Market Assessment Study to evaluate the trends of Immuno-oncology drug prescription for Melanoma in the US market

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Disease Overview

Melanoma	• Melanoma is an invasive neoplasm of melanocytes, the melanin-producing cells, and accounts for ~1% of all skin cancers
Demography	• The prevalence in 2016 was 1.17M • ~76k new cases in melanoma out of which 5% are Stage lV • Out of the total new cases in 2016, 61% were male and 39% female
Diagnosis	• Biopsy (Shave, Punch, Incisional and Excisional, Optical; FNA(Fine Needle Aspiration), Surgical Lymph Node, Sentinel Lymph Node) • Imaging test • Blood test
Characteristics	• The edges are irregular, ragged, notched, or blurred. • The colour is not the same all over (Ugly Duckling Sign), May include different shades of brown or black, or sometimes with patches of pink, red, white, or blue. • The spot is larger than 6mm across, although melanomas can sometimes be smaller than this. The mole is changing in size, shape, or colour.
Treatment	• **Primary treatment options:** Surgery, Radiation therapy, Chemotherapy • **Further therapy options:** Immunotherapy, Targeted Therapy, Oncolytic Virus Therapy
Prognosis	• Average 5-year survival rate is 15-20%[1] and average 10-year survival rate is 10% for Stage lV melanoma

Disease Burden (2015)

- **According to the World Health Organization:** 132,000 new cases of melanoma are diagnosed worldwide each year
- In the US, percentage of people who develop melanoma has more than doubled in the past 30 years

Category	Incidence (Per 100,000)
Non-Hispanic Whites	27
Hispanic	5
African- American	1
Asian/Pacific Islanders	1

Age Group	Condition
<50 years	Female> Male
By 65 years	Male: Female= 2:1
By 80 years	Male: Female= 3:1

Race[2]	Lifetime Risk of getting Melanoma (Per 100,000)
Caucasians	2500
Hispanics	500
African-Americans	100

- The incidence of Malignant Melanoma in Caucasian populations generally increases with decreasing latitude, with the highest recorded incidence occurring in Australia, where the annual rates of melanoma are 10 and over 20 times the rates in Europe for women and men respectively

Melanoma of the Skin (US): SEER Estimated Facts (2018)

	Number			Percentage of Total Cancer
Estimated New Cases	178,560	Non- Invasive	87,290	5.3%
		Invasive	91,270	
Estimated Deaths	9,320	Male	5,990	1.5%
		Female	3,330	

Table showing 5-Year Relative Survival Rate according to Stages

SEER Stage	AJCC Stage	5-year relative survival rate
Localized	Stage I & II	98%
Regional	Stage III	64%
Distant	Stage IV	23%
All SEER stages combined	All stages combined	92%

Methodology

RESEARCH QUESTION

What are the current market trends and scope in Immuno-oncology drug for Melanoma in US Market?

OBJECTIVES:

1. To evaluate the current trends and scope of IO for Melanoma in US Market
2. To study the full IO clinical trials pipeline of Melanoma

MATERIAL AND METHODS:

- **Study Design:** Analytical and Observational
- **Setting:** US Market
- **Study Population:** NA
- **Sampling Technique:** Quota Sampling

- **Data Collection Procedure:**
  - Primary Data provided by the client
  - Secondary Data from the Oncology studies and Government sites
- **Duration of Study:** 3 months

Immuno-oncology drugs approve for Melanoma

Immunotherapies

- Intron A (high-dose interferon alfa-2b)
- Sylatron (peginterferon alfa-2b)
- Proleukin / IL-2 (interleukin-2)
- Keytruda (pembrolizumab): Anti PD-1 Antibody
- Opdivo (nivolumab): Anti PD-1 Antibody
- Opdivo (nivolumab) and YERVOY (ipilimumab) Combination
- Yervoy (ipilimumab): Anti CTLA-4 Antibody

Targeted Therapies

- Braftovi (encorafenib) and Mektovi (binimetinib) Combination
- Cotellic (cobimetinib) and Zelboraf (vemurafenib) Combination
- Mekinist (trametinib): MEK Inhibitor
- Mekinist (trametinib) and Tafinlar (dabrafenib) Combination
- Tafinlar (dabrafenib): B-RAF Inhibitor
- Zelboraf (vemurafenib): B-RAF Inhibitor

Inline Products Profile

Drug (Molecular Name)	Approval Date	Attributes
Opdivo (nivolumab) PD-1 Inhibitor	2014	• Indicated for the treatment of patients with BRAF V600 wild as well as mutation type unresectable or metastatic and adjuvant melanoma • According to Keynote-067 study, The OS of the patients were significantly improved
Yervoy (ipilimumab) **PD-L1 Inhibitor**	2011	• Indicated for the treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older) with Lymph Node Involvement • Results from studies and clinical trials found that ipilimumab prolongs overall survival compared to a vaccine, leading to approximately 20 percent of patients being alive years later • Ipilimumab extends the amount of time before cancer returned by an average of 9 months

