COUNTING CARDS IN BIOTECH

A Checklist for Improving the Odds of Success in Early Stage Targeted Therapies in Cancer

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DRIEHAUS CAPITAL MANAGEMENT LLC

OUR ARGUMENT: IF INVESTING IN EARLY STAGE BIOTECH COMPANIES IS A GAMBLE, THEN LET'S COUNT CARDS

Many people believe early stage biotech is a gamble

"The harsh truth is that investing in a small or even medium sized biotech company is a lot like gambling in Las Vegas. You are either going to win big or lose big and – short of a true medical breakthrough – it is almost impossible to predict in advance what will happen. Even the companies don't know what will happen."

Robert Langreth, *Forbes*, December 2010

We acknowledge biotech is risky…

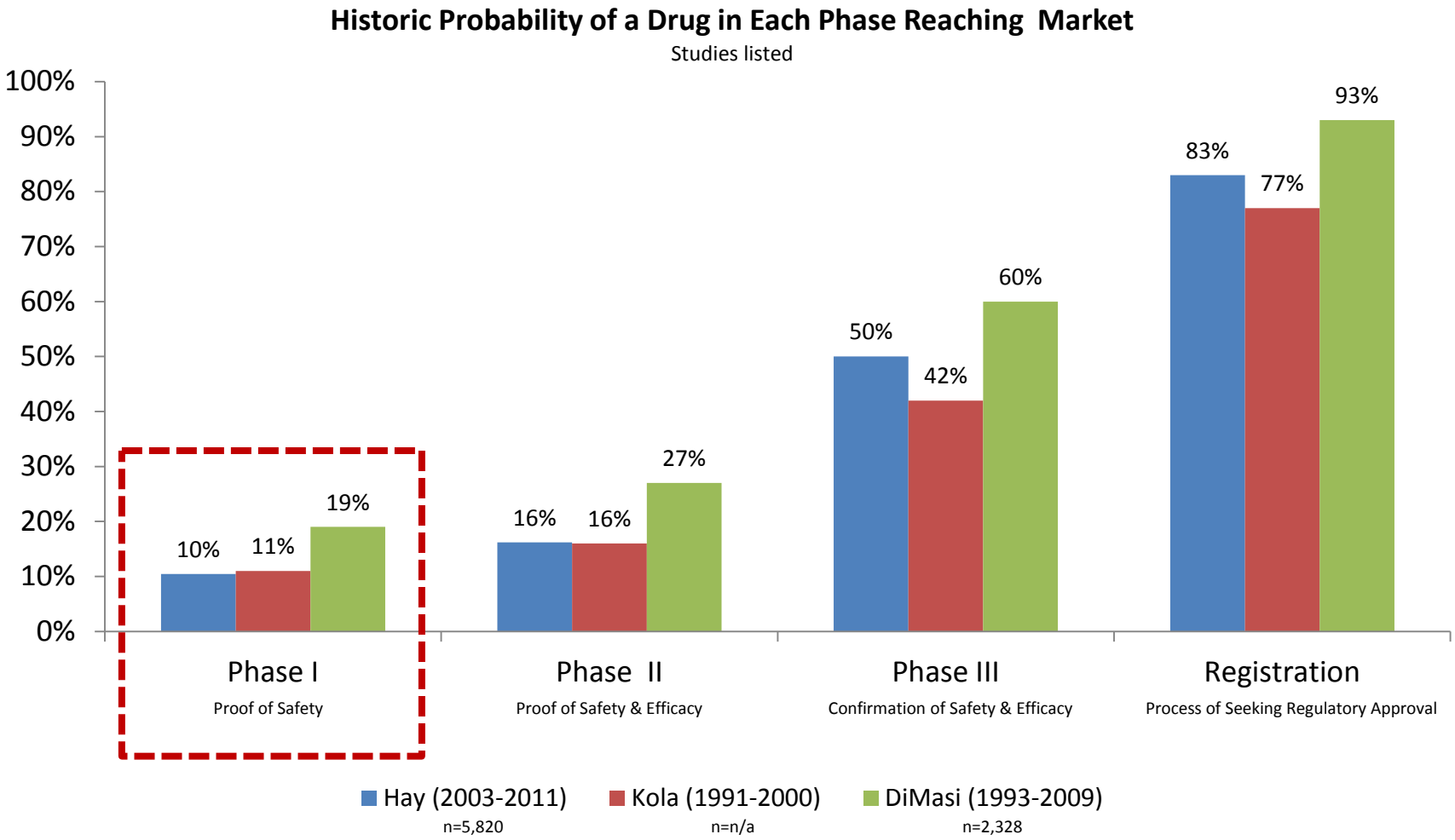
- Historically, novel drugs entering human trials have succeeded in making it to market between 10-19% of the time
- Oncology drugs have been particularly unsuccessful; study from 2014 reviewing the success rates of 2,541 therapies found that only ~7% of novel oncology drugs made it to market

…However, development features have emerged that mitigate risk

- Evidence is accumulating that five features are strongly associated with clinical success for a specific class of oncology drugs
- These features include patient selection criteria, the presence of tumor-initiating mutations, tumor composition, drug selectivity and drug properties

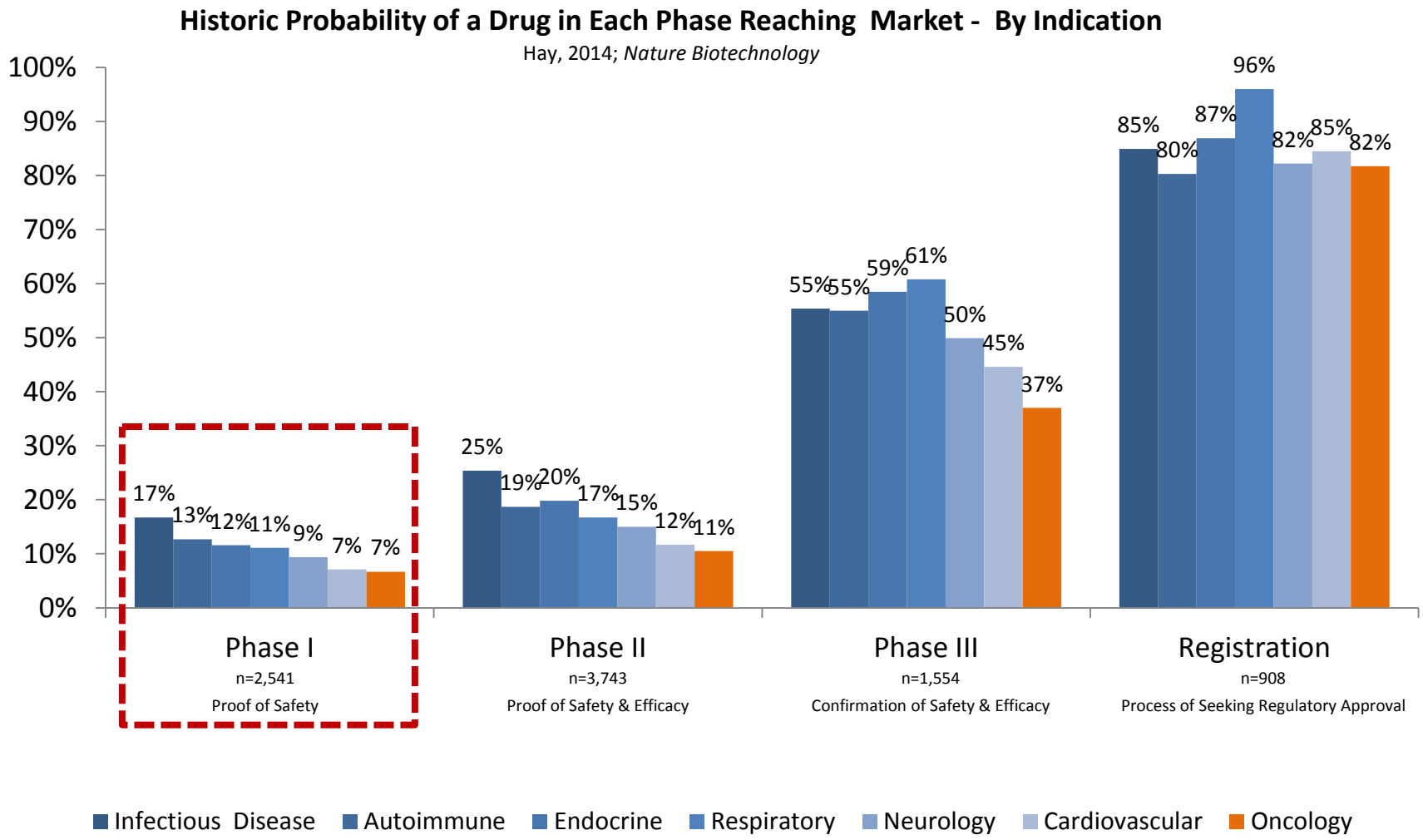
By seeking programs that incorporate the five features we highlight, we believe we can prospectively avoid many early-stage clinical trial failures and concentrate our investments in much higher probability clinical programs

TWO DECADES OF CLINICAL TRIAL DATA TELL US THAT PROBABILITY OF SUCCESS FOR EARLY STAGE DRUGS IS LOW



Sources: *Hay, "Clinical development success rates for investigational drugs," Nature Biotechnology, 2014. Kola, "Can the pharmaceutical industry reduce attrition rates? Nat. Rev. Drug Discov., 2004. DiMasi, "Pharmaceutical innovation in the 21st century: new drug approvals in the first decade, 2000–2009." Clin. Pharmacol. Ther., 2011.*

