

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



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Center for Drug Evaluation and Research
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STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA #: 202429
Supplement #: 16
Drug Name: Zelboraf (vemurafenib);
Indication(s): To evaluate the efficacy of vemurafenib in patients with cancers harboring BRAF V600 mutations as response rate (RR) at Week 8 determined by the investigator using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST, v1.1).
Applicant: Hoffman La Roche/Genetech, Inc
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EXECUTIVE SUMMARY

On June 7th, 2017, the applicant, Hoffmann-La Roche/Genentech, Inc, submitted a new efficacy supplement for NDA202429 Zelboraf (vemurafenib). The sponsor is proposing a new indication in patients with Erdheim Chester Disease (ECD) with BRAF V600 mutation.

The supplement was an open-label, multicenter, multinational, phase II study. 208 patients were enrolled into 7 different cohorts and twenty-two subjects enrolled in Cohort 7a had ECD. The proposed indication is based on these 22 ECD patients. The primary efficacy endpoint was the overall response rate (ORR) by investigator. ORR is defined as a complete response, partial response on two occasions ≥ 4 weeks apart, as assessed by the investigator.

The ORR was 54.5% (12 out of 22 subjects; 95% CI= [32.2,75.6]). One subject had a complete response and eleven had partial responses. For the rest, nine subjects had stable disease and one patient's outcome was not measurable.

Based on the data submitted, this reviewer confirms the results for patients with ECD known to harbor BRAF V600 mutations, however, whether the results represent a favorable benefit to risk ratio to support an approval of vemurafenib will be deferred to clinical judgment.

1 INTRODUCTION

1.1 Background

Erdheim-Chester Disease (ECD) is a rare, non-Langerhans histiocytosis characterized by organ infiltration by CD68+, CD163+, and CD1a- non-Langerhans foamy histiocytes. Currently, there are no universally accepted guidelines for the diagnosis and treatment of ECD.

Vemurafenib is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test in August 2011.

In April 2017, FDA granted the Breakthrough therapy designation to vemurafenib for the treatment of patients with ECD with BRAF V600 mutation.

This submission is to support the proposed indication in the package insert:

- *Vemurafenib is indicated for the treatment of patients with Erdheim-Chester Disease with BRAF V600 mutation.*

1.2 Statistical Analysis Plan Critical Amendments

The initiation date of study MO28072 was April 11, 2012 and the completion date was October 27, 2016. The data cut-off date was Jan 12, 2017. The protocol MO28072 version 1 was finalized on November 30, 2011. The last version, version 6, was finalized on January 13, 2015.

1.3 Clinical Studies

The applicant proposes that vemurafenib is indicated for the treatment of patients with ECD with BRAF V600 mutations.

To support the above proposed indication, the applicant conducted one phase II study. The major study design characteristics of this study are summarized in Table 1.

Table 1 Study Overview

Study Name	Study Description	Treatment Groups	No. of Subjects
MO28072	An open-label, multicenter, multinational, phase II study exploring the efficacy and safety of vemurafenib in a diverse population of patients with cancers known to harbor BRAF V600 mutations and for whom vemurafenib is deemed the best option in the opinion of the investigator.	Oral dose of vemurafenib 960 mg b.i.d.	22 subjects in Cohort 7A that has ECD

1.4 Data Sources

Data were provided electronically with the standard analysis data formats. SAS programs used to create key efficacy and safety endpoints and analyses for Study MO28072 were submitted electronically with this application.

