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SCIENCE MEDICINES HEALTH

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Procedure Management and Committees Support Division

## Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

### **Avastin**

bevacizumab

Procedure No. EMEA/H/C/000582/P46/083

### **Note**

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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# 1. Introduction

On 16 November 2015 the MAH submitted a completed paediatric study for Avastin in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

## 2. Scientific discussion

### 2.1. Information on the development program

The MAH stated that study BO20924 (BERNIE) is a standalone study. A line listing of all studies included in the development program has been provided.

Product Name: Avastin                      Active substance: Bevacizumab  
Indication: Metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma

Study title	Study number	Date of completion	Date of submission of final study report
Open-label, multi-center, randomized, phase II study evaluating the addition of bevacizumab to chemotherapy in childhood and adolescent patients presenting with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma.	BO20924	Recruitment completed: 31 October 2013	16 November 2015: CSR (primary analysis) based on the clinical cut off of 31 May 2015, approximately 19 months after the last patient was randomized. Following completion of the analyses included in this CSR, Study BO20924 is continuing and patients will be followed for a minimum of 47 months for overall survival (OS) and the long-term effects of treatment.

The Avastin BERNIE study is part of an approved PIP EMEA-000056-PIP01-07-MO2 for the treatment of rhabdomyosarcoma and soft tissue sarcoma.

The first patient was randomized in Study BO20924 on 29 July 2008. Patient recruitment was completed on 31 October 2013, after a total of 154 patients had been randomized. The primary analysis was EFS, and this CSR is based on the clinical cut off of 31 May 2015, approximately 19 months after the last patient was randomized. Following completion of the analyses included in this CSR, Study BO20924 is continuing and patients will be followed for a minimum of 47 months for overall survival (OS) and the long-term effects of treatment.

The Sponsor will submit a CSR addendum with the final analysis results (EFS and OS) for the BERNIE study in 2019.

The Avastin BERNIE study failed to meet the primary endpoint and no new safety signals have been identified. Therefore, the MAH will not be seeking an indication nor amending existing indications.

## **2.2. Information on the pharmaceutical formulation used in the study**

Avastin is provided as an 25 mg/ml concentrate for solution for intravenous infusion, this is considered an adequate formulation for paediatric use.

## **2.3. Clinical aspects**

### **2.3.1. Introduction**

The MAH submitted a clinical study report for:

- BO20924 (BERNIE) a randomized, comparative, open-label, multi-center Phase II study evaluating the benefit of the addition of bevacizumab to chemotherapy in children and adolescent patients presenting with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma.

### **2.3.2. Clinical study**

#### **Study BO20924 (BERNIE)**

Open-label, multi-center, randomized, phase II study evaluating the addition of bevacizumab to chemotherapy in children and adolescent patients presenting with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma – Report No.: 1065302 .November 2015.

#### **Description**

#### **Methods**

##### **Objectives**

##### Overall Objective

The objective of Study BO20924 was to evaluate the role of anti-angiogenic therapy with bevacizumab as part of the multi-modality treatment of patients presenting with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma.

##### Primary Objective

To evaluate the efficacy of the addition of bevacizumab to chemotherapy as compared to chemotherapy alone in children and adolescent patients presenting with metastatic RMS and NRSTS as assessed by Independent Review Committee (IRC)-evaluated Event-Free Survival (EFS)

##### Secondary Objectives

To determine the safety, tolerability and efficacy of the addition of bevacizumab to chemotherapy as compared to chemotherapy alone in patients presenting with metastatic RMS and NRSTS, as assessed by:

- . Adverse event profile
- . Discontinuation or modification or delay of any treatment element
- . Objective response rate (according to RECIST v1.0) prior to local therapy
- . Overall survival (OS)
- . Duration of response (DoR)

To characterize the pharmacokinetic (PK) profile of bevacizumab across all age subsets of the study population

Exploratory Objective

Correlation of biomarker assessments with risk factors and treatment outcome

### **Study design**

A randomized, comparative, open-label, multi-center Phase II study evaluating the benefit of the addition of bevacizumab to chemotherapy in children and adolescent patients presenting with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma. Patients who fulfilled the inclusion and exclusion criteria and completed the screening assessments were randomized 1:1 to receive combined modality therapy with or without bevacizumab.

### **Study population**

150 patients between 6 months and 18 years of age with a histologically established diagnosis of metastatic or unresectable soft tissue sarcoma (STS), either rhabdomyosarcoma (RMS) or non-rhabdomyosarcoma

### **Sample size**

STS 150 patients planned. 154 patients enrolled; (74 patients in the Bv + Chemo arm and 80 patients in the Chemo arm).

### **Treatments**

Patients randomized to the experimental arm received bevacizumab every three weeks at a dose of 2.5 mg/kg/week in addition to chemotherapy (IVADo) and local therapy (radiation and/or surgery) as appropriate during the induction phase. Bevacizumab dosing was maintained at the same dose intensity during the maintenance phase with cyclophosphamide and vinorelbine.

### **Outcomes/endpoints**

#### Efficacy:

#### *Primary Endpoints*

The primary endpoint of Study BO20924 was EFS, defined as the time between randomization and any of the following:

- Disease progression (as evaluated by a central independent image review committee), or
- Recurrence (as evaluated by a central independent image review committee)
- No documented evidence of response after three cycles of induction chemotherapy (as derived from central independent image review committee visit response data)
- Second primary cancer
- Death due to any cause

#### *Secondary Endpoints*

- Overall response (OR) prior to local therapy, defined as complete response (CR) or partial response (PR) determined on two consecutive occasions  $\geq 4$  weeks apart
- Overall survival, defined as the time between randomization and death due to any cause

- Duration of Response, defined as time between the first tumor assessment that supported patient's OR and the occurrence of an event contributing to primary EFS.

#### Pharmacodynamics

##### *Exploratory endpoint*

Analyses of biomarkers (for available patients), including:

- Correlation of baseline placental growth factor (PIGF)
- Correlation of tumor VEGFA with EFS, OS, and risk factors
- Analyses changes of PIGF over time
- Correlation of PIGF with risk factors

#### Pharmacokinetics

##### *Secondary endpoint*

The pharmacokinetics (PK) of bevacizumab for PK-evaluable paediatric patients in Study BO20924, using a paediatric population PK model

#### Safety

##### *Secondary endpoint*

To determine the safety, tolerability and efficacy of the addition of bevacizumab to chemotherapy as compared to chemotherapy alone in patients presenting with metastatic RMS and NRSTS, as assessed by:

- Adverse event analyses.
- Discontinuation or modification or delay of any treatment element

Clinical assessments included:

- Signs and symptoms, weight, height (sitting and standing), head circumference, and menstrual status.
- Reporting of adverse events (AEs) as per NCI CTCAE version 3
- Standard laboratory investigations including hematology, biochemistry, urinalysis, and a pregnancy test when clinically indicated
- Special investigations (ECG) and echocardiography
- X-ray of the left hand, including the wrist (as assessment of epiphyseal/metaphyseal development), and bone age assessments.

#### **Statistical Methods**

##### *Primary endpoint*

- EFS: data for patients who had not experienced an event by the time of clinical cut-off (31 May 2015) were censored at the date of the last disease assessment prior to the clinical cut-off date. Data for patients who did not have any post-baseline disease assessments were censored at the time of randomization. The two-sided stratified log-rank test was used to compare EFS between the two treatment arms.

