



Phase 1b/2 study of ompenaclid, a first-in-class oral inhibitor of the creatine transporter SLC6A8, in combination with FOLFIRI and bevacizumab in RAS-mutated second-line advanced/metastatic colorectal cancer

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Introduction

- Colorectal cancer (CRC) is the 2nd most common cause of cancer death, causing almost 1 million deaths/year.¹
- Up to 45% of patients with metastatic CRC (mCRC) have RAS-mutant (RAS-mut) tumors.²
- SLC6A8, which imports creatine and phosphocreatine (PCr), is upregulated in mCRC cells to aid survival under hypoxia.
- Ompenaclid (RGX-202-01) is a first-in-class oral SLC6A8 inhibitor that reduces intracellular PCr and adenosine triphosphate (ATP) leading to tumor cell apoptosis (Fig 1).³

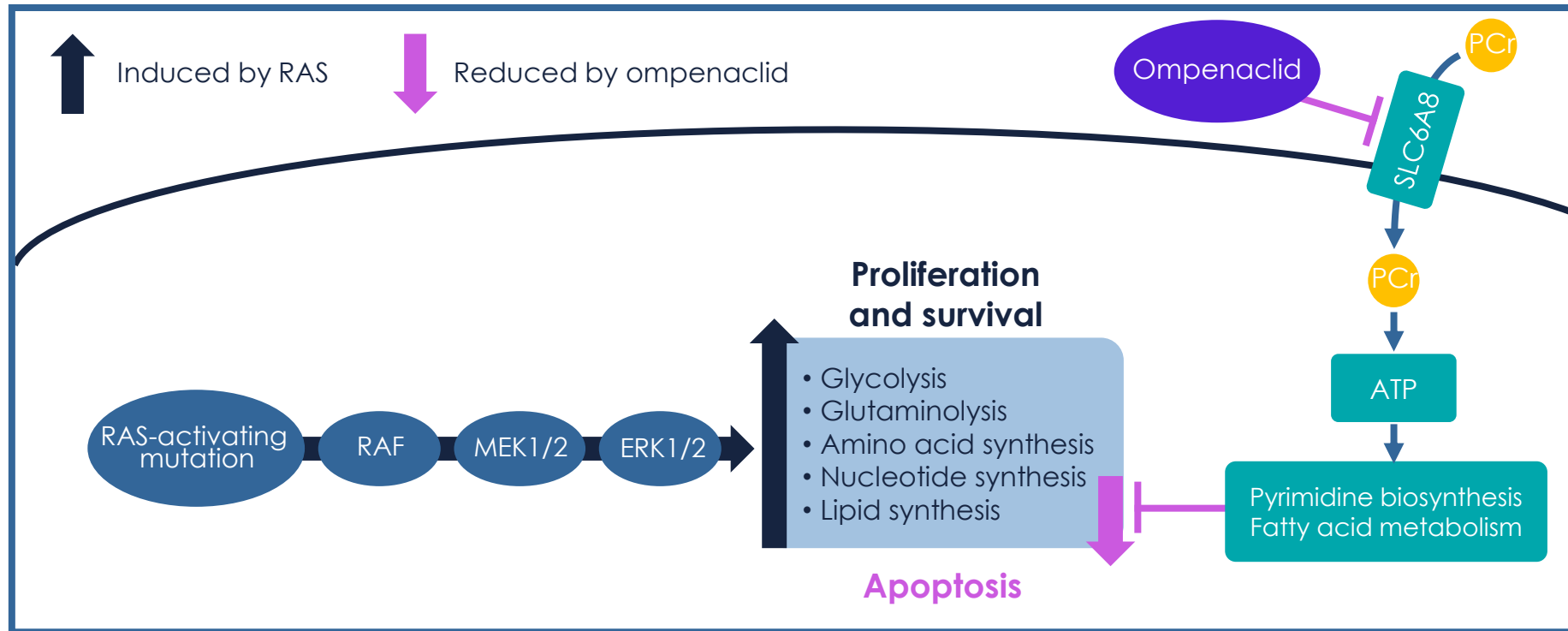
Introduction (continued)

- Targeting the metabolic dependencies of RAS-mut mCRC broadens the therapeutic approach, regardless of a specific RAS pathway mutation.
- On target resistance to SLC6A8 has not been observed with ompenaclid in preclinical models.
- In animal models, ompenaclid monotherapy demonstrated robust anti-tumor activity and exhibited synergistic efficacy with 5-fluorouracil (5-FU).⁴
- In patients with RAS-mut mCRC, ompenaclid monotherapy demonstrated anti-tumor activity with a favorable safety profile without dose-limiting toxicities (DLTs).⁵

Introduction (continued)

- Clinical data suggest robust and maximal pharmacodynamic effects are achieved with ompenacrid \geq 2400 mg twice daily (BID).^{5,6}
- Preliminary efficacy data suggest that ompenacrid has activity in RAS-mut mCRC regardless of the specific mutation.⁶
- FOLFIRI/bevacizumab (BEV) is a standard-of-care (SOC) 2nd line regimen for mCRC, which provides overall response rate (ORR) of ~15%, median progression-free survival (mPFS) of ~5–6 months and median overall survival (mOS) of ~11–18 months.⁷
- The aims of this phase 1b/2 study are to evaluate safety, pharmacodynamics and pharmacokinetics (PK/PD) and efficacy of ompenacrid plus SOC (FOLFIRI/BEV) in 2nd line RAS-mut mCRC.

