MASSACHUSETTS
INSTITUTE OF
TECHNOLOGY

Benefit Risk Analysis Of Decision-Making: Oncology

G.K. Raju, Ph.D.

December 13th 2016

Outline

- Background
- Approach
- Application to Oncology
  - Non-Small Cell Lung Cancer
  - Learnings & Ongoing Work
  - Acknowledgements

Decisions & Benefit-Risk

NSCLC (Crizotinib)

"The FDA granted regular approval to crizotinib based on a favorable benefit-risk assessment for the indication of treatment of patients with NSCLC whose tumors are ALK positive, as detected by an FDA-approved test."

Source: Dickran Kazandjian, Gideon M. Blumenthal, [...], and Richard Pazdur, "FDA Approval Summary: Crizotinib for the Treatment of Metastatic Non-Small Cell Lung Cancer With Anaplastic Lymphoma Kinase Rearrangements", Oncologist. 2014 Oct; 19(10): e5–e11. Published online 2014 Aug 28. doi: 10.1634/theoncologist.2014-0241

Multiple Myeloma (Bortezomib)

"The dose and schedule studied in the protocol confer clear clinical benefits of disease control and survival improvement with well-characterized, acceptable, and manageable safety. "

Source: Medical Review Section 1.2 Risk Benefit Analysis

CML (Omacetaxine)

"Omacetaxine has a positive risk-benefit assessment for patients with CML-CP or CML-AP who have previously received at least two prior TKIs "

Source: Medical Review Section 1.2 Risk Benefit Analysis

Decisions & Benefit-Risk

Breast Cancer (Avastin)

"The modest benefit observed with Avastin together with the substantial adverse reactions observed in breast cancer trials to date fail to provide a favorable risk-benefit profile to support continued marketing of Avastin for a first-line metastatic breast cancer indication."*

***FDA Memorandum to the File BLA 125085 Avastin (bevacizumab) Dated December 15, 2010**

Breast Cancer (Palbociclib)

"The basis for this recommendation is a favorable benefit-risk profile for palbociclib when added to letrozole in first-line ER-positive, HER2-negative advanced breast cancer"

Source: Medical Review Section 1.1 Recommendation on Regulatory Action

Melanoma (Ipilimumab)

"The benefits of ipilimumab, which is demonstration of a reproducible increase in overall survival time, outweighs the sometimes substantial and unique adverse reactions of this product."

Source: Division Director Summary Review, Section 13.Decision/Action/Risk Benefit Assessment

Decision-Making & Benefit-Risk

Decisions	• Accelerated Approval • Non-Approval • Full Approval • Withdrawal
Benefit Risk	
Disciplines	• Efficacy • Safety • CMC • Clinical Microbiology • Pharmacokinetics • Pharmacodynamics

Decisions & Benefit-Risk

- **FDA Benefit-Risk Framework**
  - **Analysis of Condition**
  - **Alternate Treatments**
  - **Benefits**
  - **Risks**
  - **Risk Management**

- **PDUFA**

Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making Draft PDUFA V Implementation Plan - February 2013 Fiscal Years 2013-2017

Current clinical reviews can be rather lengthy, highly detailed documents. Distilling such an extensive document down to a short and concise summary can be challenging and may also highlight the need for an additional type of training. Over time, CDER and CBER will build a database of worked examples of benefit-risk frameworks that can be used as a reference for reviewers. Such a database can serve a dual purpose of providing examples of high quality frameworks as well as establishing an easily accessible set of regulatory precedents that can be a future reference when similar regulatory decisions must be made.

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Approach

STATE OF THE ART

Benefit-Risk Analysis for Decision-Making: An Approach

GK Raju[1,2], K Gurumurthi[1] and R Domike[1]

The analysis of benefit and risk is an important aspect of decision-making throughout the drug lifecycle. In this work, the use of a benefit-risk analysis approach to support decision-making was explored. The proposed approach builds on the qualitative US Food and Drug Administration (FDA) approach to include a more explicit analysis based on international standards and guidance that enables aggregation and comparison of benefit and risk on a common basis and a lifecycle focus. The approach is demonstrated on six decisions over the lifecycle (e.g., accelerated approval, withdrawal, and traditional approval) using two case studies: natalizumab for multiple sclerosis (MS) and bedaquiline for multidrug-resistant tuberculosis (MDR-TB).

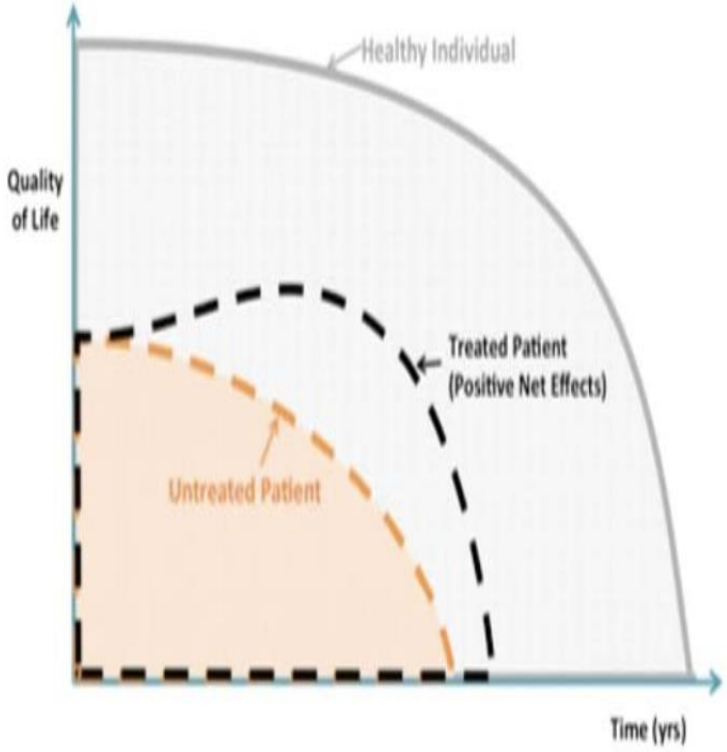
The availability of safe and effective medicines is crucial to patients and the broader population, and can substantially impact life, health, and economic outcomes.[1] Benefit-risk approaches have the potential to facilitate stakeholder (patients, sponsors, regulators, providers, payers, etc.) decision-making throughout the drug lifecycle, and thereby facilitate the accessibility of safe and effective medicines.[2] Prior work[3–5] has discussed a number of desirable attributes of benefit-risk frameworks and highlighted

online). In this work, the qualitative FDA approach[6] is extended to include a more explicit analysis based on international standards[12] and guidance[13] that enables aggregation and weighing of benefits and risk and a lifecycle focus.[14,15] The analysis approach is demonstrated using two case studies. Our focus on the FDA decision-making is related but also distinct from decision-making to support Health Technology Assessment that also includes economic and other considerations.[16,17]