### *Secondary endpoints:*

- Objective response rate: patients who had no post-baseline record of tumor assessment were counted as non-responders. Patients without measurable disease at baseline were excluded from the analysis. The difference in objective response rate between the treatment arms was tested in an exploratory manner, using a chi-square test with Schouten correction.
- Overall survival: data for patients without an event at the time of the clinical cut-off were censored at the date they were last known to be alive. Data for patients who did not have any post-baseline information were censored at the date of randomization. The statistical methods used for the OS analysis were the same as those described for the primary endpoint of EFS. As a sensitivity analysis, unstratified analysis of OS was also performed.
- Duration of response: as DoR was only calculated for patients who had an objective response, patients without measurable disease at baseline were excluded from the analysis. The censoring method for DoR was the same as that for EFS. The Kaplan-Meier approach was used to estimate median DoR for each treatment arm. The 95% CI of the median DoR was estimated using the Brookmeyer and Crowley method.

## **Results**

### ***Recruitment/ Number analysed***

The analysis was conducted on the 154 patients in the intent-to-treat population (80 patients in the Chemo arm and 74 patients in the Bv + Chemo arm) unless otherwise specified.

### ***Baseline data***

Baseline disease characteristics were balanced between the study treatment arms. In terms of patients' surgical status at baseline, the primary tumor was intact in the majority of patients. The primary tumor was intact in 55/80 patients in the Chemo arm and 53/74 patients in the Bv + Chemo arm. The most common histological subtype of metastatic RMS in the high- risk group was alveolar RMS (31/40 [77.5%] patients in the Chemo arm and 24/38 patients [63.2%] in the Bv + Chemo arm). The most common histological subtype of RMS in the non highrisk group was embryonal RMS (10/13 patients [76.9%] in the Chemo arm and 8/12 [66.7%] patients in the Bv + Chemo arm).

About one-third of patients had NRSTS: 26 patients (32.5%) in the Chemo arm and 23 patients (31.1%) in the Bv + Chemo arm. Among patients with NRSTS, the most common histological subtype diagnosis was desmoplastic small round cell tumor (7/26 patients [26.9%] in the Chemo arm and 5/23 patients [21.7%] in the Bv + Chemo arm).

**Table 11 Demographics and Baseline Characteristics: Intent-to-Treat Patients**

Demographics and Baseline Characteristics, Intent-to-Treat Patients  
Protocol: BO20924

	Chemo (N=80)	Ev+Chemo (N=74)	Total (N=154)
<b>Sex</b>			
n	80	74	154
Male	40 (50.0%)	45 (60.8%)	85 (55.2%)
Female	40 (50.0%)	29 (39.2%)	69 (44.8%)
<b>Age (years)</b>			
n	80	74	154
Mean (SD)	10.5 (4.8)	10.3 (4.9)	10.4 (4.9)
Median	11.3	11.0	11.1
Q1 - Q3	6.4 - 14.6	5.9 - 14.8	6.1 - 14.6
Min - Max	1 - 18	1 - 18	1 - 18
<b>Age Group - Randomisation Stratification</b>			
n	80	74	154
0.5-<2 years	3 (3.8%)	3 (4.1%)	6 (3.9%)
2-<12 years	39 (48.8%)	38 (51.4%)	77 (50.0%)
12-<18 years	38 (47.5%)	33 (44.6%)	71 (46.1%)
<b>Age Group - Key Binding Element</b>			
n	80	74	154
0.5-<2 years	3 (3.8%)	3 (4.1%)	6 (3.9%)
2-<6 years	15 (18.8%)	16 (21.6%)	31 (20.1%)
6-<10 years	18 (22.5%)	15 (20.3%)	33 (21.4%)
10-<18 years	44 (55.0%)	40 (54.1%)	84 (54.5%)
<b>Age Group - Analysis Stratification</b>			
n	80	74	154
<10 years	36 (45.0%)	34 (45.9%)	70 (45.5%)
>=10 years	44 (55.0%)	40 (54.1%)	84 (54.5%)
<b>Bone Age (Epiphyseal Maturation) at BL</b>			
n	56	51	107
Mean (SD)	10.0 (5.1)	9.9 (5.2)	10.0 (5.1)
Median	10.5	10.0	10.0
Q1 - Q3	5.3 - 14.3	5.0 - 15.0	5.0 - 15.0
Min - Max	2 - 19	2 - 18	2 - 19
<b>Race Category</b>			
n	80	74	154
Asian	1 (1.3%)	1 (1.4%)	2 (1.3%)
Black	2 (2.5%)	1 (1.4%)	3 (1.9%)
Unknown	24 (30.0%)	35 (47.3%)	59 (38.3%)
White	53 (66.3%)	37 (50.0%)	90 (58.4%)

Note: Two patients with missing histology in the data base which were later found to be Wilms tumor for one patient and Ewing's sarcoma for the other one

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Demographics and Baseline Characteristics, Intent-to-Treat Patients  
 Protocol: B020924

	Chemo (N=80)	Ev+Chemo (N=74)	Total (N=154)
<b>Weight at Baseline (kg)</b>			
n	80	74	154
Mean (SD)	38.6 (19.4)	38.4 (19.9)	38.5 (19.6)
Median	36.8	33.0	35.1
Q1 - Q3	21.2 - 52.8	20.2 - 55.0	20.2 - 53.5
Min - Max	10 - 80	10 - 78	10 - 80
<b>Height at Baseline - sitting (cm)</b>			
n	49	40	89
Mean (SD)	74.2 (14.4)	71.6 (13.3)	73.0 (13.9)
Median	76.0	73.0	74.0
Q1 - Q3	63.0 - 85.0	59.0 - 82.0	60.0 - 83.0
Min - Max	49 - 112	52 - 95	49 - 112
<b>Height at Baseline - standing (cm)</b>			
n	79	72	151
Mean (SD)	140.2 (28.3)	141.3 (28.3)	140.7 (28.2)
Median	147.0	144.5	145.0
Q1 - Q3	115.0 - 164.0	119.0 - 166.0	115.0 - 165.0
Min - Max	79 - 185	82 - 191	79 - 191
<b>Head circumference at Baseline (cm)</b>			
n	49	46	95
Mean (SD)	52.9 (3.0)	53.3 (2.7)	53.1 (2.9)
Median	53.0	53.5	53.0
Q1 - Q3	51.0 - 55.0	51.5 - 55.0	51.0 - 55.0
Min - Max	45 - 59	45 - 60	45 - 60
<b>Body Surface Area at Baseline (m2)</b>			
n	79	72	151
Mean (SD)	1.22 (0.43)	1.22 (0.44)	1.22 (0.43)
Median	1.24	1.18	1.21
Q1 - Q3	0.80 - 1.59	0.82 - 1.61	0.82 - 1.59
Min - Max	0.5 - 2.0	0.5 - 2.0	0.5 - 2.0
<b>Performance Status - Karnofsky (%)</b>			
n	36	32	68
10-50	4 (11.1%)	2 (6.3%)	6 (8.8%)
60-70	5 (13.9%)	7 (21.9%)	12 (17.6%)
80-100	27 (75.0%)	23 (71.9%)	50 (73.5%)
<b>Performance Status - Lansky (%)</b>			
n	44	41	85
10-50	4 (9.1%)	3 (7.3%)	7 (8.2%)
60-70	5 (11.4%)	7 (17.1%)	12 (14.1%)
80-100	35 (79.5%)	31 (75.6%)	66 (77.6%)
<b>Randomisation to 1st TRT Dose (days)</b>			
n	79	71	150
Mean (SD)	1.8 (0.9)	1.9 (1.1)	1.9 (1.0)
Median	2.0	2.0	2.0
Q1 - Q3	1.0 - 2.0	1.0 - 2.0	1.0 - 2.0
Min - Max	0 - 4	1 - 5	0 - 5
<b>Randomisation to 1st TRT Dose - Category</b>			
n	79	71	150
<=3 days	75 (94.9%)	61 (85.9%)	136 (90.7%)
>3 days	4 (5.1%)	10 (14.1%)	14 (9.3%)
<b>Histology/Disease Risk</b>			
n	80	74	154
High risk metastatic RMS	40 (50.0%)	38 (51.4%)	78 (50.6%)
Non-high risk metastatic RMS	13 (16.3%)	12 (16.2%)	25 (16.2%)
NRSTS	26 (32.5%)	23 (31.1%)	49 (31.8%)
Missing	1 (1.3%)	1 (1.4%)	2 (1.3%)

