ALEXION®

7th annual Temple Analytics Challenge

WHAT MAKES RARE DISEASE CLINICAL TRIALS SUCCESSFUL?

For the 2019 Alexion Analytics challenge, we looked into the rare disease clinical research landscape to address:

Scientific and monetary success
Trial trends by condtion
Sampling characteristics for success
Funding mechanisms for success
The future of rare disease clinical trials

WHAT IS A RARE DISEASE?

*A rare disease is any disease or disorder bearing some serious life threatening condition that affects:

UNITED STATES
<200,000 people

EUROPE
1 in 2,000 people

*different countries have different definitions of a rare disease

7,000+ Unique rare diseases identified

80% are genetic disorders

25-30 million Americans are living with rare diseases

WHAT ARE CLINICAL TRIALS?

clinical trials are experiments or observations conducted that are pertinent to gather medical knolwedge and are helpful to determine whether a medical surgery, drug, or device is safe to use or consume by humans.

KEY CHALLENGES IN RARE DISEASE TRIALS

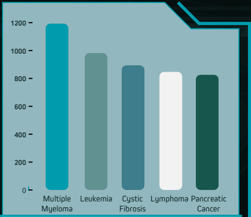
- Smaller populations diminish opportunity for study + replication
- Difficulty identifying homogenious trial participants
- Study design limitations [can't always be gold standard*]

*By gold standard, we mean a randomized, double blind, controlled trial.

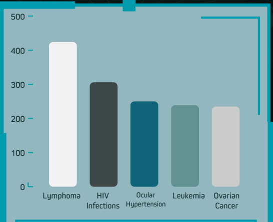
THESE CHALLENGES LEAD TO DIFFICULTY PROVING SAFETY & EFFICACY

only
5%
of rare diseases have an FDA approved treatment

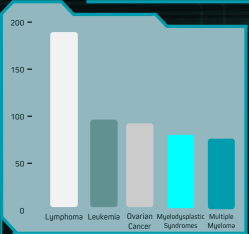
SO, WHICH RARE DISEASES HAD THE MOST TRIALS?



Top 5 Primary Conditions
Count of Rare Trials



Top 5 Secondary Conditions
Count of Rare Trials



Top 5 Tertiary Conditions
Count of Rare Trials

After cleaning duplicates and deliminating on conditions we determined **multiple myeloma** to be the primary condition with the greatest frequency

HOW SHOULD WE MEASURE RARE DISEASE TRIAL SUCCESS?

1. SCIENTIFIC SUCCESS

2. MONETARY SUCCESS

We define rare disease trial success from a ***SCIENTIFIC STANDPOINT*** as any phase I, II, or III interventional trial where the primary intervention of interest goes on to receive approval for marketing.

SCIENTIFIC SUCCESS IN RARE DISEASE TRIALS

Meet Trial Outcome Measures

[Phase I and II]

→

Prove Efficacy + Safety

[Phase III]

→

APPROVED

Get Approved for Marketing

BREAKING DOWN SAMPLING CHARACTERISTICS OF ■ SCIENTIFIC SUCCESS ■

*see appendix for success dataset methodology

ENROLLMENT SAMPLE SIZE

Size of enrollment plays a huge part in a study's ability to prove efficacy. We used median as our measure of central tendency to mitigate the impact of outliers

33 subjects

Phase 1 Median Enrollment

42 subjects

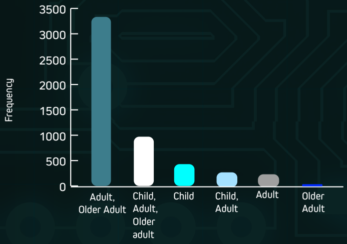
Phase 2 Median Enrollment

225 subjects

Phase 3 Median Enrollment

AGE OF STUDY PARTICIPANTS

Age Criterion Frequency

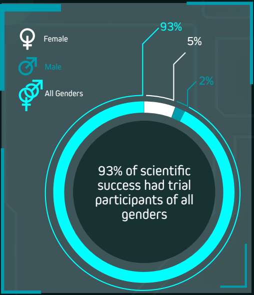


Of the phase I, II, & III trials where the intervention of interest go approval for marketing, **63%** had participants in the **adult + older age bracket**

NOTE: Accurate diagnosis of a rare disease from symptom onset is 4.8 years. One can deduct that it is easier to find homogeneous trial participants who are adults, which is why more scientific trial successes studied adults and older adults.

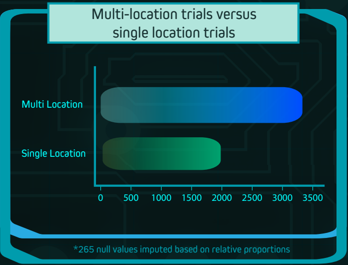
GENDER CRITERION

Although the vast majority of trials in our success data set had criterion evaluating all genders, trials should also take into consideration the proportion of male versus female within all gender studies, as interventions may affect males and females differently.



93% of scientific success had trial participants of all genders

LOCATIONS OF TRIALS


Multi-location trials versus single location trials

*265 null values imputed based on relative proportions

For successful trials with multiple locations, the average number of trial sites was 36, with values ranging from 2 to 748.

Multi-location rare disease trials had more scientific success, likely due to having higher enrollment.

Phase	Multi Location Median of Enrollment	Single Location Median of Enrollment
I	49	26
II	58	34
III	226	136.5

*Median enrollment derived by phase and location excludes 265 null values

HOW ARE SCIENTIFIC SUCCESSES FUNDED?

Based on the analysis of our scientific success dataset, we found that there are more successful trials with single funding sources

58%

were trials with single funding sources

33.5%

were industry single funded

HOW SHOULD WE MEASURE RARE DISEASE TRIAL SUCCESS?