EARLY STAGE ONCOLOGY STUDIES HAVE AN EVEN LOWER PROBABILITY OF SUCCESS, IN AGGREGATE



Sources: *Hay, Nature Biotechnology, 2014.*

KNOWING THE CLINICAL RISKS, WE FOCUS OUR APPROACH ON TARGETED THERAPIES – SPECIFICALLY KINASE INHIBITORS

Cancer Treatment Modalities

	Surgery	Radiation	Chemotherapy	Targeted Therapies	Immuno-Therapy
How does it work?	Cut out accessible tumor cells to stop their growth and prevent their spread	Use highly concentrated X-rays or radioactive isotopes to kill cancerous cells	Use cytotoxic drugs to kill or inhibit fast-dividing cells	Interfere with a mechanism required for, or that supports, tumor growth	Support the immune system's innate ability to recognize and eliminate tumor cells
Since when?	1800s	Early 1900s	Late 1940s	1990s	2010s
Examples	n/a	n/a	Platinum agents	Gleevec	Opdivo
Opportunity? (e.g. new applications to be explored)	Limited	Limited	Limited	Large	Very Large
Relative Development Risk? (e.g. risk based on our understanding of how the drug works in the body)	Very Low	Very Low	Moderate	Low	High

- Nearly 50% of the oncology drugs approved in the United States in the last 5 years have been targeted therapies, the bulk of which have been **kinase inhibitors** (see next page for an introduction)

***Note**: Immuno-therapy is a promising, evolving space that warrants further examination. However, it is beyond the scope of this presentation.*
***Sources:** Adapted from the Cancer Research Institute's website. http://www.cancerresearch.org/grants-programs/clinical-accelerator/mission.*

KINASE INHIBITORS ARE A TYPE OF TARGETED THERAPY

Introduction to Kinases

What is a kinase?

- Kinases are cellular switches that regulate cell growth.
- There are over 500 kinases.

How are kinases implicated in cancer?

- Kinases that have mutated to be permanently switched "on" can cause cancer.
- Therefore, inhibiting (stopping) these "always on" kinases is an established and effective therapeutic approach.

Why is inhibiting specific kinases difficult?

- Kinases are structurally very similar to one another. Two kinases may differ by only one amino acid, yet have very different functions.
- The structural similarity makes it difficult to design inhibitors of just a single kinase.

What are "promiscuous" kinase inhibitors, and why do they matter?

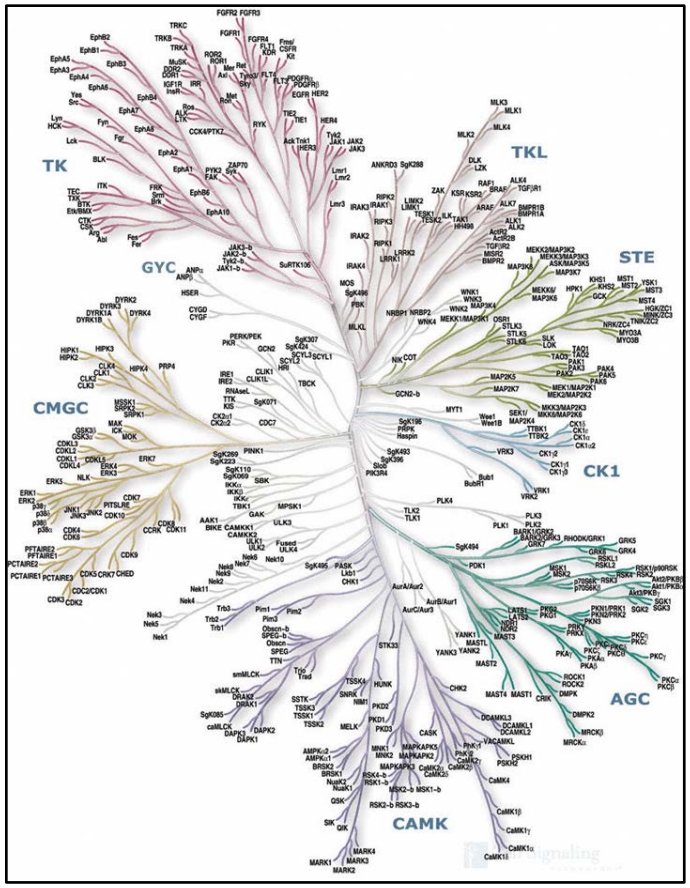
- An inhibitor is considered 'promiscuous' if it inhibits multiple kinases with similar potency.
- "Promiscuous" inhibitors can produce problematic side-effects due to the inhibition of kinases distinct from the target.

What is selectivity, and why does it matter?

- An inhibitor is considered "selective" if it inhibits a single kinase with potency distinctive from any other kinase.
- Designing an inhibitor that hits only the desired target and nothing else ideally will inhibit tumor growth without significant side effects.

Kinome Tree

A visual schematic of all 500 kinases



The schematic demonstrates the challenge associated with inhibiting a single kinase. Closer proximity on the tree represents higher similarity.

Sources: *Schematic is from Cell Signaling Technology's website. Accessed July 2016 from http://www.cstj.co.jp/reference/kinase/images/kinome.jpg.*

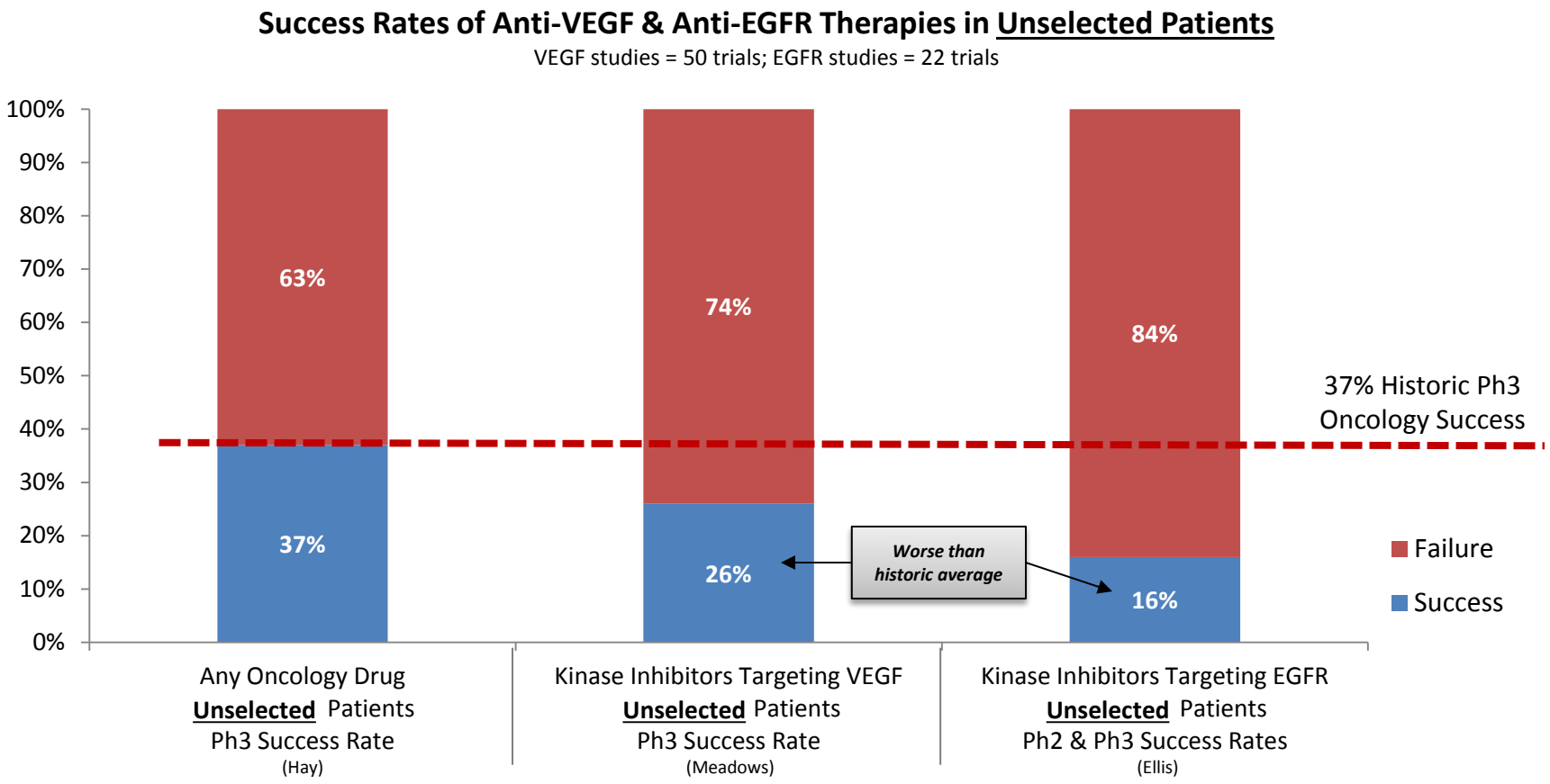
AT LEAST FIVE FEATURES INCREASE PROBABILITY OF SUCCESS FOR KINASE INHIBITORS ENTERING CLINICAL DEVELOPMENT

