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内容:治療歴のある淡明細胞型腎細胞がんには低酸素誘導因子 2α 阻害薬 belzutifan が有用

出典:Belzutifan versus Everolimus for Advanced Renal-Cell Carcinoma.

The New England journal of medicine. 2024 Aug 22;391(8);710-721.

https://pubmed.ncbi.nlm.nih.gov/39167807/

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免疫チェックポイント阻害薬(ICI)と血管新生阻害薬(VEGFR-TKI)による治療歴のある進行淡明細胞型腎細胞がん患者の治療において、エベロリムスと比較して低酸素誘導因子 2α 阻害薬 belzutifan は有用か、米国・ダナファーバーがん研究所の研究者らが実施した「LITESPARK-005 試験」で示された。研究の成果は、NEJM 誌 2024 年 8 月 22 日号で報告された。

世界 6 地域(日本を含む)の 147 施設で実施した非盲検無作為化実薬対照第 III 相試験であり、2020 年 3 月～2022 年 1 月の期間に参加者の無作為化を行った。年齢 18 歳以上、StageIV の淡明細胞型腎細胞がんと診断され、ICI と VEGFR-TKI の逐次投与または同時併用投与を受けた後に、病勢が進行した患者を対象とした。belzutifan 120mg またはエベロリムス 10mg を 1 日 1 回、経口投与する群に 1 対 1 の割合で無作為に割り付け、主要評価項目は、無増悪生存期間と全生存期間とした。746 例を登録し、374 例を belzutifan 群(年齢中央値 62.0 歳、男性 79.4%)、372 例をエベロリムス群(63.0 歳、76.3%)に割り付けた。全体の 43.3%が 2 ライン、42.8%が 3 ラインの前治療を受けていた。2 回目の中間解析(追跡期間中央値 25.7 ヵ月)の時点における全生存期間中央値は、belzutifan 群が 21.4 ヵ月、エベロリムス群は 18.1 ヵ月であり、18 ヵ月時の生存率はそれぞれ 55.2%および 50.6%と両群間に差を認めなかった(ハザード比[HR]:0.88、95%信頼区間[CI]:0.73～1.07、両側の p=0.20)が、客観的奏効率は、エベロリムス群が 3.5%(95%CI:1.9～5.9)であったのに対し、belzutifan 群は 21.9%(17.8～26.5)と有意に優れた(p<0.001)。

本試験は、有効な治療メカニズムとして低酸素誘導因子 2α の阻害を導入し、免疫チェックポイント阻害薬と血管新生阻害薬の両方の治療を受けた進行腎細胞がん患者の治療選択肢として、belzutifan を確立した。

The NEW ENGLAND JOURNAL of MEDICINE

Belzutifan vs. Everolimus for Advanced Renal-Cell Carcinoma

A PLAIN-LANGUAGE SUMMARY

Based on the NEJM publication Belzutifan versus Everolimus for Advanced Renal-Cell Carcinoma
by T.K. Choueiri et al. (published August 22, 2024)

In this trial, researchers compared the efficacy and safety of belzutifan with those of everolimus in persons with advanced clear-cell renal-cell carcinoma that progressed after immune checkpoint and antiangiogenic therapies.

Belzutifan is a small molecule inhibitor of hypoxia-inducible factor 2α (HIF-2α). HIF-2α up-regulates the expression of genes that encode proteins associated with the growth and progression of renal-cell carcinoma.

WHY WAS THE TRIAL DONE?

Recent advances in first-line therapy for clear-cell renal-cell carcinoma, including immune checkpoint and antiangiogenic agents, have led to knowledge gaps in selecting subsequent therapy for patients with disease progression. Therefore, there is a need for medications with new therapeutic mechanisms for these patients. The HIF-2α inhibitor belzutifan has shown clinical activity in clear-cell renal-cell carcinoma in early-phase studies, but additional data are needed.

Advanced Renal-Cell Carcinoma

HOW WAS THE TRIAL CONDUCTED?

A total of 746 adults with stage IV clear-cell renal-cell carcinoma that had progressed after treatment with a programmed cell death protein 1 or programmed death ligand 1 inhibitor, along with a vascular endothelial growth factor receptor–tyrosine kinase inhibitor, were assigned to receive belzutifan (120 mg) or everolimus (10 mg) orally once daily until disease progression or unacceptable toxic effects occurred. The dual primary end points were progression-free survival and overall survival.

Belzutifan
120 mg
(tablet)

174 Participants

Everolimus
10 mg
(tablet)

172 Participants

PARTICIPANTS

WHO: 746 adults
Median age, 63.3 years
Men: 70%; Women: 22%

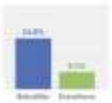
CLINICAL SETTING: Stage IV clear-cell renal-cell carcinoma
At least one measurable lesion
Karnofsky performance-status score of at least 70 out of 100 (lower scores indicate greater disability)
Disease progression during or after most recent therapy; no previous everolimus or HIF-2α inhibitor therapy

TRIAL DESIGN

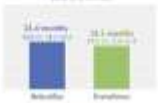
RESULTS

At the first interim analysis, the estimated progression-free survival over time was significantly greater in the belzutifan group than in the everolimus group. At the second interim analysis, overall survival did not differ significantly between the groups.

Estimated Progression-Free Survival at 18 Months



Overall Survival



The incidence of grade 3 or higher adverse events was similar in the two groups. Belzutifan recipients were less likely than everolimus recipients to discontinue treatment because of adverse events.

Grade 3 or Higher Adverse Event

Adverse Event Leading to Treatment Discontinuation

OBJECTIVE RESPONSE

At the first interim analysis, 22.9% of the participants in the belzutifan group and 1.5% of those in the everolimus group had a confirmed objective response (a key secondary end point).

LIMITATIONS AND REMAINING QUESTIONS

- The choice of everolimus as the comparator may be a limitation, because other agents are also available and used in the treatment of clear-cell renal-cell carcinoma.
- Black persons were underrepresented, accounting for only 1.1% of the participants.
- Results from the trial's final analysis are pending.

LINKED FULL ARTICLE | VIEW QUICK TAKE

CONCLUSIONS

In participants with advanced clear-cell renal-cell carcinoma that progressed after immune checkpoint and antiangiogenic therapies, the HIF-2α inhibitor belzutifan showed a benefit over everolimus with respect to progression-free survival and objective response.

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT04195750
Trial funding: Merck Sharp and Dohme, a subsidiary of Merck
Full citation: Choueiri TK, Powles T, Peltola K, et al. Belzutifan versus everolimus for advanced renal-cell carcinoma. N Engl J Med 2024;391:720-31. DOI: 10.1056/NEJMoa2313998