Fig 1. Ompenaclid mechanism of action

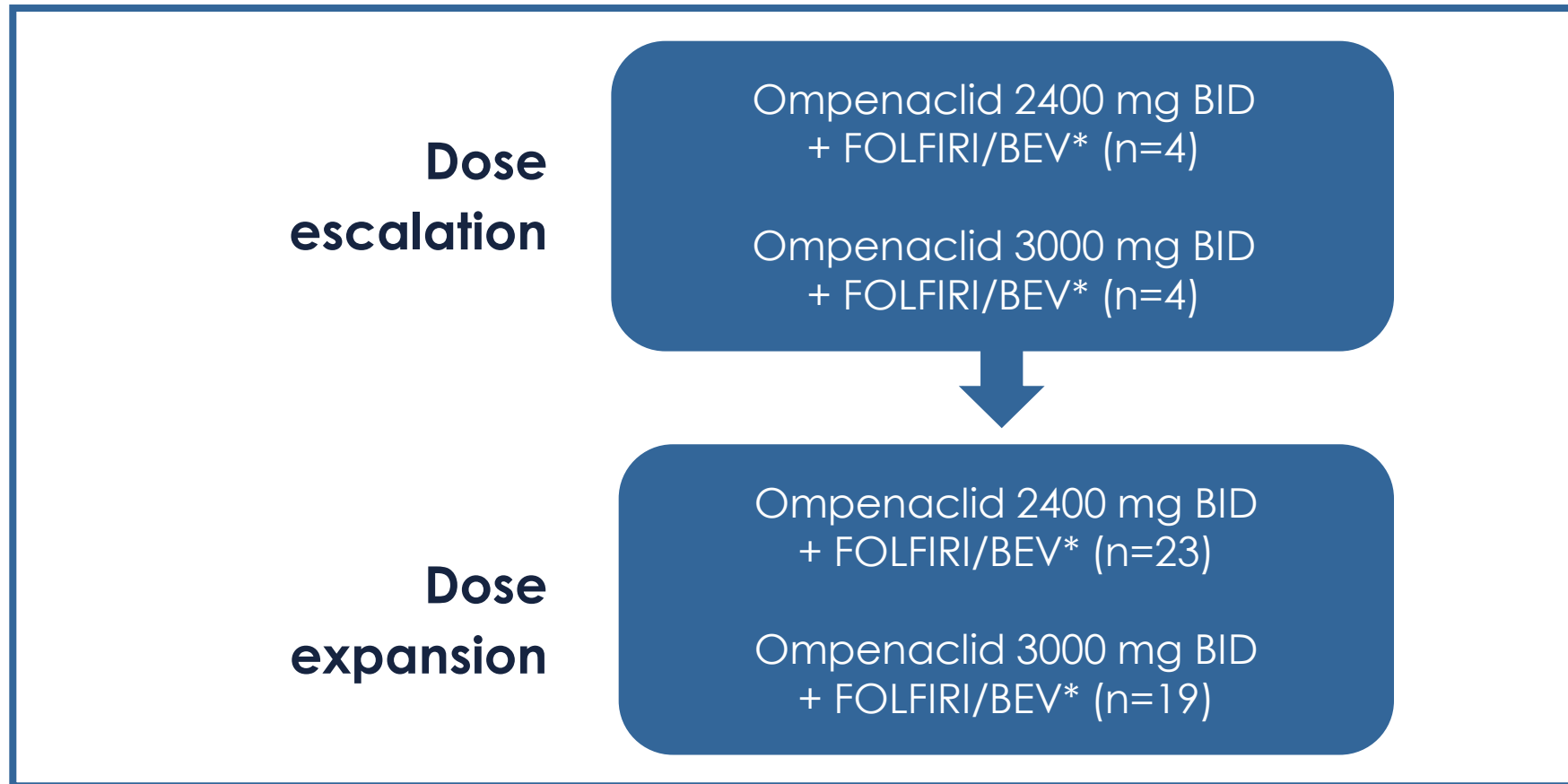


By depleting intracellular ATP levels, ompenaclid inhibits multiple pathways, including pyrimidine synthesis and fatty acid metabolism. These pathways generate critical building blocks upon which RAS-mut tumors depend for growth and survival. Unlike other RAS-mut targeting agents, ompenaclid's mechanism of action interferes with multiple downstream biosynthetic pathways.

Key eligibility criteria

- Advanced (adv) or metastatic RAS-mut CRC; wild type (WT) patients were also initially enrolled.
- Measurable disease by Response Evaluation Criteria in Solid Tumour (RECIST) version 1.1, Eastern Cooperative Oncology Group (ECOG) ≤ 1 .
- Demonstrated progression with an oxaliplatin-based regimen.
- Only 1 prior line of therapy for adv/mCRC with the following exception:
 - Patients were eligible if they had recurrence within 12 months of completion of an oxaliplatin-based adjuvant therapy and no treatment for adv/mCRC.