1. SCIENTIFIC SUCCESS

2. MONETARY SUCCESS

We define rare disease trials as successful from a **MONTETARY STANDPOINT** as interventions for rare diseases that go on to receive **subsequent indications** and at least one **orphan designation.**

SUBSEQUENT INDCATIONS

- Intervention recieves regulatory approval to treat a disease other than original indication

OR

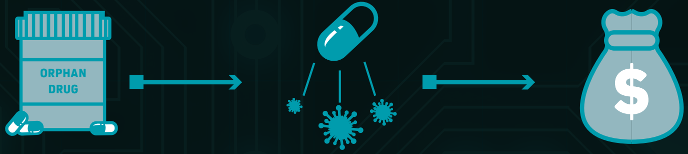
- Intervention receives approval to treat a new population within the same disease

ORPHAN DRUG ACT OF 1983

The orphan drug act plays a huge role in rare disease monetary success through financial incentives

- Tax Incentives
- 7 years market exclusivity
- Clinical research subsidies

MONETARY SUCCESS IN RARE DISEASE TRIALS



Orphan Designations
[Defend market exclusivity]

Subsequent Indications
[Expand total addressable market]

Increased Revenues

CASING A MONETARY SUCCESS

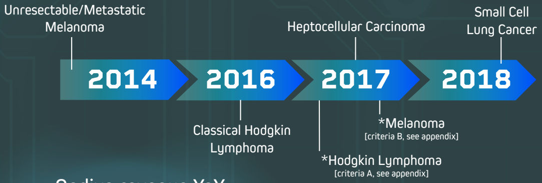
OPDIVO [NIVOLUMAB]

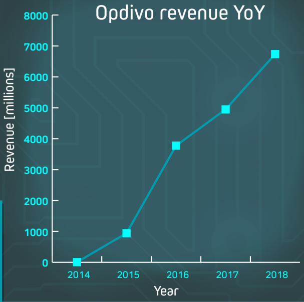
Immune checkpoint inhibitor
Subsequent Indications: 10
Number of Orphan Drug approvals: 6

Opdivo is an intervention which targets the cellular pathway known as PD-1-PD-L1.

Through harnessing the body's own immune system, Opdivo has gone on to receive approvals and orphan drug classifications across multiple rare cancers

Opdivo approved orphan indications:


Unresectable/Metastatic Melanoma
Heptocellular Carcinoma
Small Cell Lung Cancer
2014
2016
2017
2018
Classical Hodgkin Lymphoma
*Melanoma
[criteria B, see appendix]
*Hodgkin Lymphoma
[criteria A, see appendix]



By focusing on a cellular pathway instead of a specific rare cancer, Opdivo went on to receive subsequent indications and immense revenue growth.

FUTURE CONSIDERATIONS IN CLINICAL TRIALS

VIRTUAL CLINICAL TRIALS

- Brings research to patients via in-home visits to support patient-centric trial design and reducing the burden for caregivers and patients
- Using virtual enrollment can increase enrollment size and decrease time in finding patients as well as keep subjects engaged [roughly **40%** of patients of phase III trial subjects become disengaged and drop out of studies.

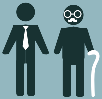
HOW CAN ALEXION MAXIMIZE TRIAL SUCCESS AS THEY DIVERSIFY INTO RARE DISEASES?

EMPHASIS ON

1

Trials for all genders

2



Adult + Older Adult age categories

3

Multi-location trials to increase median enrollment

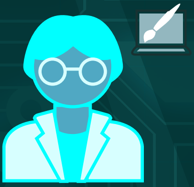
4

Focus on cellular pathways

1. Focus on trials that encompass all genders.
2. When conducting trials, set age eligibility criterion for the adult + older adult category. This can help mitigate the challenge of identifying homogenous trial participants who have not yet been diagnosed. Once approved, target other age groups within the population to attain subsequent indications.
3. Utilize multiple trial sites and seek methods of breaking physical barriers to increase median enrollment.
4. Focus on cellular pathways within your core competence areas to increase the liklihood of subsequent approvals & orphan designations across indications. This will lead to increased revenues.

Jake Green
tug62544
Fox School of Business
and Management

Rohit Bobby
tud12377
Fox School of Business
and Management



Lauren Remy
tuj89255
Klein College of Media and
Communication

SOURCES

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APPENDIX

Approved label indication - **Criteria 1**: Treatment of adult patients with Classical Hodgkin lymphoma that has relapsed or progressed after 3 or more lines of systemic therapy that includes autologous HSCT

Approved label indication - **Criteria 2:** Adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection

METHODOLOGY

Our analysis of which rare diseases had the most clinical trials represents the dataset provided for the challenge de-duplicated on NCT, keeping the record with the most recent updated date. Our scientific success dataset (used in sampling scientific success and funding scientific success) was derived by joining the provided dataset on NCT with a dataset we curated from clinicaltrials.gov. The curated dataset filter criteria was for interventional trials that were completed, with results, and obtained an eventual approval for marketing for the primary intervention of interest (phase 1, 2, and 3). We included all funder types, age groups, and genders. After combining these curated record into one large data-set, we joined it on NCIT with the de-duplicated version of the provided dataset. This left us with our success dataset of n=5279. All records in our success set were representative of rare disease interventional trials where the primary intervention of interest went on to receive approval for marketing, across all phases. Phase 1|2 records were regrouped into phase 1. Phase 2|3 records were grouped into phase 2. Our rationale regarding the accuracy of these reclassification was based upon a reputable and highly cited research study conducted and posted in the Orphanet Journal of Rare Disease which utilized the same methodology to produce summary statistics for rare disease trials.