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PD-1 and PD-L1 Inhibitors: A Single Center Medication Assistance Program (MAP) Experience

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Background

In 2014, the PD-1 inhibitors Opdivo (nivolumab) and Keytruda (pembrolizumab), became FDA approved for treatment of melanoma.[1,2] Since then, numerous other agents in the class including the PD-1 inhibitor Libtayo (cemiplimab) and the PD-L1 inhibitors Imfinzi (durvalumab) and Tecentriq (atezolizumab) have also become FDA approved for various malignancies. These immunotherapy agents work by targeting two proteins called programmed death-1 (PD-1) expressed on the surface of immune T cells and programmed death ligand-1 (PD-L1) on tumor cells. By binding to these sites, PD-1 and PD-L1 inhibitors enhance anti-cancer immune response thereby serving as a unique treatment modality.[3]

Lee, HT, et al

The Medication Assistance Program (MAP) at Providence Health and Services allows patients access to free medications direct from the manufacturer when they would otherwise be unable to afford them due to lack of insurance coverage and/or off label use. In particular, many MAP patients are able to utilize this program to receive PD-1 and PD-L1 infusions for advanced stage cancers frequently failing first line regimens. This study will evaluate MAP patients on PD-1 and PD-L1 inhibitors for both labeled and unlabeled indications to determine safety and efficacy.

Objectives

Primary Objective
Determine labeled vs unlabeled indications for which MAP patients are receiving PD-1 and PD-L1 inhibitors
(Labeled = FDA approved indication when patient initiated therapy)
(Unlabeled = not FDA approved indication when patient initiated therapy)

Secondary Objectives
Determine time to progression of targeted cancer
Determine incidence of adverse drug reactions
Determine financial impact for institution and patient

Hypothesis
The majority of MAP patients will be using PD-1 and PD-L1 immunotherapy agents for unlabeled indications.
PD-1 and PD-L1 immunotherapy agents will be effective when used for unlabeled indications.

Methods

Study Design
- Report of Providence patients on MAP for PD-1 and PD-L1 therapies will be pulled by the MAP technician in the time frame of 10/1/2017 to 8/1/2019.
- From this report, up to 100 patients will be collected and analyzed reverse chronologically for the following:
  - Indication
  - Concurrent cancer treatment
  - Time period on the medication
  - Labeled or unlabeled usage
  - Disease progression as measured by mortality or metastases on imaging
  - Side effect incident, onset and duration will be determined by lab tests and prescription fill history
  - Total amount of PD-1 or PD-L1 medication
- Evaluate data compared to published literature for labeled indications.