The path to the CDER Electronic Document Room (EDR) data is:
\\CDSESUB1\evsprod\NDA202429\0186\m5\datasets\mo28072

2 STATISTICAL EVALUATION

2.1 Data and Analysis Quality

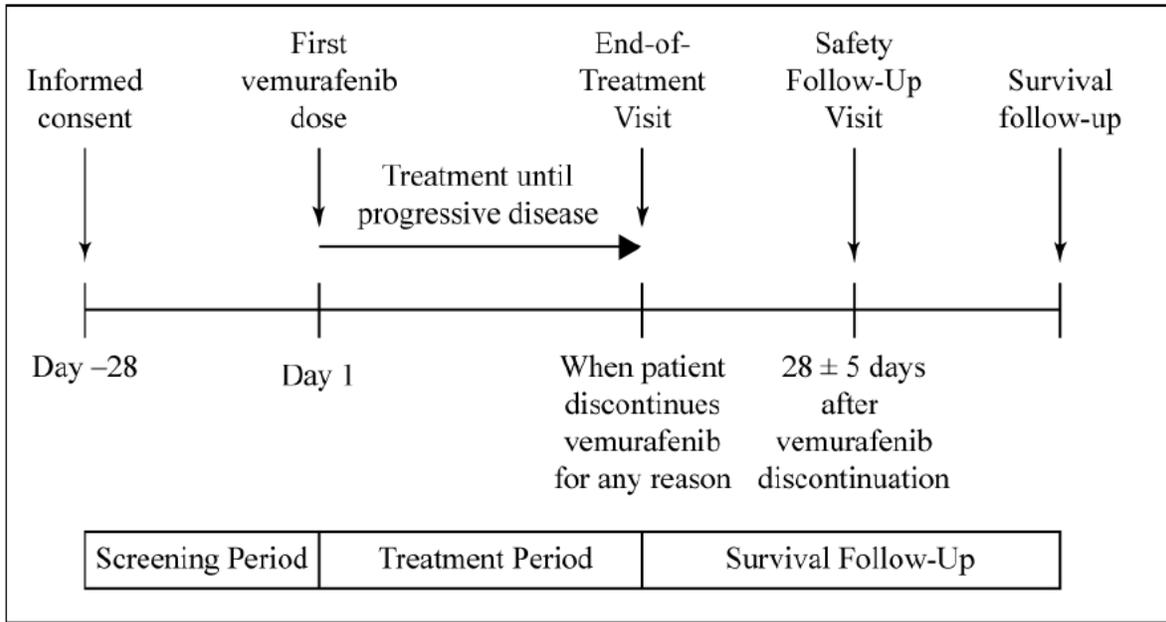
Data from study MO28072 was provided with SDTM and ADAM formats. Documentations on datasets and programming for the key study endpoints were included with sufficient details for verifications.

