A Multi-Center Phase II Study on High Dose IL-2 (HD IL-2) Sequenced with Vemurafenib in Patients with BRAF-V600E Mutation Positive Advanced Melanoma

Adapted from a poster
presented at the ASCO 2015

Joseph I. Clark[1], Marc S. Ernstoff[2], Mohammed M. Milhem[3], Christopher D. Lao[4], David H. Lawson[5], Lawrence E. Flaherty[6], Theresa L. Luna[7], Hong Hua[7], Jessica Perritt[7], and Sandra Aung[7]

1. Loyola University Medical Center, Maywood, IL; 2. Dartmouth Hitchcock Medial Center/Norris Cotton Cancer Center, Lebanon, NH; 3. University of Iowa Hospitals and Clinics, Iowa City, IA; 4. University of Michigan, Ann Arbor, MI; 5. Emory University School of Medicine, Atlanta, GA; 6. Wayne State University, Detroit, MI; 7. Prometheus Laboratories Inc, San Diego

A Multi-Center Phase II Study on High Dose IL-2 (HD IL-2) Sequenced with Vemurafenib in Patients with BRAF-V600E Mutation Positive Advanced Melanoma

BACKGROUND

Progression after a period of tumor response is common with single-agent BRAF-inhibitor therapy after a median progression-free survival of 6 to 7 months[1,2]. Preclinical studies have suggested that BRAF inhibitors may enhance immune-cell function and antigen presentation[3-6]. Therefore, ample rationale to investigate the combining of vemurafenib with an immunotherapy exists. The combination of targeted agents with immunotherapies may result in heightened disease control rate and longer survival time, however concerns for toxicities have limited their use. Vemurafenib gives rise to a high response rate in BRAFv600 mutated melanoma patients, but responses are relatively short-lived. Durable unmaintained remissions are consistently observed in a small percentage of patients with metastatic melanoma (mM) treated with HD IL-2. Using both vemurafenib and HD IL-2 in sequence may complement the individual strengths of each therapy. The safety and efficacy results of a multi-center phase II study of high dose IL-2 (HD IL-2) sequenced with vemurafenib in patients with BRAFv600 mutation positive advanced melanoma is reported here.

ELIGIBILITY CRITERIA

- Metastatic melanoma with BRAFv600 mutation
- 18 years of age or older
- Met requirements for HD IL-2 and vemurafenib per institutional guidelines
- PROCLAIM registry participation (PROCLAIM is a US-based multi-center patient database designed to capture real-world clinical data on patients with metastatic melanoma and/or metastatic renal cell carcinoma who are treated with HD IL-2)
- Patients with brain metastases were excluded
- Prior treatment with HD IL-2, ipilimumab, or a BRAF inhibitor excluded
- Prior treatment with anti-PD-1/PD-L1 acceptable

OBJECTIVES

Primary

Assess Complete Response (CR) rate at assessment 1 (10 weeks ± 3) and assessment 2 (26 weeks ± 3) from the start of HD IL-2

Secondary

- Progression-free survival (PFS) and overall survival (OS):
- Treatment tolerability
- Treatment-related safety and immune-related adverse events
- Explore potential correlative biomarkers or diagnostics
- Treatment response to retreatment with vemurafenib in "CR" patients progressing on no therapy