Inline Products

Drug (Molecular Name)	Approval Date	Attributes
Keytruda (pembrolizumab) PD-1 Inhibitor	2014	• Indicated for the treatment of patients with unresectable or metastatic melanoma • The median length of study follow-up for all patients from initiation of pembrolizumab was 10.5 months (range, 0–25.1 month). • Survival probabilities at 12 and 24 months were 61% and 44% overall, respectively whereas by pembrolizumab line of therapy, the survival probabilities at 12 months were 68% , 64%, and 49% for first-line, second-line, and third-line (or later) therapy, respectively.
Braftovi (encorafenib) BRAF Inhibitor	2018	• Indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation • Not indicated for treatment of patients with wild-type BRAF melanoma • Clinical Trials showed 47% OS at 3 years

Inline Products

Drug (Molecular Name)	Approval Date	Attributes
Mektovi (binimetinib) MEK Inhibitor	2018	• Indicated in combination with encorafenib for patients with unresectable or metastatic melanoma with the BRAF V600E or V600K mutations • In the COLUMBUS Trials studies, The OS, RFS were significantly increased in combination with encorafenib for the advanced stage Melanoma
Tafinlar (dabrafenib) BRAF Inhibitor	2013	• Indicated as a single agent or in combination with Trametinib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation • Delays disease worsening and patients experienced full or partial shrinkage of the tumours • **Limitation:** The most common side effects of treatment are fatigue, nausea, vomiting, abdominal pain and joint pain