***Clinical Pharmacology & Therapeutics*, Oct 2016**

Approach: Impact on Quantity and Quality of Life

Positive Net Effects



Negative Net Effects

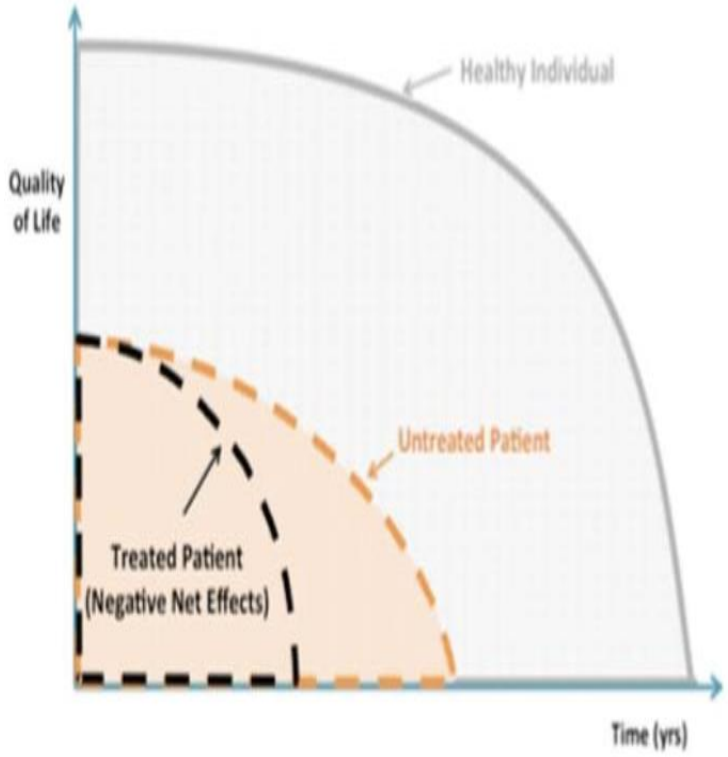


Figure 1 Impact on quality of life over time due to disease and treatment (hypothetical). Scenario A1: positive net effects; scenario B1: negative net effects.

Approach: Benefit-Risk Analysis (Hypothetical)

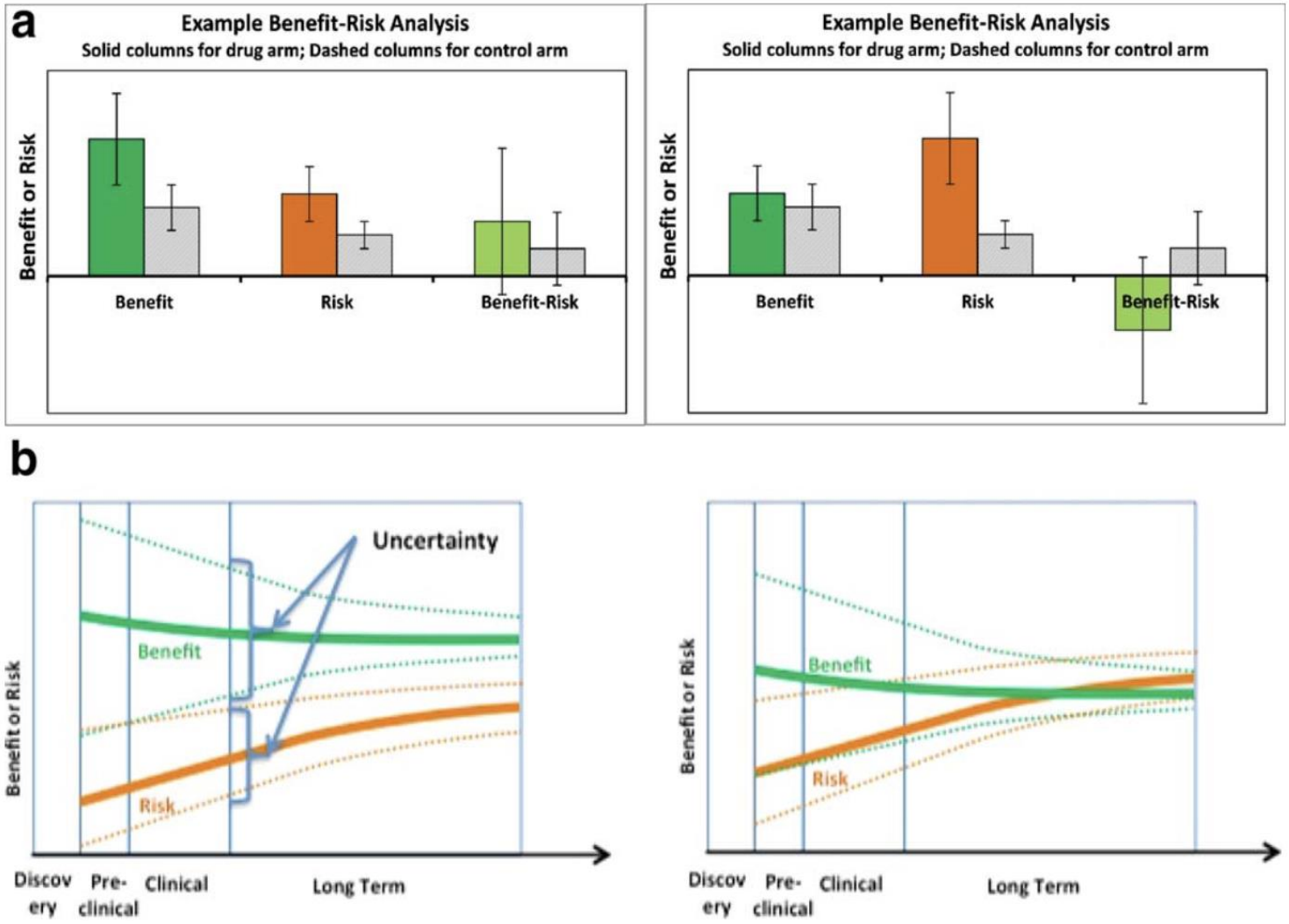


Figure 2 (**a**) Benefit-risk analysis (hypothetical). Scenario A1: positive net effects (expected). Scenario B1: negative net effects (expected). (**b**) Benefit-risk changes over phases of a lifecycle (hypothetical). Scenario A2: positive benefit-risk profile over time; scenario B2: positive to negative benefit-risk.

