Study on Estimating Market Potential of Immunotherapy and Chemotherapeutics in 2018

By

Utkarsh Misra

Dissertation submitted in partial fulfillment of the requirements of the degree

MBA Hospital and Health Management

Academic year, 2017-2019

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INSTITUTE OF HEALTH MANAGEMENT RESEARCH
(WHO Collaborating Centre for District Health System Based on Primary Health Care)

IIHMR UNIVERSITY

TO WHOMSOEVER MAY CONCERN

This is to certify that **Dr. Utkarsh Misra** student of MBA Health and Hospital Management from The IIHMR University, Jaipur has undergone internship training at **PharmaACE Innovations , Pune** from **4st February 2019 to 3rd May, 2019.**

The Candidate has successfully carried out the study on **'The study on estimating market potential of immunotherapy and chemotherapeutics in 2018'** designated to his during internship training and his approach to the study has been sincere, scientific and analytical.
The Internship is in fulfillment of the course requirements.

I wish him all success in all his future endeavors.

(Col) Dr. Ashok Kaushik
Dean, Academic and Student Affairs
The IIHMR University, Jaipur
17 May 2019

Dr. Monika Chaudhary
Professor, Guide
The IIHMR University, Jaipur

PharmaACE

The certificate is awarded to

Mr. Utkarsh Misra

In recognition of having successfully completed his internship in the department of

Market Research

And has successfully completed his project on

"The study on Estimating Market Size of Immunotherapy over Chemotherapy in Cancer Therapeutics for 2018"

3rd May 2019

He comes across as a committed, sincere and diligent person who has a strong drive and zeal for learning.

We wish him all the best for his future endeavors!

For PharmaACE Innovations LLP

Rashi Chawla

HR Lead

THE IIHMR UNIVERSITY, JAIPUR

CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled :**The study on estimating market potential of immunotherapy and chemotherapeutics in 2018** and submitted by **Utkarsh Misra** Enrolment No **IIHMR-U/01/2017-19/0686** under the supervision of **Dr. Monika Chaudhary** for award of MBA in Hospital and Health Management in Health and Hospitals of the University carried out during the period from **4th February 2019 to 3rd May 2019** embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other institute or other similar institution of higher learning.

Signature

ACKNOWLEDGEMENT

I am very indebted to get a chance to work in an organization which is JCI and NABH accredited, in which I learned a lot and everyone was highly cooperative and provided me necessary information regarding my project as well the functioning of this organization.

I would like to pay my sincere regard and gratitude to **Rashi Chawla (HR MANAGER)** who gave me the opportunity to do dissertation training in their esteemed organization. He also gave his time and advice very nicely.

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I solemnly acknowledge my sincere gratitude to all those who have directly or indirectly supported me during this Internship.

Sincerely,

Utkarsh Misra

TABLE OF CONTENTS:

ABRREVIATIONS/DEFINATIONS:

IO –Immuno-Oncology

PD– Programmed death

CD4+ - Glycoprotein found on the surface of immune cells

helper T cells– type of cells in adaptive immunity

(irRC)- Immune-related Response Criteria

TITLE -The study on estimating market potential of immunotherapy and chemotherapeutics in 2018

RESEARCH QUESTION

- What was market size of cancer drugs in USA in the year 2018?
- What therapy area is contributing most in terms of annual revenues?

OBJECTIVE:

- To estimate the market potential for US market of Immunotherapy and Chemotherapy in terms of market share
- To calculate revenue share contribution for US market of Immunotherapy and Chemotherapy for the year 2018

EXECUTIVE SUMMARY

ADVANCES IN IO medicine

In the course of recent years sixty-three IO drug, each and every one endorsed in at least one than one tumors, have wedged the treatment of twenty-four totally extraordinary disease sorts. the expansion of immuno-oncology since the essential dispatches in 2014 has been for the most part centered around the PD-1 and PD-L1 components, assumed checkpoint inhibitors, that have wide effectivity crosswise over strong tumors and are utilized crosswise over twenty-three totally extraordinary tumor sorts.

Of the fourteen New Active Substance disease medication propelled in 2018 alone, every one of them were focused on treatments and eleven of them were conceded Breakthrough treatment assignment by the Food and Drug Administration – showing potential for generous improvement over existing treatments on one or extra clinically significant endpoints. Clinical points of interest in wording ranges from complete reduction rates higher than 50 percent or gradual survival favorable circumstances to augmentations of by and large survival. The methodology of including different medicine amid a treatment program is being stretched out to join various immuno-oncology checkpoint inhibitors in blend regimens. Persistent treatment conventions are detailed dependent on the ID of immuno-oncologic biomarkers that are re-characterizing disease into a great deal of exact classes, with improved reaction rates, higher results and extra fair medications.

GEOGRAPHIC INEQUALITY

Just patients inside the United States of America, European country and Britain approach more than forty of the fifty five prescription meds principally propelled somewhere in the range of 2012 and 2016 in light of medication creators not petitioning for administrative endorsement, postponements or refusals of endorsement, or

medication producers anticipating the aftereffects of repayment dealings before propelling the medication inside the nation.

- The range of oncologists accessible to treat patients varies three-fold relative to population across developed countries, probably impacting access to treatment.

PIPELINE AND PROSPECTS FOR CLINICAL DEVELOPMENT

- In excess of 700 malignancy medicine are in late-arrange advancement – up over 60% from 10 years past. Over third of preliminaries are including biomarkers to stratify patients, focusing to even extra tweaked (and successful) malignancy medicines inside what's to come. The pipeline of immunotherapies is particularly dynamic and incorporates almost three hundred atoms with sixty separate instruments being assessed in stage I clinical preliminary or stage II clinical preliminary clinical preliminaries, that could be a significant hop from the four components of such prescription in stage III preliminaries or experiencing administrative audit. Immunotherapy clinical preliminaries are being led crosswise over thirty four totally extraordinary tumor sorts, showing the wide based use of this new way to deal with malignant growth treatment. about 700 firms or associations have at least one than one malignant growth drug in late stage improvement, speaking to an astoundingly assorted arrangement of elements following advances in immuno-oncology space, and fourteen of the world's biggest pharmaceutical firms have at least third of their late-organize R&D action fixated on disease prescription.

ADVANCES IN CANCER MEDICINE

- new active substances launched of targeted therapies of Food and Drug Administration status
- The new medicines launched their important clinical advances
- Over the past 5 years there are seventy eight new indication approvals for NAS, with some treating multiple tumour sorts
- uptake of checkpoint inhibitors
- Checkpoint inhibitors are getting used across many alternative tumour sorts
- use of multiple immuno-oncology stop inhibitors
- Biomarkers ar getting used to redefine cancer a lot of exactly
- Immuno-oncology currently encompasses a spread of mechanisms
- Therapies work effectively in specific sub-groups of patients across multiple solid and blood-based tumours.

INTRODUCTION:

Disease medicines giving clinical advantage and raised particularity through biomarker choice enormously moving the course of treatment. the measure of treatments, nature of meds, finance access to medications, flood in development, openness of prognosticative

biomarkers and symptomatic tests, remedial pipeline and troublesome innovations are drawing an a ton of exact course of treatment to the malignant growth quiet.

tumor immunology has been coordinated to know the components of the framework that are indispensable for neoplasm resistant reconnaissance and neoplasm dismissal to get a handle on how, when, and why they flop in instances of clinical disease. (4)

Immunotherapy, that includes fortifying the disease patient's resistant framework by upgrading its capacity to perceive the neoplasm or giving a missing invulnerable effector activity

cancer– safe framework collaborations have unveiled that each prestigious natural and versatile invulnerable effector instrument takes an interest in neoplasm acknowledgment and the board. the essential few changed cells are identified by NK cells through their experience with explicit ligands on neoplasm cells. This winds up in the devastation of some re-demonstrated cells and furthermore the take-up and preparing of their parts by macrophages and dendritic cells. Thus, these macrophages and dendritic cells are actuated to discharge a few incendiary cytokines and exchange malignant growth cell-inferred atoms to T-and B cells. Initiation of T-and B cells results in the get together of additional cytokines that moreover advance actuation of normal insusceptibility and bolster the development and creation of tumor-explicit T cells and antibodies, all the while. the total intensity of the accommodating framework winds up in the disposal of residual neoplasm cells and, fundamentally, to the age of invulnerable memory to explicit neoplasm components which will serve to stop neoplasm return.