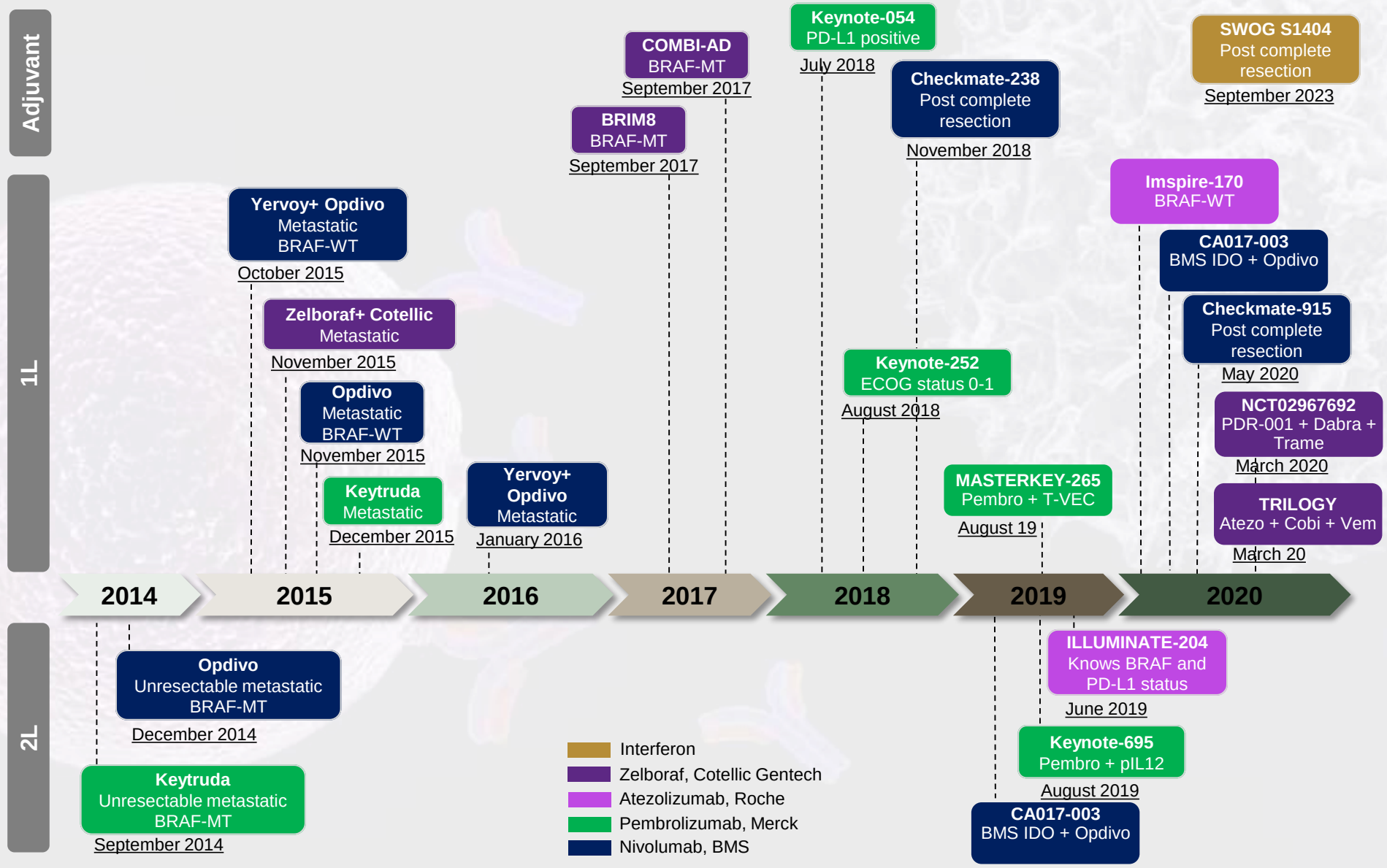
Inline Products

Drug (Molecular Name)	Approval Date	Attributes
Mekinist (trametinib) MEK Inhibitor	2013	• Indicated, as a single agent or in combination with dabrafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations involving lymph node and complete resection • PFS at 48 months and 60 months was 13% vs 3% in Tafinlar + Mekinist vs Chemotherapy respectively
Cotellic (cobimetiniob) MEK Inhibitor	2015	• Indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation, in combination with vemurafenib • Not indicated for treatment of patients with wild-type BRAF melanoma • Median RFS in the BRAF Mutant type patients is 15-24 months with a follow-up of 3 years • On observing for 5 years, the 5 years survival rate of Stage IV patients are 27%

Inline Products

Drug (Molecular Name)	Approval Date	Attributes
Zelboraf (vemurafenib) BRAF Inhibitor	2011	• Indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation • Not recommended for use in patients with wild-type BRAF melanoma • Median RFS in the BRAF Mutant type patients is 15-24 months with a follow-up of 3 years • On observing for 5 years, the 5 years survival rate of Stage IV patients are 27%

Drug Approval Timeline



Pipeline Overview

Drugs	NCT ID Company	# Pts, Pt Population	Phase	Study Completion Date (CT.gov)	Study Completion Date (CT.gov)
PDR001+ Dabrafenib+ Trametinib	NCT02967692 Novartis Pharmaceuticals	538 Unresectable or metastatic BRAF V600 mutant melanoma	3	July 2023	• The median PFS was 9.3 months in the dabrafenib-trametinib group and 8.8 months in the dabrafenib-only group • Hazard ratio for progression or death in the dabrafenib-trametinib group, 0.75 • The overall response rate was 67% in the dabrafenib-trametinib group and 51% in the dabrafenib-only group At 6 months, the interim overall survival rate was 93% with dabrafenib-trametinib and 85% with dabrafenib alone

Pipeline Overview

Drugs	NCT ID Company	# Pts, Pt Population	Phase	Study Completion Date (CT.gov)	Study Completion Date (CT.gov)
Cobimetinib+ Atezolizumab	NCT03108131 Genentech, Inc.	60 Metastatic Melanoma	2	April 2020	• Atezolizumab + cobimetinib had manageable safety and clinical activity irrespective of KRAS/BRAF status CONS: The most common all-grade treatment-related adverse events (AEs) were diarrhea (67%), rash (48%) and fatigue (40%)
LN- 144	NCT02360579 Iovance Biotherapeutics, Inc.	164 Metastatic Melanoma	2	Dec 2024	• No serious adverse effect was reported • Therapeutic responses included complete remission as well as partial remission

Pipeline Overview

Drugs	NCT ID Company	# Pts, Pt Population	Phase	Study Completion Date (CT.gov)	Study Completion Date (CT.gov)
NKTR-214 + nivolumab + ipilimumab	NCT02983045 Bristol-Myers Squibb	480 Metastatic melanoma	1|2	Jun 2021	• Responses were observed in 7/11 (63%) efficacy-evaluable patients (2 CR and 5 PR)◊. Median time to response was 1.7 months. DCR, also known as disease control rate (CR + PR + 3 SD)
CMP-001+ Pembrolizumab	NCT03084640 Checkmate Pharmaceuticals	76 Previously received an anti-PD-1/PD-L1 therapy for advanced cutaneous melanoma	1	Dec 2019	• Combining CMP-001 with Keytruda resulted in objective, durable tumor responses without triggering major toxicity issues in PD-1-resistant advanced melanoma patients, the study reports. **CONS:** • Acute adverse effects related to treatment mainly included fever, nausea and/or vomiting, headache, hypotension, and rigors