Study Setting
Large tertiary medical center

Inclusion Criteria
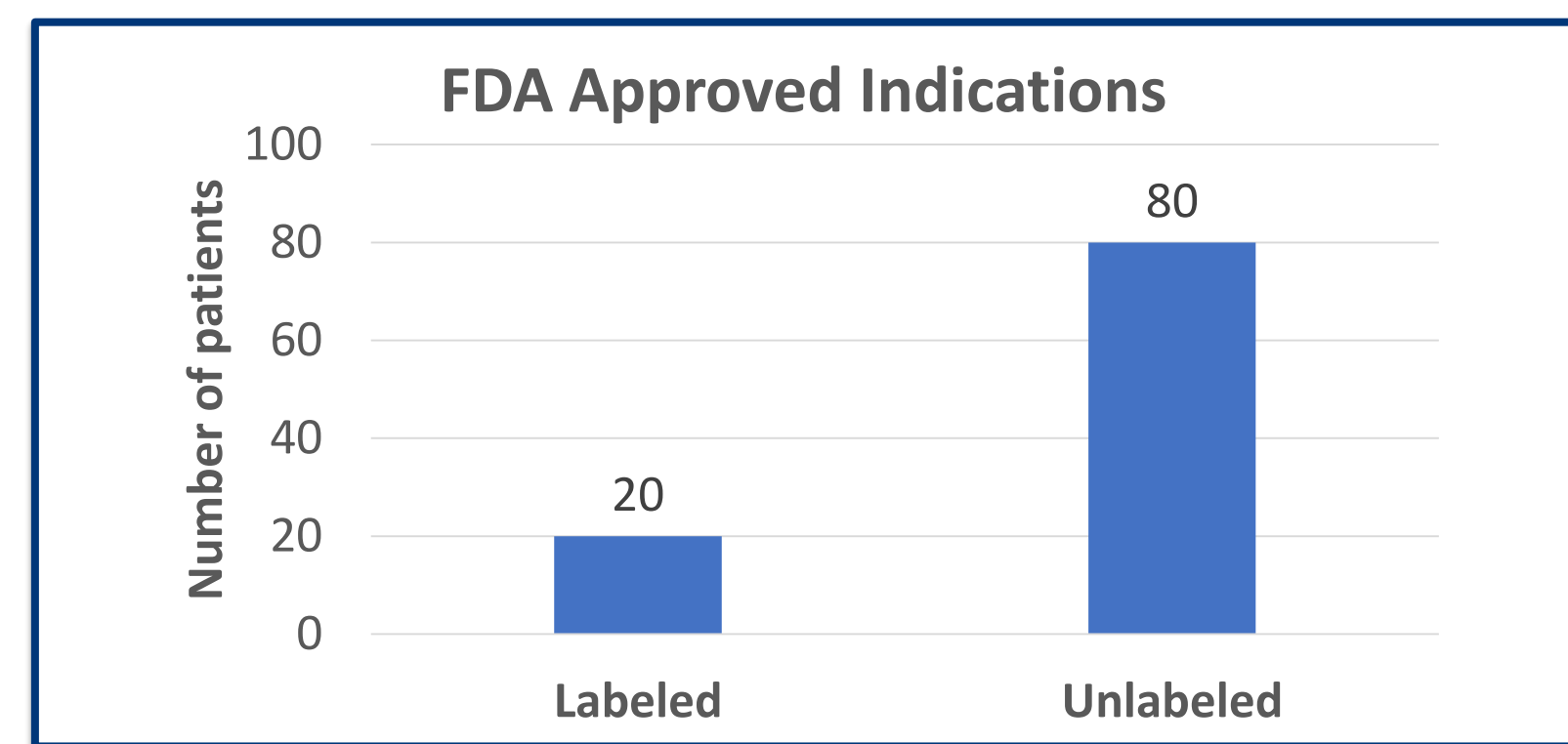