

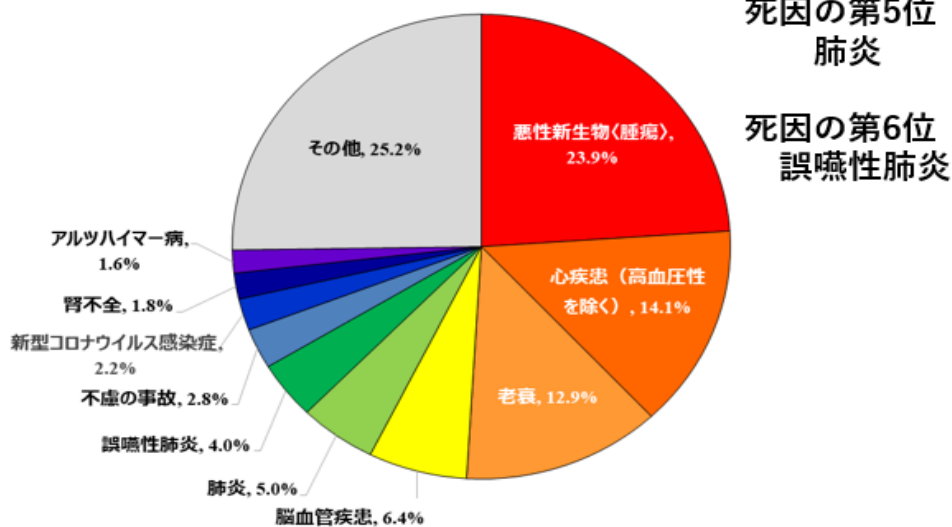
RAS(ON)multi inhibitor

膵癌：新たな抗がん剤 Revolution Medicine

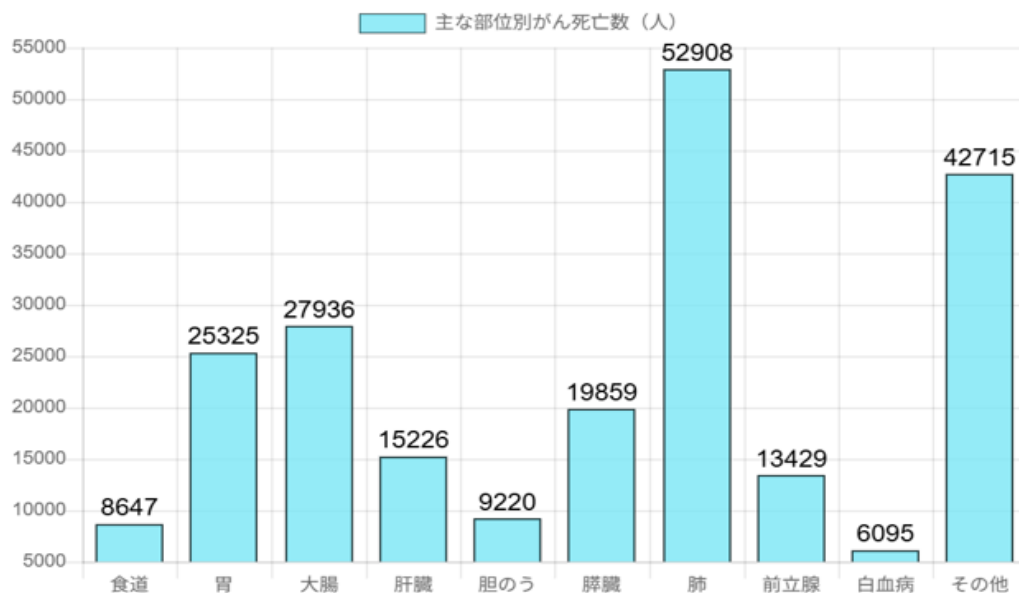
RAS(ON) Multi-Selective Inhibitor :
Daraxonrasib