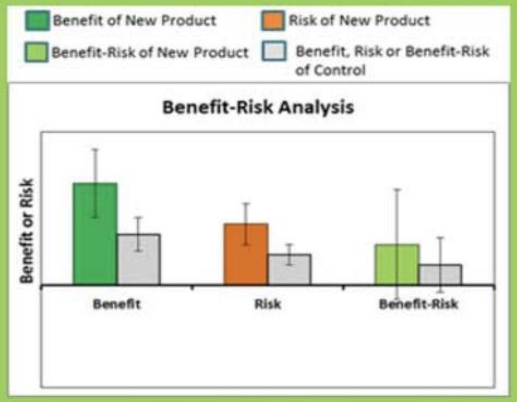
Approach: Benefit Risk Knowledge Mgmt

Unknown Knowns
(Benefits/Harms Discovered But Not Yet in Context (e.g. lab, animal trials))

- Disease (e.g. Models of)
- Benefits & Risks (e.g. based on lab and animal studies)
- 'Benefit'& Risk Management (e.g. System Maturity)

"Translation" Release Data (Integrate into Decision Making)

Known Knowns
(Benefits/Harms Characterized)



- Disease (e.g. Disability, Survival)
- 'Benefit' & Risk (e.g. Magnitude/Severity, Occurrence)
- 'Benefit'& Risk Management (e.g. System Maturity)

"Continuous Improvement" Refinement (Additional Clinical Trials, Surveillance)

Known Unknowns
(Benefits/Harms Identified But Not YetCharacterized/Certain)

- Disease (e.g. Disability, Life Expectancy by sub-population)
- 'Benefit' & Risk (e.g. Magnitude/Severity , Occurrence by sub-population)
- 'Benefit'& Risk Management (e.g. site-wise maturity)

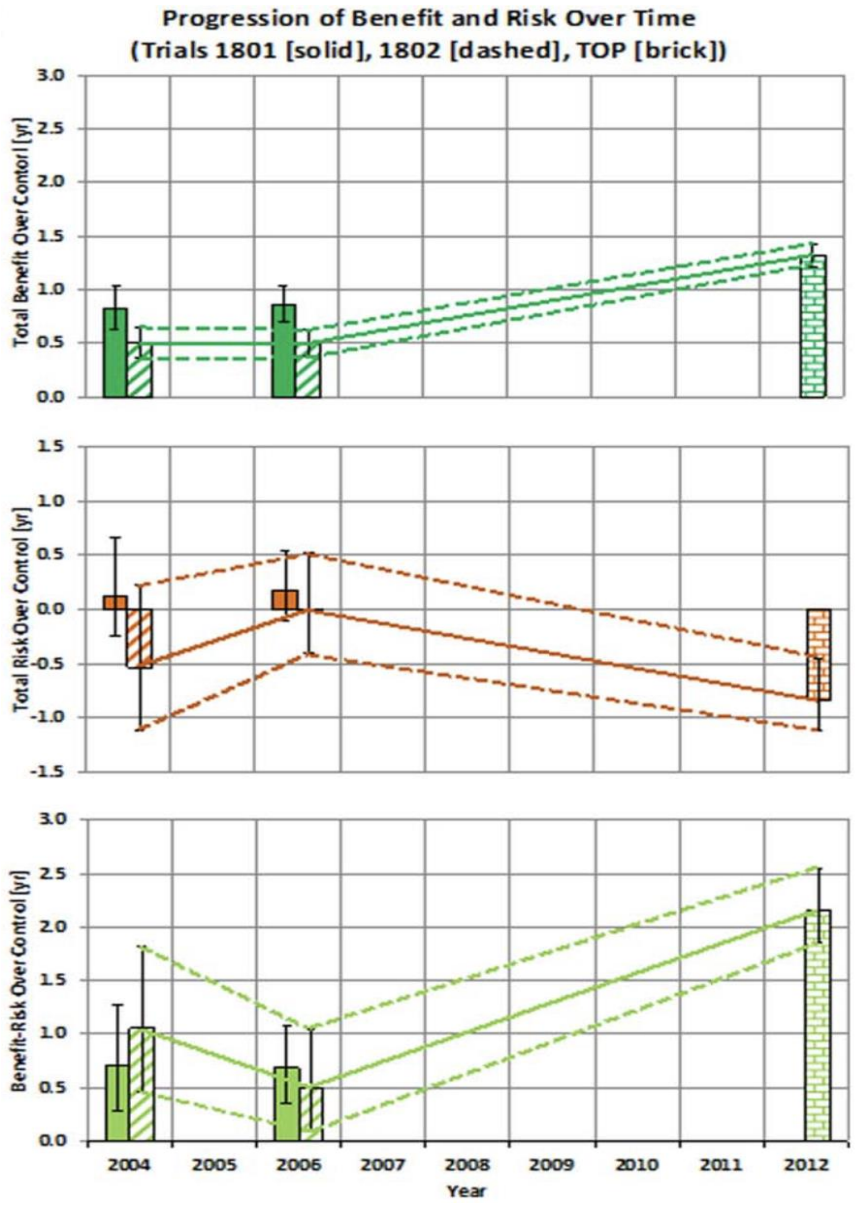
Discovery

Unknown Unknowns
(Benefits/Harms Not Yet Discovered)