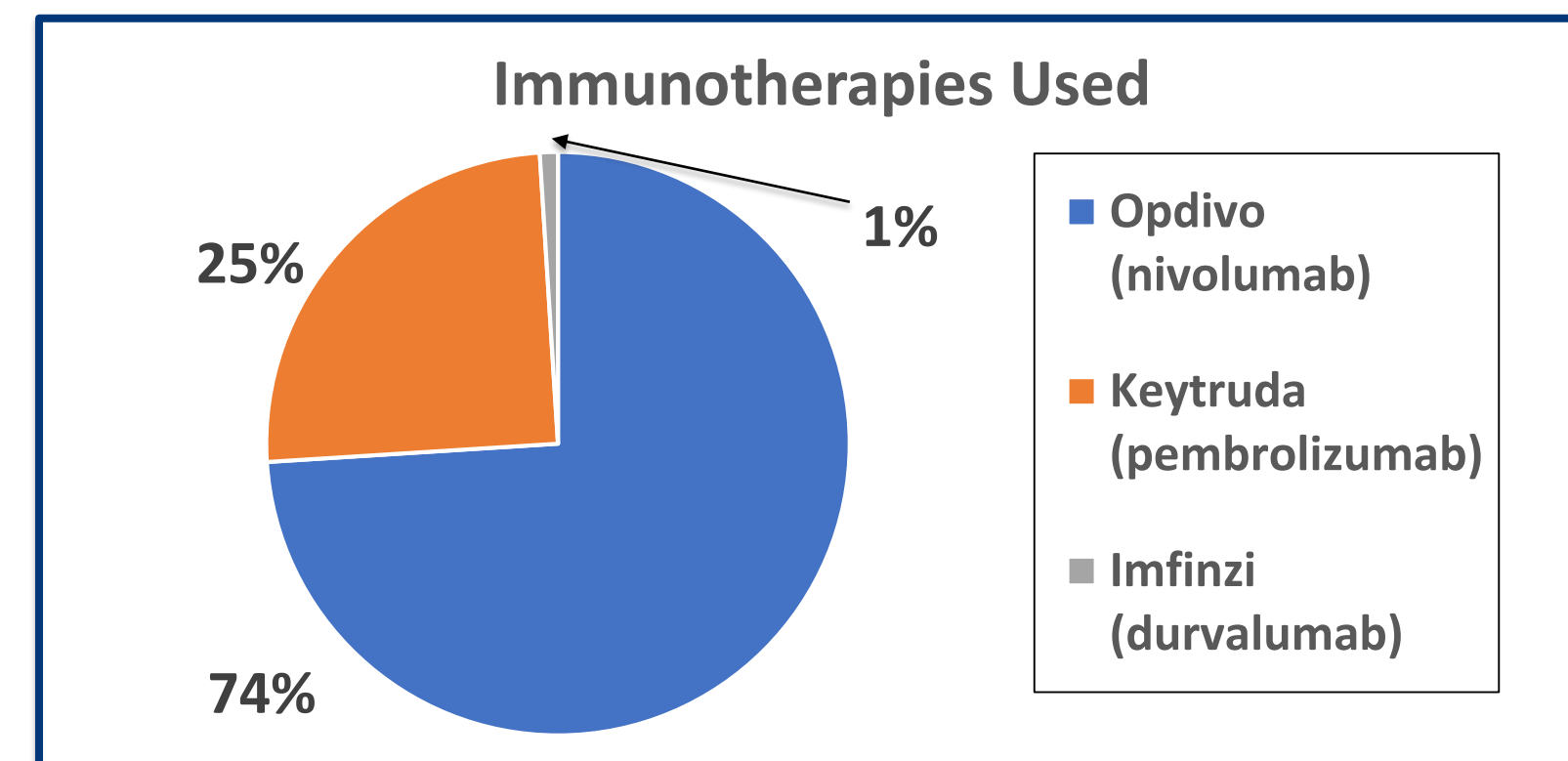Any patient getting a PD-1 or PD-L1 inhibitor through MAP

