Sotorasib, panitumumab, and FOLFIRI in the first-line setting for *KRAS* G12C–mutated metastatic colorectal cancer: safety and efficacy analysis from the phase 1b CodeBreaK 101 study

Salvatore Siena,[1] Kensei Yamaguchi,[2] Jose Ruffinelli,[3] Elena Corral,[4] Yasutoshi Kuboki,[5] Chiara Cremolini,[6] Ivan Victoria,[7] Elena Elez,[8] John Strickler,[9] Muhammad Furqan,[10] Babar Bashir,[11] Chidozie Nduka,[12] Jane Hippenmeyer,[13] Emily Chan,[14] Caihong Xia,[14] Toshiki Masuishi[15]

[1]Università degli Studi di Milano and Grande Ospedale Metropolitano Niguarda, Milan, Italy; [2]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [3]Catalan Institute of Oncology, Hospital Duran i Reynals, Barcelona, Spain; [4]Hospital Universitario Ramón y Cajal, Madrid, Spain; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]University of Pisa, Pisa, Italy; [7]Hospital Clinic of Barcelona, Barcelona, Spain; [8]Vall d'Hebron University Hospital and Institute of Oncology, Universitat Autònoma de Barcelona, Barcelona, Spain; [9]Duke University Medical Center, Durham, NC, USA; [10]University of Iowa, Iowa City, IA, USA; [11]Sidney Kimmel Cancer Center, Thomas Jefferson University Hospital, Philadelphia, PA, USA; [12]Amgen Uxbridge, Uxbridge, UK; [13]Amgen Europe, Rotkreuz, Switzerland; [14]Amgen Inc., Thousand Oaks, CA, USA; [15]Aichi Cancer Center Hospital, Nagoya, Japan

As Presented at European Society for Medical Oncology (ESMO) Annual Meeting September 13-17, 2024; Barcelona, Spain

SC-AT-AMG 510-00294 09.24

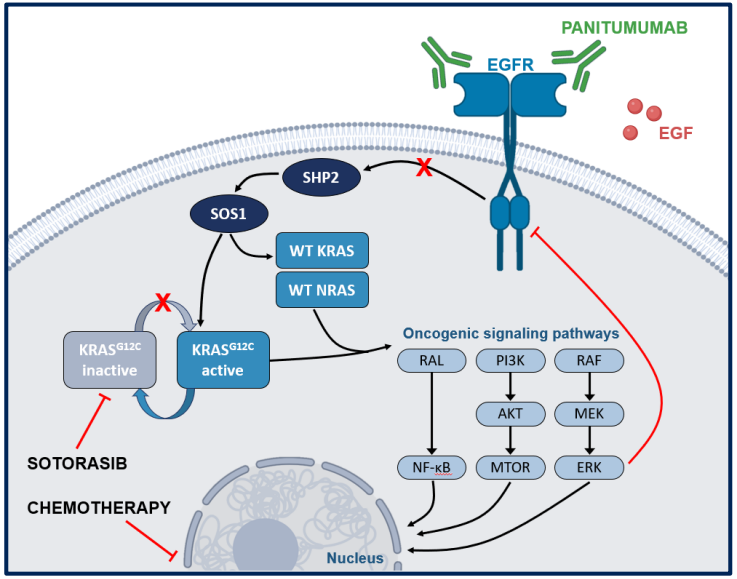
SC-AT-NP-00098 10.23

Declaration of Interests

Dr Salvatore Siena reports participating on advisory boards (personal) for Agenus, AstraZeneca, Bayer, Bristol Myers Squibb, CheckmAb, Daiichi-Sankyo, GlaxoSmithKline, MSD, Merck, Novartis, Pierre-Fabre, Seagen, and T-One Therapeutics

Background

- Approximately 3% of patients with CRC have an oncogenic *KRAS* G12C mutation[1]
- In **CodeBreaK 300** (NCT05198934), sotorasib plus panitumumab significantly improved PFS compared with investigator's choice in patients with chemorefractory *KRAS* G12C–mutated mCRC[2]
  - The final analysis of CodeBreaK 300 showed an ORR of 30% for the combination of sotorasib plus panitumumab[3]
- In the phase 1b **CodeBreaK 101** (NCT04185883) study, the addition of FOLFIRI to sotorasib plus panitumumab demonstrated an acceptable safety profile and a promising ORR of 60% for patients with previously treated *KRAS* G12C–mutated mCRC[4]

