	7 (17.5%)	2 (8.70%)
PD-L1 Status:			
PD-□1 positive	3 (33.3%)	2 (28.6%)	1 (50.0%)
PD-□1 negative□not detected	4 (44.4%)	3 (42.9%)	1 (50.0%)
□nknown□results pending	2 (22.2%)	2 (28.6%)	0 (0.00%)
% EGFR Tested:	50 (79.4%)	34 (85.0%)	16 (69.6%)
EGFR Status:			
Mutation positive	5 (10.0%)	3 (8.82%)	2 (12.5%)
Mutation negative (wild-type)	45 (90.0%)	31 (91.2%)	14 (87.5%)
% ALK Tested:	46 (73.0%)	31 (77.5%)	15 (65.2%)
ALK Status:			
□□□ positive	1 (2.17%)	1 (3.23%)	0 (0.00%)
□□□ negative□not detected	44 (95.7%)	30 (96.8%)	14 (93.3%)
□nknown□results pending	1 (2.17%)	0 (0.00%)	1 (6.67%)

Note: One patient, who received a PD-1 inhibitor followed by Cyramza followed by a different PD-1 inhibitor, was considered in both cohorts.

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Baseline patient characteristics

Overall NSCLC cohort and ramucirumab / PD-1 cohort

	Overall* N=23,139	PD1/Cyramza Cohort N=63
Gender:		
Female	11019 (47.6%)	26 (41.3%)
Male	12120 (52.4%)	37 (58.7%)
Group stage at diagnosis:		
Stage 0-II	3009 (13.0%)	6 (9.52%)
Stage III	4578 (19.8%)	13 (20.6%)
Stage IV	14421 (62.3%)	43 (68.3%)
Group stage is not reported	1131 (4.89%)	1 (1.59%)
Histology:		
Non-squamous cell carcinoma	15831 (68.4%)	48 (76.2%)
Squamous cell carcinoma	5823 (25.2%)	15 (23.8%)
Smoking status:		
History of smoking	19626 (84.8%)	52 (82.5%)
No history of smoking	2800 (12.1%)	11 (17.5%)
□nknown□not documented	713 (3.08%)	0 (0.00%)
Age at advanced diagnosis (years), Median [IQR]	69.0 [61.0;76.0]	62.0 [59.0;68.0]
Follow-up time from advanced diagnosis (months), Median [IQR]	6.71 [2.50;15.0]	20.0 [13.1;27.2]
% deceased	12617 (54.5%)	15 (23.8%)

*Overall includes patients in Flatiron's network diagnosed advanced NSCLC, and includes patients in the PD1/Cyramza cohort

Note: One patient, who received a PD-1 inhibitor followed by Cyramza followed by a different PD-1 inhibitor, was considered in both cohorts.

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Baseline patient characteristics

Overall NSCLC cohort and ramucirumab / PD-1 cohort

	Overall* N=23,139	PD1/Cyramza Cohort N=63
% PD-L1 Tested:	□□□ □□□□9□ □	9 □□□□□□□ □
PD-L1 Status:		
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*Overall includes patients in Flatiron's network diagnosed with advanced NSCLC, and includes patients in the PD1/Cyramza c□h□rt □□te□□ne patient□□h□ recei□e□ a □□□□ inhi□it□r □ll□□e□ □□ □□ra□ □a □ll□□e□ □□a □i□erent □□□□ inhi□it□r□□as c□nsi□ere□ in □□th c□h□rts□

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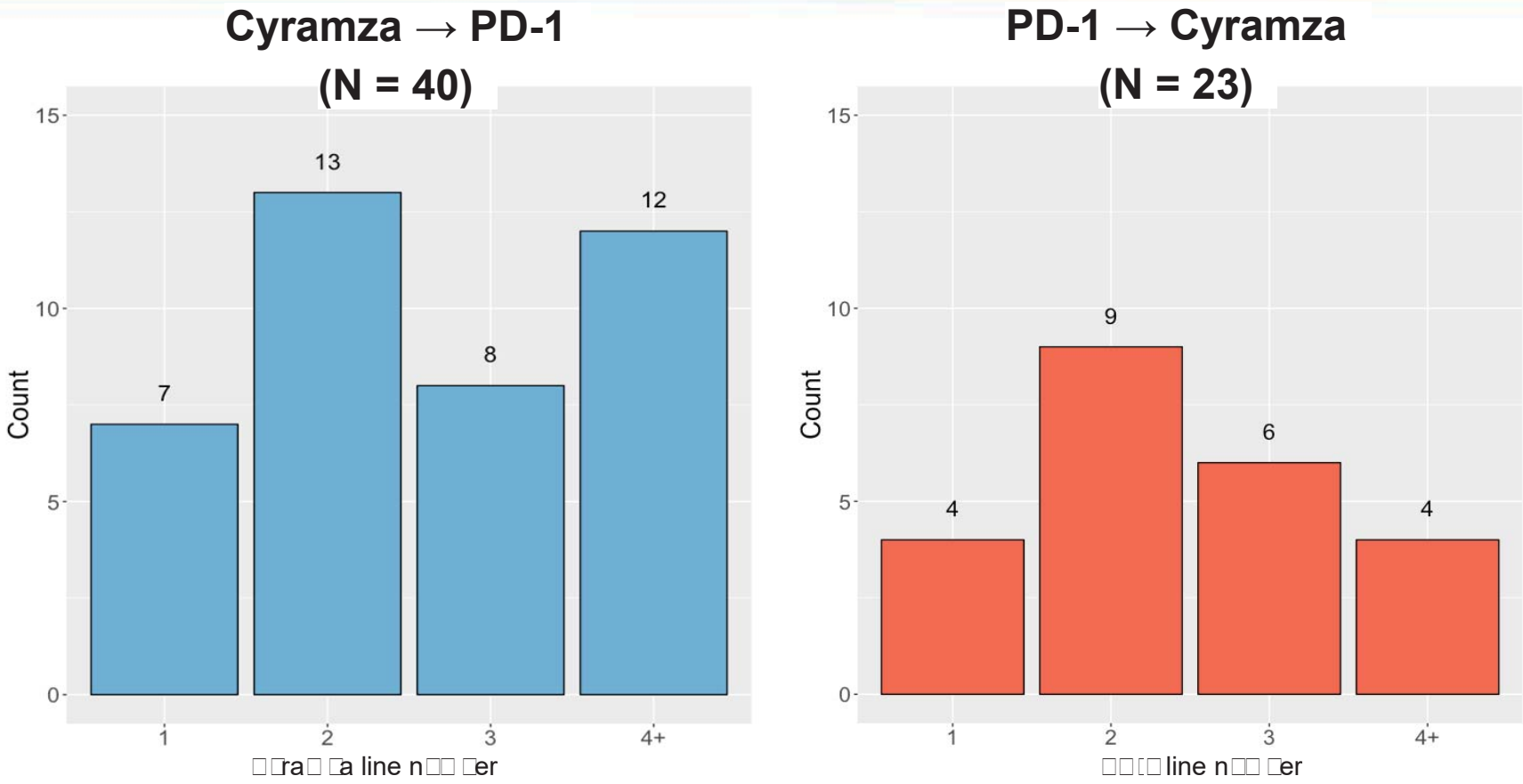

Key takeaways:

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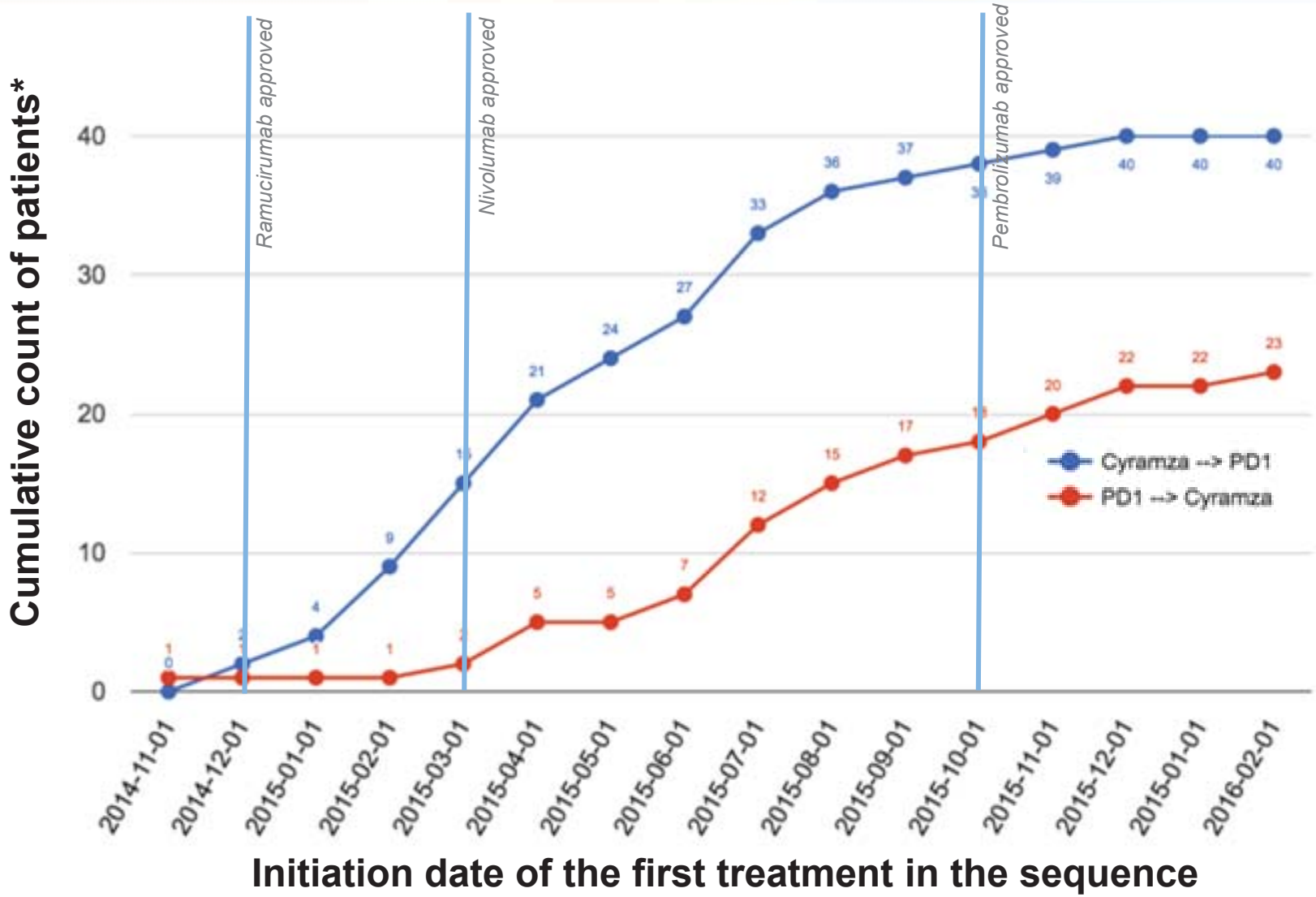
Uptake of different sequences over time