Exclusion Criteria
Patients <18 years old
Pregnant patients
Prisoners

Results

Table 1: Baseline Demographics

	Total	Labeled (n=20)	Unlabeled (n=80)
Age			
<50	10	0	10
50-59	24	5	19
60-69	28	7	21
>70	38	8	30
Gender			
M	65	10	55
F	35	10	25
Cancer Staging			
I	14	0	14
II	5	0	5
III	18	2	16
IV	63	18	45
Combination therapy			
Y	33	5	28
N	66	14	52
Lost to follow up	1	1	0
Research Protocol			
Y	18	0	18
N	82	20	62

Immunotherapies Used
- Opdivo (nivolumab): 74%
- Keytruda (pembrolizumab): 25%
- Imfinzi (durvalumab): 1%

FDA Approved Indications (Number of patients)
- Labeled: 20
- Unlabeled: 80

Results

Unlabeled Treatment Duration (Treatment Duration (Months) vs Indications)
Indications: Breast, Head & Neck, Gastroesophageal, O, C, M, NSCLC, Prostate, Other
O= ovarian cancer, C= colorectal cancer, M = melanoma
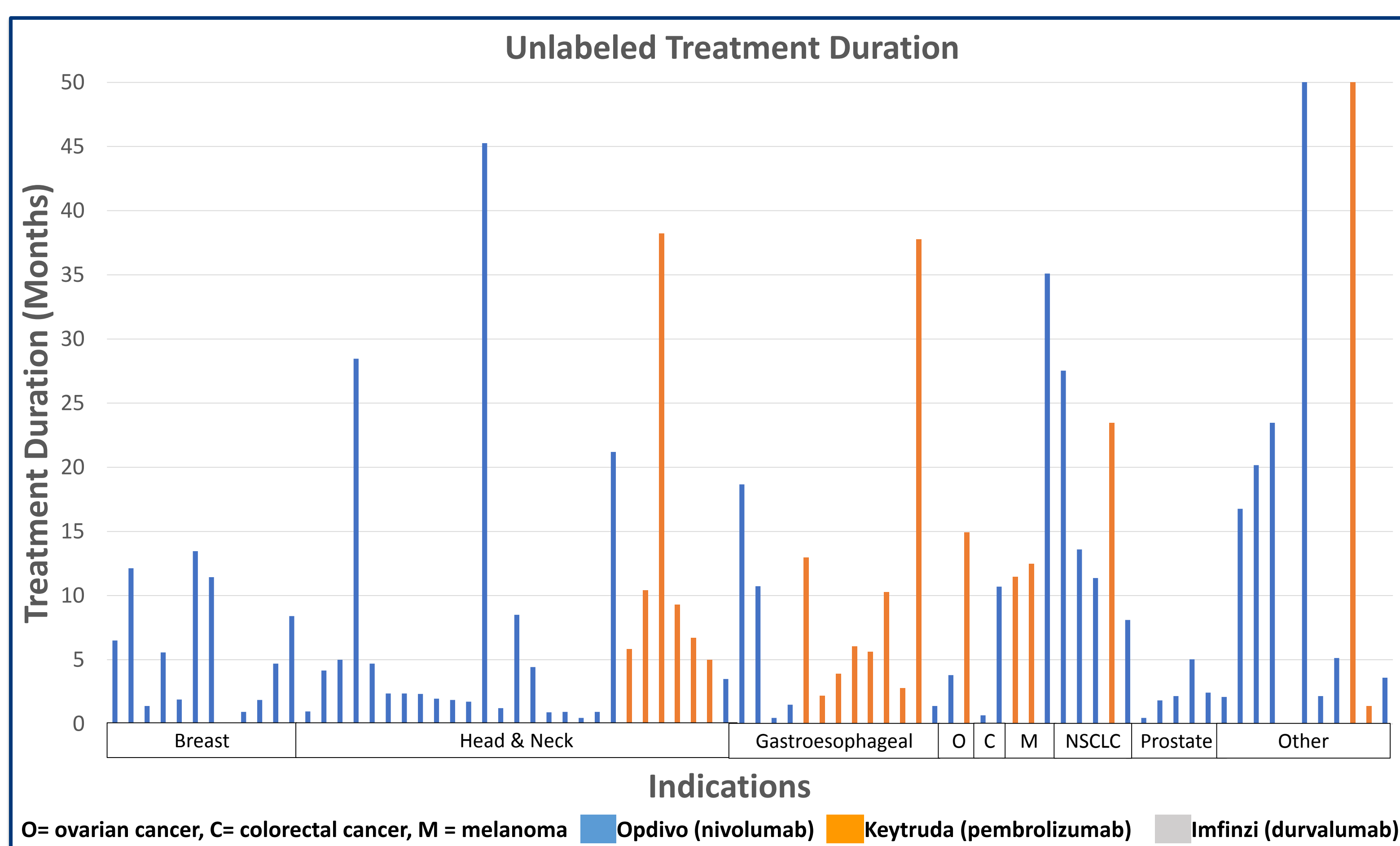Opdivo (nivolumab) | Keytruda (pembrolizumab) | Imfinzi (durvalumab)

Table 2: Average Time to Disease Progression (ATDP)

Cancer Types	Stage	Labeled ATDP (Months)	Unlabeled ATDP (Months)
Breast (n=12)			
	II	--	8.3
	III	--	N/A
	IV	--	7.3
Head and Neck (n=35)			
	I	--	3.1
	II	--	N/A
	III	--	N/A
	IV	7.3	8.6
Gastroesophageal (n=17)			
	I	--	14.8
	III	--	8.4
	IV	1.1	2.7
Ovarian (n=2)			
	IV	--	13.5
Colon (n=2)			
	IV	N/A	1.4
Melanoma (n=5)			
	II	--	N/A
	III	18.3	N/A
	IV	--	35.9
Non-small Cell Lung Cancer (n=9)			
	III	N/A	22.7
	IV	0.5	12.9
Prostate (n=5)			
	IV	--	12.7
Hodgkin Lymphoma (n=1)	IV	--	N/A
Cutaneous SCC (n=1)	IV	--	N/A
Pancreatic (n=2)	IV	--	10.3
Epitheliod mesothelioma lung (n=1)	I	--	N/A
Cervical (n=1)	III	--	1.9
Endometrial (n=1)	IV	--	N/A
Procarcinoma sweat gland (n=1)	IV	--	4.6
Neuroendocrine (n=1)	IV	--	2.0
Merkel cell carcinoma (n=1)	IV	--	9.4
Adnexal (n=1)	IV	--	3.8
Renal Cell Carcinoma (n=1)	IV	5.8	--
Thymus (n=1)	IV	N/A	--

Labeled Treatment Duration (Treatment Duration (Months) vs Indications)
Indications: Head & Neck, Gastroesophageal, C, M, NSCLC, Other
Opdivo(nivolumab) | Keytruda (pembrolizumab) | Imfinzi (durvalumab)