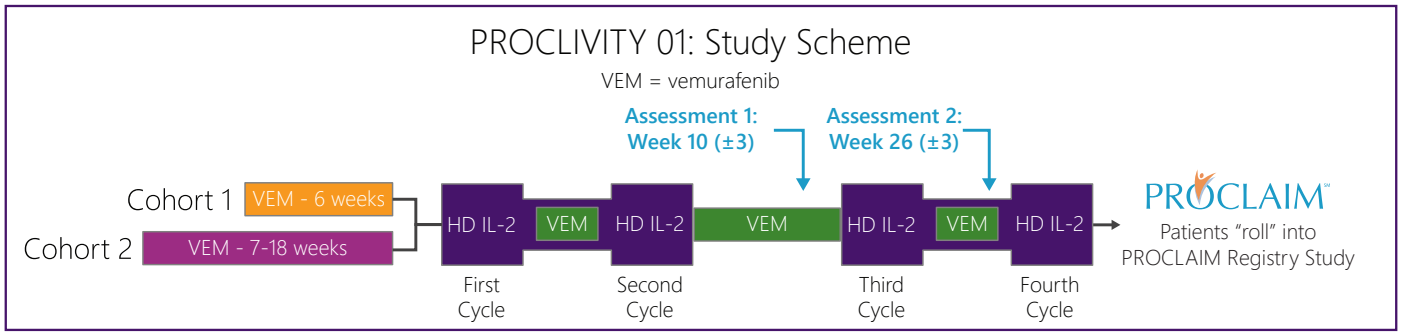
STUDY DESIGN

PROCLIVITY 01 (PROleukin® Combined with IpiLImumab, VemurafinIb or Other Targeted Agents in the Treatment of MalignancY) is an open-label, uncontrolled two-arm, multi-center study in patients with metastatic melanoma with BRAFV600 oncogene mutations. Patients initially received treatment with vemurafenib interspersed with two courses of High Dose IL-2 (HD IL-2). Patients were eligible for the study if they had melanoma positive for a BRAFV600 mutation, had been on vemurafenib therapy for 0-18 weeks, had responding or stable disease if on vemurafenib, and met the requirements for dosing with HD IL-2 and all protocol inclusion and exclusion criteria (Figure 1).

Cohort 1

Consists of 30 evaluable patients naïve to vemurafenib and HD IL-2 therapy. Patients had an initial evaluation and received a defined 6 (±1) week course of vemurafenib before beginning HD IL-2. This cohort was used to define study size and statistical validity with the comparator being historical controls using data from BRAF positive patients from the Melanoma SELECT study (NCT01288963). The initial design was to enroll 135 subjects in cohort 1. Based on a one-sample binomial test (using normal approximation), a sample size of 123 would have 80% power to detect a

Figure 1. Study Scheme



significant difference using a one-sided test with a = 0.05% if the true CR rate for naïve subjects treated with 6 weeks of vemurafenib prior to adding HD IL-2 is twice the CR rate of the historical control for HD IL-2 (12% vs 6%). However, due to poor accrual in the study, the number of evaluable number of patients was 30.

Cohort 2

Consists of 14 evaluable patients who were on vemurafenib therapy for >7 to 18 weeks with stable or responding disease before starting HD IL-2. This cohort was designed to evaluate whether additive or synergistic clinical benefit or toxicity is observed in BRAFV600 mutation positive metastatic melanoma patients treated with vemurafenib as a single agent for >7 to 18 weeks prior to the first course of HD IL-2 therapy in conjunction with continued vemurafenib.

Table 1. Cohorts

	Cohort 1	Cohort 2
Safety Population	31	15
Evaluable Population	30	14

Table 1. The safety population consists of all subjects who received at least one dose of HD IL-2. The evaluable population consists of all subjects who had measureable disease at baseline, received at least one dose of study drug, and had their disease re-evaluated. Subjects who exhibited objective disease progression or died prior to the end of cycle 1 were also considered evaluable.

ASSESSMENTS

Tumor assessment was collected prior to dosing with vemurafenib and prior to the first dose of HD IL-2 (PE, X-ray or CT scan data in the medical records). Patients in both cohorts discontinued vemurafenib prior to each treatment with HD IL-2 and resumed dosing after each discharge. Patients received up to two courses (4 cycles) of HD IL-2 and were evaluated for disease responses at Assessment 1 (week 10 ± 3 weeks) from the start of HD IL-2 dosing, and at Assessment 2 (week 26 ± 3 weeks) from the start of HD Il-2 dosing. QTc intervals were reviewed daily for changes during each cycle of HD IL-2 dosing. Administration of vemurafenib and HD IL-2 were according to the respective Package Inserts and according to the Institution's standard of care. The investigator determined the number of HD IL-2 cycles each patient received, according to investigator's discretion and medical judgment.

Table 2. Patient Demographics

Characteristic	Cohort 1 Vemurafenib (6 wks) N=31	Cohort 2 Vemurafenib (7-18 wks) (N=15)
Age (yr)		
Mean	48.1	48.47
Median	49.0	48.0
Range	21-67	26-67
Gender – no. (%)		
Male	21 (68)	9 (60)
Female	10 (32)	6 (40)
Race - No. (%)		
White	30 (97)	15 (100)
Decline	1 (3)	0
Location of Metastases - no. (%)		
Bone	7 (9.46)	4 (11.76)
Skin	8 (10.81)	3 (8.82)
Lungs	17 (22.97)	6 (17.65)
Liver	7 (9.46)	3 (8.82)
Lymph Nodes	20 (27.03)	9 (26.47)
Brain	2 (2.7)	3 (8.82)
Soft Tissue	10 (13.51)	2 (5.88)
Other	3 (4.05)	4 (11.76)
Prior Therapy - no. (%)		
Surgery	60 (86.96)	31 (72.09)
Radiation	7 (10.14)	10 (23.26)
Chemotherapy	2 (2.9)	2 (4.65)
Mutation - no. (%)		
BRAF	31 (100)	
cKIT	1 (3.22)	15 (100)
Other	3 (9.68)	
ECOG Performance Status - no. (%)		
0	21 (67.74)	8 (53.33)
1	10 (32.26)	7 (46.67)