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*Cumulative denotes total number of patients that have initiated the first treatment in the sequence as of X month

□e□ □uestions for □iscussion

- □ hat kind of information □ould be helpful for prescribers to address both efficac□ and safet□ of different sequencin□□
  - □ hat endpoints should be considered □□ □□r□□□□r□□□□
  - □o□ should to□icit□ be assessed□
- □ hat is a sufficient sample si□e for each arm□
  - □re the numbers needed different for a safet□ question versus an efficac□ question□
  - □ hat other options are available to ans□er these questions in the absence of adequate patient counts□
    - A pragmatic trial may "force" the randomization if we are unable to get enough Cyramza → PD□1 patients
- □re data of sufficient qualit□ to be considered credible for stakeholders□
- □ hat t□pes of action □ould be taken based upon this information□
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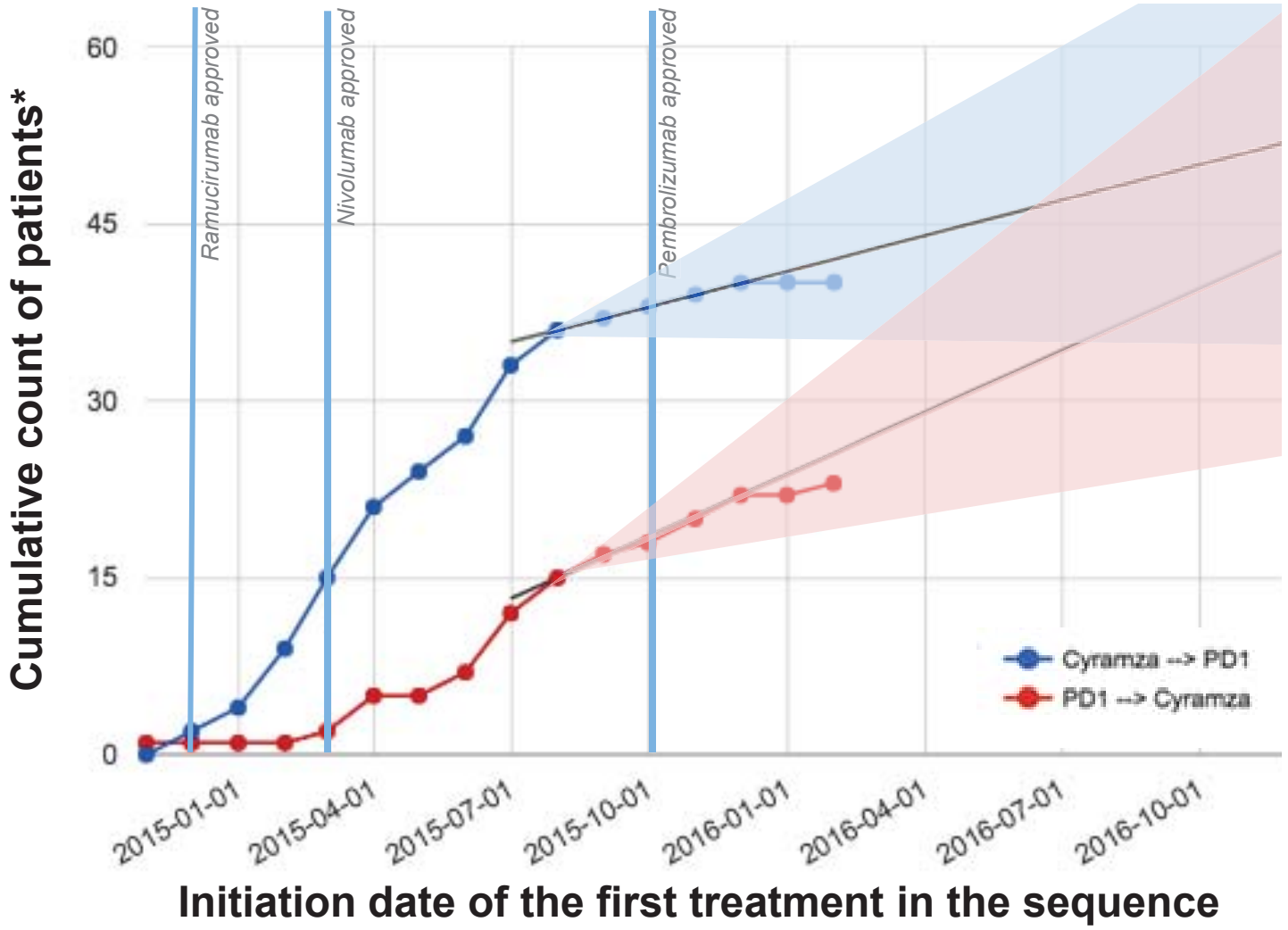
□□pected uptake of sequences over time



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*Cumulative denotes total number of patients that have initiated the first treatment in the sequence as of X month

□e□ □uestions □□eprise□and □e□t □teps

Key Questions for Discussion

- □s the dominant question efficac□or to□icit□□
- □ hat is a sufficient sample si□e for each arm□
- □re data of sufficient qualit□to be considered credible for stakeholders□
- □ hat t□pes of action □ould be taken based upon this information□

Next Steps

- Incorporate feedback from today's discussion into the study design
- □etermine timeline for full stud□ □*depe□d□o□ □ample □ize re□uired*□
- □evelop statistical anal□sis plan

FLATIRON

A Blueprint for Breakthrough: Exploring Utility of Real World Evidence

Maria Koehler MD PhD
Vice President Strategy, Innovation and Collaboration
Pfizer Oncology NY, NY

Pfizer Oncology

Panel 1: Identify Case Studies and Explore Characteristics of Data Quality to Improve Collection

Crizotinib for ALK-positive NSCLC: Yesterday's Development and Today's Proposal

1. Brief overview of crizotinib early development that led to accelerated approval (pre-BTD era through Breakthrough Designation era)
2. FDA discussions/agreements and post approval commitments
3. Post-approval real world data
4. Alternative development challenge

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Discovery of EML4-ALK Fusion Gene in 2007

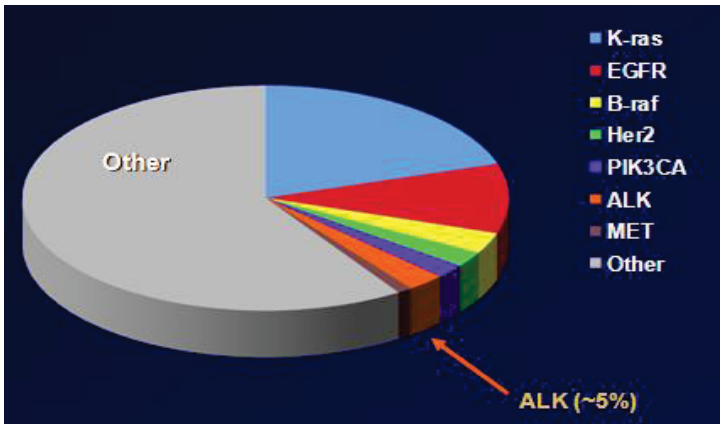
Soda, et al., Nature □□□□ □□ugust □, □□□□□

Vol 448|2 August 2007|doi:10.1038/nature05945 nature

ARTICLES

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]



□□K □ anaplastic lymphoma □inase□□□FR □ epidermal growth factor receptor□□er□ □ human epidermal growth factor receptor □□ PIK□C□ □ phosphoinositide□□□□inase, catalytic, alpha polypeptide

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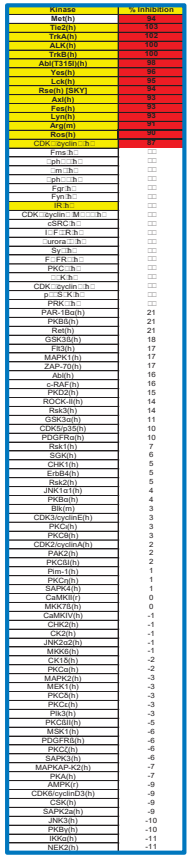
Crizotinib: Selective Inhibitor of ALK, MET and ROS1