Fig 2. Treatment cohorts



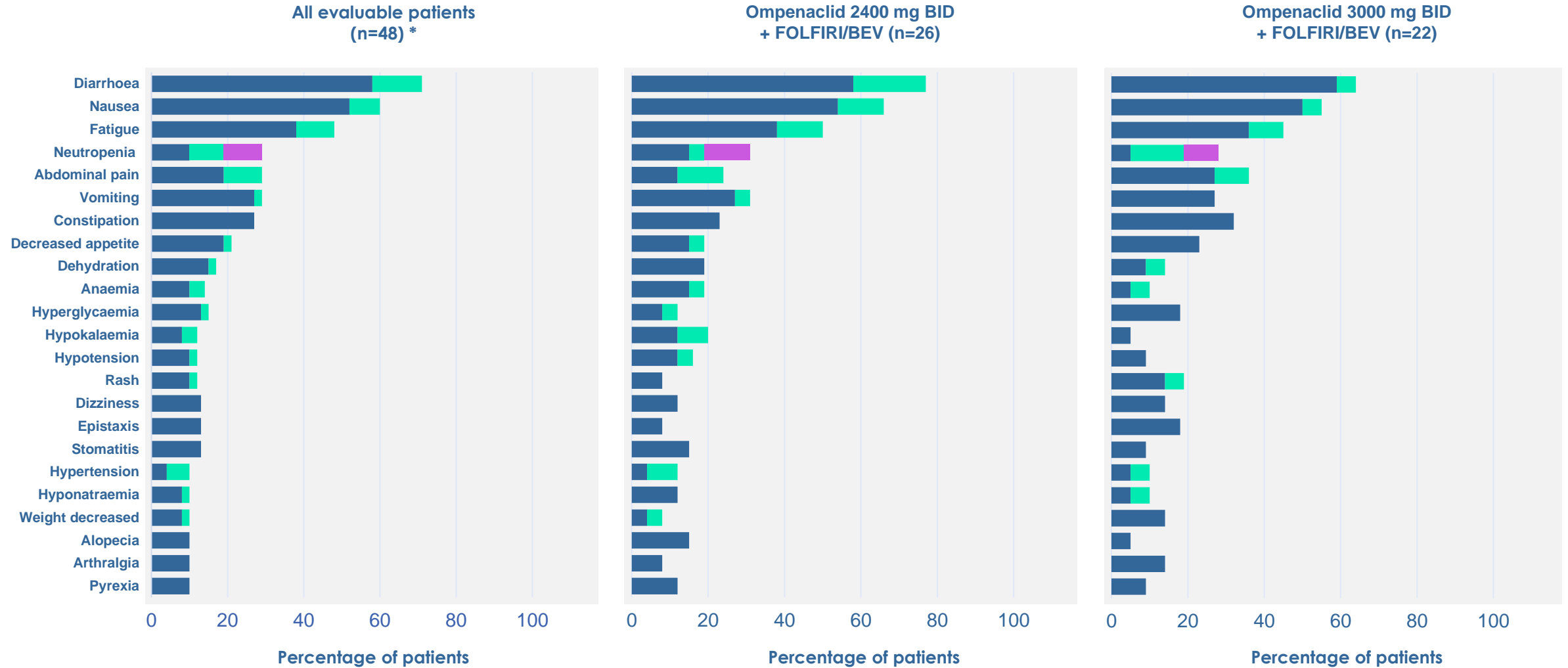
* BEV intravenous (IV) 5 mg/kg, followed by irinotecan 180 mg/m² IV concurrently with folinic acid 400 mg/m² IV, followed by 5-FU 2400 mg/m² IV over 46 hours on days 1 and 15 of each 28-day cycle.

ClinicalTrials.gov: NCT03597581

Table 1. Baseline characteristics

RAS status (n)		RAS-mut (n=41)	WT (n=9)
Median age, years (range)		58 (43–82)	63 (32–85)
Race, n (%)	White	32 (78)	6 (67)
	African American	7 (17)	1 (11)
	Asian	1 (2)	0
	Not reported / other	1 (2)	2 (22)
Sex, n (%)	Male	25 (61)	6 (67)
	Female	16 (39)	3 (33)
ECOG, n (%)	0	20 (49)	4 (44)
	1	21 (51)	5 (56)
≥ 2 metastatic organ sites, n (%)		34 (83)	9 (100)
Prior therapies, n (%)	Oxaliplatin + 5-FU	41 (100)	9 (100)
	BEV	28 (68)	8 (89)