Abbreviations: ECOG, Eastern Cooperative Oncology Group

Table 3. Clinical Response

	Cohort 1 Vemurafenib (6 wks)		Cohort 2 Vemurafenib (7-18 wks)	
	Assessment 1 n=27 No. (%)	Assessment 2 n=9 No. (%)	Assessment 1 n=13 No. (%)	Assessment 2 n=6 No. (%)
CR	1 (3.70)	1 (11.11)	1 (7.69)	0 (0)
PR	3 (11.11)	0 (0)	1 (7.69)	0 (0)
SD	10 (37.04)	4 (44.44)	7 (53.85)	3 (50)
PD	13 (48.15)	4 (44.44)	4 (30.77)	3 (50)
CR+PR	4 (14.81)	1 (11.11)	2 (15.38)	0 (0)
CR+PR+SD	14 (51.85)	5 (55.56)	9 (69.23)	3 (50)

Table 3. Clinical Response. Tumor response was collected at 10 weeks (assessment 1) and at 26 weeks (assessment 2) from the start of HD IL-2 dosing. The immune-related response criteria (irRC) was used (Wolchok JD et al, 2009)[7]. For cohort 1, response rates were available for 27 patients at assessment 1 and 9 patients at assessment 2. For cohort 2, response rates were available for 13 patients at assessment 1 and 6 patients at assessment 2. Response was obtained from the evaluable population.

Table 4. Treatment Duration

	Cohort 1 Vemurafenib (6 wks)		Cohort 2 Vemurafenib (7-18 wks)	
	Days on Vemurafenib	Days on HD IL-2	Days on Vemurafenib	Days on HD IL-2
Mean (95% CI)	82.6 (61.07, 104.13)	11.66 (9.76, 13.55)	151 (110.76, 191.24)	11.5 (8.86, 14.14)
Median	67	10	140	10.5
Range	28, 278	5, 22	43, 288	5, 20

Table 4. Treatment duration. The duration of vemurafenib and HD IL-2 therapies for cohort 1 and cohort 2 are depicted. Duration of treatment was based on the evaluable population.

Figure 2A. Kaplan Meier overall progression-free survival (PFS)

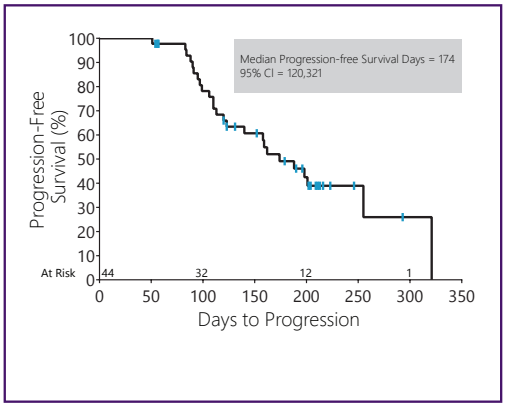


Figure 2A. Kaplan Meier overall progression-free survival (PFS) for the efficacy evaluable population. The efficacy evaluable population consisted of all subjects who had measurable disease present at baseline, had received at least one dose of study treatment, and had their disease re-evaluated. PFS is defined as the duration of time from initiation of vemuafenib to time of objective disease progression. Vertical bars represent censored subjects.

Figure 2B. Kaplan Meier overall progression-free survival (PFS)

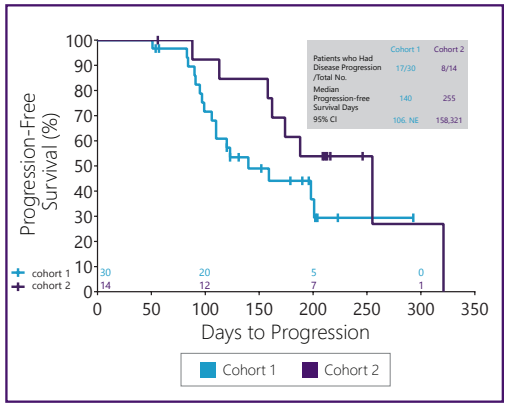


Figure 2B. Kaplan Meier overall progression-free survival for the efficacy evaluable population stratified by cohort. Median progression-free survival was 140 days for cohort 1 and 255 days for cohort 2. Vertical bars represent censored subjects.

