Report on the Deliberation Results

November 6, 2020

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	(a) Braftovi Capsules 50 mg (b) Braftovi Capsules 75 mg
Non-proprietary Name	Encorafenib (JAN*)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	(a) March 4, 2020 (b) August 26, 2020

Results of Deliberation

In its meeting held on October 30, 2020, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 5 years and 10 months.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

October 21, 2020
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	(a) Braftovi Capsules 50 mg (b) Braftovi Capsules 75 mg
Non-proprietary Name	Encorafenib
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	(a) March 4, 2020 (b) August 26, 2020
Dosage Form/Strength	(a) Capsules: Each capsule contains 50 mg of encorafenib (b) Capsules: Each capsule contains 75 mg of encorafenib
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	Priority review (PSEHB/PED Notification No. 0424-2 dated April 24, 2020, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that encorafenib in combination with binimetinib and cetuximab (genetical recombination) or with cetuximab (genetical recombination) has efficacy in the treatment of patients with unresectable advanced or recurrent colorectal cancer with B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) mutation that has progressed after cancer chemotherapy, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. The choice between the above treatment regimens needs to be further investigated.

Indications

○ Unresectable malignant melanoma with *BRAF* mutation

○ Unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy

(Underline denotes additions.)

Dosage and Administration

Unresectable malignant melanoma with *BRAF* mutation

In combination with binimetinib, the usual adult dosage is 450 mg of encorafenib administered orally once daily. The dose may be reduced according to the patient's condition.

Unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy

In combination with cetuximab (genetical recombination) or with binimetinib and cetuximab (genetical recombination), the usual adult dosage is 300 mg of encorafenib administered orally once daily. The dose may be reduced according to the patient's condition.

(Underline denotes additions.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

September 9, 2020

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

(a) Brand Name	(1) Braftovi Capsules 50 mg (2) Braftovi Capsules 75 mg
Non-proprietary Name	Encorafenib
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	(1) March 4, 2020 (2) August 26, 2020
Dosage Form/Strength	(1) Capsules: Each capsule contains 50 mg of encorafenib (2) Capsules: Each capsule contains 75 mg of encorafenib
Proposed Indications	○ Unresectable malignant melanoma with *BRAF* mutation ○ Unresectable advanced or recurrent colorectal cancer with *BRAF* mutation (Underline denote additions.)

Proposed Dosage and Administration

Unresectable malignant melanoma

In combination with binimetinib, the usual adult dosage is 450 mg of encorafenib administered orally once daily. The dose may be reduced according to the patient's condition.

Unresectable advanced or recurrent colorectal cancer

In combination with binimetinib and cetuximab, the usual adult dosage is 300 mg of encorafenib administered orally once daily. The dose may be reduced according to the patient's condition.

(Underline denotes additions.)

(b) Brand Name	Mektovi Tablets 15 mg
Non-proprietary Name	Binimetinib
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	March 4, 2020
Dosage Form/Strength	Tablets: Each tablet contains 15 mg of binimetinib

Proposed Indications

○ Unresectable malignant melanoma with *BRAF* mutation

○ Unresectable advanced or recurrent colorectal cancer with *BRAF* mutation

(Underline denotes additions.)

Proposed Dosage and Administration

Unresectable malignant melanoma

In combination with encorafenib, the usual adult dosage is 45 mg of binimetinib administered orally twice daily. The dose may be reduced according to the patient's condition.

Unresectable advanced or recurrent colorectal cancer

In combination with encorafenib and cetuximab, the usual adult dosage is 45 mg of binimetinib administered orally twice daily. The dose may be reduced according to the patient's condition.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) mutations have been found in approximately 4.6% to 20.6% and 4.7% to 6.7%, respectively, of patients with colorectal cancer in Western countries and in Japan (*Cancer*. 2011;17:4623-32, *BMC Cancer.* 2015;15:258, etc.). Mutations in *BRAF* gene are considered to constitutively activate BRAF, the serine/threonine kinase involved in the activation of mitogen-activated protein kinase (MAPK) pathway, resulting in the enhancement of tumor cell growth, suppression of apoptosis, etc., through activation of MAPK pathway mediated by phosphorylation of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase (MEK), etc., in the downstream (*Nat Med*. 2013;19:1401-9, *Nat Rev Cancer.* 2017;17:676-91, etc.).

Encorafenib (ENCO), a low molecular weight compound discovered by Novartis (Switzerland), is considered to suppress the growth of tumor with *BRAF* mutations by inhibiting the kinase activity of BRAF.

Binimetinib (BINI), a low molecular weight compound discovered by Array BioPharma (US), is considered to suppress the growth of tumor with *BRAF* mutations by inhibiting the kinase activity of MEK.

In Japan, ENCO and BINI were approved in January 2019 for the indication “unresectable malignant melanoma with *BRAF* mutation.”

1.2 Development history etc.

In the clinical development of a combination therapy of ENCO and BINI (ENCO/BINI) for the treatment of unresectable advanced or recurrent colorectal cancer with *BRAF* mutation, a global phase Ib/II study (Study CLGX818X2103 [Study X2103]) was initiated in November 2012 by Novartis AG (Switzerland) with a combination therapy of ENCO and cetuximab (genetical recombination) (Cmab) (ENCO/Cmab) in patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that had progressed after standard therapies. Subsequently, a global phase III study (Study ARRAY-818-302 [the BEACON CRC study]) was initiated in October 2016 by Array BioPharma (US) with a combination therapy of ENCO, BINI, and Cmab (ENCO/BINI/Cmab) in patients with unresectable advanced or recurrent colorectal cancer with “BRAF mutation involving amino acid substitution of valine to glutamic acid at codon 600” (BRAF V600E mutation) that had progressed after the first- or second-line therapy.

In the US and EU, an application for ENCO and BINI was submitted in October 2019 for the combination of ENCO/BINI/Cmab, with the BEACON CRC study as the pivotal study. During the review process, the application of BINI was withdrawn. The combination of ENCO/Cmab was approved for the indication “BRAFTOVI is indicated, in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.” in April 2020 in the US, and for the indication “Encorafenib is indicated in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.” in June 2020 in the EU.

As of July 2020, ENCO is approved for the indication of colorectal cancer with *BRAF* mutation in 32 countries or regions, whereas BINI has not been approved in any country or region.

In Japan, enrollment of patients in Study X2103 and the BEACON CRC study was initiated in [redacted] 20[redacted] and in [redacted] 20[redacted], respectively.

Recently, an application for partial changes (partial change application) was submitted to add the indication "unresectable advanced or recurrent colorectal cancer with *BRAF* mutation" and the dosage and administration for ENCO and BINI, based on the results of the BEACON CRC study as the pivotal data.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Since the present application relates to the new indication and new dosage, no new data relating to quality were submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 ENCO

3.1.1 Primary pharmacodynamics

3.1.1.1 Growth-inhibitory effect against malignant tumor-derived cell lines

3.1.1.1.1 *In vivo* (ENCO, CTD 4.2.1.1-2, 4.2.1.1-3)

Using nude mice subcutaneously transplanted with human colorectal cancer-derived COLO 205 cell lines that harbor BRAF V600E mutation (n = 10/group), the tumor growth-inhibitory effect of ENCO was investigated. Starting from 8 days after the transplantation, ENCO 5, 25, or 150 mg/kg BID or ENCO 10, 50, or 300 mg/kg QD was administered orally for 28 days, and tumor volume was calculated. On Day 28, a statistically significant tumor growth-inhibitory effect was observed in all ENCO groups compared with the control (vehicle[1)]) group ($P < 0.01$, Dunn test for all ENCO groups).

Using nude mice subcutaneously transplanted with human colorectal cancer-derived LS411N cell lines that harbor BRAF V600E mutation (n = 10/group), the tumor growth-inhibitory effect of ENCO was investigated. Starting from 7 days after the transplantation, ENCO 5, 25, or 150 mg/kg BID or ENCO 10, 50, or 300 mg/kg QD was administered orally for 28 days, and tumor volume was calculated. On Day 28, a statistically significant tumor growth-inhibitory effect was observed in the ENCO 5, 25, and 150 mg/kg BID groups compared with the control (vehicle[1)]) group ($P < 0.05$ by Dunnett's multiple comparison).

3.2 BINI

3.2.1 Primary pharmacodynamics

3.2.1.1 Growth-inhibitory effect against malignant tumor-derived cell lines

3.2.1.1.1 *In vivo* (BINI, CTD 4.2.1.1-1)

Using nude mice subcutaneously transplanted with COLO 205 cell lines (n = 7/group), the tumor growth-inhibitory effect of BINI was investigated. Starting from 5 days after the transplantation, BINI

1) 0.5 w/v% carboxymethylcellulose (CMC) containing 0.5% polysorbate 80.

3, 10, or 30 mg/kg was administered orally QD for 19 days, and tumor volume was calculated. Tumor growth-inhibition (TGI)[2)] on Day 19 was 33%, 59%, and 85%, respectively, in the BINI 3, 10, and 30 mg/kg groups.

3.3 ENCO/BINI

3.3.1 Primary pharmacodynamics

3.3.1.1 Growth-inhibitory effect against malignant tumor-derived cell lines

3.3.1.1.1 *In vitro* (ENCO, CTD 4.2.1.1-5; BINI, CTD 4.2.1.1-2)

The growth-inhibitory effect of ENCO/BINI against 10 different types of human colorectal cancer-derived cell lines was investigated with adenosine triphosphate (ATP) content in viable cells as the index. Table 1 shows IC_{50} of ENCO and BINI. The combined effect[3)] of ENCO and BINI was observed in all cell lines investigated.

Table 1. Growth inhibitory effect against human colorectal cancer-derived cell lines

Cell line	Type of BRAF mutation	IC_{50} (nmol/L)		Synergy Score	Combination Index
		ENCO	BINI		
OUMS23	V600E	>2,700	>2,700	0.17	—
SW1417		15.0	24.01	2.55	1.34
COLO 205		3.7	15.71	2.05	1.05
LS411N		3.6	19.42	2.01	0.89
HT-29		4.1	32.00	3.32	1.43
KM12	None	>2,700	231.6	0.19	1.30
CW2		>2,700	>2,700	0.14	—
NCIH716		>2,700	>2,700	0.93	—
C2BBE1		>2,700	>2,700	0.50	0.63
SNUC1		>2,700	10.2	0.35	2.23

n = 1; —, Not calculated.

3.3.1.1.2 *In vivo* (ENCO, CTD 4.2.1.1-7, 4.2.1.1-8, 4.2.1.1-9; BINI, CTD 4.2.1.1-3, 4.2.1.1-4, 4.2.1.1-5)

Using nude mice subcutaneously transplanted with human colorectal cancer HT-29 cell lines that harbor BRAF V600E mutation (n = 8 or 9/group), the tumor growth-inhibitory effect of ENCO/BINI/Cmab was investigated. Starting from 22 days after the transplantation, ENCO 20 mg/kg QD and BINI 3.5 mg/kg BID were administered orally and Cmab 20 mg/kg twice weekly intraperitoneally, for 21 days, and tumor volume was calculated. On Day 21, a statistically significant tumor growth-inhibitory effect was observed in the ENCO/Cmab group, the BINI and Cmab (BINI/Cmab) group, and the ENCO/BINI/Cmab group compared with the control (vehicle[4)]) group and the Cmab group. Also, a statistically significant tumor growth-inhibitory effect was observed in the ENCO/BINI/Cmab group compared with the ENCO group (Figure 1).

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2) Tumor growth-inhibition rate (%) = (1 – [tumor volume in the BINI group/tumor volume in the control (0.5w/v% CMC containing 0.5% polysorbate 80) group]) × 100

3) The combined effect was assumed if any of the following was met (*Nat Biotechnol.* 2009;27:659-66).
- Synergy Score >2.0 AND Combination Index <0.5
- Synergy Score >2.0 AND Combination Index >0.5, OR Synergy Score >1.0 and <2.0 AND Combination Index <0.5
- Synergy Score<1.0 AND Combination Index<0.5, OR Synergy Score<2.0 AND Combination Index>0.5

4) 1 w/v% CMC containing 0.5% polysorbate 80

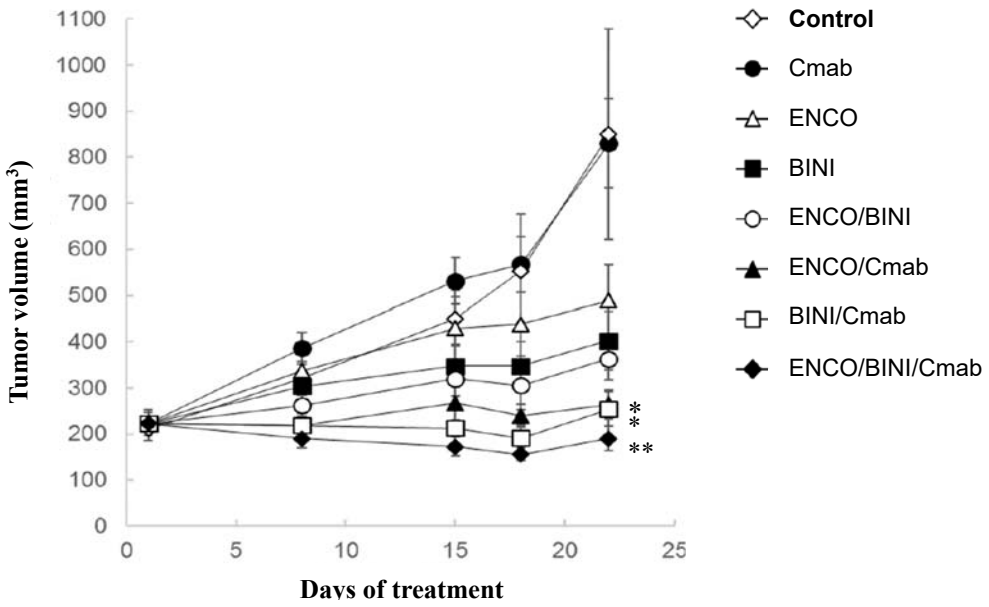


Figure 1. Tumor growth-inhibitory effect of ENCO/BINI/Cmab in nude mice subcutaneously transplanted with cell line HT-29

n = 8 or 9; Mean ± standard error; * $P < 0.05$ against the control group and the Cmab group; ** $P < 0.05$ against the control group, the Cmab group, and the ENCO group

Using nude mice subcutaneously transplanted with CRC563 or CRC769 tumor tissue slice derived from patients with colorectal cancer with BRAF V600E mutation (n = 8/group), the tumor growth inhibitory effect of ENCO/BINI/Cmab was investigated. Starting from the time point when tumor volume reached 200 ± 40 mm^3, ENCO 20 mg/kg QD and BINI 3.5 mg/kg BID were administered orally, and Cmab 20 mg/kg twice weekly intraperitoneally, for 21 days, and tumor volume was calculated. TGI[5)] on Day 21 was 45% in the ENCO group, 68% in the BINI group, 0% in the Cmab group, 58% in the ENCO/BINI group, 43% in the ENCO/Cmab group, 59% in the BINI/Cmab group, and 75% in the ENCO/BINI/Cmab with CRC563 tumor tissue slice, and 56% in the ENCO group, 43% in the BINI group, 0% in the Cmab group, 76% in the ENCO/BINI group, 56% in the ENCO/Cmab group, 48% in the BINI/Cmab group, and 80% in the ENCO/BINI/Cmab with CRC769 tumor tissue slice.

3.R Outline of the review conducted by PMDA

On the basis of the data submitted and on the results of the reviews in the following sections, PMDA concluded that the applicant's explanation about the nonclinical pharmacology of ENCO and BINI is acceptable.

3.R.1 Efficacy of ENCO and BINI against colorectal cancer with *BRAF* gene mutation

The applicant's explanation about the efficacy of ENCO and BINI against colorectal cancer with *BRAF* mutation:

In light of the following observations, co-administration of Cmab, ENCO, and BINI is expected to be effective against colorectal cancer with *BRAF* mutation.

- While monotherapy with epidermal growth factor receptor (EGFR) inhibitor or BRAF inhibitor has only a limited tumor growth-inhibitory effect against colorectal cancer with *BRAF* mutation, co-

5) Tumor growth inhibition rate (%) = (1 – [tumor volume in each group/tumor volume in control (1 w/v% CMC containing 0.5% polysorbate 80) group]) × 100

administration of EGFR inhibitor and BRAF inhibitor continuously inhibited MAPK-mediated signaling, leading to an enhanced tumor growth-inhibitory effect (*Nature.* 2012;483:100-3, *Cancer Discov*. 2012;2:227-35, etc.).

- In colorectal cancer-derived cell line that have acquired resistance to BRAF inhibitors, reactivation of MAPK pathway, such as amplification of v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS)* and *BRAF* genes, is observed (*Cancer Discov.* 2015;5:358-67). Co-administration of BRAF and MEK inhibitors is expected to delay the resistance acquisition through the reactivation of MAPK pathway.
- BRAF V600E mutation accounts for most (90%) of *BRAF* mutations observed in colorectal cancer (*J Gastrointest Oncol.* 2015;6:660-7). Both ENCO and BINI inhibited the growth of human colorectal cancer-derived cell lines with BRAF V600E mutation [see Sections 3.1.1 and 3.2.1]. Co-administration of ENCO, BINI, and Cmab showed an enhanced tumor growth-inhibitory effect compared to monotherapy with either of them [see Section 3.3.1].

PMDA accepted the explanation of the applicant.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application relates to the new indication and new dosage, no new study data were submitted on the ground that non-clinical pharmacokinetics data has been reviewed at the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application relates to the new indication and new dosage, no new data relating to toxicity were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

Although the present application relates to the new indication and new dosage, no new study data were submitted on the ground that data on biopharmaceutic studies and associated analytical methods have been reviewed at the initial approval.

6.1 Clinical pharmacology

Pharmacokinetics (PK) of ENCO and BINI after administration of ENCO/BINI/Cmab was investigated in patients with cancer.

6.1.1 Global phase III study (CTD 5.3.5.1-1.1, the BEACON CRC study [ongoing since October 2016 (data cut-off February 11, 2019)])

This study consisted of a safety lead-in part and a phase III part. In the safety lead-in part, an open-label, uncontrolled study was conducted to investigate PK, etc., of ENCO and BINI. The study was conducted in 37 patients (37 patients included in the PK analysis) with unresectable advanced or recurrent colorectal cancer with BRAF V600E mutation that has progressed after the first- or second-line therapy. ENCO 300 mg QD and BINI 45 mg BID were administered orally in combination with Cmab, and plasma ENCO and BINI concentrations were measured.

Table 2 shows PK parameter values of ENCO and BINI. Reduced exposure to ENCO, supposedly due to CYP3A self-induction by ENCO, was observed after multiple administration of ENCO, as was observed in previous studies (see "Review Report of Braftovi Capsules 50 mg, dated November 19, 2018").

Table 2. PK parameters of ENCO ad BINI

	Day of measurement	n	C_{max} (ng/mL)	t_{max}^{*} (h)	AUC_{last} (ng•h/mL)
ENCO	1	34	3,950 ± 2,270	2.00 (0.883, 6.25)	13,100 ± 7,170
	29	29	3,010 ± 1,750	2.00 (0.950, 5.73)	7,650 ± 3,980
BINI	1	35	731 ± 369	1.98 (0.883, 5.67)	2,140 ± 920
	29	26	624 ± 366	1.04 (0.900, 4.00)	1,680 ± 714

Mean ± standard deviation (SD); * Median (range)

6.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA concluded that the applicant's explanation about the clinical pharmacology of ENCO and BINI is acceptable.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results data from a total of 3 studies consisting of 1 global phase Ib/II study, 1 global phase III study, and 1 foreign phase Ib/II study, as shown in Table 3. The applicant also submitted the results of a total of 3 studies consisting of 1 Japanese phase I study, 1 global phase I study, and 1 foreign phase I study as reference data. Since the data of the Japanese phase I study (Study CMEK162X1101 [Study X1101]), the global phase I study (Study CLGX818X2101 [Study X2101]), the foreign phase I study (Study ARRAY-162-111 [Study 162-111]), and the foreign phase Ib/II study (Study CMEK162X2110 [Study X2110]) were evaluated by PMDA at the review for the initial approval of ENCO and BINI, they are omitted from the description here (see "Review Report of Braftovi Capsules 50 mg, dated November 19, 2018" and "Review Report of Mektovi Tablets 15 mg, dated November 19, 2018").

Table 3. List of clinical studies on efficacy and safety

Data category	Region	Study	Phase	Study population	Number of enrollments	Dosage regimen	Main endpoints
Evaluation	Global	X2103	Ib/II	Patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after standard therapies	ENCO/Cmab Phase Ib part 26 Phase II part 50	Phase Ib part ENCO 100, 200, 400, or 450 mg orally QD and Cmab intravenously QW Phase II part ENCO 200 mg orally QD and Cmab intravenously QW	Tolerability Safety Efficacy
	Global	BEACON CRC	III	Patients with unresectable advanced or recurrent colorectal cancer with BRAF V600E mutation that had progressed after the first- or second-line therapy	Safety lead-in part 37 Phase III part (a) 224 (b) 220 (c) 221	Safety lead-in part ENCO 300 mg orally QD, BINI 45 mg orally BID, and Cmab intravenously QW Phase III part (a) ENCO 300 mg orally QD, BINI 45 mg orally BID, and Cmab intravenously QW (b) ENCO 300 mg orally QD and Cmab intravenously QW (c) Cmab intravenously QW in combination with IRI or FOLFIRI	Efficacy Safety
	Foreign	X2110	Ib/II	Patients with advanced solid cancer[*1] with BRAF V600 mutation	Phase Ib part 47 Phase II part 79	Phase Ib part ENCO 50, 100, 200, 400, 450, 600, or 800 mg orally QD and BINI 45 mg orally BID Phase II part ENCO 450 or 600 mg orally QD and BINI 45 mg orally BID	PK Tolerability Safety Efficacy
Reference	Japan	X1101	I	Patients with advanced solid cancer[*2]	Dose titration part 14 Dose expansion part 7	Dose titration part BINI 15 mg orally QD on Day 1 and BINI 30 or 45 mg orally BID from Day 2 Dose expansion part BINI 45 mg orally BID	PK Tolerability Safety
	Global	X2101	I	Patients with advanced solid cancer[*1] with BRAF V600 mutation	Dose titration part 54 Dose expansion part 53	Dose titration part ENCO 50, 100, 150, 200, 300, 450, 550, or 700 mg orally QD or ENCO 75, 100 or 150 mg orally BID Dose expansion part ENCO 300 mg orally QD from Day 1 to Day 14 and 450 mg QD from Day 15	PK Tolerability Safety
	Foreign	162-111	I	Patients with advanced solid cancer[*3]	Dose titration part 19 Dose expansion part 74	Dose titration part BINI 30, 45, 60, or 80 mg orally QD on Day 1 and orally BID from Day 2 Dose expansion part BINI 45 or 60 mg orally BID	PK Tolerability Safety

*1 In the phase Ib or dose titration part, patients with unresectable malignant melanoma were enrolled. In the dose expansion or phase II part, patients with unresectable malignant melanoma and patients with unresectable advanced or recurrent colorectal cancer were enrolled.

*2 In the dose expansion part, patients with advanced solid cancer with *KRAS*, neuroblastoma RAS viral oncogene homolog gene (*NRAS)* or *BRAF* mutation (except for patients with pancreatic cancer) were enrolled. Patients with pancreatic cancer were enrolled regardless of the above mutations.

*3 In the dose expansion part, patients with biliary tract cancer and patients with colorectal cancer with *KRAS* or *BRAF* mutation were enrolled.

The outline of each clinical study is as described below. Table 4 shows the dosage regimen of antineoplastic agents other than ENCO and BINI used in each clinical study. Main adverse events other than death observed in clinical studies are summarized in Section "7.2 Adverse events, etc., observed in clinical studies."