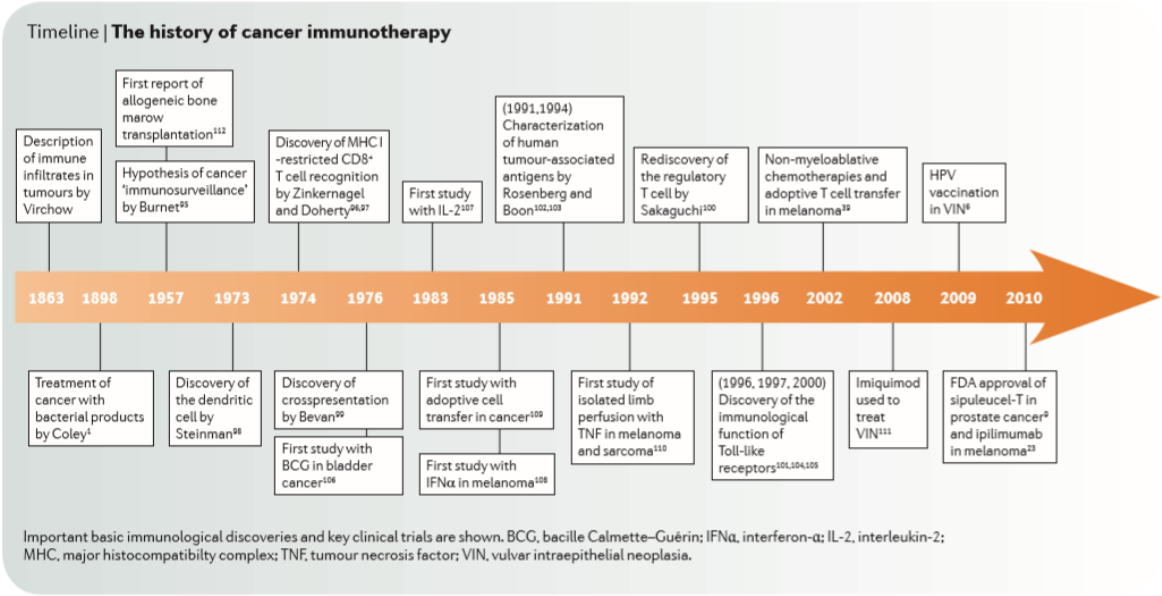
Effectors of versatile resistance, as CD4+ partner T cells, CD8+ cytotoxic T cells, and antibodies, explicitly target tumor antigens; for example particles communicated in tumor cells, anyway not in customary cells.

Not at all like chemo-treatment, that demonstrations straightforwardly on the tumor, malignant growth immunotherapies apply their impacts on the bodies invulnerable framework and exhibit new mechanics that include building a cell insusceptible response, trailed by changes in tumor weight or patient survival.

Somewhere in the range of 2004 and 2009, a few activities encouraged by the Cancer Immunotherapy Consortium of the Cancer Research Institute and accomplice associations deliberately assessed an immunotherapy-centered clinical improvement worldview and made the standards for rethinking preliminary endpoints.

BACKGROUND

Figure 1:TIME LINE



Traditional treatments apply their belongings by legitimately focusing on disease cells and ordinarily instigate quantifiable effect on neoplasm development not long after organization or not under any Indication. In qualification, treatments focusing on the insusceptible framework especially incite hostile to tumoral impacts in a roundabout way by at first invigorating the bodies safe reaction and second bringing about a more extensive scope of reaction mechanics just as deferred impacts (after increment of existing malignant growth injuries or event of more sores most likely inspired by resistant penetrates) or adjustment of present disease sores.

For the survival end point, Kaplan-Meier bends from randomized immunotherapy clinical preliminaries may demonstrate a deferred detachment when contrasted with chemotherapy in months

Measurable models utilized in randomized preliminaries with standard treatments, wherever partition of bends happens early when treatment started, by and large expect a proceeding with danger proportion after some time (corresponding risks). Diverse connected factual models custom fitted to manage the postponed partition of bends must be constrained to consider that all occasions before the detachment don't add to the separation between study arms after the division, bringing about loss of measurable power. Such new connected factual models should offer some kind of reparation for this loss of intensity. they will part the risk proportion into an early and a late component when the partition of bends.

utilizing tumor shrinkage as their assessment of movement. due to the new science spoke to over, the reaction examples of immunotherapy stretch out on the far side those of chemotherapy, and show once a measure of stable term of illness is come to or after starting tumor load increment or presence of new sores, which may cause invasion of lymphocytes into the development.

Information arranged four examples of reaction. (1) Immediate reaction; (2) solid stable un wellbeing with potential moderate decrease in tumor trouble; (3) reaction after tumor load increment (conceivable WBC invasion); and (4) reaction inside the nearness of new sores. The last reaction criteria, named invulnerable related reaction criteria (irRC) ar normally upheld by World Health Organization and RECIST criteria, depict tumor load as a constant variable over the long run, represent new injuries inside the general tumor trouble and inspire affirmation of movement like the set up affirmation of reaction at an ensuing time point after starting discovery.

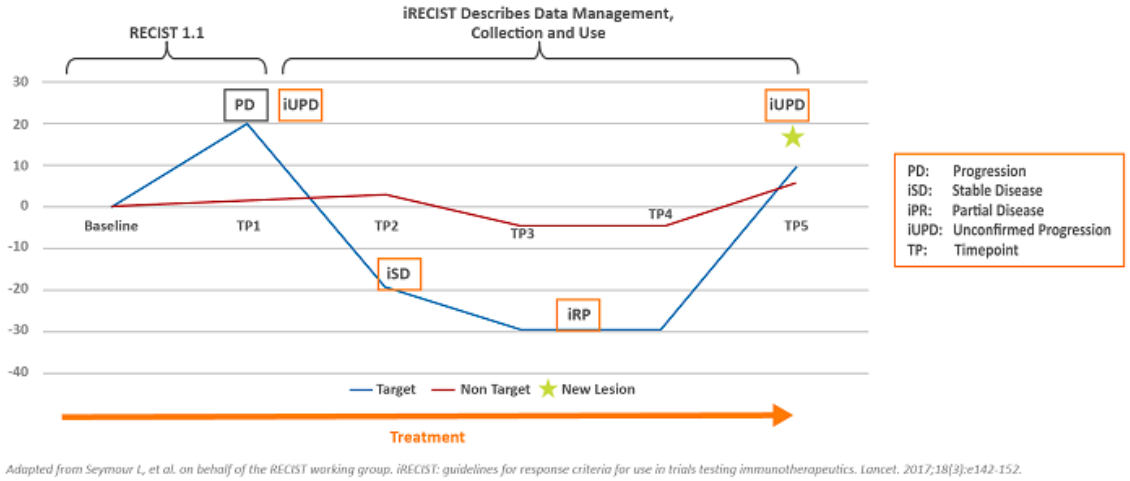
A NEW SET OF RULES: IRECIST

In 2017, another arrangement of insusceptible related reaction criteria was anticipated by a RECIST social unit involved individuals from industry, the scholarly community, the U.S. Sustenance and Drug Administration (FDA) and furthermore the European Medicines Agency (EMA). This agreement rule—called Immune RECIST (iRECIST)—institutionalizes and approves immunologic reaction criteria to aid basic leadership identifying with continuation of restorative consideration in clinical preliminaries.

iRECIST includes the use of changed RECIST in malignant growth treatment preliminaries and portrays a uniform way to deal with measure strong developments and molding target change in tumor estimate for clinical trials.2 iRECIST furthermore presents a spic and span reaction standard called invulnerable unverified movement of ailment (iUPD), which depicts new in general reaction.