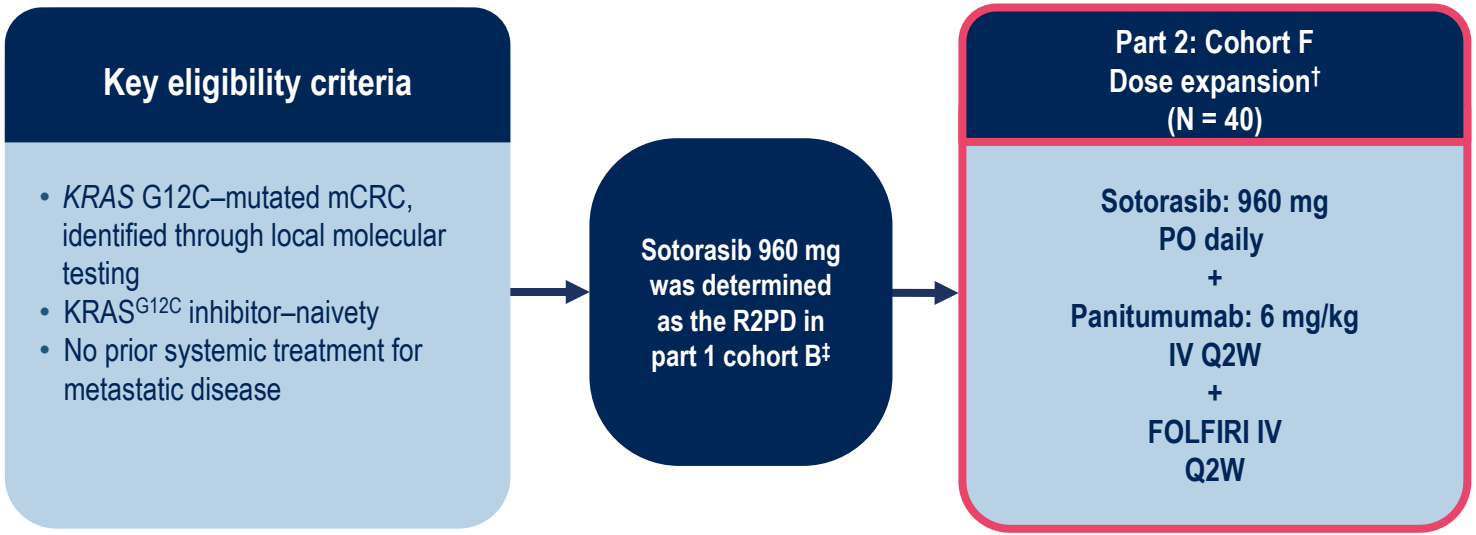


Here we evaluated the safety and efficacy of sotorasib, panitumumab, and FOLFIRI in the first-line setting for mCRC disease

AKT, protein kinase B; **CRC**, colorectal cancer; **EGFR**, epidermal growth factor receptor; **ERK**, extracellular signal-regulated kinase; **FOLFIRI**, irinotecan, leucovorin plus 5-fluorouracil; **KRAS**, Kirsten rat sarcoma virus; **mCRC**, metastatic colorectal cancer; **MEK**, mitogen-activated extracellular signal-regulated kinase; **MTOR**, mammalian target of rapamycin; **NF-κB**, nuclear factor kappa B; **NRAS**, neuroblastoma Ras viral oncogene homolog; **ORR**, objective response rate; **PFS**, progression-free survival; **PI3K**, phosphatidylinositol 3-kinase; **RAF**, rapidly accelerated fibrosarcoma; **RAL**, Ras-related protein; **SHP2**, Src homology region 2-containing protein tyrosine phosphatase 2; **SOS1**, son of sevenless homolog 1; **WT**, wild type.

