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THE HEART OF MEDICAL EDUCATION

PRECISION ONCOLOGY CONNECT

RECENT ADVANCES IN PRECISION ONCOLOGY AND FUTURE IMPLICATIONS

Prof. David Hong, MD

MD Anderson Cancer Center, Houston, United States

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EDUCATIONAL OBJECTIVES

1. Drive a deeper awareness and understanding of current and future developments in precision oncology and the future clinical implications
2. Enhance knowledge of precision oncology and biomarker testing across patient, caregiver and HCP communities

HCP, healthcare professionals

CLINICAL TAKEAWAYS

- Ongoing research is uncovering new, precise, and reliable tumour biomarkers. This has improved advanced precision medicine, promising better outcomes for people with cancer
- Inhibitors for *KRAS* mutations (e.g. sotorasib/adagrasib) have provided new treatment options for cancer in certain subpopulations (i.e. $KRAS^{G12C}$ mutated); other agents targeting specific patient subsets (e.g. those with MTAP loss) may expand targeted therapy options
- Evolving targets like *NTRK* and *HER2* are benefiting multiple cancer types
- The expansion of new biomarkers and targeted therapies highlights the importance of molecular profiling using NGS and knowing which treatment option is best suited to individual patients

HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma virus; MTAP, methylthioadenosine phosphorylase; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase

INTRODUCTION

- As research continues to evolve, identifying key molecular targets plays a critical role in the development of effective therapies for cancer.[1] New precision targets and therapies continue to emerge,[2] and more established targets are expanding their indications[2]
- **New and emerging targets:**
  - ***RAS* (*KRAS*, *NRAS* and *HRAS*)** is the most frequently mutated gene family in cancers, and researchers have sought an effective RAS inhibitor for more than 30 years.[3] Two $KRAS^{G12C}$ inhibitors, sotorasib[4] and adagrasib,[5] are now FDA approved for NSCLC and a number of RAS(ON) inhibitors are in development targeting variants of RAS proteins including $KRAS^{G12D}$[6,7,8]
  - **Protein arginine methyltransferase 5 (PRMT5)** inhibitors have emerged as a promising treatment for solid tumours with methylthioadenosine phosphorylase (MTAP) deficiency[9]
- **Older, established targets:**
  - **HER2*:*** long-established as a key target in breast cancer[10] and recently gained a histology-agnostic approval of the anti-HER2 antibody–drug conjugate trastuzumab deruxtecan for patients with HER2-overexpressing solid tumours[11]
  - ***NTRK:*** targeting *NTRK* gene fusions with tyrosine kinase inhibitors has provided significant benefits in precision oncology.[12] New data continues to emerge for the first generation TRK inhibitors[12] and novel second-generation *TRK* inhibitors are in development[13]

FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HRAS, Harvey RAS; KRAS, Kirsten RAS; NRAS, Neuroblastoma RAS; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; RAS, rat sarcoma virus; TRK, tropomyosin receptor kinase

1. Min HY and Lee HY. Exp Mol Med. 2022;54:1670-1694; 2. Malone ER, et al. Genome Med. 2020;12:8; 3. CAS. Emerging trends in targeting “undruggable” RAS protein for cancer treatment. Available here (accessed December 2024); 4. FDA grants accelerated approval to sotorasib for KRAS G12C mutated NSCLC. Available here (accessed December 2024); 5. FDA grants accelerated approval to adagrasib for KRAS G12C-mutated NSCLC. Available here (accessed December 2024); 6. Nokin M-J, et al. Nat Commun. 2024; 15: 7554; 7. Akhave NS, et al. Mol Cancer Ther. 2022;21:1645-1651; 8. Arbour KC, et al. Ann Oncol. 2023;34(Supplement 2):S458-S497. Presented at ESMO 2023. Abstr 6520, oral presentation; 9. Rodon J, et al. Eur J Cancer. 2024;211 (suppl 1):114981. Presented at ENA 2024 (EORTC NCI AACR 36th Symposium). 503LBA (oral presentation); 10. Meric-Bernstam F, et al. J Clin Oncol. 2023;42:47-58; 11. Yoon J, et al. Nat Rev Clin Oncol. 2024; 21:675-700; 12. Hong DS, et al. Ann Oncol. 34 (supplement 2):S469. Presented at ESMO 2023 (Poster 667P); 13. Sheng J, et al. NPJ Precis Oncol. 2024;8:198

NEW TARGETS: *KRAS*

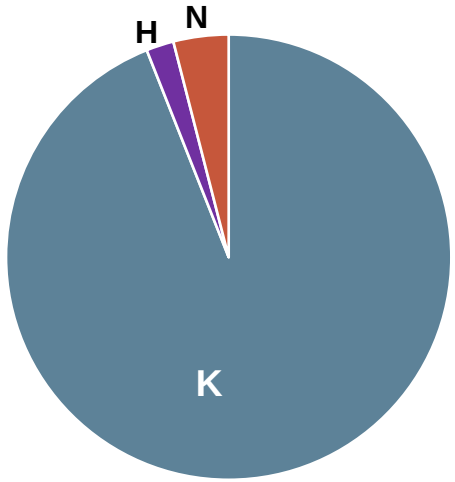
KRAS, Kirsten rat sarcoma virus

RAS MUTANT CANCERS: TARGETS FOR PRECISION ONCOLOGY?

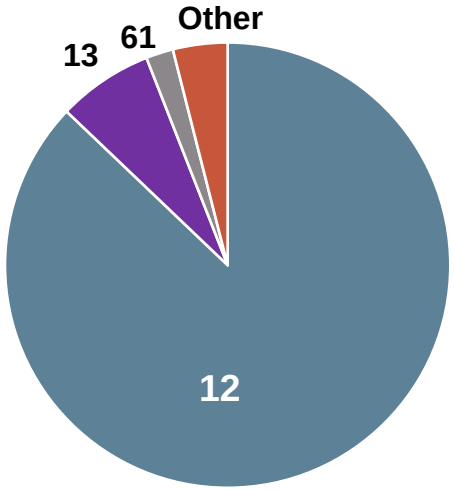
Different mutant alleles are found in different cancer types. Pancreatic cancer has the most *KRAS* mutations

PAN-TUMOUR

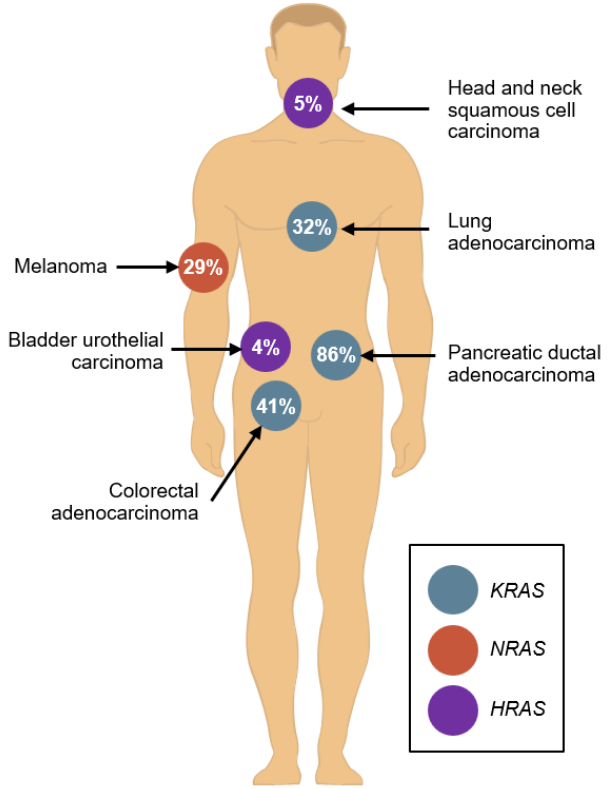
RAS mutation isoforms



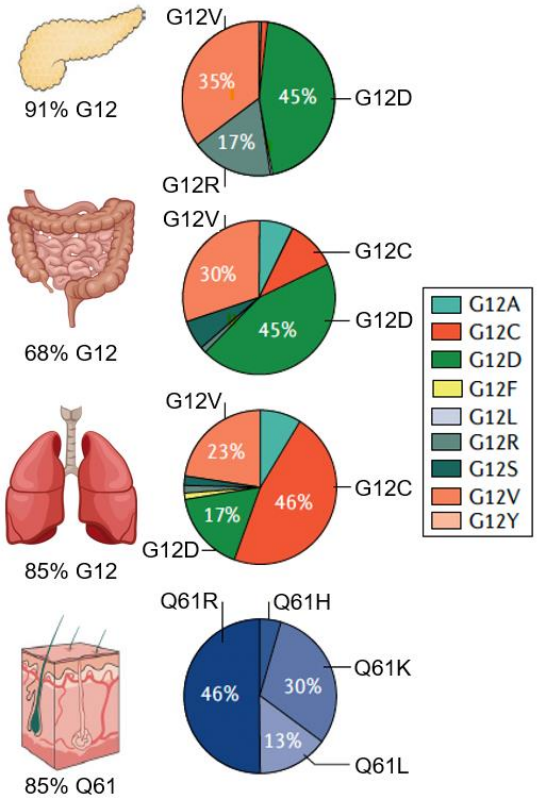
KRAS mutation codons



Distribution and frequency of *RAS* isoform across tumour



Percentages of *KRAS* mutations in codon 12 by tissue and tumour type



HRAS, Harvey RAS; KRAS, Kirsten RAS; NRAS, Neuroblastoma RAS; RAS, rat sarcoma virus