	Feature	Strength of Evidence	Evidence Base
1	**Biomarker-Selected Patient Population** A biomarker driven patient-selection strategy leads to high clinical success rates	Strong	Clinical Success Rates of VEGF Therapies in 50+ Phase 3 Trials Source: Meadows, *Cold Spring Harbor Perspectives*, 2012; Authors' Analysis Clinical Success Rates for 190+ Drugs in Lung Cancer from 1998-2012 Source: Falconi, *Journal of Thoracic Oncology*, 2014
2	**Oncogenic Driver Mutation** An oncogenic driver mutation is one that is known to 'Initiate and Maintain' cancer, and therefore is a good target	Strong	Meta-Analysis of Response Rates for Targeted Therapies in 13,000+ PhI Pts Source: Schwaederle, ASCO Presentation, 2016 Response Rates for 23 ALK Inhibitor Studies Source: Authors' Analysis from ASCO 2011-2016
3	**Tumor Homogeneity** Tumors comprised of more uniform cells are more likely to respond favorably to targeted therapies	Emerging	BRAFm Tumor Response Rate to Targeted Therapy Vemurafenib, Based on Mutation Burden Source: Lebbe, *Melanoma Res.*, 2014
4	**Selective Inhibitor** A selective inhibitor is a drug that blocks its target without blocking other biological functions, enabling one to inhibit a target with greater potency	Emerging	Case Study of AZD9291 Source: Morgan, Conference on Improving R&D Productivity, Brookings Institute 2015
5	**Favorable Drug Properties** A drug with favorable properties is absorbed, distributed, metabolized and excreted in a safe and reliable manner	Strong	Review of 94 Drug Failures, AstraZeneca Source: Cook, *Nature Reviews Drug Discovery* 2014 Case Study Comparison of AZD9291 and CO-1686 Source: FDA April 2016 ODAC Briefing Materials

We believe kinase Inhibitors with these features have a greater likelihood of clinical success than those that lack these features

Note: *Probability of success refers to clinical probability of success..*
Definition: *A "biomarker" is a functional biochemical or molecular indicator of a biologic or disease process that has predictive, diagnostic, and/or prognostic utility.*

1 KINASE INHIBITORS HAVE SUCCESS RATES WORSE THAN HISTORIC AVERAGES WHEN PATIENTS ARE NOT SELECTED BY BIOMARKERS



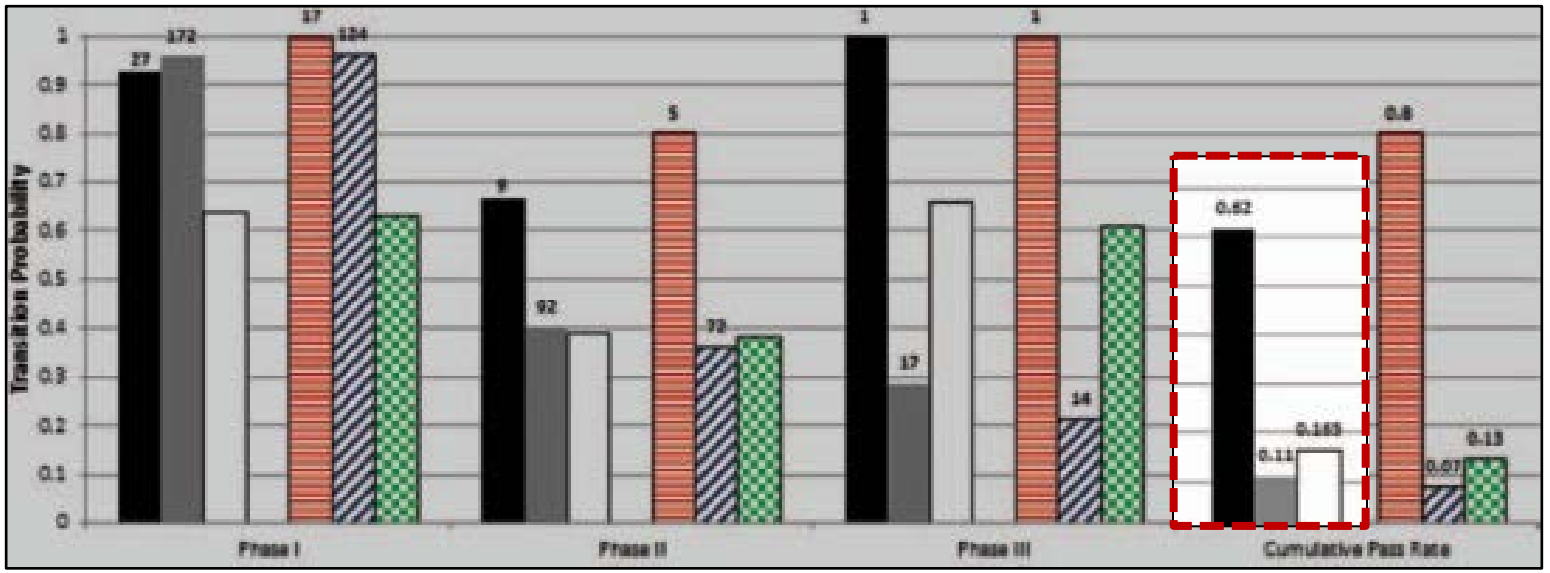
Kinase inhibitors are well established therapeutic options in oncology, however the chart above shows that when used in unselected populations, they have a success rate that is actually worse than average

Sources: *Hay, Nature Biotechnology, 2014. Meadows, "Anti-VEGF therapies in the clinic," Cold Spring Harb Perspect Med. 2012. Ellis, "Use of the epidermal growth factor receptor inhibitors gefitinib, erlotinib, afatinib, dacomitinib, and icotinib in the treatment of non-small-cell lung cancer: a systematic review," Current Oncology, June 2015.*

1 IN CONTRAST, A BIOMARKER DRIVEN PATIENT-SELECTION STRATEGY RESULTS IN HIGHER CLINICAL SUCCESS RATES

Clinical Trial Success Rates for Biomarker Targeted and Non-Biomarker Targeted Therapy for Advanced NSCLC

Falconi, 2014; n=199 compounds from 1998-2012.
"Success" per phase was defined as advancing to the next stage of development.



Strategy	Cumulative Pass Rate
Biomarker Targeted Therapy -- All Compound Types	62%
Non-Biomarker Targeted Therapy – All Compound Types	11%
Industry Expectations (DiMasi) – All Compound Types	15%

The boxed data show that the clinical success rate moves meaningfully higher when a biomarker is utilized in selecting which patients to treat

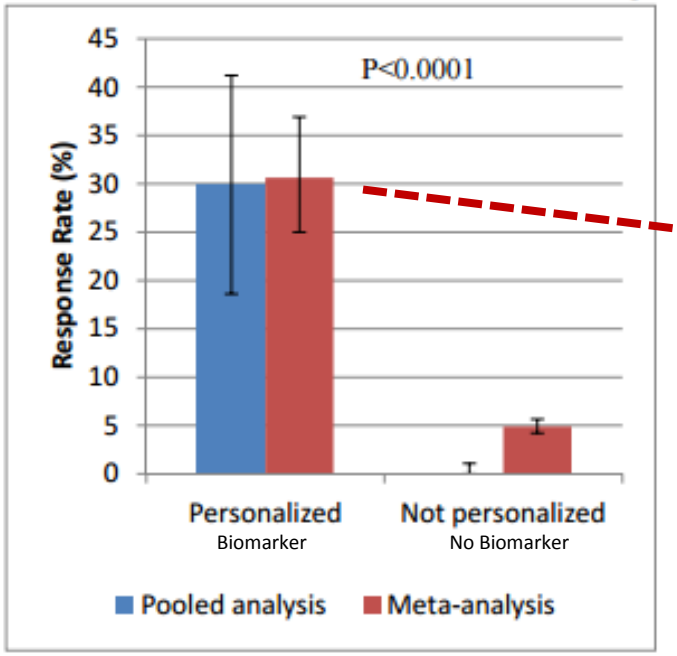
Source: *Falconi, "Biomarkers and Receptor Targeted Therapies Reduce Clinical Trial Risk in Non–Small-Cell Lung Cancer," Journal of Thoracic Oncology, 2014.*

2 SELECTING PATIENTS USING A GENOMIC BIOMARKER LEADS TO LARGER SIGNALS OF EFFICACY THAN THE AVERAGE BIOMARKER

Association of Biomarker-Based Treatment Strategies With Response Rates and Progression-Free Survival in Refractory Malignant Neoplasms

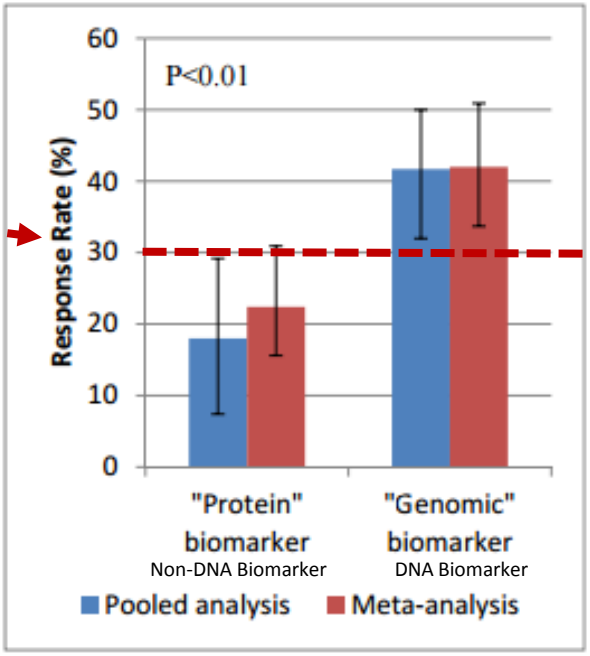
Schwaederle, 2016

Figure 1B



1B. Any Biomarker ("Personalized") is Better Than No Biomarker ("Not Personalized")

Figure 1C



1C. But a Genomic Biomarker is Better than a Non-Genomic Biomarker

Average of 30% Response Rate Using Any Biomarker

The chart on the left recapitulates the conclusion from the prior slide that use of a biomarker meaningfully improves the success rate in clinical trials, while the chart on the right indicates that the signal of efficacy can be enhanced further by using a genomic biomarker instead of a protein biomarker.