Upstate 102 Kinase Panel



Kinase	% Inhibition
Met(h)	96
Tie2(h)	103
TrkA(h)	102
ALK(h)	100
TrkB(h)	100
Abl(T315I)(h)	98
Yes(h)	96
Lck(h)	95
Rse(h) [SKY]	94
Axl(h)	93
Fes(h)	93
Lyn(h)	93
Arg(m)	91
Ros(h)	90
CDK□/cyclin□/h□	87
Fms/h□	□□
□ph□□/h□	□□
□m□/h□	□□
□ph□□/h□	□□
Fgr/h□	□□
Fyn/h□	□□
IR/h□	□□
CDK□/cyclin□M□□/h□	□□
cSRC/h□	□□
I□F□/Kh□	□□
Aurora□/h□	□□
Syc/h□	□□
F□FR□/h□	□□
PKC□/h□	□□
□□K/h□	□□
CDK□/cyclin□/h□	□□
p□□S□K/h□	□□
PRK□/h□	□□
PAR-1Bα(h)	21
PKBβ(h)	21
Ret(h)	21
GSK3β(h)	18
Flt3(h)	17
MAPK1(h)	17
ZAP-70(h)	17
Abl(h)	16
c-RAF(h)	16
PKD2(h)	15
ROCK-II(h)	14
Rsk3(h)	14
GSK3α(h)	11
CDK5/p35(h)	10
PDGFRα(h)	10
Rsk1(h)	7
SGK(h)	6
CHK1(h)	5
ErbB4(h)	5
Rsk2(h)	5
JNK1α1(h)	4
PKBα(h)	4
Blk(m)	3
CDK3/cyclinE(h)	3
PKCι(h)	3
PKCθ(h)	3
CDK2/cyclinA(h)	2
PAK2(h)	2
PKCδ(h)	2
Pim-1(h)	1
PKCη(h)	1
SAPK4(h)	1
CaMKII(r)	0
MKK7δ(h)	0
CaMKIV(h)	-1
CHK2(h)	-1
CK2(h)	-1
JNK2α2(h)	-1
MKK6(h)	-1
CK1δ(h)	-2
PKCαi(h)	-2
MAPK2(h)	-3
MEK1(h)	-3
PKCδ(h)	-3
PKCε(h)	-3
Plk3(h)	-3
PKCβII(h)	-5
MSK1(h)	-6
PDGFRδ(h)	-6
PKC(h)	-6
SAPK3(h)	-6
MAPKAP-K2(h)	-7
PKA(h)	-7
AMPK(r)	-9
CDK6/cyclinD3(h)	-9
CSK(h)	-9
SAPK2a(h)	-9
JNK3(h)	-10
PKBγ(h)	-10
IKKα(h)	-11
NEK2(h)	-11

13 'Hits' <100X Selective for Met

Cellular Selectivity on 10 of 13 Relevant Hits

Kinase	IC50 (nM) Mean*	Selectivity Ratio
Met	□	–
□□K	□□–□□	□–□□
ROS□	□□	□□
RON	□□	□□□
□□l	□□□	□□□
	□□□	□□□
□ie□	□□□	□□□
□bl	□,□□□	□□□□
IRK	□,□□□	□□□□
□c□	□,□□□	□□□□
S□y	□□□,□□□	□□□□□□
V□□FR□	□□□,□□□	□□□□□□
PD□FRβ	□□□,□□□	□□□□□□

High Probability of ALK, MET and ROS1 Inhibition at Clinically Relevant Doses

□ang Y, et al□□ Clin Oncol □□□□□□□□suppl □□□s □abstr □□http□□meetinglibrary□asco□org□content□□□□□□□media□vm

□Measured using □□IS□ capture method

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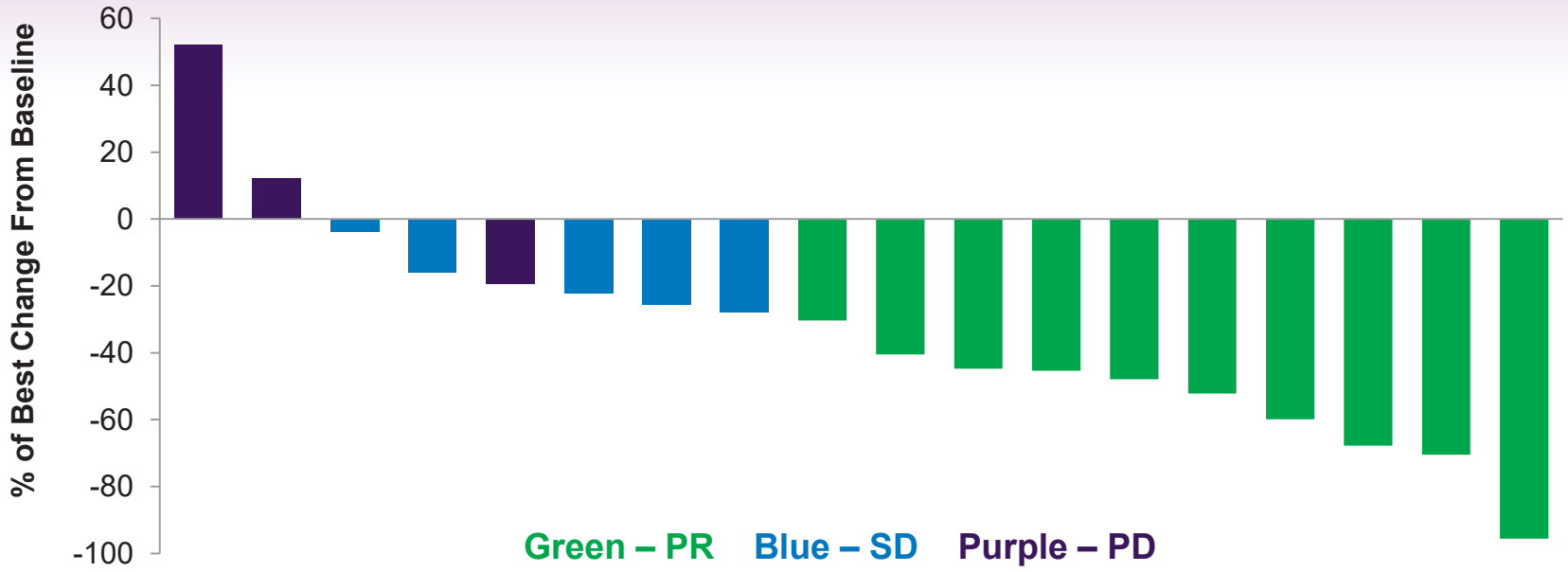
Study A8081001: Tumor Responses to Crizotinib for NSCLC Evaluable Patients with ALK Fusions

Tumor Size Change



One patient had clinical progression and discontinued without radiographic confirmation

Kwak et al ASCO 2009

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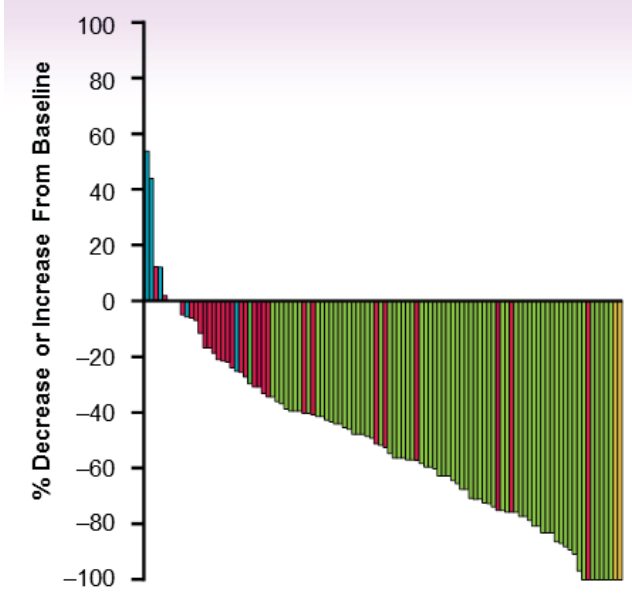
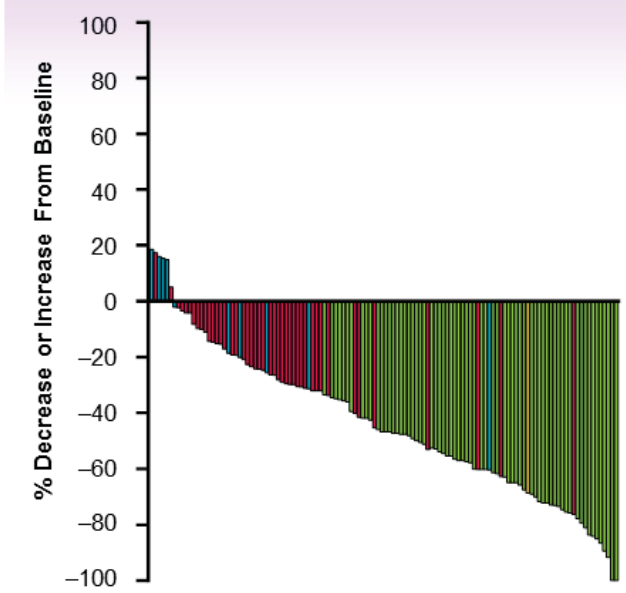
ALK-Positive Non-Small Cell Lung Cancer Tumor Responses to Crizotinib by Patient

Study A8081001 – n=106[1]



Study A8081005 – n=123[2]



PD SD PR CR

[1]Camidge DR, oral presentation at ASCO 2011; abstract 2501
[2]Riely GJ, oral presentation at WCLC 2011; abstract 1618

- RR for chemotherapeutic agents approved for the treatment of metastatic NSCLC is ~30–35% in first-line chemotherapy

Complete Response	1	2
Partial Response	67	69
Duration of Response Median	41.9 weeks (6.1, 42.1)	48.1 weeks (4.1, 76.6)

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Crizotinib US NDA Approval

Crizotinib FDA approval

- Accelerated approval (AA) based on data from two studies
  - **A8081001:** Phase I with □□tension phase NSCLC
  - **A8081005:** Single Arm Phase II
- **NDA approved August 26th, 2011 – in 4.9 mo**
  - Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (AL□)-positive as detected by an FDA-approved test
- Abbott's Dx PMA simultaneously approved
  - The □ysis AL□ □reak Apart FIS□ Probe □it is a □ualitative test to detect rearrangements involving the AL□ gene via FIS□ in FFP□ NSCLC tissue specimens to aid in identifying those patients eligible for treatment with □AL□ORI (cri□otinib)