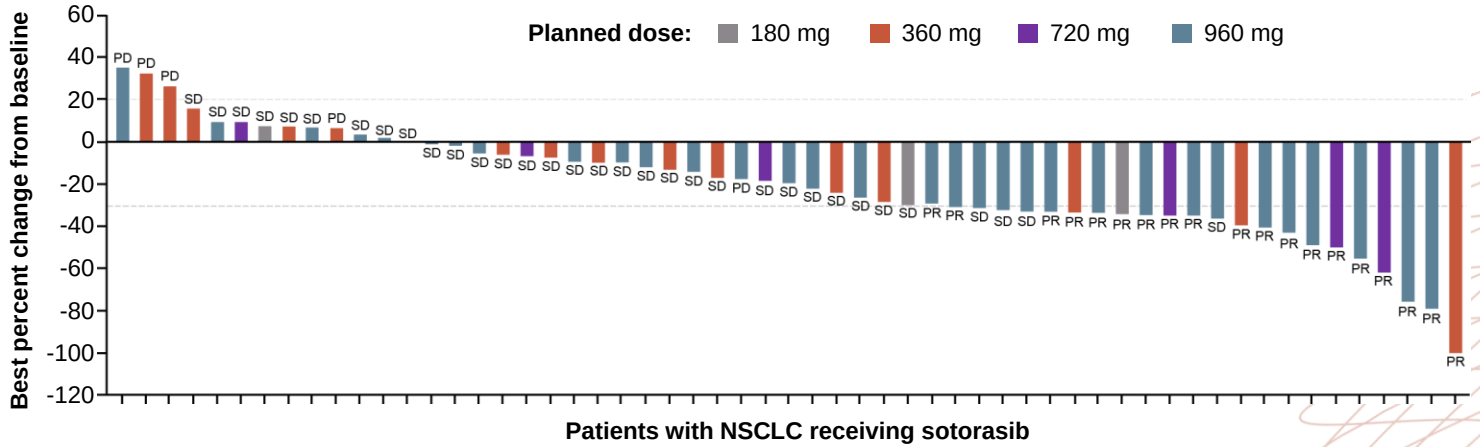
Moore A, et al. Nat Rev Drug Discovery. 2020;19:553-552

KRAS^{G12C} INHIBITION WITH SOTORASIB IN ADVANCED SOLID TUMOURS (EFFICACY)

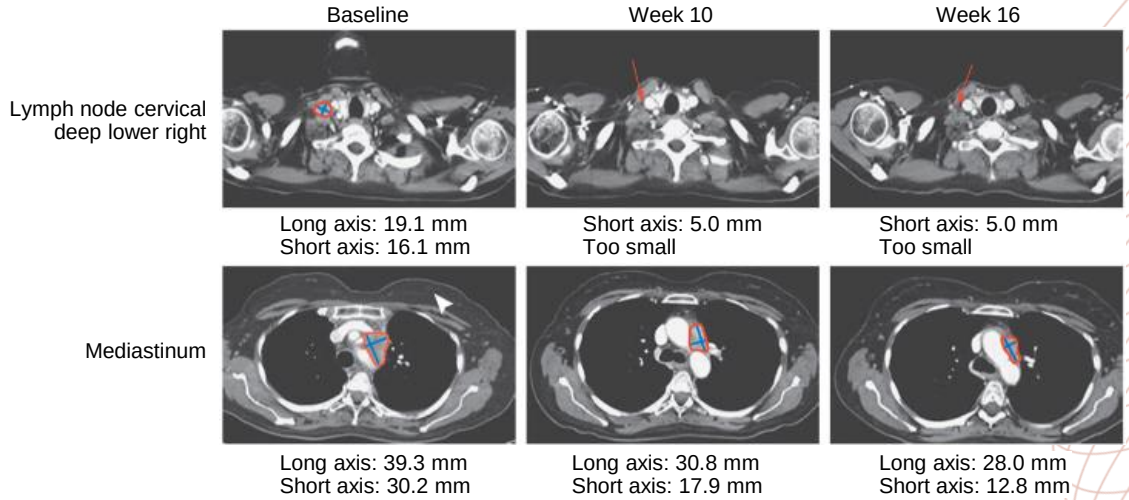
EFFICACY OF SOTORASIB IN ALL TUMOUR TYPES

	NSCLC (N=59)	Colorectal cancer (N=42)	Other (N=28)
Best overall response, n (%)			
Confirmed CR	0	0	0
Confirmed PR	19 (32.2)	3 (7.1)	4 (14.3)
SD	33 (55.9)	28 (66.7)	17 (60.7)
PD	5 (8.5)	10 (23.8)	4 (14.3)
Could not be evaluated	1 (1.7)	0	1 (3.6)
No assessment[a]	1 (1.7)	1 (2.4)	2 (7.1)
Objective response, %[b] (95% CI)	32.2 (20.62-45.64)	7.1 (1.50-19.48)	14.3 (4.03-32.67)
Disease control, %[c] (95% CI)	88.1 (77.07-95.09)	73.8 (57.96-86.14)	75.0 (55.13-89.31)

CHANGE FROM BASELINE IN TUMOUR BURDEN



EFFECT OF SOTORASIB IN A PATIENT WITH NSCLC



[a] One patient with NSCLC withdrew consent before tumour assessment. One patient with colorectal cancer and two patients with other tumour types had clinical progression
[b] Objective response was defined as a complete or partial response
[c] Disease control was defined as a complete response, a partial response, or stable disease

CI, confidence interval; CR, complete response; KRAS, Kirsten rat sarcoma virus; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease

Hong DS, et al. N Engl J Med. 2020;383:1207-1217

$KRAS^{G12C}$ INHIBITION WITH SOTORASIB IN ADVANCED SOLID TUMOURS (SAFETY)

Events	Any Grade	Grade ≥3	Grade ≥4	Grade 5: Fatal
Adverse events of any cause that occurred during treatment, n (%)				
Any	125 (96.9)	68 (52.7)	26 (20.2)	22 (17.1)
Serious	58 (45.0)	51 (39.5)	25 (19.4)	22 (17.1)
Resulting in discontinuation of treatment[a]	9 (7.0)	9 (7.0)	4 (3.1)	4 (3.1)
Adverse events of any cause that occurred during treatment ≥10% of patients, n (%)				
Diarrhoea	38 (29.5)	5 (3.9)	0	0
Fatigue	30 (23.3)	3 (2.3)	0	0
Nausea	27 (20.9)	2 (1.6)	0	0
Vomiting	23 (17.8)	5 (3.9)	0	0
Abdominal pain	23 (17.8)	4 (3.1)	0	0
Dyspnoea	21 (16.3)	3 (2.3)	1 (0.8)	1 (0.8)
Cough	20 (15.5)	0	0	0
Back pain	19 (14.7)	2 (1.6)	0	0
Decreased appetite	19 (14.7)	1 (0.8)	0	0
Headache	18 (14.0)	0	0	0
Aspartate aminotransferase increase	17 (13.2)	3 (2.3)	0	0
Anaemia	17 (13.2)	6 (4.7)	0	0
Dizziness	17 (13.2)	0	0	0
Alanine aminotransferase increase	15 (11.6)	6 (4.7)	1 (0.8)	0
Constipation	15 (11.6)	0	0	0
Pyrexia	14 (10.9)	0	0	0
Insomnia	14 (10.9)	0	0	0
Myalgia	13 (10.1)	0	0	0
Peripheral oedema	13 (10.1)	0	0	0
Arthralgia	13 (10.1)	2 (1.6)	0	0

[a] Among the 22 patients who had fatal adverse events of any cause during treatment, four patients discontinued treatment directly because of those adverse events. The remaining patients discontinued treatment before the fatal adverse event occurred, and therefore the fatal adverse event was not recorded as the reason for treatment discontinuation for those patients.

