Sponsor
Novartis Pharmaceuticals

Generic Drug Name

Nivolumab, Pembrolizumab, Dabrafenib+Trametinib, Ipilimumab+Nivolumab, Vemurafenib+Cobimetinib, Encorafenib+Binimetinib

Trial Indication(s)
Melanoma

Protocol Number

CTMT212AUS55

Protocol Title
Real-World Treatment Patterns and Outcomes of Targeted Therapy and Immunotherapy among BRAF-Positive Melanoma Patients Treated in the Adjuvant Setting and among BRAF-Positive Metastatic Melanoma Patients with Low Tumor Burden: An Observational Study

Clinical Trial Phase
IV

Phase of Drug Development
NA

Study Start/End Dates
Study start date: 16/06/2020
Study Completion date: 03/12/2021

Reason for Termination
NA

Study Design/Methodology

The NOBLE database was built from the harmonization of two customized oncology specific EHR databases: Flatiron Health Spotlight and Concerto Custom Patient360. BRAF v600 mutated advanced (i.e., stage III or IV) patients treated at oncology practices across the US were identified in these two databases for potential inclusion. Both the Flatiron Health EHR-derived database and the Concerto Patient360 database contain clinical, demographic, treatment, and mortality information for melanoma patients from the time of initial diagnosis until death or the most recent data cut-off, which is August 31, 2020 (for population 1), and May 31, 2020 (for population 2).

For population 1 (patients treated in the adjuvant setting): included patients were aged more than or equal to 18 years, were required to have a diagnosis of melanoma (ICD-9 172.x & ICD-10 C43.x or D03.x), pathologic stage III disease, evidence of resection, adjuvant treatment with Immunotherapy (IO) (e.g., Nivolumab (nivo) or Pembrolizumab (pembro)) or Targeted Therapy (TT) (e.g., Dabrafenib+ Trametinib (dab+tram)) on or after January 1, 2014 and prior to August 30,2020 (data cut-off), and any evidence of a BRAF+ result. Patients were required to have at least 6 months of follow-up after initiation of adjuvant treatment. Patients were followed until the earlier of death, data cut-off, loss of follow-up, or received MM diagnosis. While the first systemic therapy approved for use in the adjuvant melanoma setting occurred in 2015, the study period of interest begins on January 1, 2014, to include any potential off-label use of these therapies as adjuvant therapies.

For population 2 (patients with Low tumor burden (LTB) treated in the metastatic setting): included patients were aged more than or equal to 18 years, and were required to have a diagnosis of melanoma (ICD-9 172.x & ICD-10 C43 or D03x), a pathologic stage IV diagnosis, treatment with IO (e.g. Ipilimumab (ipi), nivo, pembro, ipi+nivo) or TT (dab+tram, Vemurafenib+Cobimetinib, Encorafenib+Binimetinib (vem+cobi, enco+bini) on or after January 1, 2014 and prior to May 31, 2020 (data cut-off), and evidence of a BRAF+ result after therapy initiation. Patients were required to be classified as LTB at the time of stage IV diagnosis. LTB was defined as having normal LDH and <3 metastatic sites at the time of stage IV diagnosis. To align with recent FDA approvals for combination therapies use in the MM setting, the study period of interest began on January 1, 2014. Furthermore, this sampling interval allowed for a maximum of 6 years of follow-up from the start of study period.

Centers

Novartis Investigative Site

Objectives:

This study was conducted in two populations of interest. All objectives described below were assessed separately in the two study populations.
Population 1: BRAF+ melanoma patients treated with either TT or IO in the adjuvant setting
Population 2: BRAF+ melanoma patients with LTB treated with TT or IO in the metastatic setting

Primary objective:

- Describe treatment patterns among patients prescribed with TT versus IO

Secondary objectives:

- Evaluate discontinuation rates and reasons for discontinuation of treatment among patients receiving TT or IO
- Estimate time to treatment failure from initiation of first-line (1L) and subsequent-lines of therapy among patients treated with TT or IO

- Estimate the overall survival (OS) from initiation of 1L therapy among patients treated with TT or IO
- Estimate the recurrence free survival (RFS) [population 1] or progression free survival (PFS) [population 2] from initiation of 1L therapy among patients treated with TT or IO