Fig 3. TEAEs occurring in $\geq 10\%$ of patients

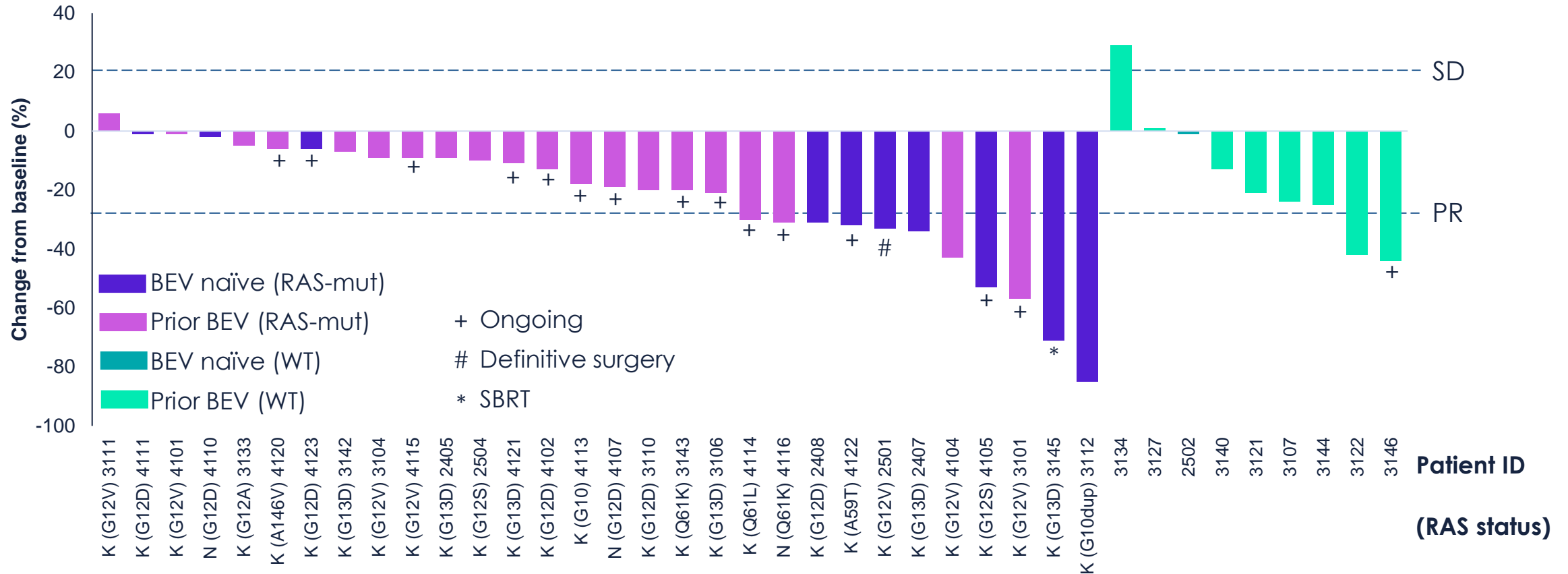


* Includes all patients who have discontinued study treatment and patients with study treatment ongoing who have completed ≥ 1 cycle with AE data entered. Data cut-off 18 Sep 2023.

Safety (continued)

- In the Dose Escalation Phase, there were no DLTs observed for either the 2400 mg BID or 3000 mg BID dose with the combination.
- The most common Grade ≤ 2 TEAEs were diarrhea (58%) and nausea (52%).
- The most frequent Grade ≥ 3 TEAEs were neutropenia (18%), diarrhea (13%), fatigue (10%) and abdominal pain (10%).
- The only Grade 5 TEAE was 1 patient (2% of total patients) with an intestinal perforation, deemed related to BEV.
- At the evaluated dose levels, ompenacilid added to FOLFIRI/BEV was well tolerated.

Fig 4. Best response in all evaluable patients (n=39)



Percentage change from baseline of tumors in evaluable patients. Graph shows patient RAS status (N=NRAS, K=KRAS) and best overall response after ompenaclicid + FOLFIRI/BEV treatment. Data cut-off 18 Sep 2023; open database.

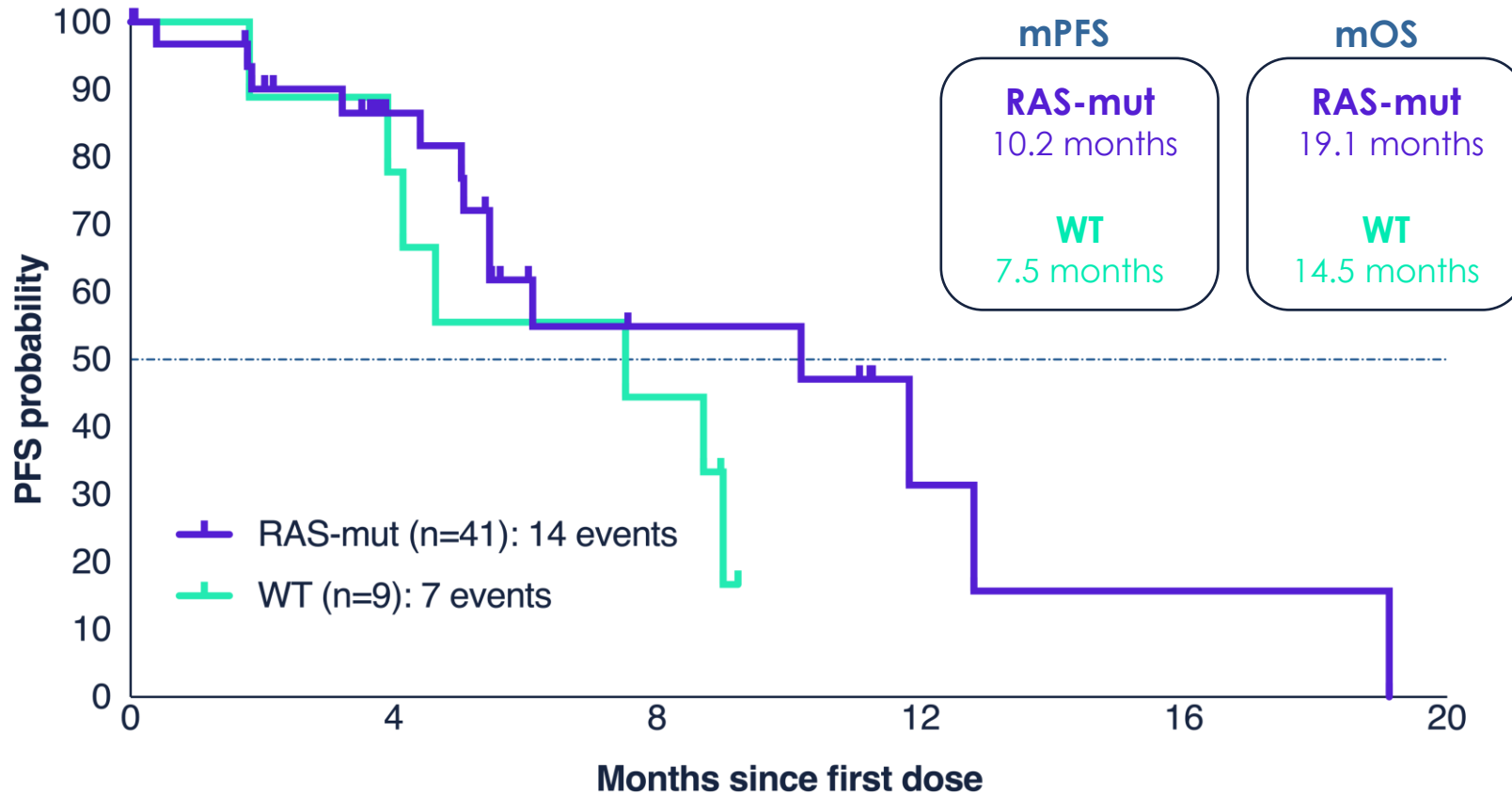
Table 2. Best response

RAS status (evaluable patients)	RAS-mut (n=30)	WT (n=9)
PR , n (%)	11 (37)	2 (22)
Confirmed PR, n	8*	1*
Unconfirmed PR, n	3**	1†
SD , n (%)	19 (63)	6 (67)
PD , n (%)	0	1 (11)

Preferential activity in RAS-mut vs WT is consistent with preclinical and Phase 1 data.