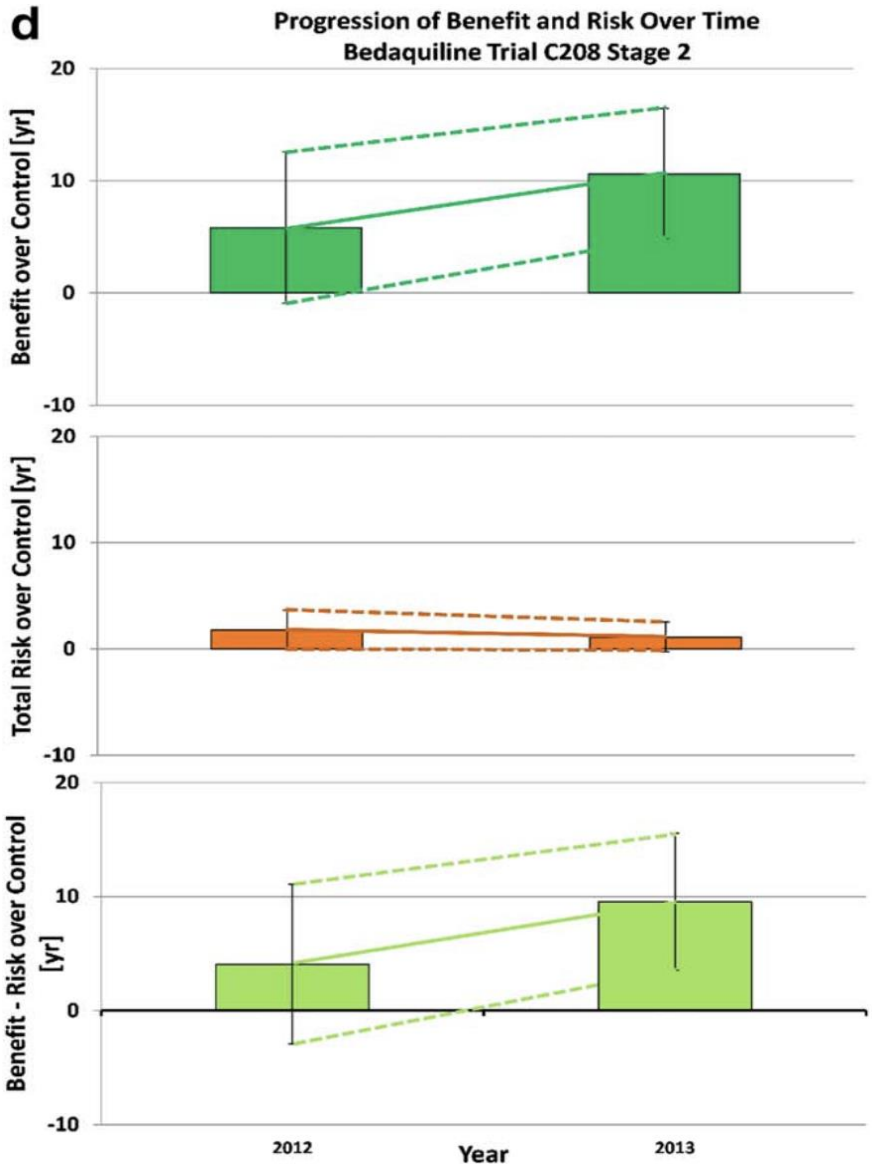
- Disease (e.g. variants of)
- Benefits & Risk (e.g. as yet unidentified)
- 'Benefit'& Risk Management (e.g. System Maturity of very new organizations)

Approach: Demonstration: MS and MDR-TB

Multiple Sclerosis (Tysabri)



MDR-TB (Bedaquiline)



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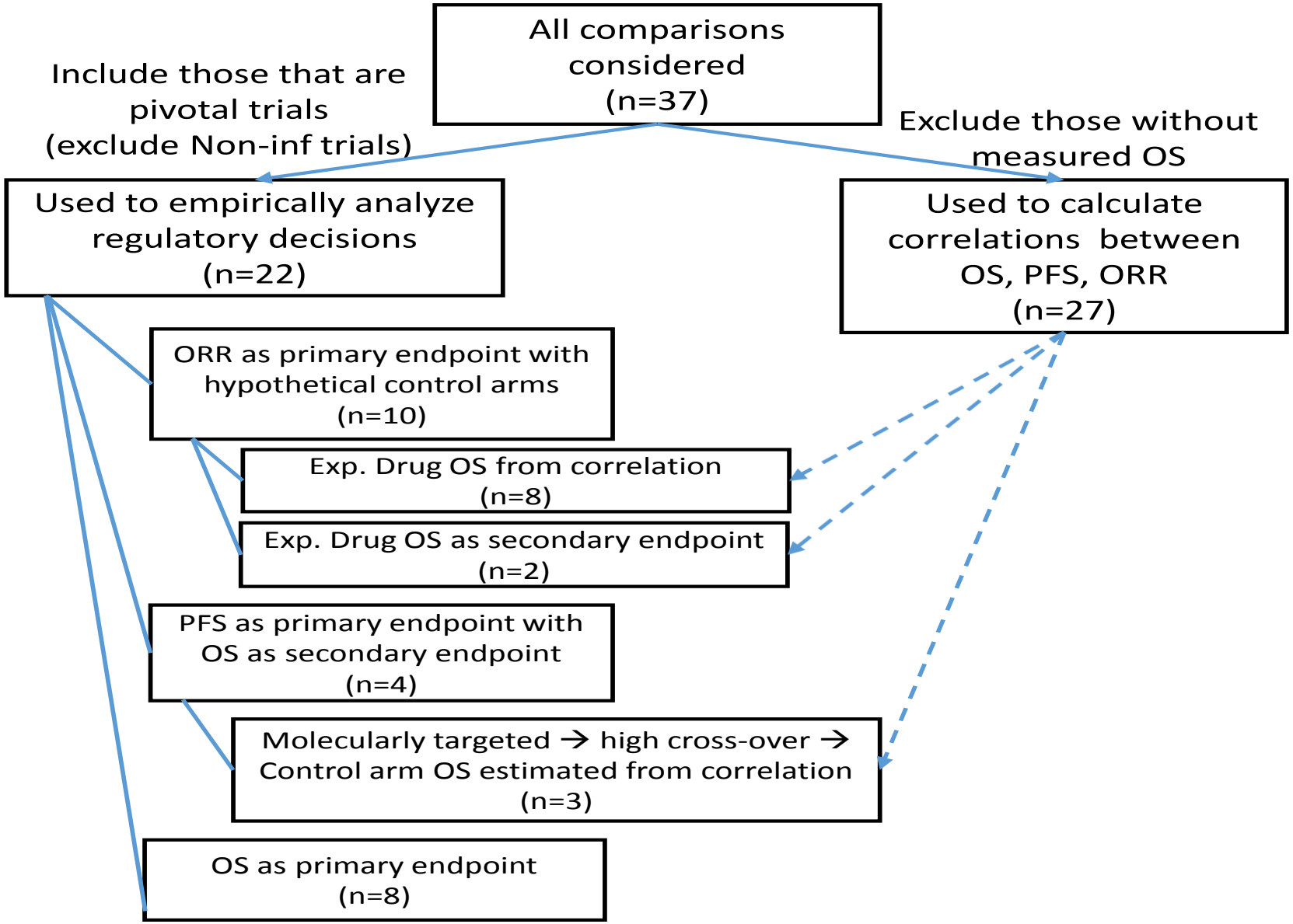
NSCLC Studies: Analyzing Benefit