背景：米国 膵癌5年生存率 3%
毎年6万人発生 5万人死亡
RAS: renin angiotensin system

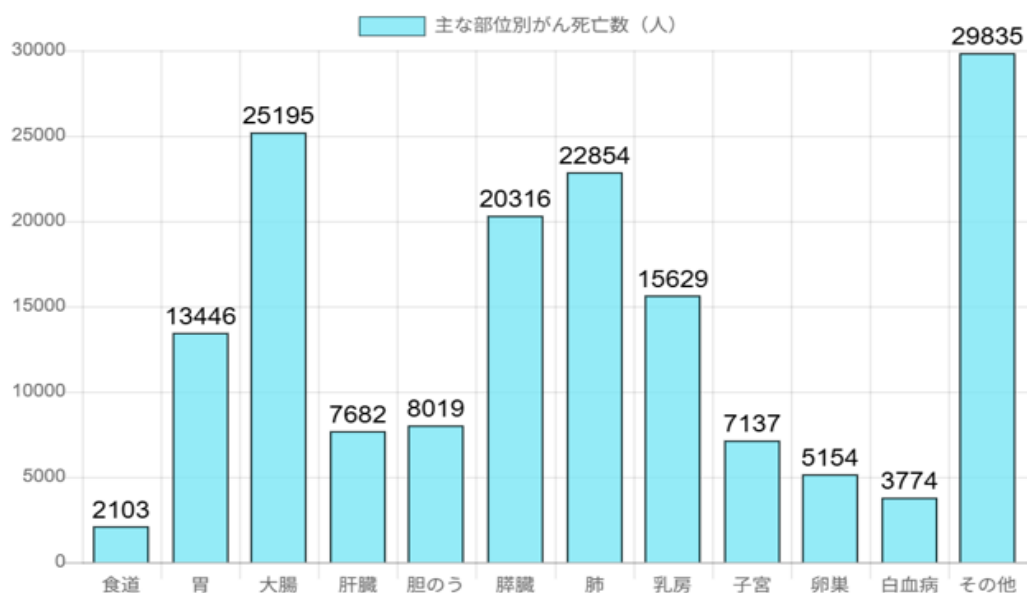
令和6年（2024年）主な死因の構成割合



(出典：「令和6年（2024年）人口動態統計月報年計（概数）」厚生労働省 2025.6.4 より作図)



部位別がん死亡数（2023年）男性



部位別がん死亡数（2023年）女性

細胞内外の情報伝達機構

細胞外伝達系

ホルモン系、神経系、免疫系

種々の系で情報伝達：種々の外的刺激、内的刺激、免疫系の情報が担当
細胞に伝達各細胞膜には受容体の存在

細胞内伝達系

RAS：細胞内伝達系の代表

細胞外の伝達系は種々あるも、細胞内伝達系は比較的一元化

細胞内伝達系は細胞外伝達系より情報が緩やかで調整されながら情報が伝達

その情報をもとに 細胞が成長、分化、分裂

RAS proteins とは

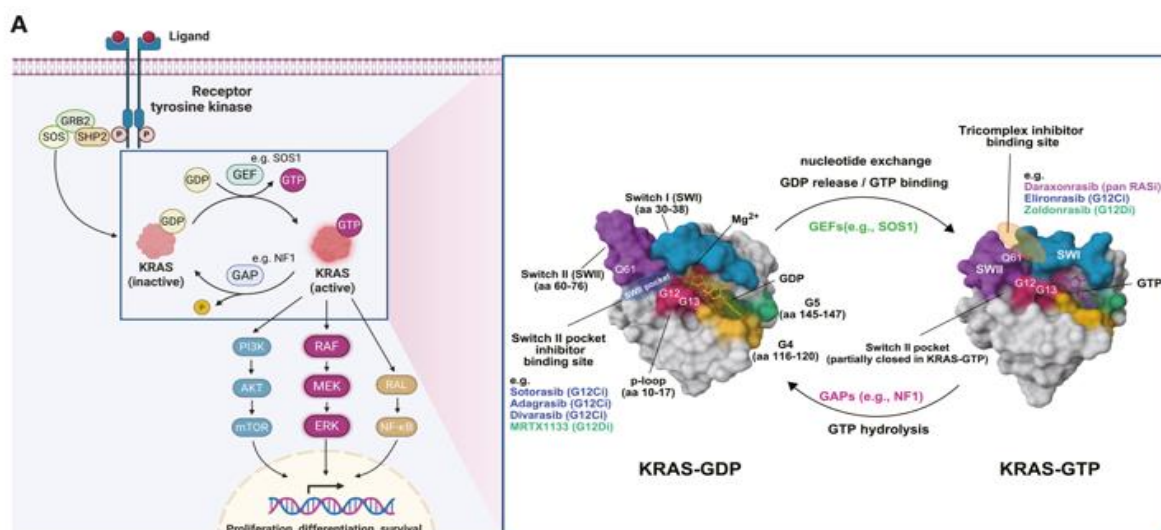
細胞内情報伝達系を担う代表

• RAS 細胞膜に存在

• RAS：GDP とGTP細胞内信号をつかさどる中核調整因子

• 正常では何らかの外的刺激=RASとGTPがくっつくと、細胞内信号
活性化情報がdown stream 的にDNAに伝わり細胞の成長、細胞分化、
細胞分裂(生存)