Table 4: Side Effects

Adverse Drug Reactions (ADR)	Labeled (n=20) n	Labeled %	Unlabeled (n=80) n	Unlabeled %
1 ADR	6	30%	25	31.3%
2 ADRs	2	10%	9	11.3%
3 ADRs	1	5%	3	3.8%
Total Incidence ADR	9	45%	37	46.3%
Types of ADRs				
Infusion	0	0%	0	0.0%
Dermatological	0	0%	2	2.5%
Thyroid	5	25%	16	20.0%
GI	2	10%	5	6.3%
Pneumonitis	3	15%	8	10.0%
Hepatitis	1	5%	8	10.0%
Neurological	1	5%	4	5.0%
Ocular	0	0%	3	3.8%
Myocardial	0	0%	0	0.0%
Other	1	5%	6	7.5%

Table 3: Outcomes

	Labeled (n=20)	Unlabeled (n=80)
ATDP (months)	8.9	4.3
Disease Progression Outcomes		
Death (n, %)	5, 25%	18, 22.5%
Metastases (n, %)	4, 20%	22, 27.5%
Average amount of medication received (mg)	2986.75	960
Average amount of medication received as MAP patient (mg)	2612	960

Results

Indications
- MAP patients on PD-1 and PD-L1 inhibitors are primarily using these immunotherapies for unlabeled indications (80%) and the majority (74%) of patients are on Opdivo (nivolumab).
- Sixty six percent of patients are receiving monotherapy, commonly for later stage cancers (stage III 18% and stage IV 63%).
- Head and neck (35%), gastroesophageal (17%), and breast cancer (12%) are the three highest indications overall. For unlabeled indications, head and neck, gastroesophageal and breast cancer were the highest indications.

Efficacy
- In stage IV head and neck, gastroesophageal, and NSCLC, unlabeled PD-1 and PD-L1 inhibitors demonstrated a greater ATDP compared to labeled indications (8.6 vs 7.3 months, 2.7 vs 1.1 months, and 12.9 vs 0.5 months).
- Twelve patients were treated with PD-1 and PD-L1 inhibitors for stage II-IV breast cancer with some success. ATDP was 8.3 months for stage II and 7.3 months for stage IV.

Side effects
- The percentage of patients that experience grade 2 or 3 toxicities requiring medication management and delays in immunotherapy treatment are comparable between the two groups at 45% for labeled and 46.3% for unlabeled indications.
- The most common ADR noted was hypothyroidism at 25% for labeled patients and 20% for unlabeled patients. These patients were usually prescribed levothyroxine and then immunotherapy treatment was delayed.
- Other notable ADRs include GI (10% labeled vs 6.3% unlabeled) and pneumonitis (15% labeled vs 10% unlabeled). Diarrhea and GI upset were the most commonly noted ADRs per physician notes although it was generally not severe enough to warrant delays in immunotherapy treatment.

Economics
- Some patients initially covered by MAP later transitioned to private insurance. This is seen in discrepancy between median amount of medication received and median amount of medication received on MAP. This represents a financial gain, especially with 340B program, in these patients.

Discussion
- High usage of immunotherapy for late stage cancer fits the clinical picture as the majority of research for PD-1 and PD-L1 inhibitors is for stage III and IV cancers. Early stage cancers are usually treated with first line regimens.
- High counts of gastroesophageal cancer could be because diagnosis usually occurs in patients ~ 65 years old which is the majority of the patient population in this study (66% >60 YO).[6, 7]
- Third line therapy for gastroesophageal cancer is Keytruda so this could account for the high amounts for this indication.[8] Patient population could also be impacted by provider specialties. At this institution, the same provider treats gastroesophageal and head and neck cancers. Many of these patients are enrolled in the same clinical trial under this physician.
- PD-1 and PD-L1 for breast cancer is an area that is still being researched so it is something to continue tracking to see if the data supports usage.
- Given that combination therapy was in 25% of labeled patients and 35% of unlabeled patients, it is interesting that total incidence of ADR was similar between groups. This could be due to variation in supportive medications or radiation.
- MAP represents an opportunity to serve those who may not be able to afford high cost medications.
- MAP data is an opportunity to gain insight to indications that are unlabeled because research protocols may not always account for real world scenarios. Only 18 of the 80 unlabeled patients were on formal research studies.
- Without going through MAP, treating each patient will likely result in the institution absorbing the drug acquisition cost (median ~$100000-190000).[1,2]

Next Steps
- Subgroup analysis of unlabeled indications to determine which medications have since changed indication from labeled to unlabeled
- Evaluate side effects compared to literature incident rate and onset of common ADRs related to immunotherapy with PD-1 and PD-L1 inhibitors
- Economic analysis in progress to determine medication spend

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