Test Product (s), Dose(s), and Mode(s) of Administration
NA

Statistical Methods
Baseline demographic and clinical characteristics, as well as treatment patterns, were analyzed descriptively for all patients and stratified by type of treatment. Descriptive analyses were summarized using counts and percentages for dichotomous and categorical variables, while measures of means with standard deviations (SD) or medians with interquartile range (IQR) were used for continuous variables as appropriate. Kaplan-Meier survival curves were used to describe RFS, PFS, and OS.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

Population 1(patients treated in the adjuvant setting)

- Diagnosis of melanoma (ICD-9 172.x & ICD-10 C43.x or D03.x)
- Pathologic stage III on or after 2011
- Evidence of resection
- Adjuvant treatment with IO (nivo, pembro) or TT (dab+tram) on or after 1/1/2014 and prior to 8/31/2020
- At least 6 months of follow-up time (until death, end of data cut-off, loss-of-follow-up, or progressed to stage IV diagnosis) from the initiation of therapy
- Evidence of a BRAF+ result ≤30 days after therapy initiation in the adjuvant setting
- At least 18 years of age at the time of initiation of treatment
- No documented receipt of a clinical trial treatment for cancer at any time on or after January 1, 2014

Population 2 (patients with LTB treated in the metastatic setting)

- Diagnosis of melanoma (ICD-9 172.x & ICD-10 C43.x or D03.x)
- Pathologic stage IV at initial diagnosis on or after 1/1/2011, or earlier stage disease accompanied by development of a first locoregional recurrence on or after 1/1/2011
- 1L treatment with IO (ipi, nivo, pembro, ipi+nivo) or TT (dab+tram, vemu+cobi, enco+bini) on or after 1/1/2014 and prior to 5/31/2020

- At least 6 months of follow-up time (until death, loss of follow-up, or end of data cut-off) from the initiation of therapy
- Evidence of a BRAF+ result ≤30 days after 1L therapy initiation
- LTB, defined as having <3 involved organ sites and normal LDH test (less than upper limit of normal) at the time of receiving MM diagnosis
- At least 18 years of age at the time of initiation of 1L treatment
- No documented receipt of a clinical trial treatment for cancer at any time on or after 1/1/2014

Exclusion criteria

- None

Participant Flow

Population 1 (patients treated in the adjuvant setting)

A total of 318 patients from the NOBLE data met the study inclusion criteria. Table 10-1 provides additional details describing the sample selection process. Among the 318 included patients, 215 (68%) received nivo, 58 (18%) received DT, and 45 (14%) received pembro as 1L therapy.

Description	N
Step 1 - Diagnosis of melanoma (ICD-9 172.x or ICD-10 C43) with at least two documented clinical visits on or after 1/1/2011, and pathologic stages IIIA to IIID at initial diagnosis OR earlier stage at initial diagnosis with a known loco-regional recurrence on or after January 1, 2011	**5,641**
Step 2 - Treatment with IO (nivo, pembro) OR TT (dab+tram) as adjuvant therapy and confirmation of successful resection on or after January 1, 2014	**1,975**
Step 3 - Evidence of a BRAF test and a positive result	**348**
Step 4 - Patients ≥18 years of age as of initial diagnosis	**348**
Exclusion	
Exclude patients enrolled in a clinical trial (n=4)	**344**
Exclude patients who had unresectable status prior to developing metastasis (n=2)	**342**
Exclude patients who had a metastatic diagnosis prior to initiation of adjuvant therapy (n=4)	**338**
Exclude patients who did not initiate IO or TT as 1L adjuvant therapy (n=20)	**318**
Final sample	**318**

Population 2 (patients with LTB treated in the metastatic setting)
A total of 1,961 MM patients met the selection criteria and initiated 1L IO or TT, of which 422 had LTB

Description	N
Step 1 - Diagnosis of melanoma (ICD-9 172.x or ICD-10 C43) with at least two documented clinical visits on or after 1/1/2011, and pathologic stages III or IV at initial diagnosis OR earlier stage at initial diagnosis with a known loco-regional recurrence on or after 1/1/2011	**11,821**
Step 2 - Treatment with IO (ipi, nivo, pemrbo, ipi+nivo) or TT (dab+tram, enco+bini, vem+cobi) as 1L on or after 1/1/2014 and prior to 5/31/2020 (to allow at least 6 months of follow-up)	**4,543**
Step 3 - Evidence of BRAF test and a positive result	**1,742**
Step 4 - Patients ≥18 years of age as of initial diagnosis	**1,741**
Exclusion	
Exclude patients enrolled in a clinical trial (n=254)	**1,487**
Total patients in the NOBLE database	**1,487**
Final sample: LTB patients in the NOBLE database	**422**

