

PROSPER: A first in human study of FMC-376, a KRAS G12C equipotent ON+OFF inhibitor in patients with advanced KRAS G12C mutant solid tumors, with a focus on NSCLC

M.V. Negrao¹, J. Luo², A. Parsonson³, P. Munster⁴, A. Spira⁵, L. Sun⁶, K. Papadopoulos⁷, P. Neupane⁸, L. Bazhenova⁹, D. Mahadevan¹⁰, B. Shim¹¹, B.C. Cho¹², S. Singh¹³, L. Warburton¹⁴, K. Webster¹⁵, A. Weitzman¹⁵

1. The University of Texas – MD Anderson Cancer Center, Houston, TX, USA; 2. Dana Farber Cancer Institute, Boston, USA;
3. Macquarie University, New South Wales, Australia; 4. UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA;
5. NEXT Oncology – Virginia, Fairfax, USA; 6. University Of Pennsylvania, Philadelphia, USA; 7. The START Center for Cancer Care, San Antonio, USA; 8. University of Kansas Medical Center, Kansas City, USA; 9. Moores Cancer Center - UC San Diego Health, La Jolla, USA; 10. University of Texas Health Science Center, San Antonio, USA;
11. The Catholic University of Korea - St. Vincent's Hospital, Suwon, Republic of Korea;
12. Severance Hospital Yonsei University Health System, Seoul, Republic of Korea;
13. Northwest Cancer Centers, Indiana, USA; 14. Linear Clinical Research, Nedlands West, Australia; 15. Frontier Medicines, Boston, USA

25October2026

Disclosures

M.V. Negrao

Research grants to institution: Lilly, Mirati, BMS, Novartis, Alaunos, AstraZeneca, Pfizer, Genentech, Navire, Frontier, Verastem