CI, confidence interval; KRAS, Kirsten rat sarcoma virus; NSCLC, non-small cell lung cancer

Hong DS, et al. N Engl J Med. 2020;383:1207-1217

KRAS^{G12C} ALLELE SPECIFIC INHIBITORS – SINGLE ARM STUDIES

Agent	Sotorasib[1] 960 mg daily	Adagrasib[2] 600 mg BID	Fulzerasib[3] (IBI351) 600 mg BID	Divarasib[4] (GDC-6036) 50-400 mg QD	Garsorasib[5] (D-1553) 600 mg BID	Opnurasib[6] (JDQ443) 200 mg BID	Glecirasib[7] (JAB-81822) 800 mg QD	Olomorasib[8] (LY3537982) 50-200 mg BID
N	124	112	116	60[a]	123	14[a]	119	39[a]
Confirmed ORR, %	37.1	43	49.1	53.4	52.0	57.1	47.9	41
Median DoR, months	11.1	8.5	NR	14.0	12.5	–	–	–
Median PFS, months	6.8	6.5	9.7	13.1	9.1	–	8.2	8.1
Grade 3-4 TRAE, %	20.6	43	33.6	18	51.2	5.9	38.7	7
Dose reduction for TRAE, %	–	52	6.9	14	30.1	2.9	–	5
Dose modification/ Interruption, %	22.2	61	33.6	50	41.5	–	–	13
Discontinued for TRAE, %	7.1	7	6.0	3	0	–	5.0	1

[a]NSCLC cohort for efficacy and full dataset for safety

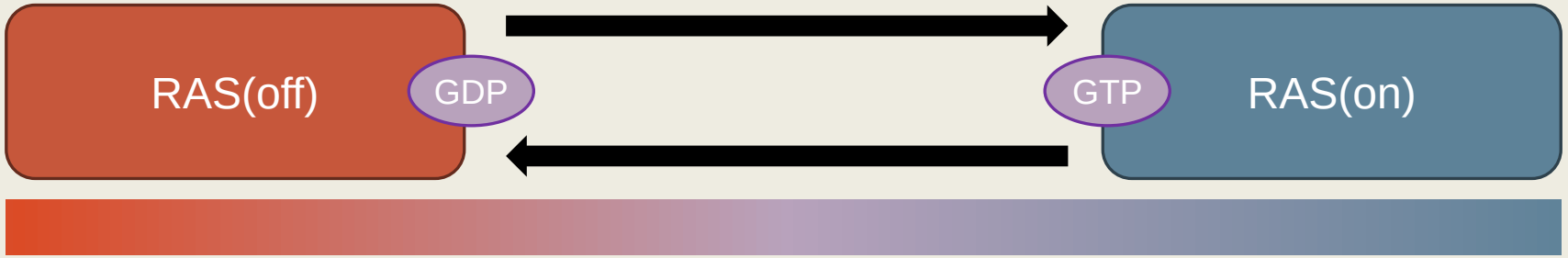
BID, twice a day; DoR, duration of response; KRAS, Kirsten rat sarcoma virus; ORR, objective response rate; PFS, progression-free survival; QD, once daily; RP2D, recommended phase 2 dose; TRAE, treatment-related adverse event

1. Skoulidis F, et al. N Engl J Med 2021; 384: 2371-81; 2. Spira AI, et al. J Clin Oncol. 2022;40 (16 suppl):9002. (ASCO 2022 oral presentation); 3. Zhou Q, et al. Journal of Thoracic Oncology 2024; 19: 1630-1639; 4. Sacher A, et al N Engl J Med. 2023;389:710-721; 5. Li Z, et al. J Thorac Oncol. 2024;19(10 Suppl):S40-S41 (WCLC 2024 oral presentation); 6. Cassier P, et al. J. Clin Oncol 2023; 41 (16_suppl): 9007 (Miguel M, ASCO 2023 oral presentation); 7. Shi Y, et al. J Clin Oncol. 2024;42(36 Suppl):468214 (ASCO 2024 oral presentation); 8. Heist RS, et al. J Clin Oncol 2024;42 (16_suppl):3007 (ASCO 2024 oral presentation)

Modified from Leighl NB, 2024. Slides presented at ESMO 2024

DO THE LESSONS FROM KRAS^{G12C} APPLY TO THE NEXT GENERATION OF INHIBITORS?

SPECTRUM OF THERAPEUTIC APPROACHES TO TARGET KRAS



Mutation-specific direct KRAS therapies

Advantages:

- Wide therapeutic index supporting combination trials

Disadvantages:

- Narrow target population for each agent
- Unclear efficacy/safety of non-covalent inhibitors
- Beyond KRAS^{G12C} inhibitors, all other inhibitors remain in pre-clinical testing

Indirect Pan-RAS therapies

Advantages:

- Large patient population, including ability to target other RAS proteins (e.g. HRAS, NRAS) or non-mutated oncogenic alterations (e.g. *KRAS* amplification)
- Bypass acquired resistance mechanisms to KRAS^{G12C} inhibitors

Disadvantages:

- Possibility for unanticipated off-target or on-target effects that could narrow therapeutic index

Mutation-independent direct KRAS therapies

GDP, guanosine diphosphate; GTP, guanosine triphosphate; HRAS, Harvey RAS; KRAS, Kirsten RAS; NRAS, Neuroblastoma RAS; RAS, rat sarcoma virus

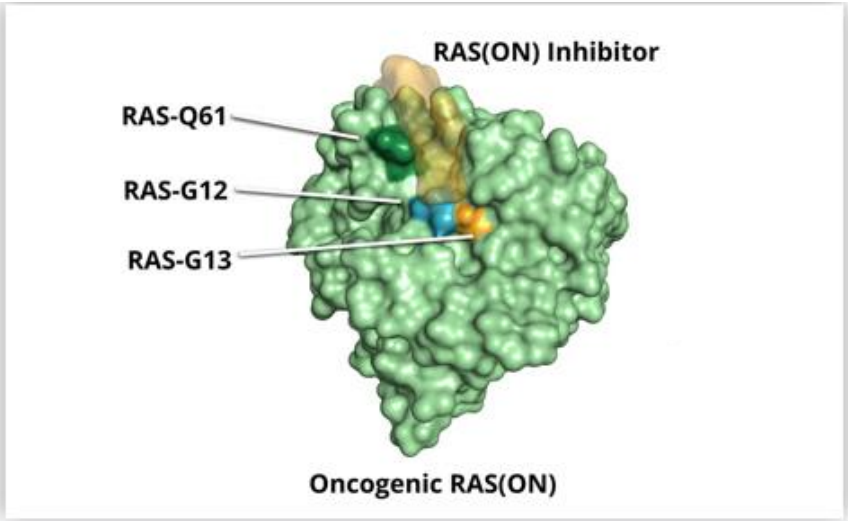
Akhave NS, et al. Mol Cancer Ther. 2022;21:1645-1651

DO THE LESSONS FROM KRAS^{G12C} APPLY TO THE NEXT GENERATION OF INHIBITORS?

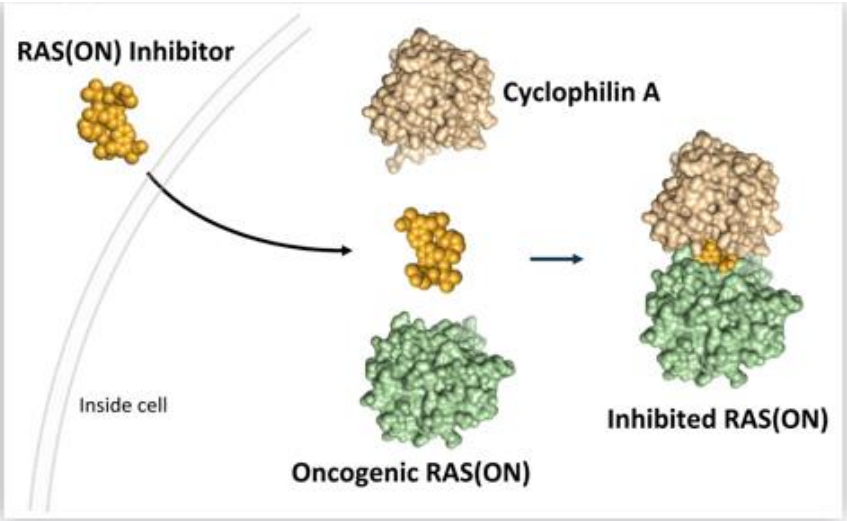
FIRST-IN-CLASS RAS(ON) INHIBITORS, INCLUDING RAS(ON) G12D-SELECTIVE AND RAS(ON) MULTI-SELECTIVE INHIBITORS[1,2]

Amino acid positions that, according to mutation, determine potential for inhibitor interaction

Bind[2]



Suppress[1,3]