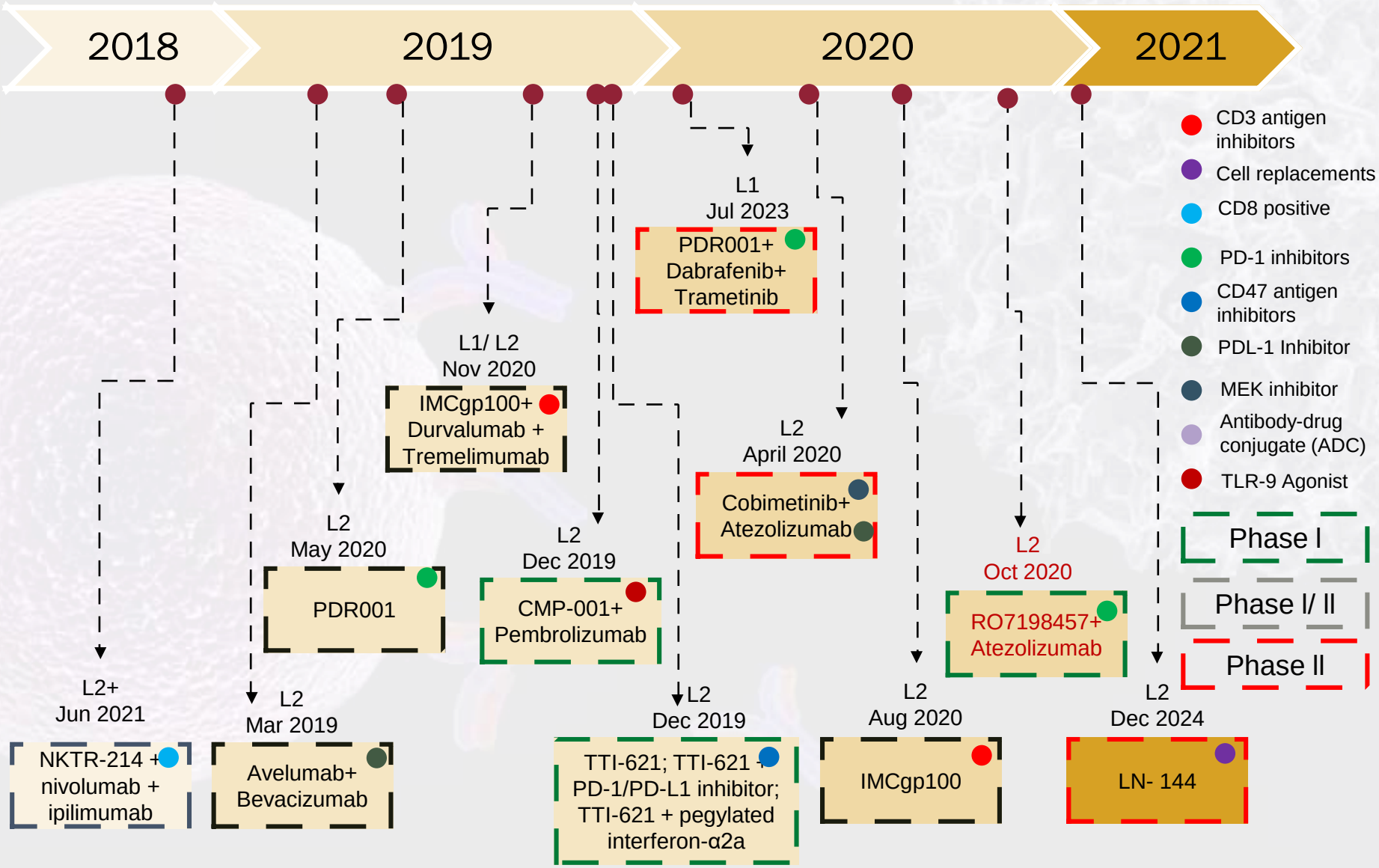
Pipeline Overview

Drugs	NCT ID Company	# Pts, Pt Population	Phase	Study Completion Date (CT.gov)	Study Completion Date (CT.gov)
Avelumab+ Bevacizumab	NCT03167177 NantKwest, Inc.	67 Metastatic Melanoma progressed on or after chemotherapy and anti-PD-1/PD-L1 therapy	1|2	Mar 2019	• Avelumab showed durable responses, promising survival outcomes, and an acceptable safety profile in patients with previously treated metastatic melanoma • The confirmed ORR was 21.6%, complete response, 7.8%; partial response, 13.7%). Median PFS and OS were 3.1 months and 17.2 months respectively • Thirty-nine patients (76.5%) had a treatment-related adverse event (TRAE), most commonly infusion-related reaction (29.4%), fatigue (17.6%), and chills (11.8%); 4 patients (7.8%) had a grade 3 TRAE. Five patients (9.8%) had an immune-related TRAE (all were grade 1/2). No grade 4 TRAEs or treatment-related deaths were reported.