With iRECIST, the bar for movement resets if RECIST-characterized dynamic infection (PD) is pursued at following time point (TP) by tumor shrinkage, as observed in TP2

inside the figure beneath.



Adapted from Seymour L, et al. on behalf of the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet. 2017;18(3):e142-152.

Figure 2: Assessing tumor response using iRECIST

iRECIST has not yet been validated and should not be used as a guideline for treatment decisions. However, iRECIST can be used in conjunction with RECIST in later-phase studies, and may be used as primary response criteria in exploratory, early-phase studies.

Patrons of malignant growth immunotherapy drugs who need to utilize iRECIST rules in their examinations should prepare their operational group and discuss intimately with the Data and Safety Monitoring Board (DSMB) to guarantee that all partners comprehend that these specialists work uniquely in contrast to cytotoxic treatments.

Validating Biomarkers

Current patient reaction rates and toxicities related with immunotherapies have made a feeling of earnestness to figure out which patients would most profit by these specialists. Until this point in time, the biomarkers for immunotherapy incorporate immunohistochemistry, stream cytometry and cutting edge sequencing, every one of which has its upsides and downsides. The distinguishing proof of insusceptible explicit biomarkers will fill learning holes by giving significant prescient and prognostic data, just as bits of knowledge on the basic systems of treatment reaction and obstruction.

A noteworthy obstacle to the recognizable proof and improvement of clinically significant biomarkers is the way that insusceptible tweak influences numerous phone types and includes complex collaborations among the host, malignancy cells and tumor microenvironment.3 The Society for Immunotherapy of Cancer (SITC) Biomarkers Task Force has distributed a progression of white papers on the approval procedure and

administrative contemplations related with biomarkers in immunotherapy, just as novel innovations and developing biomarkers pertinent to individualized disease treatment.

Table 1 : CLASSIFICATION (1)

Class Under Immunotherapy	Mechanism of action & Major benefit	Major disadvantages
Cytokines		
IL-2	-Activates the body's immune system	-Low response rates
		-considerable risk of severe systemic inflammation
IFN-α	-Activates the body's immune system	-Low response rates
	-Durable responses	-Large amount of dose toxicity
Cell-based therapies		
Vaccines	-Activates the host's immune system	-Lack of common antigens and model immunization protocols results in poor efficacy and response
	-minimum toxicity (e.g., sipuleucel-T)	
	-Can be given in the outpatient clinic	
Adoptive cellular therapy	-eliminates the process of reducing tolerance to tumour antigens	-usage only in melanoma
	-Produces a remarkable avidity in effector T cells	-Safety profile, severe adverse effects, and deficient of long enduring responses in many patients
	-Lymphodepleting indicating treatment prior to TIL infusion enhances efficacy	-needs time to develop the required cell populations
	-Genetic T cell engineering widens TIL to malignant tumours except melanoma	-High cost
Immune checkpoint blockade		
Anti-CTLA-4 monoclonal antibodies	-set free pre-existing anticancer T cell responses and maybe triggers new	-Only a comparatively little portion of patients gain clinical benefit
	-shows strong antitumor properties	-Severe immune-related adverse events have been observed in up to 35 % of patients
	-extension of overall survival	
Anti-PD1 and anti-PD-	-adequate clinical responses	-Only a quite small portion

L1 antibodies	that are regularly long-lasting	of patients obtain clinical benefit
	-curative responses in patients with wide range of human cancers	
	-Decreased toxicity in contrast to anti-CTLA-4 antibodies	
Combination immunotherapy (immune checkpoint blockade as the backbone)	-enhancement of anti-tumor responses/immunity	-May cause increase in the magnitude, rate of recurrence, and start of side effects

Farkona et al. BMC Medicine (2016) 14:73 DOI 10.1186/s12916-016-0623-5

Table 2: MAJOR DRUGS APPROVED

Generic Name (Brand, Manufacturer)	FDA Approval	Target	Structure/Description	Indication(s)†
Alemtuzumab (Campath, Genzyme)	2001	CD52	Humanized IgG1	B-cell CLL
Atezolizumab*(Tecentriq, Genentech)	2016	PD-L1	Humanized IgG1	Locally advanced or metastatic UC; metastatic NSCLC
Avelumab* (Bavencio, EMD Serono)	2017	PD-L1	Human IgG1	Merkel cell carcinoma; UC
Bevacizumab (Avastin, Genentech)	2004	VEGF	Humanized IgG1	Metastatic CRC and RCC; NSCLC; glioblastoma; cervical cancer; epithelial ovarian, fallopian tube, or primary peritoneal cancer

Blinatumomab (Blincyto, Amgen)	2014	CD19/CD3	BiTE	B-cell ALL
Brentuximab vedotin (Adcetris, Seattle Genetics)	2011	CD30	Chimeric IgG1 conjugated with mitotic toxin MMAE	HL; systemic anaplastic large cell lymphoma
Cetuximab (Erbitux, Eli Lilly)	2004	EGFR	Chimeric IgG1	CRC; HNSCC
Daratumumab (Darzalex, Janssen Biotech)	2015	CD38	Humanized IgG1	MM
Durvalumab* (Imfinzi, AstraZeneca)	2017	PD-L1	Human IgG1	UC
Ibritumomab tiuxetan (Zevalin, Spectrum Pharmaceuticals)	2002	CD20	Mouse IgG1 conjugated with radionuclide Y90	B-cell NHL
Ipilimumab* (Yervoy, Bristol-Myers Squibb)	2011	CTLA-4	Human IgG1	Metastatic melanoma
Nivolumab* (Opdivo, Bristol-Myers Squibb)	2014	PD-1	Human IgG4	Metastatic melanoma; metastatic NSCLC; advanced RCC; HL; HNSCC; advanced or metastatic UC
Obinutuzumab (Gazyva, Genentech)	2013	CD20	Glycoengineered IgG1	CLL; follicular lymphoma
Ofatumumab (Arzerra, Novartis)	2009	CD20	Human IgG1	CLL
Olaratumab (Lartruvo, Eli Lilly)	2016	PDGFR-α	Human IgG1	Soft tissue sarcoma

Panitumumab (Vectibix, Amgen)	2006	EGFR	Human IgG2	Metastatic CRC
Pembrolizumab*(Keytruda, Merck Sharp & Dohme)	2014	PD-1	Humanized IgG4	Metastatic melanoma; NSCLC; metastatic HNSCC; HL; UC; MSI-H or dMMR CRC
Pertuzumab (Perjeta, Genentech)	2012	HER-2	Humanized IgG1	Breast cancer
Rituxumab (Rituxan, Genentech)	1997	CD20	Chimeric IgG1	NHL; CLL
Ramucirumab (Cyramza, Eli Lilly)	2014	VEGFR2	Human IgG1	NSCLC; gastric cancer; metastatic CRC
Siltuximab (Sylvant, Janssen Biotech)	2014	IL-6	Chimeric IgG1	Multicentric Castleman's disease
Trastuzumab (Herceptin, Genentech)	1998	HER-2	Humanized IgG1	Breast cancer; metastatic gastric or gastroesophageal junction adenocarcinoma
Trastuzumab emtansine (Kadcyla, Genentech)	2013	HER-2	Humanized IgG1	Metastatic breast cancer

MARKET ANALYSIS:

TOP CHEMO 2017

1. Revlimid

Manufacturer: Celgene

Indication or Diseases treated: Multiple myeloma

Global sales: $4.2 billion

Generic name: Lenalidomide

2. Gleevec

Manufacturer: Novartis

Indication or Diseases treated: Chronic myeloid leukemia, gastrointestinal stromal tumors

Global sales: $4.7 billion

Generic name: Imatinib

3. Velcade

Manufacturer: Johnson & Johnson/Takeda

Indication or Diseases treated: Multiple myeloma, mantle cell lymphoma

Global sales: $2.6 billion

Generic name: Bortezomib

4. Xtandi

Manufacturer: Astellas Pharma/Pfizer

Indication or Diseases treated: Prostate cancer

Global sales: $2.371 billion

Generic name: Enzalutamide

5. Alimta

Manufacturer: Eli Lilly

Indication or Diseases treated: Non-small cell lung cancer

Global sales: $2.5 billion

Generic name: Pemetrexed

TOP IO DRUGS 2017:

1. Keytruda

Manufacturer: Merck.