Fig 5. PFS in RAS-mut vs WT mCRC

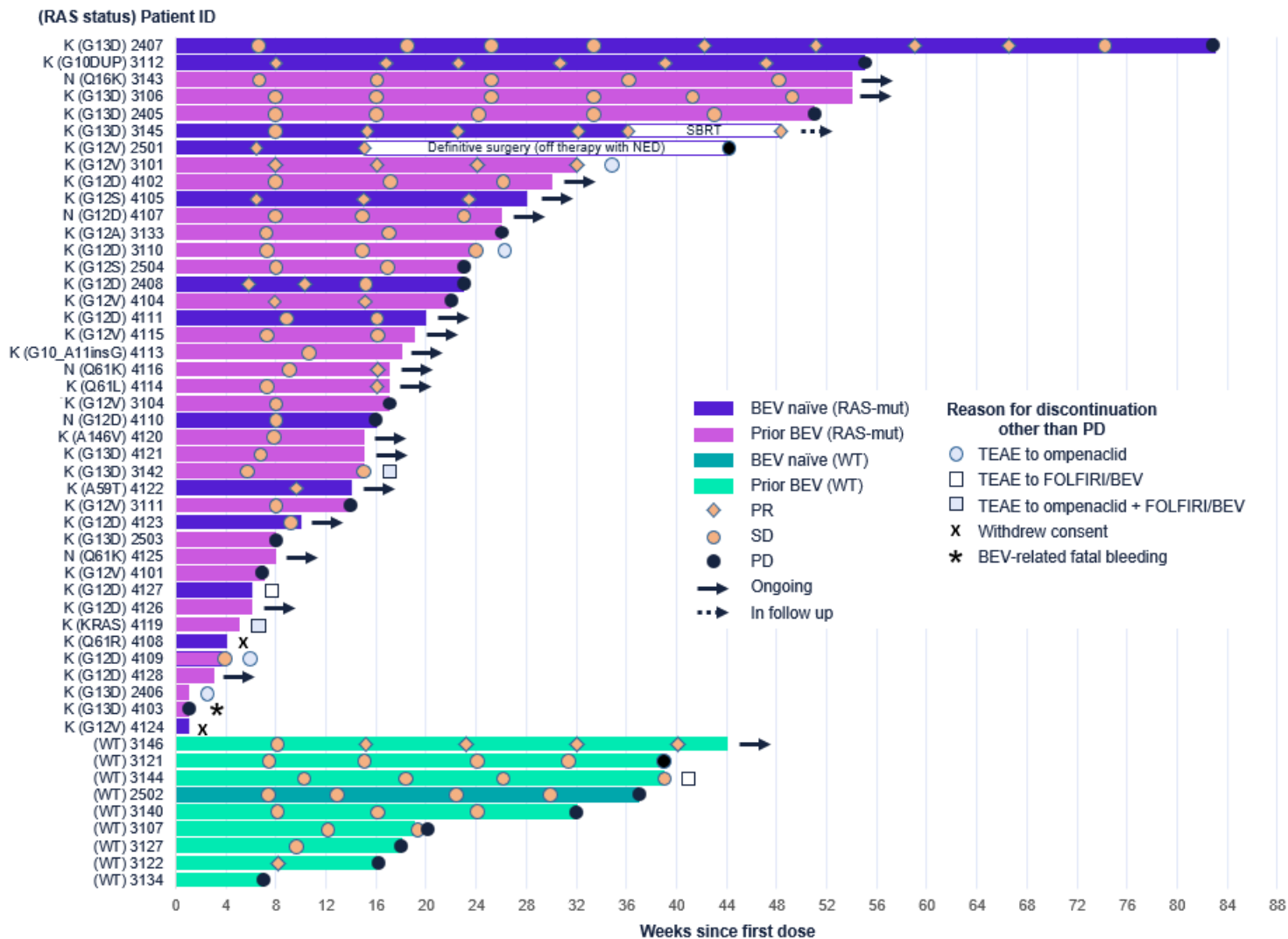
Ompenaclid + SOC increased PFS and OS in RAS-mut vs WT mCRC.



PFS analysis included all patients enrolled (n=50). PFS data are not yet final as of the cut-off date 18 Sep 2023 due to continuing patient follow-up and the limited number of PD events.

Fig 6. Duration of treatment and response in all patients (n=50)

Graph shows patient RAS status (N=NRAS, K=KRAS). Data cut-off 18 Sep 2023; open database, data subject to change.



Summary of efficacy

- Patients with RAS-mut mCRC experienced durable clinical benefit with an ORR of 37% and mPFS of 10.2 months.
- Clinical benefit (PRs and durable SDs) was observed in patients with diverse KRAS and NRAS mutations.
- Patients with WT mCRC had an ORR of 22% and a mPFS of 7.5 months.
- Patients not previously treated with BEV experienced a higher response rate.

