Dokumentvorlage, Version vom 16.12.2021

Dossier zur Nutzenbewertung gemäß § 35a SGB V

Ivosidenib (Tibsovo®)

Servier Deutschland GmbH

Modul 4B – Anhang 4-I

Erwachsene Patienten mit lokal fortgeschrittenem oder metastasiertem Cholangiokarzinom mit einer Isocitrat-Dehydrogenase-1 (IDH1)-R132-Mutation, die zuvor bereits mit mindestens einer systemischen Therapie behandelt worden sind

Medizinischer Nutzen und
medizinischer Zusatznutzen,
Patientengruppen mit therapeutisch
bedeutsamem Zusatznutzen

Stand: 13.07.2023

Table 14.1.6.4
Baseline Characteristics Among Subsets of Population

	AG120 N=126 n (%)	Placebo N=61 n (%)	Placebo without CO N=18 n (%)	Placebo with CO N=43 n (%)	Placebo with CO - prior to CO [1] N=43 n (%)
Randomization Strata					
1 Prior Line of Therapy	66 (52.4)	33 (54.1)	8 (44.4)	25 (58.1)	25 (58.1)
2 Prior Lines of Therapy	60 (47.6)	28 (45.9)	10 (55.6)	18 (41.9)	18 (41.9)
IDH Allele Types [2]					
R132C	86 (68.3)	45 (73.8)	14 (77.8)	31 (72.1)	31 (72.1)
R132G	17 (13.5)	6 (9.8)	2 (11.1)	4 (9.3)	4 (9.3)
R132H	0	2 (3.3)	0	2 (4.7)	2 (4.7)
R132L	21 (16.7)	7 (11.5)	2 (11.1)	5 (11.6)	5 (11.6)
R132S	2 (1.6)	1 (1.6)	0	1 (2.3)	1 (2.3)
ECOG at Baseline					
0	50 (39.7)	19 (31.1)	0	19 (44.2)	12 (27.9)
1	75 (59.5)	41 (67.2)	17 (94.4)	24 (55.8)	31 (72.1)
2	0	1 (1.6)	1 (5.6)	0	0
3	1 (0.8)	0	0	0	0

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[2] From IDH1 central testing.
Subject with both local/regional and metastatic is considered as metastatic.
Percentages are calculated with the number of subjects in the ITT Set in each column as the denominator.

Table 14.1.6.4
Baseline Characteristics Among Subsets of Population

	AG120 N=126 n (%)	Placebo N=61 n (%)	Placebo without CO N=18 n (%)	Placebo with CO N=43 n (%)	Placebo with CO - prior to CO [1] N=43 n (%)
Aspartate Aminotransferase (U/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	47.0 (34.13)	47.8 (43.16)	70.3 (63.83)	38.4 (26.55)	43.1 (24.00)
Median	37.5	34.0	48.5	30.0	37.0
Min, Max	14.0, 274.0	14.0, 268.0	20.0, 268.0	14.0, 146.0	17.0, 121.0
Alanine Aminotransferase (U/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	35.9 (29.27)	29.7 (18.88)	34.3 (14.22)	27.8 (20.35)	25.3 (18.75)
Median	25.0	26.0	34.0	22.0	21.0
Min, Max	7.0, 151.0	7.0, 114.0	10.0, 59.0	7.0, 114.0	5.0, 92.0
Serum Bilirubin (umol/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	14.2 (16.75)	14.1 (22.46)	21.7 (40.33)	11.0 (5.21)	11.9 (8.14)
Median	10.3	10.3	11.6	10.3	10.1
Min, Max	3.4, 184.7	1.7, 181.3	1.7, 181.3	3.1, 29.4	3.4, 41.0

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Table 14.1.6.4
Baseline Characteristics Among Subsets of Population

	AG120 N=126 n (%)	Placebo N=61 n (%)	Placebo without CO N=18 n (%)	Placebo with CO N=43 n (%)	Placebo with CO - prior to CO [1] N=43 n (%)
Albumin (g/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	42.8 (43.83)	44.0 (46.14)	33.8 (5.91)	48.3 (54.43)	45.6 (46.43)
Median	39.0	39.0	32.5	40.7	40.0
Min, Max	5.0, 402.0	25.0, 396.0	25.0, 44.0	30.0, 396.0	26.0, 341.0
Alkaline Phosphatase (U/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	243.6 (197.92)	226.5 (217.35)	377.8 (331.26)	163.1 (95.60)	208.9 (134.31)
Median	167.5	162.0	262.0	140.0	170.0
Min, Max	53.0, 1029	57.0, 1414	104.0, 1414	57.0, 552.0	61.0, 716.0
Direct Bilirubin (umol/L) at Baseline					
N	120	58	17	41	42
Mean (SD)	6.8 (12.91)	6.8 (16.11)	12.5 (29.27)	4.4 (2.67)	5.4 (3.89)
Median	3.4	3.4	3.8	3.4	3.4
Min, Max	0.0, 138.5	0.0, 124.8	0.0, 124.8	1.5, 12.5	1.7, 22.2

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Subject with both local/regional and metastatic is considered as metastatic.
Percentages are calculated with the number of subjects in the ITT Set in each column as the denominator.

Table 14.1.6.4
Baseline Characteristics Among Subsets of Population

	AG120 N=126 n (%)	Placebo N=61 n (%)	Placebo without CO N=18 n (%)	Placebo with CO N=43 n (%)	Placebo with CO - prior to CO [1] N=43 n (%)
Calcium (mmol/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	2.4 (0.17)	2.4 (0.17)	2.4 (0.22)	2.4 (0.14)	2.5 (0.22)
Median	2.4	2.4	2.4	2.4	2.4
Min, Max	2.0, 3.1	2.1, 2.8	2.1, 2.8	2.2, 2.8	2.2, 3.2
Creatinine (umol/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	68.8 (20.47)	81.0 (29.85)	95.0 (35.07)	75.1 (25.60)	73.6 (26.25)
Median	67.1	70.7	90.2	70.7	70.7
Min, Max	30.0, 132.6	23.9, 150.3	46.0, 150.3	23.9, 148.5	30.1, 158.2
Serum Glucose (mmol/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	6.9 (2.50)	6.4 (1.65)	7.0 (2.00)	6.2 (1.44)	6.6 (2.08)
Median	6.2	6.0	6.5	5.9	6.1
Min, Max	3.9, 19.0	4.1, 11.9	4.7, 11.9	4.1, 10.6	4.4, 16.7

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Percentages are calculated with the number of subjects in the ITT Set in each column as the denominator.

Table 14.1.6.4
Baseline Characteristics Among Subsets of Population

	AG120 N=126 n (%)	Placebo N=61 n (%)	Placebo without CO N=18 n (%)	Placebo with CO N=43 n (%)	Placebo with CO - prior to CO [1] N=43 n (%)
Hemoglobin (g/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	118.7 (15.13)	120.0 (15.92)	114.2 (18.40)	122.5 (14.29)	120.6 (16.24)
Median	118.0	120.0	115.5	122.0	122.0
Min, Max	84.0, 151.0	80.0, 164.0	80.0, 164.0	86.0, 149.0	87.0, 155.0
Potassium (mmol/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	4.1 (0.43)	4.2 (0.45)	4.3 (0.49)	4.2 (0.43)	4.1 (0.43)
Median	4.1	4.2	4.3	4.1	4.1
Min, Max	2.9, 5.6	3.3, 5.4	3.3, 5.2	3.3, 5.4	3.0, 5.1
Lactate Dehydrogenase (U/L) at Baseline					
N	124	60	18	42	43
Mean (SD)	274.8 (137.81)	349.5 (542.19)	538.1 (943.92)	268.7 (176.91)	269.9 (170.40)
Median	226.0	211.0	256.5	195.5	208.0
Min, Max	87.0, 852.0	112.0, 4258	118.0, 4258	112.0, 995.0	115.0, 1125

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Percentages are calculated with the number of subjects in the ITT Set in each column as the denominator.

Table 14.1.6.4
Baseline Characteristics Among Subsets of Population

	AG120 N=126 n (%)	Placebo N=61 n (%)	Placebo without CO N=18 n (%)	Placebo with CO N=43 n (%)	Placebo with CO - prior to CO [1] N=43 n (%)
Lymphocytes (10^9/L) at Baseline					
N	120	59	17	42	43
Mean (SD)	11.0 (107.62)	1.4 (0.99)	1.4 (0.80)	1.4 (1.07)	1.3 (0.84)
Median	1.1	1.1	1.1	1.1	1.0
Min, Max	0.2, 1180	0.3, 5.4	0.4, 3.7	0.3, 5.4	0.4, 3.7
Lymphocytes/Leukocytes (fraction of 1) at Baseline					
N	109	56	16	40	41
Mean (SD)	0.2 (0.09)	0.2 (0.07)	0.1 (0.06)	0.2 (0.07)	0.2 (0.08)
Median	0.2	0.2	0.1	0.2	0.1
Min, Max	0.0, 0.5	0.0, 0.4	0.0, 0.2	0.1, 0.4	0.0, 0.3
Magnesium (mmol/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	0.8 (0.10)	0.8 (0.13)	0.8 (0.15)	0.8 (0.12)	0.8 (0.14)
Median	0.8	0.8	0.8	0.8	0.8
Min, Max	0.4, 1.1	0.5, 1.3	0.5, 1.1	0.6, 1.3	0.6, 1.3

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[2] From IDH1 central testing.
Subject with both local/regional and metastatic is considered as metastatic.
Percentages are calculated with the number of subjects in the ITT Set in each column as the denominator.

Table 14.1.6.4
Baseline Characteristics Among Subsets of Population

	AG120 N=126 n (%)	Placebo N=61 n (%)	Placebo without CO N=18 n (%)	Placebo with CO N=43 n (%)	Placebo with CO - prior to CO [1] N=43 n (%)
Neutrophils (10^9/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	110.0 (1175.49)	6.3 (3.50)	9.0 (3.93)	5.1 (2.59)	6.5 (4.49)
Median	4.4	5.2	7.8	4.6	5.2
Min, Max	1.2, 13200	2.1, 17.7	4.9, 17.7	2.1, 12.8	1.3, 21.0
Neutrophils Band Form/Leukocytes (fraction of 1) at Baseline					
N	33	18	3	15	17
Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.01)	0.0 (0.00)	0.0 (0.00)
Median	0.0	0.0	0.0	0.0	0.0
Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0
Neutrophils/Leukocytes (fraction of 1) at Baseline					
N	111	59	17	42	42
Mean (SD)	0.7 (0.13)	0.7 (0.15)	0.8 (0.08)	0.7 (0.16)	0.7 (0.19)
Median	0.7	0.7	0.8	0.7	0.7
Min, Max	0.0, 1.0	0.0, 0.9	0.6, 0.9	0.0, 0.9	0.0, 0.9

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[2] From IDH1 central testing.
Subject with both local/regional and metastatic is considered as metastatic.
Percentages are calculated with the number of subjects in the ITT Set in each column as the denominator.

Table 14.1.6.4
Baseline Characteristics Among Subsets of Population

	AG120 N=126 n (%)	Placebo N=61 n (%)	Placebo without CO N=18 n (%)	Placebo with CO N=43 n (%)	Placebo with CO - prior to CO [1] N=43 n (%)
Phosphate (mmol/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	1.1 (0.21)	1.1 (0.18)	1.1 (0.20)	1.1 (0.17)	1.0 (0.19)
Median	1.0	1.1	1.1	1.1	1.0
Min, Max	0.5, 1.7	0.7, 1.5	0.7, 1.5	0.8, 1.5	0.6, 1.3
Platelets (10^9/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	191.9 (65.72)	194.4 (82.14)	224.5 (71.46)	181.8 (83.79)	196.7 (90.16)
Median	183.5	194.0	220.5	181.0	185.0
Min, Max	82.0, 425.0	73.0, 538.0	81.0, 363.0	73.0, 538.0	79.0, 544.0
Plasma Erythrocytes (10^12/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	3.9 (0.51)	4.0 (0.51)	3.8 (0.62)	4.1 (0.45)	4.1 (0.50)
Median	4.0	4.1	3.8	4.2	4.1
Min, Max	3.0, 5.2	2.6, 5.1	2.6, 5.0	3.1, 5.1	3.1, 5.4

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Table 14.1.6.4
Baseline Characteristics Among Subsets of Population

	AG120 N=126 n (%)	Placebo N=61 n (%)	Placebo without CO N=18 n (%)	Placebo with CO N=43 n (%)	Placebo with CO - prior to CO [1] N=43 n (%)
Sodium (mmol/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	138.1 (3.29)	138.1 (4.33)	135.5 (5.60)	139.1 (3.19)	137.9 (3.59)
Median	139.0	139.0	136.0	139.0	138.0
Min, Max	124.0, 144.0	123.0, 146.0	123.0, 143.0	128.0, 146.0	126.0, 145.0
Urate (umol/L) at Baseline					
N	115	55	16	39	40
Mean (SD)	301.4 (103.87)	321.1 (110.02)	364.4 (97.65)	303.3 (111.03)	304.2 (112.19)
Median	285.5	285.5	342.0	279.6	291.5
Min, Max	107.1, 773.2	148.7, 690.0	255.8, 535.3	148.7, 690.0	142.8, 624.5
Urea Nitrogen (mmol/L) at Baseline					
N	119	58	16	42	42
Mean (SD)	5.8 (2.63)	6.9 (3.73)	9.0 (5.06)	6.1 (2.78)	6.0 (2.54)
Median	5.4	5.8	7.5	5.6	5.4
Min, Max	1.5, 18.6	1.8, 22.1	4.3, 22.1	1.8, 16.1	1.8, 13.9

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Table 14.1.6.4
Baseline Characteristics Among Subsets of Population

	AG120 N=126 n (%)	Placebo N=61 n (%)	Placebo without CO N=18 n (%)	Placebo with CO N=43 n (%)	Placebo with CO - prior to CO [1] N=43 n (%)
Plasma Leukocytes (10^9/L) at Baseline					
N	126	61	18	43	43
Mean (SD)	7.3 (3.64)	8.5 (4.19)	11.7 (4.67)	7.2 (3.16)	8.7 (5.23)
Median	6.4	7.3	10.7	6.4	6.8
Min, Max	3.0, 25.3	3.0, 24.4	6.7, 24.4	3.0, 16.7	3.1, 24.7
Cholangiocarcinoma Type at Diagnosis					
Intrahepatic	113 (89.7)	58 (95.1)	18 (100)	40 (93.0)	40 (93.0)
Extrahepatic	1 (0.8)	1 (1.6)	0	1 (2.3)	1 (2.3)
Perihilar	4 (3.2)	0	0	0	0
Unknown	8 (6.3)	2 (3.3)	0	2 (4.7)	2 (4.7)
T (Tumor) Stage at Initial Diagnosis					
T0	0	1 (1.6)	0	1 (2.3)	1 (2.3)
T1	13 (10.3)	9 (14.8)	2 (11.1)	7 (16.3)	7 (16.3)
T2	54 (42.9)	25 (41.0)	8 (44.4)	17 (39.5)	17 (39.5)
T3	13 (10.3)	11 (18.0)	1 (5.6)	10 (23.3)	10 (23.3)
T4	13 (10.3)	5 (8.2)	2 (11.1)	3 (7.0)	3 (7.0)
Tx	27 (21.4)	8 (13.1)	5 (27.8)	3 (7.0)	3 (7.0)
Missing	6 (4.8)	2 (3.3)	0	2 (4.7)	2 (4.7)

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Table 14.1.6.4
Baseline Characteristics Among Subsets of Population

	AG120 N=126 n (%)	Placebo N=61 n (%)	Placebo without CO N=18 n (%)	Placebo with CO N=43 n (%)	Placebo with CO - prior to CO [1] N=43 n (%)
N (Lymph node) Stage at Initial Diagnosis					
N0	40 (31.7)	23 (37.7)	3 (16.7)	20 (46.5)	20 (46.5)
N1	45 (35.7)	19 (31.1)	11 (61.1)	8 (18.6)	8 (18.6)
N2	1 (0.8)	1 (1.6)	0	1 (2.3)	1 (2.3)
Nx	33 (26.2)	16 (26.2)	4 (22.2)	12 (27.9)	12 (27.9)
Missing	7 (5.6)	2 (3.3)	0	2 (4.7)	2 (4.7)
M (Metastasis) Stage at Initial Diagnosis					
M0	47 (37.3)	33 (54.1)	9 (50.0)	24 (55.8)	24 (55.8)
M1	63 (50.0)	23 (37.7)	8 (44.4)	15 (34.9)	15 (34.9)
Mx	11 (8.7)	4 (6.6)	1 (5.6)	3 (7.0)	3 (7.0)
Missing	5 (4.0)	1 (1.6)	0	1 (2.3)	1 (2.3)
Grade at Initial Diagnosis					
Well Differentiated	8 (6.3)	4 (6.6)	0	4 (9.3)	4 (9.3)
Moderately Differentiated	47 (37.3)	28 (45.9)	5 (27.8)	23 (53.5)	23 (53.5)
Poorly Differentiated	39 (31.0)	16 (26.2)	10 (55.6)	6 (14.0)	6 (14.0)
Undifferentiated	1 (0.8)	0	0	0	0
Unknown	31 (24.6)	13 (21.3)	3 (16.7)	10 (23.3)	10 (23.3)

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Table 14.1.6.4
Baseline Characteristics Among Subsets of Population

	AG120 N=126 n (%)	Placebo N=61 n (%)	Placebo without CO N=18 n (%)	Placebo with CO N=43 n (%)	Placebo with CO - prior to CO [1] N=43 n (%)
Extent of Disease at Screening					
Local/Regional	9 (7.1)	5 (8.2)	1 (5.6)	4 (9.3)	4 (9.3)
Metastatic	117 (92.9)	56 (91.8)	17 (94.4)	39 (90.7)	39 (90.7)
Liver Cirrhosis at Screening					
Yes	6 (4.8)	3 (4.9)	1 (5.6)	2 (4.7)	2 (4.7)
Hepatitis B	1 (0.8)	0	0	0	0
Hepatitis C	0	1 (1.6)	0	1 (2.3)	1 (2.3)
Alcohol	1 (0.8)	0	0	0	0
Other	4 (3.2)	2 (3.3)	1 (5.6)	1 (2.3)	1 (2.3)
No	120 (95.2)	58 (95.1)	17 (94.4)	41 (95.3)	41 (95.3)
Presence of Biliary Stent at Screening					
Yes	13 (10.3)	7 (11.5)	1 (5.6)	6 (14.0)	6 (14.0)
No	113 (89.7)	54 (88.5)	17 (94.4)	37 (86.0)	37 (86.0)
Presence of Ascites at Screening					
Yes	34 (27.0)	13 (21.3)	9 (50.0)	4 (9.3)	4 (9.3)
No	92 (73.0)	48 (78.7)	9 (50.0)	39 (90.7)	39 (90.7)

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Subject with both local/regional and metastatic is considered as metastatic.
Percentages are calculated with the number of subjects in the ITT Set in each column as the denominator.

Table 14.1.6.4
Baseline Characteristics Among Subsets of Population

	AG120 N=126 n (%)	Placebo N=61 n (%)	Placebo without CO N=18 n (%)	Placebo with CO N=43 n (%)	Placebo with CO - prior to CO [1] N=43 n (%)
Ascites related to Cholangiocarcinoma within the past 3 months of Screening					
Yes	37 (29.4)	13 (21.3)	9 (50.0)	4 (9.3)	4 (9.3)
No	89 (70.6)	48 (78.7)	9 (50.0)	39 (90.7)	39 (90.7)
Paracentesis within the past 3 months of Screening	11 (8.7)	5 (8.2)	4 (22.2)	1 (2.3)	1 (2.3)
Pleural effusion related to Cholangiocarcinoma within the past 3 months of Screening					
Yes	13 (10.3)	7 (11.5)	4 (22.2)	3 (7.0)	3 (7.0)
No	113 (89.7)	54 (88.5)	14 (77.8)	40 (93.0)	40 (93.0)
Thoracentesis within the past 3 months of Screening	2 (1.6)	1 (1.6)	0	1 (2.3)	1 (2.3)
Subjects with at Least 1 prior local or regional therapy	45 (35.7)	20 (32.8)	5 (27.8)	15 (34.9)	15 (34.9)

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Table 14.1.7.1.5
Summary of Subsequent Therapy (ITT)

	Ivosidenib N=126	Placebo without Crossover N=18	Placebo Crossover to Ivosidenib N=43
Patients Who Received Subsequent Systemic Anti-Cancer Therapy	49 (38.9)	1 (5.6)	14 (32.6)
Number of Subsequent Therapies, Median (Min, Max)	1 (1, 4)	1 (1, 1)	1 (1, 4)
Type of Subsequent Therapy			
Chemotherapy	39 (31.0)	0	11 (25.6)
Folfox	11 (8.7)	0	5 (11.6)
Folfiri	9 (7.1)	0	1 (2.3)
Other 5-FU or Capecitabine Based Regimen	7 (5.6)	0	2 (4.7)
Gemcitabine	3 (2.4)	0	0
Gemcitabine + Platinum	15 (11.9)	0	1 (2.3)
Other Gemcitabine Based Regimen	5 (4.0)	0	3 (7.0)
Immunotherapy	10 (7.9)	0	3 (7.0)
Other Investigational Drug	11 (8.7)	1 (5.6)	3 (7.0)
Other Targeted Therapy	11 (8.7)	0	4 (9.3)

ITT: All subjects who are randomized, with the treatment group designated according to the randomization.
Number of subsequent therapies and types of subsequent therapies are determined by medical review.
Percentages are based on the number of subjects in the ITT Set by treatment groups.