Table 5. Adverse Events Related to HD IL-2

	Cohort 1 N=31				Cohort 2 N=15				Total N=46			
	no of events	%	no of events	%	no of events	%	no of events	%	no of events	%	no of events	%
	13		0		22		1		35		1	
Blood bilirubin increased	1	7.69	0	0	2	9.09	0	0	3	8.57	0	0
Confusional state	1	7.69	0	0	0	0	0	0	1	2.86	0	0
Delirium	2	15.38	0	0	0	0	0	0	2	5.71	0	0
Dermatitis bullous	1	7.69	0	0	0	0	0	0	1	2.86	0	0
Dry skin	0	0	0	0	1	4.55	0	0	1	2.86	0	0
Dyspnoea	1	7.69	0	0	0	0	0	0	1	2.86	0	0
Electrocardiogram qt prolonged	0	0	0	0	1	4.55	0	0	1	2.86	0	0
Electrolyte imbalance	0	0	0	0	1	4.55	0	0	1	2.86	0	0
Fatigue	0	0	0	0	1	4.55	0	0	1	2.86	0	0
Hyperbilirubinaemia	1	7.69	0	0	0	0	0	0	1	2.86	0	0
Hypersensitivity	0	0	0	0	1	4.55	0	0	1	2.86	0	0
Hypokalaemia	0	0	0	0	1	4.55	0	0	1	2.86	0	0
Hypophosphataemia	0	0	0	0	2	9.09	0	0	2	5.71	0	0
Hypotension	1	7.69	0	0	2	9.09	0	0	3	8.57	0	0
Leukocytosis	0	0	0	0	1	4.55	0	0	1	2.86	0	0
Lymphopenia	0	0	0	0	1	4.55	0	0	1	2.86	0	0
Metabolic acidosis	0	0	0	0	2	9.09	0	0	2	5.71	0	0
Neuropathy peripheral	0	0	0	0	1	4.55	0	0	1	2.86	0	0
Oedema peripheral	1	7.69	0	0	0	0	0	0	1	2.86	0	0
Oliguria	0	0	0	0	1	4.55	0	0	1	2.86	0	0
Pruritus	0	0	0	0	1	4.55	0	0	1	2.86	0	0
Renal failure	0	0	0	0	2	9.09	0	0	2	5.71	0	0
Renal failure acute	1	7.69	0	0	0	0	0	0	1	2.86	0	0
Sinus tachycardia	1	7.69	0	0	0	0	0	0	1	2.86	0	0
Staphylococcal bacteraemia	1	7.69	0	0	0	0	0	0	1	2.86	0	0
Thrombocytopenia	1	7.69	0	0	1	4.55	0	0	2	5.71	0	0
Lymphocyte count decreased	0	0	0	0	0	0	1	100	0	0	1	100

Table 5. Adverse Events Related to HD IL-2. The safety population was used for all analyses of safety data. All subjects who received at least one dose of HD IL-2 were included in the safety population. All investigator reported terms for adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA). AE and serious adverse event (SAE) incidence summaries are presented by prefer term and cohort. Number of events reported within a column may not add up to the total number of patients. The highest grade was counted for each patient based on preferred term. If there were more than one highest grade based on preferred term, these were counted for each patient.

Table 6. Adverse Events related to Vemurafenib

	Cohort 1 n=31				Cohort 2 n=15				Total n=46			
	no of events	%	no of events	%	no of events	%	no of events	%	no of events	%	no of events	%
Rash	1	100	0	0	1	100	0	0	2	100	0	0

Table 6. Adverse Events related to Vemurafenib. The safety population was used for all analyses of safety data. AEs were stratified into cohorts.