2.2 Evaluation of Efficacy

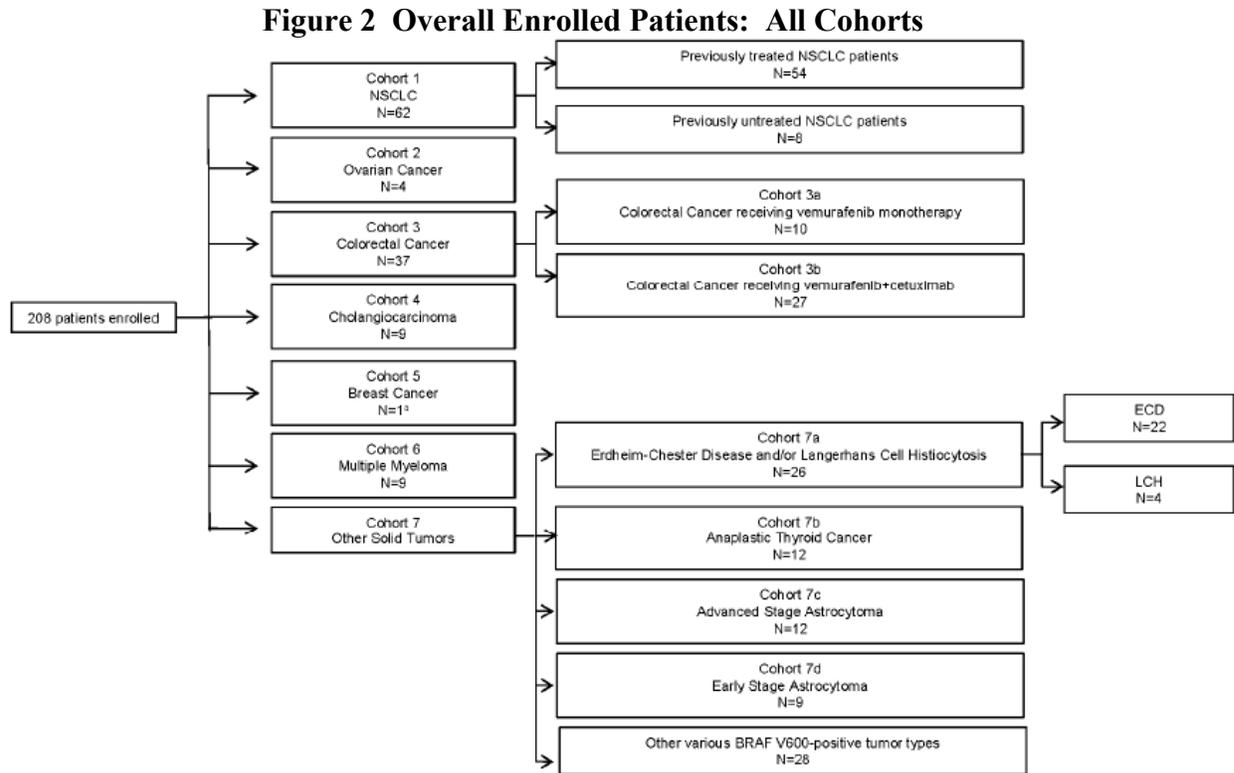
2.2.1 Study Design

This was an open-label, multicenter, multinational, phase II study exploring the efficacy and safety of vemurafenib in a diverse population of patients with cancers known to harbor BRAF V600 mutations and for whom vemurafenib is deemed the best option in the opinion of the investigator

Figure 1 Study Schema



Source: Figure 1 in Section 3.1 of Applicant's CSR



Source: Figure 2 in Section 4 of Applicant's CSR

Study Treatment:

- 960 mg (four 240 mg tablets) orally every 12 hours

Primary Efficacy Endpoint:

- Overall Response Rate (ORR) assessed by Investigator using RECIST v1.1: defined as a complete response, partial response on two occasions ≥ 4 weeks apart as assessed by the investigator.

Key Secondary Efficacy Endpoints:

- Progression-free survival (PFS)
- Time to progression (TTP)
- Best of Response (BOR)
- Clinical benefit rate (CBR)
- Time to Response (TTR)
- Duration of Response (DOR)
- Overall Survival (OS)

2.2.2 Statistical Methodologies**Sample Size and Power Determination:**

22 subjects in the Cohort 7A with ECD will be included in the analysis

Reviewer’s Comment: *This is a single arm study; no formal statistical hypothesis was proposed.*

Efficacy Analysis Populations:

Intent-to-Treat (ITT) population: only the patients whose tumors were diagnosed as ECD cohort.

Efficacy Analyses:

There is no formal statistical hypothesis. The number and percentage of responders with corresponding exact 95% CI are presented.

2.2.3 Patient Disposition, Demographic and Baseline Characteristics**Subject Disposition:**

100% of the ECD patients (22/22) were no longer receiving study treatment and all patients had discontinued from the study. The most common reason for study discontinuation was “Other” (59.1%), followed by withdrawal by subject (27.3%), loss to follow-up (9.1%), and death (4.5%). The median time to study discontinuation was 26.64 months. The most common reason for treatment discontinuation was “Other” (40.9%) as well, followed by Progressive Disease (31.8%), followed by withdrawal by subject (22.7%), physician decision (4.5%). The median time to treatment discontinuation was 14.16 months.