Note: Two patients with missing histology in the data base which were later found to be Wilms tumor for one patient and Ewing's sarcoma for the other one

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### ***Pharmacokinetic results***

The PK of bevacizumab for the 70 PK-evaluable paediatric patients from the analysis of Study BO20924 was well characterized by a comprehensive paediatric PopPK model (two-compartment with linear elimination and allometric scaling) consisting of data from 152 paediatric patients across 4 clinical studies. The paediatric PopPK model included data from 39 paediatric patients in Study BO20924 that were initially reported in the planned interim Futility Analysis for the study.

Covariates associated with bevacizumab PK in paediatric patients were similar to those found with adults with body weight (BW), sex (gender), and albumin levels having significant impact on bevacizumab exposure. Compared to BW, body-surface area (BSA) was not found to significantly improve data fitting by the Paed PopPK mode. Importantly, age was not found to be associated with bevacizumab PK when BW was taken into account. No other PK associated covariates were observed for patients in Study BO20924 based on comparisons of key PK parameters between Ped PopPK final model predictions and estimations of observed data. Due to the influence of BW on PK parameters as described in the comprehensive Paed PopPK model, there was a trend toward lower concentrations (C<sub>min</sub> and C<sub>max</sub>) and exposure (AUC) as BW decreased.

Based on observed data from the PK-evaluable paediatric patients in Study BO20924, paediatric PopPK predictions of bevacizumab steady-state trough concentrations (C<sub>ss-min</sub>) were generally found to fall within the 90% prediction intervals (90% PI) of adults when administered the same dosing regimen (7.5 mg/kg q3w [induction therapy phase]). Although bevacizumab concentrations were generally lower in paediatric patients than adults, the Paed PopPK model predicted C<sub>ss-min</sub> to be ~30 mcg/mL or greater, which is similar to adults administered the Study BO20924 dose regimen. Bevacizumab steady-state peak concentrations (C<sub>ss-max</sub>) and exposure (AUC<sub>ss</sub>) tended to fall below the 90% PI of adults as BW decreased. The cause for C<sub>max</sub> and AUC to fall below the 90% PI for adults is unknown as there are no adult patients with sarcomas represented in the Adult PopPK model to compare against paediatric patients with sarcomas.

### ***Efficacy results***

#### **Primary endpoint**

No statistically significant improvement was seen in the Bv + Chemo arm over the Chemo arm with respect to the primary endpoint of EFS as assessed by IRC. HR was 0.93 (95% CI: 0.61, 1.41; p-value = 0.72).

**Table 13 Event-Free Survival: Intent-to-Treat Patients (IRC Assessment)**

Time to Event Summary for Event-Free Survival (IRC Assessed), Intent-to-Treat Patients  
 Protocol: BO20924

	Chemo (N=80)	Bv+Chemo (N=74)
Patients with event (%)	42 (52.5%)	51 (68.9%)
Earliest contributing event		
Death	18	22
No evidence of response after 3 cycles	5	0
Tumor progression	18	28
Tumor recurrence	1	1
Patients without event (%)	38 (47.5%)	23 (31.1%)
Time to event (months)		
Median	14.85	20.63
95% CI for Median	(10.84, 35.88)	(15.15, 24.87)
25% and 75%-ile	7.29, NE	12.52, 35.91
Range	0.0 to 62.8	0.0 to 60.6
Stratified Analysis		
p-value (log-rank)		0.7189
Hazard Ratio		0.93
95% CI		(0.61, 1.41)
Unstratified Analysis		
p-value (log-rank)		0.9393
Hazard Ratio		0.98
95% CI		(0.65, 1.48)

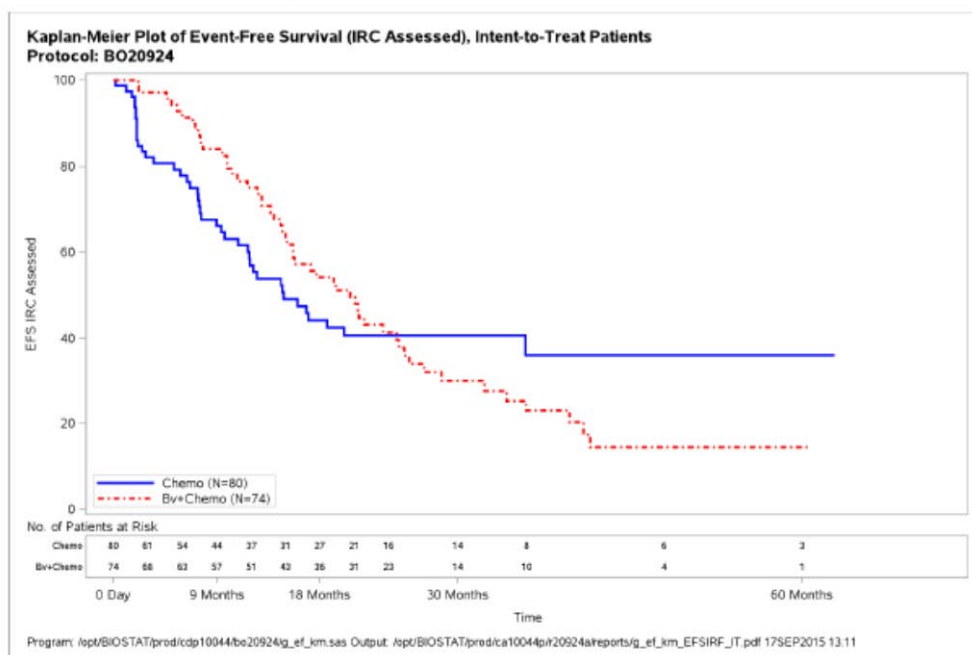
Event: Tumor progression (IRC assessed), tumor recurrence (IRC assessed), second primary cancer, no evidence of response after 3 cycles of induction, or death due to any cause;  
 Censoring: last tumor assessment of non-PD, or at randomization for those without post-BL assessment  
 Summaries of Time-to-Event Endpoint (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: Age and Histology/Disease Risk. Hazard ratios were estimated by Cox regression. Adjusted hazard ratios and p-values are adjusted for covariates Age and Histology/Disease Risk.