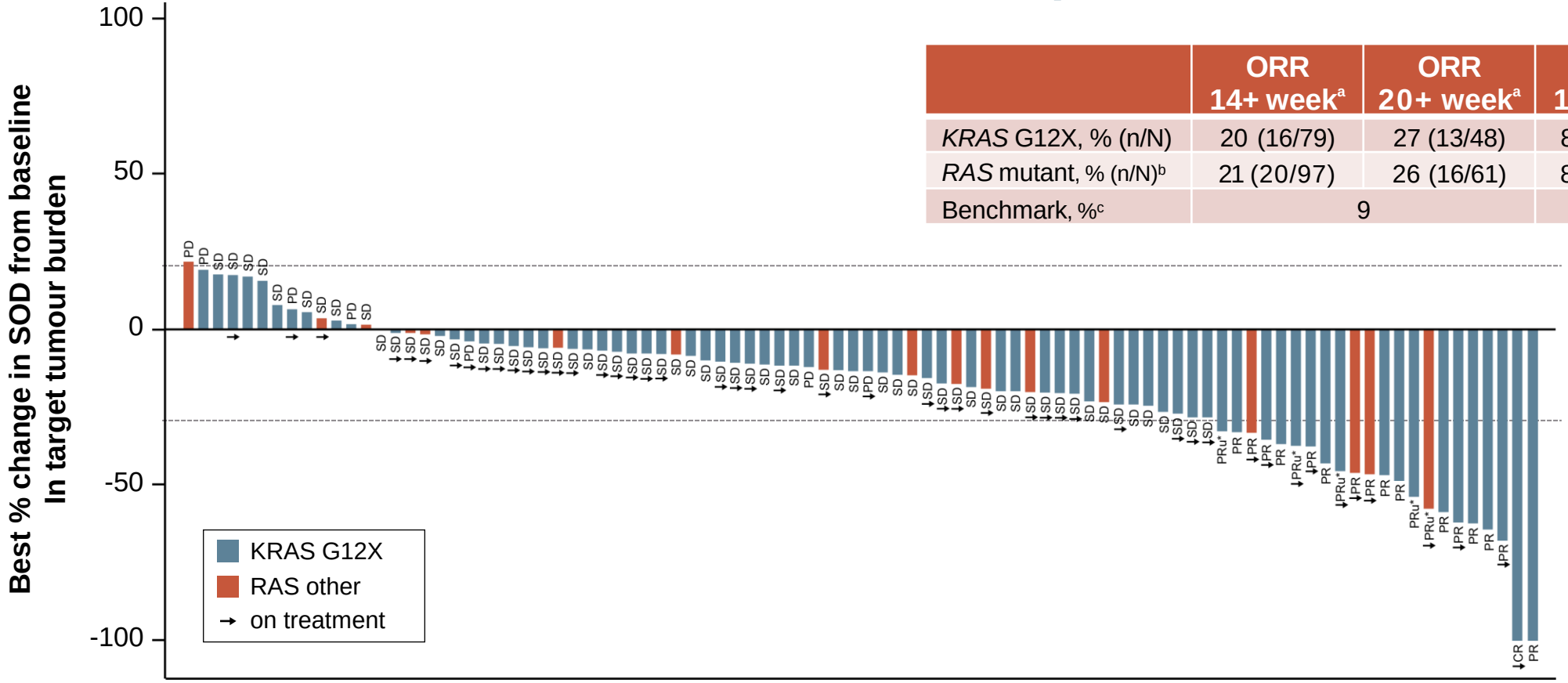


Preclinical studies have demonstrated deep and sustained regressions across multiple *RAS*^{MUT} tumour types, particularly PDAC and NSCLC harbouring *KRAS* G12X mutations[2]

KRAS, Kirsten RAS; MUT, mutated; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; RAS, rat sarcoma virus

1. On Target to Outsmart Cancer. Revolution Medicines. Available at: https://ir.revmed.com/static-files/1980f6ca-cb1d-4568-94a7-623ccc8c0cf2 (accessed December 2024); 2. Arbour KC, et al. Ann Oncol. 2023;34(Supplement 2):S458-S497. Presented at ESMO 2023 (oral presentation) 3. Koltun E, et al. Presented at AACR 2022. Available at: https://www.revmed.com/wp-content/uploads/2023/09/AACR_2022_Koltun.pdf (accessed December 2024);

BEST PERCENTAGE CHANGE IN TUMOUR SIZE FROM BASELINE AND OBJECTIVE RESPONSE RATE IN 2L+ PDAC (RMC-6236 160-300 mg)



	ORR 14+ week[a]	ORR 20+ week[a]	DCR 14+ week[a]
KRAS G12X, % (n/N)	20 (16/79)	27 (13/48)	87 (69/79)
RAS mutant, % (n/N)[b]	21 (20/97)	26 (16/61)	88 (85/97)
Benchmark, %[c]	9		NA

Unconfirmed PRs (PRu) with treatment discontinued (will never confirm) are not considered responders but remain in the denominator (n=5)

[a] "ORR 14+ week" and "DCR 14+ week" analyses include all patients who received first dose of RMC-6236 at least 14 weeks prior to data cutoff date (to allow two potential scans). "ORR 20+ week" analysis is similarly defined to allow three potential scans. Five patients included in the denominator of the '14+ week' analyses are not displayed on waterfall due to lack of post-baseline target lesion assessment (four patients discontinued treatment without post-baseline scans: three due to death, one due to subject request to withdraw from treatment, and one patient had documented PD due to new lesion without target lesion assessment); ORR (by RECISTv1.1) includes confirmed CRs/PRs and unconfirmed CRs/PRs who are still on treatment and may yet confirm; 2L in the metastatic setting includes patients who progressed on prior therapy in an earlier setting within 6 months of last dose

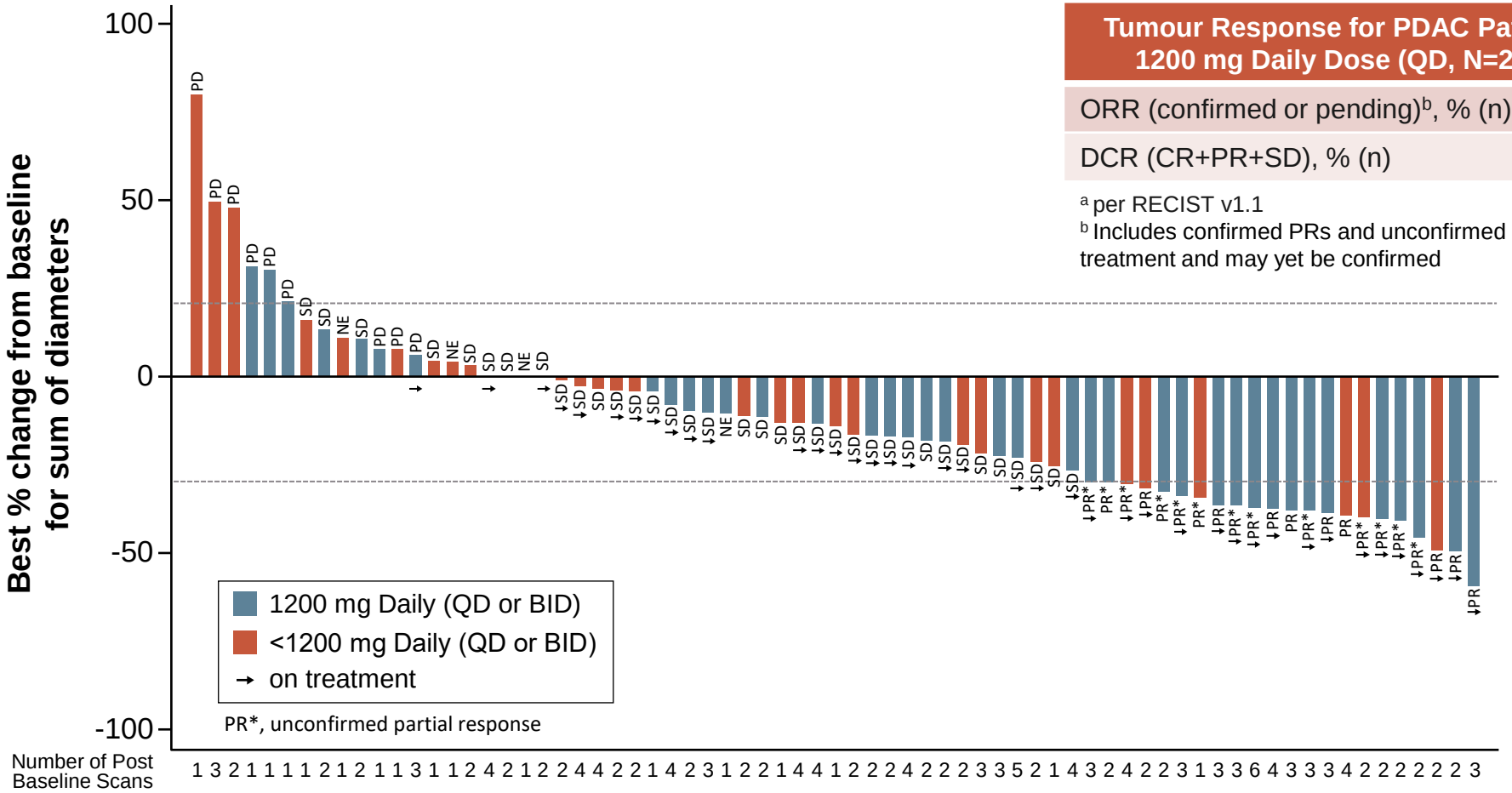
[b] *RAS* mutant defined as patients with G12X, G13X or Q61X PDAC