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Post-Marketing Requirements & Commitments

- □ ith rapid development and approval, come Post-Marketing Re□uirements (PMRs) □ Commitments (PMCs)
- 314.510 Subpart □ Post-Marketing Re□uirements
  - Study A8081007 □2nd Line Phase 3 randomi□ed vs chemo
  - Study A8081014 □1st Line Phase 3 randomi□ed vs chemo
- Other safety □ non-safety related PMRs □ PMCs
  - Assess visual effects
  - Dose adjustment strategy for hepatic and renal (severe) impairment
  - Dose adjustment strategy for C□P3A inhibitors□inducers
  - Dosing strategy with gastric p□ elevating agents
  - Response in AL□-negative NSCLC (20 additional patients in 1001)
    - Including assessment of other biomarkers
  - Final □Tc prolongation potential evaluation
  - □□posure-Response analyses of Phase 3 trials

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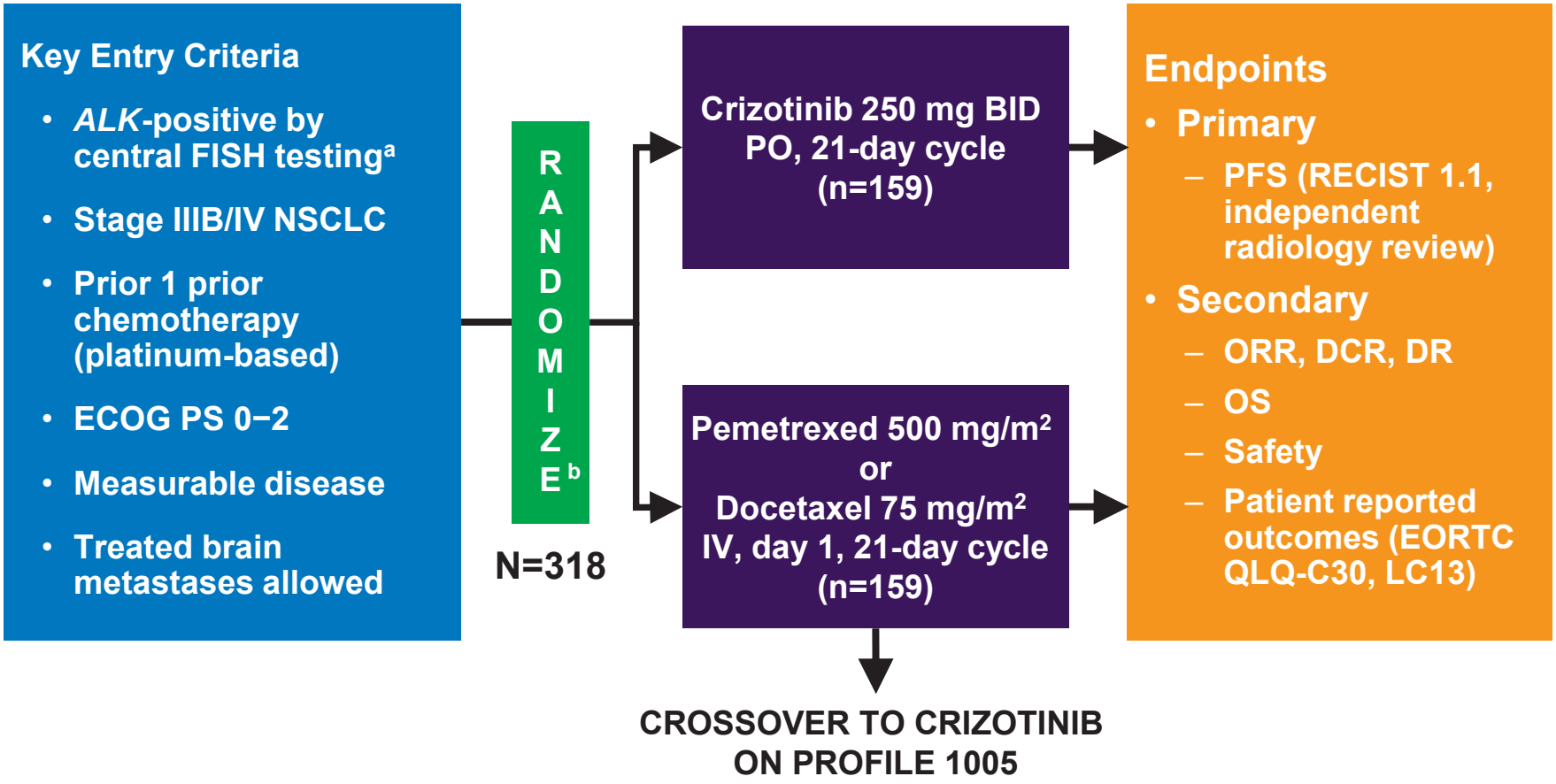
PROFILE 1007: Phase 3 Second-line Study of Crizotinib vs. Pemetrexed or Docetaxel in *ALK*-Positive NSCLC



[a]ALK status determined using standard ALK break-apart FISH assay [b]Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no)

Shaw et al., ESMO 2012

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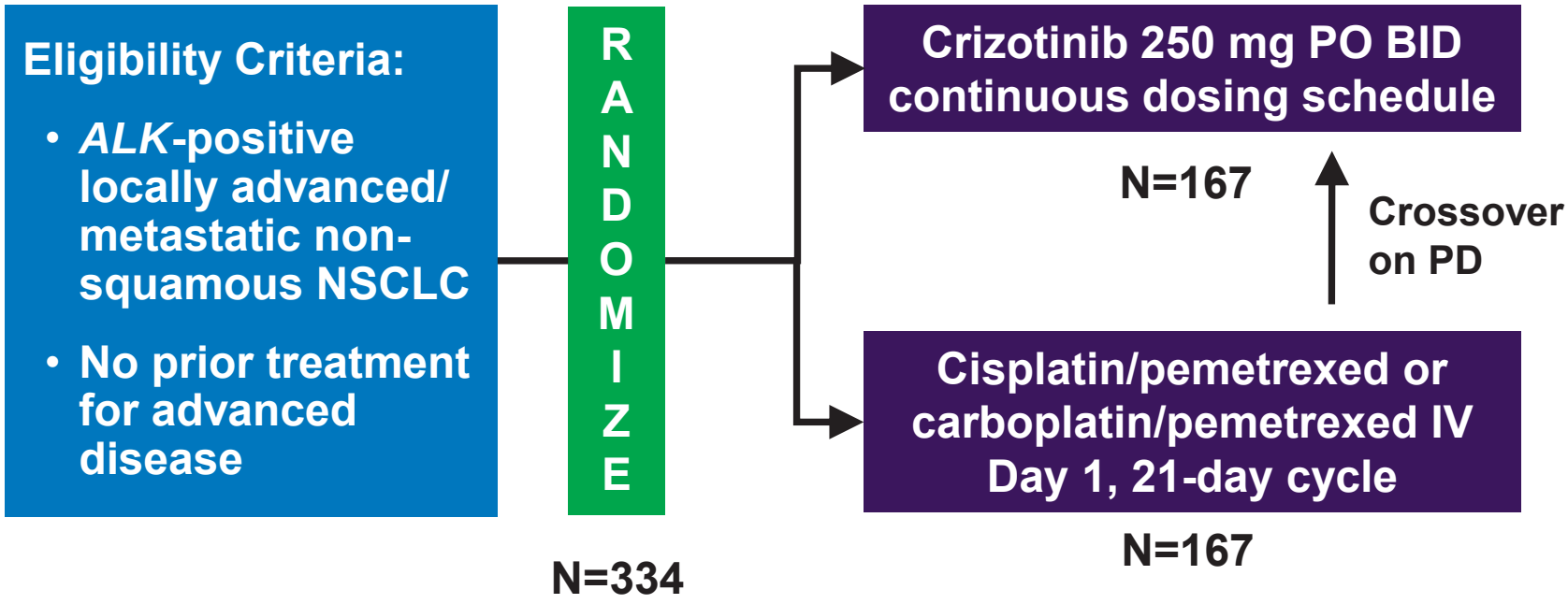
PROFILE 1014: Phase 3 First-line Study of Crizotinib vs. Platinum/Pemetrexed in *ALK*-Positive NSCLC



- Primary endpoint: PFS□
- Secondary endpoints: OS, ORR□, □R, safety, □oL, lung cancer-specific symptoms

□□ased on RECIST v 1.1 and confirmed by independent radiology review
ClinicalTrials.gov I□: □CT011□□1□0

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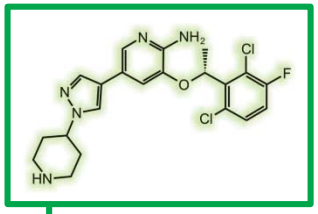
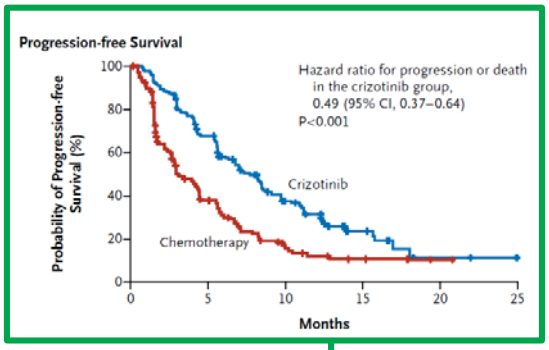
Crizotinib: Rapid Timeline From Compound Identification to Approval and Challenges with Post-approval Development

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,3], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[3], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[4], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]





…treatment of patients with locally advanced/ metastatic NSCLC that is ALK+ as detected by an FDA-approved test[3]