Table 4. List of dosage regimens for antineoplastic agents other than ENCO and BINI used in each clinical study

	Dosage regimen
Cmab	The first dose of 400 mg/m^2 was administered intravenously QW over 120 minutes, and the second and each of subsequent doses of 250 mg/m^2 were administered intravenously QW over 60 minutes.
FOLFIRI	On Day 1 of each 2-week cycle, (a) IRI 180 mg/m^2 was administered intravenously over 90 minutes, (b) LV 400 mg/m^2 was administered intravenously over 120 minutes, and (c) 5-FU 400 mg/m^2 was bolus-administered intravenously, followed by intravenous administration of 5-FU 2,400 mg/m^2 over 46 to 48 hours.
IRI	In each of the 2-week cycles, IRI 180 mg/m^2 was administered intravenously over 90 minutes.

7.1 Evaluation data

7.1.1 Global studies

7.1.1.1 Global phase Ib/II study (CTD 5.3.5.2-1.1, Study X2103 [ongoing since November 2012 (data cut-off [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the tolerability, safety, efficacy, etc., of ENCO/Cmab and combination of ENCO, Cmab, and alpelisib (ENCO/Cmab/alpelisib) (alpelisib is unapproved in Japan) at 28 study sites in 12 countries including Japan. The study is conducted in patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutations[6)] that had progressed after standard therapies[7)] (target sample size, approximately 24 patients in the phase Ib part, 100 patients in the phase II part) (in this review report, data on the ENCO/Cmab group are described for Study X2103).

In the ENCO/Cmab group, ENCO 100, 200, 400, or 450 mg was administered orally QD and Cmab was administered intravenously QW in the phase Ib part, and ENCO 200 mg was administered orally QD and Cmab was administered intravenously QW in the phase II part. The treatment was continued until disease progression or any of the criteria for treatment discontinuation was met.

All of the 76 patients enrolled in the ENCO/Cmab group of the study (26[8)] in the phase Ib part, 50 in the phase II part) received the study drugs and were included in the population for safety and efficacy analysis (6 Japanese patients were included in the phase II part).

In the phase Ib part, tolerability was evaluated during the dose-limiting toxicity (DLT) assessment period of 28 days from the start of study drug administration. DLT was observed in 1 of 7 patients in the ENCO 200 mg cohort (Grade 3 arthralgia), 1 of 9 patients in the 400 mg cohort (Grade 3 vomiting), and 1 of 8 patients in the 450 mg cohort (Grade 3 electrocardiogram QT prolonged), but maximum tolerated dose (MTD) was not reached. As a result, the recommended Phase 2 dose (RP2D) of ENCO in combination with Cmab was determined to be 400 mg based on Bayesian model-based estimation, safety, etc. However, taking account of the finding that RP2D of ENCO in ENCO/Cmab/alpelisib had been

6) Patients with *BRAF* mutations other than BRAF mutation involving amino acid substitution of valine to other amino acid at codon 600 (BRAF V600 mutation) were enrolled in the phase Ib part upon consultation with the sponsor.

7) Patients who showed aggravation after ≥1 standard therapies and patients resistant to IRI were enrolled. In the phase Ib part, patients deemed to be nonresponsive to any standard therapy by the investigator was enrolled. In the phase II part, patients with a prior treatment with EGFR inhibitor, RAF proto-oncogene serine/threonine-protein kinase (RAF) inhibitor, phosphoinositide 3-kinase (PI3K) inhibitor, or MEK inhibitor were excluded.

8) Using Bayesian logistic regression model, 3 to 6 patients were enrolled in each dose cohort for the dose titration study. At least 6 patients were to be enrolled in the cohort of the suspected RP2D. As a result, 2, 7, 9, and 8 patients were enrolled in the ENCO 100, 200, 400, and 450 mg cohorts, respectively.

determined to be 200 mg, the dose of ENCO in the ENCO/Cmab group in the phase II part was determined to be 200 mg.

Death during, or within 30 days after the end of, the study drug administration was observed in 5 of 26 patients (19.2%) in the phase Ib part and in 7 of 50 patients (14.0%) in the phase II part (no death was observed among Japanese patients). The cause of death, except for death due to disease progression (4 patients in the phase Ib part, 6 patients in the phase II part) was cardiac arrest in 1 patient each in the phase Ib part and the phase II part. A causal relationship of the death to the study drugs was denied for both patients.

7.1.1.2 Global phase III study (CTD 5.3.5.1-1.1, the BEACON CRC study [ongoing since October 2016 (data cut-off February 11, 2019)])

A study consisting of a safety lead-in part (open label, uncontrolled study) to investigate the tolerability, safety, etc., of ENCO/BINI/Cmab and a phase III part (open-label, randomized, controlled study) to compare the efficacy and safety of ENCO/BINI/Cmab, ENCO/Cmab, and investigator's choice (IC) was conducted at 221 study sites in 28 countries including Japan. The study was conducted in patients with unresectable advanced or recurrent colorectal cancer with BRAF V600E mutation[9)] that had progressed after the first- or second-line therapy[10)] (target sample size, 31-36[11)] patients in the safety lead-in part, 615 patients in the phase III part).

Patients received the study drugs according to the following dosage regimens until disease progression or the patient met the criteria for study discontinuation:

- ENCO/BINI/Cmab group: oral administration of ENCO 300 mg QD and BINI 45 mg BID, and intravenous administration of Cmab QW
- ENCO/Cmab group: oral administration of ENCO 300 mg QD and intravenous administration of Cmab QW
- IC group: intravenous administration of Cmab QW in combination with irinotecan hydrochloride hydrate (IRI) or in combination with 5-fluorouracil (5-FU), folinate (LV), and IRI (FOLFIRI)

All of the 37 patients enrolled in the safety lead-in part of the study (30 in the foreign safety lead-in part, 7 in the Japanese safety lead-in part) received ENCO/BINI/Cmab. After confirmation of the tolerability, safety, etc., of ENCO/BINI/Cmab, patients were enrolled in the phase III part.

In the safety lead-in part, tolerability was evaluated in the DLT assessment period of 28 days after the start of the study drug. Although DLT was observed in 5 of 30 patients in the foreign safety lead-in

9) Patients who were confirmed to have *BRAF* mutation by the test at the study site or the central laboratory were enrolled. Of patients enrolled based on the results of tests performed by the study site, ≥37 patients were not confirmed to have BRAF V600E mutation when tested by the central laboratory. Thereafter, patients were enrolled based on the results of the test by the central laboratory according to the predefined protocol. Plasma samples at baseline were submitted by 29 of 39 patients with unconfirmed BRAF V600E mutation by the test of the central laboratory, and BRAF V600E mutation was detected in 25 of 29 samples.

10) Patients with a prior treatment with BRAF inhibitor, MEK inhibitor, or EGFR inhibitor (including Cmab and panitumumab [genetical recombination] [Pmab]) were excluded. As for patients who had received the second-line treatment, patients who had a prior treatment with oxaliplatin (L-OHP) or had refused L-OHP were enrolled at the maximum of 215 patients (35% of total).

11) Conducted in foreign countries (target sample size, 25-30 patients) and in Japan (target sample size, 6 patients)

part[12] (Grade 2 retinal detachment in 2 patients, Grade 3 hypersensitivity,[13] Grade 2 hypersensitivity,[13] and Grade 2 ejection fraction decreased in 1 patient each) and in 1 of 6 patients in the Japanese safety lead-in part (Grade 3 blood creatinine increased), ENCO/BINI/Cmab was assessed to be tolerable.

All of the 665 patients enrolled in the phase III part and randomized (224 in the ENCO/BINI/Cmab group, 220 in the ENCO/Cmab group, 221 in the IC group) were included in the full analysis set (FAS) (Japanese patients; 3 in the ENCO/BINI/Cmab group, 6 in the ENCO/Cmab group, 11 in the IC group). Among the patients in FAS, the first 331 patients enrolled (111 in the ENCO/BINI/Cmab group, 113 in the ENCO/Cmab group, 107 in the IC group) were included in the response efficacy set (RES) (no Japanese patients in any treatment group). FAS and RES were subjected to efficacy analysis. RES was the primary population for the analysis of the response rate, and FAS was the primary population for the analysis of other efficacy endpoints (including overall survival [OS]). Of the patients in FAS, 631 patients (222 in the ENCO/BINI/Cmab group, 216 in the ENCO/Cmab group, 193 in the IC group), excluding 34 patients (2 in the ENCO/BINI/Cmab group, 4 in the ENCO/Cmab group, 28 in the IC group) who did not receive the study drug, were included in the safety analysis population (Japanese patients; 3 in the ENCO/BINI/Cmab group, 6 in the ENCO/Cmab group, 11 in the IC group).

The primary endpoint in the phase III part of the study had been OS at the start of the study, and an interim analysis had been planned to compare OS between the ENCO/BINI/Cmab group and the IC group to evaluate the futility. Later, the response rate was included in the primary endpoints in addition to OS, because an exploratory evaluation of the efficacy of ENCO/BINI/Cmab in the foreign safety lead-in part of the study showed that the response rate by blinded independent central review (BICR) assessment based on Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1, the secondary endpoint in the study, tended to be higher than the rate reported for existing treatments *(J Clin Oncol*. 2019;37:1460-9). In addition, it was determined to conduct an interim analysis and a final analysis, at the following time point, for the primary analysis of the response rate and for the evaluation of the futility or superiority of OS (comparison between the ENCO/BINI/Cmab group and the IC group) (clinical study protocol, ver. [redacted] [dated [redacted], 20[redacted]]):

- The primary analysis of the response rate and the interim analysis of OS were to be conducted at the time point when all of the following conditions were met:
  - 9 months after randomization of the 330th patient (110 patients per group)
  - ≥188 OS events occurred both in the ENCO/BINI/Cmab group and in the IC group.
  - ≥169 OS events occurred both in the ENCO/ Cmab group and in the IC group.
- The final analysis of OS was to be conducted at the time point when both of the following conditions were met:
  - ≥268 OS events occurred both in the ENCO/BINI/Cmab group and in the IC group.
  - ≥338 OS events occurred both in the ENCO/Cmab group and in the IC group.

The test for the primary and secondary endpoints of the study and the assignment of the significance level were to be performed according to the following order: (a) The response rate in RES to verify the

[12] If DLT occurred in <3 of the first 9 patients and was determined to be tolerable by the independent data monitoring committee (IDMC), the safety lead-in part was to be expanded to add an additional 16 to 21 patients. Because DLT was observed in 1 of the first 9 patients (Grade 2 hypersensitivity), and it was determined to be tolerable by IDMC, an additional 21 patients were included in the safety lead-in part.

[13] Occurred after intravenous administration of Cmab.

superiority of the ENCO/BINI/Cmab group to the IC group, (b) hypothesis testing on OS in FAS, followed by secondary analyses (c) to (f) below in a hierarchical manner. The probability of type 1 error of the entire study was adjusted to a one-sided significance level of 0.025 (Figure 2). The probability of type 1 error associated with the interim analysis was adjusted by the alpha spending function of O'Brien-Fleming type based on Lan & DeMets method.

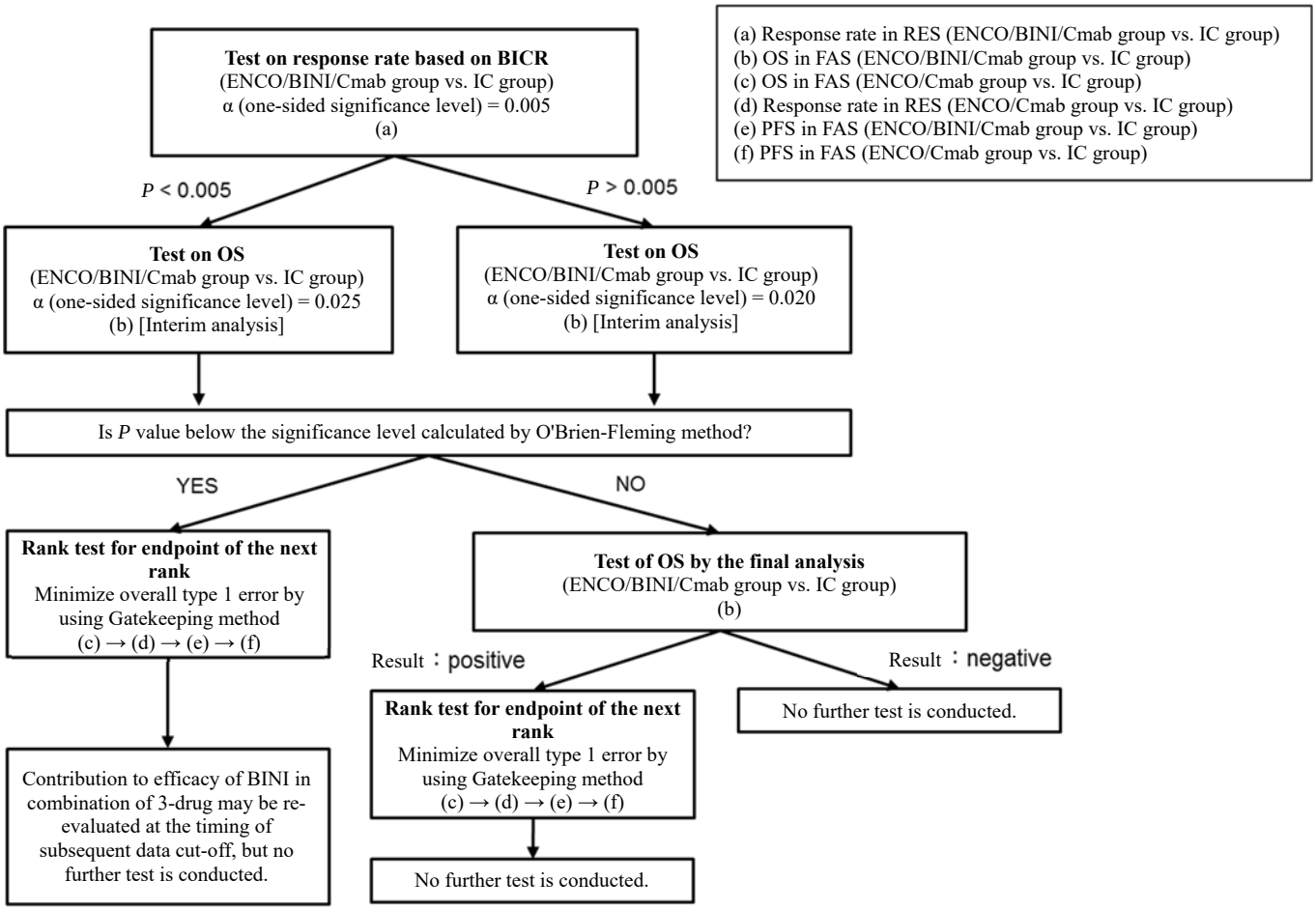


Figure 2. Testing procedures and assignment of significance level (one-sided) in the BEACON CRC study

Table 5 shows the results of a primary analysis of the response rate assessed by BICR based on RECIST ver. 1.1, one of the primary endpoints (data cut-off February 11, 2019), which confirmed the superiority of the ENCO/BINI/Cmab group to the IC group. A statistically significant difference was observed in the response rate between the ENCO/BINI/Cmab group and the IC group.

Table 5. Best overall response and response rate
(RECIST ver. 1.1, phase III part, RES, BICR assessment, data cut-off February 11, 2019)

Best overall response	Number of patients (%)		
	ENCO/BINI/Cmab (n = 111)	ENCO/Cmab (n = 113)	IC (n = 107)
CR	4 (3.6)	6 (5.3)	0
PR	25 (22.5)	17 (15.0)	2 (1.9)
SD	41 (36.9)	57 (50.4)	26 (24.3)
PD	11 (9.9)	8 (7.1)	36 (33.6)
Non-CR/Non-PD	6 (5.4)	4 (3.5)	5 (4.7)
NE	24 (21.6)	21 (18.6)	38 (35.5)
Response (CR + PR) (Response rate [95% CI[*1]] [%])	29 (26.1 [18.2, 35.3])	23 (20.4 [13.4, 29.0])	2 (1.9 [0.2, 6.6])
P value (one-sided)[*2]	<0.0001[*3]	<0.0001[*4]	

*1 Clopper-Pearson method
*2 Cochran-Mantel-Haenszel test with Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0, 1), prior treatment with IRI (yes, no), and source of Cmab (US, Europe) as stratification factors (comparison with the IC group)
*3 Significance level (one-sided) 0.005
*4 Significance level (one-sided) 0.025

Table 6 and Figure 3 show the results of the interim analysis of OS, another primary endpoint (data cut-off February 11, 2019), and Kaplan-Meier curves, respectively, which demonstrated the superiority of the ENCO/BINI/Cmab group to the IC group. A statistically significant prolongation of OS in the ENCO/Cmab group to the IC group was observed (Table 6 and Figure 4).

Table 6. Results of the interim analysis of OS (phase III part, FAS, data cut-off February 11, 2019)

	ENCO/BINI/Cmab	ENCO/Cmab	IC
Number of patients	224	220	221
Number of events (%)	90 (40.2)	93 (42.3)	114 (51.6)
Median [95% CI] (months)	9.0 [8.0, 11.4]	8.4 [7.5, 11.0]	5.4 [4.8, 6.6]
Hazard ratio [95% CI][*1]	0.52 [0.39, 0.70]	0.60 [0.45, 0.79]	
P value (one-sided)[*2]	<0.0001[*3]	0.0002[*4]	

*1 Stratified Cox proportional hazard model with ECOG PS (0, 1), prior treatment with IRI (yes, no), and source of Cmab (US, Europe) as stratification factors (comparison with the IC group)
*2 Stratified log-rank test with ECOG PS (0, 1), prior treatment with IRI (yes, no), and source of Cmab (US, Europe) as stratification factors (comparison with the IC group)
*3 Significance level (one-sided) 0.0102
*4 Significance level (one-sided) 0.0042

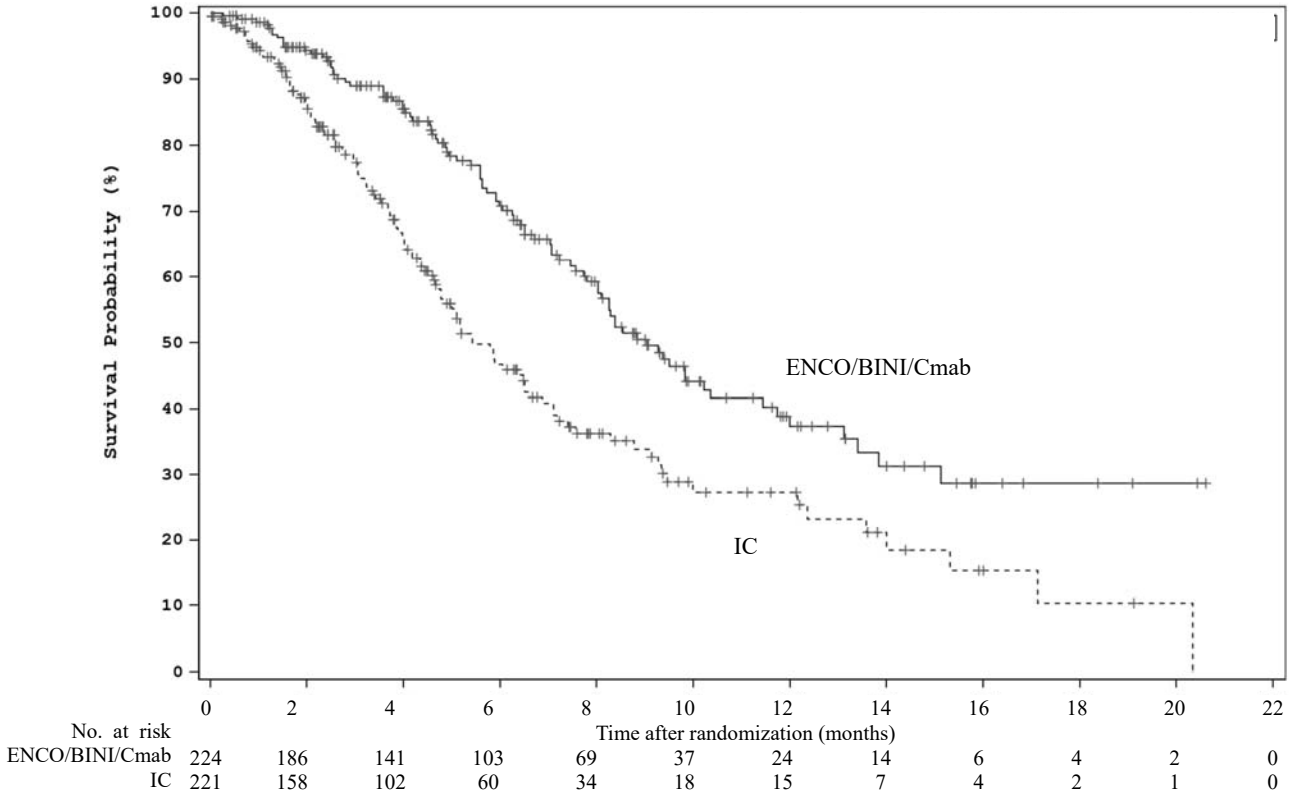


Figure 3. Kaplan-Meier curve of OS at the interim analysis (phase III part, FAS, data cut-off February 11, 2019)

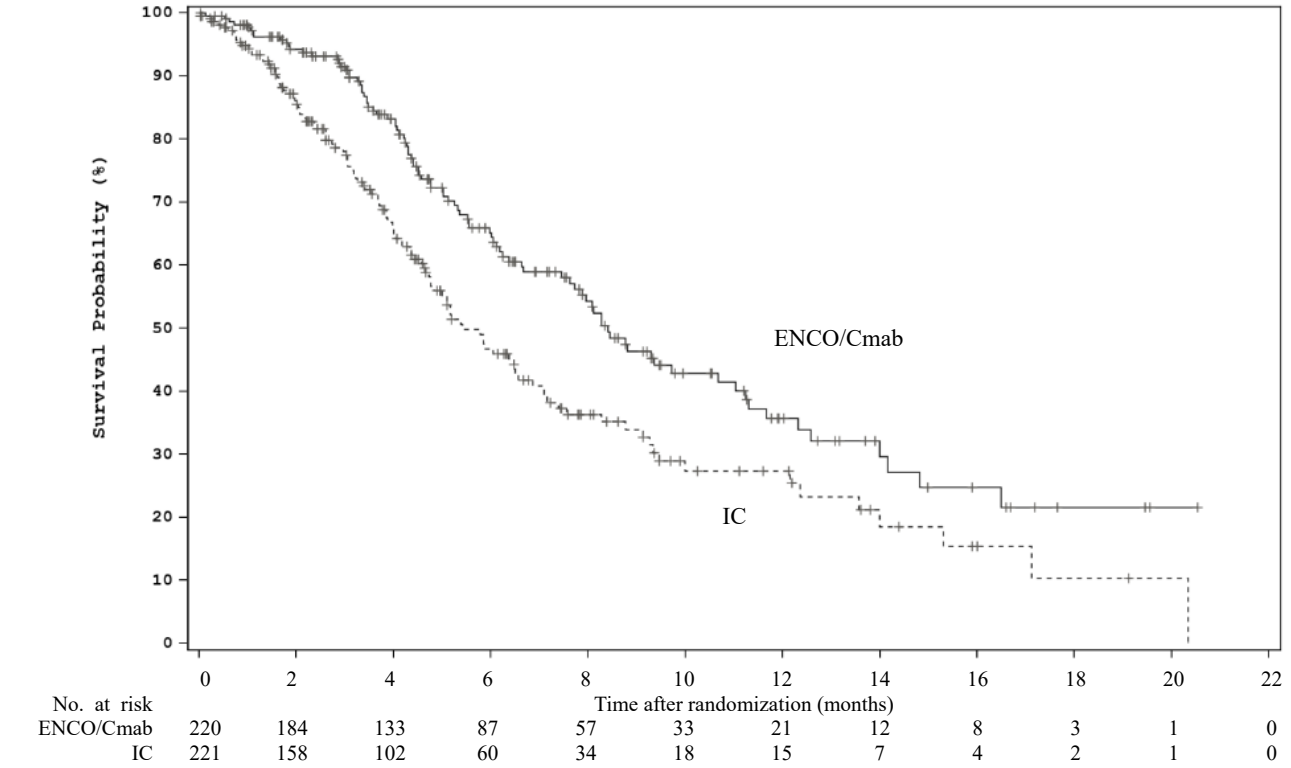


Figure 4. Kaplan-Meier curve of OS at the interim analysis (phase III part, FAS, data cut-off February 11, 2019)

Death during, or within 30 days after the end of, the study drug administration was observed in 5 of 37 patients (13.5%) in the safety lead-in period. The cause of death was disease progression in all of them, and a causal relationship to the study drug was denied (no death occurred in Japanese patients). In the phase III part, death during, or within 30 days after the end of, the study drug administration was observed in 23 of 222 patients (10.4%) in the ENCO/BINI/Cmab group, 32 of 216 patients (14.8%) in the ENCO/Cmab group, and 26 of 193 patients (13.5%) in the IC group (no death occurred in Japanese patients). The causes of death, except for death due to disease progression (14 patients in the ENCO/BINI/Cmab group, 26 patients in the ENCO/Cmab group, 18 patients in the IC group), were hepatic failure and death in 2 patients each, ileus, gastrointestinal perforation, large intestine perforation, cardiac arrest, and intestinal obstruction in 1 patient each in the ENCO/BINI/Cmab group; aspiration in 2 patients, sepsis, large intestine perforation, cardiac arrest, and gastrointestinal haemorrhage in 1 patient each in the ENCO/Cmab group; and subileus, respiratory distress, cerebral ischaemia, anaphylactic reaction, peritonitis, respiratory tract infection, cardio-respiratory arrest, and respiratory failure in 1 patient each in the IC group. A causal relationship to the study drug could not be ruled out for large intestine perforation in 1 patient in the ENCO/BINI/Cmab group and for anaphylactic reaction and respiratory failure in 1 patient each in the IC group.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA concluded that, among the evaluation data submitted, the important clinical study for evaluating the efficacy and safety of ENCO/BINI/Cmab and ENCO/Cmab was the global phase III study (the BEACON CRC study) in patients with unresectable advanced or recurrent colorectal cancer with BRAF V600E mutation that had progressed after the first- or second-line therapy, and decided to evaluate the submitted data focusing on this study.