[c] Benchmark mean ORR derived from published reports

2L, second line; CR, complete response; DCR, disease control rate; KRAS, Kirsten rat sarcoma virus; NA, not available; ORR, objective response rate; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PR(u), (unconfirmed) partial response; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; SOD, sum of diameters

RMC-6236: Pancreatic Cancer Update to Support Pivotal Phase 3 Trial. Revolution Medicines. Available at: https://ir.revmed.com/static-files/eeeb0690-0ef4-44b8-b5fe-8d11d8df3c9a (accessed December 2024)

ORR AND DCR IN PATIENTS WITH KRAS G12D PDAC TREATED WITH RMC-9805



Tumour Response for PDAC Patients Treated with 1200 mg Daily Dose (QD, N=20 or BID, N=20)[a]	
ORR (confirmed or pending)[b], % (n)	30 (12)
DCR (CR+PR+SD), % (n)	80 (32)

[a] per RECIST v1.1
[b] Includes confirmed PRs and unconfirmed PRs who were still on treatment and may yet be confirmed

Data cutoff: 02 Sep 2024; All treated patients with PDAC who received a first daily dose at least 14 weeks prior to data cutoff date (applies to Waterfall plot and ORR table); three additional patients (N=2 at 1200 mg daily; N=1 at <1200 mg daily) are not displayed on the Waterfall plot due to withdrawal of consent or clinical progression. Among patients with a response (confirmed or unconfirmed), 55% of first response occurred after 2 months of RMC-9805 treatment (all dose levels)

BID, twice a day; CR, complete response; DCR, disease control rate; KRAS, Kirsten rat sarcoma virus; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease

Hong DS, et al. Presented at ENA 2024 (EORTC NCI AACR 36th Symposium): Available at: https://www.revmed.com/wp-content/uploads/2024/10/ENA-LBA514-Hong-etal-FINAL-2024_1018.pdf (accessed December 2024)

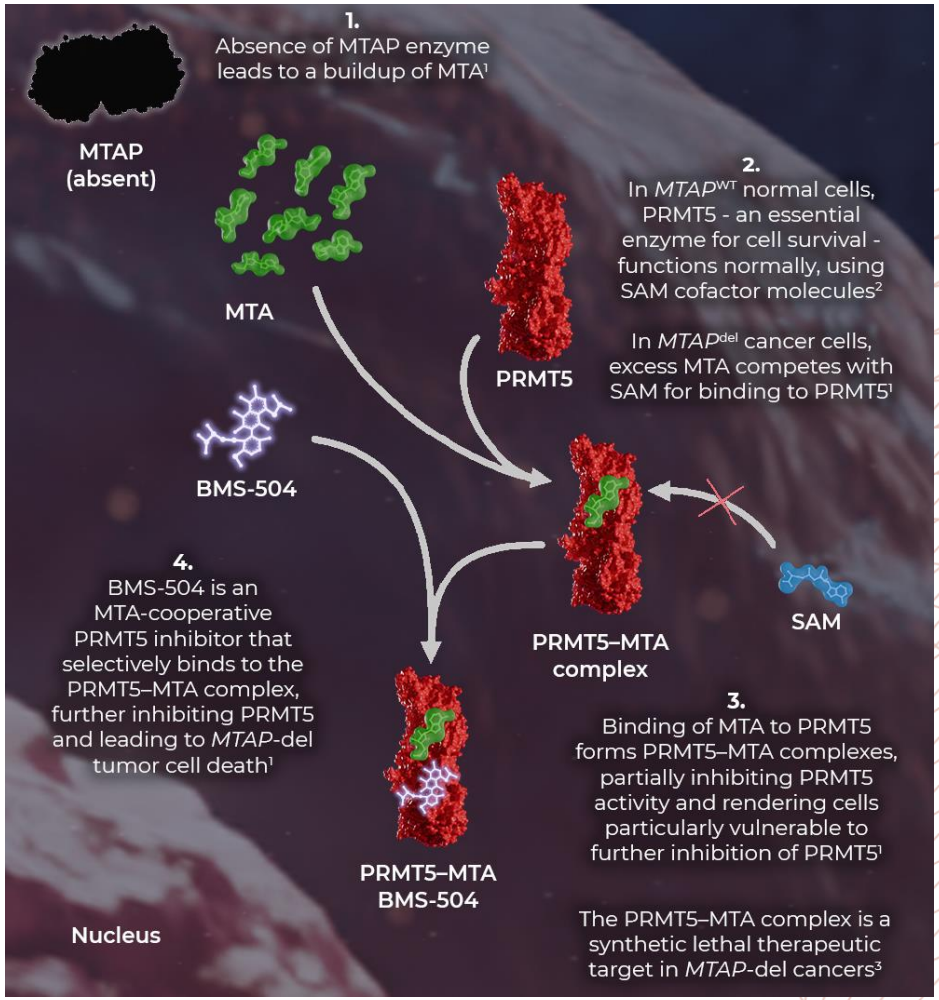
NEW TARGETS:
MTAP

MTAP, methylthioadenosine phosphorylase

BACKGROUND

- Homozygous *MTAP*-del occurs in 10–15% of all cancers,[1] and in up to 50% of tumours such as GBM[2] and mesothelioma[3]
- Patients with homozygous *MTAP*-del have a poorer prognosis[4]
- BMS-986504 (MRTX1719) is a first-in-class MTA-cooperative PRMT5 inhibitor[5,6] that selectively binds to the PRMT5-MTA complex[6]
- The PRMT5-MTA complex is a synthetic lethal target in *MTAP*-del cancer cells, but not in *MTAP*–wild-type cells[7]
- CA240-0007 is a phase 1/2 study of BMS-986504 in patients with advanced solid tumours with homozygous *MTAP*-del[5,8]
  - Early clinical activity has been reported across a range of doses and tumour types[5]

MTAP-del CANCER CELL



del, deleted; GBM, glioblastoma multiforme; (MTA)P, (methylthioadenosine) phosphorylase; PRMT5, protein arginine methyltransferase 5; SAM, S-adenosylmethionine

1. Rodon J, et al. Ann Oncol. 2024;35:1138-1147; 2. Barekatain Y, et al. Nature Commun. 2021;12:4228; 3. Sharkey A, et al. J Thorac Oncol. 2017;12(no. 15):P3.03-005; 4. Han G, et al. Nat Commun 2021;12:5606; 5. Engstrom LD, et al. Cancer Discov. 2023;13:2412-2431; 6. Smith CR, et al. Mol Cancer Ther. 2021;20 (12_Supplement): P165; 7. Smith CR, et al. J Med Chem. 2022;65:1749-1766; 8. ClinicalTrials.gov identifier: NCT05245500. Available at: https://clinicaltrials.gov/study/NCT05245500 (accessed December 2024)

Rodon J, et al. Eur J Cancer. 2024; 211 (suppl 1):114981. Presented at ENA 2024 (EORTC NCI AACR 36th Symposium). 503LBA (oral presentation)

CA240-0007[a] PHASE 1 FIRST-IN-HUMAN STUDY OF BMS-986504 (PRMT5 INHIBITOR)

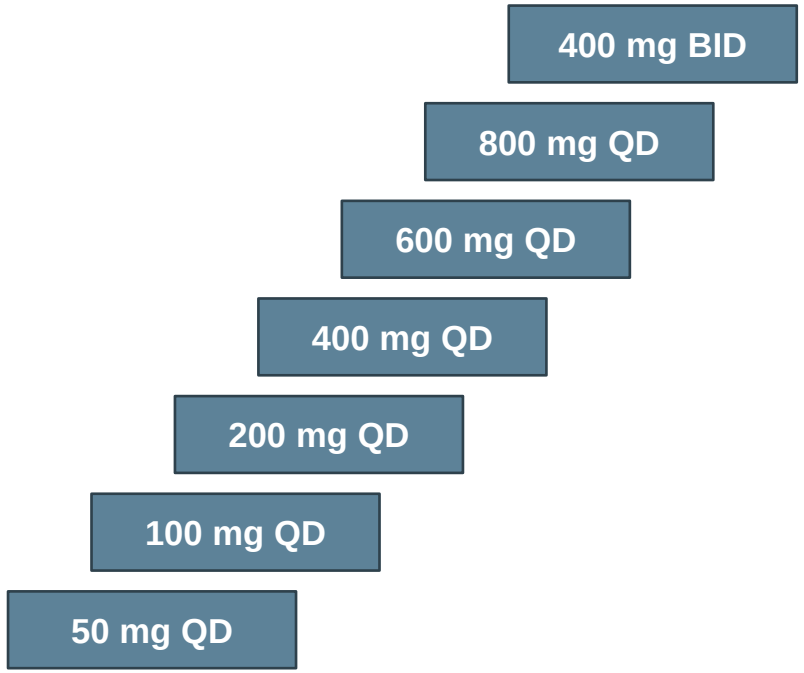
Key eligibility criteria

- Advanced, unresectable, or metastatic solid tumours with homozygous *MTAP*-del[b]
- Measurable or evaluable disease[c]
- Disease progression on or after the most recent treatment
- No available treatment with curative intent