Table 2 Subject Disposition

	ECD (N=22)
Study Discontinuation Reasons	
N	22
Death	1 (4.5%)

Lost to Follow-up	2 (9.1%)
Withdrawal by Subject	6 (27.3%)
Other	13 (59.1%)
Time to Study Discontinuation (months)	
N	22
Mean (SD)	22.7 (12.98)
Median	26.6
Min - Max	3.1 – 44.3
Vemurafenib Discontinuation Reasons	
N	22
Progressive Disease	0
Adverse Event	7 (31.8%)
Death	0
Withdrawal by Subject	5 (22.7%)
Physician Decision	1 (4.5%)
Other	9 (40.9%)
Time to Vemurafenib Discontinuation (months)	
N	22
Mean (SD)	17.2 (13.35)
Median	14.2
Min - Max	1.6 – 44.2

Demographics Characteristics:

The median age of the 22 subjects was 58.5 years. 54.5% of the subjects were (b) (6) and (b) (6) out of 22 subjects were (b) (6). Fifteen subjects (68.2%) had at least one prior systemic therapy.

Table 3 Demographics

	ECD (n=22)
Age (years)	
Mean (SD)	59.9 (11.8)
Median	58.5
Min-Max	(b) (6)
Sex	
Male	(b) (6)
Female	(b) (6)
Race	
White	(b) (6)
Asian	(b) (6)
ECOG Status	
0	4 (18.2%)
1	12 (54.5%)
2	5 (22.7%)
NA	1 (4.6%)
Prior Systemic Therapy	

0	7 (31.8%)
1	7 (31.8%)
2	5 (22.7%)
3 or more	3 (13.7%)

2.2.4 Efficacy Results

Overall Response Rate:

The ORR was 54.5% (12/22) with 95% CI was (32.21%, 75.61%). One patient had a complete response (4.5%), eleven patients had a partial response (50.0%), nine had stable disease (40.9%), and one patient's disease status was not measurable (4.5%). Out of the twelve responders, the median time to response was ~11 months with 95% CI of 4 and 15 months. The median duration of response was not reached at the time of study cutoff.

Table 4 Overall Response Rate by Investigator

Efficacy Result	ECD patients (N=22)
Median duration of follow-up (months) (Min, Max)	26.64 (3.0, 44.3)
ORR by Investigator (95% CI)	12 (54.5%) (32.21, 75.61)
Complete response	1 (4.5%)
Partial response	11 (50.0%)
Stable disease	9 (40.9%)
Progressive disease	0
Not Measurable	1 (4.5%)
Duration of Response	
Number of responders	12 (54.5%)
Median (months) (95%CI)	NE (NE)
Time to Response	
Number of responders	12 (54.5%)
Median (months) (95%CI)	10.97 (3.68, 14.55)
Progression Free Survival (PFS)	
Number of events	3 (13.6%)
Median (months) (95%CI)	NE (NE)
Overall Survival (OS)	
Number of events	1 (4.5%)
Median (months) (95%CI)	NE (NE)

Time-to-Event Outcomes:

Three out of twenty-two patients had PFS events (13.6%), One patients (4.5%) died (Table 4).

2.3 Evaluation of Safety

Please refer to clinical review on the safety issues of study MO28072.

3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses presented in this section are considered exploratory.

Subgroup Analyses by Age, Gender, Race and Region:

The difference of ORR between the subgroups and their associated wide 95% CI are the result of small sample size.

Table 5 Subgroup Analysis of ORR

Subgroup	N	ORR	95% CI for ORR
Gender			
Men	(b) (6)	5 (41.7%)	(15.17%, 72.33%)
Women	(b) (6)	7 (70.0%)	(34.75%, 93.33%)
Age (years)			
<65 years old	(b) (6)	9 (64.3%)	(35.14%, 87.24%)
≥65 years old	(b) (6)	3 (37.5%)	(8.52%, 75.51%)

Reviewer's Comment: (b) (6) of 22 patients were white and (b) (6) of 22 patients were from (b) (6) the by- race and by-country subset analyses would not be reasonable and provide any substantial insight.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

This study does not have a formal statistical hypothesis due to the single arm study design and small sample size of 22 patients in the ECD cohort.

4.2 Conclusions and Recommendations

Based on the data submitted, this reviewer confirms the results for patients with ECD known to harbor BRAF V600 mutations, however, whether the results represent a favorable benefit to risk ratio to support an approval of vemurafenib will be deferred to clinical judgment.

4.3 Labeling Recommendations

NA.

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/s/

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10/02/2017

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