Indication or Diseases treated: Advanced melanoma; non-small cell lung cancer; head and neck squamous cell cancer

Global sales: $1.402 billion

Generic name: Pembrolizumab

2. OPDIVO

Manufacturer: Bristol-Myers Squibb; Ono Pharmaceutical

Indication or Diseases treated: Non-small cell lung cancer; metastatic melanoma; renal cell carcinoma; classical Hodgkin lymphoma

Global sales: $4.7 billion

Generic name: Nivolumab

Table 3: Upcoming Unmet Needs in the form of new incidence cases (7)

SITE	Total	Male	Female
Oral cavity & pharynx			
Tongue	17,060	12,550	4,510
Mouth	14,310	8,430	5,880
Pharynx	17,870	14,450	3,420
Other oral cavity	3,760	2,710	1,050
Digestive system			
Oesophagus	17,650	13,750	3,900
Stomach	27,510	17,230	10,280
Small intestine	10,590	5,610	4,980
Colon	101,420	51,690	49,730
Rectum	44,180	26,810	17,370
Anus, anal canal, & anorectum	8,300	2,770	5,530
Liver & intrahepatic bile duct	42,030	29,480	12,550
Gallbladder & other biliary	12,360	5,810	6,550
Pancreas	56,770	29,940	26,830
Other digestive organs	7,220	2,990	4,230
Respiratory system			
Larynx	12,410	9,860	2,550
Lung & bronchus	228,150	116,440	111,710
Other respiratory organs	5,880	4,070	1,810
Bones & joints	**3,500**	**2,030**	**1,470**
Soft tissue (including heart)	**12,750**	**7,240**	**5,510**
Skin (excluding basal & squamous)			
Melanoma of the skin	96,480	57,220	39,260
Other nonepithelial skin	7,870	5,100	2,770
Breast	**271,270**	**2,670**	**268,600**
Genital system			
Uterine cervix	13,170		13,170
Uterine corpus	61,880		61,880
Ovary	22,530		22,530

Vulva	6,070		6,070
Vagina & other genital, female	5,350		5,350
Prostate	174,650	174,650	
Testis	9,560	9,560	
Penis & other genital, male	2,080	2,080	
Urinary system			
Urinary bladder	80,470	61,700	18,770
Kidney & renal pelvis	73,820	44,120	29,700
Ureter & other urinary organs	3,930	2,630	1,300
Eye & orbit	**3,360**	**1,860**	**1,500**
Brain & other nervous system	**23,820**	**13,410**	**10,410**
Endocrine system			
Thyroid	52,070	14,260	37,810
Other endocrine	2,670	1,390	1,280
Lymphoma			
Hodgkin lymphoma	8,110	4,570	3,540
Non-Hodgkin lymphoma	74,200	41,090	33,110
Myeloma	**32,110**	**18,130**	**13,980**
Leukaemia			
Acute lymphocytic leukaemia	5,930	3,280	2,650
Chronic lymphocytic leukaemia	20,720	12,880	7,840
Acute myeloid leukaemia	21,450	11,650	9,800
Chronic myeloid leukaemia	8,990	5,250	3,740
Other leukaemia	4,690	2,860	1,830
Other & unspecified primary sites	**31,480**	**16,750**	**14,730**
All sites	**1,762,450**	**870,970**	**891,480**

Table 4 :5-year survival rates

Cancer Type	5-year Relative Survival (%)
Prostate	97.3 (97.2-97.4)
Thyroid	96.8 (96.7-96.9)
Testis	95.3 (95.1-95.5)
Melanomas of the Skin	89.3 (89.2-89.4)
Female Breast	88.6 (88.6-88.7)
Hodgkin Lymphoma	83.5 (83.2-83.8)
Corpus and Uterus, NOS	80.6 (80.5-80.8)
Urinary Bladder	74.8 (74.7-75)
Kidney and Renal Pelvis	71.2 (71.1-71.4)
Non-Hodgkin Lymphoma	67.9 (67.8-68.1)

Cervix	67.6 (67.3-67.9)
All Cancer Sites Combined	65.6 (65.6-65.6)
Colon and Rectum	63.4 (63.3-63.5)
Oral Cavity and Pharynx	60.6 (60.4-60.8)
Larynx	59 (58.7-59.4)
Leukemias	54.7 (54.5-54.9)
Ovary	46.1 (45.9-46.4)
Myeloma	45.3 (45-45.6)
Brain and Other Nervous System	32.7 (32.5-32.9)
Stomach	29.2 (29-29.5)
Lung and Bronchus	18.2 (18.1-18.3)
Esophagus	18.1 (17.8-18.3)
Liver and Intrahepatic Bile Duct	17.2 (17-17.4)
Pancreas	8.5 (8.3-8.6)

Table 5: FDA Approval

	IO Drug	FDA Approval Date
Frontline treatment of advanced melanoma	Ipilimumab and Nivolumab	October 2015
Second-line treatment for lung cancer	Pembrolizumab	October 2015
Non-squamous NSCLC (Post Chemotharapy)	Nivolumab	October 2015
Metastatic squamous NSCLC	Nivolumab	November 2015
3L or more multiple myeloma	Daratumumab	November 2015
Metastatic renal cell carcinoma	Nivolumab	November 2015
Multiple myeloma	Elotuzumab	November 2015
Chronic lymphocytic leukemia (CLL)	Ofatumumab	January 2016
Follicular lymphoma	Obinutuzumab	February 2016
Classical Hodgkin lymphoma (chl)	Nivolumab	May 2016
Bladder cancer	Atezolizumab	May 2016
Metastatc head and neck Carcinoma (HNSCC)	Pembrolizumab	August 2016
Metastatic, chemotherapy-resistant (NSCLC)	Atezolizumab	October 2016

Pd-l1 (nsclc)	Pembrolizumab	October 2016
Metastatc head and neck Carcinoma (HNSCC)	Nivolumab	November 2016
Bladder cancer	Nivolumab	February 2016

METHODOLOGY:

Descriptive study is performed to identify the potential of different cancer therapy areas available to the patients on the basis of certain characteristics drug have to be an effective treatment. First criteria considered is the effectiveness proved in clinical trials before the drug is approved by FDA as the more effective drug gains major position in the market. Second criteria is the appearance of side effects due to the treatment. Third is the length of the treatment that a patient must undergo in a hope to get treated. Finally, the fourth criteria is the average cost of the treatment which the patient or the reimbursement agencies has to bear.

Secondary data is collected on the four criteria to score them according to the potential of the therapy area to gain the market. Various Research articles are referred to gain the data over the advances in each therapy areas. Major clinical trials and past launched products provided the insight to score the criteria out of 1.

Each criteria is subjectively weighted according to the inputs from previous market researches. Then normalizing the score to gain the final market potential in terms of market share in percentages.