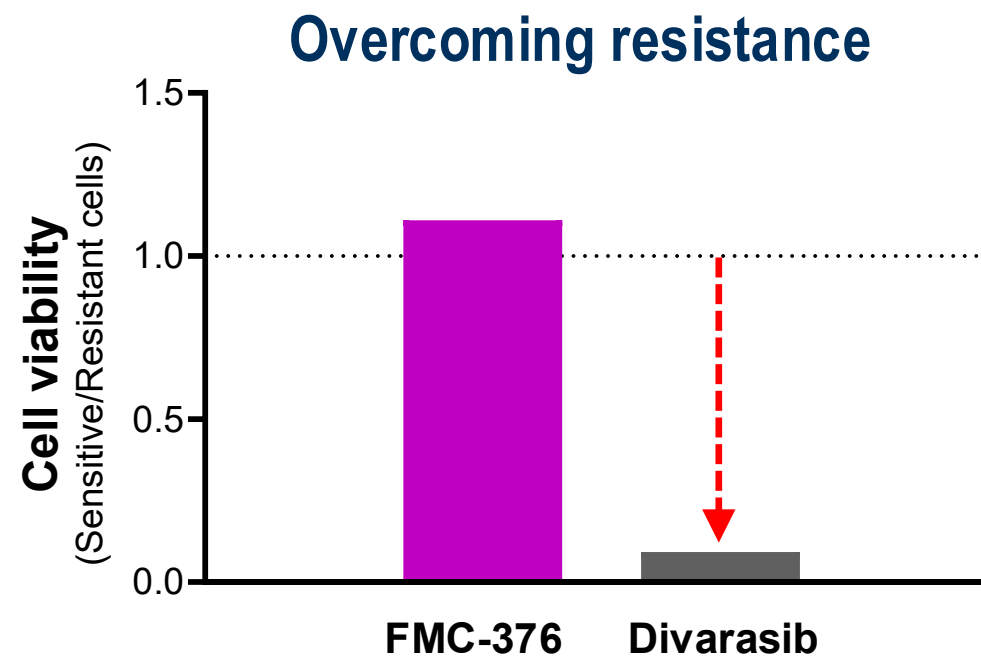
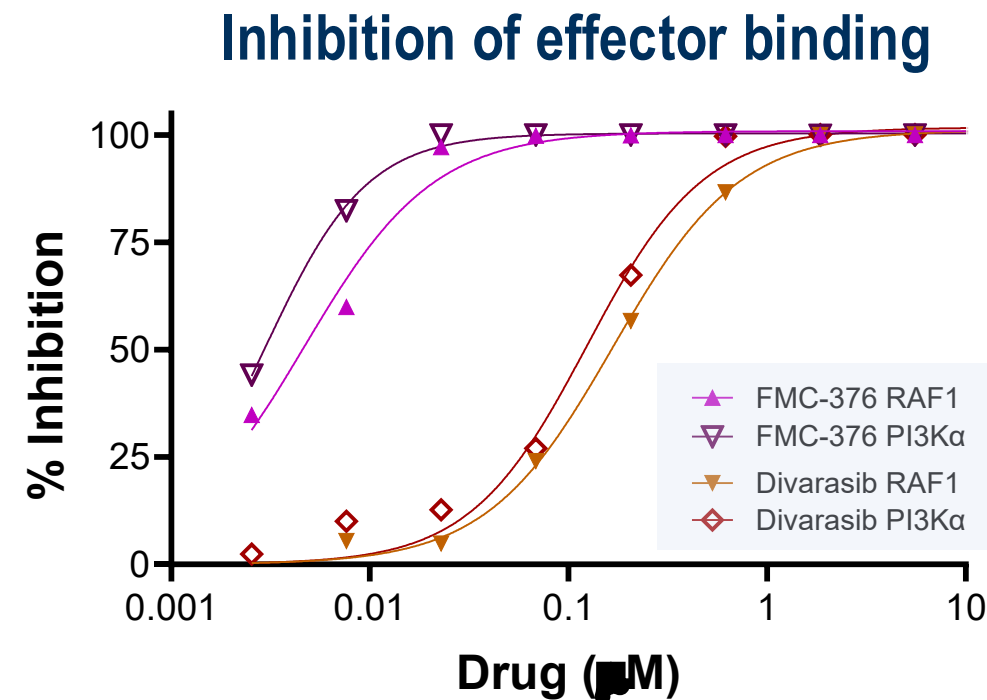
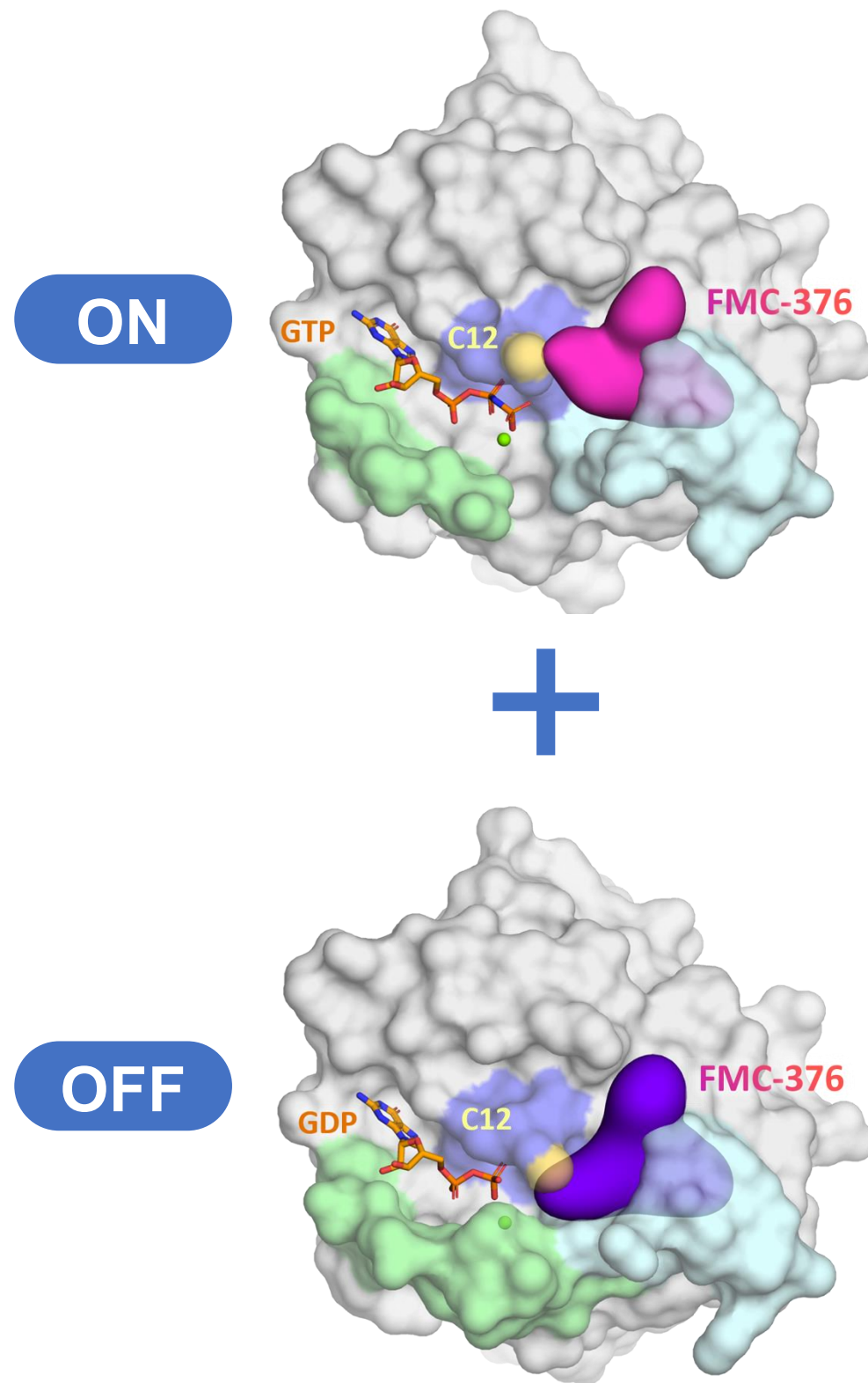
Consulting fees / advisory boards: Genentech, Sanofi, Pfizer, AstraZeneca, BMS, Guardant, Lilly, Verastem