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**Figure 6 Kaplan-Meier Plot of IRC-Assessed Event-Free Survival: Intent-to-Treat Population**



Source: [g\\_ef\\_km\\_EFSIRF\\_IT](#)

The median EFS was 14.9 months (95% CI 10.8, 35.9) in the Chemo arm and 20.6 months (95% CI 15.2, 24.9) in the Bv + Chemo arm. KM estimate for event-free survival rate at 12 months was 57.0% in the Chemo arm and 75.2% in the Bv + Chemo arm; and at 18 months was 44.3% in the Chemo arm and 54.3% in the Bv + Chemo arm. The Kaplan-Meier (KM) curves crossed at approximately 24 months after randomization

**Table 14 Kaplan-Meier Estimate Rates for Event-Free Survival (IRC Assessed) over Time, Intent-to-Treat Patients**

Kaplan-Meier Event-Free Rates for Event-Free Survival (IRC Assessed) over Time, Intent-to-Treat Patients  
Protocol: B020924

	Time Point	Patients at Risk	Number of Events	Patients Censored	KM-Estimate for Event-free Rate (%)	95% CI for KM-Estimate
Chemo (N=80)	Day 1	80	0	1	100.00	NE
	1/2 Year	54	17	9	77.93	(66.88, 85.67)
	1 Year	37	31	12	57.01	(44.62, 67.62)
	1 1/2 Years	27	39	14	44.30	(32.22, 55.69)
	2 Years	16	41	23	40.74	(28.82, 52.31)
Bv+Chemo (N=74)	Day 1	74	0	2	100.00	NE
	1/2 Year	64	6	5	91.36	(81.78, 96.03)
	1 Year	51	17	6	75.18	(63.10, 83.76)
	1 1/2 Years	36	31	7	54.26	(41.68, 65.23)
	2 Years	23	39	12	41.42	(29.41, 53.00)

Event: Tumor progression (IRC assessed), tumor recurrence (IRC assessed), second primary cancer, no evidence of response after 3 cycles of induction, or death due to any cause;  
Censoring: last tumor assessment of non-PD, or at randomization for those without post-BL assessment  
Z-test using the standard errors for the KM-estimates computed via the Greenwood method

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Four sensitivity analyses of EFS were performed to assess the robustness of the primary analysis:

- Investigator-evaluated EFS

Investigator-evaluated EFS was similar to the IRC-evaluated EFS, and was not significantly different between treatment arms: HR was 0.71 (95% CI: 0.47, 1.07; pvalue = 0.10). The Kaplan-Meier estimate of the median EFS was 12.5 months (95% CI: 9.3, 18.6) in the Chemo arm and 18.9 months (95% CI: 14.7, 25.4) in the Bv + Chemo arm.

A concordance analysis was performed on the ITT population. The concordance rates (i.e., for EFS events assessed with less than 14 days apart between investigator and IRC assessment, or agreement on the absence of event assessed by either) were 63.8% (51/80) for patients in the Chemo arm and 45.9% (34/74) for patients in the Bv + Chemo arm.

For 14 patients in the Chemo arm and 22 patients in the Bv+ Chemo Arm, the EFS event as assessed by IRC occurred later than the investigator-assessed EFS event. A time-sensitive radiological review committee was responsible for the confirmation of the patient's status of "treatment failure," after 3 cycles of induction therapy. This review was performed in an ongoing manner at the request of the investigator.

- There were 7 patients who were assessed by the investigator as having experienced insufficient therapeutic response. The investigator's assessment was confirmed by the committee in 5 cases. Unstratified EFS



Using a Cox proportional hazards model, the unstratified analysis of the IRC-assessed EFS gave similar results to the stratified analysis: HR was 0.98 (95% CI: 0.65, 1.48; p-value = 0.94). See table13 above

- IRC-evaluated EFS, censoring EFS at initiation of non-protocol anti-cancer treatment

A sensitivity analysis was performed with data censored at the time patients started a non-protocol anti-cancer therapy (before experiencing an EFS event). This analysis was stratified by age and histology/disease risk. The HR was 0.85 (95% CI 0.49, 1.46; p-value = 0.56). This EFS estimate was consistent with the results of the primary analysis.

**Table 16 EFS Evaluated by IRC: Data Censored at the Time Patients Began a New Anti-Cancer Therapy before Experiencing an EFS Event (Intent-to-Treat Population)**

Time to Event Summary for Event-Free Survival (IRC Assessed) Censored at the Time Patients Begin a New Anti-Cancer Therapy Before Experiencing an Event-Free Survival Event, Intent-to-Treat Patients  
Protocol: B020924

	Chemo (N=80)	Bv+Chemo (N=74)
Patients with event (%)	27 (33.8%)	30 (40.5%)
Earliest contributing event		
Death	5	3
No evidence of response after 3 cycles	5	0
Tumor progression	17	26
Tumor recurrence	0	1
Patients without event (%)	53 (66.3%)	44 (59.5%)
Time to event (months)		
Median	35.88	23.49
95% CI for Median	(12.16, NE)	(15.67, 39.69)
25% and 75%-ile	7.36, NE	13.67, NE
Range	0.0 to 62.8	0.0 to 60.6
Stratified Analysis		
p-value (log-rank)		0.5556
Hazard Ratio		0.85
95% CI		(0.49, 1.46)
Unstratified Analysis		
p-value (log-rank)		0.7174
Hazard Ratio		0.91
95% CI		(0.54, 1.53)

Event: Tumor progression (IRC assessed), tumor recurrence (IRC assessed), second primary cancer, no evidence of response after 3 cycles of induction, or death due to any cause; Censoring: new anti-cancer therapy, or last tumor assessment of non-PD, or at randomization for those without post-BL assessment  
Summaries of Time-to-Event Endpoint (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: Age and Histology/Disease Risk. Hazard ratios were estimated by Cox regression. Adjusted hazard ratios and p-values are adjusted for covariates Age and Histology/Disease Risk.

Program: /opt/BIOSAT/prod/cdpl0044/bo20924/t\_ef\_tte.sas  
Output: /opt/BIOSAT/prod/cal0044p/r20924a/reports/t\_ef\_tte\_EFSANI\_II.out  
19AUG2015 17:07

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- IRC-evaluated EFS, censoring EFS at early discontinuation of all study treatment.

A sensitivity analysis was performed with data censored at the time patients discontinued all study treatment early for any reason (before experiencing an EFS event). This analysis was stratified by age and histology/disease risk. The HR was 1.19 (95% CI 0.74, 1.93; p-value = 0.48).

**Table 17 EFS Evaluated by IRC: Data Censored at the Time Patients Discontinued Study Treatment due to Any Reason before Experiencing an EFS Event (Intent-to-Treat Patients)**

Time to Event Summary for Event-Free Survival (IRC Assessed) Censored at the Time Patients Discontinue Study Treatment Due to any Reason Before Experiencing an Event-Free Survival Event, Intent-to-Treat Patients  
Protocol: BO20924

	Chemo (N=80)	Bv+Chemo (N=74)
Patients with event (%)	28 (35.0%)	47 (63.5%)
Earliest contributing event		
Death	12	19
No evidence of response after 3 cycles	1	0
Tumor progression	14	27
Tumor recurrence	1	1
Patients without event (%)	52 (65.0%)	27 (36.5%)
Time to event (months)		
Median	20.07	21.29
95% CI for Median	(12.48, NE)	(15.15, 25.76)
25% and 75%-ile	9.66, NE	12.91, 35.91
Range	0.0 to 62.6	0.0 to 60.6
Stratified Analysis		
p-value (log-rank)		0.4784
Hazard Ratio		1.19
95% CI		(0.74, 1.93)
Unstratified Analysis		
p-value (log-rank)		0.2914
Hazard Ratio		1.29
95% CI		(0.80, 2.06)

Event: Tumor progression (IRC assessed), tumor recurrence (IRC assessed), second primary cancer, no evidence of response after 3 cycles of induction, or death due to any cause; Censoring: discontinue study treatment, or last tumor assessment of non-PD, or at randomisation for those without post-BL assessment  
Summaries of Time-to-Event Endpoint (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: Age and Histology/Disease Risk. Hazard ratios were estimated by Cox regression. Adjusted hazard ratios and p-values are adjusted for covariates Age and Histology/Disease Risk.