…treatment of adults with previously treated ALK+ advanced NSCLC[4]

Re□□ compo□□□ ie□tifie□

□i□ic□□ testi□□ □e i□s

□isco□e□y of *EML4–ALK* f□sio□ □e□e□

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2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014

Now Crizotinib is on the Market

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Crizotinib Efficacy Across Phase 1, 2 and 3 Studies in ALK-Positive NSCLC was very similar

Approval and Post-approval Commitments

	PROFILE 1001[1] (N=143)	PROFILE 1005[2] (N=259)	PROFILE 1007[3] (N=172)	PROFILE 1014[4] (N=172)
Phase	1	2	3	3
Line of therapy	Any line	2nd line and beyond	2nd line	1st line
ORR	61%	60%	65%	74%
DOR, median (mo)	11.3	10.5	7.4	11.3
PFS, median (mo)	9.7	8.1	7.7	10.9

[1]Camidge et al., Lancet Onc 13(10): 1011-9, 2012
[2]Kim et al., ASCO 2012
[3]Shaw et al., NEJM 368(25): 2385-94 , 2013
[4]Solomon et al., NEJM 371(23): 2167-77, 2014

ASCO 2016 abs 9066
OS HR 0.85 – cross over

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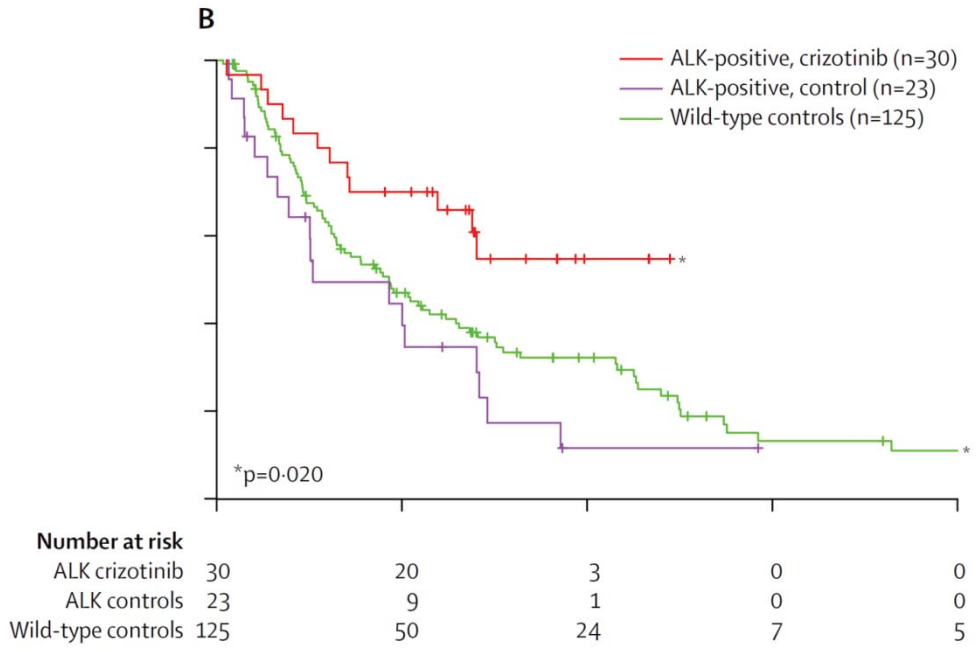
What did subsequent studies in real world teach us?

Confirmation of Crizotinib's Effect Thru Retrospective Analysis

Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring *ALK* gene rearrangement: a retrospective analysis

Alice T Shaw, Beow Y Yeap, Benjamin J Solomon, Gregory J Riely, Justin Gainor, Jeffrey A Engelman, Geoffrey I Shapiro, Daniel B Costa, Sai-Hong I Ou, Mohit Butaney, Ravi Salgia, Robert G Maki, Marileila Varella-Garcia, Robert C Doebele, Yung-Jue Bang, Kimary Kulig, Paulina Selaru, Yiyun Tang, Keith D Wilner, Eunice L Kwak, Jeffrey W Clark, A John Iafrate, D Ross Camidge

***Lancet Oncol* 2011; 12: 1004–12**



This analysis, performed while the Ph 3 confirmatory trials were ongoing, confirms crizotinib's effect vs historical chemotherapy treated control pts

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US/Canada Crizotinib Retrospective Chart Review

Methods

- Retrospective cohort st□dy in 212 patient (de-identified)
- Physicians (N□107 in □S, N□40 in Canada) treating patients with NSCLC were recr□ited
- For patients meeting the st□dy incl□sion criteria, data were retrospectively abstracted by the participating physicians □sing a sec□re, web-based data collection form

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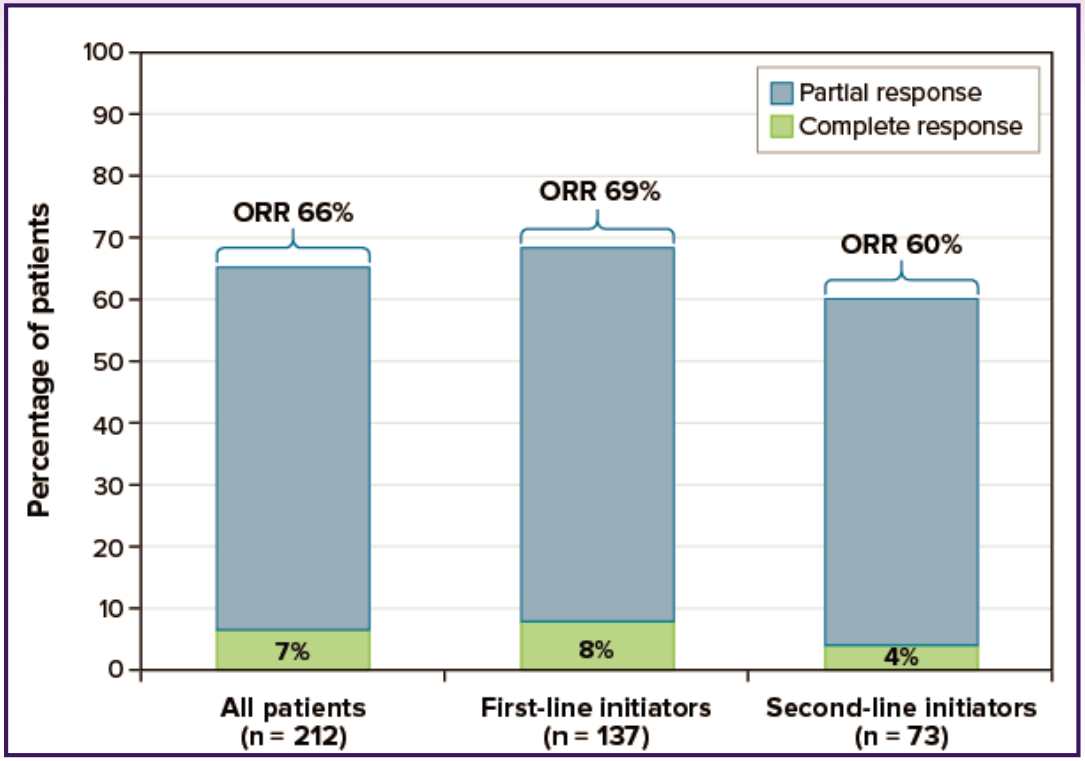
US/Canada Crizotinib Chart Review

Results: Response Rate During Crizotinib Treatment

- The estimated crizotinib ORR was 66% for the overall cohort (69% for first-line initiators vs. 60% for second later-line initiators)



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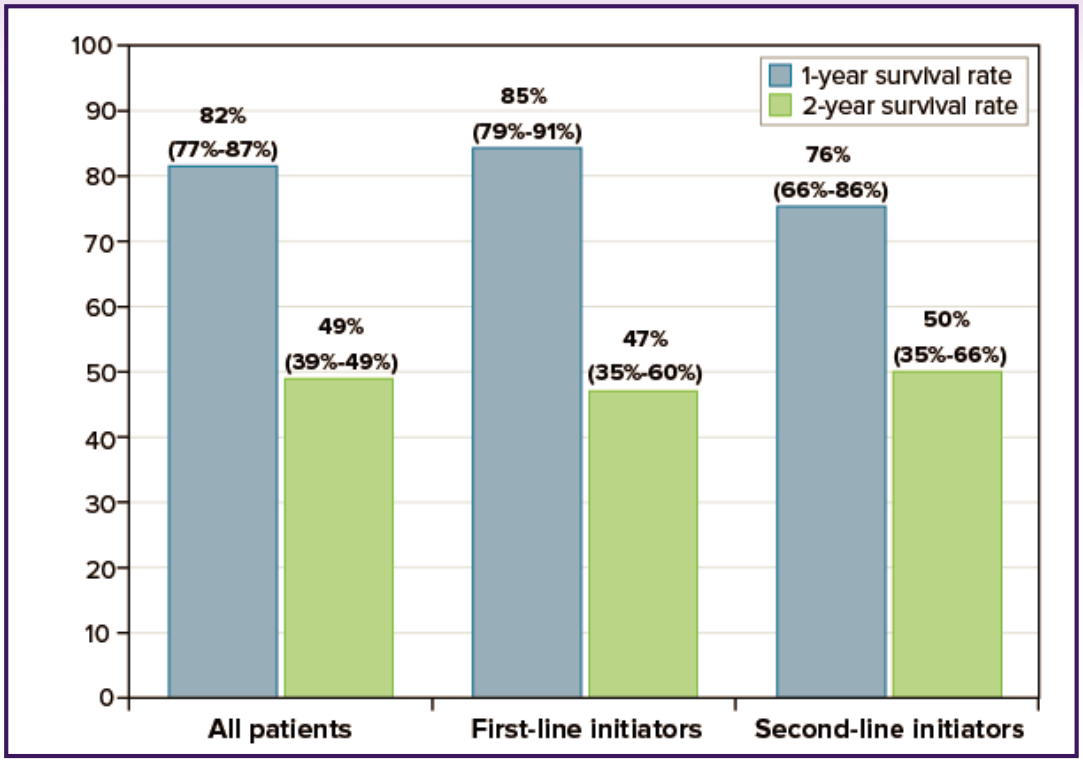
US/Canada Crizotinib Chart Review