• RASとGDPがくっつくと 細胞内信号不活性化



RASON(GTP)になればdown stream
に情報が伝わり
DNAに到達：増殖 分化 生存

RASOFF(GDP)なればDNAへ
の情報伝達遅延

ON(GTPRAS)

細胞内伝達：ON
RAS-GTP経路

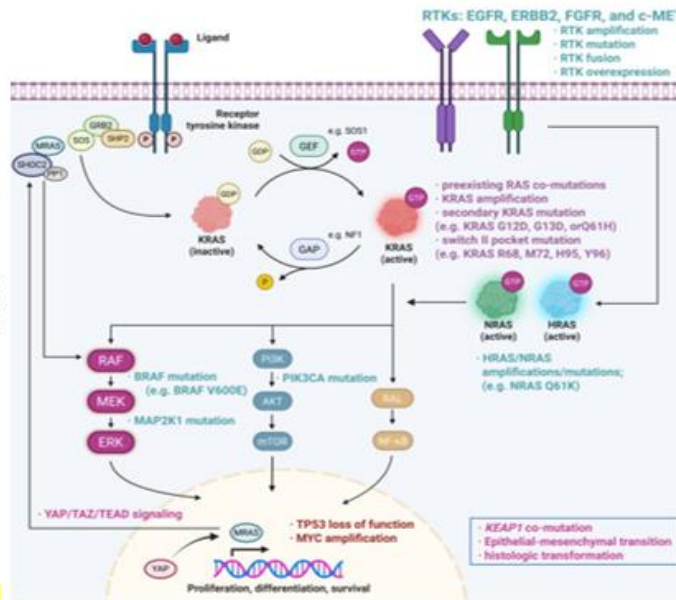
細胞内伝達：OFF
RAS-GDP経路

RAS-GTP ONの
状態になると
下部の経路が盛ん
となり

細胞の成長、増殖
分化、分裂、生存
につながる

RAS-ONとdown
stream effectors

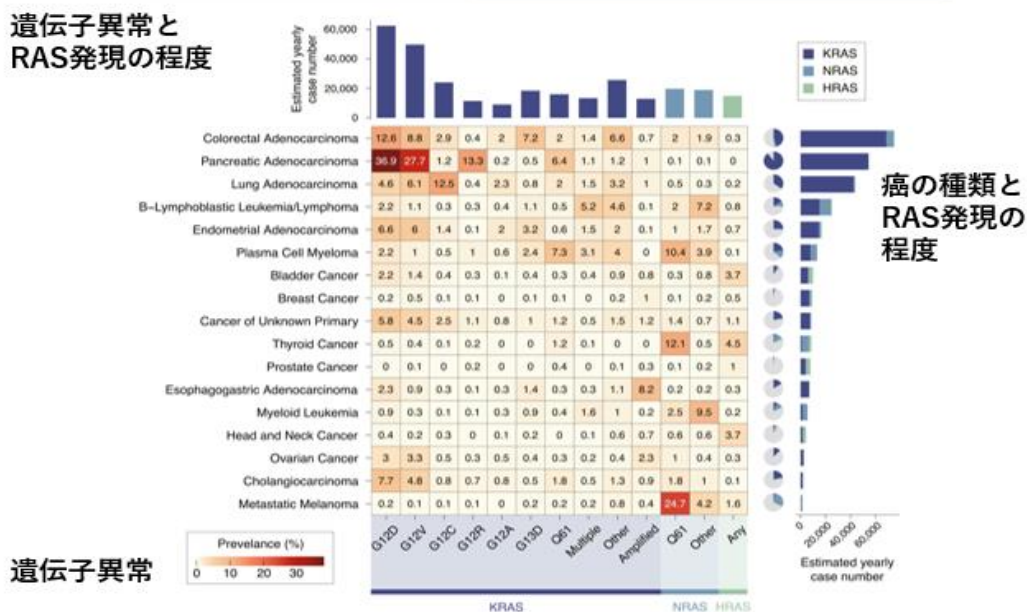
RAS(ON) multi-
selective inhibitor
: RASONとdown
stream effectorsを
阻害