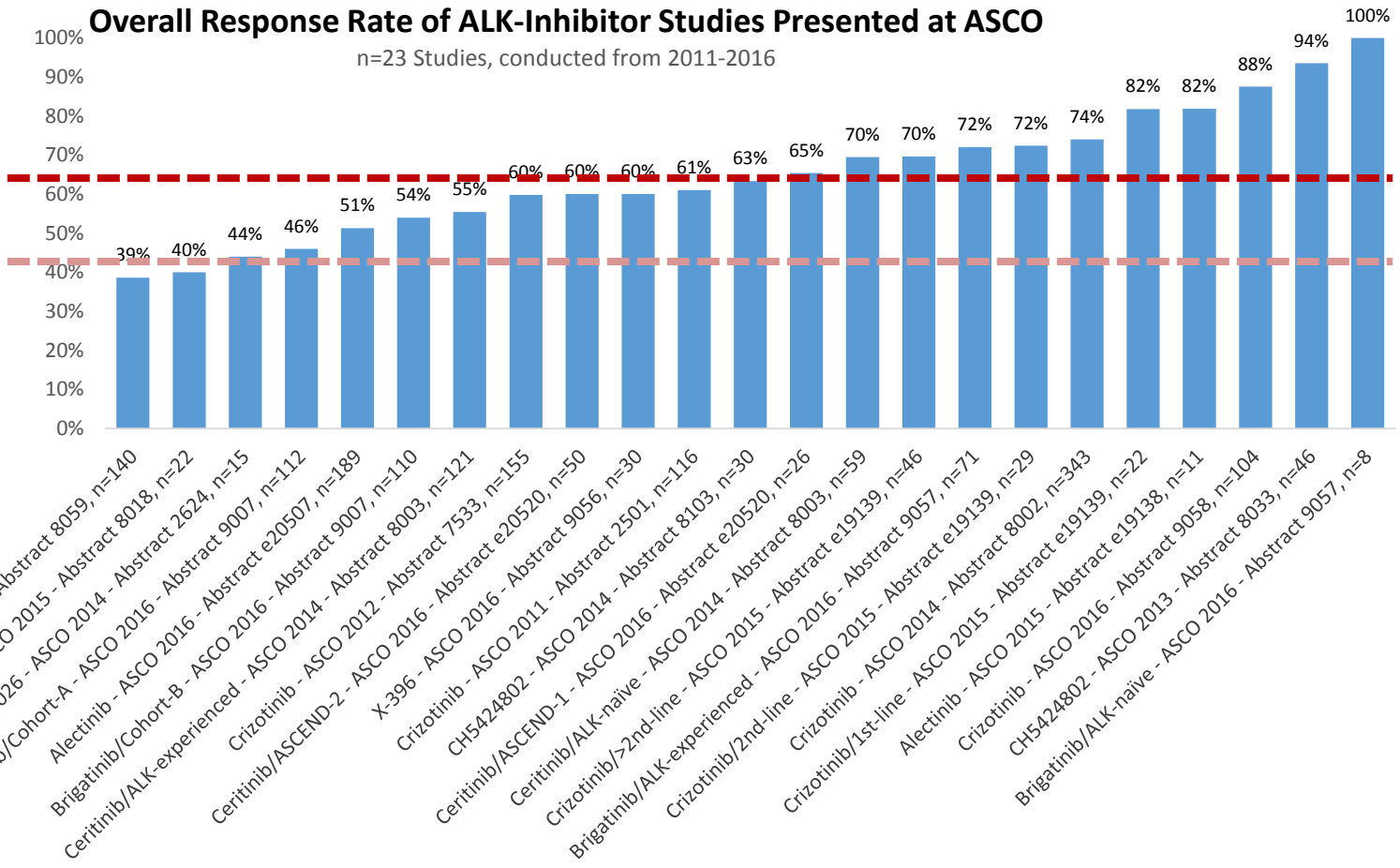
Note: *A "Genomic" biomarker is a specific genetic sequence.*

Source: *Schwaederle, "Association of Biomarker-Based Treatment Strategies With Response Rates and Progression-Free Survival in Refractory Malignant Neoplasms: A Meta-analysis," JAMA Oncology, 2016.*

2 SELECTING PATIENTS WITH AN ONCOGENIC DRIVER MUTATION AS THE GENOMIC BIOMARKER YIELDS AN EVEN LARGER SIGNAL

>63% Median Response Rate for Oncogenic Driver Mutation

42% Response Rate for Genomic Biomarker (Schwaederle, 2016)



ALK is an established oncogenic driver mutation. The chart above shows 23 distinct studies of ALK inhibitors presented at ASCO since 2011, and the result suggests that the use of an oncogenic driver as a biomarker can enhance the signal of efficacy beyond the use of a genomic biomarker.

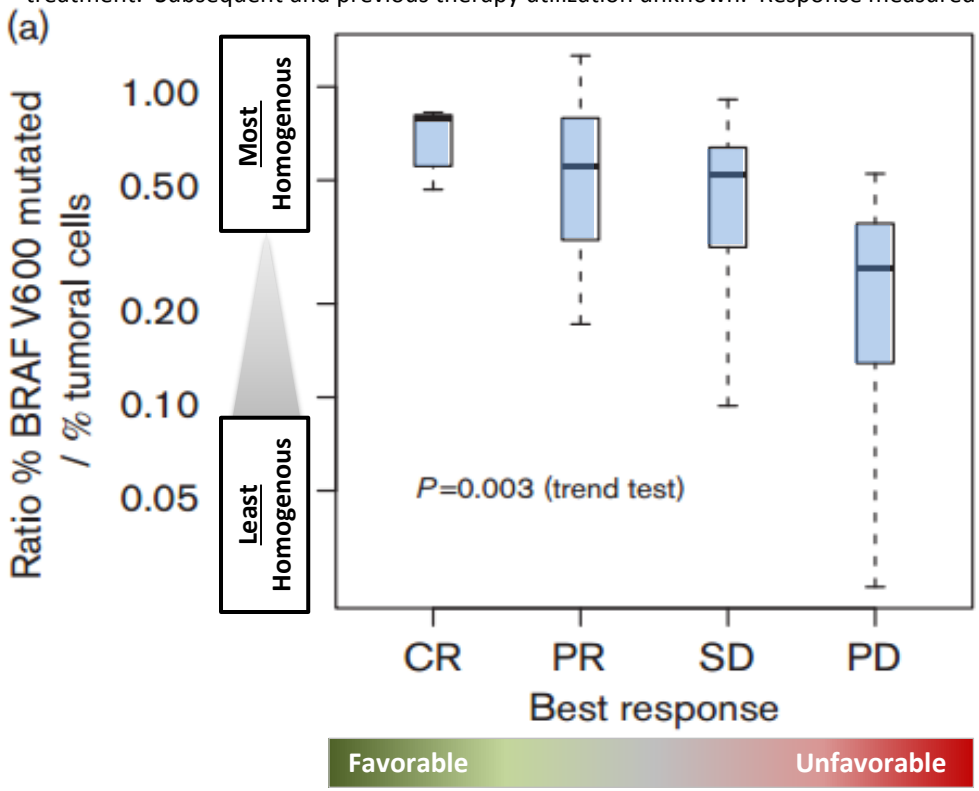
Note: *An oncogenic driver mutation is one that is known to 'initiate and maintain' cancer.*

Sources: *Listed in the table. Most can be found at ASCO.org.*

3 MOST TUMORS ARE NOT HOMOGENOUS; THE ONES THAT ARE HOMOGENOUS RESPOND VERY WELL TO TARGETED THERAPY

Tumor Response Rate to Targeted Therapy, Based on Mutation Burden

Lebbe, 2013. Biopsies sourced from 44 patients with $BRAF_{V600}$ mutated melanoma treated with vemurafenib at recommended dose. Patients split between 1-3L of treatment. Subsequent and previous therapy utilization unknown. Response measured according to RECIST criteria.



Rough RECIST Definitions:
"CR" means Complete Response, or disappearance of tumor.
"PR" means Partial Response, or >30% decrease in tumor size.
"SD" means Stable Disease, <20% growth and <30% tumor shrinkage.
"PD" means Progressive Disease , or >20% increase in tumor size.