The efficacy in Japanese patients was investigated in a systemic manner based on the BEACON CRC study, etc., by taking account of “Basic Principles on Global Clinical Trials (PFSB/ELD Notification No. 0928010, dated September 28, 2007),” “Basic Principles on Global Clinical Trials (Reference Cases)” (Administrative Notice dated September 5, 2012), and “General Principles for Planning and Design of Multi-Regional Clinical Trials” (PSEHB/PED Notification No. 0612-1, dated June 12, 2018), among others.

7.R.2 Efficacy

On the basis of the following review, PMDA has concluded that the efficacy of ENCO/BINI/Cmab and ENCO/Cmab is demonstrated in patients with unresectable advanced or recurrent colorectal cancer with BRAF V600E mutation that had progressed after the first- or second-line therapy.

7.R.2.1 Control group

The applicant’s explanation about justification for the control group chosen for the BEACON CRC study:

At the time of planning the BEACON CRC study, Japanese and non-Japanese clinical practice guidelines such as National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Colon Cancer (NCCN Guidelines [colon cancer]) (v.2.2016) recommended, as the second-line therapy

for unresectable advanced or recurrent colorectal cancer, a combination therapy consisting of (1) antineoplastics, either of oxaliplatin (L-OHP) and IRI not used in the first regimen and (2) either of molecular targeted therapeutics (anti-vascular endothelial growth factor [VEGF] antibody drugs[14)] [bevacizumab (genetical recombination) (BV), ramucirumab (genetical recombination) (RAM), or aflibercept beta (genetical recombination) (AFL)] or anti-EGFR antibody drugs[15)] [Cmab or panitumumab (genetical recombination) (Pmab)]. When the disease progressed after the first-line therapy including L-OHP, patients were treated with combination of IRI and Cmab (IRI/Cmab), combination of FOLFIRI and Cmab (FOLFIRI/Cmab), or a combination of FOLFIRI and anti-VEGF antibody drug. For patients requiring the third- or later-line therapy, IRI/Cmab, regorafenib hydrate (regorafenib), trifluridine/tipiracil hydrochloride (FTD/TPI), etc. were administered.

For patients with the target disease for the BEACON CRC study, namely patients with unresectable advanced or recurrent colorectal cancer with BRAF V600E mutation that had progressed after the first- or second-line therapy and not previously treated with anti-EGFR antibody drug, IRI/Cmab was selected as the second- or third-line therapy, regardless of the prior treatment with IRI, because it was recommended to preferentially give treatment combined with anti-EGFR antibody drug according to the treatment algorithm for patients with wild type rat sarcoma viral oncogene homologue (*RAS)* gene, taking into account that, in colorectal cancer, *BRAF* mutation and *RAS* mutation are mutually exclusive (Japanese Society of Medical Oncology: Guidance for gene-related testing in colorectal cancer patients [in Japanese], third edition, etc.).

Thus, target patients for the study are considered to have received IRI/Cmab or FOLFIRI/Cmab as the standard therapy. Therefore, for the control group in the BEACON CRC study, the investigator was to use either IRI/Cmab or FOLFIRI/Cmab.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints and evaluation results

The applicant's explanation about the appropriateness of the primary endpoints in the BEACON CRC study:

OS and the response rate were appropriate primary endpoints in the BEACON CRC study, given the following:

- Treatment of patients with unresectable advanced or recurrent colorectal cancer is performed with the expectation for sustainment of life.
- In patients with unresectable advanced or recurrent colorectal cancer, improvement in clinical conditions associated with tumor shrinkage, improvement in activities of daily living (ADL) and quality of life (QOL), etc., are expected in responders (*J Clin Oncol*. 2008;26:2311-9, etc.), suggesting clinical significance.

The applicant's explanation about the results of efficacy evaluation in the BEACON CRC study:

14) RAM and AFL were recommended for use in combination with FOLFIRI in the second-line therapy.
15) Indicated only for patients with wild-type *RAS* gene.

The primary endpoints, response rate and OS, were demonstrated to be superior in the ENCO/BINI/Cmab group compared with the IC group [see Section 7.1.1.2]. Secondary analyses were performed according to the testing procedures specified in the protocol. Results showed a statistically significantly higher response rate and a statistically significant OS prolongation in the ENCO/Cmab group compared with the IC group [see Section 7.1.1.2].

The median OS [95% confidence interval (CI)] with each treatment selected in the IC group (IRI/Cmab and FOLFIRI/Cmab) was 4.8 [3.9, 7.1] months for IRI/Cmab and 5.9 [5.1, 7.2] months for FOLFIRI/Cmab, and the hazard ratio[16)] [95% CI] of OS with ENCO/BINI/Cmab and ENCO/Cmab to IRI/Cmab and FOLFIRI/Cmab was 0.45 [0.31, 0.64] and 0.51 [0.35, 0.74] for IRI/Cmab and 0.54 [0.38, 0.76] and 0.62 [0.44, 0.87] for FOLFIRI/Cmab, showing no difference that could affect efficacy evaluation of ENCO/BINI/Cmab and ENCO/Cmab between the treatments selected for the IC group.

Table 7 shows the results of OS, classified by the number of prior treatments and by the presence/absence of prior treatment with IRI. No clear difference was observed between any of the subpopulations and the entire population.

Table 7. OS classified by the number of prior treatments and by prior treatment with IRI (Phase III part, FAS, data cut-off February 11, 2019)

		Median [95% CI] (months)			Hazard ratio [95% CI]*	
		ENCO/BINI/Cmab	ENCO/Cmab	IC	ENCO/BINI/Cmab	ENCO/Cmab
Number of prior treatments	1	9.0 [8.0, 12.0]	9.4 [8.1, 11.7]	5.9 [5.0, 7.6]	0.54 [0.38, 0.77]	0.55 [0.38, 0.78]
	≥2	9.3 [6.5, 13.8]	6.1 [4.4, 8.1]	4.7 [3.7, 6.9]	0.53 [0.34, 0.82]	0.71 [0.46, 1.11]
Prior treatment with IRI	No	9.0 [8.0, 15.1]	11.0 [8.1, 14.0]	5.9 [5.0, 7.6]	0.53 [0.35, 0.79]	0.50 [0.33, 0.74]
	Yes	9.3 [6.5, 11.4]	6.0 [4.8, 8.4]	5.1 [4.0, 6.9]	0.55 [0.37, 0.80]	0.75 [0.52, 1.10]

* Unstratified Cox proportional hazard model (comparison with the IC group)

Table 8 and Figure 5 show the results of the analysis of OS and Kaplan-Meier curves in Japanese population in the phase III part of the BEACON CRC study. No patients in the Japanese population showed a response by BICR assessment regardless of the treatment group.

16) Stratified Cox proportional hazard model with ECOG PS (0, 1), prior treatment with IRI (yes, no), and source of Cmab (US, Europe) as stratification factors.

Table 8. Results of the analysis of OS in Japanese population (phase III part, FAS, data cut-off February 11, 2019)

	ENCO/BINI/Cmab	ENCO/Cmab	IC
Number of patients	3	6	11
Number of events (%)	1 (33.3)	1 (16.7)	1 (9.1)
Median [95% CI] (months)	7.1 [—, —]	— [—, —]	— [2.04, —]
Hazard ratio [95% CI][*1]	— [—, —]	1.58 [0.09, 27.19]	
P value (one-sided)[*2]	—	0.6248	

—, Not estimable

*1 Stratified Cox proportional hazard model with ECOG PS (0, 1), prior treatment with IRI (yes, no), and source of Cmab (US, Europe) as stratification factors (comparison with the IC group)

*2 Stratified log-rank test with ECOG PS (0, 1), prior treatment with IRI (yes, no), and source of Cmab (US, Europe) as stratification factors (comparison with the IC group)

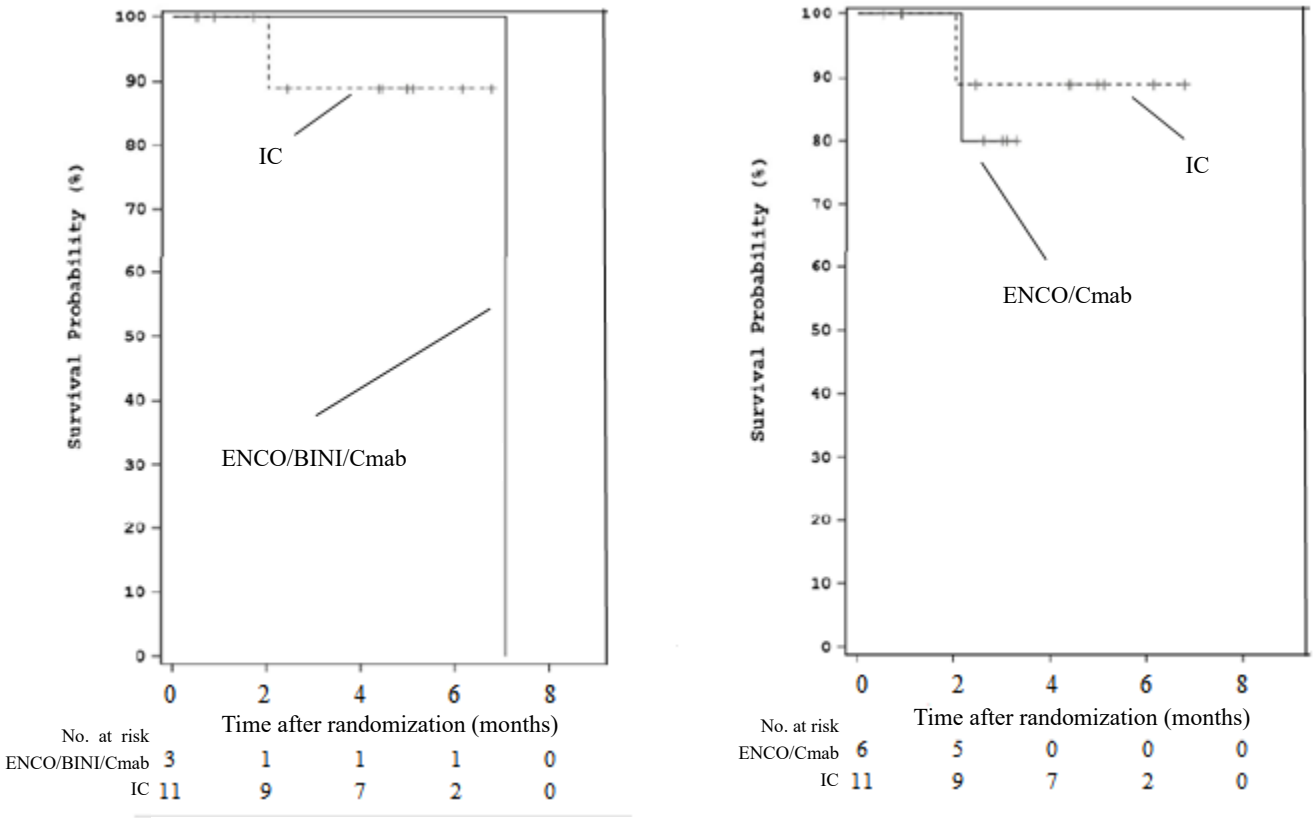


Figure 5. Kaplan-Meier curves of OS in Japanese population (phase III part, FAS, data cut-off February 11, 2019)

Taking into account of the consultation results with the foreign regulatory agency, an additional analysis was conducted when all patients in FAS of the phase III part had been followed up for ≥6 months (data cut-off August 15, 2019), albeit not included in the pre-specified analyses. Table 9 and Figure 6 show the results of the additional analysis of OS and Kaplan-Meier curves, which showed no difference from the results of the interim analysis [Section 7.1.1.2 Table 6 and Figures 3 and 4].

Table 9. Additional analysis of OS (phase III part, FAS, data cut-off August 15, 2019)

	ENCO/BINI/Cmab	ENCO/Cmab	IC
Number of patients	224	220	221
Number of events (%)	137 (61.2)	128 (58.2)	157 (71.0)
Median [95% CI] (months)	9.3 [8.3, 10.8]	9.3 [8.1, 11.3]	5.9 [5.1, 7.1]
Hazard ratio [95% CI][*1]	0.60 [0.47, 0.75]	0.61 [0.48, 0.77]	-
P value (one-sided)[*2]	<0.0001	<0.0001	

*1 Stratified Cox proportional hazard model with ECOG PS (0, 1), prior treatment with IRI (yes, no), and source of Cmab (US, Europe) as stratification factors (comparison with the IC group)

*2 Stratified log-rank test with ECOG PS (0, 1), prior treatment with IRI (yes, no), and source of Cmab (US, Europe) as stratification factors (comparison with the IC group)

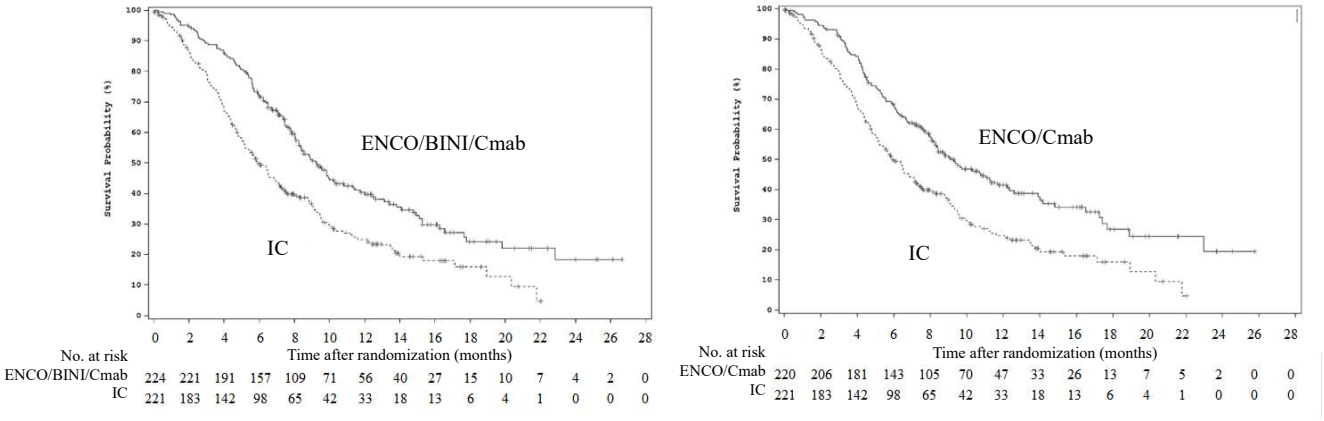


Figure 6. Kaplan-Meier curves of OS at additional analysis (phase III part, FAS, data cut-off August 15, 2019)

PMDA's view:

The BEACON CRC study demonstrated the efficacy of ENCO/BINI/Cmab and ENCO/Cmab in patients investigated, for the following findings:

- The study demonstrated the superiority of the ENCO/BINI/Cmab group to the IC group in the primary analysis of OS, a primary endpoint.
- The study showed a statistically significant prolongation of OS in the ENCO/Cmab group compared with the IC group, as determined by the secondary analysis conducted according to the prespecified testing procedures.

Because of an extremely small number of Japanese patients enrolled in the BEACON CRC study, there are limitations to evaluating the efficacy of ENCO/BINI/Cmab and ENCO/Cmab in Japanese patients based on the comparison with the results in the entire population of the BEACON CRC study. Nevertheless, ENCO/BINI/Cmab and ENCO/Cmab are expected to show efficacy in Japanese patients as well, considering the demonstrated efficacy of ENCO/BINI/Cmab and ENCO/Cmab in the entire population of the BEACON CRC study [see Section 7.1.1.2], and from the following findings:

- In the safety lead-in part, BICR-assessed efficacy was observed in 3 of 7 Japanese patients receiving ENCO/BINI/Cmab. There was no clear difference between the Japanese population and the non-Japanese population in the response rate in the safety lead-in part (42.9% [3 of 7] in Japanese population, 41.4% [12 of 29] in non-Japanese population).
- In the additional analysis (data cut-off August 15, 2019), BICR-assessed efficacy was observed in 1 of 6 Japanese patients (16.7%) enrolled in the ENCO/Cmab group in the phase III part.

- No intrinsic or extrinsic ethnic factors were identified that would affect the treatment effect of ENCO/BINI/Cmab or ENCO/Cmab against colorectal cancer with *BRAF* mutation.
- No clear difference was observed in PK of ENCO or BINI between Japanese and non-Japanese subjects (see "Review Report of Braftovi Capsules 50 mg, dated November 19, 2018" and "Review Report of Mektovi Tablets 15 mg, dated November 19, 2018").
- No clear difference is observed between Japan and foreign countries in the diagnosis and treatment algorithm for unresectable advanced or recurrent colorectal cancer that has progressed after the first- or second-line therapy.

7.R.3 Safety [for adverse events, see Section "7.2 Adverse events, etc., observed in clinical studies"]

On the basis of the following review, PMDA concluded that adverse events requiring particular attention in treatment with ENCO/BINI/Cmab or ENCO/Cmab in patients with unresectable advanced or recurrent colorectal cancer with BRAF V600E mutation that has progressed after the first- or second-line therapy are events that were considered to require particular caution at the initial approval of ENCO and BINI (eye disorders, cardiac dysfunction, hepatic dysfunction, rhabdomyolysis, cutaneous malignancies, hypertension, haemorrhage, and palmar-plantar erythrodysaesthesia syndrome) (see "Review Report of Braftovi Capsules 50 mg, dated November 19, 2018" and "Review Report of Mektovi Tablets 15 mg, dated November 19, 2018"). Particular caution should be exercised against occurrence of the above adverse events in using ENCO/BINI/Cmab or ENCO/Cmab.

PMDA also concluded that although attention should be paid to the occurrence of the above adverse events in using ENCO/BINI/Cmab or ENCO/Cmab, the treatment with ENCO/BINI/Cmab or ENCO/Cmab is tolerable for patients with colorectal cancer provided that appropriate measures, such as monitoring and management of the above adverse events, and interruption, dose reduction or discontinuation of ENCO, BINI and/or Cmab, are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

7.R.3.1 Safety profiles of ENCO/BINI/Cmab and ENCO/Cmab

The applicant's explanation about the safety profiles of ENCO/BINI/Cmab and ENCO/Cmab based on the safety information obtained in the phase III part of the BEACON CRC study (only data on phase III part of the BEACON CRC study are provided in this section):

Table 10 shows the summary of safety in the BEACON CRC study.

Table 10. Summary of safety (phase III part of the BEACON CRC study)

	Number of patients (%)		
	ENCO/BINI/Cmab (n = 222)	ENCO/Cmab (n = 216)	IC (n = 193)
All adverse events	217 (97.7)	212 (98.1)	188 (97.4)
Grade ≥3 adverse events	128 (57.7)	108 (50.0)	117 (60.6)
Adverse events leading to death	9 (4.1)	7 (3.2)	8 (4.1)
Serious adverse events	93 (41.9)	71 (32.9)	71 (36.8)
Adverse events leading to treatment discontinuation*	33 (14.9)	25 (11.6)	33 (17.1)
ENCO	21 (9.5)	21 (9.7)	—
BINI	24 (10.8)	—	—
Cmab	25 (11.3)	19 (8.8)	26 (13.5)
Adverse events leading to treatment interruption*	146 (65.8)	98 (45.4)	103 (53.4)
ENCO	119 (53.6)	72 (33.3)	—
BINI	127 (57.2)	—	—
Cmab	96 (43.2)	66 (30.6)	79 (40.9)
Adverse events leading to dose reduction	68 (30.6)	22 (10.2)	58 (30.1)
ENCO	39 (17.6)	19 (8.8)	—
BINI	60 (27.0)	—	—
Cmab	13 (5.9)	5 (2.3)	11 (5.7)

* Adverse events leading to discontinuation, interruption, or dose reduction of any of the study drugs.

(a) Comparison between the ENCO/BINI/Cmab group and the IC group:

In the BEACON CRC study, all-Grade adverse events with a ≥10% higher incidence in the ENCO/BINI/Cmab group than in the IC group were diarrhoea (137 patients [61.7%] in the ENCO/BINI/Cmab group, 93 patients [48.2%] in the IC group), anaemia (80 patients [36.0%], 37 patients [19.2%]), dry skin (46 patients [20.7%], 13 patients [6.7%]), and vision blurred (25 patients [11.3%], 1 patient [0.5%]). Grade ≥3 adverse event with a ≥5% higher incidence was anaemia (37 patients [16.7%], 12 patients [6.2%]). Serious adverse events with a ≥2% higher incidence were acute kidney injury (7 patients [3.2%], 1 patient [0.5%]) and nausea (7 patients [3.2%], 1 patient [0.5%]). Adverse events leading to interruption of the study drug with a ≥2% higher incidence were diarrhoea (41 patients [18.5%], 18 patients [9.3%]), vomiting (19 patients [8.6%], 6 patients [3.1%]), queasy (16 patients [7. 2%], 3 patients [1.6%]), anaemia (12 patients [5.4%], 2 patients [1.6%]), pyrexia (10 patients [4.5%], 4 patients [2.1%]), blood creatinine increased (9 patients [4.1%], 1 patient [0.5%]), blood creatine phosphokinase (CK) increased (8 patients [3.6%], 0 patients), rash pustular (6 patients [2.7%], 1 patient [0.5%]), urinary tract infection (6 patients [2.7%], 0 patients), and vision blurred (6 patients [2.7%], 0 patients). There were no adverse events leading to death, discontinuation or dose reduction of the study drug that occurred with a ≥2% higher incidence in the ENCO/BINI/Cmab group than in the IC group.

(b) Comparison between the ENCO/Cmab group and the IC group:

All-Grade adverse events with a ≥10% higher incidence in the ENCO/Cmab group than in the IC group were headache (42 patients [19.4%] in the ENCO/Cmab group, 5 patients [2.6%] in the IC group), arthralgia (41 patients [19.0%], 1 patient [0.5%]), melanocytic naevus (31 patients [14.4%], 0 patients), myalgia (29 patients [13.4%], 4 patients [2.1%]), and musculoskeletal pain (27 patients [12.5%], 3 patients [1.6%])]. The adverse event leading to interruption of the study drug with a ≥2% higher incidence was queasy (8 patients [3.7%], 3 patients [1.6%]). There were no Grade ≥3 adverse events that occurred with a ≥5% higher incidence, adverse events leading to death, serious adverse events, or adverse events leading to discontinuation or dose reduction of the study drugs that occurred with a ≥2% higher incidence in the ENCO/Cmab group than in the IC group.