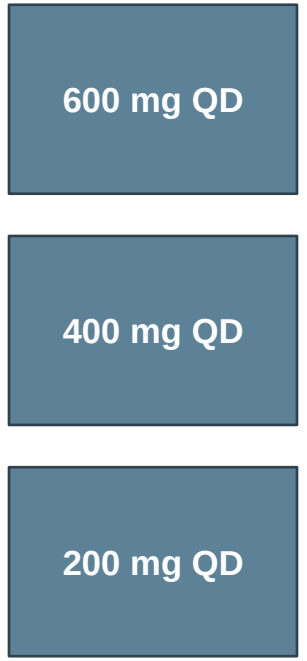
Tumour types assessed

- NSCLC
- PDAC
- CCA
- Meso
- MPNST
- HNSCC
- BC
- MEL
- Other[d]

Phase 1 dose escalation[e]



Phase 1b dose expansion[f]



Endpoints: safety, pharmacokinetics, and clinical activity/efficacy

Data cutoff date: September 19, 2024; median follow-up (95% CI): 7.6 (6.8–8.3) months.

[a] NCT05245500. [b] Dose escalation only: patients with tumours with homozygous *CDKN2A*-del per a sponsor-approved test were eligible if *MTAP*-del was unknown or present but assessed using a test not approved by the sponsor and *MTAP*-wild type was not present on the test establishing *CDKN2A*-del. [c] Patients with evaluable disease were eligible only in dose escalation. [d] Included acinic cell carcinoma, acinic cell carcinoma of the parotid gland, ampulla of the vater cancer, apocrine carcinoma, chondrosarcoma, esophageal adenocarcinoma, gallbladder cancer, GIST, GBM, large cell neuroendocrine tumour, malignant TGCT, metastatic ampullary adenocarcinoma, neuroendocrine cancer, osteosarcoma, pancreatic cancer (invasive carcinoma with adenosquamous features and neuroendocrine), pleomorphic adenoma of parotid gland, RCC, rectal cancer, spindle cell sarcoma, undifferentiated pleomorphic sarcoma, and UC. [e] Doses increased by 100% increments until ≥1 DLTs occurred and then in increments of 40–50% afterwards. Depending on safety observations, smaller dose increments were used. In the event the MTD was exceeded, dose levels below the MTD but above the previous dose level would be evaluated using smaller dose increments. n ≥ 3 per cohort. [f] Enrolment to dose expansion cohorts is ongoing.

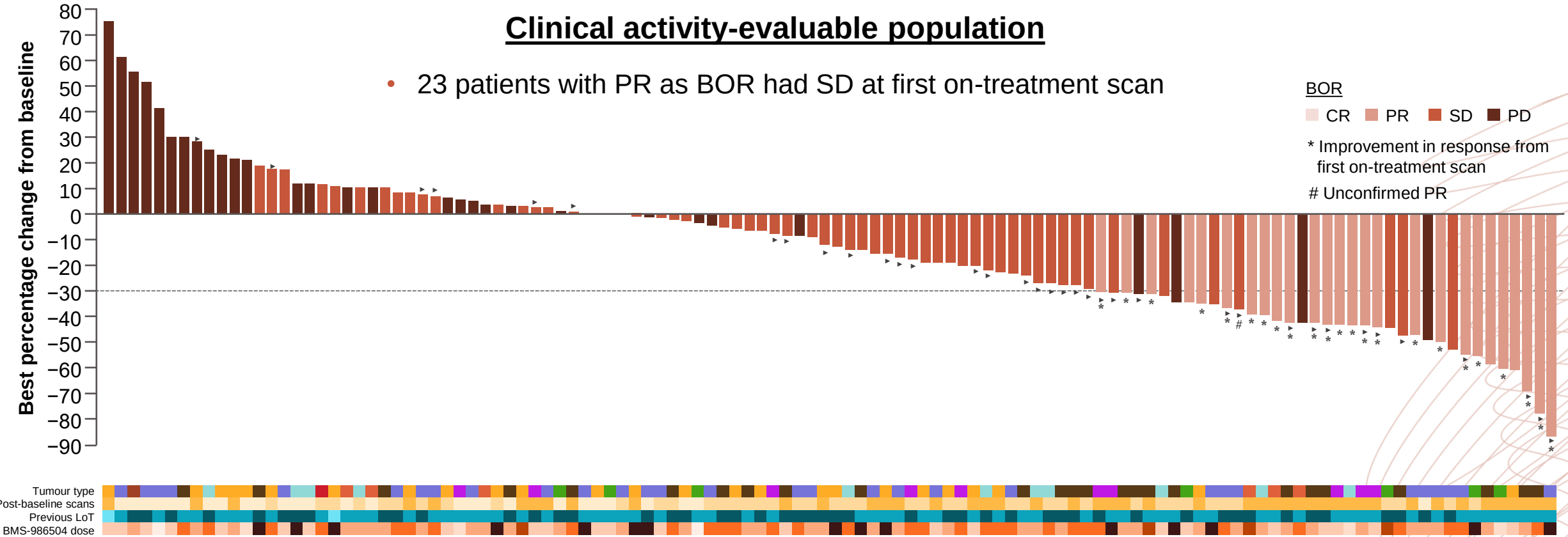
BC, breast cancer; BID, twice daily; CCA, cholangiocarcinoma; CDKN2A, cyclin-dependent kinase inhibitor 2A; CI, confidence interval; del, deleted; DLT, dose-limiting toxicity; GBM, glioblastoma multiforme; GIST, gastrointestinal stromal tumour; HNSCC, head and neck squamous cell carcinoma; MEL, melanoma; meso, mesothelioma; MPNST, malignant peripheral nerve sheath tumour; MTAP, methylthioadenosine phosphorylase; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; PRMT5, protein arginine methyltransferase 5; QD, once daily; RCC, renal cell carcinoma; TGCT, tenosynovial giant cell tumour; UC, uterine carcinosarcoma

Rodon J, et al. Eur J Cancer. 2024; 211 (suppl 1):114981. Presented at ENA 2024 (EORTC NCI AACR 36th Symposium). 503LBA (oral presentation)

BEST PERCENT CHANGE IN SUM OF TARGET LESION MEASUREMENTS

Clinical activity-evaluable population

- 23 patients with PR as BOR had SD at first on-treatment scan



Median follow-up (95% CI): 7.6 (6.8–8.3) months.

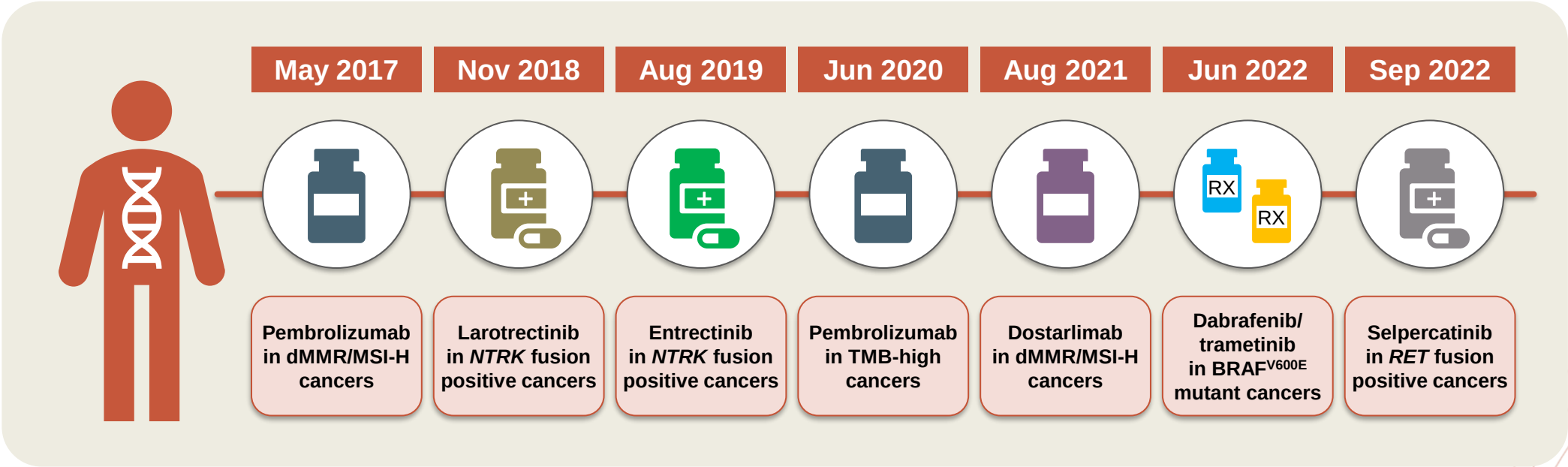
Clinical activity-evaluable population (n = 124): patients who received ≥1 dose of BMS-986504 in this study, had homozygous *MTAP*-del confirmed by a sponsor-approved assay, and had ≥ 1 on-study disease assessment prior to discontinuation, any subsequent anti-cancer therapies, or death. Patients with NE as BOR or for which change of baseline is missing due to lack of post-baseline measurement (n = 8) were not included.