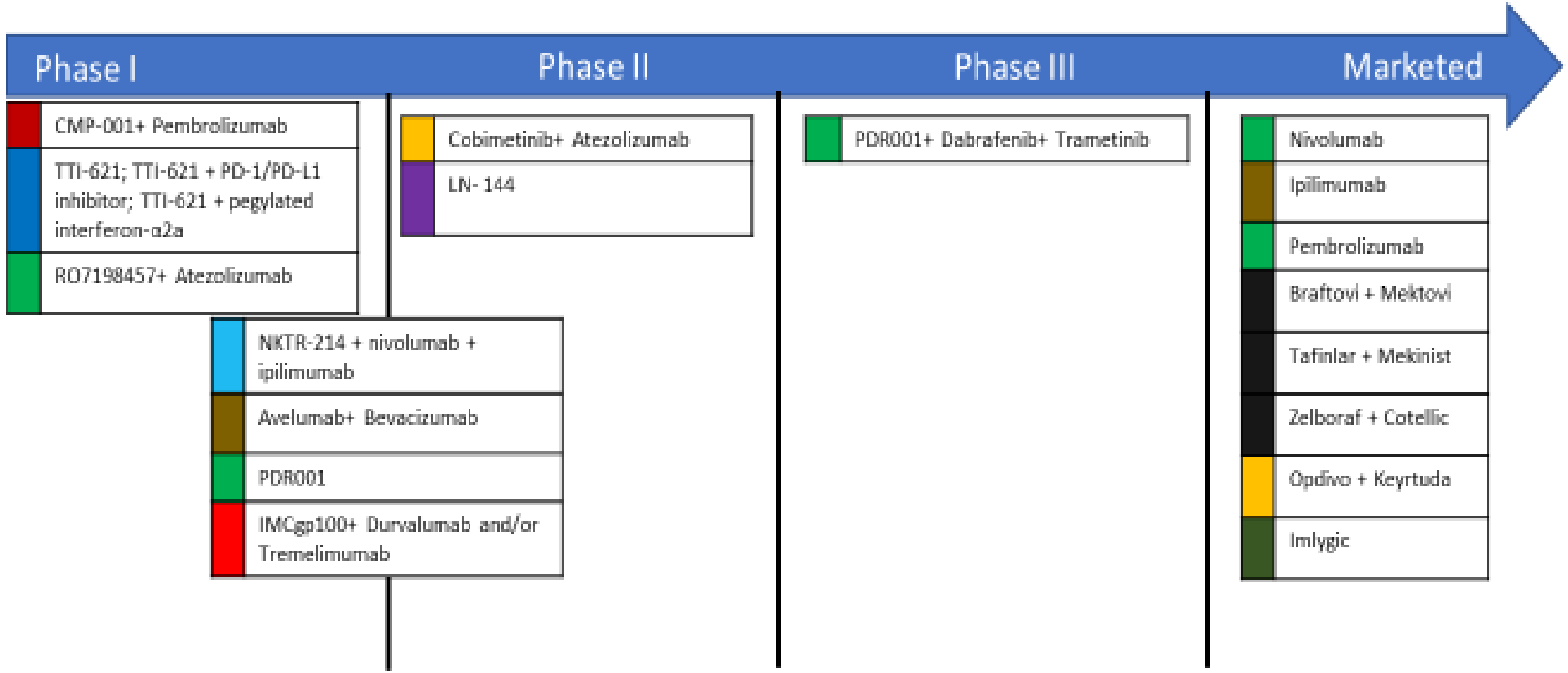
Pipeline Overview

Drugs	NCT ID Company	# Pts, Pt Population	Phase	Study Completion Date (CT.gov)	Study Completion Date (CT.gov)
PDR001	NCT02404441 Novartis Pharmaceuticals	319 Metastatic Melanoma	1|2	May 2020	• Preliminary trial results suggested that the drug is well-tolerated and safe • ORRs were higher in PD-L1+ pts, corroborating previous findings that PD-L1 expression enriches for response to anti-PD1 agents in certain tumor types
IMCgp100+ Durvalumab and/or Tremelimumab	NCT02535078 Immunocore. Ltd	85 Advanced Melanoma	1|2	Nov 2020	• The therapy was safe and triggered long-lasting responses in patients with both skin and eye melanoma • Patients experienced a prolonged response to treatment and longer survival times. • Seventy-three percent survived for a year after treatment, compared with 25 to 45 percent with other treatments