Study Schema

CodeBreaK 101 subprotocol H phase 1b, multicenter, open-label study*: sotorasib + panitumumab + FOLFIRI in first-line *KRAS* G12C–mutated mCRC



Primary endpoint: Safety and tolerability

Secondary endpoints: Anti-tumor efficacy (ORR, DCR, DOR, TTR, PFS per RECIST v1.1, and OS) and PK

*NCT04185883. †Treatment until disease progression, withdrawal of consent, or end of study. ‡No dose adjustment was needed. **DCR**, disease control rate; **DOR**, duration of response; **FOLFIRI**, irinotecan, leucovorin plus 5-fluorouracil; **IV**, intravenous; **KRAS**, Kirsten rat sarcoma virus; **mCRC**, metastatic colorectal cancer; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **PK**, pharmacokinetics; **PO**, orally; **Q2W**, every 2 weeks; **RECIST**, Response Evaluation Criteria in Solid Tumors; **RP2D**, recommended phase 2 dose; **TTR**, time to response.

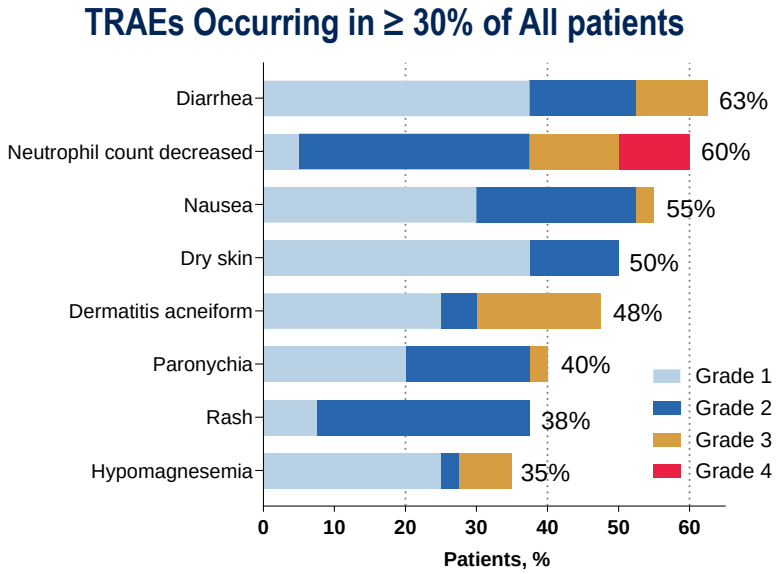
Baseline Characteristics

	Sotorasib + Panitumumab + FOLFIRI (N = 40)
Median age, years (range)	60 (23–80)
Male	23 (58)
White / Asian / Black or African American / Other	22 (55) / 15 (38) / 2 (5) / 1 (3)
ECOG performance status 0 / 1	27 (68) / 13 (33)
Liver metastasis	26 (65)
Liver metastasis only	7 (18)
Lung metastasis	24 (60)
Lymph node metastasis	16 (40)
Peritoneal metastasis	17 (43)
Tumor sidedness, left / right / unknown	27 (68) / 10 (25) / 3 (8)
Prior fluoropyrimidine	8 (20)
Prior oxaliplatin	8 (20)
Prior irinotecan†	1 (3)
Prior fluoropyrimidine, oxaliplatin, and irinotecan	1 (3)
Prior radiotherapy / surgery for current malignancy	3 (8) / 25 (63)

Data cutoff, July 15, 2024. Baseline characteristics shown as n (%) unless otherwise stated. †Patient received FOLFIRINOX in the neoadjuvant setting. **ECOG**, Eastern Cooperative Oncology Group; **FOLFIRI**, irinotecan, leucovorin plus 5-fluorouracil.

Treatment-Related Adverse Events

	Sotorasib + Panitumumab + FOLFIRI (N = 40)
Any-grade TRAEs, n (%)	40 (100)
Grade ≥ 3	23 (58)
Leading to dose reduction / interruption	35 (88)
Sotorasib	20 (50)
Panitumumab	26 (65)
5-fluorouracil	28 (70)
Irinotecan	25 (63)
Leading to discontinuation	7 (18)
Sotorasib	1 (3)
Panitumumab	2 (5)
5-fluorouracil	5 (13)
Irinotecan	4 (10)
Discontinued all study therapy	1 (3)