Analyzing Risks

Medical Review

Safety

Deaths
- Those not due to disease progression

•**Level 5 Harms**

Non-fatal Serious Adverse Events
- Life threatening (e.g. Myocardial Infarction, Cerebrovascular Accident):
- Very Disabling but not Life Threatening
- (e.g. Gastrointestinal bleeding, fractures)
- Other

•**Level 4 Harms**

• **Level 3 Harms**

Common Adverse Events
- Other than deaths and non-fatal Serious AEs

• **Level 2 Harms**

• **Level 1 Harms**

$$\text{Risk}_i = \text{Magnitude of Harm}_i * \text{Probability of Occurrence of Harm}_i$$

$$\text{Risk} = \Sigma_i \, (\text{Magnitude of Harm}_i * \text{Occurrence of Harm}_i)$$

Occurrence of Harm of Grade i = Number of Patients experiencing Adverse Events of Grade i/Total Number of Patients

Severity & Seriousness

Level	Description	Seriousness (%)
5	Death	100%
4	Moderate to high, chronic disability or Life Threatening/Shortening Condition	10%
3	Moderate to high disability	1%
2	Mild Disability	0.1%
1	Very Mild Disability	0.01%

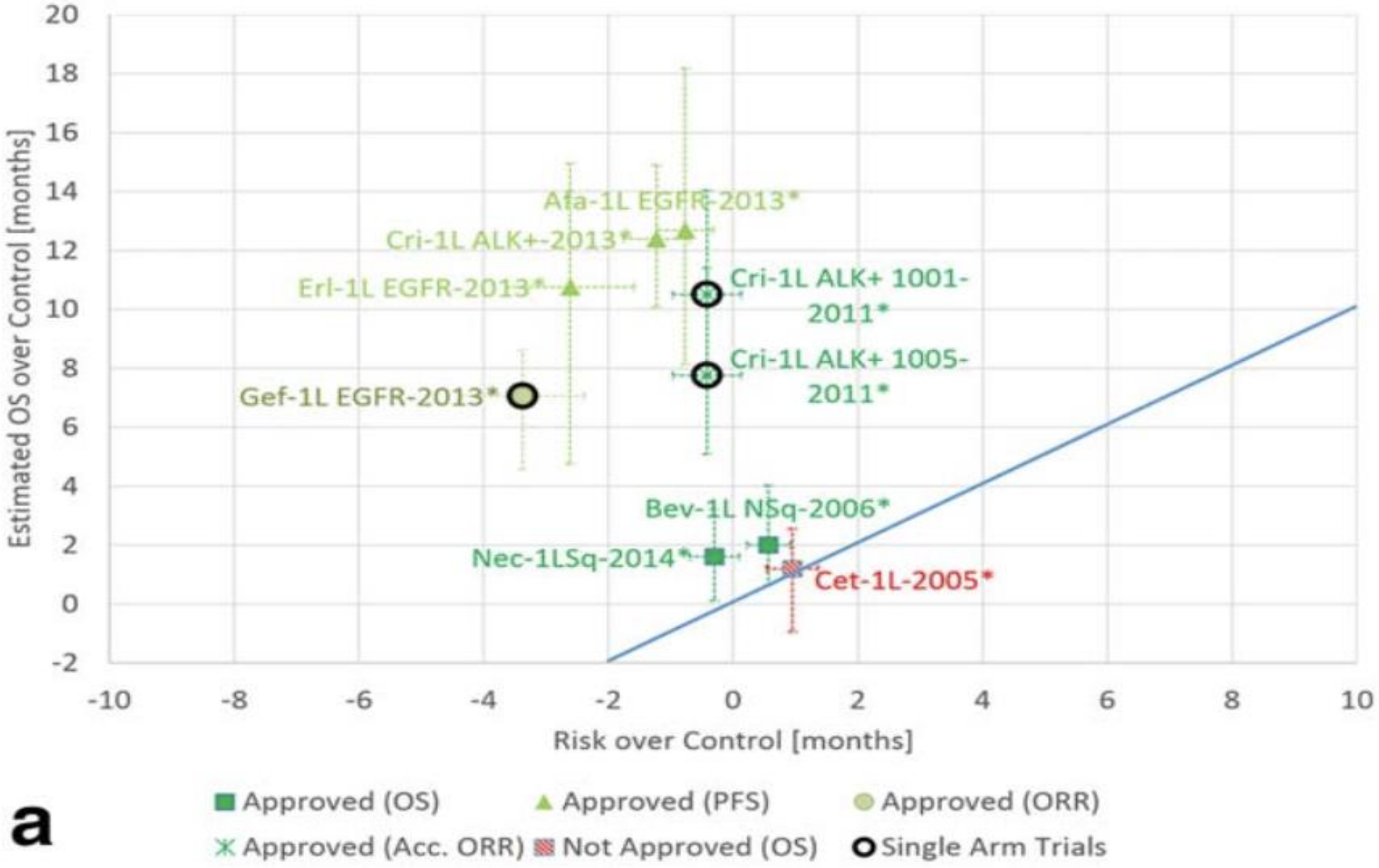
% of Life Expectancy e.g.. 3 years for some metastatic cancers

- **Analogous to Severity Scale**
  - **Common Toxicity Criteria Adverse Event (CTCAE)**
- **Severity and Seriousness**