This chart establishes that complete responses (disappearance of tumor) were concentrated in the patients that had the most homogeneous tumors. In contrast, progressive disease was seen in the patients that had the least homogenous tumors.

Note: *In this study, the PFS patients with high mutation burden treated with vemurafenib was stastically significantly longer than that of the treated patients with low mutation burden. However, the OS was not. We believe these survival findings are potentially confounded by the unreported differences in the two arms with respect to previous therapy, subsequent therapy, and line of therapy.* ***Source:*** *Lebbe, "BRAFV600 mutation levels predict response to vemurafenib in metastatic melanoma," Melanoma Res., 2014.*

4 SELECTIVE INHIBITION AVOIDS SIDE EFFECTS, ENABLING MAXIMAL INHIBITION OF THE ONCOGENIC DRIVER MUTATION

This table shows the potency of five compounds against five targets. In this case, the objective is to maximally inhibit the kinase driving the cancer (EGFRm+) while avoiding the kinases that cause negative side effects (EGFR wild type, IR, IGFR). Compound 5 (AZD921) is most selective for mutant EGFR, as represented by the ratio of 194 in green.

Optimising Target and Compound Selection to Enhance Early Stage Decision-Making

Morgan, 2015

Right Safety: Insulin Receptor affinity removed from AZD9291 profile – removes potential hyperglycaemia risk

	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5 (AZD9291)
EGFRm+ sensitising mutation cell IC50 (pEGF μM)	0.39	0.016	0.021	0.002	0.017
EGFRm+/T790M double mutation cell IC50 (pEGF μM)	0.091	0.002	0.004	0.0007	0.015
EGFR wild type cell IC50 (pEGFR μM)	23.0	0.36	0.94	0.15	0.48
IR Kinase IC50 (μM)	0.016	0.014	0.022	0.15	0.91
IGFR cell IC50 (pIGFR μM)	0.099	0.16	0.49	0.10	3.3
Ratio SM/IGFR cell selectivity	**0.25**	**10**	**23**	**48**	**194**

Definitions:
"IC50" is a measure of target binding. The lower the number is, the better the binding.
"EGFR" is Epidermal Growth Factor Receptor, a kinase whose mutation (denoted "m+") can cause cancer. T790 is a type of EGFR mutation.
"EGFR Wild Type" is the non-mutated form of EGFR. Inhibiting this causes rash and diarrhea.
"IGFR" is Insulin –like Growth Factor Receptor. Inhibiting this causes hyperglycemia (often associated with diabetes).

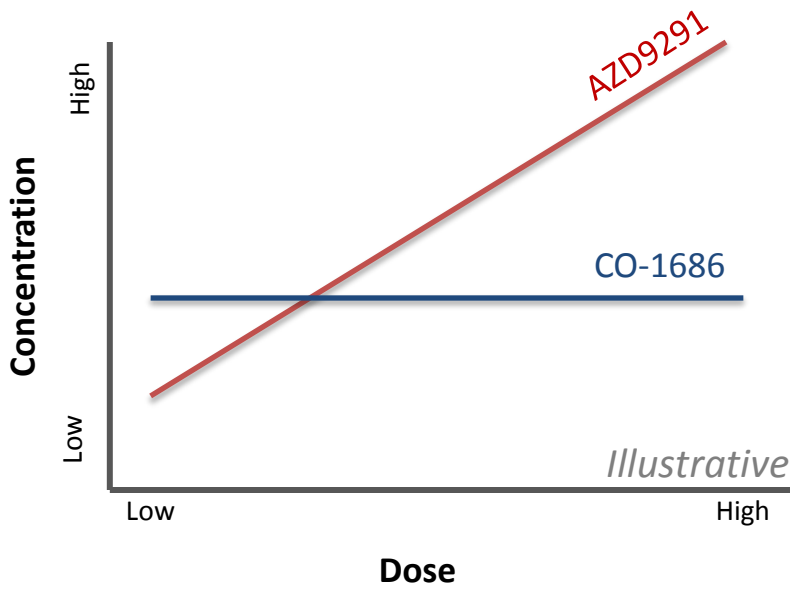
"The target was known.[…] From the outset, we were focused on what the profile of what a suitable compound would be, specifically a 'mutant-selective' profile. In other words, a compound more active against the mutant form of EGFR than the wild-type [the target that causes rash and diarrhea.].[…] The profile of the required compound was clear: inhibit the mutant receptor and have a margin to wild-type."

Dr. Richard Ward, Principal Scientist and Computational Chemist, AstraZeneca

Sources: *AstraZeneca, "Osimertinib (AZD9291) and the 5R framework." Published on the AstraZeneca website. Accessed July 2016. Morgan, "Optimising target and compound selection to enhance early stage decision-making," From "Conference on Improving R&D Productivity," hosted by the Brookings Institute, July 2015.*

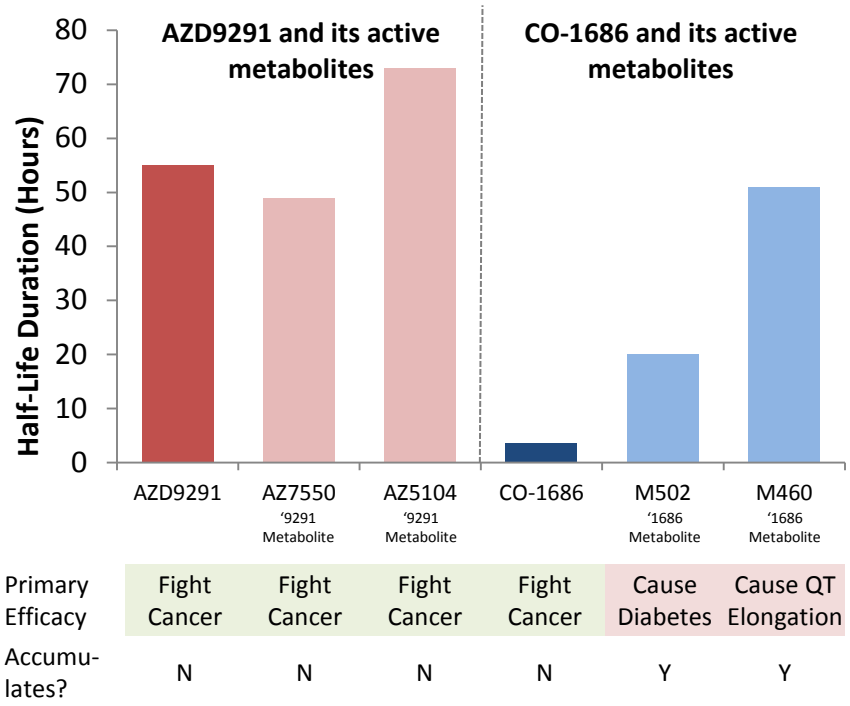
5 SIDE EFFECTS CAN ALSO RESULT FROM POOR DRUG PROPERTIES; BELOW WE COMPARE THE PROPERTIES OF TWO COMPETING DRUGS

Absorption



Finding: There is a dose-proportional (higher dose = higher concentration) relationship between AZD9291 dose and plasma concentration; however, this did not exist for CO-1686, suggesting a pharmacology issue with CO-1686.

Metabolism

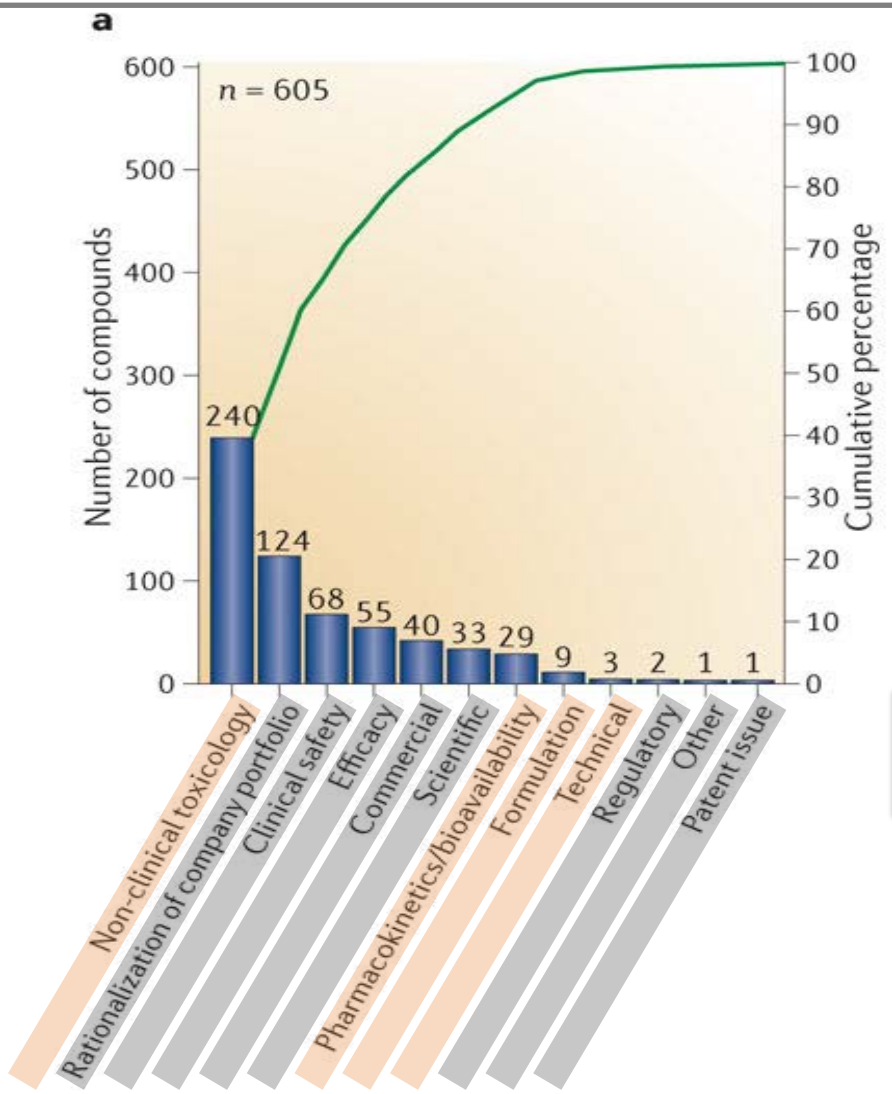


Finding: Not only is CO-1686's half-life shorter than AZD9291 and its metabolites, but AZD9291 and its metabolites fight cancer, whereas CO-1686's metabolites cause harsh side-effects and have longer half-lives.