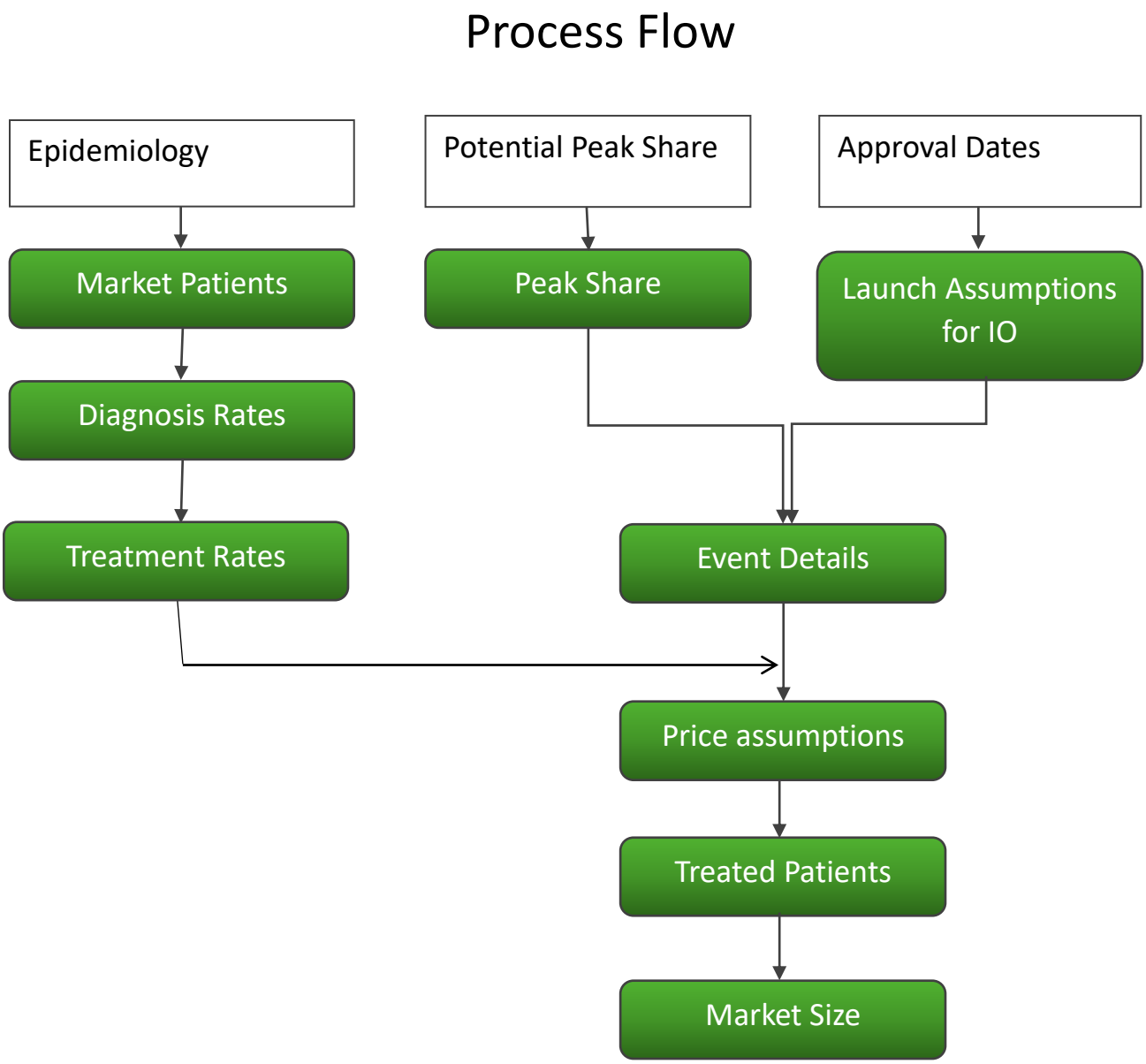
To estimate the revenues major inputs and assumptions are identified and processed to give a market size distribution in terms of revenues (US dollars). Major indications across cancer therapy are evaluated to get the complete market size

Inputs required are

- Epidemiological data of major cancer indications
- Potential peak share of the therapy area
- Approved drugs under each therapy area
- Diagnosis rates and Treatment rate
- Average length of the treatment (DoT)
- Average cost of the treatment in major indications

Mapping the process flow to get the final revenues across each indication:

FIGURE 3: Process flow



Assessing Criteria to establish market potential in terms of market share

CRITERIA 1. CHEMOTHERAPY VS IMMUNOTHERAPY – EFFECTIVENESS

Immunotherapy is a novel methodology that demonstrates extraordinary guarantee in the treatment of malignant growth. For instance, immunotherapeutic operators affirmed for the treatment of non little cell lung malignancy incorporate pembrolizumab (Keytruda, Merck), nivolumab (Opdivo, Bristol-Myers Squibb), and atezolizumab(Tecentriq, Genentech). For lung malignant growth that has spread broadly, the main line

treatment is pembrolizumab for patients with elevated amounts of modified demise ligand 1 (PD-L1), which is identified with reaction to resistant checkpoint barricade. In the KEYNOTE-024 preliminary, the reaction rate with the principal line pembrolizumab in tumors with at any rate half PD-L1 was 44.8% contrasted and 27.8% for the chemotherapy gathering. Patients treated with the second-line pembrolizumab (KEYNOTE-010 preliminary) had a middle generally speaking survival term of 10.4 months (at a portion of 2 mg/kg) or 12.7 months (at a portion of 10 mg/kg) contrasted and 8.5 months for docetaxel. In the CheckMate-57 preliminary, patients who got nivolumab as a second-line treatment after platinum-based doublet chemotherapy had a middle in general survival length of 12.2 months contrasted and 9.4 months in patients treated with docetaxel. At last, in the OAK preliminary, patients who got atezolizumab as a second-line treatment had a middle generally survival length of 13.8 months contrasted and 9.6 months for those treated with docetaxel.

<u>CRITERIA 2.</u> CHEMOTHERAPY VS IMMUNOTHERAPY - SIDE EFFECTS

Side effects of chemotherapy:

- Are more likely to have infections
- Become tired more easily
- Bleed too much, even during everyday activities
- Feel pain or numbness from nerve damage
- Have a dry mouth, mouth sores, or swelling in the mouth
- Have a poor appetite or lose weight
- Have an upset stomach, vomiting, or diarrhoea
- Lose their hair
- Have problems with thinking and memory ("chemo brain")

Referred study results: (2) (3)

The normal predominance of reactions was 54% over the accomplice. Chest torment had the most reduced predominance (4% in general) while weakness had the most noteworthy (73% in general) and pervasiveness was comparable over the disease types.

As the second-line treatment choices for lung malignancy, pembrolizumab, nivolumab, and atezolizumab all have preferable wellbeing profiles over chemotherapy. Treatment-related unfavorable occasions (AEs) of any evaluation were accounted for in 63% of patients in the pembrolizumab gathering (accepting a portion of 2 mg/kg) contrasted and 81% in the chemotherapy gathering. The relating AE rates were 69% in the nivolumab bunch contrasted and 88% in the docetaxel gathering and 64% in the atezolizumab bunch contrasted and 86% in the docetaxel gathering. Not many patients suspended treatment attributable to treatment-related AEs. The rates were 5% for pembrolizumab, 5% for nivolumab, and 1% for atezolizumab. In the main line setting, the rate of treatment-related AEs of any evaluation was 73.4% for pembrolizumab contrasted and 90% for chemotherapy

FIGURE 4: Prevalence (Proportions Of Follow –Up Visists At Which The Specific Side Effect Was Reported) Of Self –Reported Side Effects,By Cancer Type, During Elemnts Of Cancer Care Study Period>. (2)