Case Studies: NSCLC: First Line

Experimental Drug Arm	Control Arm	Patient Population	Study Title	Date	Chart Alias	Primary Endpoint	Estimated Benefit: Hazard Ratio for Primary Endpoint Point Estimate (LCL, UCL); p-value	Estimated Benefit: Median OS Exp. Drug - Control Median Difference (LCL, UCL) [months]	Estimated Total Risk: Exp. Drug - Control Mean Estimate (LCL, UCL) [months]	Regulatory Decision
Afatinib*	Pemetrexed/Cisplatin	1L EGFRm	1200.32	Apr-13	Afa-1L EGFR-2013*	PFS	0.58 (0.43, 0.78); 0.0003	*12.65* *(8.04, 18.2)*	-0.77 (-1.23, -0.31)	Approved
Bevacizumab + Carboplatin + Paclitaxel*	Carboplatin+Paclitaxel	1L NSq	E4599	Oct-06	Bev-1L NSq-2006*	OS	0.8 (0.68, 0.94); 0.013	2 (0.63, 4.02)	0.57 (0.22, 0.91)	Approved
Cetuximab + Cisplatin + Vinorelbine*	Cisplatin + Vinorelbine	1L	FLEX (Phase III)	Sep-05	Cet-1L-2005*	OS	0.87 (0.76, 1); 0.044	1.2 (-0.95, 2.56)	0.95 (0.54, 1.36)	Not Approved
Crizotinib*	None (Single Arm) (Hypothetical control same as Cri-1L ALK+-2013*)	1L ALK+	1005	Aug-11	Cri-1L ALK+ 1005-2011*	ORR	None (Single Arm)	*7.97* *(5.27, 11.67)*	*-0.42* *(-0.97, 0.13)*	Accelerated Approval
Crizotinib*	None (Single Arm) (Hypothetical control same as Cri-1L ALK+-2013*)	1L ALK+	1001	Aug-11	Cri-1L ALK+ 1001-2011*	ORR	None (Single Arm)	*10.71* *(7.88, 14.32)*	*-0.42* *(-0.97, 0.13)*	
Crizotinib*	Docetaxel or Pemetrexed	1L ALK+	1007	Oct-13	Cri-1L ALK+-2013*	PFS	0.49 (0.37, 0.64); <0.0001	*12.65* *(10.31, 15.25)*	-1.23 (-1.76, -0.69)	Approved
Erlotinib(EGFRm)*	Platinum based Doublet Chemotherapy	1L EGFRm	ML20650 (EURTAC)	Apr-13	Erl-1L EGFR-2013*	PFS	0.34 (0.23, 0.49); <0.0001	*10.85* *(4.83, 15.06)*	-2.61 (-3.63, -1.59)	Approved
Gefitinib(EGFRm)*	None (Single Arm) (Hypothetical control same as Erl-1L EGFR-2013*)	1L EGFRm	IFUM	Nov-13	Gef-1L EGFR-2013*	ORR	None (Single Arm)	*7.15* *(4.64, 8.75)*	*-3.38* *(-4.37, -2.39)*	Approved
Necitumumab + Gemcitabine + Cisplatin*	Gemcitabine + Cisplatin	1LSq	SQUIRE	Jul-14	Nec-1LSq-2014*	OS	0.84 (0.74, 0.96); 0.012	1.6 (0.11, 3.23)	-0.3 (-0.7, 0.09)	Approved (ODAC)

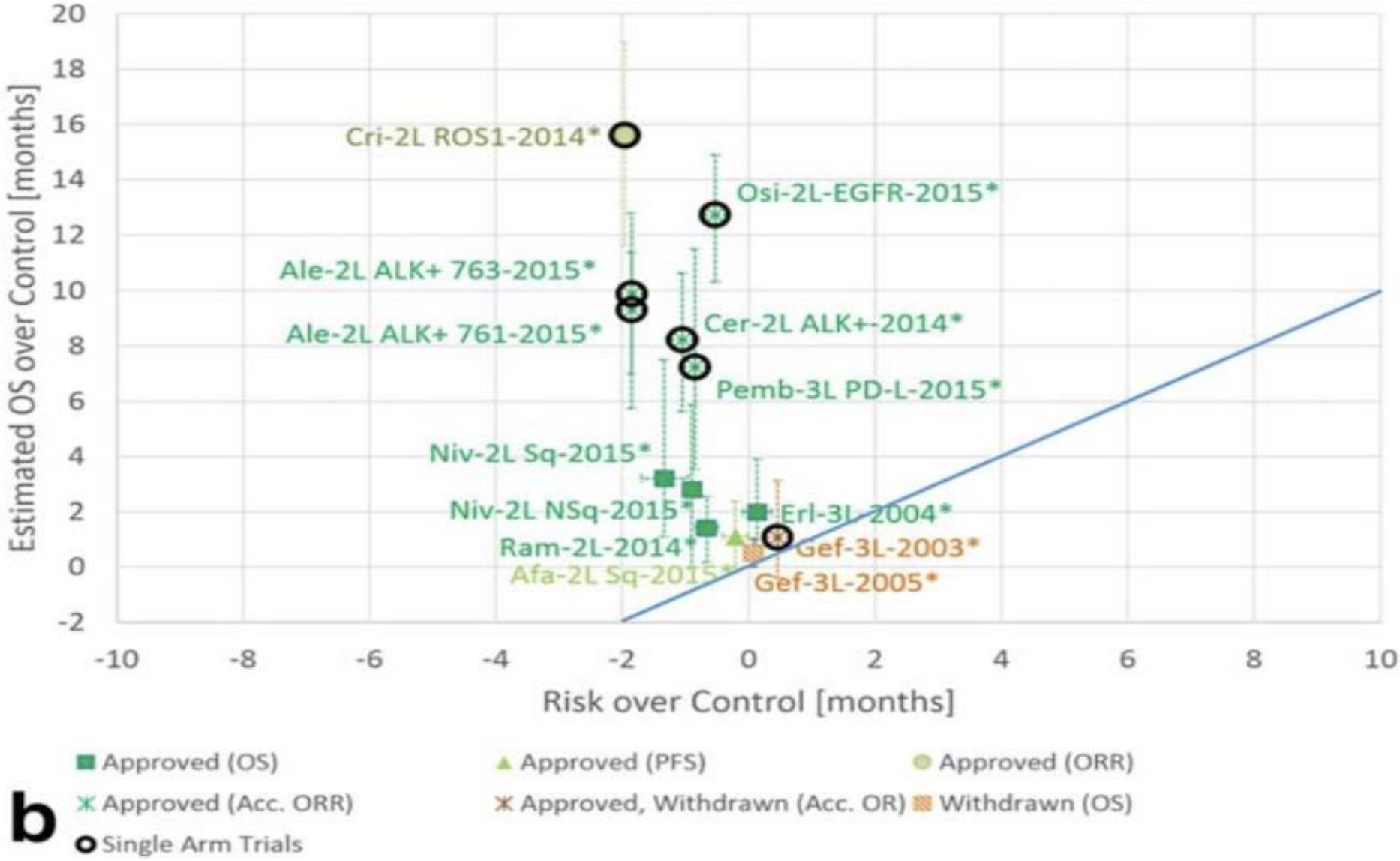
Benefit Risk Analysis: NSLCLC: First Line