Definition: *Active metabolite results when a drug is metabolized by the body into a modified form which continues to produce effects in the body.*

Source: *FDA ODAC Committee Meeting, "NDA 208542: Rociletinib," April 12, 2016. Published on the FDA website. Accessed July 2016*

5 PRODUCING FAVORABLE DRUG PROPERTIES IS MORE DIFFICULT THAN ONE MIGHT THINK...



An analysis of the attrition of drug candidates from four major pharmaceutical companies, 2000-2010

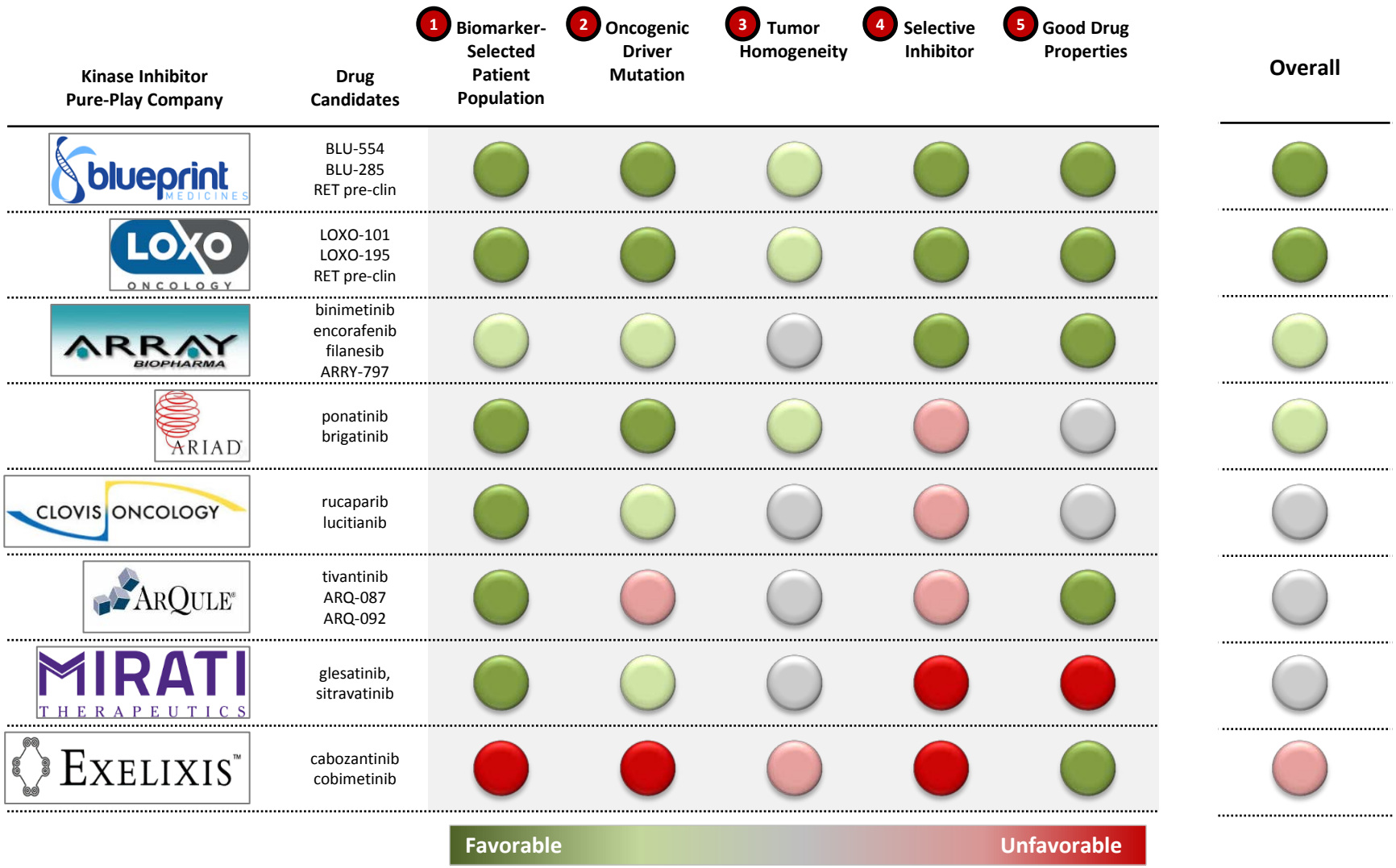
Waring, *Nature Reviews Drug Discovery* 2015

Reason for attrition, 605 drugs	
Non-Clinical Toxicology	40%
Pharmacokinetics/Availability	5%
Formulation	1%
Technical	<1%
Attrition Potentially Due to Unfavorable Drug Properties	**46%**

This chart shows that nearly half of all drug attrition may be due to unfavorable drug properties

Source: *Waring, "An analysis of the attrition of drug candidates from four major pharmaceutical companies," Nature Reviews Drug Discovery, 2015.*

FRAMEWORK APPLICATION: COMPANY LEVEL



Note: As of August 9, 2016, Driehaus Capital Management is the beneficial owner of shares of Blueprint Medicines, Loxo Oncology, Array BioPharma and Exelixis. Holdings are subject to change and we assume no obligation to update this information to reflect subsequent changes. This information should not be viewed as a recommendation to buy or sell any securities.

FRAMEWORK APPLICATION: PRODUCT LEVEL

	Indication	1 Biomarker-Selected Patient Population	2 Oncogenic Driver Mutation	3 Tumor Homogeneity	4 Selective Inhibitor	5 Good Drug Properties
BLU-285	KIT Exon 17 D816V mutated Systemic Mastocytosis	●	●	●	●	●
BLU-285	PDGFRα D842V and KIT Exon 17 mutated Gastrointestinal Stromal Tumors	●	●	●	●	●
BLU-554	FGF19 altered Hepatocellular Carcinoma	●	○	○	●	●
BLU-667	RET mutated solid tumors	●	●	◐	●	○
LOXO-101	TRK mutated solid tumors	●	●	●	●	●
LOXO-195	TRK mutated solid tumors	●	●	●	●	○
RET Inhibitor	RET mutated solid tumors	●	●	◐	●	○
FGFR2/3 Inhibitor	FGFR2/3 translocated solid tumors	●	●	◐	●	○

Favorable — Unfavorable

APPENDIX

A. Tumor Heterogeneity
B. Targeted Therapies and Immune Therapies
C. Glossary
D. About the Authors

A TUMOR HETEROGENEITY: RESISTANCE MUTATIONS CURRENTLY LIMIT TREATMENT, BUT COULD POTENTIALLY BE HARNESSED IN THE FUTURE

Resistance Mutations Cause Kinase Resistance, Limiting Response Durability

"Despite the success of targeted therapies in the treatment of cancer, the development of resistance limits the ability to translate this method into a curative treatment."

Turner, "Genetic heterogeneity and cancer drug resistance," *Lancet Oncology* 2012

Multiple Therapies Can Extend Durability, But Resistance Eventually Surfaces

"While systemic therapy can have some initial success, it is rarely durable. Typically, populations of cancer cells resistant to therapy emerge quickly requiring progressively less effective 2nd, 3rd, and 4th line therapies until the patient succumbs."