(c) Comparison between the ENCO/BINI/Cmab group and the ENCO/Cmab group:

All-Grade adverse events with a ≥10% higher incidence in the ENCO/BINI/Cmab group than in the ENCO/Cmab group were diarrhoea (137 patients [61.7%] in the ENCO/BINI/Cmab group, 72 patients [33.3%] in the ENCO/Cmab group), dermatitis acneiform (108 patients [48.6%], 63 patients [29.2%]), nausea (100 patients [45.0%], 74 patients [34.3%]), vomiting (85 patients [38.3%]), 46 patients [21.3%]), and anaemia (80 patients [36.0%], 35 patients [16.2%]). Grade ≥3 adverse events with a ≥5% higher incidence were anaemia (37 patients [16.7%], 10 patients [4.6%]) and diarrhoea (22 patients [9.9%], 4 patients [1.9%]). Serious adverse events with a ≥2% higher incidence were pulmonary embolism (8 patients [3.6%], 3 patients [1.4%]) and diarrhoea (8 patients [3.6%], 0 patients). Adverse events leading to interruption of the study drug with a ≥2% higher incidence were diarrhoea (41 patients [18.5%], 6 patients [2.8%)), vomiting (19 patients [8.6%], 9 patients [4.2%]), queasy (16 patients [7.2%], 8 patients [3.7%]), anaemia (12 patients [5.4%], 3 patients [1.4%]), asthenia (10 patients [4.5%], 5 patients [2.3%]), blood creatinine increased (9 patients [4.1%], 0 patients), blood CK increased (8 patients [3.6%], 0 patients), rash pustular (6 patients [2.7%]), 1 patient [0.5%]), and vision blurred (6 patients [2.7%], 1 patient [0.5%]). The adverse event leading to dose reduction of the study drug with a ≥2% higher incidence was diarrhoea (23 patients [10.4%], 1 patient [0.5%]). There were no adverse events leading to death or discontinuation of the study drug that occurred with a ≥2% higher incidence in the ENCO/BINI/Cmab group than in the ENCO/Cmab group.

All-Grade adverse events with a ≥10% higher incidence in the ENCO/Cmab group than in the ENCO/BINI/Cmab group were headache (42 patients [19.4%] in the ENCO/Cmab group, 16 patients [7.2%] in the ENCO/BINI/Cmab group) and melanocytic naevus (31 patients [14.4%], 1 patient [0.5%]). The adverse event leading to death that occurred with a ≥2% higher incidence was disease progression (20 patients [9.3%], 10 patients [4.5%]). The adverse event leading to interruption of the study drug that occurred with a ≥2% higher incidence was infusion related reaction (10 patients [4.6%], 2 patients [0.9%]). There were no Grade ≥3 adverse events with a ≥5% higher incidence in the ENCO/Cmab group than in the ENCO/BINI/Cmab group, serious adverse events or adverse events leading to discontinuation or dose reduction of the study drug that occurred with a ≥2% higher incidence.

The applicant's explanation about the difference in the safety profiles of ENCO and BINI between patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that had progressed after the first- or second-line therapy (BEACON CRC study) and patients with unresectable malignant melanoma with *BRAF* gene mutation, the approved indication (global phase III study [Study CMEK162B2301 (Study B2301)]):

Table 11 shows the summary of safety in the ENCO/BINI/Cmab group and the ENCO/Cmab group in the phase III part of the BEACON CRC study and in the ENCO/BINI group in Study B2301.

Table 11. Summary of safety in the BEACON CRC study and Study B2301

	Number of patients (%)		
	Colorectal cancer (the BEACON CRC study)		Malignant melanoma (Study B2301)
	ENCO/BINI/Cmab[*1] (n = 222)	ENCO/Cmab[*2] (n = 216)	ENCO/BINI[*3] (n = 192)
All adverse events	217 (97.7)	212 (98.1)	189 (98.4)
Grade ≥3 adverse events	128 (57.7)	108 (50.0)	111 (57.8)
Adverse events leading to death	9 (4.1)	7 (3.2)	9 (4.7)
Serious adverse events	93 (41.9)	71 (32.9)	66 (34.4)
Adverse events leading to treatment discontinuation[*4]	33 (14.9)	25 (11.6)	24 (12.5)
Adverse events leading to treatment interruption[*4]	146 (65.8)	98 (45.4)	88 (45.8)
Adverse events leading to dose reduction[*4]	68 (30.6)	22 (10.2)	22 (11.5)

*1 ENCO 300 mg QD and BINI 45 mg BID were administered orally.
*2 ENCO 300 mg QD was administered orally.
*3 ENCO 450 mg QD and BINI 45 mg BID were administered orally.
*4 Adverse events that led to discontinuation, interruption, or dose reduction of any of the study drugs.

All-Grade adverse events with a ≥10% higher incidence in the ENCO/BINI/Cmab group of the BEACON CRC study than in the ENCO/BINI group of Study B2301 were diarrhoea (137 patients [61.7%] in the ENCO/BINI/Cmab group of the BEACON CRC study, 70 patients [36.5%] in the ENCO/BINI group of Study B2301), dermatitis acneiform (108 patients [48.6%], 5 patients [2.6%]), anaemia (80 patients [36.0%], 29 patients [15.1%]), abdominal pain (65 patients [29.3%], 32 patients [16.7%]), decreased appetite (63 patients [28.4%], 16 patients [8.3%]), and stomatitis (31 patients [14.0%], 4 patients [2.1%]). Grade ≥3 adverse events with a ≥5% higher incidence were anaemia (37 patients [16.7%], 8 patients [4.2%]) and diarrhoea (22 patients [9.9%], 5 patients [2.6%]). Serious adverse events with a ≥2% higher incidence were pulmonary embolism (8 patients [3.6%], 3 patients [1.6%]), diarrhoea (8 patients [3.6%], 1 patient [0.5%]), nausea (7 patients [3.2%], 2 patients [1.0%]), intestinal obstruction (6 patients [2.7%], 0 patients), and ileus (5 patients [2.3%], 0 patients). Adverse events leading to interruption of the study drug with a ≥2% higher incidence were diarrhoea (41 patients [18.5%], 6 patients [3.1%]), anaemia (12 patients [5.4%], 4 patients [2.1%]), asthenia (10 patients [4.5%], 1 patient [0.5%]), vision blurred (6 patients [2.7%], 0 patients), rash pustular (5 patients [2.3%], 0 patients), and hypomagnesemia (5 patients [2.3%], 0 patients). The adverse event leading to dose reduction of the study drug with a ≥5% higher incidence was diarrhoea (23 patients [10.4%], 1 patient [0.5%]). There were no adverse events leading to death or discontinuation of the study drug that occurred with a ≥2% higher incidence.

All-Grade adverse events with a ≥10% higher incidence in the ENCO/Cmab group of the BEACON CRC study than in the ENCO/BINI group of Study B2301 were dermatitis acneiform (63 patients [29.2%] in the ENCO/Cmab group of the BEACON CRC study, 5 patients [2.6%] in the ENCO/BINI group of Study B2301), decreased appetite (58 patients [26.9%], 16 patients [8.3%]), melanocytic naevus (31 patients [14.4%], 3 patients [1.6%]), and hypomagnesemia (22 patients [10.2%], 0 patients). Serious adverse events with a ≥2% higher incidence were intestinal obstruction (10 patients [4.6%], 0 patients) and cancer pain (5 patients [2.3%], 0 patients). Adverse events leading to interruption of the study drug with a ≥2% higher incidence were infusion related reaction (10 patients [4.6%], 0 patients) and intestinal obstruction (7 patients [3.2%], 0 patients). There were no Grade ≥3 adverse events that occurred with a ≥5% higher incidence, adverse events leading to death, adverse events leading to discontinuation or dose reduction of the study drug that occurred with a ≥2% higher incidence.

PMDA's view:

Given the following findings, ENCO/BINI/Cmab and ENCO/Cmab are tolerable for patients with colorectal cancer as well, provided that appropriate measures, such as monitoring and management of adverse events, interruption, or dose reduction of ENCO, BINI and/or Cmab, are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

- In the BEACON CRC study, there were adverse events with a higher incidence in the ENCO/BINI/Cmab group or the ENCO/Cmab group than in the IC group. However, they were known adverse events for ENCO, BINI, or Cmab.
- Although there were adverse events with a higher incidence in patients with colorectal cancer than in patients with malignant melanoma (approved indication), there was no tendency of a higher incidence in adverse events leading to death or in serious adverse events.

7.R.3.2 Difference in safety between Japanese and non-Japanese patients

The applicant's explanation about the difference in the safety of ENCO/BINI/Cmab and ENCO/Cmab between Japanese and non-Japanese patients, based on the safety information obtained from the safety lead-in part and the phase III part of the BEACON CRC study:

Table 12 shows the summary of safety in Japanese and non-Japanese patients in the ENCO/BINI/Cmab group (safety lead-in part and the phase III part), and in the ENCO/Cmab group (phase III part) of the BEACON CRC study.

Table 12. Summary of safety in Japanese and non-Japanese patients (the BEACON CRC study)

	Number of patients (%)			
	ENCO/BINI/Cmab (Safety lead-in part and phase III part combined)		ENCO/Cmab (Phase III part)	
	Japanese (n = 10)	Non-Japanese (n = 249)	Japanese (n = 6)	Non-Japanese (n = 210)
All adverse events	9 (90.0)	245 (98.4)	6 (100)	206 (98.1)
Grade ≥3 adverse events	6 (60.0)	148 (59.4)	2 (33.3)	106 (50.5)
Adverse events leading to death	0	2 (0.8)	0	7 (3.3)
Serious adverse events	4 (40.0)	111 (44.6)	1 (16.7)	70 (33.3)
Adverse events leading to treatment discontinuation*	0	41 (16.5)	0	25 (11.9)
Adverse events leading to treatment interruption*	8 (80.0)	168 (67.5)	4 (66.7)	94 (44.8)
Adverse events leading to dose reduction*	5 (50.0)	79 (31.7)	2 (33.3)	20 (9.5)

* Adverse events that led to discontinuation, interruption, or dose reduction of any of the study drugs.

All-Grade adverse events with a higher incidence in Japanese than in non-Japanese patients that were reported by ≥3 Japanese patients in the ENCO/BINI/Cmab group were dermatitis acneiform (7 Japanese patients [70.0%], 126 non-Japanese patients [50.6%]), pyrexia (4 patients [40.0%], 56 patients [22.5%]), decreased appetite (3 patients [30.0%], 74 patients [29.7%]), dry skin (3 patients [30.0%], 62 patients [24.9%]), stomatitis (3 patients [30.0%], 34 patients [13.7%]), vision blurred (3 patients [30.0%], 34 patients [13.7%]), blood CK increased (3 patients [30.0%], 30 patients [12.0%]), blood creatinine increased (3 patients [30.0%], 26 patients [10.4%]), and alanine aminotransferase (ALT) increased (3 patients [30.0%], 18 patients [7.2%]). Grade ≥3 adverse events reported by ≥2 Japanese patients were anaemia (2 patients [20.0%], 40 patients [16.1%]) and blood creatinine increased (2 patients [20.0%], 5

patients [2.0%]). Serious adverse events reported by ≥1 Japanese patients were diarrhoea (1 patient [10.0%], 8 patients [3.2%]), large intestine perforation (1 patient [10.0%], 3 patients [1.2%]), colitis (1 patient [10.0%], 2 patients [0.8%]), hydronephrosis (1 patient [10.0%], 1 patient [0.4%]), and blood CK increased (1 patient [10.0%], 0 patient). Adverse events leading to interruption of the study drug in ≥2 Japanese patients were diarrhoea (2 patients [20.0%], 46 patients [18.5%]), blood creatinine increased (2 patients [20.0%], 15 patients [6.0%]), pyrexia (2 patients [20.0%], 13 patients [5.2%]), decreased appetite (2 patients [20.0%], 5 patients [2.0%]), colitis (2 patients [20.0%], 2 patients [0.8%]), and macular oedema (2 patients [20.0%], 0 patients). The adverse event leading to dose reduction of the study drug in ≥2 Japanese patients was decreased appetite (2 patients [20.0%], 3 patients [1.2%]). There were no adverse events leading to death or discontinuation of the study drug in Japanese patients.

All-Grade adverse events with a higher incidence in Japanese than in non-Japanese patients that were reported by ≥2 Japanese patients in the ENCO/Cmab group were malaise (5 Japanese patients [83.3%], 60 non-Japanese patients [28.6%]), nausea (3 patients [50.0%], 71 patients [33.8%]), diarrhoea (2 patients [33.3%], 70 patients [33.3%]), decreased appetite (2 patients [33.3%], 56 patients [26.7%]), headache (2 patients [33.3%], 40 patients [19.0%]), and constipation (2 patients [33.3%], 31 patients [14.8%]). Serious adverse events reported by ≥1 Japanese patients were pulmonary embolism (1 patient [16.7%], 2 patients [1.0%]), skin infection (1 patient [16.7%], 0 patient), and dehydration (1 patient [16.7%], 0 patient). Adverse events leading to interruption of the study drug in ≥2 Japanese patients were malaise (2 patients [33.3%], 4 patients [1.9%]) and decreased appetite (2 patients [33.3%], 0 patients). The adverse event leading to dose reduction of the study drug in ≥2 Japanese patients was decreased appetite (2 patients [33.3%], 0 patients). There were no Grade ≥3 adverse events reported by ≥2 Japanese patients. There were no adverse events leading to death or discontinuation of the study drug in Japanese patients.

PMDA's view:
Because of the small number of Japanese patients investigated in the BEACON CRC study, there are limitations to comparing safety between Japanese and non-Japanese patients. However, taking account of the lack of any clear difference between Japanese and non-Japanese patients in the incidence of Grade ≥3 adverse events or serious adverse events, ENCO/BINI/Cmab and ENCO/Cmab are tolerable in Japanese patients provided that appropriate measures such as treatment interruption or dose reduction of each drug are taken.

Because of the limited safety information available in Japanese patients, relevant information should be collected after the launch of ENCO and BINI, and once available, new information should be provided appropriately to healthcare professionals.

7.R.4 Clinical positioning and indications

The proposed indication for ENCO and BINI was "unresectable advanced or recurrent colorectal cancer with *BRAF* mutation." The following descriptions were included the "Precautions Concerning Indications" section:

- ENCO and BINI should be administered to patients with *BRAF* mutation confirmed by tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic should be used in the test.
- Suitable patients should be selected based on a thorough understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of ENCO and BINI.
- The efficacy and safety of ENCO and BINI in adjuvant chemotherapy have not been established.
- The efficacy and safety of ENCO and BINI in the first-line therapy have not been established.
- The efficacy and safety of ENCO and BINI in neoadjuvant chemotherapy of rectal cancer have not been established.

On the basis of the review in Sections "7.R.2 Efficacy" and "7.R.3 Safety" and in the following sections, PMDA concluded that the indication for ENCO and BINI should be modified as "unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy," with the following cautions in the "Precautions Concerning Indications" section:

- ENCO and BINI should be administered to patients with *BRAF* mutation confirmed by tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic or medical device should be used in the test.
- Suitable patients should be selected based on a thorough understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of ENCO and BINI.
- The efficacy and safety of ENCO and BINI in adjuvant chemotherapy have not been established.
- The efficacy and safety of ENCO and BINI in the first-line therapy have not been established.

7.R.4.1 Clinical positioning of ENCO/BINI/Cmab and ENCO/Cmab

In Japanese and foreign clinical practice guidelines and leading clinical oncology textbooks, descriptions on ENCO/BINI/Cmab and ENCO/Cmab in the treatment of patients with unresectable advanced or recurrent colorectal cancer with BRAF V600E mutation that has progressed after the first- or second-line therapy are as shown below.

Clinical practice guidelines

- NCCN Guidelines (colorectal cancer) (v.3.2020):
  Co-administration of ENCO and anti-EGFR antibody drug (Cmab or Pmab) is recommended as a secondary or subsequent lines of therapy for patients with unresectable advanced or recurrent colorectal cancer with BRAF V600E mutation.

The applicant's explanation about the clinical positioning of ENCO/BINI/Cmab and ENCO/Cmab from the viewpoint of (a) clinical significance of co-administration of ENCO, BINI, and Cmab in patients investigated in the BEACON CRC study and (b) benefit-risk balance based on the results of the BEACON CRC study:

(a) Clinical significance of co-administration of ENCO, BINI, and Cmab in patients investigated in the BEACON CRC study:

The following are the background and the reasons for co-administering (i) ENCO and Cmab and (ii) ENCO, BINI, and Cmab in the BEACON CRC study.

(i) The following findings suggested that co-administration of ENCO (a BRAF inhibitor) and Cmab (an anti-EGFR antibody drug) would lead to enhanced tumor growth-inhibitory activity.

- EGFR is more highly expressed in colorectal cancer with *BRAF* mutation than in malignant melanoma with *BRAF* mutation. Inhibition of BRAF induces activation of EGFR-mediated MAPK pathway, resulting in limited suppression of tumor growth-inhibitory activity by BRAF inhibitor monotherapy, whereas co-administration of BRAF inhibitor and EGFR inhibitor leads to an enhanced tumor growth-inhibitory effect (*Nature.* 2012;483:100-3, *Cancer Discov.* 2012;2:227-35, etc.).
- In Study X2101, the response rate to ENCO monotherapy was 5.6% (1 of 18) of patients with unresectable advanced or recurrent colorectal cancer with BRAF V600E mutation, whereas in Study X2103, the response rate to ENCO/Cmab was 22.0% (12 of 50) of patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation.

(ii) In addition to (i) above, the following observations suggested that further co-administration of BINI (a MEK inhibitor) with ENCO/Cmab would lead to a still higher efficacy.

- In colorectal cancer-derived cell lines with *BRAF* mutation, co-administration of ENCO and BINI exhibited an enhanced tumor growth-inhibitory effect [see Section 3.3.1.1.1]. In colorectal cancer-derived cell line that has acquired resistance to BRAF inhibitor, reactivation of MAPK pathway due to *KRAF* gene amplification, *BRAF* gene amplification, etc., is observed (*Cancer Discov.* 2015;5:358-67). These results suggest that co-administration of BRAF and MEK inhibitors would delay the resistance acquisition due to reactivation of MAPK pathway.
- In the study using mice subcutaneously transplanted with colorectal cancer-derived cell line with BRAF V600E mutation, the tumor growth-inhibitory effect of ENCO/BINI/Cmab tended to be higher than that caused by ENCO, BINI, or Cmab alone or by combination of any 2 of them [see Section 3.3.1.1.2].
- In Study X2101, the response rate to ENCO monotherapy was 5.6% (1 of 18) of patients with unresectable advanced or recurrent colorectal cancer with BRAF V600E mutation, whereas in Study X2110 in patients with the same disease, the response rate to ENCO/BINI was 18.2% (2 of 11) of patients. These results suggest that co-administration of ENCO and BINI leads to an enhanced tumor growth-inhibitory effect.

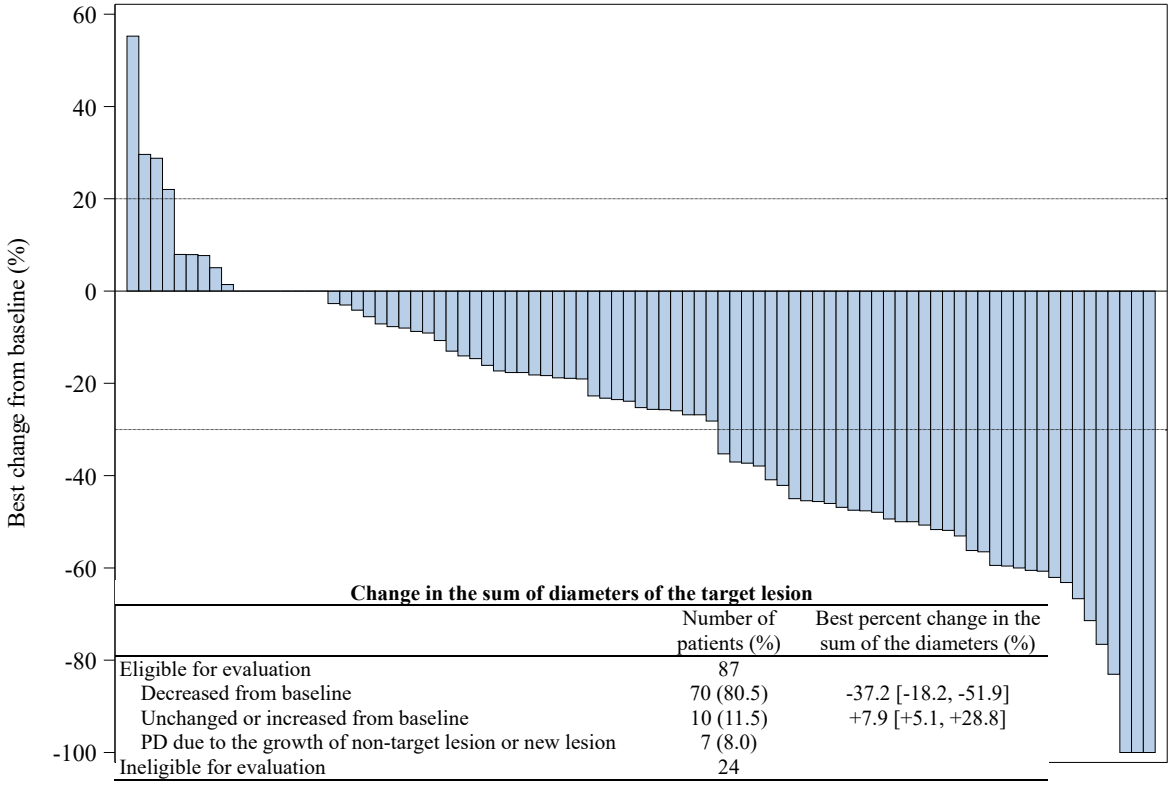
(b) Benefit-risk balance of ENCO/BINI/Cmab and ENCO/Cmab based on the results of the BEACON CRC study:

Results of the clinical study described in Sections “7.R.2 Efficacy” and “7.R.3 Safety” suggested to demonstrate the clinical benefit of both ENCO/BINI/Cmab and ENCO/Cmab in patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after the first- or second-line therapy. The main objective of the BEACON CRC study is not to compare the efficacy and safety for ENCO/BINI/Cmab and ENCO/Cmab, but the benefit-risk balance of

ENCO/BINI/Cmab was compared with that of ENCO/Cmab based on the results of the exploratory analysis of this study as shown below.