Case Studies: NSCLC: Non First Line

Experimental Drug Arm	Control Arm	Patient Population	Study Title	Date	Chart Alias	Primary Endpoint	Estimated Benefit: Hazard Ratio for Primary Endpoint Point Estimate (LCL, UCL); p-value	Estimated Benefit: Median OS Exp. Drug - Control Median Difference (LCL, UCL) [months]	Estimated Total Risk: Exp. Drug - Control Mean Estimate (LCL, UCL) [months]	Regulatory Decision
Afatinib*	Erlotinib	2L Sq	LUX-Lung8	Jul-15	Afa-2L Sq-2015*	PFS	0.81 (0.69, 0.96); 0.0103	1.1 (-0.04, 2.38)	-0.21 (-0.41, -0.01)	Approved
Alectinib*	None(Single Arm) (Hypothetical Control same as that of Pem 2L)	2L ALK+ Progression on Crizotinib	NP28761	Nov-15	Ale-2L ALK+ 761-2015*	ORR	None (Single Arm)	*9.3* *(5.75, 12.78)*	*-1.85* *(-2.08, -1.62)*	Accelerated Approval
Alectinib*	None(Single Arm) (Hypothetical Control same as that of Pem 2L)	2L ALK+ Progression on Crizotinib	NP28763	Nov-15	Ale-2L ALK+ 763-2015*	ORR	None (Single Arm)	*9.88* *(7, 11.38)*	*-1.85* *(-2.08, -1.62)*	
Ceritinib*	None(Single Arm) (Hypothetical Control same as that of Pem 2L)	2L ALK+ P/I to Crizotinib	X2101	Mar-14	Cer-2L ALK+-2014*	ORR	None (Single Arm)	*8.21* *(5.63, 10.64)*	*-1.05* *(-1.3, -0.8)*	Accelerated Approval
Crizotinib*	None(Single Arm) (Hypothetical Control same as that of Pem 2L)	2L ROS1+	NCT00585195	Nov-14	Cri-2L ROS1-2014*	ORR	None (Single Arm)	*15.6* *(11.62, 18.98)*	*-1.96* *(-2.19, -1.73)*	Approved
Erlotinib*	Placebo	3L	BR.21	Sep-04	Erl-3L-2004*	OS	0.73 (0.6, 0.87); 0.001	1.97 (0.68, 3.91)	0.14 (-0.09, 0.36)	Approved
Gefitinib*	Placebo	3L	ISEL	Nov-05	Gef-3L-2005*	OS	0.89 (0.77, 1.02); 0.087	0.5 (-0.01, 1.03)	0.08 (0, 0.16)	Withdrawn (ODAC)
Gefitnib*	None (Single Arm) (Hypothetical control same as Gef-3L-2005*)	3L	39	May-03	Gef-3L-2003*	ORR	None (Single Arm)	*1.07* *(-0.39, 3.12)*	*0.46* *(0.24, 0.69)*	Approval (ODAC) (subsequently withdrawn)
Nivolumab*	Docetaxel	2L	CA209017	Mar-15	Niv-2L Sq-2015*	OS	0.59 (0.44, 0.79); 0.00025	3.2 (1.1, 7.5)	-1.33 (-1.7, -0.97)	Approved
Nivolumab*	Docetaxel	2L	CheckMate 057	Sep-15	Niv-2L NSq-2015*	OS	0.73 (0.59, 0.89); 0.002	2.8 (-0.02, 5.89)	-0.89 (-0.99, -0.79)	Approved
Osimertinib*	None(Single Arm) (Hypothetical Control same as that of Pem 2L)	2L-EGFRm	AURA 2	Oct-15	Osi-2L-EGFR-2015*	ORR	None (Single Arm)	*12.74* *(10.31, 14.89)*	*-0.53* *(-0.7, -0.36)*	Accelerated Approval
Pembrolizumab*	None(Single Arm) (Hypothetical Control same as that of Pemb 3L Doc)	3L PD-L1	KEYNOTE 001	Oct-15	Pemb-3L PD-L-2015*	ORR	None (Single Arm)	*7.24* *(3.54, 11.5)*	*-0.85* *(-1.02, -0.68)*	Accelerated Approval
Ramucirumab + Docataxel*	Placebo+Docataxel	2L	I4T-MC-JVBA	Dec-14	Ram-2L-2014*	OS	0.86 (0.75, 0.98); 0.024	1.4 (0.18, 2.54)	-0.66 (-0.83, -0.49)	Approved