Program: /opt/BIOSTAT/prod/cdp10044/bo20924/t\_ef\_tte.sas  
Output: /opt/BIOSTAT/prod/cal0044p/r20924a/reports/t\_ef\_tte\_EFS\_DSC\_IT.out  
19AUG2015 17:08

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## **Secondary endpoints**

### *Overall survival*

As of the clinical cutoff date, 31 May 2015, 37 patients (46.3%) in the Chemo arm and 34 patients (45.9%) in the Bv + Chemo arm had died. The OS analysis at this stage is not mature as over 50% of the patients are still alive. The HR was estimated using a Cox proportional hazards model stratified by age and histology/disease risk. The addition of bevacizumab to standard of care chemotherapy did not result in a significant reduction in the risk of death (HR 0.79, 95% CI 0.49, 1.26; p-value = 0.32) (Table 18). Similar results were obtained from the unstratified analysis.

**Table 18 Time to Event Summary for Overall Survival: Intent-to-Treat Patients**

Time to Event Summary for Overall Survival, Intent-to-Treat Patients  
Protocol: B020924

	Chemo (N=80)	Bv+Chemo (N=74)
Patients with event (%)	37 (46.3%)	34 (45.9%)
Earliest contributing event		
Death	37	34
Patients without event (%)	43 (53.6%)	40 (54.1%)
Time to event (months)		
Median	42.18	32.30
95% CI for Median	(18.63, NE)	(25.33, NE)
25% and 75%-ile	13.08, NE	19.22, NE
Range	0.0 to 77.1	0.0 to 68.2
Stratified Analysis		
p-value (log-rank)		0.3207
Hazard Ratio		0.79
95% CI		(0.49, 1.26)
Unstratified Analysis		
p-value (log-rank)		0.4302
Hazard Ratio		0.63
95% CI		(0.52, 1.32)

Event: Death due to any cause; Censoring: time patient last known to be alive  
Summaries of Time-to-Event Endpoint (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: Age and Histology/Disease Risk. Hazard ratios were estimated by Cox regression. Adjusted hazard ratios and p-values are adjusted for covariates Age and Histology/Disease Risk.

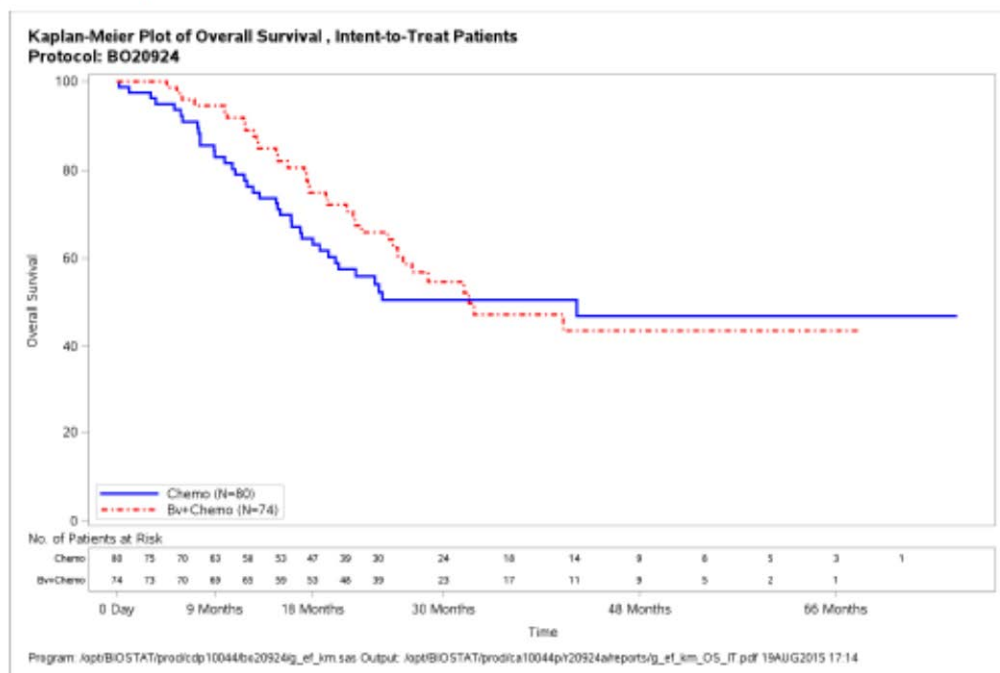
Program: /opt/BIOSTAT/prod/cdpl0044/b020924/t\_ef\_tte.sas  
Output: /opt/BIOSTAT/prod/cal0044p/r20924a/reports/t\_ef\_tte\_OS\_IT.out  
19AUG2015 17:09

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Source: [t\\_ef\\_tte\\_OS\\_IT](#)

The Kaplan-Meier plots of OS are shown in [Figure 8](#).

**Figure 8 Kaplan-Meier Plot of Overall Survival: Intent-to-Treat Patients**



Source: [g\\_ef\\_km\\_OS\\_IT](#)

## Objective Response Rate

Objective response prior to first local therapy was defined as a complete response (CR) or partial response (PR) determined on two consecutive occasions  $\geq 4$  weeks apart as assessed by RECIST v1.0. For the ORR analysis, patients without measurable disease at baseline were excluded.

Per IRC, clinically meaningful difference in ORR was seen between the two treatment arms: 27/75 patients (36.0%, 95% Clopper-Pearson CI: 25.2%, 47.9%) in the Chemo arm and 34/63 patients (54.0%, 95% Clopper-Pearson CI: 40.9%, 66.6%) in the Bv + Chemo arm were assessed as having had a confirmed response prior to receiving any local therapy in Study BO20924. The difference in response rates between arms was 18.0% (95% Hauck-Anderson CI: 0.6%, 35.3%; p-value = 0.04).

**Table 19 Objective Response Rate Prior to First Local Therapy (IRC Assessed): Intent-to-Treat Patients**

Objective Response Rate Prior to First Local Therapy (IRC assessed), Intent-to-Treat Patients  
Protocol: BO20924

	Chemo (N=80)	Bv+Chemo (N=74)
Responders	27 (36.0%)	34 (54.0%)
Non-Responders	48 (64.0%)	29 (46.0%)
95% CI for Response Rate (Clopper-Pearson)	(25.23, 47.91)	(40.94, 66.61)
Difference in Response Rates		17.97
95% CI for Difference in Response Rates (Hauck-Anderson)		(0.64, 35.30)
p-Value (Chi-square with Schouten Correction)		0.0422
Odds Ratio*		2.08
95% CI for Odds Ratio*		(1.05, 4.13)

Patients with a measurable disease at Baseline are included.

Patients without a Post-Baseline tumor assessment are considered as Non-Responders.

\* Wald confidence interval/test

Program: /opt/BIOSTAT/prod/cdpl0044/bo20924/t\_ef\_orr.sas  
Output: /opt/BIOSTAT/prod/cal0044p/r20924a/reports/t\_ef\_orr\_IT.out  
17SEP2015 15:55

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Source: [t\\_ef\\_orr\\_IT](#)

## Duration of Response

Twenty-seven patients in the Chemo arm and 34 patients in the Bv + Chemo arm had an objective response and were included in the analysis of DoR, defined as the time from the first tumor assessment that supported assessment of a confirmed overall response, until the occurrence of an event contributing to the primary endpoint of EFS. Of the patients included in the DoR analysis, 11/27 patients (40.7%) in the Chemo arm and 26/34 patients (76.5%) in the Bv + Chemo arm had experienced EFS events after their confirmed objective response. The KM curve of DoR in the Chemo arm did not cross 50%. The Kaplan-Meier estimate of median DoR was 17.5 months (Brookmeyer-Crowley 95% CI: 12.3, 25.2) in the Bv + Chemo arm. The censoring methods for the DoR analysis were the same as those used for patients in the EFS analysis.