Travel support: Ideology, DAVA Oncology, Targeted Oncology, Frontier

Speaker bureaus: OncLive, Ideology, BIO Brasil, DAVA Oncology, Targeted Oncology

Medical writing support: ApotheCom and Ashfield Healthcare

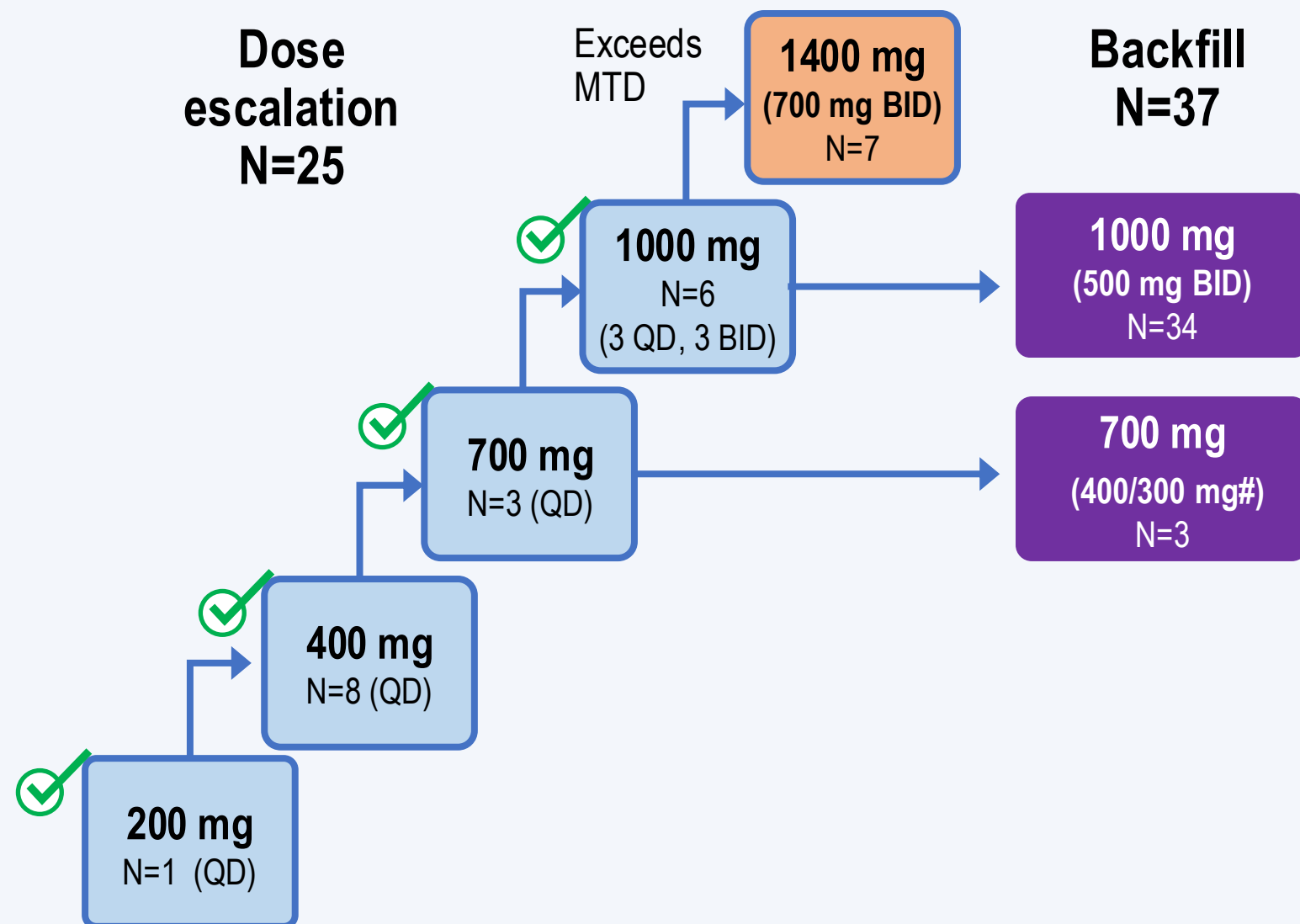
FMC-376 is designed to be a novel oral equipotent ON+OFF KRAS G12C inhibitor