(i) Efficacy

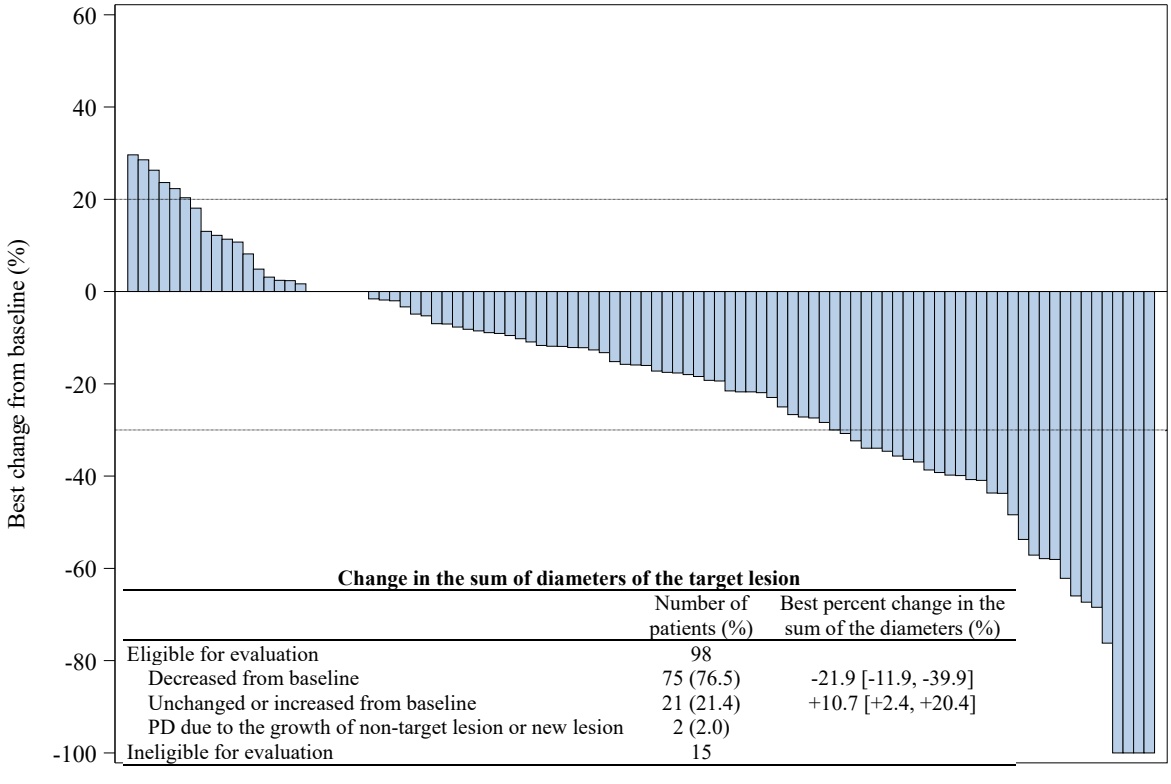
In the BEACON CRC study, the response rate in the ENCO/BINI/Cmab group and the ENCO/Cmab group was 26.1% (29 of 111 patients) and 20.4% (23 of 113 patients), respectively, showing a higher tendency in the ENCO/BINI/Cmab group than in the ENCO/Cmab group [see Section 7.1.1.2]. Figures 7 and 8 show the best percent change in the sum of the diameters of the target lesion, assessed by BICR based on RECIST ver. 1.1 (data cut-off February 11, 2019).



Change in the sum of diameters of the target lesion

	Number of patients (%)	Best percent change in the sum of the diameters (%)
Eligible for evaluation	87	
Decreased from baseline	70 (80.5)	-37.2 [-18.2, -51.9]
Unchanged or increased from baseline	10 (11.5)	+7.9 [+5.1, +28.8]
PD due to the growth of non-target lesion or new lesion	7 (8.0)	
Ineligible for evaluation	24	

Figure 7. Best percent change in the sum of the diameters of the target lesion (ENCO/BINI/Cmab group) (RECIST ver. 1.1, Phase III part, RES, BICR assessment, data cut-off February 11, 2019)



Change in the sum of diameters of the target lesion

	Number of patients (%)	Best percent change in the sum of the diameters (%)
Eligible for evaluation	98	
Decreased from baseline	75 (76.5)	-21.9 [-11.9, -39.9]
Unchanged or increased from baseline	21 (21.4)	+10.7 [+2.4, +20.4]
PD due to the growth of non-target lesion or new lesion	2 (2.0)	
Ineligible for evaluation	15	

Figure 8. Best percent change in the sum of the diameters of the target lesion (ENCO/Cmab group) (RECIST ver. 1.1, Phase III part, RES, BICR assessment, data cut-off February 11, 2019)

The hazard ratio [95% CI] of the ENCO/BINI/Cmab group to the ENCO/Cmab group at the interim analysis was 0.79 [0.59, 1.06], showing a tendency of prolonging OS in the ENCO/BINI/Cmab group, whereas at the additional analysis (data cut-off August 15, 2019), the hazard ratio [95% CI] was 0.95 [0.74, 1.21].

The possibility that the imbalance of the patient characteristics between the treatment groups affected the results of the analysis of OS was investigated by a univariate Cox regression model. Results identified 5 factors (CRP >1 mg/dL, hepatic metastasis, CEA >5 μg/L, CA19-9 >35 U/mL, and number of organs involved ≥3), with each factor showing distribution differences between the treatment groups.[17)] Table 13 shows the results of the sensitivity analysis of OS adjusted for the distribution of 5 factors above between the treatment groups. The adjusted hazard ratio of the ENCO/BINI/Cmab group to the ENCO/Cmab group tended to be similar to that observed at the interim analysis.

Table 13. Sensitivity analysis of OS (phase III part, FAS)

	Hazard ratio [95% CI]*	
	Unadjusted	Adjusted
At the time of interim analysis (data cut-off February 11, 2019)		
Comparison between ENCO/BINI/Cmab and IC	0.52 [0.39, 0.70]	0.45 [0.33, 0.60]
Comparison between ENCO/Cmab and IC	0.60 [0.45, 0.79]	0.55 [0.41, 0.74]
Comparison between ENCO/BINI/Cmab and ENCO/Cmab	0.79 [0.59, 1.06]	0.73 [0.54, 1.00]
At the time of additional analysis (data cut-off August 15, 2019)		
Comparison between ENCO/BINI/Cmab and IC	0.60 [0.47, 0.75]	0.50 [0.39, 0.63]
Comparison between ENCO/Cmab and IC	0.61 [0.48, 0.77]	0.59 [0.46, 0.76]
Comparison between ENCO/BINI/Cmab and ENCO/Cmab	0.95 [0.74, 1.21]	0.84 [0.65, 1.08]

*, Stratified Cox proportional hazard model with ECOG PS (0, 1), prior treatment with IRI (yes, no), and source of Cmab (US, Europe) as stratification factors

(ii) Safety

The combination use of BRAF and MEK inhibitors decreases the incidences of skin-related adverse events such as cutaneous proliferative lesions and palmar-plantar erythrodysaesthesia syndrome that are supposedly caused by BRAF inhibitor (*N Engl J Med*. 2014;371:1877-88, etc.), suggesting a difference in the safety profile between the ENCO/BINI/Cmab and ENCO/Cmab groups. Results of the BEACON CRC study showed that the incidences of diarrhoea, vomiting, and anaemia were higher in the ENCO/BINI/Cmab group whereas the incidences of headache, arthralgia, and skin-related adverse events such as melanocytic naevus tended to be higher in the ENCO/Cmab group, showing a difference in the safety profile between the treatment groups. All of these adverse events are known to be associated with the use of ENCO or BINI, posing no novel safety concerns. Thus, they were considered to be manageable by the interruption, dose reduction, and discontinuation of ENCO or BINI. The incidences of serious adverse events and adverse events that led to interruption or dose reduction of the study drug tended to be higher in the ENCO/BINI/Cmab group than in the ENCO/Cmab group. However, no clear difference was observed between the treatment groups in the incidence of adverse events resulting in the discontinuation of all of the study drugs, which suggested that adverse events associated with ENCO/BINI/Cmab and with ENCO/Cmab are both manageable.

17) The percentage of patients with each factor in the ENCO/BINI/Cmab group, the ENCO/Cmab group, and the IC group was as follows:
- CRP >1 mg/dL: 95 patients (42.4%), 79 patients (35.9%), and 90 patients (40.7%)
- Hepatic metastasis: 144 patients (64.3%), 134 patients (60.9%), and 128 patients (57.9%)
- CEA >5 μg/L: 179 patients (79.9%), 153 patients (69.5%), and 178 patients (80.5%)
- CA19-9 >35 U/mL: 159 patients (71.0%), 149 patients (67.7%), and 156 patients (70.6%)
- Number of organs involved ≥3: 110 patients (49.1%), 103 patients (46.8%), 98 patients (44.3%)

The results discussed in (i) and (ii) above suggest a favorable benefit-risk balance for both ENCO/BINI/Cmab and ENCO/Cmab. However, given the following findings, ENCO/BINI/Cmab appears to be preferable than ENCO/Cmab in patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after the first- or second-line therapy.

- Results of the exploratory analysis suggest that the response rate is higher with a tendency of more prolonged OS in the ENCO/BINI/Cmab group than in the ENCO/Cmab group.
- Among patients with colorectal cancer, patients with *BRAF* mutation are characterized by a higher proportion of patients with component of poorly differentiated adenocarcinoma or mucinous carcinoma, a large tumor diameter, and peritoneal dissemination, and they are prone to aggravation of clinical symptoms such as intestinal obstruction associated with tumor enlargement, pain, etc., and to rapid disease progression (*Br J Cancer*. 2011;104:856-62, *Ann Oncol*. 2016;27:1746-53, etc.). In these patients, it is critical to control the disease progression at the earlier stage by shrinking the tumor. ENCO/BINI/Cmab, which showed a tendency of a higher tumor shrinking effect than ENCO/Cmab, may possibly provide benefits of improving clinical symptoms, ADL, and QOL (*J Clin Oncol*. 2008;26:2311-9, etc.)
- Patients with colorectal cancer with *BRAF* mutation who poorly respond to conventional treatments can be treated with ENCO/Cmab, the treatment regimen with shown clinical usefulness in this group of patients, even if continued treatment with ENCO/BINI/Cmab is no longer feasible due to adverse events associated with BINI. Results of the BEACON CRC study showed that 3 of 4 patients responded to continued treatment with ENCO/BINI after discontinuation of Cmab, suggesting the usefulness of continued treatment with ENCO/BINI [see Section 7.R.5.1].

There are no clinical data available on the comparison of the efficacy and safety between (1) ENCO/BINI/Cmab or ENCO/Cmab and (2) combination of FOLFIRI and RAM (FOLFIRI/RAM), combination of FOLFIRI and AFL (FOLFIRI/AFL), regorafenib, FTD/TPI, etc. in patients with unresectable advanced or recurrent colorectal cancer with BRAF V600E mutation that has progressed after the first- or second-line therapy. However, given the following findings, ENCO/BINI/Cmab and ENCO/Cmab appear to be preferable than these treatments.

- In the global phase III study in patients with unresectable advanced or recurrent colorectal cancer that has progressed after the first-line therapy including L-OHP, FOLFIRI/RAM and FOLFIRI/AFL exhibited a statistically significant OS prolongation compared with FOLFIRI (*Lancet Oncol.* 2015;16:499-508, *J Clin Oncol.* 2012;30:3499-506). However, their efficacy in patients with *BRAF* mutation has not been demonstrated.
- NCCN Guidelines (colorectal cancer) (v.3.2020) recommends ENCO/Cmab in preference to regorafenib and FTD/TPI, taking account of the results of the following clinical studies:
  - In the global phase III study comparing the efficacy and safety between regorafenib and placebo in patients with unresectable advanced or recurrent colorectal cancer that has progressed after the standard therapy,[18] the response rate in the regorafenib group was 1.0% (*Lancet.* 2013;381:303-12).

[18] Patients with a prior treatment with (a) fluoropyrimidine-based antineoplastic agent, (b) L-OHP, (c) IRI, (d) BV, or (e) Cmab or Pmab (in patients with wild-type RAS) were enrolled in the study.

- In the global phase III study comparing the efficacy and safety between FTD/TPI and placebo in patients with unresectable advanced or recurrent colorectal cancer that has progressed after the standard therapy,[17] the response rate in the FTD/TPI group was 1.6% (*N Engl J Med.* 2015;372:1909-19).

PMDA's view:
The results of the BEACON CRC study demonstrated the clinical usefulness of ENCO/BINI/Cmab and ENCO/Cmab in patients with unresectable advanced or recurrent colorectal cancer that has progressed after the first- or second-line therapy. On the other hand, it is difficult to conclude the superior efficacy of ENCO/BINI/Cmab relative to ENCO/Cmab, given that comparison between the ENCO/BINI/Cmab group and the ENCO/Cmab group was performed as an exploratory analysis in the BEACON CRC study. Nevertheless, taking account of (1) the explanation of the applicant, (2) the finding that ENCO/BINI/Cmab showed a tendency of a higher tumor shrinking effect than ENCO/Cmab, and (3) the following situation, there is a certain clinical significance in providing ENCO/BINI/Cmab as a treatment option in addition to ENCO/Cmab.

- Colorectal cancer with *BRAF* mutation that has become refractory or resistant to the first- or second-line therapy is a serious disease condition. Given this disease condition and the characteristics of the clinical course in afflicted patients, a certain number of patients are presumed to have urgent need for tumor shrinkage aimed at symptom alleviation and QOL improvement.

However, given the above situations, it is inappropriate to conclude currently that ENCO/BINI/Cmab should be the preferred choice in all patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after the first- or second-line therapy. The treatment should be selected by physicians with adequate knowledge and experience in cancer chemotherapy who have fully understood the efficacy and safety of ENCO/BINI/Cmab and ENCO/Cmab, based on the general condition, disease state, and the purpose of the treatment in individual patients. So that patients for whom ENCO/BINI/Cmab or ENCO/Cmab is the most desirable treatment may be selected, beneficial information for selection and treatment of patients should be collected continuously, and once available, new information should be provided appropriately to healthcare professionals.

There are no data of clinical studies that compared the efficacy and safety between (1) ENCO/BINI/Cmab or ENCO/Cmab and (2) FOLFIRI/RAM, FOLFIRI/AFL, etc., in patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation. Therefore, which of these treatments should be used in these patients is unknown at present. The most suitable treatment option should be selected according to the conditions of individual patients upon thorough understanding of the efficacy and safety of these drugs.

7.R.4.2 Indication for ENCO/BINI/Cmab and ENCO/Cmab

The applicant's explanation about the target patients and the indication of ENCO/BINI/Cmab and ENCO/Cmab in patients with unresectable advanced or recurrent colorectal cancer:
Taking into account that BRAF V600E mutation accounts for approximately 90% of *BRAF* mutations in colorectal cancer (*J Gastrointest Oncol*. 2015;6:660-7), the subjects in the BEACON CRC study were limited to patients with confirmed BRAF V600E mutation. Given the following findings, etc.,

ENCO/BINI/Cmab and ENCO/Cmab are expected to be effective also in patients with *BRAF* mutations other than BRAF V600E, as determined from the aspect of the mechanism of action.

- ENCO alone and ENCO/BINI exhibit tumor growth-inhibitory activity against cell lines derived from malignant melanoma, non-small cell lung cancer, colorectal cancer, etc., with *BRAF* mutations other than BRAF V600E (*Clin Cancer Res.* 2018;24:6438-94, etc.).

In the BEACON CRC study, (i) patients with a prior treatment with EGFR inhibitor (including anti-EGFR antibody drug such as Cmab and Pmab) and (ii) patients without a prior chemotherapy were excluded. Neither ENCO/BINI/Cmab nor ENCO/Cmab is recommended in these patients because no data are available on clinical usefulness of these treatments in patient groups (i) and (ii). However, since there is no particular safety problem in re-administering anti-EGFR antibody drug to patients with unresectable advanced or recurrent colorectal cancer (*Cancer Treat Rev*. 2019;73:41-53), it is unnecessary to exclude patients in category (i) from treatment with ENCO/BINI/Cmab and ENCO/Cmab at the discretion of the attending physician.

Use of ENCO/BINI/Cmab and ENCO/Cmab as an adjuvant or neoadjuvant therapy is not recommended because there are no data on the clinical usefulness of such treatment.

On the basis of the above, the indication for ENCO and BINI is proposed as "unresectable advanced or recurrent colorectal cancer with *BRAF* mutation," with the following caution statement included in the "Precautions Concerning Indications" section, and the description of the type of *BRAF* mutation, prior treatment, etc., of patients enrolled in the BEACON CRC study in the "Clinical Studies" section of the package insert.

- Suitable patients should be selected based on a thorough understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of ENCO and BINI.
- The efficacy and safety of ENCO and BINI in adjuvant chemotherapy have not been established.
- The efficacy and safety of ENCO and BINI in the first-line therapy have not been established.
- The efficacy and safety of ENCO and BINI in neoadjuvant chemotherapy of rectal cancer have not been established.

PMDA's view:

PMDA generally accepted the above explanation of the applicant. However, given that the BEACON CRC study was conducted in patients whose disease had progressed after the first- or second-line therapy and did not include chemotherapy-naïve patients, it should be clearly indicated that ENCO/BINI/Cmab and ENCO/Cmab are intended to be used in patients whose disease has progressed after chemotherapy. Since no neoadjuvant therapy has been established as the standard treatment for rectal cancer in Japan, the precautionary statement "the efficacy and safety of ENCO and BINI in neoadjuvant chemotherapy of rectal cancer have not been established" is unnecessary.

On the basis of the above, the indication for ENCO and BINI should be "unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy," and that the following precautions should be included in the "Precautions Concerning Indications" section:

- Suitable patients should be selected based on a thorough understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of ENCO and BINI.
- The efficacy and safety of ENCO and BINI in adjuvant chemotherapy have not been established.
- The efficacy and safety of ENCO and BINI in the first-line therapy have not been established.

7.R.4.3 Test for *BRAF* mutation

The applicant's explanation about the test for *BRAF* mutation to be used in the selection of patients suitable for treatment with ENCO/BINI/Cmab or ENCO/Cmab:

In the BEACON CRC study, patients in the efficacy and safety analysis population were patients determined to have BRAF V600E mutation based on (1) the histological test conducted at the study site or (2) the histological test conducted using therascreen BRAF V600E PCR Kit (Qiagen K.K.) by the central laboratory[10)] [see Section 7.1.1.2]. Both "therascreen BRAF V600E RGQ PCR Kit" of Qiagen K.K. and "MEBGEN RASKET-B Kit" of Medical & Biological Laboratories Co., Ltd., were applied as companion diagnostics, etc., to assist the judgement on whether ENCO and BINI are indicated for individual patients. They demonstrated a favorable concordance rate with the test performed at the central laboratory and at the study site in the BEACON CRC study, when subjected to comparability test using the screening samples obtained in the BEACON CRC study. These proposed test kits will be able to identify patients for whom ENCO/BINI/Cmab and ENCO/Cmab are expected to be safe and effective.

On the basis of the above, suitable patients for the treatment with ENCO/BINI/Cmab or ENCO/Cmab should be selected using "therascreen BRAF V600E RGQ PCR Kit" or "MEBGEN RASKET-B Kit," and the following precautionary statement should be included in the "Precautions Concerning Indications" section.

- ENCO and BINI should be administered to patients with *BRAF* mutation confirmed by tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic should be used in the test.

PMDA's view:

The explanation of the applicant is acceptable. The "Precautions Concerning Indications" section should be modified as follows:

- ENCO and BINI should be administered to patients with *BRAF* mutation confirmed by tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic or medical device should be used in the test.

7.R.5 Dosage and administration

In this partial change application, the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections of ENCO and BINI for the treatment of unresectable advanced or recurrent colorectal cancer with *BRAF* mutation were proposed as follows:

	Dosage and Administration	Precautions Concerning Dosage and Administration
ENCO	In combination with BINI and Cmab, the usual adult dosage is 300 mg of ENCO administered orally once daily. The dose may be reduced according to the patient's condition.	[Common among indications] • Guide for interruption, dose reduction, and discontinuation of ENCO in case of adverse drug reactions [Unresectable advanced or recurrent colorectal cancer] • When both BINI and Cmab are interrupted or discontinued, ENCO should also be interrupted or discontinued, respectively.
BINI	In combination with ENCO and Cmab, the usual adult dosage is 45 mg of BINI administered orally twice daily. The dose may be reduced according to the patient's condition.	[Common among indications] • Guide for interruption, dose reduction, and discontinuation of BINI in case of adverse drug reactions [Unresectable advanced or recurrent colorectal cancer] • When ENCO is discontinued, BINI should also be discontinued. • When both ENCO and Cmab are interrupted, BINI should also be interrupted.

As a result of the review in Sections "7.R.2 Efficacy" and "7.R.3 Safety" and in the following sections, PMDA concluded that the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections of ENCO and BINI should be specified as shown in the following table.

	Dosage and Administration	Precautions Concerning Dosage and Administration
ENCO	In combination with Cmab or with BINI and Cmab, the usual adult dosage is 300 mg of ENCO administered orally once daily. The dose may be reduced according to the patient's condition.	[Common among indications] • Guide for interruption, dose reduction, and discontinuation of ENCO in case of adverse drug reactions [Unresectable advanced or recurrent colorectal cancer] • In combination with BINI and Cmab, when both BINI and Cmab are interrupted or discontinued, ENCO should also be interrupted or discontinued, respectively. • In combination with Cmab, when Cmab is interrupted or discontinued, ENCO should also be interrupted or discontinued, respectively. • Other antineoplastic agents to be co-administered should be selected with sufficient understanding of the content in the "Clinical Studies" section.
BINI	In combination with ENCO and Cmab, the usual adult dosage is 45 mg of BINI administered orally twice daily. The dose may be reduced according to the patient's condition.	[Common among indications] • Guide for interruption, dose reduction, and discontinuation of BINI in case of adverse drug reactions • When ENCO is interrupted or discontinued, BINI should also be interrupted or discontinued, respectively.

7.R.5.1 Dosage and administration of ENCO and BINI

The applicant's explanation of justification for the proposed dosage and administration of ENCO and BINI for the treatment of unresectable advanced or recurrent colorectal cancer with *BRAF* mutation:

In the phase III part of the BEACON CRC study conducted using the dosage regimen determined based on the following study results, etc., clinical usefulness of ENCO/BINI/Cmab and ENCO/Cmab was demonstrated in patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation. Therefore, the dosage and administration of ENCO and BINI were proposed based on those used in the BEACON CRC study.

- In the phase Ib part of the global phase Ib/II study (Study X2103), RP2D of ENCO in combination with Cmab was determined to be 400 mg QD. However, in the global phase I study (Study X2101), RP2D of ENCO monotherapy was 300 mg QD (see "Review Report of Braftovi Capsules 50 mg, dated November 19, 2018," "Review Report of Mektovi Tablets 15 mg, dated November 19, 2018"). For the safety in combination with Cmab, ENCO 300 mg QD was considered to be the preferred dosage regimen for the BEACON CRC study.

- In the foreign phase I study (Study 162-111), RP2D in BINI monotherapy was determined to be 45 mg BID (see "Review Report of Braftovi Capsules 50 mg, dated November 19, 2018" and "Review Report of Mektovi Tablets 15 mg, dated November 19, 2018").
- In the safety lead-in part of the BEACON CRC study, the tolerability of co-administration of ENCO 300 mg QD, BINI 45 mg BID, and Cmab was demonstrated [see Section 7.1.1.2].

In addition, given the following study results, even if continuation of treatment using BINI or Cmab becomes difficult due to adverse events after the start of treatment with ENCO/BINI/Cmab, treatment with ENCO/Cmab or ENCO/BINI is still expected to delay the disease progression. It is thus recommended to start with ENCO/BINI/Cmab. The combination use of ENCO/BINI/Cmab as a dosage regimen of ENCO and BINI should therefore be appropriate.

- The BEACON CRC study showed a statistically significant OS prolongation in the ENCO/Cmab group than in the IC group.
- Response was observed in 2 of 11 patients with colorectal cancer with *BRAF* mutation receiving ENCO/BINI in the phase II part of the foreign phase Ib/II study (Study X2110) and in 3 of 4 patients receiving ENCO/BINI for ≥2 weeks after discontinuation of Cmab in the ENCO/BINI/Cmab group in the phase III part of the BEACON CRC study.

Also, the following precautionary statements (a) and (b) are included in the "Precautions Concerning Dosage and Administration" section for reasons described below.

(a) When both BINI and Cmab are interrupted or discontinued, ENCO should also be interrupted or discontinued, respectively.
(b) When ENCO is discontinued, BINI also should be discontinued, and when both ENCO and Cmab are interrupted, BINI also should be interrupted.

- Given the following study results, the efficacy or safety of ENCO or BINI monotherapy in patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation has not been established:
  - In the dose expansion part of the global phase I study (Study X2101), the response rate was 5.6% (1 of 18 patients) among patients with colorectal cancer with *BRAF* mutation receiving ENCO 300 or 450 mg QD.
  - In the dose expansion part of the foreign phase I study (Study 162-111), the response rate was 0% (0 of 15 patients) among patients with colorectal cancer with *BRAF* mutation receiving BINI 45 mg BID.
- In the BEACON CRC study, continued administration of ENCO, BINI, or Cmab alone was not permitted. The protocol had specified that at least 2 of them be administered in combination.
- There are no data available on the clinical usefulness of BINI/Cmab in patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation. Continued treatment with BINI/Cmab is not recommended.