**Table 20 Duration of Response: Intent-to-Treat Patients**

Duration of Response (IRC Assessed), Intent-to-Treat Patients  
 Protocol: B020924

	Chemo (N=80)	Bv+Chemo (N=74)
Patients included in analysis	27 (100.0%)	34 (100.0%)
Patients with event (%)	11 ( 40.7%)	26 ( 76.5%)
Earliest contributing event		
Death	6	10
Tumor progression	5	16
Patients without event (%)	16 ( 59.3%)	8 ( 23.5%)
Time to event (months)		
Median	NE	17.48
95% CI for Median	(10.18, NE)	(12.29, 25.23)
25% and 75%-ile	10.02, NE	11.04, 30.49
Range	4.2 to 60.7	5.0 to 57.4

Event: Tumor progression (IRC assessed), tumor recurrence (IRC assessed), second primary cancer, no evidence of response after 3 cycles of induction, or death due to any cause;  
 Censoring: last tumor assessment of non-PD  
 Summaries of Time-to-Event Endpoint (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.

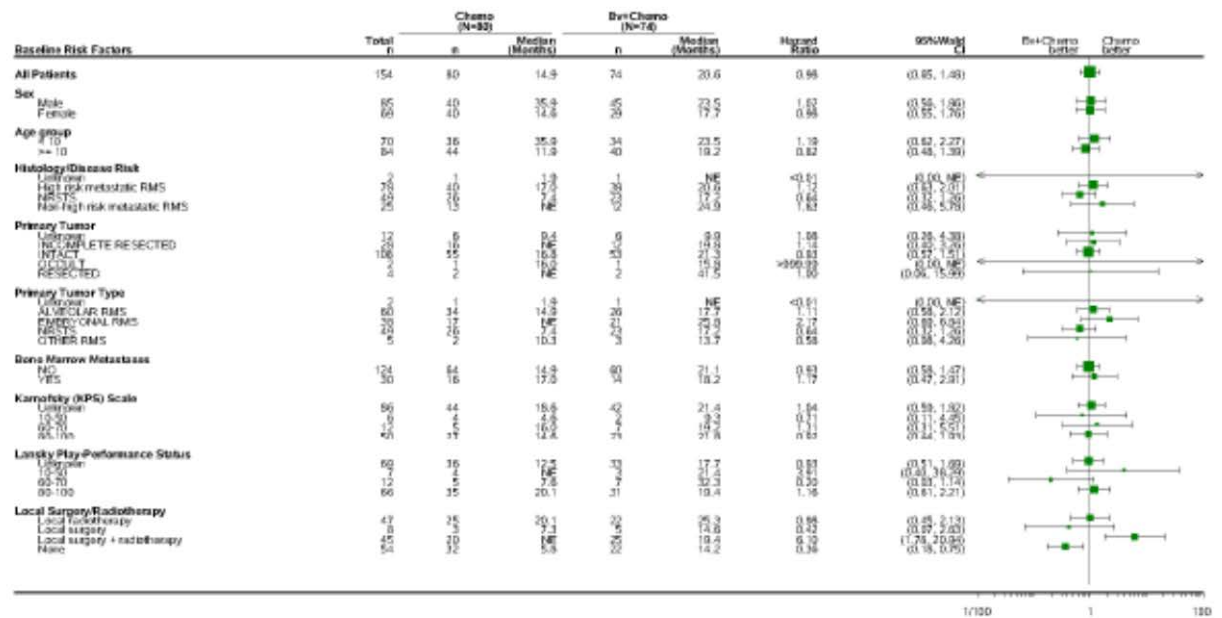
Program: /opt/BIOSTAT/prod/cdpl0044/bo20924/t\_ef\_tte.sas  
 Output: /opt/BIOSTAT/prod/cal0044p/r20924a/reports/t\_ef\_tte\_DORIRF\_IT.out  
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 Source: t\_ef\_tte\_DORIRF\_IT

### Subgroup Analyses

Subgroup analyses were performed for IRC-assessed EFS using the following factors: sex, age group, histology/disease risk, status of primary tumor, primary tumor type, and presence of bone marrow metastases, Karnofsky scale, Lansky Play-Performance Status, and history of local surgery/radiotherapy during the study. The results for these subgroups were consistent with the results of the primary analysis (see Figure 9) except for patients with local surgery and radiotherapy and patients without any local therapy. Due to small numbers of patients in these subgroups, no conclusion could be drawn.

**Figure 9 Forest Plot of Hazard Ratio for Event-Free Survival (IRC Assessed) by Subgroup: Intent-to-Treat Patients**

**Forest Plot of Hazard Ratio for Event-Free Survival (IRC Assessed) by Subgroup, Intent-to-Treat Patients  
Protocol: BO20924**



RMS reported by primary tumor type can be either high risk or non-high risk metastatic RMS as defined in the protocol. Other RMS include SPINDLE CELLS/LEIOMIOMATOUS RMS, BOTRYOID RMS, and NOT OTHERWISE SPECIFY RMS.  
Program: /opt/BIOSTAT/prod/cdp10044/bo20924/ig\_ef\_fp.sas Output: /opt/BIOSTAT/prod/cdp10044pr20924a/reports/ig\_ef\_fp\_EFSIRF\_FT.pdf 26OCT2015 12:34

**Subsequent Treatment after Study Treatment Discontinuation**

Drug Therapies for Cancer Among the patients in the ITT population, 38 patients in the Chemo arm (47.5%) and 30 patients (40.5%) in the Bv + Chemo arm received subsequent treatment for cancer after discontinuation of study treatment in Study BO20924.

Among the patients in the ITT population, 22 patients in the Chemo arm (27.5%) and 18 patients (24.3%) in the Bv + Chemo arm underwent additional radiotherapy after discontinuation of study treatment in Study BO20924. In the cases where a site was specified, the most common location of therapy was bone (6 patients [7.5%] in the Chemo arm and 4 patients [5.4%] in the Bv + Chemo arm).

Among the patients in the ITT population, 12 patients in the Chemo arm (15.0%) and 11 patients (14.9%) in the Bv + Chemo arm underwent a surgical procedure after discontinuation of study treatment in Study BO20924. Three patients (3.8%) who had participated in the Chemo arm of Study BO20924 underwent an additional surgical procedure: aspiration biopsy, cystoscopy, and ureteroscopy, respectively. No additional surgical procedures were reported among patients who had participated in the Bv + Chemo arm.

Eleven patients (13.8%) in the Chemo arm and 11 patients (14.9%) in the Bv + Chemo arm underwent additional surgeries after discontinuation of study treatment.

## Biomarker analyses

Biomarker analyses were performed on patients from the ITT population who consented to participate in the translational research program and for whom samples were available at baseline. A total of 77 patients (48 in the Chemo arm and 29 in the Bv + Chemo arm) had PIGF measurements at baseline and on study (Cycle 5 Day 1) and 52 patients (29 in the Chemo arm and 23 in the Bv + Chemo arm) had tumor VEGF-A (tVEGFA) measurements at baseline.