- FMC-376 is **>10-fold more potent** than divarasilb
- **Effective in settings of resistance** to other KRAS inhibitors
- **ON+OFF inhibition MOA** delivered activity in drug resistant settings
- Potential to produce improved response rates and duration of response in KRAS G12C-mutant solid tumors

Study design: Dose escalation to NSCLC expansion

Total enrolled*: 62 patients (500 mg BID - N=37)



- Study initially included all-comers with KRAS G12C mutation
- **Current focus: NSCLC** - patients naïve to or with prior treatment with OFF-state KRAS G12Ci
- **500 mg BID expanded to backfill:** achieves desired target coverage

	Total (N=62)
Gender	Male: 58% (36); Female: 42% (26)
Age in years, median (range)	64 (37-83)
ECOG performance status	0: 35% (22); 1: 65% (40)
Tumor type, % (n)	NSCLC: 68% (42) ; CRC: 22% (14); Pancreatic: 5% (3); Other: 5% (3)
NSCLC patients	N=42
Treated at 500 mg BID	29
Response evaluable [^]	22
Prior chemo-IO in metastatic setting	18
Prior chemo-IO subgroup	N=18
Prior lines – median (range)	3 (1-7)
Prior treatment with OFF-state G12Ci	50% (9)
≥1 known resistance conferring alteration ^{&}	83% (15)

*Patients enrolled as of April 30, 2026 # 700 mg split as 400 mg AM and 300 mg PM
Note: Preliminary data from the ongoing PROSPER trial; subject to change with additional follow-up.