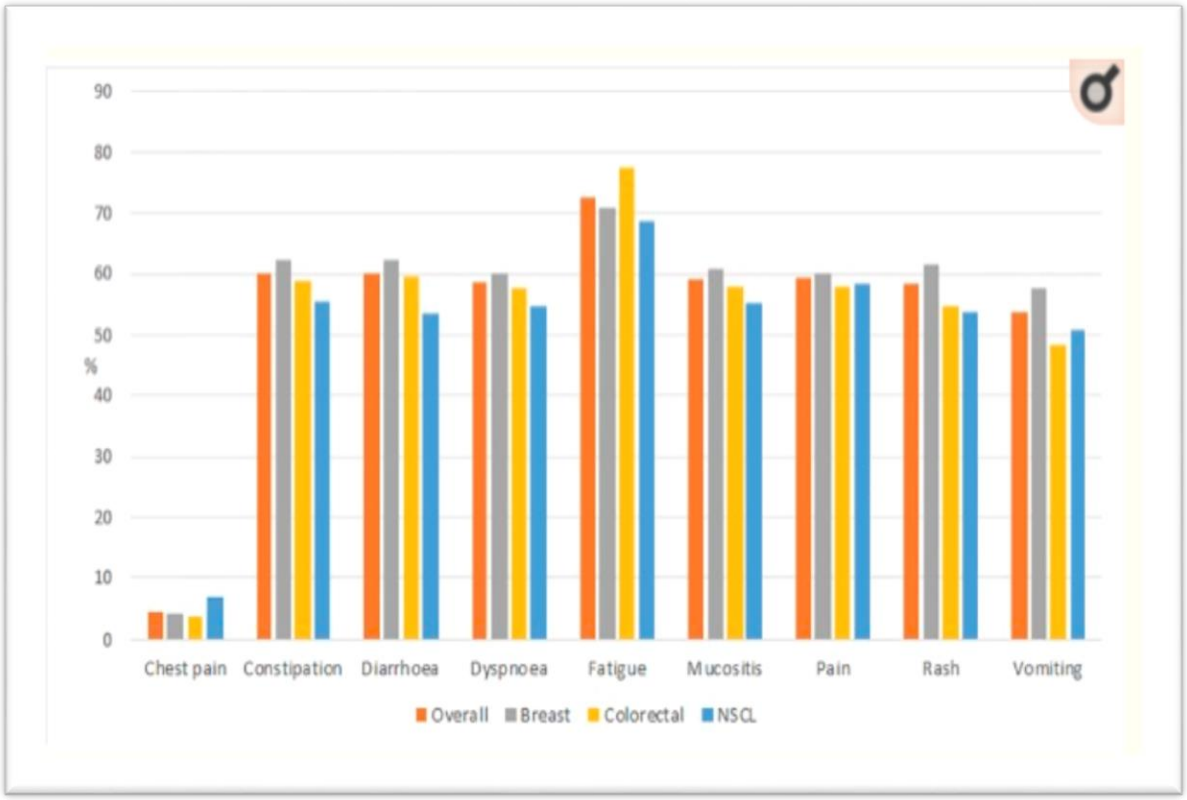
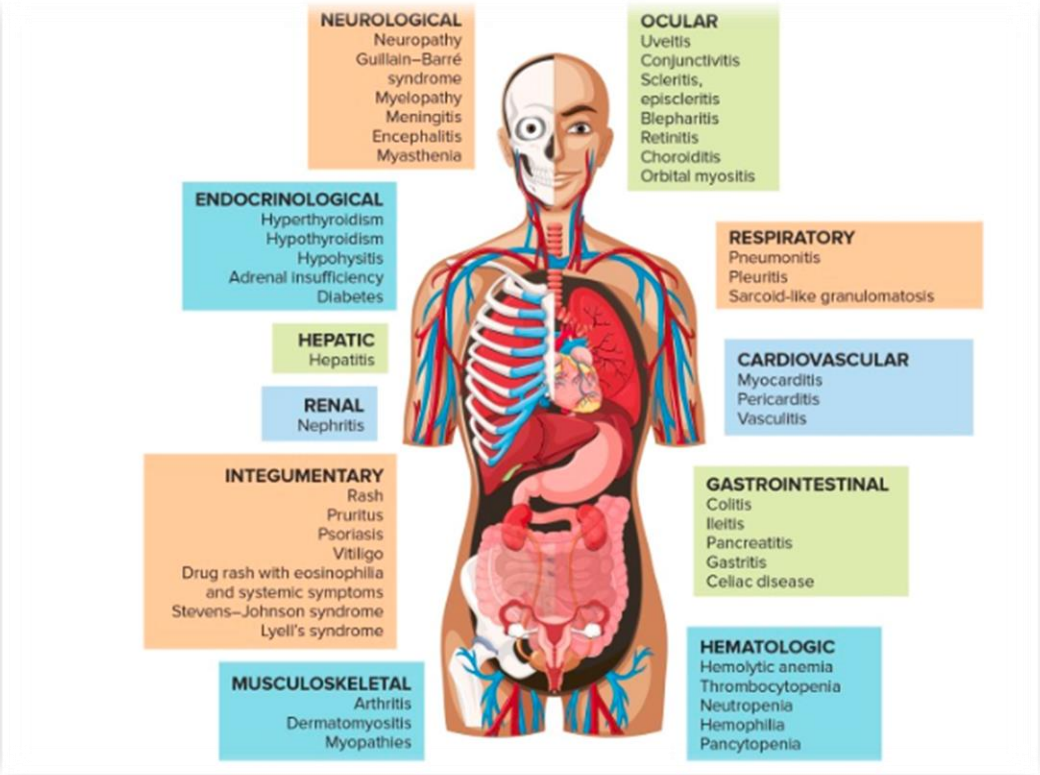


FIGURE 5: Representative Immune –Related Adverse Events Observed with Immnue Checkpoints Blockers (2)



CRITERIA 3. CHEMOTHERAPY VS IMMUNOTHERAPY - LENGTH OF TREATMENT

Length of the treatment also called the duration of the treatment is calculated on applying a factor of 90% to the progression free survival of the disease which represents patients has progressed to the advanced stages of cancer while on drugs.

Table 6: Duration of the treatment

	Indication	Dot (months)	PFS			Indication	Dot (months)	PFS
Opdivo	Melanoma	4.59	5.1		Temozolomide	melanoma	6.93	7.7
	Squamous non-small cell lung cancer	5.04	5.6		Cisplatin	squamous non-small cell lung cancer	4.23	4.7
	Renal cell carcinoma	10.44	11.6		Sunitinib	Renal cell carcinoma	7.56	8.4
	Colorectal cancer	8.64	9.6		Folfox4	colorectal cancer	6.66	7.4
	Hepatocellular carcinoma				Sorafenib	hepatocellular carcinoma	3.33	3.7
Pembrolizumab	Merkel-cell carcinoma	15.12	16.8		Cisplatin	Merkel-cell carcinoma	4.14	4.6
	Primary mediastinal B-cell lymphoma	1.98	2.2		Doxorubicin	primary mediastinal B-cell lymphoma	3.24	3.6
	Stomach cancer	4.5	5		Paclitaxel	stomach cancer	4.95	5.5

Criteria 4. Chemotherapy Vs Immunotherapy - Cost Comparison

Immunotherapies in particular often cost more than $100,000 per patient per year. Doctors now use immunotherapies in combination, which means those costs can quickly double or triple. For some of the newest immunotherapies, the price tag is even steeper: When you include the value of the medical support necessary to deliver these treatments, a price tag of $850,000 per patient is estimated

Table 7: Cost Comparison (5)

Indication	Year	Yearly Cost IO	Yearly Cost Chemo
Head and neck cancers	2017	$73,463	$26,133
	2018	$174,800	$57,000
Non-small cell lung cancer	2016	$107631	$30049
	2017	$100,791	$48182
Recurrent RCC	2017	$211,407	$167,405
	2018	$197089	$163,902
Melanoma	2017	$206,435	$146,775

PROVIDING WEIGHTS TO CRITERIA

The weights are provided to each criterion by their relevance to the criteria required to be fulfilled before the drug is launched. Thus drug effectiveness is the most important criteria that the drug is actually benefiting the patients in terms of their over all survival and progression free survival. Then the safety of the drug measured in the form of what drug does to the body and the side effects. The cost of the treatment plays a role in becoming the established regime if it is affordable and included in reimbursement schedules of insurance companies.