Results: Kaplan-Meier Survival Estimates by Line of Crizotinib Treatment

- Based on Kaplan-Meier estimation, **1- and 2-year survival rates from crizotinib initiation were 82% (95% CI, 77%-87%) and 49% (95% CI, 39%-60%), respectively**
- **Median PFS from crizotinib initiation was 9.5 months** (95% confidence interval [CI], 8.7-10.1 months), in the overall cohort
- **Median OS from crizotinib initiation was 23.4 months** (95% CI, 19.5 months to not reached), or 2 years (95% CI, 1.6 years to not reached), for the overall cohort



Note: 95% confidence interval shown in parentheses

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Retrospective Chart Review Indicates Concordance Between the Real World Clinical Effectiveness and Clinical Trial Efficacy Results

	PROFILE 1001[1] (N=143)	PROFILE 1005[2] (N=259)	PROFILE 1007[3] (N=172)	PROFILE 1014[4] (N=172)
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[2]Kim et al., ASCO 2012
[3]Shaw et al., NEJM 368(25): 2385-94 , 2013
[4]Solomon et al., NEJM 371(23): 2167-77, 2014

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Crizotinib Retrospective Analysis Sept 2015

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 • DENVER, COLORADO, USA

Abstract 1355
Crizotinib outcome and post-progression management in *ALK*+ NSCLC: IFCT-1302 CLINALK

Michaël Duruisseaux,[1] Benjamin Besse,[2] Jacques Cadranel,[3] Maurice Pérol,[4] Elisabeth Quoix,[5] Julien Mazières,[6] Renaud Descourt,[7] Eric Dansin,[8] Clarisse Audigier-Valette,[9] Lionel Moreau,[10] José Hureaux,[11] Remi Veillon,[12] Josiane Otto,[13] Anne Madroszyk,[14] Alexis B. Cortot,[15] Francois Guichard,[16] Pascaline Boudou-Rouquette,[17] Alexandra Langlais,[18] Pascale Missy,[18] Franck Morin,[18] Gérard Zalcman,[19] Denis Moro-Sibilot [20]

On behalf of the French Cooperative Thoracic Intergroup IFCT

[1]CHU de Grenoble, Grenoble, France; [2]Institut Gustave Roussy, Villejuif, France; [3]Hôpital Tenon/AP-HP, Paris, France; [4]Centre Léon Bérard, Lyon, France; [5]CHU de Strasbourg, Strasbourg, France; [6]CHU de Toulouse, Toulouse, France; [7]CHU Morvan, Brest, France; [8]Centre Oscar Lambret, Lille, France; [9]CHITS de Toulon Sainte-Musse, Toulon, France; [10]CH de Colmar, Colmar, France; [11]CHU d'Angers, Angers, France; [12]CHU de Bordeaux, Bordeaux, France; [13]CRLCC de Nice, Nice, France; [14]CRLCC de Marseille, Marseille, France; [15]CHU de Lille, Lille, France; [16]Polyclinique de Bordeaux, Bordeaux, France; [17]Hôpital Cochin/AP-HP, Paris, France; [18]French Cooperative Thoracic Intergroup (IFCT), Paris, France; [19]Hôpital Bichat/AP-HP, Paris, France; [20]CHU de Grenoble, Grenoble, France

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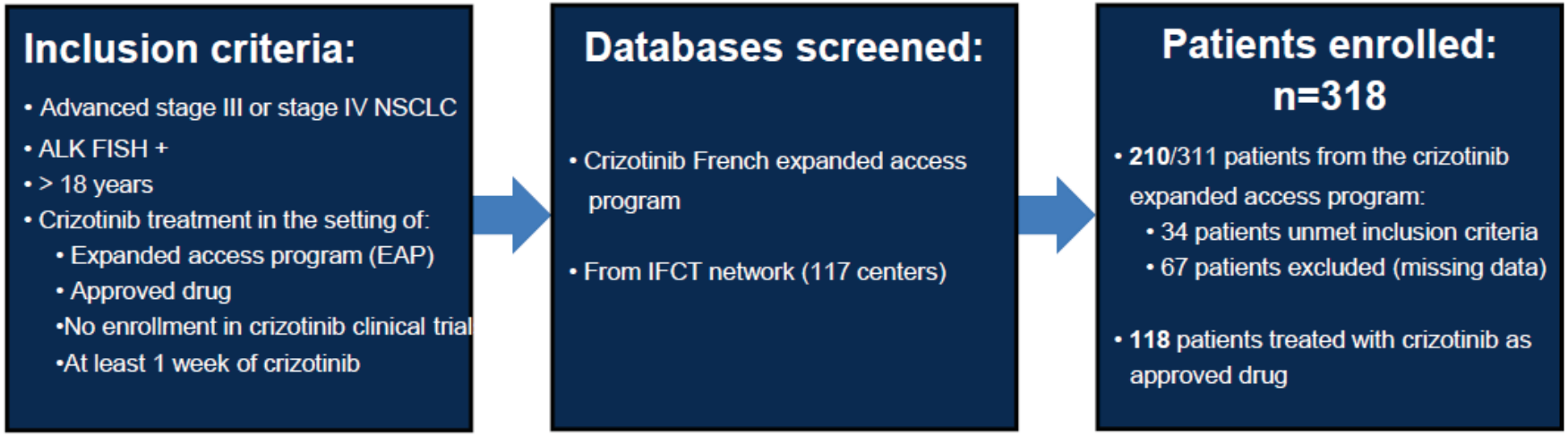
Study Design

- Non-interventional, retrospective, multicenter study
- **Primary endpoint: Overall Survival** measured from the start of crizotinib
- **Secondary endpoints**: PFS, ORR at 3 months (RECIST 1.1), efficacy of subsequent systemic therapies
- **Statistical analysis**: stratified Cox regression model for risk of death, logistic regression model for probability of objective response in evaluable patients
- **Inclusion period**: from November 18 2011 to December 31 2013



PFS: progression free survival; ORR: overall response rate; FISH: Fluorescent In Situ Hybridization;

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Baseline Characteristics at Time of Crizotinib Treatment Start

Baseline characteristics, n (%)		n=318
Age (years)	Median (range)	**58.4** (19.2-88.4)
Gender	**Female** / Male	**157 (49.4)** / 161 (50.6)
Ethnicity	**Non-asian**/ Asian / MD	**282 (98.6)** / 4 (1.4) / 32
Smoking status	**Never** / Former or Current / MD	**172 (55.1)** / 140 (44.9) / 6
Current smoker at time of crizotinib initiation	**Yes** / No / MD	**30 (9.6)** / 282 (90.4) / 6
Histology	**Adenocarcinoma** / Large cell / Other / MD	**289 (91.8)** / 19 (6.0) / 7 (2.2) / 3
ECOG Performance Status (PS)	**0-1** / 2-4 / MD	**222 (78.5)** / 61 (21.5) / 35
Stage	IV / III / MD	**265 (85.0)** / 47 (15.0) / 6
Brain metastases	**Yes** / No / MD	**101 (34.9)** / 188 (65.1) / 29
Line of therapy before crizotinib	0 / **1** / 2 / >2	17 (5.3) / **171 (53.8)** / 58 (18.2) / 72 (22.7)
Drugs received before crizotinib	Platinum based / Pemetrexed based / MD	254 (89.1) / 217 (76.1) /16

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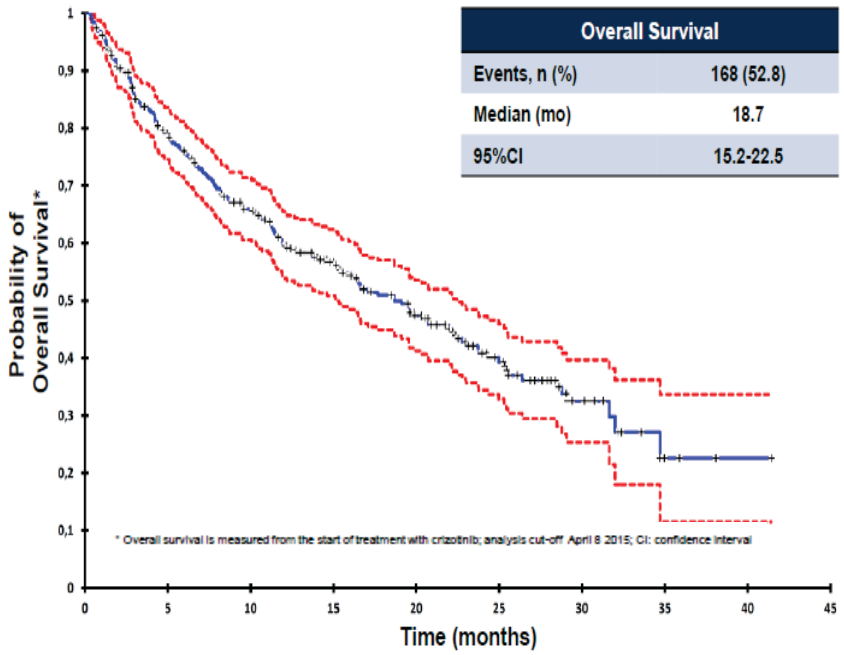
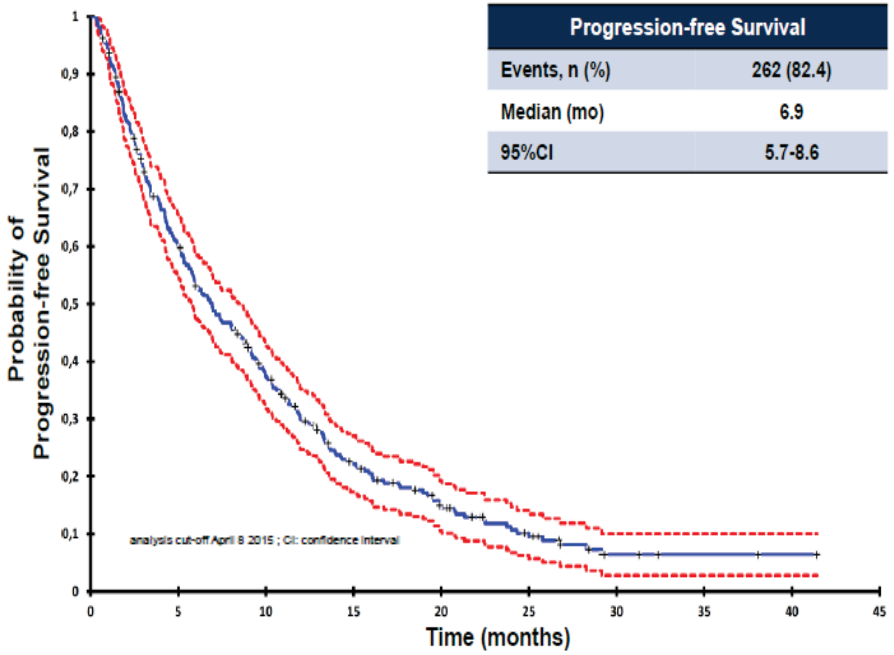
Primary and Secondary Endpoints