Benefit Risk Analysis: NSCLC: Non First Line



Sensitivity Analysis: Crizotinib

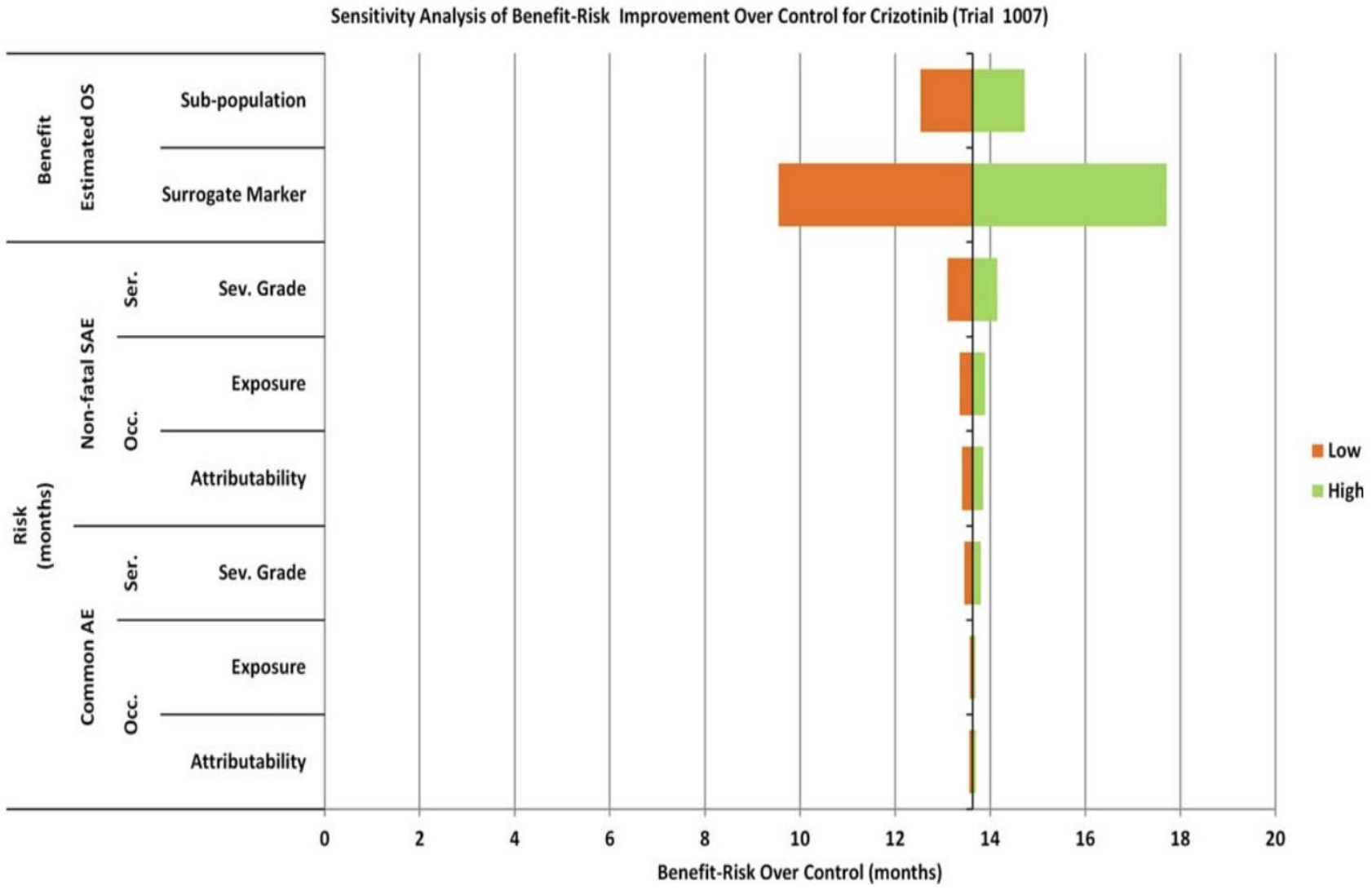


Figure 5 Sensitivity analysis of benefit–risk over control: crizotinib.

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Learnings & On-Going Work

- **Able to Capture A Benefit-Risk Rationale For Decision-Making**
- **Extensions**
  - **Other Decisions and Aspects**
  - **Lifecycle: Earlier and Later**
  - **Patient Reported Outcomes**
  - **Patient Level Analysis**
- **Other Disease Areas**
  - **Multiple Myeloma**
  - **Several Others**
- **Limitations: AE Reporting, etc.**

Application to Oncology

STATE OF THE ART

A Benefit–Risk Analysis Approach to Capture Regulatory Decision-Making: Non-Small Cell Lung Cancer

GK Raju[1], K Gurumurthi[1], R Domike[1], D Kazandjian[2], G Blumenthal[2], R Pazdur[2] and J Woodcock[2]

Drug regulators around the world make decisions about drug approvability based on qualitative benefit–risk analyses. There is much interest in quantifying regulatory approaches to benefit and risk. In this work the use of a quantitative benefit–risk analysis was applied to regulatory decision-making about new drugs to treat advanced non-small cell lung cancer (NSCLC). Benefits and risks associated with 20 US Food and Drug Administration (FDA) decisions associated with a set of candidate treatments submitted between 2003 and 2015 were analyzed. For benefit analysis, the median overall survival (OS) was used where available. When not available, OS was estimated based on overall response rate (ORR) or progression-free survival (PFS). Risks were analyzed based on magnitude (or severity) of harm and likelihood of occurrence. Additionally, a sensitivity analysis was explored to demonstrate analysis of systematic uncertainty. FDA approval decision outcomes considered were found to be consistent with the benefit–risk logic.

The availability of safe and effective medicines is crucial to individual patients and the broader population, and can substantially impact life, health, and economic outcomes.[1,2] Regulatory decisions about drug approvability are fundamentally benefit–risk assessments (as documented by representative quotations in **Supplementary Table 1**), and such assessments are also used to facilitate stakeholder (patients, sponsors, providers, payers, etc.) decision-making throughout the drug development lifecycle. The US Food and Drug Administration (FDA),[3] the European Medi-

a surrogate endpoint believed reasonably likely to predict clinical benefit.[9,10]

In this work the qualitative FDA benefit–risk framework[3] was used to create a quantitative benefit–risk model and graphical representation. Advanced NSCLC was a useful test disease area because there is one fundamental desired outcome measure (improved duration of survival) and there are existing scales for quantifying harm (adverse events) in a way that enables construction of an overall risk metric that can be compared with expected

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- Co-Authors
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- U.S. Food and Drug Administration
  - Janet Woodcock
  - Richard Pazdur

References

- Raju GK, Gurumurthi K, Domike R. Benefit-Risk Analysis for Decision-Making: An Approach. *Clinical Pharmacology & Therapeutics*, Oct, 2016.
- Raju GK, Gurumurthi K, Domike R, Kazandjian D, Blumenthal G, Pazdur R, Woodcock, J. A Benefit-Risk Analysis Approach to Capture Regulatory Decision-Making: Non-Small Cell Cancer. *Clinical Pharmacology & Therapeutics,* Oct, 2016.