Criteria 1 – Effectiveness – 50%

Criteria 2 - Side Effects – 20%

Criteria 3 - Length of treatment – 10%

Criteria 4 - Cost Comparison – 20%

SoMarket Share Potential is calculated by Scoring the assigned criteria out of 1:

Table 8: Market score

Scoring Market Share Potential	Chemo	IO	IO Combination
Criteria 1	0.25	1	-
Criteria 2	0.25	0.5	-
Criteria 3	0.25	0.25	-
Criteria 4	0.75	0.25	-

Market share Contribution Final weighted Score by multiplying Average score to weightage given and IO Combination drugs are accounted for therapies which includes Immunotherapy given in combination with chemo therapy.

Market Share Potential	Chemo	IO	IO Combination (Average of IO & Chemo)
Criteria			
Criteria 1	0.125	0.5	0.3125

Criteria 2	0.05	0.1	0.075
Criteria 3	0.025	0.025	0.025
Criteria 4	0.15	0.05	0.1

IO VS Chemo Percentage Score

	Criteria 1	Criteria 2	Criteria 3	Criteria 4
Chemo Therapy	12%	5%	2%	15%
IO Therapy	49%	10%	2%	5%

The percentage score is then normalized to get IO Vs Chemo Vs IO-Chemo Combination Final Potential to Gain the Market

	Criteria 1	Criteria 2	Criteria 3	Criteria 4
Chemo Therapy	8%	3%	2%	10%
IO Therapy	33%	7%	2%	3%
Combination Therapy	20%	5%	2%	7%

Final Proposed Market share

IO	IO + Chemo	Chemo
44%	33%	23%

Epidemiology in US

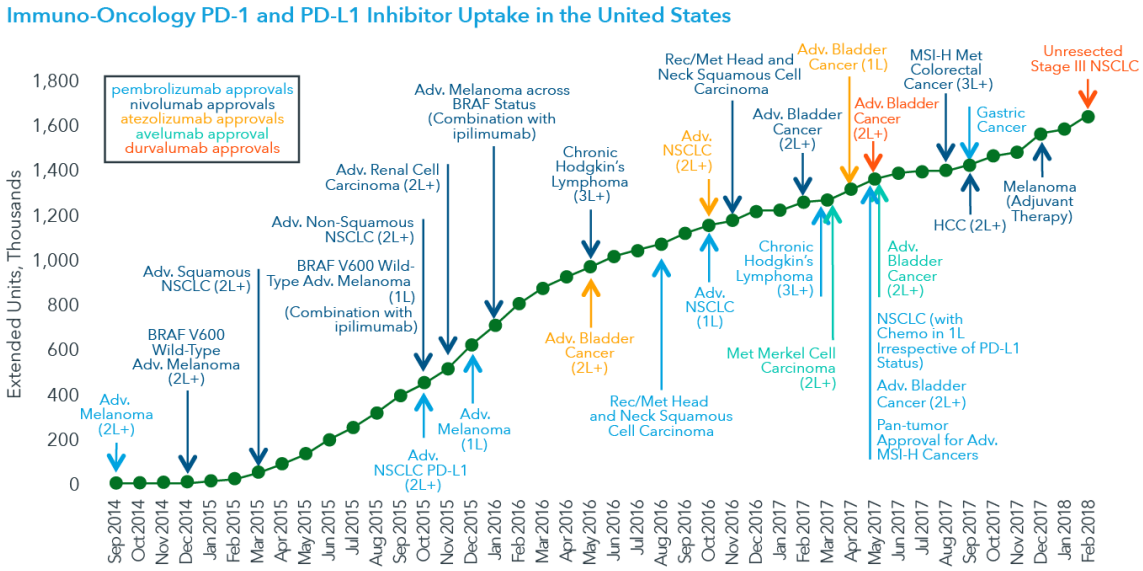
Identifying the unmet Need and the potential by the total cancer market

Table 9 :TOP 10 CANCER BY INCIDENCE:

Cancer Type	Incidence per year
Female Breast	270,000
Prostate	183,529
Lung and Bronchus	218,527
Colon and Rectum	140,788
Corpus and Uterus, NOS	54,644
Melanomas of the Skin	80,442
Urinary Bladder	73,067
Non-Hodgkin Lymphoma	67,522
Kidney and Renal Pelvis	61,816
Thyroid	48,761

https://gis.cdc.gov/Cancer/USCS/DataViz.html

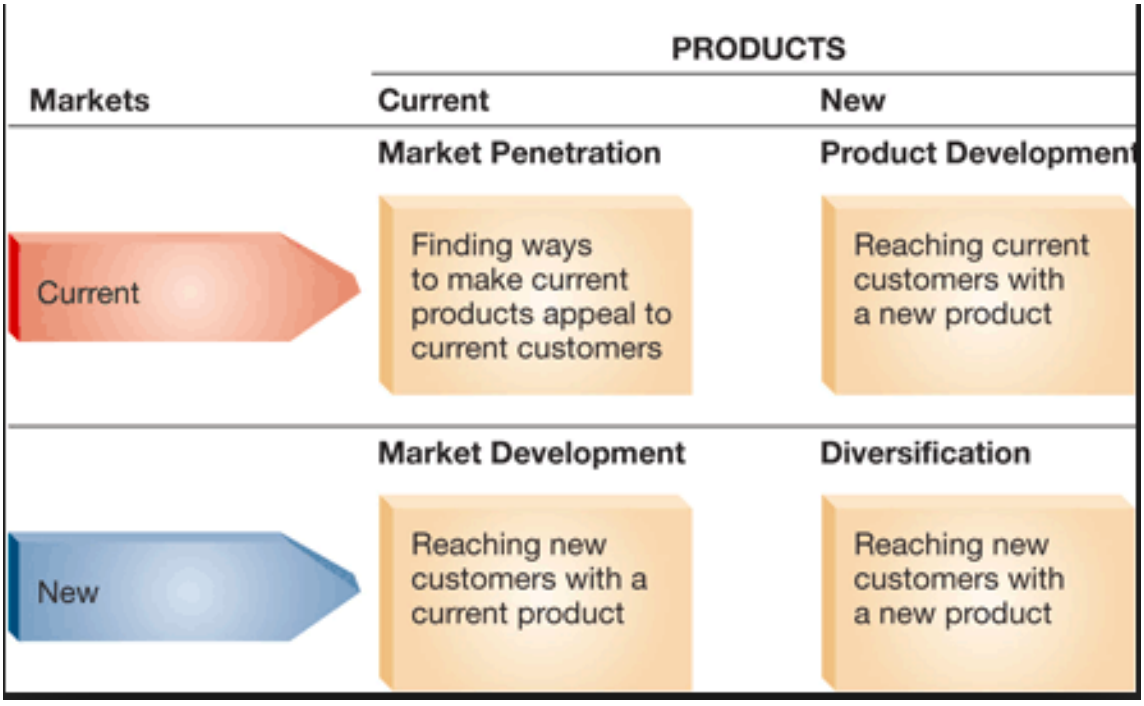
Figure 6 :**Growth of Immuno-therapy:**



https://www.iqvia.com/institute/reports/global-oncology-trends-2018

The growth of Immuno-therapy starts from the approval of first IO drug for any indication. Every new approval expands the market of IO and starts taking the patients which were earlier given the chemotherapy or established treatments. The pattern of growth is variable across the indications but usually rise with increase in the number of products approved in the indication. The penetration into the market reaches its peak until 4 or 5 products are launched and the products beyond 5 usually takes patients from current IO drugs due reason that new launched IO drugs need to show greater effectiveness over chemotherapy as well as current IO drugs in clinical trials.