BC, breast cancer; BID, twice daily; BOR, best overall response; CCA, cholangiocarcinoma; CR, complete response; del, deleted; HNSCC, head and neck squamous cell carcinomas; LoT, line of therapy; MEL, melanoma; meso, mesothelioma; MPNST, malignant peripheral nerve sheath tumour; MTAP, methylthioadenosine phosphorylase; NE, not evaluable; NSCLC, non-small cell lung cancer; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; QD, once daily; SD, stable disease

Rodon J, et al. Eur J Cancer. 2024; 211 (suppl 1):114981. Presented at ENA 2024 (EORTC NCI AACR 36th Symposium). 503LBA (oral presentation)

ESTABLISHED TARGETS

TUMOUR AGNOSTIC PRECISION MEDICINE



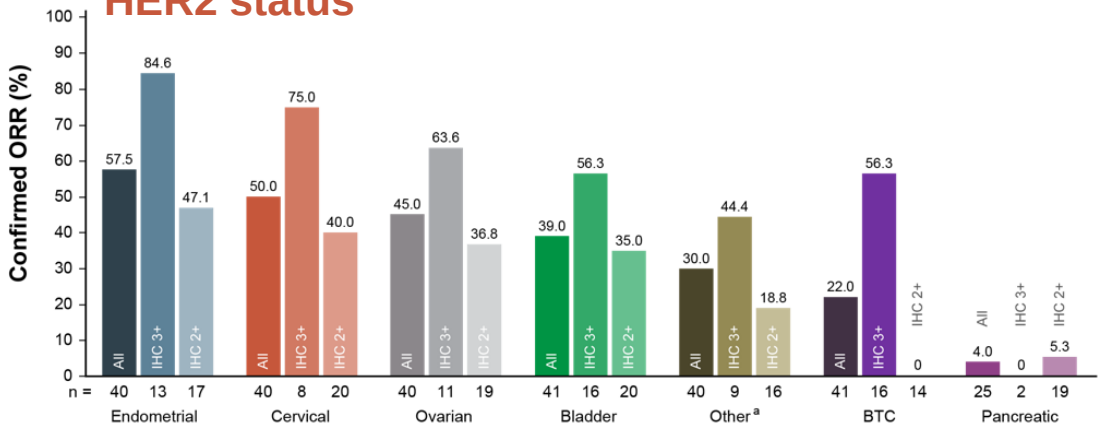
6 medicines US FDA approved for 7 tumour-agnostic indications

BRAF, proto-oncogene B-Raf; dMMR, deficient DNA mismatch repair; FDA, Food and Drug Administration; MSI-H, microsatellite instability high; NTRK, neurotrophic tropomyosin-receptor kinase; RET, rearranged during transfection; TMB, tumour mutational burden

Gouda M, et al. Clin Can Res. 2023;29:2753-2760

EFFICACY AND SAFETY OF T-DXd IN HER2-EXPRESSING SOLID TUMOURS

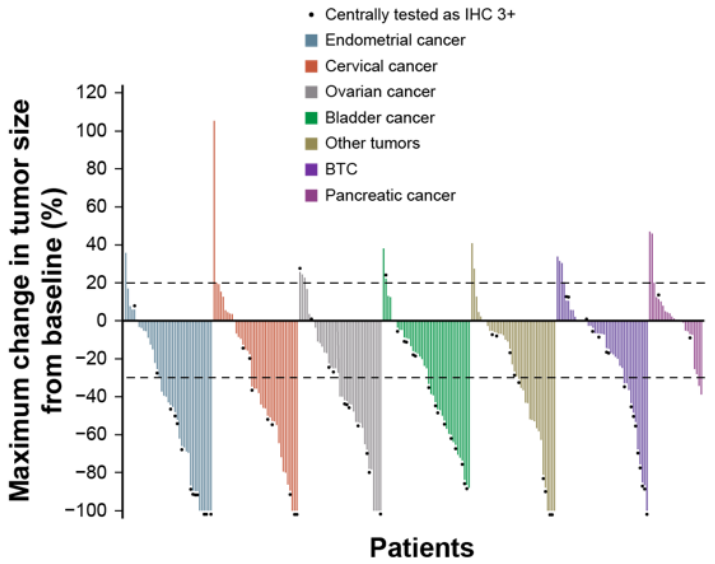
ORR across tumour cohorts, according to HER2 status



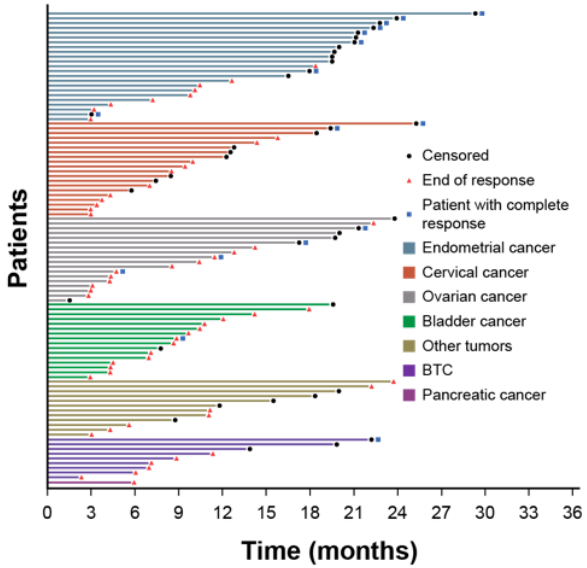
[a] Responses in the other tumours cohort include responses in extramammary Paget disease, oropharyngeal neoplasm, head and neck cancer, and salivary gland cancer