Table 7. Investigator Determined Unexpected AEs Related to HD IL-2

	Cohort 1 n=31				Cohort 2 n=15				Total n=46			
	Grade 3		Grade 4		Grade 3		Grade 4		Grade 3		Grade 4	
	no of events	%	no of events	%	no of events	%	no of events	%	no of events	%	no of events	%
All	1		0		2		0		3		0	
Electrocardiogram qt prolonged	0	0	0	0	1	50	0	0	1	33.3	0	0
Neuropathy peripheral	0	0	0	0	1	50	0	0	1	33.3	0	0
Staphylococcal bacteraemia	1	100	0	0	0	0	0	0	1	33.3	0	0

Table 7. Investigator determined unexpected AEs related to HD IL-2. The safety population was used for all analyses of safety data. AEs were stratified into cohorts. Note there were no unexpected investigator determined AEs related to vemurafenib.

Table 8. Treatment-related Events in the Safety Population

	Cohort 1 n=31				Cohort 2 n=15				Total n=46			
	Grade 3		Grade 4		Grade 3		Grade 4		Grade 3		Grade 4	
Treatment related AE	no of events	%	no of events	%	no of events	%	no of events	%	no of events	%	no of events	%
	33		1		46		1		79		2	
Hypotension	2	6.1	0	0	4	8.7	0	0	6	7.6	0	0
Renal failure	1	3	0	0	5	10.9	0	0	6	7.6	0	0
Blood bilirubin increased	2	6.1	0	0	3	6.5	0	0	5	6.3	0	0
Rash	2	6.1	0	0	1	2.2	0	0	3	3.8	0	0
Thrombocytopenia	1	3	0	0	2	4.3	0	0	3	3.8	0	0
Anaemia	0	0	0	0	2	4.3	0	0	2	2.5	0	0
Back pain	1	3	0	0	1	2.2	0	0	2	2.5	0	0
Chest pain	1	3	0	0	1	2.2	0	0	2	2.5	0	0
Delirium	2	6.1	0	0	0	0	0	0	2	2.5	0	0
Hypophosphataemia	0	0	0	0	2	4.3	0	0	2	2.5	0	0
Liver function test abnormal	1	3	0	0	1	2.2	0	0	2	2.5	0	0
Metabolic acidosis	0	0	0	0	2	4.3	0	0	2	2.5	0	0
Renal failure acute	2	6.1	0	0	0	0	0	0	2	2.5	0	0
Abdominal pain	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Alanine aminotransferase increased	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Arthralgia	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Aspartate aminotransferase increased	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Asthenia	1	3	0	0	0	0	0	0	1	1.3	0	0
Blood creatinine increased	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Confusional state	1	3	0	0	0	0	0	0	1	1.3	0	0
Dermatitis bullous	1	3	0	0	0	0	0	0	1	1.3	0	0
Dry skin	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Dyspnoea	1	3	0	0	0	0	0	0	1	1.3	0	0
Electrocardiogram qt prolonged	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Electrolyte imbalance	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Failure to thrive	1	3	0	0	0	0	0	0	1	1.3	0	0
Fatigue	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Gastritis	1	3	0	0	0	0	0	0	1	1.3	0	0
Headache	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Hepatotoxicity	1	3	0	0	0	0	0	0	1	1.3	0	0
Hydronephrosis	1	3	0	0	0	0	0	0	1	1.3	0	0
Hyperbilirubinaemia	1	3	0	0	0	0	0	0	1	1.3	0	0
Hypersensitivity	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Hypoaesthesia	1	3	0	0	0	0	0	0	1	1.3	0	0
Hypoglycaemia	1	3	0	0	0	0	0	0	1	1.3	0	0
Hypokalaemia	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Leukocytosis	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Lymphopenia	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Muscular weakness	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Nausea	1	3	0	0	0	0	0	0	1	1.3	0	0
Neurological decompensation	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Neuropathy peripheral	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Oedema peripheral	1	3	0	0	0	0	0	0	1	1.3	0	0
Oliguria	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Pain in extremity	1	3	0	0	0	0	0	0	1	1.3	0	0
Pleural effusion	1	3	0	0	0	0	0	0	1	1.3	0	0
Pruritus	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Radiation necrosis	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Renal failure chronic	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Sinus tachycardia	1	3	0	0	0	0	0	0	1	1.3	0	0
Skin exfoliation	1	3	0	0	0	0	0	0	1	1.3	0	0
Spinal fracture	0	0	0	0	1	2.2	0	0	1	1.3	0	0
Staphylococcal bacteraemia	1	3	0	0	0	0	0	0	1	1.3	0	0
Hyperglycaemia	0	0	1	100	0	0	0	0	0	0	1	50
Lymphocyte count decreased	0	0	0	0	0	0	1	100	0	0	1	50

Table 8. Treatment-related events in the safety population. All subjects who received at least one dose of HD IL-2 were included in the safety population. All investigator reported terms for adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA). AE and serious adverse event (SAE) incidence summaries are presented by prefer term and cohort. Number of events reported within a column may not add up to the total number of patients. The highest grade was counted for each patient based on preferred term. If there were more than one highest grade based on preferred term, these were counted for each patient. There was only 1 Patient that had a Grade 5 AE. The patient was in cohort 1 and the AE was not related to either IL-2 or Vemurafenib (AE by SOC was neoplasms benign, malignant, and unspecified (includes cysts and polyps)).