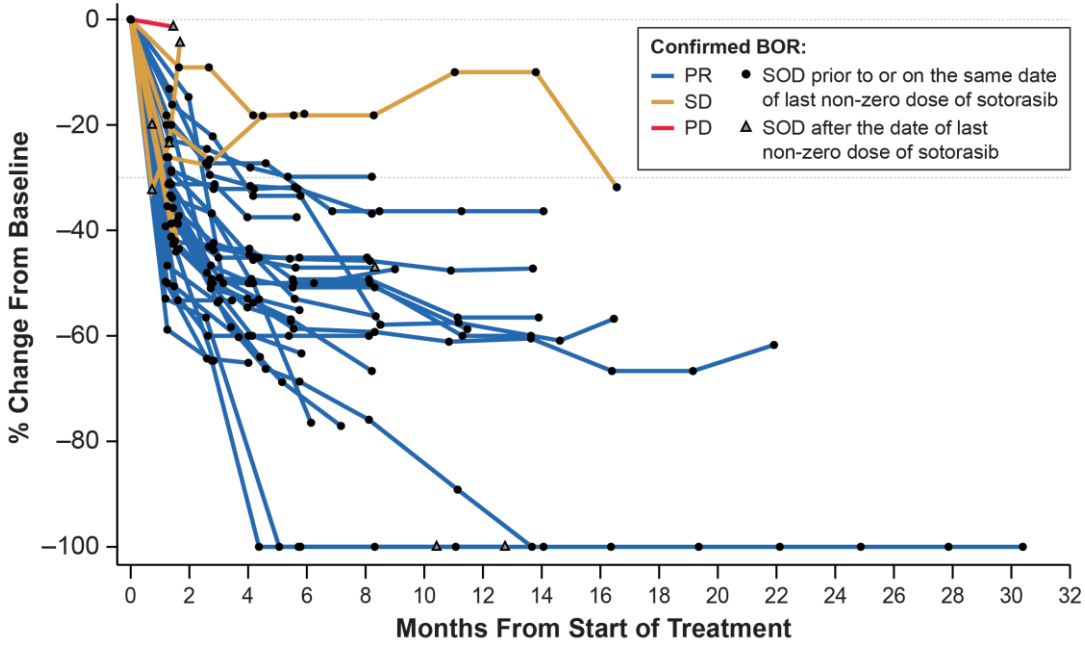
- **TRAEs were consistent with known safety profiles of sotorasib, panitumumab, and FOLFIRI**
- **No fatal TRAEs occurred**

Data cutoff, July 15, 2024. **FOLFIRI**, irinotecan, leucovorin plus 5-fluorouracil; **TRAE**, treatment-related adverse event.

Efficacy Summary

ORR by Investigator Assessment*	Sotorasib + Panitumumab + FOLFIRI (N = 40)
ORR, n (%)	31 (78)
Complete response†	0
Partial response	31 (78)
Stable disease	7 (18)
Progressive disease	1 (3)
Not evaluable‡	1 (3)
Patients with liver metastasis only, n / N (%)	7 / 7 (100)
Left-sided tumor, n / N (%)	22 / 27 (82)
Right-sided tumor, n / N (%)	6 / 10 (60)

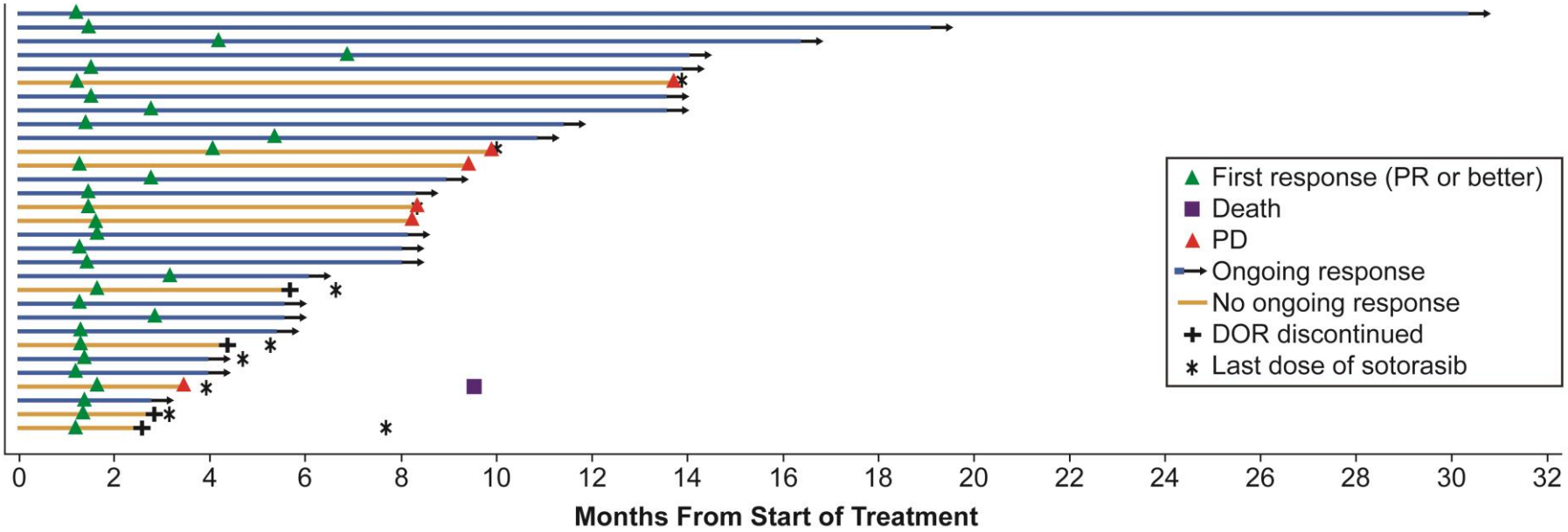
Change From Baseline in Sum of Target Lesions