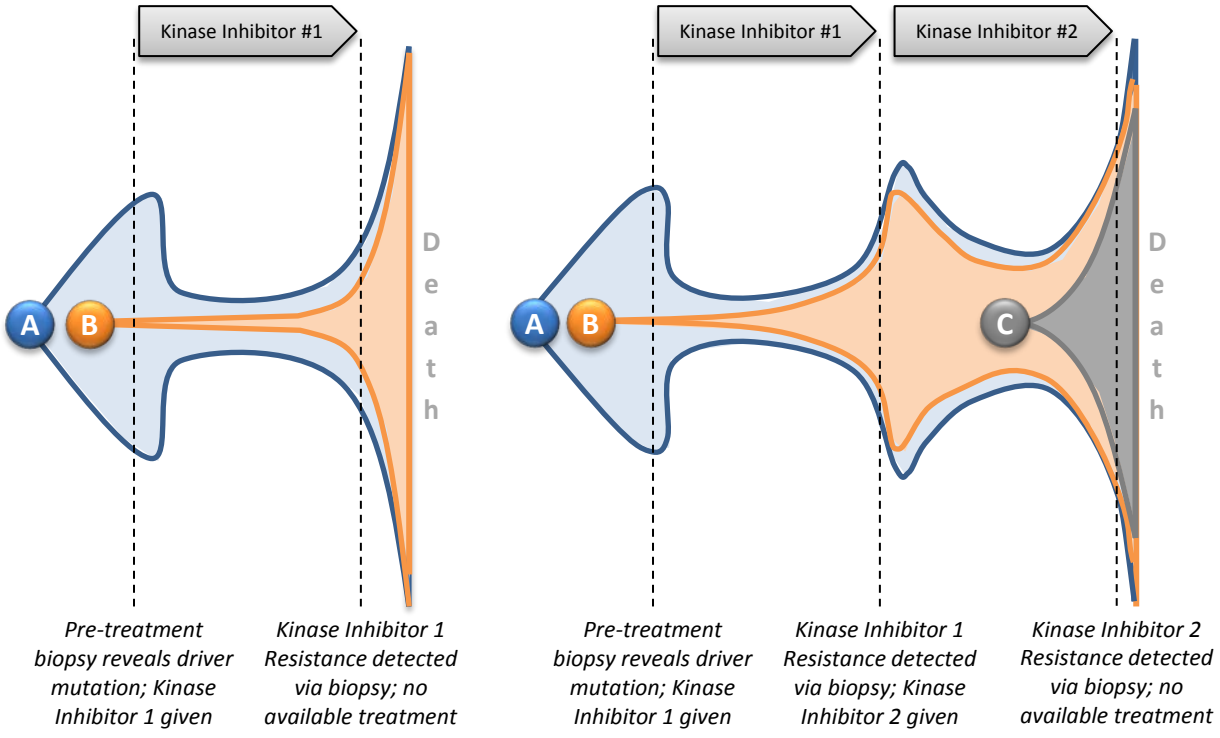
Cunningham, "Evolutionary dynamics in cancer therapy," *Mol Pharm.* 2011

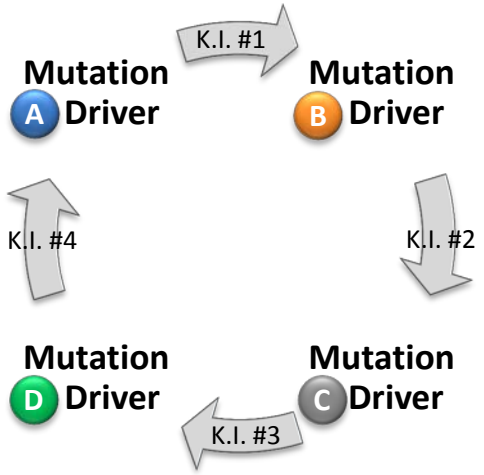
If Resistance Can Re-Sensitive Tumors, Longer Term Durability Could be Attained

Note: This remains theoretical. However, there are case studies which demonstrate intriguing signals.

*"This patient with metastatic ALK-rearranged lung cancer received multiple ALK inhibitors during her treatment course, including first-, second-, and third-generation inhibitors. Resistance to ALK inhibition was a dynamic and clonal process, originating with a founder ALK C1156Y clone in the pretreatment tumor and culminating in a double-mutant subclone (ALK C1156Y–L1198F) in the post-lorlatinib tumor that led to the relapse. This acquired L1198F mutation conferred resistance to lorlatinib, but **unexpectedly restored sensitivity to crizotinib, a less potent and less selective first-generation inhibitor.**"*

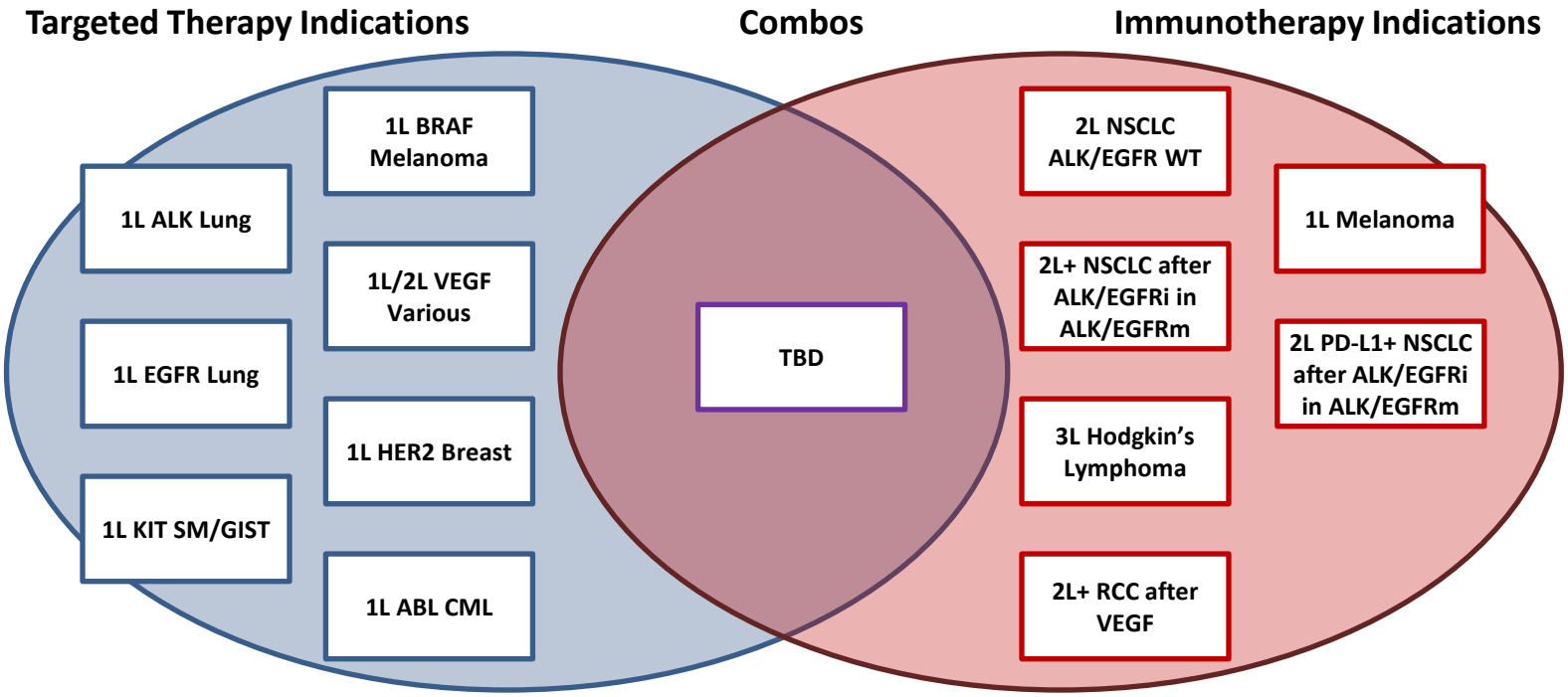
Shaw, "Resensitization to Crizotinib by the Lorlatinib ALK Resistance Mutation L1198F," NEJM 2015.





Source: *Shaw, "Resensitization to Crizotinib by the Lorlatinib ALK Resistance Mutation L1198F," NEJM 2015.*

B TARGETED THERAPIES AND IMMUNOTHERAPIES: FUTURE APPLICATIONS



- Clinicians (and investors) are increasingly excited about the potential of immuno-oncology agents (e.g. targeting PD-1, CTLA-4, others), and for good reason: some of these therapies have, in a minority of patients, induced durable responses far beyond what had been possible previously.
- Though clinical investigators are only in the early innings of exploring the potential applications of IO, **it is likely that targeted therapies will continue to play a meaningful role in the treatment of advanced cancers**, whether that is in combination with or sequenced with immuno-agents.