PMDA's view:

Taking account of the review in Section "7.R.4.1 Clinical positioning of ENCO/BINI/Cmab and ENCO/Cmab," there is little evidence for recommending ENCO/BINI/Cmab in all patients. Treatment

should be initiated after selecting either ENCO/BINI/Cmab or ENCO/Cmab according to the conditions of each patient by the physician with adequate knowledge and experience in cancer chemotherapy.

The "Dosage and Administration" and the "Precautions Concerning Dosage and Administration" sections of ENCO and BINI should be modified and specified as follows:

ENCO

- Dosage and Administration:
  In combination with Cmab or with BINI and Cmab, the usual adult dosage is 300 mg of ENCO administered orally once daily. The dose may be reduced according to the patient's condition.
- Precautions Concerning Dosage and Administration
  - Guide for interruption, dose reduction, and discontinuation of ENCO in case of adverse drug reactions
  - In combination with BINI and Cmab, when both BINI and Cmab are interrupted or discontinued, ENCO should also be interrupted or discontinued, respectively.
  - In combination with Cmab, when Cmab is interrupted or discontinued, ENCO should also be interrupted or discontinued, respectively.
  - Other antineoplastic agents to be co-administered should be selected with sufficient understanding of the content in the "Clinical Studies" section.

BINI

- Dosage and Administration
  In combination with ENCO and Cmab, the usual adult dosage is 45 mg of BINI administered orally twice daily. The dose may be reduced according to the patient's condition.
- Precautions Concerning Dosage and Administration
  - Guide for interruption, dose reduction, and discontinuation of BINI in case of adverse drug reactions
  - When ENCO is interrupted or discontinued, BINI should also be interrupted or discontinued, respectively.

7.R.5.2 Dose adjustment for ENCO and BINI

The applicant's explanation about the guide for interruption, dose reduction, and discontinuation of ENCO and BINI:

In the BEACON CRC study which was conducted using the roughly similar guide for dose adjustment in case of adverse drug reactions as those in the global phase III study (Study B2301) in patients with unresectable malignant melanoma with *BRAF* mutation, clinical usefulness of ENCO/BINI/Cmab and ENCO/Cmab was demonstrated in patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation who complied with the above guide. Therefore, the guide for interruption, dose reduction, and discontinuation were specified in the "Precautions Concerning Dosage and Administration" section of ENCO and BINI, based on the guide specified in the BEACON CRC study.

PMDA's view:

PMDA accepted the applicant's explanation. The guide for interruption, dose reduction, and discontinuation should be specified in the "Precautions Concerning Dosage and Administration" section, as shown below according to the proposal by the applicant.

ENCO

- In case of adverse drug reactions associated with ENCO, ENCO should be interrupted, reduced in dose, or discontinued by referring to the following criteria.

Table 14. Dose reduction of ENCO in continued administration

Dose reduction level*	Dose
Usual dose	300 mg QD
1-level dose reduction	225 mg QD
2-level dose reduction	150 mg QD
3-level dose reduction	Discontinue

* If the adverse event requiring dose reduction has improved to Grade ≤1, and there are no other concomitant adverse events, the dose may be increased according to the reverse steps.

Table 15. Criteria for dose adjustment in case of adverse drug reactions

Adverse drug reaction	Severity*	Measure
Retinal disease, uveitis	Grade 2	Interrupt ENCO until recovery to Grade ≤1. Resume ENCO at same dose or at 1-level lower dose.
	Grade 3	Interrupt ENCO until recovery to Grade ≤2. Resume ENCO at 1-level lower dose. Discontinue ENCO if Grade 3 persists.
	Grade 4	Discontinue ENCO.
Retinal vein occlusion	Grade ≥1	Discontinue ENCO.
Eye disorders (other than above)	Grade 3	Interrupt ENCO until recovery to Grade ≤1. If recovered within 21 days, resume ENCO at 1-level lower dose. Discontinue ENCO if not recovered within 21 days.
	Grade 4	Discontinue ENCO.
AST increased, ALT increased	Grade 2 (not accompanied by serum bilirubin increased)	If the symptom persists for >14 days, interrupt ENCO until recovery to Grade ≤1. Resume ENCO at same dose. If recurrent, interrupt ENCO until recovery and then resume at 1-level lower dose.
	Grade 2 (accompanied by serum bilirubin increased)	Interrupt ENCO until recovery to Grade ≤1. If recovered within 7 days, resume ENCO at 1-level lower dose. Discontinue ENCO if not recovered within 7 days.
	Grade 3 (not accompanied by serum bilirubin increased)	Interrupt ENCO until recovery to Grade ≤1. If recovered within 14 days, resume ENCO at same dose. If recovered after >14 days, resume ENCO at 1-level lower dose.
	Grade 3 (accompanied by serum bilirubin increased) and Grade 4	Discontinue ENCO.
Serum CK increased	Grade 3-4 (accompanied by serum creatinine increased)	Interrupt ENCO until recovery to Grade ≤1. If recovered within 21 days, resume ENCO at 1-level lower dose. Discontinue ENCO if not recovered within 21 days.
Electrocardiogram QT prolonged	QTc exceeds 500 ms, and the change from baseline is ≤60 ms.	Interrupt ENCO until QTc decreases to <500 ms. Resume ENCO at 1-level lower dose. Discontinue ENCO if recurrent.
	QTc exceeds 500 ms, and the change from baseline is >60 ms.	Discontinue ENCO.
Dermatitis	Grade 2	If the symptom persists or worsens, interrupt ENCO until recovery to Grade ≤1. Resume ENCO at same dose.
	Grade 3	Interrupt ENCO until recovery to Grade ≤1. Resume ENCO at same dose. If recurrent, interrupt ENCO until recovery and then resume at 1-level lower dose.
	Grade 4	Discontinue ENCO.
Palmar-plantar erythrodysaesthesia syndrome	Grade 2	If the symptom persists for >14 days, interrupt ENCO until recovery to Grade ≤1. Resume ENCO at same dose. If recurrent, interrupt ENCO until recovery and then consider resumption at 1-level lower dose.
	Grade 3	Interrupt ENCO until recovery to Grade ≤1. Resume ENCO at 1-level lower dose. If repeatedly recurrent, consider resumption at 1-level lower dose or discontinuation.
Other adverse drug reactions	Grade 2	If Grade 2 adverse reaction persists, consider interruption or dose reduction.
	Grade 3	Consider interruption until recovery to Grade ≤1. If recovered within 21 days, consider resumption at 1-level lower dose.
	Grade 4	Discontinue ENCO.

* Grade is determined according to NCI-CTCAE ver4.03.

BINI

- In case of adverse drug reactions associated with BINI, BINI should be interrupted, reduced in dose, or discontinued by referring to the following criteria.

Table 16. Dose reduction of BINI in continued administration (same as those for the approved indication)

Dose reduction level*	Dose
Usual dose	45 mg BID
1-level dose reduction	30 mg BID
2-level dose reduction	15 mg BID
3-level dose reduction	Discontinue

* If the adverse event requiring dose reduction has improved to Grade ≤1, and there are no other concomitant adverse events, the dose may be increased according to the reverse steps.

Table 17. Criteria for dose adjustment in case of adverse drug reactions

Adverse drug reaction	Severity*	Measure
Retinal disease, uveitis	Grade 2	Interrupt BINI until recovery to Grade ≤1. Resume BINI at same dose or at 1-level lower dose.
	Grade 3	Interrupt BINI until recovery to Grade ≤2. Resume BINI at 1-level lower dose. Discontinue BINI if Grade 3 persists.
	Grade 4	Discontinue BINI.
Retinal vein occlusion	Grade ≥1	Discontinue BINI.
Eye disorders (other than above)	Grade 3	Interrupt BINI until recovery to Grade ≤1. If recovered within 21 days, resume BINI at 1-level lower dose. Discontinue BINI if not recovered within 21 days.
	Grade 4	Discontinue BINI.
AST increased, ALT increased	Grade 2 (not accompanied by serum bilirubin increased)	Interrupt BINI until recovery to Grade ≤1. If recovered within 14 days, resume BINI at same dose. If recovered after >14 days, resume BINI at 1-level lower dose. If recurrent, interrupt BINI until recovery and then resume at 1-level lower dose.
	Grade 2 (accompanied by serum bilirubin increased)	Interrupt BINI until recovery to Grade ≤1. If recovered within 7 days, resume BINI at 1-level lower dose. Discontinue BINI if not recovered within 7 days.
	Grade 3 (not accompanied by serum bilirubin increased)	Interrupt BINI until recovery to Grade ≤1. Resume BINI at 1-level lower dose.
	Grade 3 (accompanied by serum bilirubin increased) and Grade 4	Discontinue BINI.
Serum CK increased	Grade 3 (accompanied by muscular symptom or creatinine increased) and Grade 4	Interrupt BINI until recovery to Grade ≤1. If recovered within 21 days, resume BINI at 1-level lower dose. Discontinue BINI if not recovered within 21 days.
Ejection fraction decreased	Decrease in left ventricular ejection fraction from baseline by ≥10% or to below the lower limit of normal	Interrupt BINI until recovery. If recovered within 21 days, resume BINI at 1-level lower dose. Discontinue BINI if not recovered within 21 days.
	Grade 3 to 4	Discontinue BINI.
Electrocardiogram QT prolonged	QTc exceeds 500 ms, and the change from baseline is ≤60 ms.	Interrupt BINI until QTc decreases to <500 ms. Resume BINI at 1-level lower dose. Discontinue BINI if QT prolongation recurs.
	QTc exceeds 500 ms, and the change from baseline is >60 ms.	Discontinue BINI.
Dermatitis	Grade 2	If the symptom persists or worsens, interrupt BINI until recovery to Grade ≤1. Resume BINI at same dose. If recurrent, interrupt BINI until recovery and then resume at 1-level lower dose.
	Grade 3	Interrupt BINI until recovery to Grade ≤1. Resume BINI at same dose. If recurrent, interrupt BINI until recovery and then resume at 1-level lower dose.
	Grade 4	Discontinue BINI.
Other adverse drug reactions	Grade 2	If Grade 2 symptom persists, consider interruption or dose reduction.
	Grade 3	Consider interruption until recovery to Grade ≤1. If recovered within 21 days, consider resumption at 1-level lower dose.
	Grade 4	Discontinue BINI.

* Grade is determined according to NCI-CTCAE ver4.03.

7.R.6 Post-marketing investigations

The applicant's explanation about the plan for the post-marketing investigations:
In order to evaluate the safety, etc., of ENCO/BINI/Cmab in post-marketing clinical use, the applicant plans to conduct a post-marketing surveillance in patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation treated with ENCO/BINI/Cmab.

The safety specifications for the surveillance will include the events that are chosen as the safety specifications for the approved indication (eye disorders, cardiac dysfunction, hepatic dysfunction, rhabdomyolysis, cutaneous malignancies, hypertension, haemorrhage, and palmar-plantar erythrodysaesthesia syndrome), by taking the following into consideration:

- Although there were some adverse events with a higher incidence in the ENCO/BINI/Cmab group of the BEACON CRC study than that observed in the safety profile in administration of ENCO/BINI for the approved indication, all of them were known adverse events of ENCO, BINI, or Cmab, suggesting no novel safety concerns in administering ENCO/BINI/Cmab to patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation [see Section 7.R.3].

The planned sample size and the follow-up period are 150 patients and 6 months, respectively, by taking into account the incidence of the events specified in the safety investigation as above in the ENCO/BINI/Cmab group of the BEACON CRC study.

PMDA's view:
Because of the limited safety information available on ENCO/BINI/Cmab and ENCO/Cmab in Japanese patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation, a post-marketing surveillance should be conducted in patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation treated with ENCO/BINI/Cmab or ENCO/Cmab. The safety information, etc., thus obtained should be provided to healthcare professionals in an appropriate manner. Given the review in Section "7.R.4.1 Clinical positioning of ENCO/BINI/Cmab and ENCO/Cmab," either ENCO/BINI/Cmab or ENCO/Cmab will be selected according to the conditions of individual patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation. The surveillance plan should allow collection and analysis of safety information, etc., on each treatment regimen, and the information thus obtained should be provided to healthcare professionals in an appropriate manner.

The safety specification in the surveillance is acceptable as proposed by the applicant. The planned sample size and the follow-up period should be reconsidered, by taking into account the incidence, in the ENCO/Cmab group of the BEACON CRC study, of the events that should be included in the safety specification.

7.2 Adverse events, etc., observed in clinical studies

Deaths reported in the safety evaluation data were described in Section "7.1 Evaluation data." The following subsections summarize major adverse events excluding deaths.

7.2.1 Global phase Ib/II study (Study X2103)

7.2.1.1 Phase Ib part[19)]

Adverse events were observed in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 2 of 2 patients (100%) in the ENCO 100 mg cohort, 5 of 7 patients (71.4%) in the ENCO 200 mg cohort, 7 of 9 patients (77.8%) in the ENCO 400 mg cohort, and 7 of 8 patients (87.5%) in the ENCO 450 mg cohort. Adverse events with an incidence of ≥55% in any group were nausea, fatigue, and hallucination in 2 patients (100%) each in the ENCO 100 mg cohort, dyspnoea in 4 patients (57.1%) in the ENCO 200 mg cohort, vomiting in 5 patients (55.6%) in the ENCO 400 mg cohort, constipation and fatigue in 5 patients (62.5%) each in the ENCO 450 mg cohort.

Serious adverse events were observed in 2 of 2 patients (100%) in the ENCO 100 mg cohort, 5 of 7 patients (71.4%) in the ENCO 200 mg cohort, 6 of 9 patients (66.7%) in the ENCO 400 mg cohort, and 6 of 8 patients (75.0%) in the ENCO 450 mg cohort. Serious adverse events reported were pneumonia and tumour pain in 1 patient (50.0%) each in the ENCO 100 mg cohort; cardiac arrest, congestive cardiac failure, myocardial infarction, ventricular fibrillation, abdominal pain, haematochezia, asthenia, pain, pneumonia, brain natriuretic peptide increased, dyspnea, pleural effusion, and respiratory failure in 1 patient (14.3%) each in the ENCO 200 mg cohort; abdominal pain, proctalgia, vomiting, pain, non-cardiac chest pain, hyperbilirubinaemia, pneumonia, device related infection, blood bilirubin increased, malignant melanoma, tumour pain, and respiratory arrest in 1 patient (11.1%) each in the ENCO 400 mg cohort; and abdominal pain in 3 patients (37.5%), ileus in 2 patients (25.0%), constipation, haematochezia, pyrexia, bile duct stenosis, hypersensitivity, *Escherichia* bacteraemia, blood bilirubin increased, electrocardiogram QT prolonged, lipase increased, and thrombosis in device in 1 patient (12.5%) each in the ENCO 450 mg cohort. A causal relationship to the study drug could not be ruled out for vomiting and malignant melanoma in 1 patient each in the ENCO 400 mg cohort and for pyrexia, hypersensitivity, electrocardiogram QT prolonged, and lipase increased in 1 patient each in the ENCO 450 mg cohort.

Adverse events leading to discontinuation of the study drug were observed in 0 of 2 patients in the ENCO 100 mg cohort, 1 of 7 patients (14.3%) in the ENCO 200 mg cohort, 1 of 9 patients (11.1%) in the ENCO 400 mg cohort, and 2 of 8 patients (25.0%) in the ENCO 450 mg cohort. They were cardiac arrest in 1 patient (14.3%) in the ENCO 200 mg cohort, malignant melanoma in 1 patient (11.1%) in the ENCO 400 mg cohort, nausea, blood bilirubin increased, and decreased appetite in 1 patient (12.5%) each in the ENCO 450 mg cohort. A causal relationship to the study drug could not be ruled out for malignant melanoma in 1 patient in the ENCO 400 mg cohort, nausea and decreased appetite in 1 patient each in the ENCO 450 mg cohort.

7.2.1.2 Phase II part

Adverse events were observed in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 48 of 50 patients (96.0%). Adverse events with an incidence of ≥30% were fatigue in 25 patients (50.0%), nausea in 23 patients (46.0%), abdominal pain in 21 patients (42.0%), arthralgia in 20 patients (40.0%), vomiting, decreased appetite, and headache in 17

[19)] Cmab was co-administered in all cohorts.

patients (34.0%) each, lipase increased in 16 patients (32.0%), constipation and diarrhoea in 15 patients (30.0%) each.

Serious adverse events were observed in all patients. Serious adverse events reported by ≥2 patients were abdominal pain and infusion related reaction in 5 patients (10.0%) each, pyrexia in 3 patients (6.0%), constipation, ileus, nausea, small intestinal obstruction, vomiting, malaise, pneumonia, and decreased appetite in 2 patients (4.0%) each. A causal relationship to the study dug could not be ruled out for infusion related reaction in 5 patients, and abdominal pain, nausea, pyrexia, and decreased appetite in 1 patient each.

Adverse events leading to discontinuation of the study drug were observed in 5 of 50 patients (10.0%). There were no adverse events leading to discontinuation of the study drug in ≥2 patients.

7.2.2 Global phase III study (the BEACON CRC study)

7.2.2.1 Safety lead-in part

Adverse events were observed in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 36 of 37 patients (97.3%). Adverse events with an incidence of ≥30% were diarrhoea in 28 patients (75.7%), dermatitis acneiform in 25 patients (67.6%), nausea in 22 patients (59.5%), fatigue in 20 patients (54.1%), dry skin in 19 patients (51.4%), vomiting in 18 patients (48.6%), anaemia in 16 patients (43.2%), pyrexia in 15 patients (40.5%), abdominal pain, constipation, and decreased appetite in 14 patients (37.8%) each, blood CK increased in 13 patients (35.1%), and dyspnoea in 12 patients (32.4%).

Serious adverse events were observed in 22 of 37 patients (59.5%). Adverse events reported by ≥2 patients were urinary tract infection in 4 patients (10.8%), infusion related reaction in 3 patients (8.1%), vomiting, pyrexia, aspartate aminotransferase (AST) increased, renal failure, and pleural effusion in 2 patients (5.4%) each. A causal relationship to the study drug could not be ruled out for infusion related reaction in 3 patients.

Adverse events leading to treatment discontinuation were observed in 8 of 37 patients (21.6%). Adverse events leading to treatment discontinuation reported by ≥2 patients were fatigue, infusion related reaction, and blood creatinine increased in 2 patients (5.4%) each. A causal relationship to the study drug could not be ruled out for fatigue and infusion related reaction in 2 patients each and blood creatinine increased in 1 patient.

7.2.2.2 Phase III part

Adverse events were observed in 217 of 222 patients (97.7%) in the ENCO/BINI/Cmab group, 212 of 216 patients (98.1%) in the ENCO/Cmab group, and 188 of 193 patients (97.4%) in the IC group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 208 of 222 patients (93.7%) in the ENCO/BINI/Cmab group, 191 of 216 patients (88.4%) in the ENCO/Cmab group, and 176 of 193 patients (91.2%) in the IC group. Table 18 shows adverse events with an incidence of ≥15% in any group.

Table 18. Adverse events with an incidence of ≥15% in any group

SOC PT (MedDRA ver.20.1)	Number of patients (%)					
	ENCO/BINI/Cmab (n = 222)		ENCO/Cmab (n = 216)		IC (n = 193)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	217 (97.7)	128 (57.7)	212 (98.1)	108 (50.0)	188 (97.4)	117 (60.6)
Blood and lymphatic system disorders						
Anaemia	80 (36.0)	37 (16.7)	35 (16.2)	10 (4.6)	37 (19.2)	12 (6.2)
Neutropenia	3 (1.4)	1 (0.5)	1 (0.5)	1 (0.5)	36 (18.7)	19 (9.8)
Gastrointestinal disorders						
Diarrhoea	137 (61.7)	22 (9.9)	72 (33.3)	4 (1.9)	93 (48.2)	19 (9.8)
Nausea	100 (45.0)	10 (4.5)	74 (34.3)	1 (0.5)	80 (41.5)	2 (1.0)
Vomiting	85 (38.3)	9 (4.1)	46 (21.3)	3 (1.4)	56 (29.0)	5 (2.6)
Abdominal pain	65 (29.3)	13 (5.9)	49 (22.7)	5 (2.3)	48 (24.9)	9 (4.7)
Constipation	55 (24.8)	0	33 (15.3)	0	35 (18.1)	2 (1.0)
Stomatitis	31 (14.0)	1 (0.5)	12 (5.6)	0	44 (22.8)	4 (2.1)
General disorders and administration site conditions						
Fatigue	73 (32.9)	5 (2.3)	65 (30.1)	9 (4.2)	53 (27.5)	8 (4.1)
Helplessness	55 (24.8)	7 (2.3)	46 (21.3)	7 (3.2)	49 (25.4)	9 (4.7)
Pyrexia	45 (20.3)	4 (1.8)	35 (16.2)	2 (0.9)	27 (14.0)	1 (0.5)
Metabolism and nutrition disorders						
Decreased appetite	63 (28.4)	4 (1.8)	58 (26.9)	3 (1.4)	52 (26.9)	6 (3.1)
Musculoskeletal and connective tissue disorders						
Arthralgia	23 (10.4)	0	41 (19.0)	2 (0.9)	1 (0.5)	0
Nervous system disorders						
Headache	16 (7.2)	0	42 (19.4)	0	5 (2.6)	0
Skin and subcutaneous tissue disorders						
Dermatitis acneiform	108 (48.6)	5 (2.3)	63 (29.2)	1 (0.5)	76 (39.4)	5 (2.6)
Dry skin	46 (20.7)	2 (0.9)	24 (11.1)	0	13 (6.7)	1 (0.5)
Rash	42 (18.9)	2 (0.9)	25 (11.6)	0	27 (14.0)	3 (1.6)

Serious adverse events were observed in 93 of 222 patients (41.9%) in the ENCO/BINI/Cmab group, 71 of 216 patients (32.9%) in the ENCO/Cmab group, and 71 of 193 patients (36.8%) in the IC group. Serious adverse events reported by ≥2 patients were diarrhoea and pulmonary embolism in 8 patients (3.6%) each, nausea and acute kidney injury in 7 patients (3.2%) each, intestinal obstruction in 6 patients (2.7%), ileus in 5 patients (2.3%), anaemia, abdominal pain, and pyrexia in 4 patients (1.8%) each, large intestine perforation, rectal haemorrhage, small intestinal obstruction, vomiting, hepatic failure, bacteraemia, and sepsis in 3 patients (1.4%) each, colitis, cholecystitis, bile duct obstruction, septic shock, urinary tract infection, staphylococcal bacteraemia, device related infection, dehydration, anxiety, prerenal failure, and female genital tract fistula in 2 patients (0.9%) each in the ENCO/BINI/Cmab group; intestinal obstruction in 10 patients (4.6%), urinary tract infection and cancer pain in 5 patients (2.3%) each, acute kidney injury in 4 patients (1.9%), atrial fibrillation, abdominal pain, ileus, nausea, large intestinal obstruction, bile duct obstruction, sepsis, infusion related reaction, and pulmonary embolism in 3 patients (1.4%) each, gastrointestinal haemorrhage, large intestine perforation, small intestinal obstruction, vomiting, cholangitis, drug hypersensitivity, pneumonia, hyponatraemia, malignant melanoma, and aspiration in 2 patients (0.9%) each in the ENCO/Cmab group; and diarrhoea in 10 patients (5.2%), intestinal obstruction in 7 patients (3.6%), febrile neutropenia in 5 patients (2.6%), abdominal pain, small intestinal obstruction, and pulmonary embolism in 4 patients (2.1%) each, vomiting, subileus, and respiratory failure in 3 patients (1.6%) each, ileus, large intestine perforation, pain, general physical health deterioration, bile duct obstruction, sepsis, septic shock, infusion related reaction, and hypokalaemia in 2 patients (1.0%) each in the IC group. A causal relationship to the study drug could not be ruled out for diarrhoea in 8 patients, nausea in 6, acute kidney injury in 5 patients,

vomiting, colitis, pyrexia, and pulmonary embolism in 2 patients each, anaemia, large intestine perforation, rectal haemorrhage, and dehydration in 1 each in the ENCO/BINI/Cmab group; nausea and infusion related reaction in 3 patients each, atrial fibrillation, vomiting, drug hypersensitivity, and malignant melanoma in 2 patients each, ileus and hyponatraemia in 1 patient each in the ENCO/Cmab group; and diarrhoea in 8 patients, febrile neutropenia in 5 patients, vomiting and infusion related reaction in 2 patients each, abdominal pain, hypokalaemia, and respiratory failure in 1 patient each in the IC group.