A total of 38 patients (95%) achieved disease control*, and all patients had reduction in target lesions

Data cutoff, July 15, 2024. *ORR analysis set includes all patients who received at least 1 dose of investigational products, have one or more measurable lesions at baseline assessed using RECIST 1.1, and had the opportunity to be followed for at least 7 weeks starting from day 1. †One patient had a confirmed CR after data cutoff. ‡Patient had only non-evaluable scans before end of study. *Achieved a complete response, partial response, or stable disease. **BOR**, best overall response; **CR**, complete response; **FOLFIRI**, irinotecan, leucovorin plus 5-fluorouracil; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease; **SOD**, sum of lesion diameter.

Duration of Response in Confirmed Responders



With a median follow-up time of 6.7 months, 21 out of 31 responders (68%) are still on study with ongoing response

Data cutoff, July 15, 2024. ORR analysis set includes all patients who received at least 1 dose of investigational products, have one or more measurable lesions at baseline assessed using RECIST v1.1, and had the opportunity to be followed for at least 7 weeks starting from day 1. **DOR,** duration of response; **ORR,** objective response rate; **PD,** progressive disease; **PR,** partial response; **RECIST**, Response Evaluation Criteria in Solid Tumors; **TTR**, time to response.

Conclusions

- This study, CodeBreaK 101, in the first-line setting provides the first data set on the use of a $KRAS^{G12C}$ inhibitor in the first-line treatment of *KRAS* G12C–mutated mCRC
- The addition of FOLFIRI to sotorasib plus panitumumab demonstrated a manageable safety profile and promising response rates
  - TRAEs were consistent with known safety profiles of sotorasib, panitumumab, and FOLFIRI
  - The most common grade ≥ 3 TRAEs were decreased neutrophil count (23%), dermatitis acneiform (18%), and diarrhea (10%)
  - Confirmed ORR was 78% and DCR was 95%
- These data support the ongoing global phase 3 CodeBreaK 301 study (NCT06252649) evaluating sotorasib plus panitumumab and FOLFIRI in first-line *KRAS* G12C–mutated mCRC

DCR, disease control rate; **FOLFIRI**, irinotecan, leucovorin plus 5-fluorouracil; **KRAS**, Kirsten rat sarcoma; **mCRC**, metastatic colorectal cancer; **ORR**, objective response rate; **TRAE**, treatment-related adverse event.

The authors thank the patients and their caregivers, investigators, and study staff who contributed to this study

This study was funded by Amgen Inc.

Medical writing support for this presentation was provided by Lisa Denny, PhD, of ICON plc (Blue Bell, PA, USA) and was funded by Amgen Inc.

Contact Information:
Salvatore Siena, salvatore.siena@unimi.it

References

1. Nassar AH, et al. *N Engl J Med*. 2021;384(2):185-187.
2. Fakih MG, et al. *N Engl J Med.* 2023;389(23):2125-2139.
3. Fakih MG, et al. *J Clin Oncol.* 2024;42(suppl 17):236S.
4. Masuishi T, et al. *Ann Oncol.* 2023;34:S1505.