Summary of efficacy (continued)

- ORR and mPFS observed to date in patients with RAS-mut tumors clearly exceed that expected with SOC FOLFIRI/BEV alone in 2nd line mCRC.
- Tumor regressions generally deepened over time in patients with RAS-mut tumors, with first radiographic evidence of PR appearing as late as 40 weeks after initiation of study therapy, consistent with previously presented ompenacrid monotherapy Phase 1 and preclinical efficacy data.^{4,5}

PK/PD

- Systemic exposure was comparable with both doses with up to a x48 increase in urine creatine, suggesting robust target inhibition.⁶

Conclusions

- Ompenaclid plus FOLFIRI/BEV provided encouraging efficacy and induced potent inhibition of SLC6A8.
- Treatment with ompenaclid resulted in clinical benefit, with ORR and PFS exceeding that of 2nd line SOC in RAS-mutant mCRC.
- The overall safety profile is similar to SOC and other anti-angiogenic combinations in 2nd line patients with mCRC.
- Preferential activity in patients with RAS-mutant mCRC is consistent with preclinical and Phase 1 data.

Conclusions (continued)

- Ompenaclid represents a novel approach to target pan-RAS-mutant mCRC, a population with high unmet medical need.
- An ongoing Phase 2 blinded randomized placebo-controlled trial will further explore the safety and efficacy of the combination of ompenaclid with FOLFIRI/BEV in 2nd line RAS-mutant mCRC and will include a subgroup analysis based on usage of BEV in the 1st line setting.

References

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3. Loo *et al. Cell* 160, 393-406 (2015).
4. Kurth *et al. Sci Adv* 7 (2021).
5. Bendell *et al. J Clin Oncol* 38(15) 2020 Supple 3504.
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Ompenaclicid + FOLFIRI/ Bev compared to historical SOC with FOLFIRI combined with Bev or other approved anti-angiogenic inhibitors

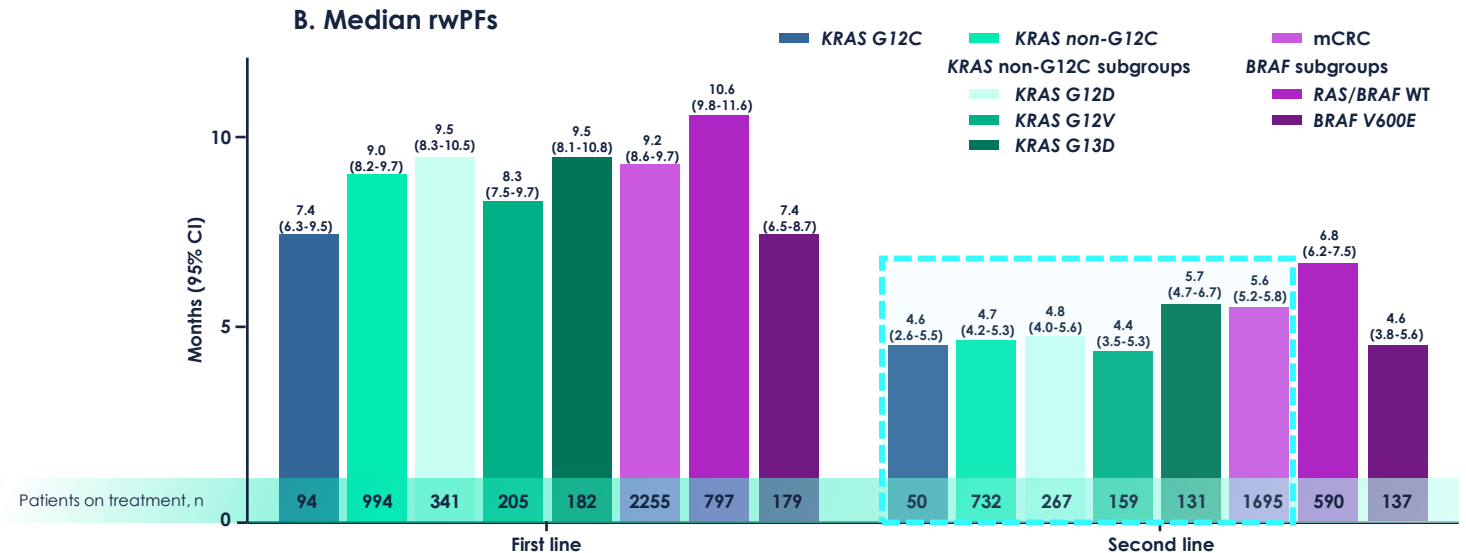
	Ompenaclicid [^] (Bevacizumab)	RAISE* (Ramucirumab)	VELOUR** (Aflibercept)	ML18147*** (Bevacizumab)
ORR (WT and RAS)	37% (RAS only)	13%	19%	5%
DCR (WT and RAS)	100% (RAS only)	74%	85%	88%
mPFS (RAS)	10.2 months	5.7 months	Unreported	5.5 months
mOS (RAS)	19.1 months	12.9 months	12.6 months	10.4 months
mPFS (WT and RAS)		5.7 months	6.9 months	5.7 months
mOS (WT and RAS)		13.3 months	13.5 months	11.2 months

* Patients had either prior Oxaliplatin- or Irinotecan- first line therapies and Investigators had the option to use either Oxaliplatin- or Irinotecan-based second line therapies

[^]ESMO 2023, Hendifar et al.