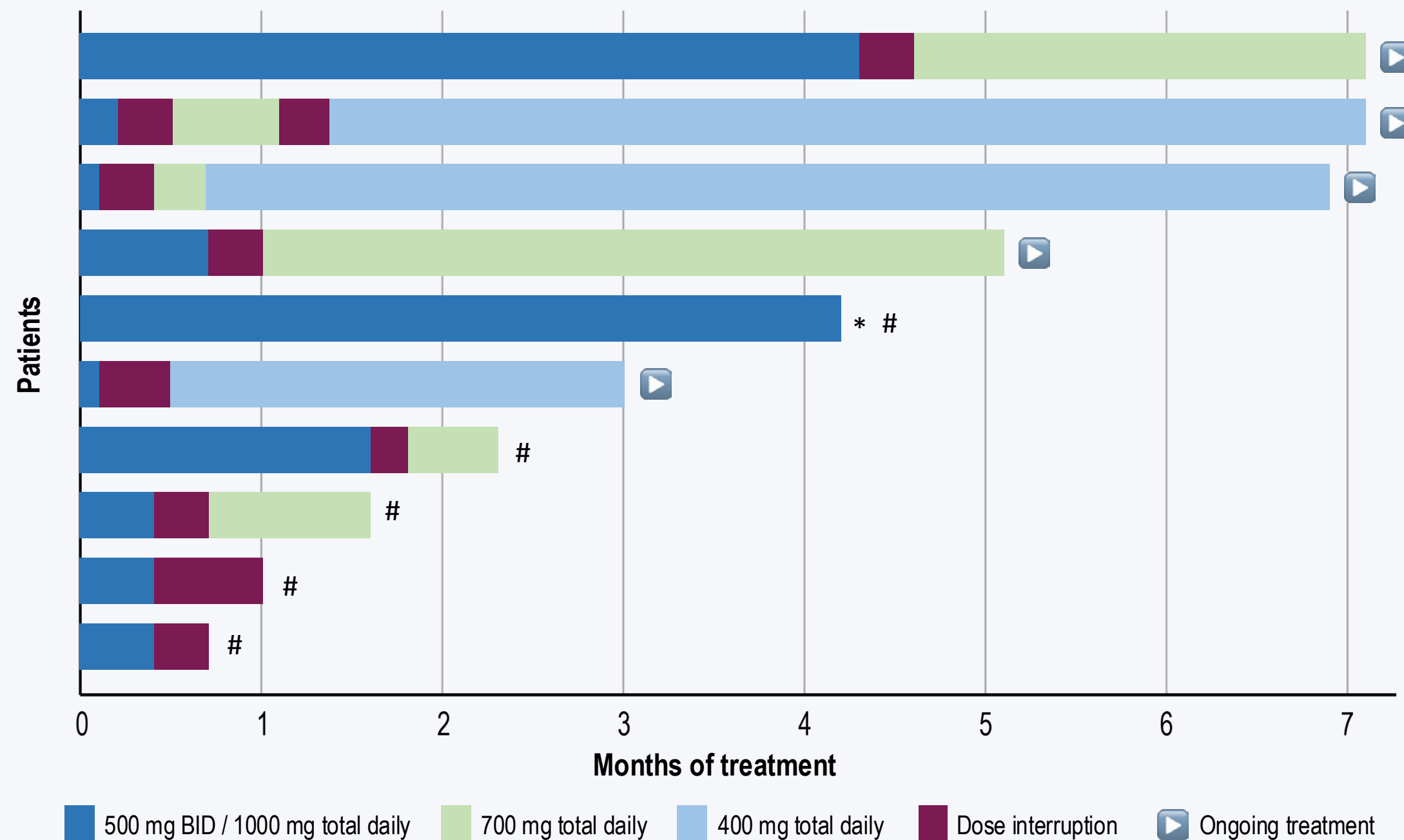
[^] at least one post-baseline scan
& conferring alterations (KRAS.G12C_amp, ATM, BRAF, CDKN2A/CDKN2B, KEAP1, PIK3CA, SMARCA4, and STK11) known to be resistant to OFF-state inhibitors.

FMC-376 was well tolerated with low rates of GI toxicity and hepatic transaminase elevations

Any TRAE*, n (%)	All doses (n=62)		500 mg BID (n=37)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Gastrointestinal				
Nausea	22 (36%)	0	12 (32%)	0
Diarrhea	10 (16%)	0	7 (19%)	0
Vomiting	10 (16%)	0	4 (11%)	0
Constitutional symptoms				
Fatigue	9 (15%)	1 (2%)	4 (11%)	0
Hepatic				
AST increased (without CPK increase)	1 (2%)	0	0	0
ALT increased (without CPK increase)	3 (5%)	0	1 (3%)**	0
Musculoskeletal				
CPK increased	24 (39%)	11 (18%)	18 (49%)	10 (27%)
AST increased (with CPK increase)	7 (11%)	1 (2%)	6 (16%)	1 (3%)
ALT increased (with CPK increase)	6 (10%)	2 (3%)	5 (14%)	2 (5%)