Baseline Characteristics

Population 1 (patients treated in the adjuvant setting)

Variable	All patients N=318	Dab+tram N=58	Nivo N=215	Pembro N=45	P-value
Age, years (mean, std)	58.4 (14.8)	57.8 (13.2)	58.2 (15.1)	60.1 (15.4)	0.690
Male (n, %)	192 (60%)	35 (60%)	135 (63%)	22 (49%)	0.222
Disease stage provided	245 (77%)	43 (74%)	167 (78%)	35 (78%)	0.844
IIIA	52 (21%)	12 (28%)	35 (21%)	5 (14%)	
IIIB	64 (26%)	9 (21%)	48 (29%)	7 (20%)	
IIIC	100 (41%)	17 (40%)	63 (38%)	20 (57%)	
IIID	4 (2%)	0 (0%)	4 (2%)	0 (0%)	
III unspecified	25 (10%)	5 (12%)	17 (10%)	3 (9%)	
Race (n, % among tested)					0.129
White	255 (89%)	47 (94%)	172 (87%)	36 (90%)	
Black or African American	3 (1%)	1 (2%)	2 (1%)	0 (0%)	
Other	28 (10%)	2 (4%)	23 (12%)	3 (8%)	
CCI (mean, std)	0.4 (0.8)	0.4 (0.7)	0.3 (0.8)	0.3 (0.7)	0.883

Variable	All patients N=318	Dab+tram N=58	Nivo N=215	Pembro N=45	P-value
Nearest ECOG status prior to initiation of 1L (n, % among tested)					0.808
0	139 (70%)	26 (72%)	97 (70%)	16 (64%)	
1	56 (28%)	10 (28%)	37 (27%)	9 (36%)	
2	1 (0.5%)	0 (0%)	1 (0.7%)	0 (0%)	
3	4 (2%)	0 (0%)	4 (3%)	0 (0%)	
PD-L1 positive (n, % among tested*)	11 (18%)	1 (20%)	6 (13%)	4 (33%)	0.270
LDH (n, %)	179 (56%)	30 (52%)	125 (58%)	24 (53%)	0.622
Normal	170 (95%)	27 (90%)	120 (96%)	23 (96%)	0.393
Elevated	9 (5%)	3 (10%)	5 (4%)	1 (4%)	
ALT	231 (73%)	41 (71%)	158 (74%)	32 (71%)	0.886
Low	95 (41%)	9 (22%)	69 (44%)	17 (53%)	0.020
Normal	109 (47%)	23 (56%)	75 (48%)	11 (34%)	
Elevated	27 (12%)	9 (22%)	14 (9%)	4 (13%)	
AST	233 (73%)	41 (71%)	160 (74%)	32 (71%)	0.799
Low	28 (12%)	6 (15%)	19 (12%)	3 (9%)	0.670
Normal	187 (80%)	30 (73%)	131 (82%)	26 (81%)	
Elevated	18 (8%)	5 (12%)	10 (6%)	3 (9%)	

Note: *62 (20%) of all patients tested for PD-L1. 1L, first-line; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-L1, programmed death-ligand 1

Population 2 (patients with LTB treated in the metastatic setting)

	All patients N= 419 N	%
Baseline demographics at initiation of 1L therapy		
Age, years (mean, std)	61	14
Male	280	67%
Race (% among tested)		
White	369	88%
Other	26	6%
Black or African American	3	1%
Missing	21	5%
CCI (mean, std)	0	1
Nearest ECOG status prior to initiation of 1L (% among tested)		
0: Fully active, able to carry on all pre-disease performance without restriction.	159	38%
1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.	95	23%
2: Ambulatory and capable of all self-care but unable to carry out any work activities.	18	4%
3 or higher: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair; or death	4	1%
Missing	143	34%
Biomarker testing		
PD-L1 positive (among tested)	18	21%
KIT positive (among tested)	3	2%
NRAS positive (among tested)	4	2%
LDH test	419	100%
Normal (among tested)	419	100%
Elevated (among tested)	0	0%
ALT test	414	99%
Low (among tested)	178	42%
Normal (among tested)	200	48%
Elevated (among tested)	36	9%
AST test	416	99%
Low (among tested)	71	17%
Normal (among tested)	325	78%
Elevated (among tested)	20	5%
Metastatic sites		
Number of metastatic sites (mean,std)	1	0
1 metastatic site	271	65%
2 metastatic sites	148	35%
History of brain metastases	89	21%
History of bone metastases	48	11%
History of lung metastases	168	40%
History of liver metastases	50	12%
History of lymph nodes metastases	102	24%