Real-world data on PFS and OS in the 2nd line RAS mutant mCRC population

- Largest and most robust RWE study in over 6000 mCRC patients, with and without RAS mutations
- Treatment patterns are generally comparable in patients in mCRC with or without the KRAS p.G12C mutation and consistent across successive LOT*
 - Since anti-VEGF therapy introduced over a decade ago in 2L CRC, standard of care has not changed



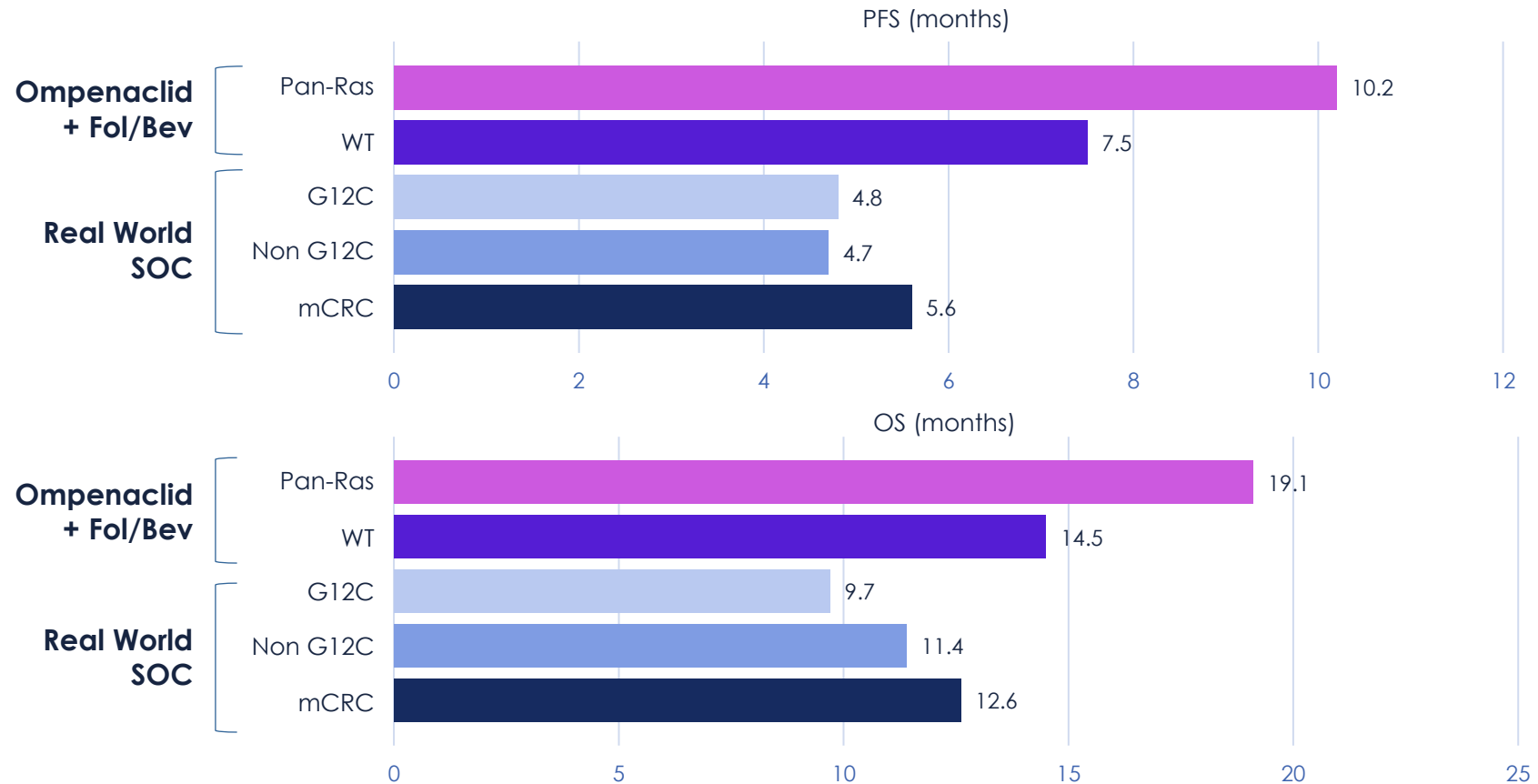
Fakih et al; Real-World Study of Characteristics and Treatment Outcomes Among Patients with KRAS p.G12C-Mutated or Other KRAS Mutated Metastatic Colorectal Cancer. The Oncologist, 2022, 27, 663–674

* LOT- line(s) of treatment

- Median (95% CI) rwPFS in second line settings
 - KRAS G12C cohort – 4.6 (2.6-5.5) months
 - KRAS non-G12C cohort – 4.7 (4.2-5.3) months
 - mCRC overall cohort – 5.6 (5.2-5.8) months