Adverse events leading to discontinuation of the study drug were observed in 33 of 222 patients (14.9%) in the ENCO/BINI/Cmab group, 25 of 216 patients (11.6%) in the ENCO/Cmab group, and 33 of 193 patients (17.1%) in the IC group. Adverse events leading to treatment discontinuation in ≥2 patients were diarrhoea and nausea in 4 patients (1.8%) each, asthenia, fatigue, hepatic failure, sepsis, blood creatinine increased, and ejection fraction decreased in 2 patients (0.9%) each in the ENCO/BINI/Cmab group; intestinal obstruction, infusion related reaction, and acute kidney injury in 2 patients (0.9%) each in the ENCO/Cmab group; and neutropenia and small intestinal obstruction in 3 patients (1.6%) each, diarrhoea, stomatitis, asthenia, general physical health deterioration, infusion related reaction, neutrophil count decreased, and hypokalaemia in 2 patients (1.0%) each in the IC group. A causal relationship to the study drug could not be ruled out for diarrhoea and nausea in 4 patients each, asthenia, fatigue, blood creatinine increased, and ejection fraction decreased in 2 patients each in the ENCO/BINI/Cmab group; infusion related reaction in 2 patients in the ENCO/Cmab group; and neutropenia in 3 patients, diarrhoea, stomatitis, asthenia, infusion related reaction, and neutrophil count decreased in 2 patients each, and hypokalaemia in 1 patient in the IC group.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, the clinical studies overall were conducted in compliance with GCP and PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following finding requiring corrective action in the sponsor (clinical trial in-country representative), although it had no significant impact on the review of the overall clinical studies. PMDA notified the sponsor (clinical trial in-country representative) to seek improvement.

Finding requiring corrective action

Sponsor (clinical trial in-country representative)

- Part of the information, including serious unexpected adverse drug reactions, was not notified to the investigator and the head of the study sites at the appropriate timing.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that ENCO/BINI/Cmab and ENCO/Cmab have efficacy in the treatment of unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy, and that ENCO/BINI/Cmab and ENCO/Cmab have acceptable safety in view of its benefit. ENCO/BINI/Cmab and ENCO/Cmab are thus considered to have clinical significance as treatment options for patients with the above disease. The clinical positioning, indication, dosage and administration of ENCO and BINI are subject to further investigation.

PMDA has concluded that both ENCO and BINI may be approved if they are not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

October 20, 2020

Product Submitted for Approval

(a) Brand Name	(1) Braftovi Capsules 50 mg (2) Braftovi Capsules 75 mg
Non-proprietary Name	Encorafenib
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	(1) March 4, 2020 (2) August 26, 2020

(b) Brand Name	Mektovi Tablets 15 mg
Non-proprietary Name	Binimetinib
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	March 4, 2020

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the products submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of its discussion in Section "7.R.2 Efficacy" in the Review Report (1), PMDA concluded that the efficacy of ENCO/BINI/Cmab and ENCO/Cmab was demonstrated in patients with unresectable advanced or recurrent colorectal cancer with BRAF V600E mutation that has progressed after the first- or second-line therapy in the global phase III study (the BEACON CRC study) that compared the efficacy and safety of ENCO/BINI/Cmab and ENCO/Cmab with those of IC, and the following results were obtained for OS, one of the primary endpoints:

- Superiority of ENCO/BINI/Cmab to IC was demonstrated by the primary analysis.
- A statistically significant prolongation of OS in the ENCO/Cmab group to that in the IC group was demonstrated by the secondary analysis conducted according to the prespecified testing procedures.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of its discussion in Section "7.R.3 Safety" in the Review Report (1), PMDA concluded that adverse events requiring particular attention in administering ENCO/BINI/Cmab and ENCO/Cmab to patients with unresectable advanced or recurrent colorectal cancer with BRAF V600E mutation that has progressed after the first- or second-line therapy are events that were identified to require caution in the prior review on the approved indication for ENCO and BINI, i.e., eye disorders, cardiac dysfunction, hepatic dysfunction, rhabdomyolysis, cutaneous malignancies, hypertension, haemorrhage, and palmar-plantar erythrodysaesthesia syndrome, and that attention should be paid to the occurrence of these adverse events in administering ENCO/BINI/Cmab or ENCO/Cmab.

PMDA also concluded that although attention should be paid to the occurrence of the above adverse events in using ENCO/BINI/Cmab or ENCO/Cmab, the treatment with ENCO/BINI/Cmab or ENCO/Cmab is tolerable for patients with colorectal cancer provided that appropriate measures, such as monitoring and management of adverse events, and interruption, dose reduction, or discontinuation of ENCO, BINI, and/or Cmab, are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication

Clinical positioning of ENCO/BINI/Cmab and ENCO/Cmab

As a result of its discussion in Sections "7.R.2 Efficacy," "7.R.3 Safety," and "7.R.4.1 Clinical positioning of ENCO/BINI/Cmab and ENCO/Cmab" in the Review Report (1), PMDA concluded that both ENCO/BINI/Cmab and ENCO/Cmab have been demonstrated to be clinically useful in the treatment of patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after the first- or second-line therapy, and that the clinical positioning of ENCO/BINI/Cmab and ENCO/Cmab should be as shown in (a) and (b) below.

(a) Since the comparison between ENCO/BINI/Cmab and ENCO/Cmab was conducted in an exploratory manner in the BEACON CRC study, it is difficult to draw a definite conclusion on the efficacy of ENCO/BINI/Cmab relative to ENCO/Cmab. However, there is a certain clinical significance in providing, as a treatment option, ENCO/BINI/Cmab which is suggested to have a tendency of higher tumor-shrinking and OS-prolonging effect compared with ENCO/Cmab, given the following situations:
   (1) Colorectal cancer with *BRAF* mutation that has become refractory or resistant to the first- or second-line therapy is a serious disease condition poorly responsive to conventional therapies.
   (2) It is suspected that there are a certain number of patients for whom the urgent need is tumor shrinkage aimed at symptom alleviation and QOL improvement.

(b) The choice between ENCO/BINI/Cmab and ENCO/Cmab should be examined by physicians with adequate knowledge and experience in cancer chemotherapy according to the general condition,

disease state, and the purpose of the treatment in individual patients, based on a good understanding of the efficacy and safety of each treatment.

The expert advisors supported PMDA's conclusions on the clinical usefulness of ENCO/BINI/Cmab and ENCO/Cmab at the Expert Discussion. The following comments on (a) and (b) above were raised by the expert advisors:

- The explanation that ENCO/BINI/Cmab is the treatment regimen with the highest efficacy with acceptable safety is understandable. However, from the results of the comparison of the response rate and OS in the submitted documents, it is difficult to conclude the clinical usefulness of BINI in combination with ENCO/Cmab. Also, there seems to be little significance in using BINI in combination with ENCO/Cmab, from the health economic aspect.
- Although study results appear to suggest a tendency of prolonging OS in the ENCO/BINI/Cmab group than in the ENCO/Cmab group, concomitant use of BINI should be carefully decided based on thorough evaluation of the balance between the expected treatment effect and adverse events, etc.
- Given the results of the sensitivity analysis of OS adjusted for the distribution of patient characteristics, the possibility cannot be excluded that patients with highly malignant cancer may not sufficiently respond to ENCO/Cmab. Since unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after the first- or second-line therapy has an extremely poor prognosis, it is worth considering to use ENCO/BINI/Cmab preferentially to avoid a risk of selecting a treatment regimen with a possibly insufficient effect.
- Although the results of the BEACON CRC study may suggest the possibility of using ENCO/Cmab and ENCO/BINI/Cmab selectively, i.e., ENCO/Cmab for life prolongation and ENCO/BINI/Cmab for tumor shrinkage, the ambiguity of choice between these treatment regimens is a problem.

Taking account of comments raised in the Expert Discussion, PMDA asked the applicant to further explain the choice between ENCO/BINI/Cmab and ENCO/Cmab.

The applicant's response:

In a similar manner as in the sensitivity analysis of OS in the entire population [see Section 7.R.4.1 of the Review Report (1)], a subpopulation analysis of OS was conducted by adjusting, between treatment groups, the distribution of 5 patient characteristics affecting OS identified by univariate Cox regression model (CRP >1 mg/dL, hepatic metastasis, CEA >5 μg/L, CA19-9 >35 U/mL, and number of organs involved ≥3) (Figure 9). Results showed that the point estimate of the hazard ratio of the ENCO/BINI/Cmab group to the ENCO/Cmab group in each subpopulation was generally less than 1, which was generally consistent with the results of the sensitivity analysis of OS in the entire population adjusted for the distribution of the above 5 factors between the treatment groups [see Section 7.R.4.1, Table 13 of the Review Report (1)].

On the other hand, in some subpopulations, a tendency of difference was suggested in the extent of the hazard ratio between subpopulations and their supplementary populations. Thus, OS tended to be superior in the ENCO/BINI/Cmab group among the subpopulations with (i) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 1, (ii) number of organs involved ≥3, (iii) CRP >1 mg/dL, or (iv) unresected or partially resected primary lesion, whereas OS was similar between the

ENCO/Cmab and the ENCO/BINI/Cmab groups among the subpopulations with (i) ECOG PS 0, (ii) number of organs involved ≤2, (iii) CRP ≤1 mg/dL, or (iv) completely resected primary lesion.

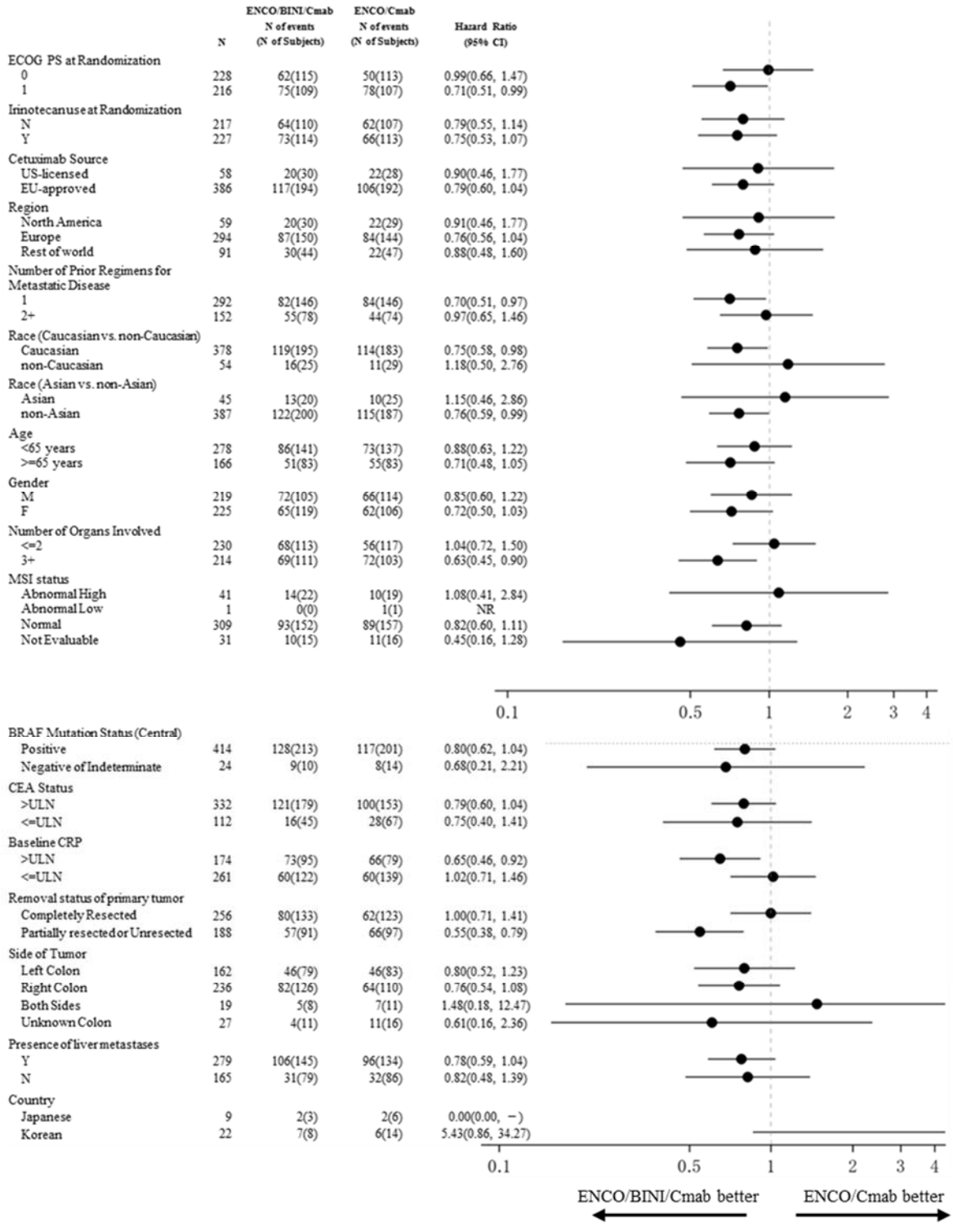


Figure 9. Subpopulation analysis results of OS adjusted for 5 patient characteristics (comparison between the ENCO/BINI/Cmab group and the ENCO/Cmab group)

Although it is difficult to draw a definite conclusion on the clinical usefulness of ENCO/BINI/Cmab relative to ENCO/Cmab from the above exploratory analysis, the following findings should be taken into account: (i) ENCO/BINI/Cmab has shown superior clinical usefulness to conventional therapies

and has consistently shown a tendency of superior OS prolongation to ENCO/Cmab in the entire population and subpopulations, and (ii) it is suggested that ENCO/BINI/Cmab has a higher therapeutic effect than ENCO/Cmab in the subpopulation with ECOG PS 1, the number of organs involved ≥3, CRP >1 mg/dL, or unresected or partially resected primary lesion. It is therefore considered appropriate to provide ENCO/BINI/Cmab as a treatment option to allow physicians to select either of the treatment regimens according to the general condition and disease state of each patient, by referring to the results of the above subpopulation analysis. The incidence of diarrhoea, vomiting, anaemia, etc., was high in the ENCO/BINI/Cmab group and the incidence of headache, arthralgia, musculoskeletal pain, skin-related adverse events such as melanocytic naevus, secondary cutaneous malignancies, etc. tended to be high in the ENCO/Cmab group. In selecting between ENCO/BINI/Cmab and ENCO/Cmab, consideration should be given to the difference in the safety profile between the treatment regimens and to incidences of adverse events in individual patients.

PMDA's view:
It is difficult to draw a definite conclusion on the choice between ENCO/BINI/Cmab and ENCO/Cmab based on the results of the submitted exploratory analysis. However, since the 5 patient characteristics used for the adjustment are generally considered to be prognostic factors for advanced or recurrent colorectal cancer (*J Natl Cancer Inst*. 2018;110:638-48, etc.), it is acceptable to compare the efficacy between ENCO/BINI/Cmab and ENCO/Cmab based on the results obtained by adjusting these factors. The applicant's explanation about the choice between these treatment options based on the results of the above comparison is therefore acceptable to a certain extent. Detailed information on the results of the BEACON CRC study, including the results of the above analysis, should be provided to healthcare professionals using materials. Also, an effort should be made to facilitate appropriate selection between ENCO/BINI/Cmab and ENCO/Cmab according to the conditions of individual patients, based on the most updated findings in relevant academic societies. In addition, information on the choice between ENCO/BINI/Cmab and ENCO/Cmab should be actively collected after the launch, and further helpful information on the choice should be provided promptly to healthcare professionals.

PMDA instructed the applicant to appropriately address the above issues, to which the applicant agreed.

Indication of ENCO/BINI/Cmab and ENCO/Cmab
As a result of the review in Sections "7.R.4.2 Indication for ENCO/BINI/Cmab and ENCO/Cmab" and "7.R.4.3 Test for *BRAF* mutation" in the Review Report (1), PMDA concluded that the indication for ENCO and BINI should be "unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy," and that the following precautions should be included in the "Precautions Concerning Indications" section.

Precautions Concerning Indications
- ENCO and BINI should be administered to patients with *BRAF* mutation confirmed by tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic or medical device should be used in the test.
- Suitable patients should be selected based on a thorough understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of ENCO and BINI.

- The efficacy and safety of ENCO and BINI in adjuvant chemotherapy have not been established.
- The efficacy and safety of ENCO and BINI in the first-line therapy have not been established.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

On the basis of the above, PMDA instructed the applicant to finalize the descriptions in the "Indication" and "Precautions Concerning Indications" sections as above. The applicant agreed.

1.4 Dosage and administration

As a result of the review in Sections "7.R.4.1 Clinical positioning of ENCO/BINI/Cmab and ENCO/Cmab" and "7.R.5.1 Dosage and administration of ENCO and BINI" in the Review Report (1), PMDA concluded that, since there is little evidence to recommend ENCO/BINI/Cmab to all patients, physicians with adequate knowledge and experience in cancer chemotherapy should initiate the treatment after selecting ENCO/BINI/Cmab or ENCO/Cmab according to the conditions of individual patients. Therefore, the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections of ENCO and BINI should be defined as shown below.

Also, for dose adjustment criteria of ENCO and BINI in case of adverse drug reactions, as a result of the review in Section "7.R.5.2 Dose adjustment for ENCO and BINI" in the Review Report (1), PMDA concluded that the guide for interruption, dose reduction, and discontinuation of ENCO and BINI should be specified based on the criteria used in the BEACON CRC study, as proposed by the applicant.

	Dosage and Administration	Precautions Concerning Dosage and Administration
ENCO	In combination with Cmab or with BINI and Cmab, the usual adult dosage is 300 mg of ENCO administered orally once daily. The dose may be reduced according to the patient's condition.	• Guide for interruption, dose reduction, and discontinuation of ENCO in case of adverse drug reactions • In combination with BINI and Cmab, when both BINI and Cmab are interrupted or discontinued, ENCO should also be interrupted or discontinued, respectively. • In combination with Cmab, when Cmab is interrupted or discontinued, ENCO should also be interrupted or discontinued, respectively. • Other antineoplastic agents to be co-administered should be selected with sufficient understanding of the content in the "Clinical Studies" section.
BINI	In combination with ENCO and Cmab, the usual adult dosage is 45 mg of BINI administered orally twice daily. The dose may be reduced according to the patient's condition.	• Guide for interruption, dose reduction, and discontinuation of BINI in case of adverse drug reactions • When ENCO is interrupted or discontinued, BINI should also be interrupted or discontinued, respectively.

The above conclusion of PMDA was generally supported by the expert advisors at the Expert Discussion.

Taking account of comments raised in the Expert Discussion described in Section "1.3 Clinical positioning and indication," PMDA concluded that the "Precautions Concerning Dosage and Administration" section of ENCO and BINI should be modified as shown below:

ENCO

- Guide for interruption, dose reduction, and discontinuation of ENCO in case of adverse drug reactions

- In combination with BINI and Cmab, when both BINI and Cmab are interrupted or discontinued, ENCO should also be interrupted or discontinued, respectively.
- In combination with Cmab, when Cmab is interrupted or discontinued, ENCO should also be interrupted or discontinued, respectively.
- Other antineoplastic agents to be co-administered should be selected with sufficient understanding of the content in the "Clinical Studies" section, and the necessity of combination with BINI should be determined according to the patient's condition and by referring to the most updated guidelines of relevant academic societies.

BINI
- Guide for interruption, dose reduction, and discontinuation of BINI in case of adverse drug reactions
- If ENCO is interrupted or discontinued, BINI should also be interrupted or discontinued, respectively.

PMDA instructed the applicant to modify the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections as above, to which the applicant agreed.

1.5 Risk management plan (draft)

In order to investigate the safety of ENCO/BINI/Cmab in clinical use after the launch, the applicant plans to conduct a post-marketing surveillance targeted at patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation treated with ENCO/BINI/Cmab, with the planned sample size of 150 patients and the follow-up period of 6 months.

On the basis of the review in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA concluded that a post-marketing surveillance should be conducted on patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation treated with ENCO/BINI/Cmab or ENCO/Cmab, and that the safety information thus obtained should be provided to healthcare professionals in an appropriate manner.

Also, PMDA concluded that the surveillance plan should be designed as follows:
- The surveillance should allow appropriate collection and analysis of safety information, etc., for each treatment regimen.
- The safety specification planned by the applicant for this surveillance is acceptable.
- The planned sample size and the follow-up period should be determined separately for patients receiving ENCO/BINI/Cmab and patients receiving ENCO/Cmab, taking account of the incidence of events to be included in the safety specification of this surveillance, in each treatment group of the BEACON CRC study.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

In view of the discussion presented in Section "1.3 Clinical positioning and indication" and the above discussions, PMDA instructed the applicant to re-consider the plan of the post-marketing surveillance, including the collection of safety information for each treatment regimen.

The applicant's response:

- The surveillance will be conducted with the aim of collecting and analyzing information on efficacy and safety of ENCO/BINI/Cmab and ENCO/Cmab in clinical use after the marketing. The safety specification, planned sample size and follow-up period, and efficacy specification will be determined for each treatment regimen.
- The planned sample size and the follow-up period of the surveillance will be 150 patients and 12 months, respectively, for patients treated with ENCO/BINI/Cmab, and 70 patients and 12 months, respectively, for patients receiving ENCO/Cmab, by taking into account the following:
  (i) The incidences of events included in the safety specification in the ENCO/BINI/Cmab and ENCO/Cmab groups of the BEACON CRC study.
  (ii) The sample size and the evaluation period that allow the evaluation of efficacy (OS and antitumor effect).

PMDA accepted the applicant's explanation.

In view of the discussion above, PMDA has also concluded that the risk management plan (draft) should include the safety and efficacy specifications presented in Tables 19 and 20, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and risk minimization activities presented in Tables 21 and 22.

Table 19. Safety and efficacy specifications in risk management plan (draft) of ENCO

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Cutaneous malignancies • Eye disorders • Palmar-plantar erythrodysaesthesia syndrome	• Secondary malignancies other than cutaneous malignancies • Cardiac dysfunction • Hypertension • Rhabdomyolysis • Hepatic dysfunction • Haemorrhage • ILD • Renal impairment • QT prolongation • Drug-drug interactions in concomitant use with CYP3A inhibitors • Embryo-fetal toxicity	Not applicable
Efficacy specification		
Efficacy in clinical use of each treatment regimen for unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy		

The underlined section is the investigation added in this review.

Table 20. Safety and efficacy specifications in risk management plan (draft) of BINI

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Cardiac dysfunction • Hypertension • Rhabdomyolysis • Hepatic dysfunction • Eye disorders • Haemorrhage	• ILD • Venous thromboembolism • Renal impairment • QT prolongation • Safety in patients with hepatic impairment • Embryo-fetal toxicity	Not applicable
Efficacy specification		
Efficacy in clinical use for unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy		

The underlined section is the investigation added in this review.