Pipeline Overview

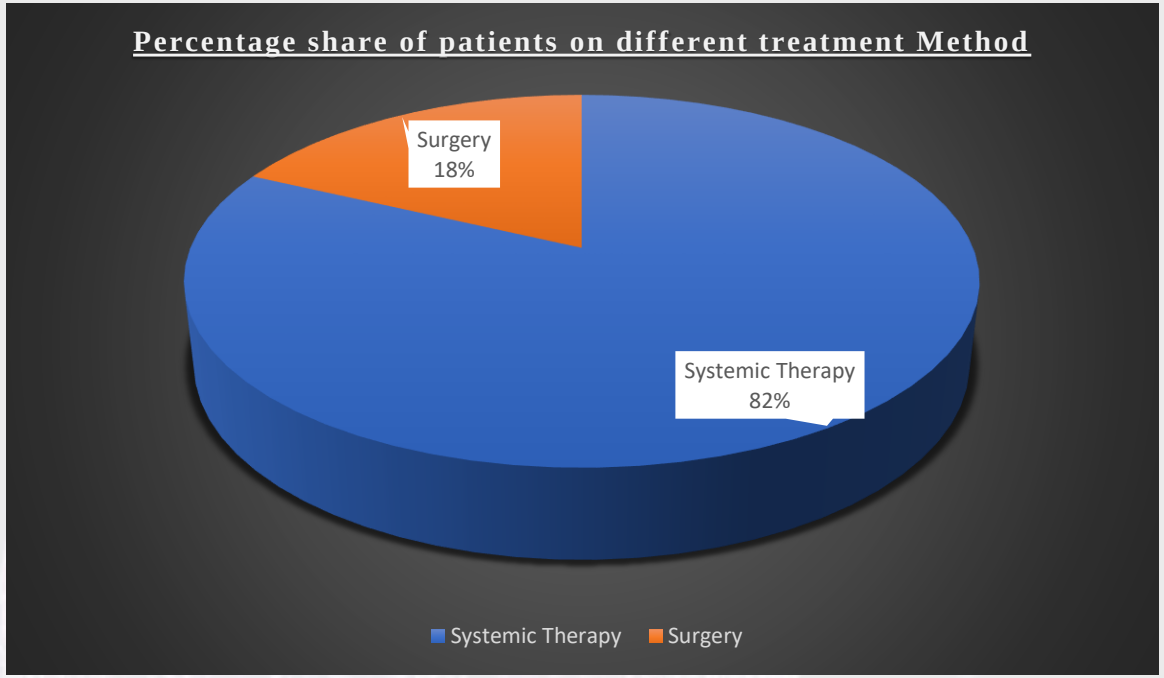


CI Landscape

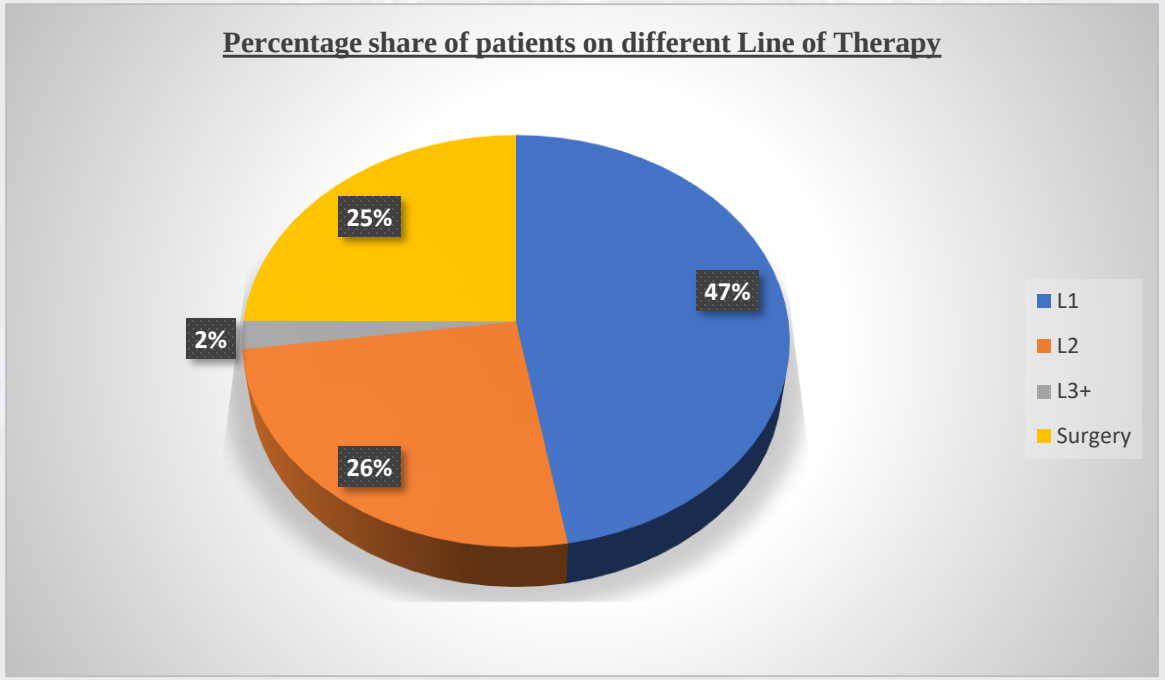


MOA	MOA	MOA
TLR-9 Agonist	PDL-1 Inhibitor	PDL-1/ PD-L1 Inhibitor
CD47 antigen inhibitors	CD3 antigen inhibitors	Protein Based
PD-1 inhibitors	BRAF/ MEK inhibitor	
CD8 positive	Antibody-drug conjugate (ADC)	