Note: 84, 182, and 170 patients had PD-L1, KIT, and NRAS tests. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1

Primary Outcome Result(s)

Treatment patterns, all patients

	All patients	
	N=	318
	N	%
1L therapy	**318**	
Time from diagnosis to 1L initiation (days)		
mean, std	148.7	225.8
median	95	
IQR	66	135
Treatment duration of 1L (days)		
mean, std	226.7	167.9
median	204.5	
IQR	88	343
Follow-up [1L initiation to cutoff] duration (days)		
mean, std	426.2	311.2
median	375	
IQR	157	628
Treatment status		
Censored at 1L	44	14%
Discontinued 1L and no 2L use until cutoff	243	76%
Discontinued 1L and continued with 2L	31	10%

Among those continued with 2L		
Dab+tram	14	45%
Nivo	7	23%
Pembro	0	0.0%
Other	10	32%
2L therapy	**31**	
Time from end of 1L to start of 2L (days)		
mean, std	39.2	51.6
median	17	
IQR	1	60
Treatment duration of 2L (days)		
mean, std	200.1	265.7
median	135	
IQR	46	265
Follow-up [1L initiation to cutoff] duration (days)		
mean, std	451.3	352.6
median	376	
IQR	263	600

Secondary Outcome Result(s)

Reasons for treatment discontinuation, by drug

	Dab+Tram		Nivo		Pembro		p-value
	N=	58	N=	215	N=	45	
	N	%	N	%	N	%	
1L therapy	**58**		**215**		**45**		
Reasons for discontinuation							
Among those with reasons provided	37		138		20		0.001
Recurrence	3	8%	24	17%	3	15%	
Toxic effect of therapy	21	57%	24	17%	5	25%	
Disease-related symptoms not due to therapy	1	3%	1	1%	1	5%	
Patient requested	0	0%	6	4%	2	10%	
Completed treatment	9	24%	79	57%	8	40%	

No evidence of disease	1	3%	1	1%	1	5%	
Other	1	3%	2	1%	0	0%	
Unknown	0	0%	1	1%	0	0%	
Financial	1	3%	0	0%	0	0%	
2L therapy	**11**		**16**		**4**		
Reasons for discontinuation							0.116
Among those with reasons provided	6		9		0		
Recurrence	1	17%	0	0%	0	0%	
Toxic effect of therapy	3	50%	8	89%	0	0%	
Completed treatment	2	33%	0	0%	0	0%	
No evidence of disease	0	0%	1	11%	0	0%	

Reasons for treatment discontinuation, by drug class

	All TT patients		All IO patients		p-value
	N=	58	N=	260	
	N	%	N	%	
1L therapy	**58**		**260**		
Reasons for discontinuation					
Among those with reasons provided	37		158		<0.001
Recurrence	3	8%	27	17%	
Toxic effect of therapy	21	57%	29	18%	
Disease-related symptoms not due to therapy	1	3%	2	1%	
Patient requested	0	0%	8	5%	
Completed treatment	9	24%	87	55%	
No evidence of disease	1	3%	2	1%	

Other	1	3%	2	1%	
Unknown	0	0%	1	1%	
Financial	1	3%	0	0%	
2L therapy	**11**		**20**		
Reasons for discontinuation					
Among those with reasons provided	6		9		
Recurrence	1	3%	0	0%	
Toxic effect of therapy	3	8%	8	5%	
Completed treatment	2	5%	0	0%	
No evidence of disease	0	0%	1	1%	

Reasons for treatment discontinuation, all patients and by drug class

	All patients		All IO patients		All TT patients	
	N= 419		N= 287		N= 132	
	N	%	N	%	N	%
Reasons of discontinuation						
Among those with reasons provided	419		287		132	
Progression	83	20%	35	12%	48	36%
Toxic effect of therapy	138	33%	100	35%	38	29%
Completed treatment	83	20%	75	26%	8	6%
Other	25	6%	14	5%	11	8%
Disease-related symptoms not due to therapy	10	2%	8	3%	2	1%
Patient requested	6	1%	5	2%	1	1%
Unknown	3	1%	3	1%	0	0%
No evidence of disease	5	1%	4	1%	1	1%
Financial	2	0%	0	0%	2	1%
Progression*	307	73%	197	69%	110	83%
Death	161	38%	92	32%	69	52%

*Progression includes clinical judgement, mortality, and treatment discontinuation because of progression. IO: Immunotherapy; TT: Targeted therapy.