Note: *Indications not exhaustive.*

GLOSSARY

Term	Definition	Source
ALK	A gene that makes a protein called anaplastic lymphoma kinase (ALK), which may be involved in cell growth. Mutated (changed) forms of the ALK gene and protein have been found in some types of cancer, including neuroblastoma, non-small cell lung cancer, and anaplastic large cell lymphoma. These changes may increase the growth of cancer cell	http://www.cancer.gov/publications/dictionaries/cancer-terms?search=alk
AZD9291	A drug used to treat non-small cell lung cancer that has spread to other parts of the body. It is used in patients whose cancer has a mutated (changed) form of a cell protein called epidermal growth factor receptor and whose disease got worse during or after treatment with an anticancer drug that blocks EGFR. It is also being studied in the treatment of other types of cancer. Osimertinib blocks this mutated protein, which may help keep cancer cells from growing and may kill them. It is a type of kinase inhibitor. Also called Tagrisso.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=776961
Biomarker	A functional biochemical or molecular indicator of a biologic or disease process that has predictive, diagnostic, and/or prognostic utility.	http://jco.ascopubs.org/cgi/glossarylookup
BRAF	A gene that makes a protein called B-RAF, which is involved in sending signals in cells and in cell growth. This gene may be mutated (changed) in many types of cancer, which causes a change in the B-RAF protein. This can increase the growth and spread of cancer cells.	http://www.cancer.gov/publications/dictionaries/cancer-terms?search=braf
BRAF V600 mutation	A specific mutation (change) in the BRAF gene, which makes a protein that is involved in sending signals in cells and in cell growth. This BRAF gene mutation may be found in some types of cancer, including melanoma and colorectal cancer. It may increase the growth and spread of cancer cells.	http://www.cancer.gov/publications/dictionaries/cancer-terms?search=braf
Clinical trial	A study that tests a therapy in humans, rather than in laboratories or on animals.	http://www.health.harvard.edu/a-through-c
CO-1686	A drug in development for EGFR-mutant lung cancer.	n/a
Complete response	The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured. Also called complete remission.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45652
Cytotoxic	A substance that kills cells, including cancer cells. These agents may stop cancer cells from dividing and growing and may cause tumors to shrink in size.	http://www.cancer.gov/publications/dictionaries/cancer-terms?search=cytotoxic
EGFR	The protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor. Also called epidermal growth factor receptor, ErbB1, and HER1.	http://www.cancer.gov/publications/dictionaries/cancer-terms?search=egfr
EGFR	a member of a family of receptors (HER2, HER3, HER4 are other members of the family) that binds to the EGF, TGF-α, and other related proteins, leading to the generation of proliferative and survival signals within the cell. EGFR (also known as HER1) also belongs to the larger family of tyrosine kinase receptors and is generally overexpressed in several solid tumors of epithelial origin.	http://jco.ascopubs.org/cgi/glossarylookup
EGFRm	Constitutively activated EGFR as a result of mutation.	n/a
EGFRm / T790M	Constitutively activated EGFR that is further mutated to avoid inhibition from first-generation EGFR inhibitors.	n/a
Genomic biomarker	A biomarker in the form of a specific genetic signature.	n/a
Half-life	The time required for the concentration of a drug to be reduced by 50%.	n/a
IC50	The concentration of a drug that is required for 50% of maximal target inhibition.	n/a
IGFR	A protein found on the surface of some types of cells that binds to insulin-like growth factor (IGF). This causes the cells to grow and divide. IGFR is found at high levels on the surface of several types of cancer cells, which causes these cells to grow rapidly in the presence of IGF. Also called insulin-like growth factor receptor.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=653124
Immunotherapy	Treating disease by enhancing or suppressing the body's immune system.	http://www.health.harvard.edu/d-through-i

GLOSSARY

Term	Definition	Source
Inhibitor	A drug that blocks the biological function of a target.	n/a
IR	Insulin receptor.	n/a
Isotope	A form of a chemical element in which the atoms have the same number of protons (part of the nucleus of an atom) but with a different number of neutrons (part of the nucleus of an atom). For example, carbon 12, carbon 13, and carbon 14 are isotopes of carbon. They all have six protons in the nucleus, but each has different number of neutrons. Isotopes may be used in certain medical tests and procedures.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=613515
Kinase	A type of enzyme (a protein that speeds up chemical reactions in the body) that adds chemicals called phosphates to other molecules, such as sugars or proteins. This may cause other molecules in the cell to become either active or inactive. Kinases are a part of many cell processes. Some cancer treatments target certain kinases that are linked to cancer.	http://www.cancer.gov/publications/dictionaries/cancer-terms?search=kinase&contains=true
Kinase Inhibitor	A substance that blocks a type of enzyme called a kinase. Human cells have many different kinases, and they help control important functions, such as cell signaling, metabolism, division, and survival. Certain kinases are more active in some types of cancer cells and blocking them may help keep the cancer cells from growing. Kinase inhibitors may also block the growth of new blood vessels that tumors need to grow. Some kinase inhibitors are used to treat cancer.	http://www.cancer.gov/publications/dictionaries/cancer-terms?search=kinase%20inhibitor&contains=true
Metabolism	The chemical reactions that occur in all living organisms to maintain life. An example is converting food into energy that the body needs to function.	http://www.health.harvard.edu/medical-dictionary-of-health-terms/j-through-p
Metabolite	A substance made or used when the body breaks down food, drugs or chemicals, or its own tissue (for example, fat or muscle tissue). This process, called metabolism, makes energy and the materials needed for growth, reproduction, and maintaining health. It also helps get rid of toxic substances.	http://www.cancer.gov/publications/dictionaries/cancer-terms?search=metabolite&contains=true
Metabolize	To break something down.	n/a
Mutation	Any change in the DNA sequence of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.	http://www.cancer.gov/publications/dictionaries/cancer-terms?search=mutation&contains=true
Oncogene	A gene that, under certain conditions, can cause cancer.	http://www.health.harvard.edu/medical-dictionary-of-health-terms/j-through-p
Oncogenic driver mutation	mutations that are causally implicated in oncogenesis or tumor survival. Such mutations have been positively selected during carcinogenesis and often show a recurrent pattern within or across tumor types. This is in contrast with passenger events, which arise from the background mutation rate and do not contribute to oncogenesis.	http://jco.ascopubs.org/cgi/glossarylookup
Partial response	A decrease in the size of a tumor, or in the extent of cancer in the body, in response to treatment. Also called partial remission.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45819
pEGF	Phosphorylated epidermal growth factor.	n/a
Phase I	The first step in testing a new treatment in humans. A phase I study tests the safety, side effects, best dose, and timing of a new treatment. It may also test the best way to give a new treatment (for example, by mouth, infusion into a vein, or injection) and how the treatment affects the body. The dose is usually increased a little at a time in order to find the highest dose that does not cause harmful side effects. Phase I clinical trials usually include only a small number of patients who have not been helped by other treatments. Sometimes they include healthy volunteers.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45830
Phase I/II	A study that tests the safety, side effects, and best dose of a new treatment. Phase I/II clinical trials also test how well a certain type of cancer or other disease responds to a new treatment. In the phase II part of the clinical trial, patients usually receive the highest dose of treatment that did not cause harmful side effects in the phase I part of the clinical trial. Combining phases I and II may allow research questions to be answered more quickly or with fewer patients.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45832

GLOSSARY

Term	Definition	Source
Phase II	A study that tests whether a new treatment works for a certain type of cancer or other disease (for example, whether it shrinks a tumor or improves blood test results). Phase II clinical trials may also provide more information about the safety of the new treatment and how the treatment affects the body.	http://www.cancer.gov/publications/dictionaries/cancer-terms?search=phase%20ii
Phase III	A study that tests the safety and how well a new treatment works compared with a standard treatment. For example, phase III clinical trials may compare which group of patients has better survival rates or fewer side effects. In most cases, treatments move into phase III trials only after they meet the goals of phase I and II trials. Phase III clinical trials may include hundreds of people.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45833
PK	The activity of drugs in the body over a period of time, including the processes by which drugs are absorbed, distributed in the body, localized in the tissues, and excreted.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=44324
Pre-clinical study	Research using animals to find out if a drug, procedure, or treatment is likely to be useful. Preclinical studies take place before any testing in humans is done.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=44517
Progressive disease	Cancer that is growing, spreading, or getting worse..	n/a
Protein biomarker	A biomarker that is a protein.	n/a
RECIST	A standard way to measure how well a cancer patient responds to treatment. It is based on whether tumors shrink, stay the same, or get bigger. To use RECIST, there must be at least one tumor that can be measured on x-rays, CT scans, or MRI scans. The types of response a patient can have are a complete response (CR), a partial response (PR), progressive disease (PD), and stable disease (SD). Also called Response Evaluation Criteria In Solid Tumors.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=691009
Registration	The process of formally seeking approval to market a drug.	n/a
Response rate	The percentage of patients whose cancer shrinks or disappears after treatment.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=43983
Selective inhibitor	An inhibitor that blocks its target, but avoids interactions with other targets or biological functions.	n/a
Small molecule drug	A substance that is able to enter cells easily because it has a low molecular weight. Once inside the cells, it can affect other molecules, such as proteins, and may cause cancer cells to die. This is different from drugs that have a large molecular weight, such as monoclonal antibodies, which are not able to get inside cells very easily. Many targeted therapies are small-molecule drugs or small molecule inhibitors.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=653146
Stable disease	Cancer that is neither decreasing nor increasing in extent or severity.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45884
Target	The object being blocked by an inhibitor, typically a protein.	n/a
Targeted therapy	A type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells. Some targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells. Other types of targeted therapies help the immune system kill cancer cells or deliver toxic substances directly to cancer cells and kill them. Targeted therapy may have fewer side effects than other types of cancer treatment. Most targeted therapies are either small molecule drugs or monoclonal antibodies.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=270742
Tx	Shorthand for 'treatment' or 'therapeutic.'	n/a
VEGF	A substance made by cells that stimulates new blood vessel formation. Also called vascular endothelial growth factor.	http://www.cancer.gov/publications/dictionaries/cancer-terms?search=vegf
Vemurafenib	A drug used to treat advanced melanoma that has a mutated (changed) form of a cell protein called BRAF. It is also being studied in the treatment of other types of cancer. Vemurafenib blocks this mutated protein, which may stop the growth of cancer cells. It is a type of kinase inhibitor and a type of targeted therapy agent. Also called BRAF (V600E) kinase inhibitor RO5185426, PLX4032, RG7204, and Zelboraf.	http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=702051
Wild type	Naturally occurring (non-mutated) DNA, RNA or protein.	n/a

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