### PIGF analysis

**Table 23 Distribution of PIGF Levels between Treatment Arms.**

Placental Growth Factor - Exploratory Biomarker, Biomarker Patients (PGF)  
Protocol: B020924

	Chemo (N=48)	Bv+Chemo (N=29)
n	48	29
Mean	147.40	90.13
SD	187.10	97.58
Median	71.31	60.92
Min - Max	9.0 - 858.4	22.4 - 470.8
25th - 75th percentile	34.36 - 159.01	41.78 - 92.11
CV (%)	126.9	108.3
SE	27.0	18.1

Program: /opt/BIOSTAT/prod/cdpl0044/bc20924/t\_bm\_pgf\_explo.sas  
Output: /opt/BIOSTAT/prod/cal0044p/s20924a/reports/t\_bm\_pgf\_explo\_BMP.out  
15OCT2015 14:56

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Source: t\_bm\_pgf\_explo BMP

EFS analysis in the PIGF-evaluable population showed corresponding results to those observed for the ITT population. An HR of 0.83 (95% CI: 0.43, 1.59) was observed in the Chemo arm vs. the Bv + Chemo arm in the PIGF-evaluable population

The ITT population results overall showed an HR of 0.93 (95% CI: 0.61, 1.41; p-value = 0.72) (Table 13). Furthermore, no significant change was seen in the EFS analysis comparing the Chemo arm with the Bv + Chemo arm for the baseline high PIGF level subgroup dichotomized at the first quartile (HR = 0.85; 95% CI: 0.38, 1.89), median (HR= 1.22; 95% CI: 0.49, 3.06) and third quartile (HR = 0.69; 95% CI: 0.18, 2.71)

OS analysis in the PIGF-evaluable population also showed similar results to those observed for the ITT population: an HR of 0.64 (95% CI: 0.30, 1.35) was observed in the Chemo arm versus the Bv + Chemo arm in this population (ITT population results: HR 0.79; 95% CI 0.49, 1.26; p-value = 0.32)]. No significant change was seen in the OS analysis comparing the Chemo arm with the Bv + Chemo arm for the baseline high PIGF level subgroup dichotomized at the first quartile (HR = 0.64; 95% CI: 0.26, 1.61), median(HR = 0.65; 95% CI: 0.21, 1.98) and third quartile (HR = 0.44; 95% CI: 0.09, 2.07).

In a Cox regression analysis for OS including trial treatment, baseline biomarker level dichotomized at quartiles and the interaction term of treatment by biomarker level, there was no indication of a treatment by biomarker level interaction.

Based on the limited data, no predictive value could be concluded for baseline PIGF as a biomarker for the efficacy of bevacizumab treatment. Additionally, the correlation was examined between PIGF levels and patient risk factors reported at baseline. A correlation was noted between PIGF levels and bone marrow metastases at baseline. Among the low PIGF level group, 37/39 patients (94.9%) did not have bone marrow metastases vs. 27/38 patients (71.1%) in the high-PIGF group (p = 0.01). Another correlation was also noted between PIGF levels and histology/disease risk at baseline. Among the high

PIGF level group, 27/38 patients (71.1%) had high risk metastatic RMS, 4/38 patients (10.5%) had NRSTS and 7/38 patients (18.4%) had non-high risk metastatic RMS vs. 14/39 patients (35.9%), 20/39 (51.3%), and 5/39 (12.8%), respectively, in the low PIGF level group ( $p = 0.01$ ).

Previous biomarker analyses have described an increase in the circulating concentration of PIGF in response to VEGF-targeted treatment as a pharmacodynamic marker but not as a predictive marker (Batchelor 2006, Rini 2008, Willett 2009). In the Bv + Chemo arm no increase in PIGF levels was observed from baseline to Cycle 5 Day 1 and maintenance therapy Cycle 5 Day1.

#### Tumor VEGFA

**Table 28 tVEGFA Levels in Biomarker-Evaluable Patients**

tVEGFA - Exploratory Biomarker, Biomarker Patients (IHC)  
Protocol: BO20924

	Chemo (N=29)	Bv+Chemo (N=23)
n	29	23
Mean	154.07	108.04
SD	73.04	47.98
Median	140.00	100.00
Min - Max	13.0 - 300.0	0.0 - 200.0
25th - 75th percentile	105.00 - 200.00	100.00 - 140.00
CV (%)	47.4	44.4
SE	13.6	10.0

Program: /opt/BIOSTAT/prod/cdp10044/bo20924/t\_bm\_vegfa\_explo.sas  
Output: /opt/BIOSTAT/prod/cal0044p/r20924a/reports/t\_bm\_vegfa\_explo\_BMI.out  
19AUG2015 17:30

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Source: t bm vegfa explo BMI

Analyses of EFS and OS by tVEGFA (IHC assessed) shows a HR of 1.48 (95% CI: 0.67, 3.28) and for OS analysis it was 0.91 (95% CI: 0.38, 2.19) in the Chemo arm vs. the Bv + Chemo arm in the tVEGFA-evaluable population. Furthermore, no significant change was seen for the baseline high tVEGFA level subgroup dichotomized at the first quartile (HR = 1.48; 95% CI: 0.50, 4.39) and median (HR= 1.36; 95% CI: 0.36, 5.10) for EFS analysis, as well for the OS analysis dichotomized at the first quartile (HR = 0.84; 95% CI: 0.25, 2.87) and median (HR = 0.81; 95% CI: 0.20, 3.28).

In a Cox regression analysis for OS including trial treatment, baseline biomarker level and the interaction term of treatment by biomarker level, there was no indication of a treatment by biomarker level interaction. Based on the limited data, no predictive value could be concluded for baseline tVEGFA as a biomarker for the efficacy of bevacizumab treatment.

#### Safety results

Of the 154 patients in the Intent-to-Treat population, 4 patients did not receive any study treatment. The remaining 150 patients were included in the safety-evaluable population (79 in the Chemo arm and 71 in the Bv + Chemo arm).

Key safety data include the following:

Overall, the toxicity profile observed in Study BO20924 patients appears to be that which might be expected in adults exposed to bevacizumab and the chemotherapy backbone in the disease under study. All patients in the safety-evaluable population experienced at least one adverse event (AE). No fatal AEs were reported. All deaths were attributed to disease progression.

68 of 79 patients (86.1%) in the Chemo arm and 66 of 71 patients (93.0%) in the Bv + Chemo arm experienced at least one SAE. The SAEs that were reported at an incidence > 5% in patients receiving Bv + Chemo were:

- Febrile neutropenia (46 patients [64.8%])
- Febrile bone marrow aplasia (19 patients [26.8%])
- Pyrexia (14 patients [19.7%])
- Mucosal inflammation (10 patients [14.1%])
- Vomiting (8 patients [11.3%])
- Weight decreased (5 patients [7.0%])
- Anaemia (4 patients [5.6%])
- Neutropenic infection (4 patients [5.6%])
- Seizure (4 patients [5.6%])
- Diarrhea (4 patients [5.6%])
- Decreased appetite (4 patients [5.6%]).

AEs that led to study chemotherapy discontinuation were reported in a total of 12 patients: 6 patients in the Chemo arm and 6 patients in the Bv + Chemo arm. AEs that led to bevacizumab discontinuation were reported in a total of 8 patients (left ventricular dysfunction most commonly reported as causing discontinuation [3/8 patients]).

79 patients [100%] in the Chemo arm and 70 patients [98.6%] in the Bv + Chemo arm experienced at least one Grade 3 – 5 AE. The total numbers of Grade 3-5 AEs were higher in the Bv + Chemo arm. Three Grade  $\geq$  3 AEs were reported with at least a 10% difference in frequency between treatment arms: neutropenia, anaemia, and febrile bone marrow aplasia, which were all more frequently reported in the Bv + Chemo arm. Forty-six patients (64.8%) in the Bv + Chemo arm experienced at least one adverse event of special interest (AESI), versus 32 patients (40.5%) in the Chemo arm. The rate of  $\geq$  Grade 3 AESIs was equivalent between the two study treatment arms: 12.7% in each arm.