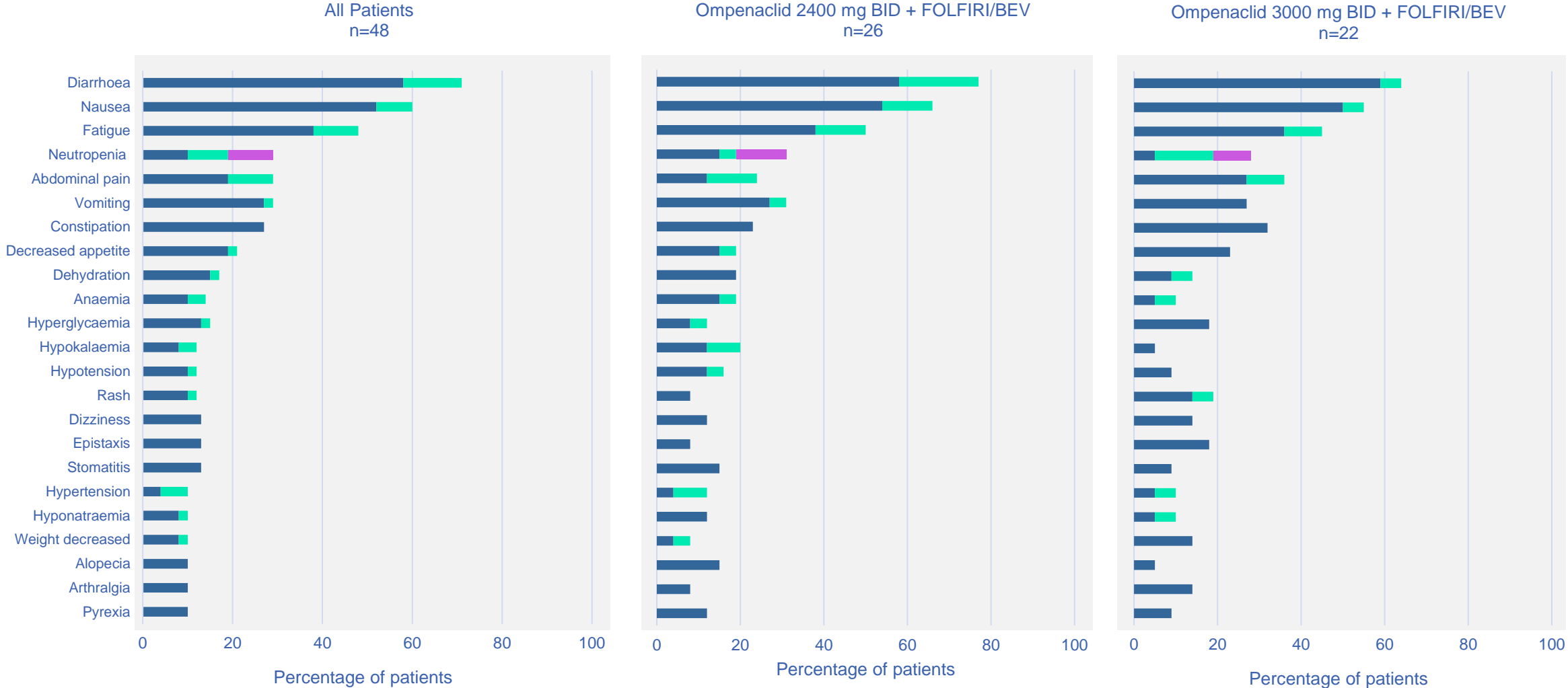
In Phase 1b/2, Ompenacnid demonstrates a meaningful clinical effect in 2L mCRC on top of standard of care of FOLFIRI + Bevacizumab

Ompenacnid phase 1b/2 compared to real world data (Fakih et al)



Ompenaclicid safety profile combined with SOC FOLFIRI/BEV

^TEAEs occurring in $\geq 10\%$ of patients



SUMMARY:

Ompenacnid safety profile combined with SOC FOLFIRI/BEV

- In the Dose Escalation Phase, there were no DLTs observed for either the 2400 mg BID or 3000 mg BID dose with the combination.
- The most common Grade ≤ 2 TEAEs were diarrhea (58%) and nausea (52%).
- The most frequent Grade ≥ 3 TEAEs were neutropenia (18%), diarrhea (13%), fatigue (10%) and abdominal pain (10%).
- The only Grade 5 TEAE was 1 patient (2% of total patients) with an intestinal perforation, deemed related to BEV.
- At the evaluated dose levels, ompenacnid added to FOLFIRI/BEV was well tolerated.
- Ompenacnid had an overall relative dose delivery of $\sim 75\%$ (this number is likely an underestimate as EDC entry of some diary dosing is still pending).
- In the phase Ib single arm study FOLFIRI and Bev were delivered with seemingly similar dose density and similar toxicity as would be expected to be seen with SOC alone.

Potential impact of prior bevacizumab treatment on efficacy and plan for stratification

- In Aflibercept's Phase 3 trial VELOUR, most patients did not receive prior Bev and a subgroup analysis showed no significant difference on either OS or PFS.
- The recent SUNLIGHT Phase 3 trial adding Bevacizumab to Lonsurf did show a greater treatment effect in Bev naïve patients compared to those who had received prior Bevacizumab, although the latter's effect was still significant compared to Lonsurf alone.
- It is important to look at this potential treatment effect and we plan to stratify and perform subgroup analyses in these two populations.

Phase 3 Dose Optimization and FDA feedback at EOP Type B meeting

- The available PK, pharmacodynamic, safety, and efficacy data from the ongoing Phase 1b/2 study of ompenacnid support a minimum effective dose of ompenacnid at 2400 mg BID to 3000 mg BID.
 - Doses below 2400 mg BID failed to consistently achieve adequate drug exposures as well as pharmacodynamic activity and exhibited non-linear PK parameters.
 - Additionally, 3600 mg BID is also considered non optimal given reduced tolerability as a single agent, which could preclude its use in combination with FOLFIRI + bevacizumab.
- Inspirna's position to the FDA at the EOP1 meeting held in June 2022 was that the 3000 mg BID dose may provide for a greater proportion of patients achieving PK and pharmacodynamic range since a dose reduction from 3000 mg BID to 2400mg BID still lands patients at an effective PD range.
- FDA requested that Inspirna explore safety and efficacy in ~15 patients at each dose prior to making a final decision, which will be discussed at a clinical pharmacology meeting in 1H 2024.

Phase 2 RCT started in Europe – current trial design

- Efficacy endpoints: ORR primary, PFS secondary
- Assumptions: 70 randomized, 40 PFS events; $\alpha=0.05$ 1-sided; 80% power for ORR, 48% power for PFS
- Interim analysis of ORR once 30 patients are evaluable for response
- Interim analysis of PFS once 20 PFS events are observed
- ORR MSD between groups $>20\%$ to yield 1-sided $p<0.05$
- PFS MSD $HR<0.59$ to yield 1-sided $p<0.05$