Primary Endpoint: Overall Survival



Overall Survival	
Events, n (%)	168 (52.8)
Median (mo)	18.7
95%CI	15.2-22.5

Secondary Endpoint: Progression-free Survival



Progression-free Survival	
Events, n (%)	262 (82.4)
Median (mo)	6.9
95%CI	5.7-8.6

Pfizer Oncology

Crizotinib: Rapid Approval, Excellent Initial Activity and Challenges with Post-approval Development Requires Alternative Solutions to Phase 3 randomized trials?

- ALK-positive advanced NSCLC is a serio□s and life-threatening disease with a high □nmet medical need
  - Orphan Dr□g Designation □ Fast □rac□ Designation
  - No e□isting therapy indicated specifically for ALK-positive NSCLC

Would that be BTD today?

- □ALKOR□provided a meaningf□l therape□tic benefit
  - □enerally safe and well tolerated
  - Associated with high, d□rable ORR
  - □hese data were reasonably li□ely to predict clinical benefit of cri□otinib in patients with ALK-positive advanced NSCLC
- Phase 3 randomi□ed trials were already □nderway
  - 2nd-line Phase 3 St□dy A8081007 – initiated Jan□ary 2010
  - 1st-line Phase 3 St□dy A8081014 – initiated Jan□ary 2011

Pfizer Oncology

Clinical Development of Crizotinib in ALK-Positive Advanced NSCLC

Protocol	Setting	Trial Design	Primary Endpoints
A8081001 Phase 1	All Lines Solid Tumors ALK-Positive NSCLC	Single-Arm, Open-Label	Safety, PK, ORR
A8081005 Phase 2	≥2nd-Line	Single-Arm, Open-Label	ORR, Safety
A8081007 Phase 3	2nd-Line	Crizotinib vs. Pemetrexed or Docetaxel, Open-Label	PFS ✓
A8081014 Phase 3	1st-Line	Crizotinib vs. Pem/Carbo or Pem/Cis, Open-Label	PFS ✓

Could we have used RWE studies as confirmatory studies in lieu of traditional randomized Phase 3 studies in as the initial evidence is strong?

What type of real world evidence would FDA accept in distinct situations: Pragmatic Randomized Trials? Contemporaneous "historical" controls? Registries?

□asis for approval – data from 255 ALK-positive NSCLC patients□✓ Completed

Pfizer Oncology

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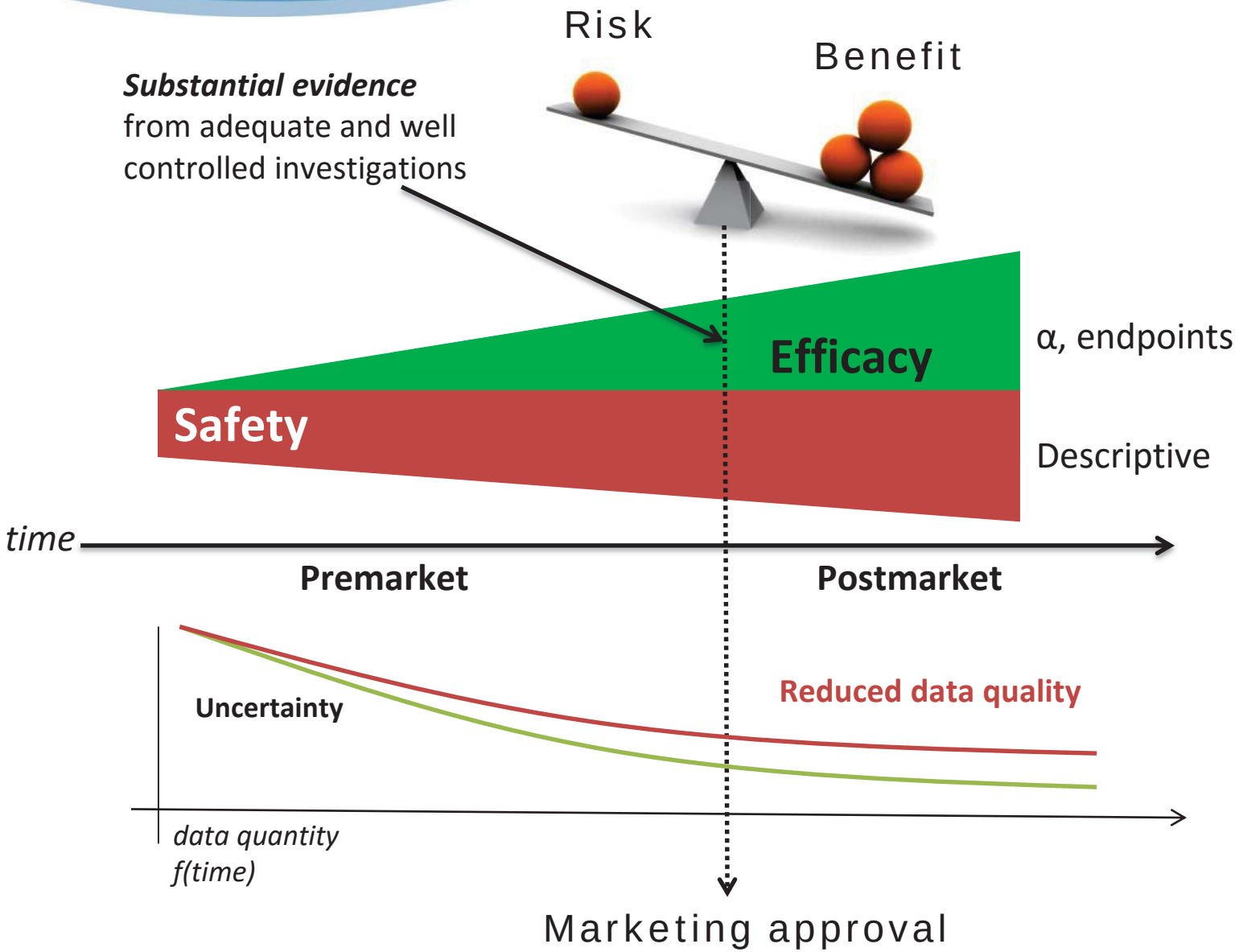
Office of Hematology and Oncology Products
Food and Drug Administration

The information in this presentation are my own and do not necessarily reflect the views and policies of FDA