Reasons for treatment discontinuation, all patients and by drug combo

	All patients		IO Combo		IO Mono		TT Combo	
	N= 419		N= 142		N= 145		N= 132	
	N	%	N	%	N	%	N	%

Reasons of discontinuation								
Among those with reasons provided	419		149		168		158	
Progression	83	20%	4	3%	31	21%	48	36%
Toxic effect of therapy	138	33%	65	46%	35	24%	38	29%
Completed treatment	83	20%	59	41%	16	11%	8	6%
Other	25	6%	3	2%	15	8.9%	11	8%
Disease-related symptoms not due to therapy	10	2%	4	3%	4	3%	2	1%
Patient requested	6	1%	2	1%	3	2%	1	1%
Unknown	3	1%	2	1%	1	1%	0	0%
No evidence of disease	5	1%	0	0%	4	3%	1	1%
Financial	2	0%	0	0%	0	0%	2	1%
Progression*	307	73%	85	60%	112	77%	110	83%
Death	161	38%	37	26%	55	37%	69	52.%

*Progression includes clinical judgement, mortality, and treatment discontinuation because of progression. IO: Immunotherapy; TT: Targeted therapy.

Rates of recurrence and death, by drug

	Dab+Tram		Nivo		Pembro		p-value
	N=	58	N=	215	N=	45	
	N	%	N	%	N	%	
1L therapy	**58**		**215**		**45**		
Recurrence							
Recurrence within 1L	4	7%	26	12%	3	7%	0.350
Recurrence within adjuvant setting	10	17%	45	21%	9	20%	0.824
First Recurrence occurred							0.005
During 1L	4	7%	26	12%	3	7%	
During 2L	1	2%	0	0%	0	0%	
After discontinued 1L, and prior to start of 2L	0	0%	2	1%	2	4%	
After discontinued 1L and no 2L use until cutoff	3	5%	17	8%	4	9%	
After discontinued 2L	2	3%	0	0%	0	0%	
Death							
Death within 1L	2	3%	1	1%	1	2.%	0.160
Death ever	9	15%	24	11%	9	20%	0.239

Rates of recurrence and death, by drug class

	All TT patients		All IO patients		p-value
	N=	58	N=	260	
	N	%	N	%	
1L therapy	**58**		**260**		
Recurrence					
Recurrence within 1L	4	7%	29	11%	0.336
Recurrence within adjuvant setting	10	17%	54	21%	0.545
First Recurrence occurred					0.002
During 1L	4	7%	29	11%	
During 2L	1	2%	0	0%	
After discontinued 1L, and prior to start of 2L	0	0%	4	2%	
After discontinued 1L and no 2L use until cutoff	3	5%	21	8%	
After discontinued 2L	2	3%	0	0%	
Death					
Death within 1L	2	3%	2	1%	0.098
Death ever	9	15%	33	13%	0.566

RFS and OS rate, based on Kaplan Meier estimation

Rate	Dab+Tram N=58	Nivol N=215	Pembro N=45
1-year RFS	87.5%	80.2%	86.2%
2-year RFS	66.2%	70.7%	68.6%
1-year OS	99.9%	94.9%	80.0%
2-year OS	76.6%	81.1%	70.0%

Progression-free and Overall survival, all patients

PFS and OS were evaluated using Kaplan-Meier estimation. In general, 40% of LTB MM patients progressed within 6 months of initiating 1L treatment. The median PFS was 10.1 months. Patients treated with IO had a longer median time to progression than patients treated with TT. The median PFS of patients treated with IO compared to those treated with TT was 11.3 months compared to 8.8 months. While the median PFS of IO combo, IO mono, and TT combo was 12.2 months, 8.5 months, and 8.8 months, respectively.

Safety Results

N/A

Other Relevant Findings

N/A

Conclusion
The conclusion was that in patients treated with Immunotherapy or dab+tram, elevated LDH level at baseline was a poor prognostic factor. Nonetheless, patients with increased LDH levels treated with these drugs gained significant benefits in terms of Progression free survival and Overall Survival. In an analysis of long-term outcomes in patients with BRAF+ MM who received dab+tram, increased Overall Survival was observed in patients with baseline normal LDH compared with patients with elevated LDH. Increased Overall Survival was also seen in patients with normal LDH and fewer than three organ sites with metastasis compared with counterparts.

Date of Clinical Study Report
25 March 2022