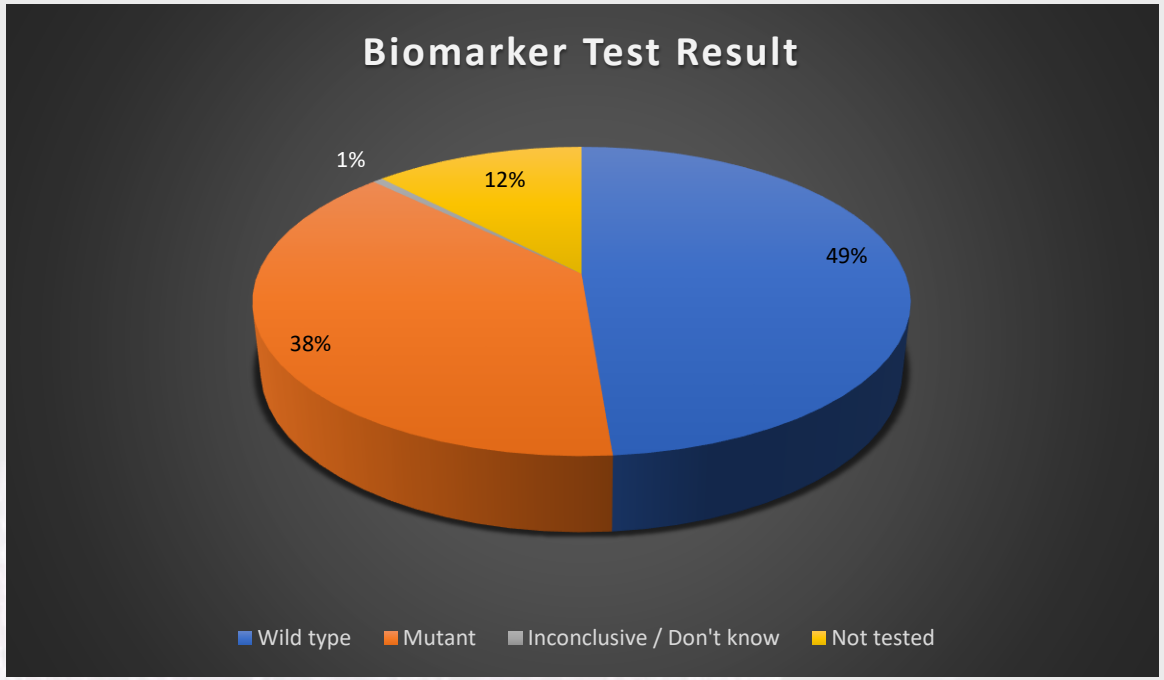
Patient Share

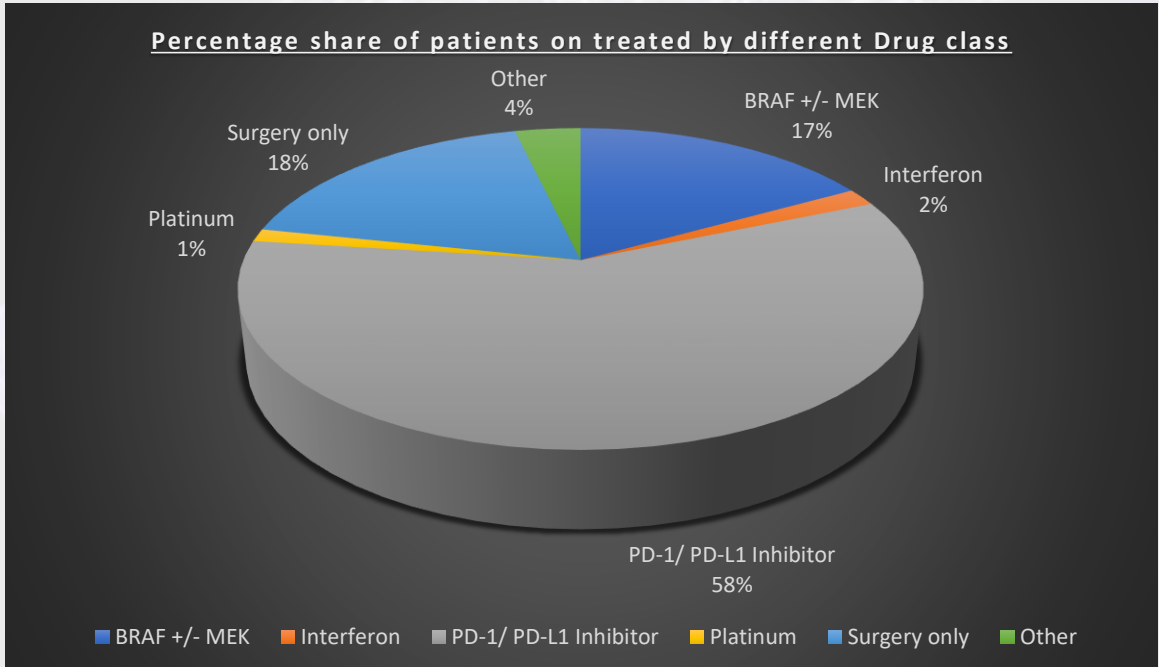


Approx. 82% patients receive Systemic Therapy for the Treatment of Melanoma



Patient Share according to Biomarker Test and Drug Class





Key Barriers and Drivers:

Key Barriers:

Technical level:

- Inadequate understanding of the biology of cancer.
- Poorly predictive pre-clinical models for cancer therapies
- Not enough patients entering RCTs (randomized controlled trials)

Public Policy Barriers:

- Reimbursement policies non- friendly to innovation.
- Rapidity of technological change threatens the ability of federal agencies to cope
- Regulations inhibit innovation and are costly to implement
- Policies for managing conflicts of interest may end up inhibiting innovation

Key Drivers:

- High level of public interest in health care issues;
- Strong public support for increasing NIH research funds;
- Substantial and increasing private investment in medical R&D, although private sector interest waxes and wanes depending on the attractiveness of other investment opportunities;
- Public expectations in the United States that patients should receive the best quality science.

Results

•There are currently 10 major drugs in the pipeline for Melanoma.
•It includes 1 drug in Phase III, 2 drugs in Phase II and & drugs in the initial stages in the pipeline
•The total CI Landscape of Melanoma along with their mechanism of action is shown
•Approx. 85% of the patients rely on Systemic Therapy for the treatment of Melanoma

BRAF Result	Percentage Share
Wild Type	49%
Mutant Type	38%
Inconclusive/ Don’t know	1%
Not Tested	12%

Drug Class	Percentage
BRAF/ MEK Inhibitor	17%
Pd-1/ PD-L1 Inhibitor	58%
Platinum Drugs	1%