Table 9A. Pre-dose QTc Measurements for Cohort 1

Cohort 1	n	Mean	Std Dev	Median	Min	Max
Screening	31	423.9	28	415	376	480
Cycle 1	27	424.4	34	430	340	490
Cycle 2	23	408.9	98	425	340	546*
Cycle 3	8	397.9	164	443	407	506*
Cycle 4	6	462.2	18	461	442	483

Table 9A. Pre-dose QTc measurements for cohort 1. *1 patient had a QTc level of >500 at cycle 2 and 3.

Table 9B. Pre-dose QTc Measurements for cohort 2

Cohort 2	n	Mean	Std Dev	Median	Min	Max
Screening	15	440.7	28	438	407	508*
Cycle 1	15	446.2	23	444	411	506*
Cycle 2	13	440.1	34	444	342	483
Cycle 3	5	443	23	444	407	470
Cycle 4	5	445	6	444	438	454

Table 9B. Pre-dose QTc measurements for cohort 2. *1 patient had a QTc level of >500 at screening and cycle 1. This patient was captured in the Protocol Deviation. QTc values were from the safety population. The CTCAE definition of Grade 3 QTc is QTc >= 501 ms on at least two separate ECGs.

SUMMARY

- This study was prematurely terminated due to slow accrual
- Sequencing of vemurafenib with HD IL-2 immunotherapy is feasible
- There were no safety concerns and patients experienced toxicities as anticipated for IL-2 or vemurafenib alone
- The overall response rate (ORR) for cohort 1 was 14.81% and 15.38% for cohort 2 at assessment 1
- Median PFS was 140 days (95% CI 106, NE) for cohort 1 and 255 days (95% CI 158, 321) for cohort 2 for the evaluable population
- There were no treatment-related deaths
- Planned correlative biomarker and diagnostic studies are on-going
- mOS data are not mature and were not reported in this analysis

CONCLUSIONS

A shift in metatstatic melanoma treatment landscape adversely affected accrual resulting in early closure of this study. The safety results of this study show vemurafenib combined with HD IL-2 did not change the known safety profile of either drug. This is relevant because safety in the concurrent administration of vemurafenib and immunotherapy with the checkpoint inhibitor, ipilimumab, reported severe hepatotoxicity in 6 of 12 patients resulting in cessation of the study[8]. The small sample size precludes definitive conclusions about any efficacy interaction between vemurafenib and HD IL-2 as administered. Durability of response and long term survival will be reported as patients continue to be followed in the PROCLAIM IL-2 database.

REFERENCES

1. Chapman PB, Hauschild A, Robert C, et al.: Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 364:2507-2516, 2011
2. Hauschild A, Grob JJ, Demidov LV, et al.: Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 380:358-365, 2012
3. Boni A, Cogdill AP, Dang P, et al.: Selective BRAFV600E inhibition enhances T-cell recognition of melanoma without affecting lymphocyte function. Cancer Res 70:5213-5219, 2010
4. Comin-Anduix B, Chodon T, Sazegar H, et al.: The oncogenic BRAF kinase inhibitor PLX4032/RG7204 does not affect the viability or function of human lymphocytes across a wide range of concentrations. Clin Cancer Res 16:6040-6048, 2010
5. Koya RC, Mok S, Otte N, et al.: BRAF inhibitor vemurafenib improves the antitumor activity of adoptive cell immunotherapy. Cancer Res 72:3928-3937, 2012
6. Liu C, Peng W, Xu C, et al.: BRAF inhibition increases tumor infiltration by T cells and enhances the antitumor activity of adoptive immunotherapy in mice. Clin Cancer Res 19:393-403, 2013
7. Wolchok JD, Hoos A, O'Day S, et al.: Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 15:7412-7420, 2009
8. Ribas A, Hodi FS, Callahan M, et al.: Hepatotoxicity with combination of vemurafenib and ipilimumab. N Engl J Med 368:1365-1366, 2013