Led to approval of T-DXd for HER2-expressing solid tumours

Maximum change in tumour size



DOR in patients with objective response

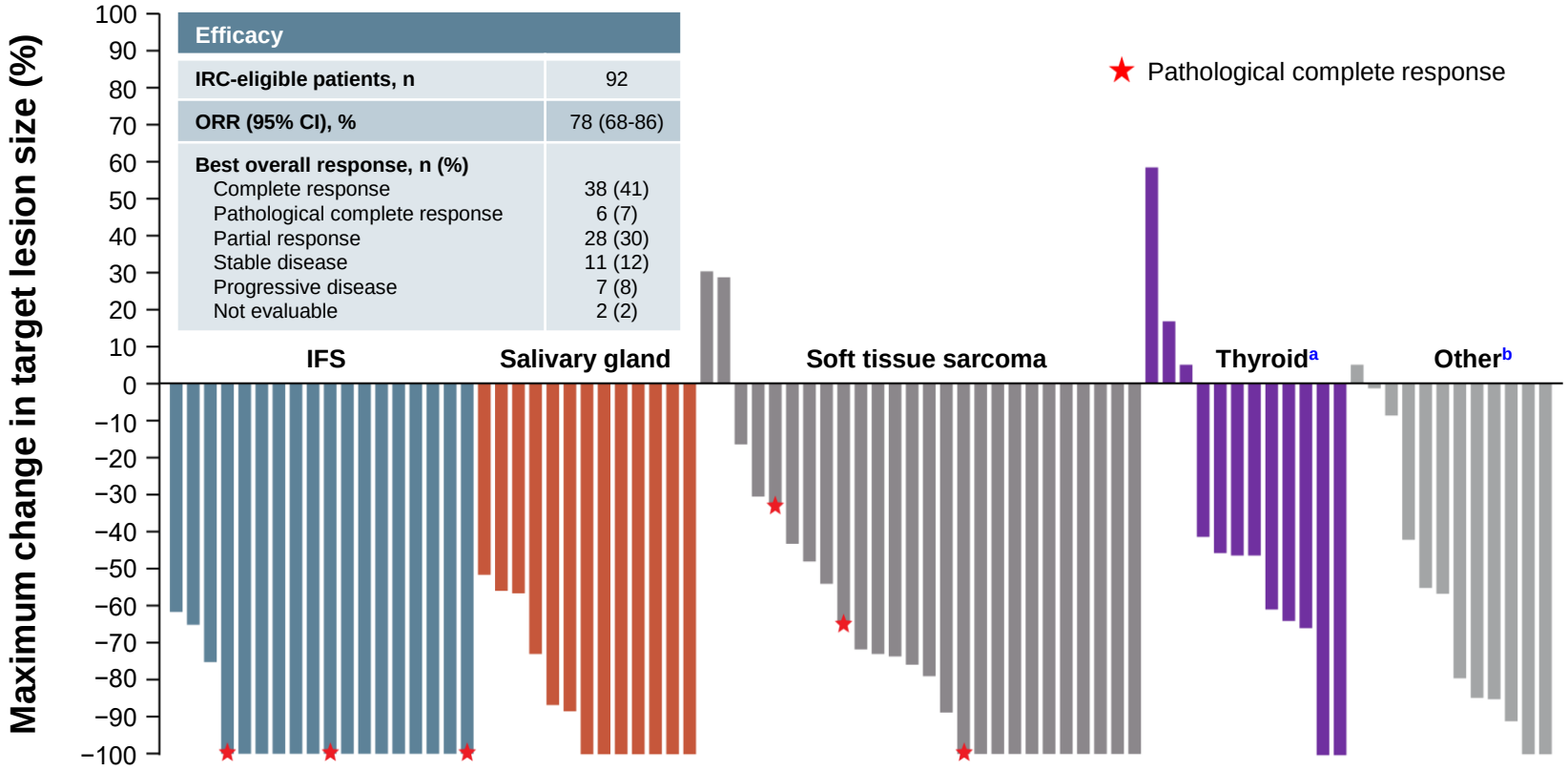


BTC, biliary tract cancer; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

Meric-Bernstam F, et al. J Clin Oncol. 2023;42:47-58

EFFICACY AND SAFETY OF LAROTRECTINIB AS FIRST-LINE TREATMENT FOR PATIENTS WITH TRK FUSION CANCER

MAXIMUM CHANGE IN TARGET LESION SIZE IN PATIENTS WITH TRK FUSION CANCER (N=92)



Not including one patient who was not eligible for IRC assessment. [a] The three patients with thyroid cancer that did not experience tumour shrinkage had anaplastic thyroid cancer. [b] Other includes two congenital mesoblastic nephroma and one each of bone sarcoma, cervix, cholangiocarcinoma, external auditory canal and lung

CI, confidence interval; IFS, infantile fibrosarcoma; IRC, independent review committee; ORR, overall response rate; TRK, tropomyosin receptor kinase

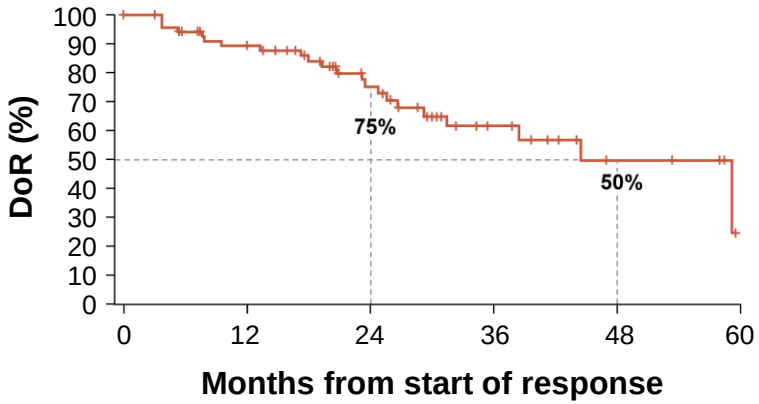
Hong DS, et al. Ann Oncol. 34 (supplement 2):S469. Presented at ESMO 2023 (Poster 667P)

EFFICACY AND SAFETY OF LAROTRECTINIB AS FIRST-LINE TREATMENT FOR PATIENTS WITH TRK FUSION CANCER

DOR, PFS AND OS IN PATIENTS WITH TRK FUSION CANCER

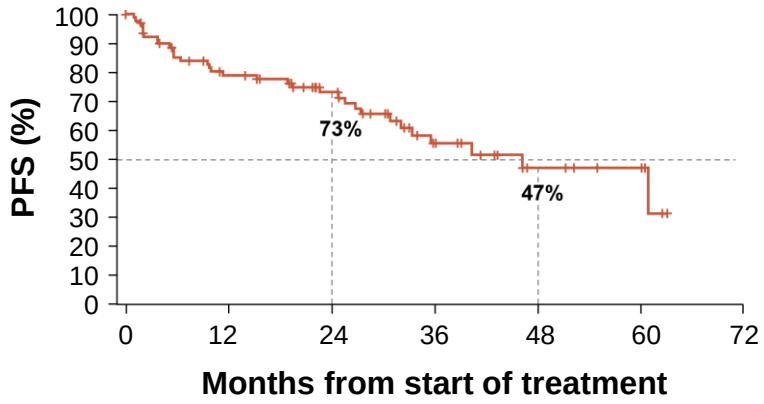
DoR

Median DoR, months (95% CI)	44.5 (29.2-NE)
Median follow-up, months	28.6
24-month DoR, % (95% CI)	75 (64-87)
48-month DoR, % (95% CI)	50 (31-69)



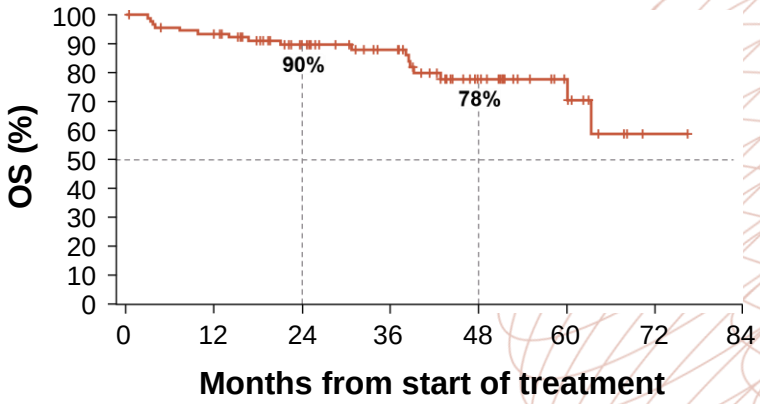
PFS

Median PFS, months (95% CI)	46.2 (32.0-NE)
Median follow-up, months	30.3
24-month PFS, % (95% CI)	73 (63-83)
48-month PFS, % (95% CI)	47 (31-62)



OS

Median OS, months (95% CI)	Not reached (63.4-NE)
Median follow-up, months	41.3
24-month OS, % (95% CI)	90 (83-96)
48-month OS, % (95% CI)	78 (67-88)



No. at risk																		
	72	54	32	14	6	0	92	60	42	19	8	5	0	92	84	63	47	23	11	1	0

CI, confidence interval; DoR, duration of response; NE, not estimable; OS, overall survival; PFS, progression-free survival; TRK, tropomyosin receptor kinase

Hong DS, et al. Ann Oncol. 34 (supplement 2):S469. Presented at ESMO 2023 (Poster 667P)

SUMMARY

- The field of precision medicine continues to evolve with the identification of new biomarkers and targeted treatments[1,2]
- Development of inhibitors such as sotorasib and adagrasib which target the *KRAS* G12C mutations have improved outcomes for NSCLC patients[3,4,5]
- Inhibitors for other *KRAS* mutations, such as *KRAS* G12D could expand treatment options for other cancers like pancreatic cancer[6,7,8]
- Other agents targeting specific patient subsets (e.g. those with MTAP loss) may expand targeted therapy options[9]
- Tumour agnostic targets such as *NTRK*[10,11] and HER2[12,13] continue to evolve and provide significant clinical benefit across a number of tumour types
- Molecular profiling by next generation sequencing is critical to ensure patients receive the most appropriate targeted therapy to improve outcomes[1,2]

KRAS, Kirsten rat sarcoma virus; MTAP, methylthioadenosine phosphorylase; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; PRMT5, protein arginine methyltransferase 5

1. Min HY and Lee HY. Exp Mol Med. 2022;54:1670-1694; 2. Malone ER, et al. Genome Med. 2020;12:8; 3. Boumelha J, et al. Clin Cancer Res. 2023;29:5012-5020; 4. FDA grants accelerated approval to sotorasib for KRAS G12C mutated NSCLC. Available here (accessed December 2024); 5. FDA grants accelerated approval to adagrasib for KRAS G12C-mutated NSCLC. Available here (accessed December 2024); 6. Nokin M-J, et al. Nat Commun. 2024; 15: 7554; 7. Akhave NS, et al. Mol Cancer Ther. 2022;21:1645-1651; 8. Arbour KC, et al. Ann Oncol. 2023;34(Supplement 2):S458-S497. Presented at ESMO 2023. Abstr 6520, oral presentation; 9. Rodon J, et al. Eur J Cancer. 2024;211 (suppl 1):114981. Presented at ENA 2024 (EORTC NCI AACR 36th Symposium). 503LBA (oral presentation); 10. Hong DS, et al. Ann Oncol. 34 (supplement 2):S469. Presented at ESMO 2023 (Poster 667P); 11. Sheng J, et al. NPJ Precis Oncol. 2024;8:198; 12. Meric-Bernstam F, et al. J Clin Oncol. 2023;42:47-58; 13. Yoon J, et al. Nat Rev Clin Oncol. 2024; 21:675-700

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