Interferon	2%
Surgery only	18%
Other	4%

Discussion

This study shows:

- Market for I-O Therapy is booming at a very fast rate
- Many new I-O combinations are coming in near future which will greatly affect the whole treatment modality of Melanoma
- With the advancement of technology, there is evolution of various new Biomarker Test, which is useful in Diagnosis as well as Treatment for Melanoma
- Majority of patients are prescribed I-O Drugs for the treatment Melanoma
- New I-O drugs are coming up which are in the Mid and Late Phase of Clinical Trials

Conclusion

- I-O has the maximum percentage of share of new patients among other treatment methods followed by Targeted Therapies
- Treatment paradigm has shifted from Conventional Methods to Targeted Therapies
- Many new drugs are in the pipeline for Melanoma
- More and more physicians are opting Biomarker Test to choose the treatment to be prescribed to the patients
- Advancement in technologies and research has paved new way for new and innovative treatment methods to evolve

Reference

- https://www.medicalnewstoday.com/articles/322765.php
- https://www.cancer.org/cancer/melanoma-skin-cancer/detection-diagnosis-staging/how-diagnosed.html
- https://www.ejso.com/article/S0748-7983(16)30866-6/fulltext
- https://www.ncbi.nlm.nih.gov/pubmed/23724867
- https://www.ncbi.nlm.nih.gov/pubmed/27454404
- https://www.tandfonline.com/doi/abs/10.1080/14737140.2017.1341315?journalCode=iery20
- https://www.cancerresearch.org/news/2018/cri-immuno-oncology-landscape-analysis-pubupdate
- https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2732329
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5402170/
- https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf