は、基準被験者集団（UGT2B17 EM 及び CYP2C19 EM 又は IM）と比較して、AUCss が3.32倍高くなると予測された。MK-6482の曝露量の範囲内で良好なリスク・ベネフィットプロファイルが認められたことから、これらの特定の代謝酵素の表現型に対して用量調節は必要ないと考えられる[2.7.2.3.3 項]。

PBPK 解析の結果、MK-6482の曝露量が高い患者において、MK-6482は中程度の CYP3A4の誘導作用があると予測された[2.7.2.3.4 項]。第 I 相試験において、MK-6482 120 mg を1日1回反復投与にミダゾラムを併用投与した際、ミダゾラムの AUC0-inf が約40%減少した。これは MK-6482が弱い CYP3A4の誘導剤であることと一貫していた[2.7.2.2 項]。

日本人集団での曝露量は非アジア人集団に比べ増加したものの、005試験において、日本人集団の有効性は概して全集団と明確に異なる傾向は認められず、日本人集団の安全性も全集団の結果と概して同様であったことから、日本人患者でも120 mg QD が適用でき、内因性要因による用量調節は必要ないと考えた[2.7.2.1.3.4 項]。

2.7.3.5　効果の持続、耐薬性

005試験の DOR の結果は[2.7.3.2.1.2.2.2 項]に示す。有効性の持続に関する追加データは得られていない。

IA1及び IA2データカットオフ時点で治験薬投与を継続していた患者の割合は、エベロリムス群と比較して MK-6482群で高かった[2.7.3.2.1.1.1 項]。

2.7.3.6　日本人集団（005試験）

本項では、005試験の有効性解析対象集団の ITT 集団のうち、日本人集団（本邦の治験実施医療機関で組み入れられた患者集団）の有効性解析結果を記載する。日本人集団の有効性に関する図表（本文中の図表を含む）は[5.3.5.4.4: P005V01_J_list]及び[5.3.5.4.5: P005V02_J_list]に示す。

なお、005試験では日本人患者を無作為化する前に、日本人での安全性及び忍容性を評価するために Safety Run-in Phase を設定した。Safety Run-in Phase には9例が登録され、日本人での安全性及び忍容性が確認された[2.7.4.7.1 項]。Safety Run-in Phase の期間の終了時点で投与継続していた8例は、その後投与を継続した。Safety Run-in Phase に登録された患者は無作為化されないため、有効性解析対象集団の ITT 集団には含めなかった。本患者の結果は[5.3.5.1.1: P005V01]に示す。

2.7.3.6.1　試験対象集団

2.7.3.6.1.1　患者の内訳

ITT 集団の日本人集団†（44例）では、MK-6482群に20例、エベロリムス群に24例が無作為割付けされ、全例が1回以上治験薬の投与を受けた。治験薬投与を継続していた患者は、IA1のデータ

カットオフ時点で16例［MK-6482群：11例（55.0%）、エベロリムス群：5例（20.8%）］（[5.3.5.4.4: P005V01_J_list] Table 1-1）、IA2のデータカットオフ時点で12例［MK-6482群：7例（35.0%）、エベロリムス群：5例（20.8%）］であった[表 2.7.3-13]。

†本邦の治験実施医療機関で組み入れられた患者集団

表 2.7.3-13　患者の内訳 005 試験 IA2（ITT）（日本人集団）

Disposition of Participants
(Japan ITT Population)

	Belzutifan		Everolimus		Total	
	n	(%)	n	(%)	n	(%)
Participant in population	20		24		44	
Status for Trial						
Discontinued	8	(40.0)	8	(33.3)	16	(36.4)
Death	8	(40.0)	8	(33.3)	16	(36.4)
Participants Ongoing	12	(60.0)	16	(66.7)	28	(63.6)
Status for Study Medication in Trial						
Started	20		24		44	
Discontinued	13	(65.0)	19	(79.2)	32	(72.7)
Adverse Event	1	(5.0)	2	(8.3)	3	(6.8)
Clinical Progression	1	(5.0)	2	(8.3)	3	(6.8)
Physician Decision	0	(0.0)	1	(4.2)	1	(2.3)
Progressive Disease	10	(50.0)	14	(58.3)	24	(54.5)
Withdrawal By Subject	1	(5.0)	0	(0.0)	1	(2.3)
Participants Ongoing	7	(35.0)	5	(20.8)	12	(27.3)

If the overall count of participant is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participant in population is used as the denominator for the percentage calculation.

Each participant is counted once for Trial Status based on the latest Survival Follow-up record.

Each participant is counted once for Study Medication Status based on the latest corresponding disposition record.

Database Cutoff Date: 13JUN2023

Source:　[P005V02MK6482: adam-adsl]

2.7.3.6.1.2　患者の人口統計学的特性及びその他のベースライン特性

全集団のベースライン時の人口統計学的特性及びその他のベースライン特性は、両投与群で同様であったが[2.7.3.2.1.1.2 項]、日本人集団では複数の患者特性に投与群間で不均衡が認められた。日本人集団においては、層別因子である IMDC リスク分類（予後良好は MK-6482群：15.0%、エベロリムス群：41.7%）及び VEGF/VEGFR 標的療法の前治療歴数（1は MK-6482群：70.0%、エベロリムス群：54.2%）に不均衡が認められた。その他の患者特性のうち、投与群間で20%を超える

不均衡が認められたものは、年齢（65歳未満はMK-6482群：55.0%、エベロリムス群：29.2%）であった[付録 2.7.3-4]。

2.7.3.6.1.3　投与状況

日本人集団の投与状況は、概して全集団と同様であった。

IA2のデータカットオフ時点で、日本人集団の投与期間の中央値は、MK-6482群［15.3ヵ月（範囲：0.5～25.7ヵ月）］でエベロリムス群［7.2ヵ月（範囲：0.9～23.3ヵ月）］より長く（[5.3.5.4.5: P005V02_J_list] Table 1-8）、フォローアップ期間の中央値は、19.8ヵ月（範囲：1.1～25.7ヵ月）で、両投与群で同程度であった（[5.3.5.4.5: P005V02_J_list] Table 1-11）。

2.7.3.6.2　有効性の結果

日本人集団の有効性に関しては、患者数及びイベント数が限られており、信頼区間の幅が広いことから、結果の解釈には注意が必要であるものの、概して全集団と明確に異なる傾向は認められなかった。

2.7.3.6.2.1　主要評価項目

2.7.3.6.2.1.1　PFS（中央判定）

IA1の日本人集団でのPFS（中央判定）のハザード比は0.59（95%信頼区間：0.26～1.34）であった。PFS（中央判定）の中央値は、MK-6482群で未到達（95%信頼区間：1.7～未到達）、エベロリムス群で5.6ヵ月（95%信頼区間：3.0～7.4）であった[表 2.7.3-14] [図 2.7.3-13]。

IA2の結果は、IA1の結果と同様であり、PFS（中央判定）のハザード比は0.61（95%信頼区間：0.29～1.27）であった。PFS（中央判定）の中央値は、MK-6482群で13.7ヵ月（95%信頼区間：1.7～未到達）、エベロリムス群で5.6ヵ月（95%信頼区間：3.0～7.4）であった[付録 2.7.3-5] [付録 2.7.3-6]。

表 2.7.3-14　PFS（中央判定）の解析 005 試験 IA1（ITT）（日本人集団）

Analysis of Progression-Free Survival (Primary Censoring Rule)
Based on BICR per RECIST 1.1
(Japan ITT Population)

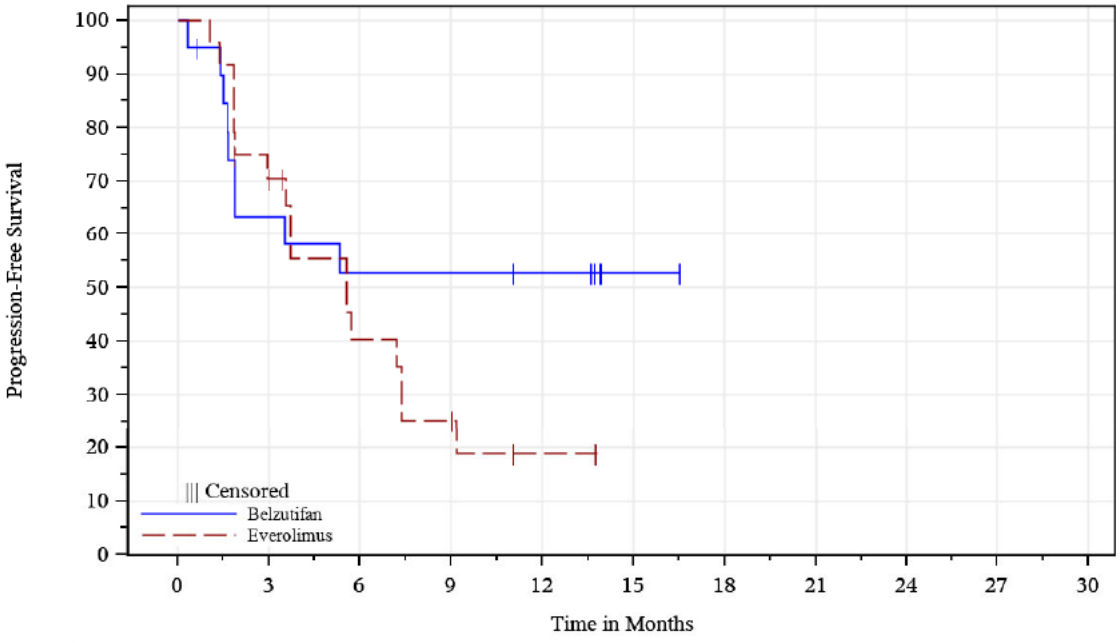
	Belzutifan (N=20)	Everolimus (N=24)
Number of Events (%)	9 (45.0)	17 (70.8)
Death	0 (0)	1 (4.2)
Documented progression	9 (45.0)	16 (66.7)
Number of Censored (%)	11 (55.0)	7 (29.2)
Last assessment showing no progression	10 (50.0)	4 (16.7)
Last radiologic assessment prior to new anti-cancer therapy showing no progression	1 (5.0)	3 (12.5)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (1.7, NR)	5.6 (3.0, 7.4)
[Q1, Q3]	[1.7, NR]	[2.4, 9.2]
Person-months	157.7	128.2
Event Rate / 100 Person-months	5.7	13.3
vs Everolimus		
Hazard Ratio (95% CI)[b]	0.59 (0.26, 1.34)	
p-value[c]	0.10370	
Rate at month 6 (%) (95% CI)	52.8 (28.8, 72.0)	40.3 (19.9, 60.0)
Rate at month 9 (%) (95% CI)	52.8 (28.8, 72.0)	25.2 (9.3, 44.9)
Rate at month 12 (%) (95% CI)	52.8 (28.8, 72.0)	18.9 (5.4, 38.8)
Rate at month 18 (%) (95% CI)	NR (NR, NR)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 01NOV2022

Source:　[P005V01MK6482: adam-adsl; adtte]

図 2.7.3-13　PFS（中央判定）の Kaplan-Meier 曲線 005 試験 IA1（ITT）（日本人集団）

Kaplan-Meier Plot of Progression-Free Survival (Primary Censoring Rule)
Based on BICR per RECIST 1.1
(Japan ITT Population)



At Risk

Belzutifan	20	12	10	10	8	2	0	0	0	0	0
Everolimus	24	16	8	5	2	0	0	0	0	0	0

Database Cutoff Date: 01NOV2022

Source:　[P005V01MK6482: adam-adsl; adtte]

2.7.3.6.2.1.2　OS

IA1の日本人集団での OS のハザード比は0.95（95%信頼区間：0.25～3.56）、OS の中央値は、MK-6482群で未到達（95%信頼区間：未到達～未到達）、エベロリムス群で未到達（95%信頼区間：14.1～未到達）であった[付録 2.7.3-2] [付録 2.7.3-3]。

IA2の日本人集団での OS のハザード比は1.18（95%信頼区間：0.44～3.15）であった。OS の中央値は、MK-6482群で23.0ヵ月（95%信頼区間：10.9～未到達）、エベロリムス群で未到達（95%信頼区間：14.1ヵ月～未到達）であった[表 2.7.3-15] [図 2.7.3-14]。

表 2.7.3-15 OS の解析 005 試験 IA2（ITT）（日本人集団）

Analysis of Overall Survival
(Japan ITT Population)

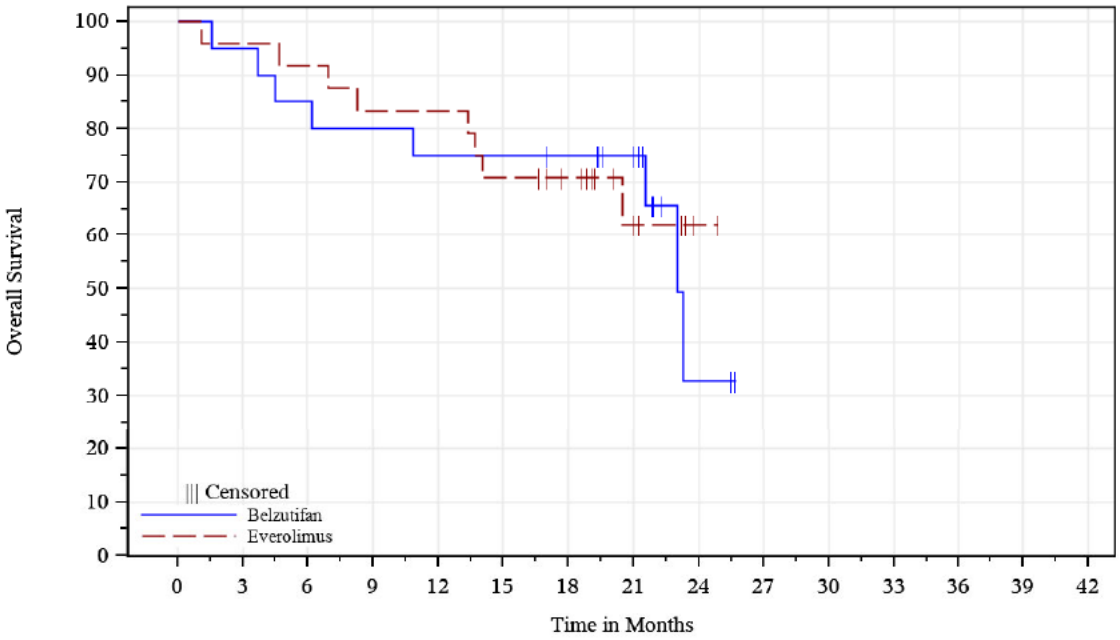
	Belzutifan (N=20)	Everolimus (N=24)
Number of Events (%)	8 (40.0)	8 (33.3)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	23.0 (10.9, NR)	NR (14.1, NR)
[Q1, Q3]	[16.2, NR]	[13.9, NR]
Person-months	351.1	409.3
Event Rate / 100 Person-months	2.3	2.0
vs Everolimus		
Hazard Ratio (95% CI)[b]	1.18 (0.44, 3.15)	
p-value[c]	0.62632	
Rate at month 6 (%) (95% CI)	85.0 (60.4, 94.9)	91.7 (70.6, 97.8)
Rate at month 12 (%) (95% CI)	75.0 (50.0, 88.7)	83.3 (61.5, 93.4)
Rate at month 18 (%) (95% CI)	75.0 (50.0, 88.7)	70.8 (48.4, 84.9)
Rate at month 24 (%) (95% CI)	32.8 (5.8, 64.7)	62.0 (35.7, 80.1)
Rate at month 30 (%) (95% CI)	NR (NR, NR)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 13JUN2023

Source: [P005V02MK6482: adam-adsl; adtte]

図 2.7.3-14　OS の Kaplan-Meier 曲線 005 試験 IA2（ITT）（日本人集団）

Kaplan-Meier Plot of Overall Survival
(Japan ITT Population)



At Risk

Belzutifan	20	19	17	16	15	15	14	10	2	0	0	0	0	0	0
Everolimus	24	23	22	20	20	17	14	6	1	0	0	0	0	0	0

Database Cutoff Date: 13JUN2023

Source:　[P005V02MK6482: adam-adsl; adtte]

2.7.3.6.2.2　副次評価項目

2.7.3.6.2.2.1　ORR（中央判定）

IA1の日本人集団での ORR（中央判定）は、MK-6482群で35.0%（95%信頼区間：15.4～59.2）、エベロリムス群で0%（95%信頼区間：0.0～14.2）であり、奏効は MK-6482群で認められたが、エベロリムス群では認められなかった[表 2.7.3-16] [表 2.7.3-17]。

IA2の結果は、IA1の結果と同様であった。IA2での ORR（中央判定）は MK-6482群で35.0%（95%信頼区間：15.4～59.2）、エベロリムス群で0%（95%信頼区間：0.0～14.2）であった[付録 2.7.3-7] [付録 2.7.3-8]。

表 2.7.3-16　ORR（中央判定）の要約 005 試験 IA1（ITT）（日本人集団）

Analysis of Objective Response (Confirmed) Based on BICR per RECIST 1.1
(Japan ITT Population)

Treatment	N	Number of Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Everolimus	
				Estimate (95% CI)[a]	p-Value[b]
Belzutifan	20	7	35.0 (15.4, 59.2)	35.0 (18.0, 57.0)	0.0009
Everolimus	24	0	0.0 (0.0, 14.2)		

Responses are based on BICR per RECIST 1.1.

[a] Based on Miettinen & Nurminen method.

[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

Database Cutoff Date: 01NOV2022

Source:　[P005V01MK6482: adam-adsl; adrs]

表 2.7.3-17　BOR（中央判定）の要約 005 試験 IA1（ITT）（日本人集団）

Summary of Best Objective Response (Confirmed) Based on BICR per RECIST 1.1
(Japan ITT Population)

	Belzutifan			Everolimus		
	n	(%)	95% CI [a]	n	(%)	95% CI [a]
Number of Participants in Population	20			24		
Complete Response (CR)	1	(5.0)	(0.1, 24.9)	0	(0.0)	(0.0, 14.2)
Partial Response (PR)	6	(30.0)	(11.9, 54.3)	0	(0.0)	(0.0, 14.2)
Overall Response (CR+PR)	**7**	**(35.0)**	**(15.4, 59.2)**	**0**	**(0.0)**	**(0.0, 14.2)**
Stable Disease (SD)	5	(25.0)	(8.7, 49.1)	19	(79.2)	(57.8, 92.9)
Disease Control (CR+PR+SD)	**12**	**(60.0)**	**(36.1, 80.9)**	**19**	**(79.2)**	**(57.8, 92.9)**
Progressive Disease (PD)	7	(35.0)	(15.4, 59.2)	4	(16.7)	(4.7, 37.4)
Not Evaluable [b]	1	(5.0)	(0.1, 24.9)	0	(0.0)	(0.0, 14.2)
No Assessment [c]	0	(0.0)	(0.0, 16.8)	1	(4.2)	(0.1, 21.1)

Responses are based on BICR assessment per RECIST 1.1.

[a] Based on the binomial exact confidence interval method for binomial data.

[b] Not Evaluable (NE) includes participants with insufficient data for assessment of response per RECIST 1.1.

[c] No Assessment includes participants without post-baseline assessment on the data cutoff date.

Stable Disease (SD) includes both SD and Non-CR/Non-PD.

Database Cutoff Date: 01NOV2022.

Source:　[P005V01MK6482: adam-adsl; adrs]

C Confidential

2.7.3.6.2.2.2　　DOR（中央判定）

IA1の日本人集団での奏効は、MK-6482群の7例で認められた。MK-6482群での DOR（中央判定）の中央値は、未到達（範囲：7.4+～14.7+ヵ月）であった。IA1の日本人集団での MK-6482群の7例の奏効例における TTR（中央判定）の中央値は、3.7ヵ月（範囲：1.8～3.8ヵ月）であった[表 2.7.3-18]。

IA2の結果は、IA1の結果と同様であった。IA2時点で奏効が確認された MK-6482群の患者7例での、DOR（中央判定）の中央値は、未到達（範囲：12.9～23.0+ヵ月）であった[付録 2.7.3-9]。

表 2.7.3-18　TTR 及び DOR の要約 005 試験 IA1（ITT）（日本人集団）

Summary of Time to Response and Duration of Response
Based on BICR per RECIST 1.1 in Participants with a Confirmed Response
(Japan ITT Population)

	Belzutifan (N=20)	Everolimus (N=24)
Number of participants with response[a]	7	0
Time to Response (months)		
Mean (SD)	3.0 (1.0)	
Median (Range)	3.7 (1.8-3.8)	
Response Duration[b] (months)		
Median (Range)	NR (7.4+ - 14.7+)	
Number (%[b]) of Participants with Extended Response Duration:		
≥6 months	7 (100.0)	0 (NR)
≥9 months	6 (100.0)	0 (NR)
≥12 months	2 (100.0)	0 (NR)

[a] Includes participants with confirmed complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cutoff Date: 01NOV2022

Source:　[P005V01MK6482: adam-adsl; adtte]

2.7.3.6.2.2.3　　PRO

PRO については、フォローアップ期間がより長い IA2の結果を主に示す。

FKSI-DRS 及び EORTC QLQ-C30スコアの変化（ベースラインから17週目まで）

IA2の日本人集団で FKSI-DRS のベースラインから17週目までの変化量の最小二乗平均値に基づく減少は、MK-6482群と比較してエベロリムス群で大きかった。最小二乗平均値

の群間差は1.24（95%信頼区間：-2.30、4.78）であった（[5.3.5.4.5: P005V02_J_list] Table 2-14）。

IA2の日本人集団でEORTC QLQ-C30全般的健康状態／QoLスコアのベースラインから17週目までの変化量の最小二乗平均値に基づく減少は、MK-6482群と比較してエベロリムス群で大きかった。最小二乗平均値の群間差は2.34（95%信頼区間：-10.59～15.27）であった（[5.3.5.4.5: P005V02_J_list] Table 2-15）。

IA1の結果は、IA2の結果と同様であった（[5.3.5.4.4: P005V01_J_list] Table 2-14、Table 2-15）。

FKSI-DRS及びEORTC QLQ-C30スコアの悪化までの期間

IA2の日本人集団でFKSI-DRSスコアの悪化が確認された患者の割合は、概してMK-6482群（25.0%）の方がエベロリムス群（34.8%）より低く、FKSI-DRSスコアの悪化が確認されるまでの期間の中央値は、MK-6482群では未到達（95%信頼区間：3.71～未到達）、エベロリムス群では未到達（95% 信頼区間：1.84～未到達）であった[付録 2.7.3-10]。

IA2の日本人集団でEORTC QLQ-C30による全般的健康状態／QoLの悪化が確認された患者の割合は、両投与群で同程度であったが（MK-6482群：55.0%、エベロリムス群：56.5%）、EORTC QLQ-C30による全般的健康状態／QoL スコアの悪化が確認されるまでの期間の中央値は、MK-6482群で15.67ヵ月（95%信頼区間：0.49～未到達）、エベロリムス群で3.75ヵ月（95%信頼区間：0.99～未到達）であり、MK-6482群の方が長かった[付録 2.7.3-11]。

IA1の結果は、IA2の結果と同様であった（[5.3.5.4.4: P005V01_J_list] Table 2-18、Table 2-19）。

EuroQoL EQ-5D-5Lに基づくVASスコア

IA2の日本人集団でEQ-5D-5L VASスコアは、いずれの投与群でも減少し悪化を示したが、MK-6482群と比較してエベロリムス群でより減少し、VASスコアのベースラインから17週目までの変化量の最小二乗平均値の群間差は1.91（95%信頼区間：-7.59～11.41）であった[付録 2.7.3-12]。

2.7.3.7　付録

2.7.3.7.1　005試験（全集団）

付録 2.7.3-1　PFS（中央判定）における 6 ヵ月以内の打切りの前治療レジメン数別の理由 005 試験 IA2（ITT）

Summary of Reasons of Censoring for Time of Censoring <= 6 months for Progression-Free-Survival
Based on BICR Assessment per RECIST 1.1 by Prior Line of Therapy
(Primary Censoring Rule)
(ITT Population)

	Belzutifan (N=374)	Everolimus (N=372)
Censored Subjects ≤ 6 months (%)	**25 (6.7)**	**79 (21.2)**
Prior 1 line	**1 (4.0)**	**10 (12.7)**
Last assessment prior to 2 or more consecutive missed assessments†	0 (0.0)	0 (0.0)
Last assessment showing no progression	0 (0.0)	0 (0.0)
Last radiologic assessment prior to new anti-cancer therapy showing no progression‡	1 (100.0)	10 (100.0)
Randomization	0 (0.0)	0 (0.0)
Prior 2 lines	**16 (64.0)**	**33 (41.8)**
Last assessment prior to 2 or more consecutive missed assessments†	1 (6.3)	3 (9.1)
Last assessment showing no progression	0 (0.0)	0 (0.0)
Last radiologic assessment prior to new anti-cancer therapy showing no progression‡	12 (75.0)	20 (60.6)
Randomization	3 (18.8)	10 (30.3)
Prior 3 lines	**8 (32.0)**	**36 (45.6)**
Last assessment prior to 2 or more consecutive missed assessments†	1 (12.5)	1 (2.8)
Last assessment showing no progression	0 (0.0)	0 (0.0)
Last radiologic assessment prior to new anti-cancer therapy showing no progression‡	6 (75.0)	30 (83.3)

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Summary of Reasons of Censoring for Time of Censoring <= 6 months for Progression-Free-Survival
Based on BICR Assessment per RECIST 1.1 by Prior Line of Therapy
(Primary Censoring Rule)
(ITT Population)

	Belzutifan (N=374)	Everolimus (N=372)
Randomization	1 (12.5)	5 (13.9)

† Censored at date of the last Non-PD scan prior to missing 2 or more consecutive disease assessments.

‡ Censored at the date of the last Non-PD scan prior to start of new anti-cancer treatment.

Database Cutoff Date: 13JUN2023

Source:　[P005V02MK6482: adam-adsl; adtte]

2.7.3.7.2 005試験（日本人集団）

2.7.3.7.2.1 IA1

付録 2.7.3-2 OS の解析 005 試験 IA1（ITT）（日本人集団）

Analysis of Overall Survival
(Japan ITT Population)

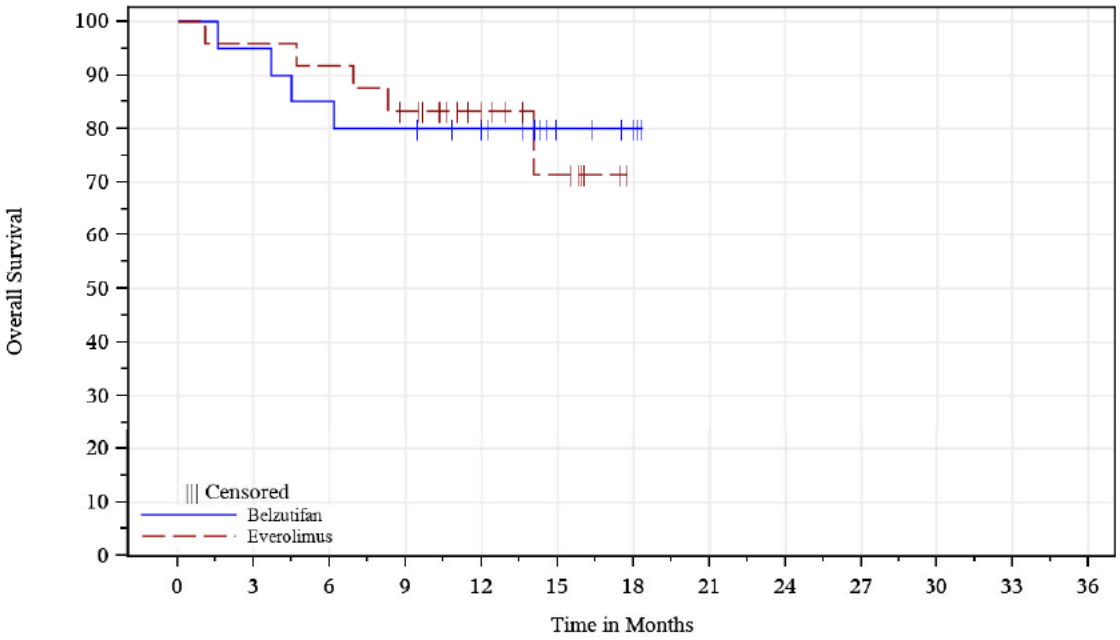
	Belzutifan (N=20)	Everolimus (N=24)
Number of Events (%)	4 (20.0)	5 (20.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (14.1, NR)
[Q1, Q3]	[NR, NR]	[14.1, NR]
Person-months	246.7	280.4
Event Rate / 100 Person-months	1.6	1.8
vs Everolimus		
Hazard Ratio (95% CI)[b]	0.95 (0.25, 3.56)	
p-value[c]	0.46954	
Rate at month 6 (%) (95% CI)	85.0 (60.4, 94.9)	91.7 (70.6, 97.8)
Rate at month 12 (%) (95% CI)	80.0 (55.1, 92.0)	83.3 (61.5, 93.4)
Rate at month 18 (%) (95% CI)	80.0 (55.1, 92.0)	NR (NR, NR)
Rate at month 24 (%) (95% CI)	NR (NR, NR)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adtte]

付録 2.7.3-3　OS の Kaplan-Meier 曲線 005 試験 IA1（ITT）（日本人集団）

Kaplan-Meier Plot of Overall Survival
(Japan ITT Population)



At Risk

Belzutifan	20	19	17	16	13	5	3	0	0	0	0	0	0
Everolimus	24	23	22	19	12	6	0	0	0	0	0	0	0

Database Cutoff Date: 01NOV2022

Source:　[P005V01MK6482: adam-adsl; adtte]

2.7.3.7.2.2　IA2

付録 2.7.3-4　患者の特性 005 試験 IA2（ITT）（日本人集団）

Participant Characteristics
(Japan ITT Population)

	Belzutifan		Everolimus		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	20		24		44	
Sex						
Male	19	(95.0)	18	(75.0)	37	(84.1)
Female	1	(5.0)	6	(25.0)	7	(15.9)
Age (Years)						
< 65	11	(55.0)	7	(29.2)	18	(40.9)
>= 65	9	(45.0)	17	(70.8)	26	(59.1)
Mean	64.0		67.7		66.0	
SD	9.8		10.1		10.0	
Median	64.0		67.0		67.0	
Range	48 to 90		38 to 84		38 to 90	
Race						
Asian	20	(100.0)	24	(100.0)	44	(100.0)
Ethnicity						
Not Hispanic Or Latino	20	(100.0)	24	(100.0)	44	(100.0)
Age (Years)						
< 65	11	(55.0)	7	(29.2)	18	(40.9)
>=65 to <75	7	(35.0)	12	(50.0)	19	(43.2)
>=75 to <85	1	(5.0)	5	(20.8)	6	(13.6)
>=85	1	(5.0)	0	(0.0)	1	(2.3)
Geographic Region of Enrolling Site						
Rest of the World	20	(100.0)	24	(100.0)	44	(100.0)
Karnofsky Performance Scale						
90/100	20	(100.0)	22	(91.7)	42	(95.5)
70/80	0	(0.0)	2	(8.3)	2	(4.5)
ECOG Performance Status						
0	14	(70.0)	19	(79.2)	33	(75.0)
1	6	(30.0)	4	(16.7)	10	(22.7)
2	0	(0.0)	1	(4.2)	1	(2.3)

Participant Characteristics
(Japan ITT Population)

	Belzutifan		Everolimus		Total	
	n	(%)	n	(%)	n	(%)
IMDC Risk Categories						
Favorable	3	(15.0)	10	(41.7)	13	(29.5)
Intermediate	17	(85.0)	14	(58.3)	31	(70.5)
IMDC Risk Categories 2						
Favorable	3	(15.0)	10	(41.7)	13	(29.5)
Intermediate or Poor	17	(85.0)	14	(58.3)	31	(70.5)
Sites of Metastatic Disease - Lung [a]						
Yes	13	(65.0)	19	(79.2)	32	(72.7)
No	7	(35.0)	5	(20.8)	12	(27.3)
Sites of Metastatic Disease - Lymph Node [a]						
Yes	7	(35.0)	8	(33.3)	15	(34.1)
No	13	(65.0)	16	(66.7)	29	(65.9)
Sites of Metastatic Disease - Bone [a]						
Yes	12	(60.0)	12	(50.0)	24	(54.5)
No	8	(40.0)	12	(50.0)	20	(45.5)
Sites of Metastatic Disease - Liver [a]						
Yes	4	(20.0)	3	(12.5)	7	(15.9)
No	16	(80.0)	21	(87.5)	37	(84.1)
Sites of Metastatic Disease - Adrenal Gland [a]						
Yes	4	(20.0)	4	(16.7)	8	(18.2)
No	16	(80.0)	20	(83.3)	36	(81.8)
Number of Organs Involved with Disease at Baseline						
1	2	(10.0)	4	(16.7)	6	(13.6)
>= 2	18	(90.0)	20	(83.3)	38	(86.4)
RCC Histology						
Clear Cell	19	(95.0)	23	(95.8)	42	(95.5)
Clear Cell Component	1	(5.0)	1	(4.2)	2	(4.5)
Sarcomatoid Feature						
Yes	1	(5.0)	2	(8.3)	3	(6.8)

Participant Characteristics
(Japan ITT Population)

	Belzutifan		Everolimus		Total	
	n	(%)	n	(%)	n	(%)
No	16	(80.0)	21	(87.5)	37	(84.1)
Unknown	3	(15.0)	1	(4.2)	4	(9.1)
RCC Stage at Initial Diagnosis						
I	2	(10.0)	3	(12.5)	5	(11.4)
II	1	(5.0)	2	(8.3)	3	(6.8)
III	7	(35.0)	5	(20.8)	12	(27.3)
IV	10	(50.0)	14	(58.3)	24	(54.5)
Prior Oncologic Radiation						
Yes	8	(40.0)	5	(20.8)	13	(29.5)
No	12	(60.0)	19	(79.2)	31	(70.5)
Prior Nephrectomy						
Yes	16	(80.0)	16	(66.7)	32	(72.7)
No	4	(20.0)	8	(33.3)	12	(27.3)
Number of prior VEGF/VEGF receptor targeted therapies						
1	14	(70.0)	13	(54.2)	27	(61.4)
2-3	6	(30.0)	11	(45.8)	17	(38.6)
Number of prior lines of therapy						
1	5	(25.0)	8	(33.3)	13	(29.5)
2	10	(50.0)	6	(25.0)	16	(36.4)
3	5	(25.0)	10	(41.7)	15	(34.1)

SD=Standard deviation.

[a]The sites are five most common metastatic sites and ordered decreasingly by the frequency in total of the two treatment arms.

Database Cutoff Date: 13JUN2023

Source:　[P005V02MK6482: adam-adsl]

付録 2.7.3-5　PFS（中央判定）の解析 005 試験 IA2（ITT）（日本人集団）

Analysis of Progression-Free Survival (Primary Censoring Rule)
Based on BICR per RECIST 1.1
(Japan ITT Population)

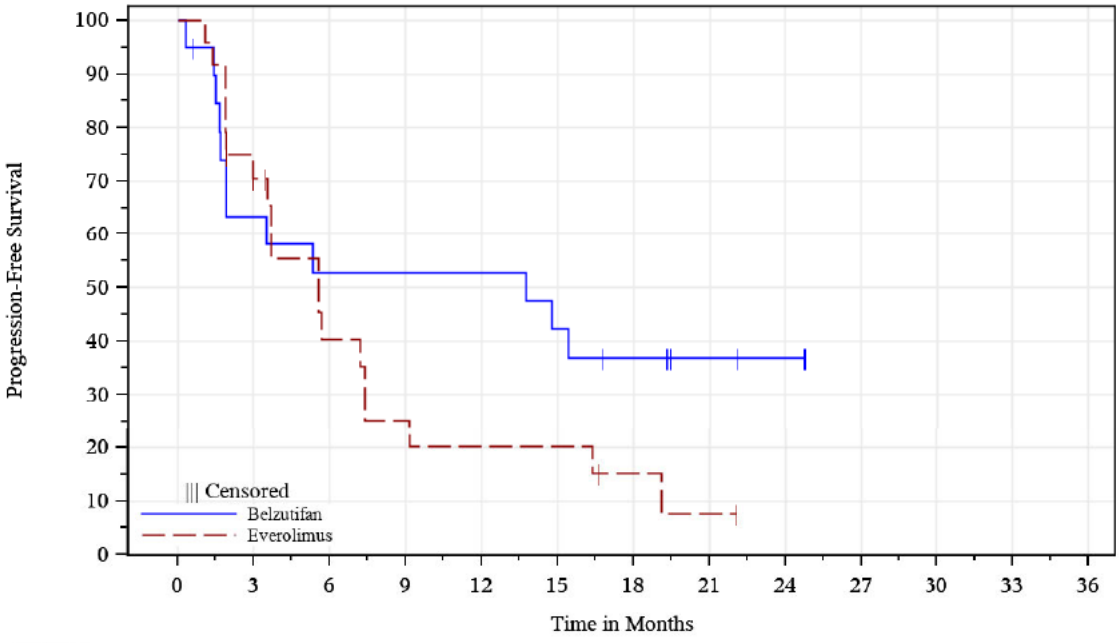
	Belzutifan (N=20)	Everolimus (N=24)
Number of Events (%)	12 (60.0)	19 (79.2)
Death	0 (0)	1 (4.2)
Documented progression	12 (60.0)	18 (75.0)
Number of Censored (%)	8 (40.0)	5 (20.8)
Last assessment showing no progression	7 (35.0)	2 (8.3)
Last radiologic assessment prior to new anti-cancer therapy showing no progression	1 (5.0)	3 (12.5)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	13.7 (1.7, NR)	5.6 (3.0, 7.4)
[Q1, Q3]	[1.7, NR]	[2.4, 9.2]
Person-months	210.5	154.7
Event Rate / 100 Person-months	5.7	12.3
vs Everolimus		
Hazard Ratio (95% CI)[b]	0.61 (0.29, 1.27)	
p-value[c]	0.09402	
Rate at month 6 (%) (95% CI)	52.8 (28.8, 72.0)	40.3 (19.9, 60.0)
Rate at month 9 (%) (95% CI)	52.8 (28.8, 72.0)	25.2 (9.3, 44.9)
Rate at month 12 (%) (95% CI)	52.8 (28.8, 72.0)	20.2 (6.4, 39.4)
Rate at month 18 (%) (95% CI)	36.9 (16.6, 57.6)	15.1 (3.8, 33.6)
Rate at month 24 (%) (95% CI)	36.9 (16.6, 57.6)	NR (NR, NR)
Rate at month 30 (%) (95% CI)	NR (NR, NR)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 13JUN2023

Source:　[P005V02MK6482: adam-adsl; adtte]

付録 2.7.3-6　PFS（中央判定）の Kaplan-Meier 曲線 005 試験 IA2（ITT）（日本人集団）

Kaplan-Meier Plot of Progression-Free Survival (Primary Censoring Rule)
Based on BICR per RECIST 1.1
(Japan ITT Population)



At Risk

Belzutifan	20	12	10	10	10	8	6	3	2	0	0	0	0
Everolimus	24	16	8	5	4	4	2	1	0	0	0	0	0

Database Cutoff Date: 13JUN2023

Source:　[P005V02MK6482: adam-adsl; adtte]

付録 2.7.3-7　ORR（中央判定）の解析 005 試験 IA2（ITT）（日本人集団）

Analysis of Objective Response (Confirmed) Based on BICR per RECIST 1.1
(Japan ITT Population)

Treatment	N	Number of Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Everolimus	
				Estimate (95% CI)[a]	p-Value[b]
Belzutifan	20	7	35.0 (15.4, 59.2)	35.0 (18.0, 57.0)	0.0009
Everolimus	24	0	0.0 (0.0, 14.2)		

Responses are based on BICR per RECIST 1.1.

[a] Based on Miettinen & Nurminen method.

[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

Database Cutoff Date: 13JUN2023

Source:　[P005V02MK6482: adam-adsl; adrs]

付録 2.7.3-8　BOR（中央判定）の要約 005 試験 IA2（ITT）（日本人集団）

Summary of Best Objective Response (Confirmed) Based on BICR per RECIST 1.1
(Japan ITT Population)

	Belzutifan			Everolimus		
	n	(%)	95% CI [a]	n	(%)	95% CI [a]
Number of Participants in Population	20			24		
Complete Response (CR)	1	(5.0)	(0.1, 24.9)	0	(0.0)	(0.0, 14.2)
Partial Response (PR)	6	(30.0)	(11.9, 54.3)	0	(0.0)	(0.0, 14.2)
Overall Response (CR+PR)	**7**	**(35.0)**	**(15.4, 59.2)**	**0**	**(0.0)**	**(0.0, 14.2)**
Stable Disease (SD)	5	(25.0)	(8.7, 49.1)	19	(79.2)	(57.8, 92.9)
Disease Control (CR+PR+SD)	**12**	**(60.0)**	**(36.1, 80.9)**	**19**	**(79.2)**	**(57.8, 92.9)**
Progressive Disease (PD)	7	(35.0)	(15.4, 59.2)	4	(16.7)	(4.7, 37.4)
Not Evaluable [b]	1	(5.0)	(0.1, 24.9)	0	(0.0)	(0.0, 14.2)
No Assessment [c]	0	(0.0)	(0.0, 16.8)	1	(4.2)	(0.1, 21.1)

Responses are based on BICR assessment per RECIST 1.1.

[a] Based on the binomial exact confidence interval method for binomial data.

[b] Not Evaluable (NE) includes participants with insufficient data for assessment of response per RECIST 1.1.

[c] No Assessment includes participants without post-baseline assessment on the data cutoff date.

Stable Disease (SD) includes both SD and Non-CR/Non-PD.

Database Cutoff Date: 13JUN2023.

Source:　[P005V02MK6482: adam-adsl; adrs]

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付録 2.7.3-9　TTR 及び DOR の要約 005 試験 IA2（ITT）（日本人集団）

Summary of Time to Response and Duration of Response
Based on BICR per RECIST 1.1 in Participants with a Confirmed Response
(Japan ITT Population)

	Belzutifan (N=20)	Everolimus (N=24)
Number of participants with response[a]	7	0
Time to Response (months)		
Mean (SD)	3.0 (1.0)	
Median (Range)	3.7 (1.8-3.8)	
Response Duration[b] (months)		
Median (Range)	NR (12.9 - 23.0+)	
Number (%[b]) of Participants with Extended Response Duration:		
≥6 months	7 (100.0)	0 (NR)
≥9 months	7 (100.0)	0 (NR)
≥12 months	7 (100.0)	0 (NR)
≥15 months	5 (71.4)	0 (NR)
≥18 months	3 (71.4)	0 (NR)
≥21 months	2 (71.4)	0 (NR)

[a] Includes participants with confirmed complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cutoff Date: 13JUN2023

Source:　[P005V02MK6482: adam-adsl; adtte]

付録 2.7.3-10 FKSI-DRS の悪化までの期間 005 試験 IA2（PRO FAS）（日本人集団）

Analysis of Time to True Deterioration for FKSI-DRS
(Japan PRO FAS Population With Baseline)

Treatment	N	Number of Events (%)	Median Time to True Deterioration [a] (months) (95% CI)
Belzutifan	20	5 (25.0)	NR (3.71, NR)
Everolimus	23	8 (34.8)	NR (1.84, NR)
Pairwise Comparisons		Hazard Ratio[b] (95% CI)[b]	p-Value
Belzutifan vs. Everolimus		0.74 (0.24, 2.26)	0.5932[d]

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

[d] Two-sided p-value based on log-rank test.

NR = Not reached.

True deterioration is defined as the time to first onset of a ≥3-points deterioration (i.e., decrease in score) from baseline with confirmation by the subsequent visit of a ≥3-point deterioration from baseline under right-censoring rule. If the first deterioration is at the last PRO assessment timepoint in the current database, then no confirmation is required.

Database Cutoff Date: 13JUN2023.

Source:　[P005V02MK6482: adam-adsl; adprotte]

付録 2.7.3-11 EORTC QLQ-C30 全般的健康状態／QoL スコアの悪化までの期間 005 試験 IA2（PRO FAS）（日本人集団）

Analysis of Time to True Deterioration for EORTC QLQ-C30 Global Health Status/QoL (Japan PRO FAS Population With Baseline)

Treatment	N	Number of Events (%)	Median Time to True Deterioration [a] (months) (95% CI)
Belzutifan	20	11 (55.0)	15.67 (0.49, NR)
Everolimus	23	13 (56.5)	3.75 (0.99, NR)
Pairwise Comparisons		Hazard Ratio[b] (95% CI)[b]	p-Value
Belzutifan vs. Everolimus		0.89 (0.39, 2.05)	0.7663[d]

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

[d] Two-sided p-value based on log-rank test.

NR = Not reached.

True deterioration is defined as the time to first onset of a ≥10-points deterioration (i.e., decrease in score) from baseline with confirmation by the subsequent visit of a ≥10-point deterioration from baseline under right-censoring rule. If the first deterioration is at the last PRO assessment timepoint in the current database, then no confirmation is required.

Database Cutoff Date: 13JUN2023.

Source:　[P005V02MK6482: adam-adsl; adprotte]

付録 2.7.3-12 EQ-5D-5L VAS スコアのベースラインから 17 週目までの変化量 005 試験 IA2（PRO FAS）（日本人集団）

Analysis of Change from Baseline in EQ-5D VAS to Week 17
(Japan PRO FAS Population)

Treatment	Baseline		Week 17		Change from Baseline to Week 17	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
Belzutifan	20	74.55 (12.11)	14	76.07 (13.84)	20	-4.04 (-11.06, 2.97)
Everolimus	23	76.09 (17.02)	16	76.31 (13.85)	24	-5.96 (-12.39, 0.48)

Pairwise Comparison	Difference in LS Means[a] (95% CI)	p-Value[a]
Belzutifan vs. Everolimus	1.91 (-7.59, 11.41)	0.6772

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by time interaction.

Two-sided p-value is based on t test.

For baseline and Week 17, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

Database Cutoff Date: 13JUN2023

Source:　[P005V02MK6482: adam-adsl; adpro]

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