Table 21. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft) for ENCO/BINI

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey in patients with unresectable malignant melanoma with *BRAF* mutation (all-case surveillance) • Specified use-results survey in patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy • Post-marketing clinical study (extension of Study ONO-7702/7703-02E*)	• Specified use-results survey in patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate materials for healthcare professionals

The underlined sections are activities to be conducted for the indication added in this review.
*, A compassionate study conducted with the BEACON CRC study as the main study

Table 22. Outline of use-results survey plan (draft)

Objective	To evaluate the efficacy and safety, separately for ENCO/BINI/Cmab and ENCO/Cmab, in post-marketing clinical use.
Survey method	Central registry system
Population	Patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy treated with ENCO/BINI/Cmab or ENCO/Cmab
Observation period	12 months
Planned sample size	Patients receiving ENCO/BINI/Cmab, 150 Patients receiving ENCO/Cmab, 70
Main survey items	Safety specifications: Eye disorders, cardiac dysfunction,* hepatic dysfunction,* rhabdomyolysis,* cutaneous malignancies, hypertension,* haemorrhage,* and palmar-plantar erythrodysaesthesia syndrome Efficacy specification: Efficacy (OS and antitumor effect) in clinical use of each treatment in patients with unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy Other main survey items: Patient characteristics (age, sex, disease stage, medical history, concurrent illness, etc.), the details on administration of ENCO, BINI, and Cmab, reason for selecting the treatment regimen (ENCO/BINI/Cmab or ENCO/Cmab), concomitant drugs, etc.

*, Events included in the safety specifications only in patients receiving ENCO/BINI/Cmab.

2. Overall Evaluation

As a result of the above review, PMDA concluded that the products may be approved for the following indication and dosage and administration with the following approval conditions, provided that appropriate cautions will be included in the package insert and information on the proper use of the products will be provided appropriately after the launch, and the proper use of the products will be ensured under the supervision of physicians with sufficient knowledge and experience in cancer

chemotherapy at medical institutions with adequate facilities for emergency care. Because this partial change application is related to the addition of an indication not designated for an orphan drug with a novel active ingredient, the re-examination period for this partial change application is 5 years and 10 months.

Braftovi Capsules 50 mg, Braftovi Capsules 75 mg

Indications (Underline denotes additions.)

○ Unresectable malignant melanoma with *BRAF* mutation

○ Unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy

Dosage and Administration (Underline denotes additions.)

Unresectable malignant melanoma with *BRAF* mutation

In combination with binimetinib, the usual adult dosage is 450 mg of encorafenib administered orally once daily. The dose may be reduced according to the patient's condition.

Unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy

In combination with cetuximab (genetical recombination) or with binimetinib and cetuximab (genetical recombination), the usual adult dosage is 300 mg of encorafenib administered orally once daily. The dose may be reduced according to the patient's condition.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Warning (no change)

Encorafenib should be administered only to patients suitable for the treatment with encorafenib under the supervision of a physician with adequate knowledge and experience in the treatment of cancer chemotherapy at a medical institution with adequate facilities for emergency care. Prior to treatment, patients or their family members should be thoroughly informed of the potential risks and benefits of the treatment, and informed consent should be obtained before starting treatment.

Contraindication (no change)

Patients with a history of hypersensitivity to encorafenib or to any of its components

Precautions Concerning Indications (Underline denotes additions. Strike-through denotes deletions.)

Common among indications

1. Encorafenib should be administered to patients with *BRAF* mutation confirmed by tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic or medical device should be used in the test.
2. Suitable patients should be selected based on a thorough understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of encorafenib.
3. The efficacy and safety of encorafenib in adjuvant chemotherapy have not been established.

Unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy

4. The efficacy and safety of encorafenib in the first-line therapy have not been established.

Precautions Concerning Dosage and Administration (Underline denotes additions.)

Unresectable malignant melanoma with *BRAF* mutation

1. In case of adverse drug reactions associated with encorafenib, encorafenib should be interrupted, reduced in dose, or discontinued by referring to the following criteria.
2. In clinical studies investigating the tolerability of encorafenib monotherapy, it is suggested that once daily administration of 450 mg may exceed the maximum tolerated dose of encorafenib. When binimetinib is interrupted or discontinued, dose reduction of encorafenib should be considered, and patient should be closely monitored for the occurrence of adverse drug reactions.

Dose reduction in continued administration

Dose reduction level[*1]	Dose
Usual dose	450 mg once daily
1-level dose reduction	300 mg once daily
2-level dose reduction	200 mg once daily
3-level dose reduction	Discontinue

[*1] If the adverse drug reaction requiring dose reduction has improved to Grade ≤1, and there are no other concomitant adverse drug reactions, the dose may be increased according to the reverse steps.

Criteria for dose adjustment in case of adverse drug reactions

Adverse drug reaction	Severity[*2]	Measure
Retinal disease, uveitis	Grade 2	Interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose or at 1-level lower dose.
	Grade 3	Interrupt encorafenib until recovery to Grade ≤2. Resume encorafenib at 1-level lower dose. Discontinue encorafenib if Grade 3 persists.
	Grade 4	Discontinue encorafenib.
Retinal vein occlusion	Grade ≥1	Discontinue encorafenib.
Eye disorders (other than above)	Grade 3	Interrupt encorafenib until recovery to Grade ≤1. If recovered within 28 days, resume encorafenib at 1-level lower dose. Discontinue encorafenib if not recovered within 28 days.
	Grade 4	Discontinue encorafenib
AST increased, ALT increased	Grade 2 (not accompanied by serum bilirubin increased)	If the symptom persists for >14 days, interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose. If recurrent, interrupt encorafenib until recovery and then resume at 1-level lower dose.
	Grade 2 (accompanied by serum bilirubin increased)	Interrupt encorafenib until recovery to Grade ≤1. If recovered within 7 days, resume encorafenib at 1-level lower dose. Discontinue encorafenib if not recovered within 7 days.
	Grade 3 (not accompanied by serum bilirubin increased)	Interrupt encorafenib until recovery to Grade ≤1. If recovered within 14 days, resume encorafenib at same dose. If recovered after >14 days, resume encorafenib at 1-level lower dose.
	Grade 3 (accompanied by serum bilirubin increased) and Grade 4	Discontinue encorafenib.
Serum CK increased	Grade 3-4 (accompanied by serum creatinine increased)	Interrupt encorafenib until recovery to Grade ≤1. If recovered within 28 days, resume encorafenib at 1-level lower dose. Discontinue encorafenib if not recovered within 28 days.
Electrocardiogram QT prolonged	QTc exceeds 500 ms, and the change from baseline is ≤60 ms.	Interrupt encorafenib until QTc decreases to <500 ms. Resume encorafenib at 1-level lower dose. Discontinue encorafenib if recurrent.
	QTc exceeds 500 ms, and the change from baseline is >60 ms.	Discontinue encorafenib.
Dermatitis	Grade 2	If the symptom persists or worsens, interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose.
	Grade 3	Interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose. If recurrent, interrupt encorafenib until recovery and then resume at 1-level lower dose.
	Grade 4	Discontinue encorafenib.
Palmar-plantar erythrodysaesthesia syndrome	Grade 2	If the symptom persists for >14 days, interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose. If recurrent, interrupt encorafenib until recovery and then consider resumption at 1-level lower dose.
	Grade 3	Interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at 1-level lower dose. If repeatedly recurrent, consider resumption at 1-level lower dose or discontinuation.
Other adverse drug reactions	Grade 2	If Grade 2 adverse reaction persists, consider interruption or dose reduction.
	Grade 3	Consider interruption until recovery to Grade ≤1. If recovered within 28 days, consider resumption at 1-level lower dose.
	Grade 4	Discontinue encorafenib.

[*2] Grade is determined according to NCI-CTCAE ver4.03.

Unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy

3. In case of adverse drug reactions associated with encorafenib, encorafenib should be interrupted, reduced in dose, or discontinued by referring to the following criteria.
4. In combination with binimetinib and cetuximab (genetical recombination), if both binimetinib and cetuximab (genetical recombination) are interrupted or discontinued, encorafenib should also be interrupted or discontinued, respectively.

5. In combination with cetuximab (genetical recombination), if cetuximab (genetical recombination) is interrupted or discontinued, encorafenib should also be interrupted or discontinued, respectively.
6. Other antineoplastic agents to be co-administered should be selected with sufficient understanding of the content in the "Clinical Studies" section, and the necessity of combination with binimetinib should be determined according to the patient's condition and by referring to the most updated guidelines of relevant academic societies.

Dose reduction in continued administration

Dose reduction level[*3]	Dose
Usual dose	300 mg QD
1-level dose reduction	225 mg QD
2-level dose reduction	150 mg QD
3-level dose reduction	Discontinue.

[*3] If the adverse drug reaction requiring dose reduction has improved to Grade ≤1, and there are no other concomitant adverse drug reactions, the dose may be increased according to the reverse steps.

Criteria for dose adjustment in case of adverse drug reactions

Adverse drug reaction	Severity*4	Measure
Retinal disease, uveitis	Grade 2	Interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose or at 1-level lower dose.
	Grade 3	Interrupt encorafenib until recovery to Grade ≤2. Resume encorafenib at 1-level lower dose. Discontinue encorafenib if Grade 3 persists.
	Grade 4	Discontinue encorafenib.
Retinal vein occlusion	Grade ≥1	Discontinue encorafenib.
Eye disorders (other than above)	Grade 3	Interrupt encorafenib until recovery to Grade ≤1. If recovered within 21 days, resume encorafenib at 1-level lower dose. Discontinue encorafenib if not recovered within 21 days.
	Grade 4	Discontinue encorafenib.
AST increased, ALT increased	Grade 2 (not accompanied by serum bilirubin increased)	If the symptom persists for >14 days, interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose. If recurrent, interrupt encorafenib until recovery and then resume at 1-level lower dose.
	Grade 2 (accompanied by serum bilirubin increased)	Interrupt encorafenib until recovery to Grade ≤1. If recovered within 7 days, resume encorafenib at 1-level lower dose. Discontinue encorafenib if not recovered within 7 days.
	Grade 3 (not accompanied by serum bilirubin increased)	Interrupt encorafenib until recovery to Grade ≤1. If recovered within 14 days, resume encorafenib at same dose. If recovered after >14 days, resume encorafenib at 1-level lower dose.
	Grade 3 (accompanied by serum bilirubin increased) and Grade 4	Discontinue encorafenib.
Serum CK increased	Grade 3-4 (accompanied by serum creatinine increased)	Interrupt encorafenib until recovery to Grade ≤1. If recovered within 21 days, resume encorafenib at 1-level lower dose. Discontinue encorafenib if not recovered within 21 days.
Electrocardiogram QT prolonged	QTc exceeds 500 ms, and the change from baseline is ≤60 ms.	Interrupt encorafenib until QTc decreases to <500 ms. Resume encorafenib at 1-level lower dose. Discontinue encorafenib if recurrent.
	QTc exceeds 500 ms, and the change from baseline is >60 ms.	Discontinue encorafenib.
Dermatitis	Grade 2	If the symptom persists or worsens, interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose.
	Grade 3	Interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose. If recurrent, interrupt encorafenib until recovery and then resume at 1-level lower dose.
	Grade 4	Discontinue encorafenib.
Palmar-plantar erythrodysaesthesia syndrome	Grade 2	If the symptom persists for >14 days, interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose. If recurrent, interrupt encorafenib until recovery and then consider resumption at 1-level lower dose.
	Grade 3	Interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at 1-level lower dose. If repeatedly recurrent, consider resumption at 1-level lower dose or discontinuation.
Other adverse drug reactions	Grade 2	If Grade 2 adverse reaction persists, consider interruption or dose reduction.
	Grade 3	Consider interruption until recovery to Grade ≤1. If recovered within 21 days, consider resumption at 1-level lower dose.
	Grade 4	Discontinue encorafenib.

*4 Grade is determined according to NCI-CTCAE ver4.03.

Mektovi Tablets 15 mg

Indications (Underline denote additions.)

○ Unresectable malignant melanoma with *BRAF* mutation

○ Unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy

Dosage and Administration (Underline denotes additions.)

Unresectable malignant melanoma with *BRAF* mutation

In combination with encorafenib, the usual adult dosage is 45 mg of binimetinib administered orally twice daily. The dose may be reduced according to the patient's condition.

Unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy

In combination with encorafenib and cetuximab (genetical recombination), the usual adult dosage is 45 mg of binimetinib administered orally twice daily. The dose may be reduced according to the patient's condition.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Warning (no change)

Binimetinib should be administered only to patients suitable for the treatment with binimetinib under the supervision of a physician with adequate knowledge and experience in the treatment of cancer chemotherapy at a medical institution with adequate facilities for emergency care. Prior to treatment, patients or their family members should be thoroughly informed of the potential risks and benefits of the treatment, and informed consent should be obtained before starting treatment.

Contraindication (no change)

Patients with a history of hypersensitivity to binimetinib or to any of its components

Precautions Concerning Indications (Underline denotes additions. Strikethrough denotes deletions.)

Common among indications

1. Binimetinib should be administered to patients with *BRAF* mutation confirmed by tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic or medical device should be used in the test.
2. Suitable patients should be selected based on a thorough understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of binimetinib.
3. The efficacy and safety of binimetinib in adjuvant chemotherapy have not been established.

Unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy

4. The efficacy and safety of binimetinib in the first-line therapy have not been established.

Precautions Concerning Dosage and Administration (Underline denotes additions.)

Unresectable malignant melanoma with *BRAF* mutation

1. In case of adverse drug reactions associated with binimetinib, binimetinib should be interrupted, reduced in dose, or discontinued by referring to the following criteria.
2. If encorafenib is interrupted or discontinued, binimetinib should also be interrupted or discontinued, respectively.

Dose reduction in continued administration

Dose reduction level[*1]	Dose
Usual dose	45 mg twice daily
1-level dose reduction	30 mg twice daily
2-level dose reduction	15 mg twice daily
3-level dose reduction	Discontinue

[*1] If the adverse drug reaction requiring dose reduction has improved to Grade ≤1, and there are no other concomitant adverse drug reactions, the dose may be increased according to the reverse steps.

Criteria for dose adjustment in case of adverse drug reactions

Adverse drug reaction	Severity[*2]	Measure to be taken
Retinal disease, uveitis	Grade 2	Interrupt binimetinib until recovery to Grade ≤1. Resume binimetinib at same dose or at 1-level lower dose.
	Grade 3	Interrupt binimetinib until recovery to Grade ≤2. Resume binimetinib at 1-level lower dose. Discontinue binimetinib if Grade 3 persists.
	Grade 4	Discontinue binimetinib.
Retinal vein occlusion	Grade ≥1	Discontinue binimetinib.
Eye disorders (other than above)	Grade 3	Interrupt binimetinib until recovery to Grade ≤1. If recovered within 28 days, resume binimetinib at 1-level lower dose. Discontinue binimetinib if not recovered within 28 days.
	Grade 4	Discontinue binimetinib.
AST increased, ALT increased	Grade 2 (not accompanied by serum bilirubin increased)	Interrupt binimetinib until recovery to Grade ≤1. If recovered within 14 days, resume binimetinib at same dose. If recovered after ≥14 days, resume binimetinib at 1-level lower dose. If recurrent, interrupt binimetinib until recovery and then resume at 1-level lower dose.
	Grade 2 (accompanied by serum bilirubin increased)	Interrupt binimetinib until recovery to Grade ≤1. If recovered within 7 days, resume binimetinib at 1-level lower dose. Discontinue binimetinib if not recovered within 7 days.
	Grade 3 (not accompanied by serum bilirubin increased)	Interrupt binimetinib until recovery to Grade ≤1. Resume binimetinib at 1-level lower dose.
	Grade 3 (accompanied by serum bilirubin increased) and Grade 4	Discontinue binimetinib.
Serum CK increased	Grade 3 (accompanied by muscular symptom or creatinine increased) and Grade 4	Interrupt binimetinib until recovery to Grade ≤1. If recovered within 28 days, resume binimetinib at 1-level lower dose. Discontinue binimetinib if not recovered within 28 days.
Ejection fraction decreased	Decrease in left ventricular ejection fraction from baseline by ≥10% or to below the lower limit of normal	Interrupt binimetinib until recovery. If recovered within 28 days, resume binimetinib at 1-level lower dose. Discontinue binimetinib if not recovered within 28 days.
	Grade 3 to 4	Discontinue binimetinib.
Electrocardiogram QT prolonged	QTc exceeds 500 ms, and the change from baseline is ≤60 ms.	Interrupt binimetinib until QTc decreases to <500 ms. Resume binimetinib at 1-level lower dose. Discontinue binimetinib if QT prolongation recurs.
	QTc exceeds 500 ms, and the change from baseline is >60 ms.	Discontinue binimetinib.
Dermatitis	Grade 2	If the symptom persists or worsens, interrupt binimetinib until recovery to Grade ≤1. Resume binimetinib at same dose. If recurrent, interrupt binimetinib until recovery and then resume at 1-level lower dose.
	Grade 3	Interrupt binimetinib until recovery to Grade ≤1. Resume binimetinib at same dose. If recurrent, interrupt binimetinib until recovery and then resume at 1-level lower dose.
	Grade 4	Discontinue binimetinib.
Other adverse drug reactions	Grade 2	If Grade 2 symptom persists, consider interruption or dose reduction.
	Grade 3	Consider interruption until recovery to Grade ≤1. If recovered within 28 days, consider resumption at 1-level lower dose.
	Grade 4	Discontinue binimetinib.

[*2] Grade is determined according to NCI-CTCAE ver4.03.

Unresectable advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy

3. In case of adverse drug reactions associated with binimetinib, binimetinib should be interrupted, reduced in dose, or discontinued by referring to the following criteria.
4. If encorafenib is interrupted or discontinued, binimetinib should also be interrupted or discontinued, respectively.

Dose reduction in continued administration

Dose reduction level*3	Dose
Usual dose	45 mg BID
1-level dose reduction	30 mg BID
2-level dose reduction	15 mg BID
3-level dose reduction	Discontinue.

*3 If the adverse drug reaction requiring dose reduction has improved to Grade ≤1, and there are no other concomitant adverse drug reactions, the dose may be increased according to the reverse steps.

Criteria for dose adjustment in case of adverse drug reactions

Adverse drug reaction	Severity*4	Measure
Retinal disease, uveitis	Grade 2	Interrupt binimetinib until recovery to Grade ≤1. Resume binimetinib at same dose or at 1-level lower dose.
	Grade 3	Interrupt binimetinib until recovery to Grade ≤2. Resume binimetinib at 1-level lower dose. Discontinue binimetinib if Grade 3 persists.
	Grade 4	Discontinue binimetinib.
Retinal vein occlusion	Grade ≥1	Discontinue binimetinib.
Eye disorders (other than above)	Grade 3	Interrupt binimetinib until recovery to Grade ≤1. If recovered within 21 days, resume binimetinib at 1-level lower dose. Discontinue binimetinib if not recovered within 21 days.
	Grade 4	Discontinue binimetinib.
AST increased, ALT increased	Grade 2 (not accompanied by serum bilirubin increased)	Interrupt binimetinib until recovery to Grade ≤1. If recovered within 14 days, resume binimetinib at same dose. If recovered after >14 days, resume binimetinib at 1-level lower dose. If recurrent, interrupt binimetinib until recovery and then resume at 1-level lower dose.
	Grade 2 (accompanied by serum bilirubin increased)	Interrupt binimetinib until recovery to Grade ≤1. If recovered within 7 days, resume binimetinib at 1-level lower dose. Discontinue binimetinib if not recovered within 7 days.
	Grade 3 (not accompanied by serum bilirubin increased)	Interrupt binimetinib until recovery to Grade ≤1. Resume binimetinib at 1-level lower dose.
	Grade 3 (accompanied by serum bilirubin increased) and Grade 4	Discontinue binimetinib.
Serum CK increased	Grade 3 (accompanied by muscular symptom or creatinine increased) and Grade 4	Interrupt binimetinib until recovery to Grade ≤1. If recovered within 21 days, resume binimetinib at 1-level lower dose. Discontinue binimetinib if not recovered within 21 days.
Ejection fraction decreased	Decrease in left ventricular ejection fraction from baseline by ≥10% or to below the lower limit of normal	Interrupt binimetinib until recovery. If recovered within 21 days, resume binimetinib at 1-level lower dose. Discontinue binimetinib if not recovered within 21 days.
	Grade 3 to 4	Discontinue binimetinib.
Electrocardiogram QT prolonged	QTc exceeds 500 ms, and the change from baseline is ≤60 ms.	Interrupt binimetinib until QTc decreases to <500 ms. Resume binimetinib at 1-level lower dose. Discontinue binimetinib if QT prolongation recurs.
	QTc exceeds 500 ms, and the change from baseline is >60 ms.	Discontinue binimetinib.
Dermatitis	Grade 2	If the symptom persists or worsens, interrupt binimetinib until recovery to Grade ≤1. Resume binimetinib at same dose. If recurrent, interrupt binimetinib until recovery and then resume at 1-level lower dose.
	Grade 3	Interrupt binimetinib until recovery to Grade ≤1. Resume binimetinib at same dose. If recurrent, interrupt binimetinib until recovery and then resume at 1-level lower dose.
	Grade 4	Discontinue binimetinib
Other adverse drug reactions	Grade 2	If Grade 2 symptom persists, consider interruption or dose reduction.
	Grade 3	Consider interruption until recovery to Grade ≤1. If recovered within 21 days, consider resumption at 1-level lower dose.
	Grade 4	Discontinue binimetinib.

*4 Grade is determined according to NCI-CTCAE ver4.03.

Appendix

List of Abbreviations

5-FU	5-fluorouracil
ADL	activities of daily living
AFL	aflibercept beta (genetical recombination)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BEACON CRC study	Study ARRAY-818-302
BICR	blinded independent central review
BID	bis in die
BINI	binimetinib
BINI/Cmab	combination of binimetinib and cetuximab (genetical recombination)
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BRAF V600 mutation	BRAF mutation involving amino acid substitution of valine to other amino acid at codon 600
BRAF V600E mutation	BRAF mutation involving amino acid substitution of valine to glutamic acid at codon 600
BV	bevacizumab (genetical recombination)
CI	confidence interval
CK	creatine phosphokinase
Cmab	cetuximab (genetical recombination)
CMC	carboxymethylcellulose
CR	complete response
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ENCO	encorafenib
ENCO/BINI	combination of ENCO and BINI
ENCO/BINI/Cmab	combination of ENCO, BINI, and Cmab
ENCO/Cmab	combination of ENCO and Cmab
ENCO/Cmab/alpelisib	combination of ENCO, Cmab, and alpelisib
FAS	full analysis set
FOLFIRI	combination of 5-FU, LV, and IRI
FOLFIRI/AFL	combination of FOLFIRI and AFL
FOLFIRI/BV	combination of FOLFIRI and BV
FOLFIRI/Cmab	combination of FOLFIRI and Cmab
FOLFIRI/RAM	combination of FOLFIRI and RAM
FTD/TPI	trifluridine/tipiracil hydrochloride
IC	investigator's choice
IDMC	independent data monitoring committee
ILD	interstitial lung disease
IRI	irinotecan hydrochloride hydrate
IRI/Cmab	combination of IRI and Cmab
Japanese clinical practice guideline	Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines for the treatment of colorectal cancer
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog gene
L-OHP	oxaliplatin
LV	folinate
MAPK	mitogen-activated protein kinase
MEK	mitogen-activated protein kinase/extracellular signal-regulated kinase
MTD	maximum tolerated dose

NCCN Guidelines (colon cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Colon Cancer
NCCN Guidelines (rectal cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Rectal Cancer
NE	not evaluable
NRAS	neuroblastoma RAS viral oncogene homolog gene
OS	overall survival
Partial change application	application for partial changes
PD	progressive disease
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetics
Pmab	panitumumab (genetical recombination)
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PS	performance status
PT	preferred term
QD	quaque die
QOL	quality of life
QT	QT interval
QW	quaque a week
RAF	RAF proto-oncogene serine/threonine-protein kinase
RAM	ramucirumab (genetical recombination)
RAS	rat sarcoma viral oncogene homologue
RECIST	Response Evaluation Criteria in Solid Tumors
Regorafenib	regorafenib hydrate
RES	response efficacy set
RP2D	recommended Phase 2 dose
SD	stable disease
SMQ	standard MedDRA queries
SOC	system organ class
Study 162-111	Study ARRAY-162-111
Study B2301	Study CMEK162B2301
Study X1101	Study CMEK162X1101
Study X2101	Study CLGX818X2101
Study X2103	Study CLGX818X2103
Study X2110	Study CMEK162X2110
VEGF	vascular endothelial growth factor