RAS-ONには
KRAS,NRAS,HRAS

刺激を受ける
receptor
の違いによる

遺伝子異常と RAS発現の程度



発がん遺伝子：腓癌

- RAS mutations : G12X, G13X and Q61X 突然遺伝子異常
- RAS ON (RASにGTP結合) が外的刺激なしに常に継続 — 癌化
ON遺伝子の発現を抑制する種々RAS阻害剤 = Daraxonrasib
- RAS mutationsを有するガン：
腓癌、非小細胞性肺癌、結腸直腸癌

RAS阻害剤 = Daraxonrasib

- 遺伝子の発現抑制とは
- RAS mutationsの遺伝子から生じるONを引き起こす様々なタンパク合成を抑制
- 従来は個別のタンパク合成阻害薬が試作されてきたが今回はそれらを網羅するだけでなくdown streamの経路を抑制

Siegel RL, et al. CA Cancer J Clin. 2024;74:12-49.

² Lee JK, Sivakumar S, Schrock AB, et al. Comprehensive pan-cancer genomic landscape of KRAS altered cancers and real-world outcomes in solid tumors. NPJ Precis Oncol. 2022;6(1):91. Doi:10.1038/s41698-022-00334-z.

³ American Cancer Society. Survival Rates for Pancreatic Cancer. Available

Daraxonrasib : 膵癌への応用の根拠と成績

- 膵管ガン : Pancreatic ductal adenocarcinoma (PDAC) is highly RAS-dependent, with over 90% of patients harboring KRAS mutations, making RAS a critical therapeutic target
- MD Anderson Hospital : second-line chemotherapy
29% response rate
overall survival of 15.6 months (vs 5-7 months control)
- Randomized, open-label Phase 3 study
Median overall survival (OS): 13.2 months vs 6.7 months
- The most common side effects : rash, oral inflammation, nausea, diarrhea, and vomiting, which can often be controlled with supportive care

Daraxonrasib vs. Chemotherapy(肝転移膵癌)

- randomized on a 1:1 basis l daraxonrasib vs the investigator's choice of chemotherapy, gemcitabine, and nab-paclitaxel (GnP); FOLFOX (leucovorin, 5-fluorouracil [5-FU], and oxaliplatin); mFOLFIRINOX (modified 5-FU, irinotecan, leucovorin, and oxaliplatin); or nanoliposomal irinotecan plus 5-FU and leucovorin.
- OS among 228 patients with RAS G12 mutations who were assigned to daraxonrasib was 13.2 months vs 6.7 months in the chemotherapy group of for the 231 patients assigned to chemotherapy. (hazard ratio (HR) for death with daraxonrasib of 0.40 (95% CI, 0.30–0.54; $P<.001$).
- The median PFS by blinded independent central review (BICR) in the RAS G12 population was 7.3 months (95% CI, 6.3–8.1 months) in the daraxonrasib group and 3.5 months (95% CI, 2.9–3.8 months), in the chemotherapy group (HR, 0.45; 95% CI, 0.34–0.59; $P<.001$).

Phase 3 Study of Daraxonrasib (RMC-6236) in Patients With Previously Treated Metastatic Pancreatic Ductal Adenocarcinoma (PDAC) (RASolute 302)
ASCO: American Society of Clinical Oncology 2026.06

RAS(ON) multi-selective inhibitor Daraxonrasib : 肝転移のある膵癌

- ・ 従来の化学療法の対照群との比較
- ・ 全体の生存率 (OS : overall survival)
13.2 months vs 6.7 months
- ・ 腫瘍無再発期間 (PFS : progression free survival)
7.3 months vs 3.5 months

Phase 3 Study of Daraxonrasib (RMC-6236) in Patients With Previously Treated Metastatic Pancreatic Ductal Adenocarcinoma (PDAC) (RASolute 302) ASCO 2026. 06

RAS: renin angiotensin system

高血圧の生じる機序として以前から認知されていたが
発がん機序にも関与

RAS(ON) Multi-Selective Inhibitor Daraxonrasib

- ・ 2025年10月 FDA 認可
- ・ RAS-addicted cancers(RAS嗜好ガンに適応)
- ・ ほぼすべての膵癌 : RAS driver mutations
- ・ Phase 3 study 施行中 : 転移のある膵癌 second lineとして
- ・ Phase 3 予定 : 転移のある膵癌 first line
切除可能膵癌 adjuvant