Figure 7: Market **strategies**



Thus major segments under the umbrella term cancer are identified by type of cancer and recording the incidence cases which will form an undifferentiated market.Over the incidence treatment rate is applied to reduce the number of patients who are not getting the treatment due to various reasons ie. affordability, bio-marker testing, age, uninsured etc.

Table 10: Market Immuno therapy penetration

Indication	Incidence (2018)	Treatment Rates	Immuno therapy launched	NO. of IO drugs approved	IO Penetration in the Market
Female Breast	270,000	70%	Y	4	67%
Prostate	183,529	70%	Y	1	18%
Lung and Bronchus	218,527	70%	Y	6	67%
Colon and Rectum	140,788	70%	Y	6	67%
Corpus and Uterus, NOS	54,644	70%	N	0	0%
Melanomas of the Skin	91,000	70%	Y	7	67%
Urinary Bladder	81,000	70%	Y	6	67%
Non-Hodgkin Lymphoma	83,000	70%	Y	9	67%
Kidney and Renal Pelvis	65,000	70%	Y	4	67%
Thyroid	48,761	70%	N	0	0%
Cervical cancer	13,000	70%	Y	2	37%
Thyroid	17,000	70%	Y	3	55%
Head and neck	65,000	70%	Y	3	55%
Leukemia	60,000	70%	Y	10	67%
Liver	42,000	70%	Y	2	37%
Myeloma	31,000	70%	Y	2	37%
Ovarian	22,000	70%	Y	1	18%
Pancreatic	55,000	70%	N	0	0%
Gastric	26000	70%	Y	3	55%
Average Number of IO drugs Launched per indication				**4**	

After applying proposed market share no. of patients is multiplied with average annual price of the treatment and average annual duration of the therapy to get the Total Market.

Indication	IO Market	Chemo Market
Female Breast	$ 8.8	$ 1.3
Prostate	$ 1.6	$ 1.7
Lung and Bronchus	$ 7.1	$ 1.1
Colon and Rectum	$ 4.6	$ 0.7
Corpus and Uterus, NOS	$ -	$ 0.6
Melanomas of the Skin	$ 3.0	$ 0.5

Urinary Bladder	$ 2.6	$ 0.4
Non-Hodgkin Lymphoma	$ 2.7	$ 0.4
Kidney and Renal Pelvis	$ 2.1	$ 0.3
Thyroid	$ -	$ 0.5
Cervical cancer	$ 0.2	$ 0.1
Thyroid	$ 0.5	$ 0.1
Head and neck	$ 1.8	$ 0.4
Leukemia	$ 2.0	$ 0.3
Liver	$ 0.8	$ 0.3
Myeloma	$ 0.6	$ 0.2
Ovarian	$ 0.2	$ 0.2
Pancreatic	$ -	$ 0.6
Gastric	$ 0.7	$ 0.2
Total	$ 39.2	$ 10.0

Figure 8: **CANNER THERAPEUTICS MARKET SIZE IN REVENUES**

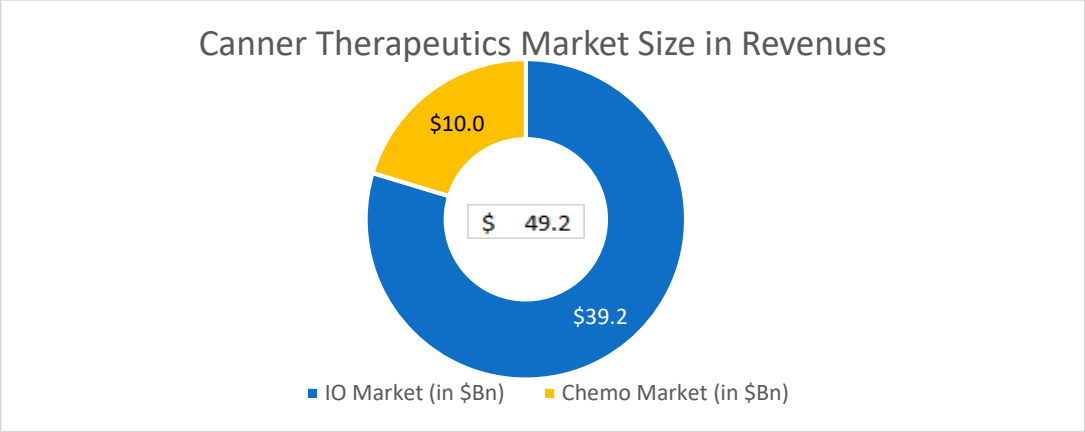
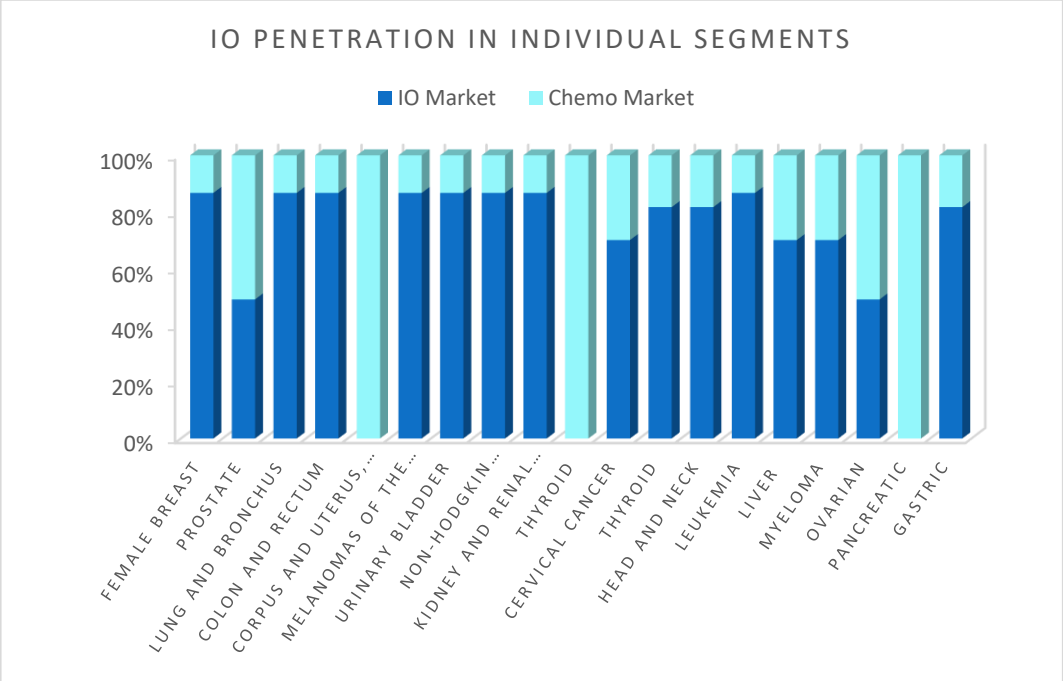


Figure 9 : **IO PENETRATION IN INDIVIDUAL SEGMENTS**



CHALLENGES:

1. Use of chemotherapy based principles for clinical development of immunologic drugs

Sol. New clinical development paradigm for immunotherapy with key components: (1) development phases for proof-of-principle and efficacy; (2) toxicity screening, (3) measuring of biological activity, (4) immunologic response activity in clinical trials, (5) dose and schedule, (6) biological process decision points, (7) trial framework in clinical trials, (8) clinical endpoints, (9) combination drug treatments

2. Clinical dynamics of immunotherapies not mirrored by standard endpoints

Sol. Adjustment of endpoints to relate immunologic responses with cancer biology

3. No recognized system to evaluate all patterns of immunologic therapy and its clinical activity

   Sol. Immunologic drug response criteria derived from RECIST and WHO: Immune-related Response Criteria (irRC)

4. High information variability for immune response observations in multi-center trials

   Sol. Harmonization criteria and quality assurance for immune response observations assays

   Requiring Improved Clinical Endpoints

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