Disclosures

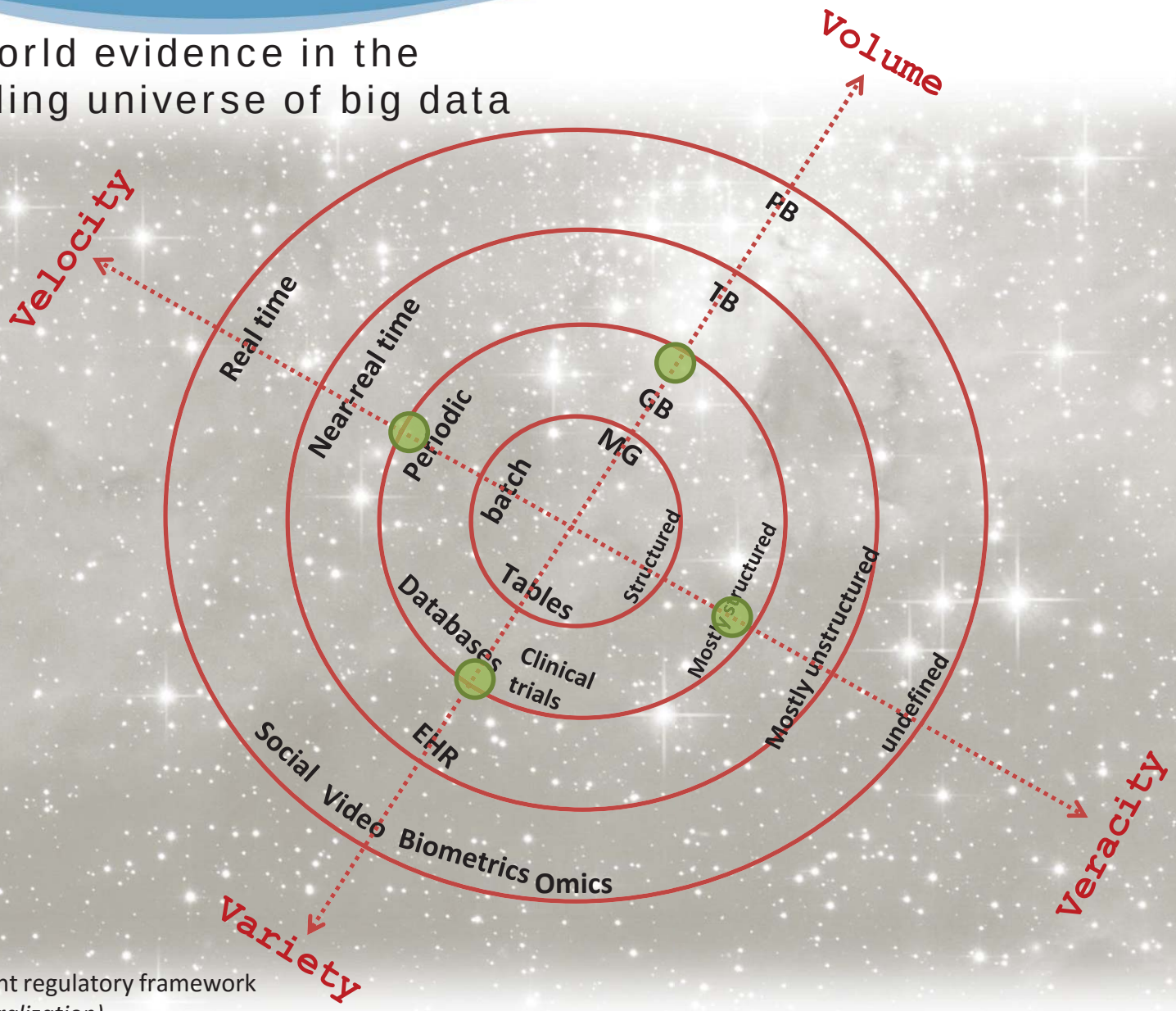
- None


Risk
Benefit
Substantial evidence
from adequate and well
controlled investigations
Efficacy
α, endpoints
Safety
Descriptive
time
Premarket
Postmarket
Uncertainty
Reduced data quality
data quantity
f(time)
Marketing approval

Uncertainty management

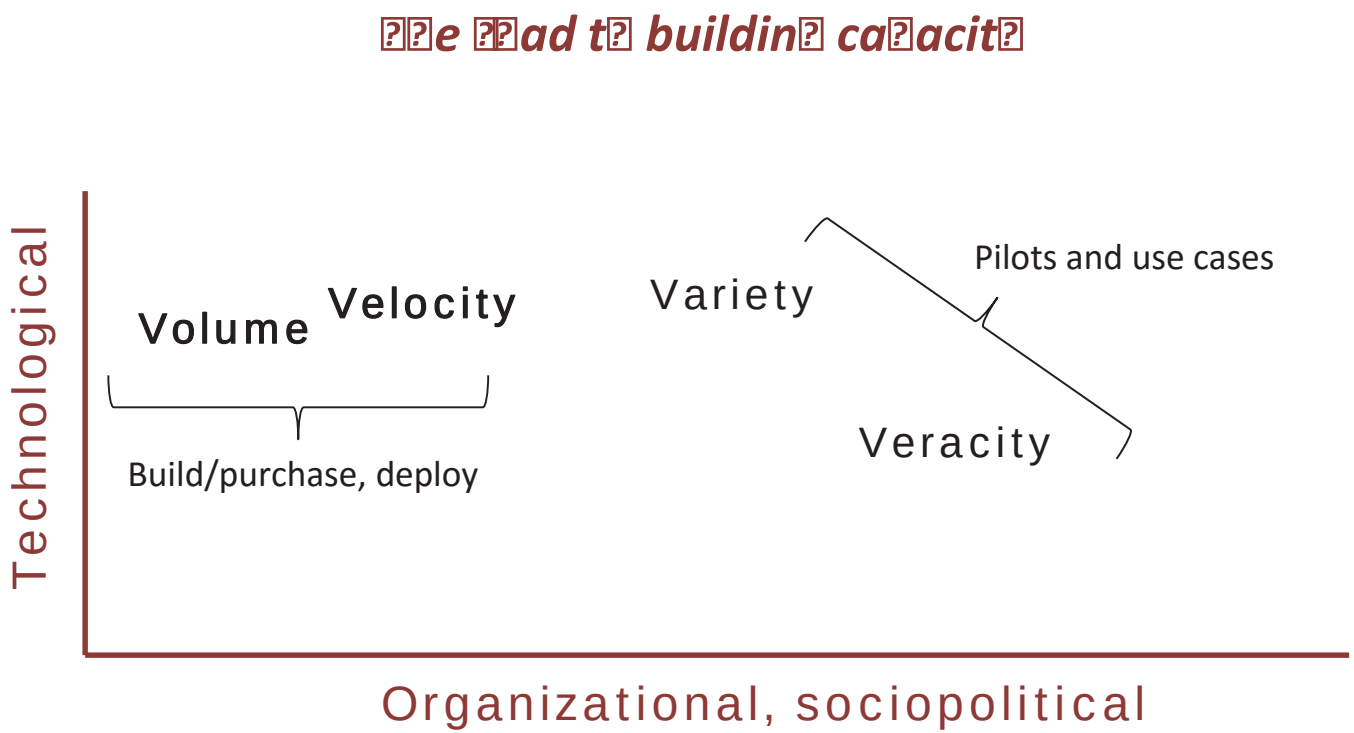
- Using novel pipelines of high quality data in regulatory decision making can reduce uncertainty
  - RWE
  - Patient reported
  - Biometrics (wearables, implantable, etc)

Real world evidence in the expanding universe of big data

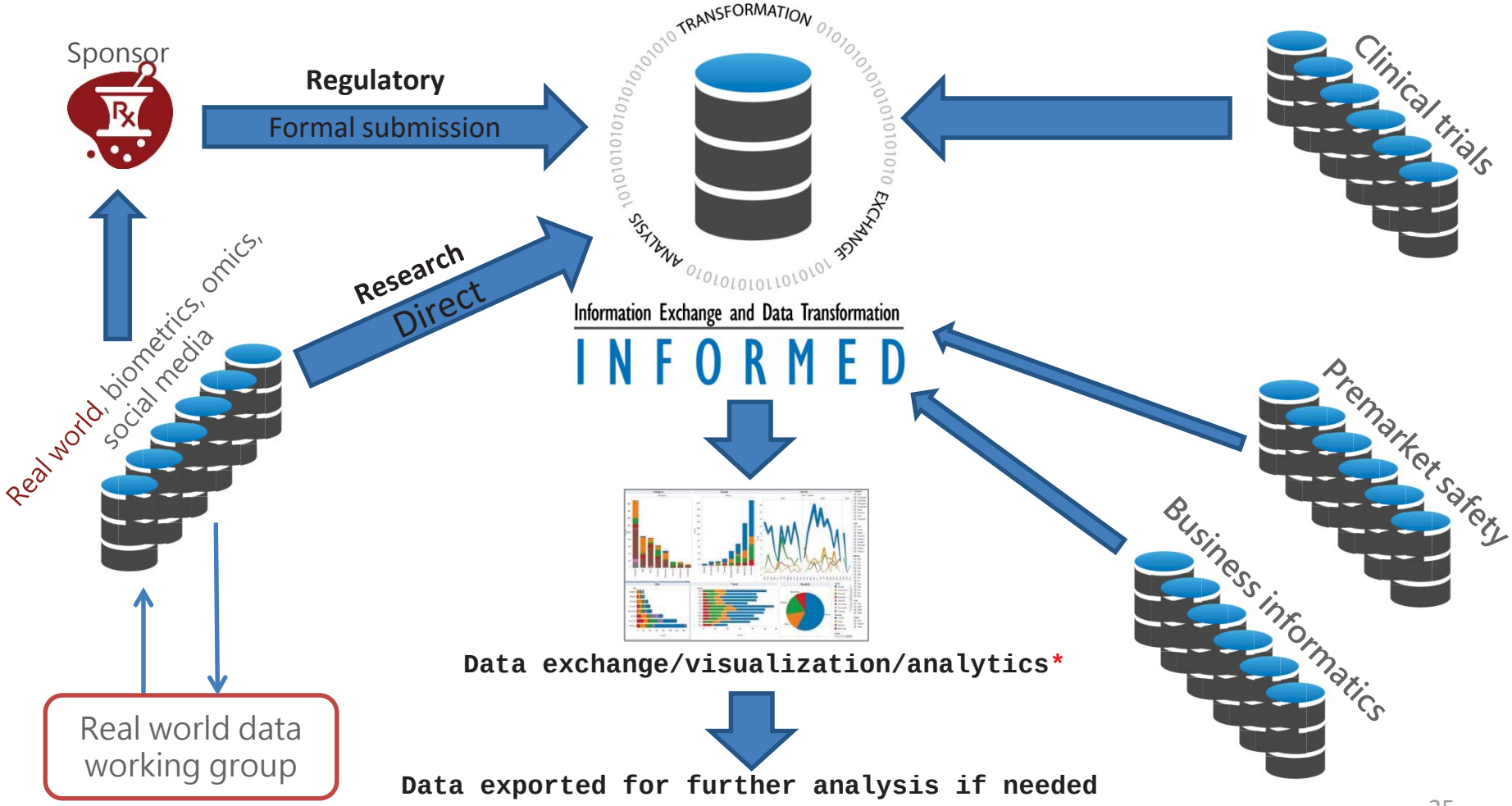


Current regulatory framework
(generalization)

The grand unified theory = learning health system



Information Exchange and Data Transformation (INFORMED)



*Technology and software development

"This is what using an EMR feels like"