2027年 日本でも治験予定

Daraxonrasib vs. Chemotherapy

Adults with metastatic PDAC who had received one prior fluoropyrimidine- or gemcitabine-based regimen for metastatic disease were enrolled. Patients were stratified by performance status (Eastern Cooperative Oncology Group score of 0 or 1), metastatic disease at diagnosis, liver metastases at baseline, and tumor mutational status. They were then randomized on a 1:1 basis to either oral daraxonrasib (300 mg daily) or the investigator's choice of chemotherapy, gemcitabine, and nab-paclitaxel (GnP); FOLFOX (leucovorin, 5-fluorouracil [5-FU], and oxaliplatin); mFOLFIRINOX (modified 5-FU, irinotecan, leucovorin, and oxaliplatin); or nanoliposomal irinotecan plus 5-FU and leucovorin.

After a median follow-up of 8.5 months, the median OS among 228 patients with RAS G12 mutations who were assigned to daraxonrasib was 13.2 months (95% confidence interval [CI], 10.0 months to not estimable [NE]) compared with 6.6 months (95% CI, 5.4–8.2 months) for the 231 patients assigned to chemotherapy. This translated into a hazard ratio (HR) for death with daraxonrasib of 0.40 (95% CI, 0.30–0.54; $P < .001$).

OS in the overall population, a key secondary endpoint, was nearly identical to that of the RAS G12 population. For those receiving daraxonrasib, it was 13.2 months (95% CI, 10.0 months to NE) compared with 6.7 months (95% CI, 5.8–8.0 months) in the chemotherapy group (HR, 0.40; 95% CI, 0.30–0.53; $P < .001$).

The median PFS by blinded independent central review (BICR) in the RAS G12 population was 7.3 months (95% CI, 6.3–8.1 months) in the daraxonrasib group and 3.5 months (95% CI, 2.9–3.8 months), in the chemotherapy group (HR, 0.45; 95% CI, 0.34–0.59; $P < .001$).

In the overall population, the median PFS was 7.2 months (95% CI, 5.7–7.5 months) with daraxonrasib compared with 3.6 months (95% CI, 2.9–4.2 months) with chemotherapy (HR, 0.49; 95% CI, 0.38–0.64; $P < .001$).

Confirmed objective response rates by BICR were also significantly higher with daraxonrasib: 33.2% (95% CI, 27.0%–39.9%) vs. 11.8% (95% CI, 7.8%–16.8%) in the RAS G12 group, and 31.6% (95% CI, 25.8%–38.0%) vs. 11.2% (95% CI, 7.5%–15.9%) in the overall population.

Good Tolerability Demonstrated

All patients who received daraxonrasib and 97.7% of those who received chemotherapy had at least one treatment-related adverse event (TRAE).

TRAEs leading to dose reduction occurred in 36.1% of patients in the daraxonrasib group and 57.5% of patients in the chemotherapy arm. Adverse events of grade 3 or higher were reported in 61.8% and 69.6%, respectively, and events leading to discontinuation occurred in 1.2% and 11.2% of patients, respectively.

As noted, the most common TRAEs leading to dose reduction in the daraxonrasib group were rash (17.4%) and stomatitis (6.6%). In the chemotherapy group, dose reductions were required due to neutropenia in 16.8% of patients, thrombocytopenia in 13.6%, fatigue in 12.6%, diarrhea in 10.3%, and peripheral neuropathy in 7.9%.

An analysis of patient-reported outcomes showed that daraxonrasib was significantly better at delaying time to deterioration in symptoms of pain and global health status/quality-of-life scores compared with chemotherapy.

“We Have a New Standard of Care”

“To me, this study is proof of principle that targeting the RAS-signaling pathway is critical in the treatment of pancreatic cancer, and as [Dr. Wolpin] mentioned, it checks all the boxes when they think about the relevant, important, and clinically meaningful outcomes,” said Dr. Shroff.

“My key takeaway point is that we have a new standard of care in the second-line setting with daraxonrasib” Dr. Knox said in her discussion.

“My other point,” she stressed, “is that RAS-targeted therapy should dominate trials across the full spectrum of pancreatic cancer clinical presentations, either as a monotherapy or in rational combinations to benefit more patients, impacting survival and quality of life.”

The RASolute 302 study was funded by Revolution Medicines.

Dr. Wolpin reported various financial relationships.

Dr. Knox reported honoraria and a consulting or advisory role from Astellas, AstraZeneca, Incyte, and Ipsen; an advisory role for MedImmune; research funding from AstraZeneca, Ipsen, and Merck; and expert testimony for AstraZeneca and Incyte.