**Table 47 Grade 3-5 Adverse Events of Special Interest by Body System and Trial Treatment, Safety-Evaluable Patients**

Grade 3-5 Adverse Events of Special Interest by Body System and Trial Treatment, Safety-Evaluable Patients  
Protocol: B020924

MedDRA System Organ Class MedDRA Preferred Term	Chemo (N=79)	Bv+Chemo (N=71)
Total number of patients with at least one adverse event	10 (12.7%)	9 (12.7%)
Overall total number of events	14	9
<b>HEMORRHAGE</b>		
Total number of patients with at least one adverse event	6 (7.6%)	2 (2.8%)
Total number of events	10	2
HAEMATURIA	3 (3.8%)	0
EPISTAXIS	1 (1.3%)	1 (1.4%)
CEREBRAL HAEMORRHAGE	0	1 (1.4%)
MENOMETRORRHAGIA	1 (1.3%)	0
METRORRHAGIA	1 (1.3%)	0
TUMOUR HAEMORRHAGE	1 (1.3%)	0
<b>THROMBOEMBOLIC EVENTS (ARTERIAL)</b>		
Total number of patients with at least one adverse event	3 (3.8%)	1 (1.4%)
Total number of events	3	1
ATRIAL THROMBOSIS	1 (1.3%)	0
EMBOLISM	1 (1.3%)	0
MONOPARESIS*	0	1 (1.4%)
PARAPARESIS*	1 (1.3%)	0
<b>CHF</b>		
Total number of patients with at least one adverse event	0	2 (2.8%)
Total number of events	0	2
CARDIAC FAILURE	0	1 (1.4%)
LEFT VENTRICULAR DYSFUNCTION	0	1 (1.4%)
<b>GI PERFORATION ABSCESS AND FISTULA</b>		
Total number of patients with at least one adverse event	0	2 (2.8%)
Total number of events	0	2
ABDOMINAL ABSCESS	0	1 (1.4%)
ANAL FISTULA	0	1 (1.4%)
<b>WOUND HEALING COMPLICATIONS</b>		
Total number of patients with at least one adverse event	0	2 (2.8%)
Total number of events	0	2
IMPAIRED HEALING	0	1 (1.4%)
WOUND DEHISCENCE	0	1 (1.4%)
<b>THROMBOEMBOLIC EVENTS (VENOUS)</b>		
Total number of patients with at least one adverse event	1 (1.3%)	0
Total number of events	1	0
VENOOCCLUSIVE DISEASE	1 (1.3%)	0

Investigator text for AEs encoded using MedDRA version 18.0  
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.  
Includes AEs with onset from first dose of study drug through 183 days after last dose of study drug. AEs may appear under more than one category.

\* The terms monoparesis and paraparesis code to the Standard MedDRA query (SMQ) of Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous which was included in the search strategy defined to identify thromboembolic events (arterial). Per protocol these events are not considered AESIs for this study.

Program: /opt/BIOSTAT/prod/cdp10044/bo20924/t\_ae\_ctc35i.sas  
Output: /opt/BIOSTAT/prod/ca10044p/r20924a/reports/t\_ae\_ctc35i\_SE.out  
28AUG2015 15:53

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As of the clinical cutoff date, no pregnancies had been reported on study.

Bone toxicity was monitored by qualitative observations from X-rays of the patient's left wrist and the development of any skeletal abnormalities, as indicated by the occurrence of symptoms, in particular pain associated with bones or joints. More patients in the Bv + Chemo arm (16 of 71 patients [22.5%]): than in the Chemo arm (12 of 79 patients [15.2%]) arm experienced at least one qualifying bone toxicity AE. Among these, the most common bone toxicities were arthralgia (10 patients [14.1%] in the Bv + Chemo arm vs. 8 patients [10.1%] in the Chemo arm); bone pain (4 patients [5.6%] in the Bv + Chemo arm vs. 2 patients [2.5%] in the Chemo arm); and foot fracture (2 patients [2.8%] in the Bv + Chemo arm vs. no patients in the Chemo arm). No AEs of osteonecrosis were reported in either treatment arm.

Seventy-nine patients in the Chemo arm (median height 147.0 cm) and 70 patients in the Bv + Chemo arm (median height 147.0 cm) were evaluated for standing height at baseline from the safety-evaluable population. At follow-up, 19 patients (24.1%) in the Chemo arm and 17 patients (23.9%) in

the Bv + Chemo arm were evaluated as pre-pubertal. No clear pattern was observed on standing height between arms.

At baseline, 49 patients in the Chemo arm and 40 patients in the Bv + Chemo arm were evaluated for sitting height. Too few patients (fewer than 20 in either arm at any time point after baseline) had subsequent evaluations performed to allow conclusions to be drawn regarding differences between treatment arms in changes from baseline. The difference in sample sizes between standing/lying and sitting height was mainly due to the patients' clinical status but also to the difficulty of measuring sitting height in a population of young patients

### **2.3.3. Conclusion on clinical aspects**

As also concluded by the MAH Study BO20924 did not meet its primary endpoint of improved EFS in the Bv + Chemo arm. HR for IRC-assessed EFS was estimated as 0.93 (95% CI: 0.61, 1.41; p-value = 0.72). Per IRC, clinically meaningful difference in ORR was seen between the two treatment arms: 27/75 patients (36.0%, 95% CI: 25.2%, 47.9%) in the Chemo arm and 34/63 patients (54.0%, 95% CI: 40.9%, 66.6%) in the Bv + Chemo arm were assessed as having had a confirmed response prior to receiving any local therapy in Study BO20924.

Additional subgroup analysis performed for the IRC assessed EFS were consistent with the primary analysis with the exception of patients with local surgery radiotherapy and patients without any local therapy. Due to small numbers of patients in these subgroups, no conclusion could be drawn.

Biomarker analyses did not show any useful results.

The safety profile observed in Study BO20924 patients appeared to be largely consistent with that which might be expected in adults exposed to bevacizumab and/or the chemotherapy backbone in the disease. The Pharmacokinetics of paediatric patients in Study BO20924 were well characterized by a paediatric PopPK model, with similar PK-associated covariates as in adults, and with the expected bevacizumab PK with a slow systemic clearance, volume of distribution that approximates the plasma volume, and long half-life.

. An addendum CSR is expected to be generated in the third quarter of 2019, when the OS endpoint has been reached and Study BO20924 has been completed. Updated OS results as well as safety data will be made available at that time and the benefit-risk reassessed.

## **3. CHMP's overall conclusion and recommendation**

Roche Registration Ltd has submitted a completed paediatric study for Avastin in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The provided study, BO20924 (BERNIE), a randomized, comparative, open-label, multi-center Phase II study evaluating the benefit of the addition of bevacizumab to chemotherapy in children and adolescent patients presenting with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma, did not meet its primary endpoint of improved EFS in the Bv + Chemo arm. It is agreed, that based on the presented data, the benefit-risk of the addition of bevacizumab to multimodal therapy in this population is not possible to assess. When the updated OS results as well as safety data will be made available in 2019 re-assessment may be conducted in order to further pursue the benefit risk in the metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma indication. The MAH has indicated that a variation is to be submitted in 2016 in order to update the SmPC with paediatric data. This is endorsed.