- No Grade 3/4 GI toxicity
- No Grade 3/4 hepatic transaminase elevations
- Most common TRAE: CPK increased (39% overall)
- CPK elevation dose limiting at >500 mg BID
- No discontinuations at 500 mg BID or below

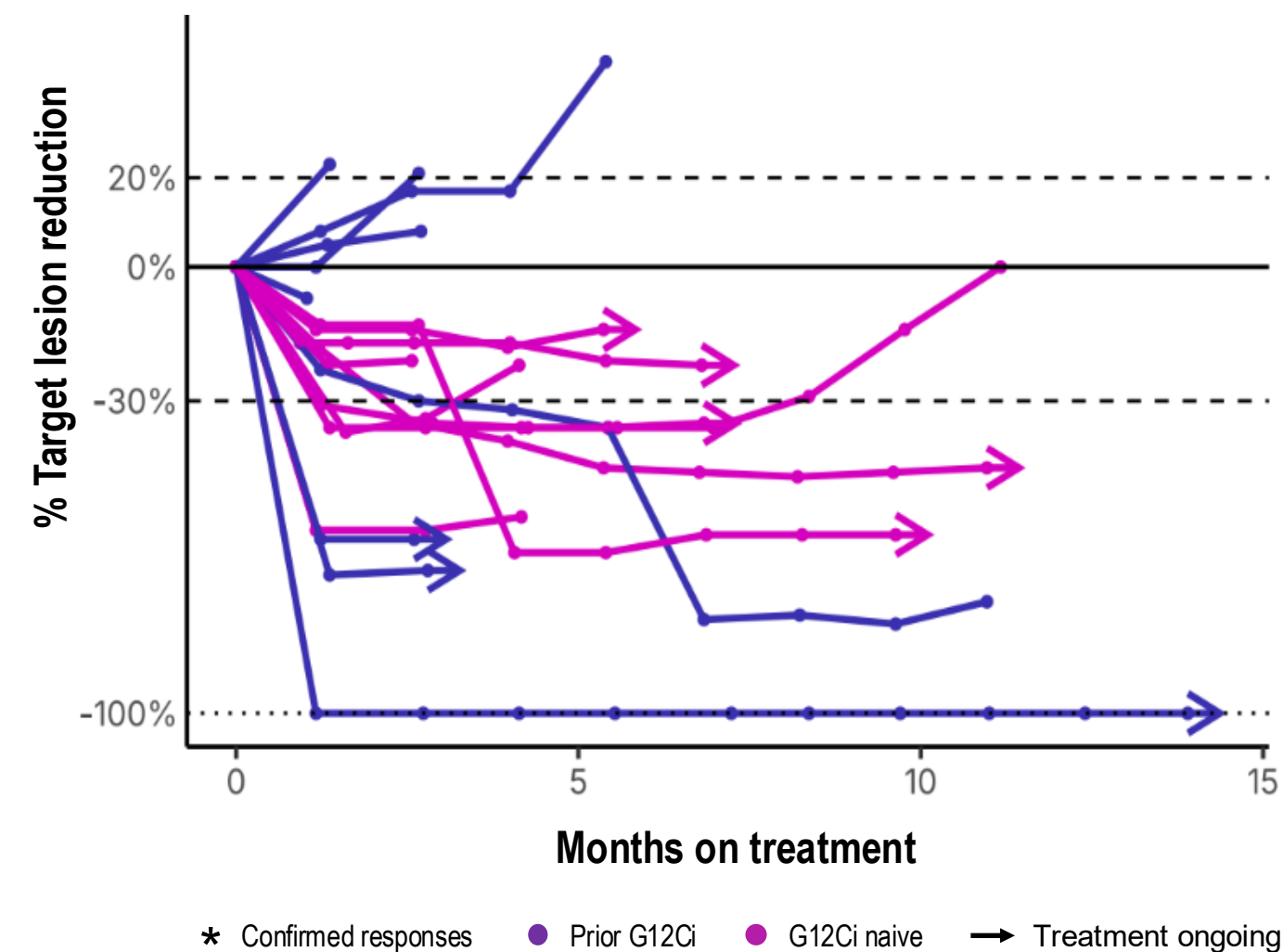
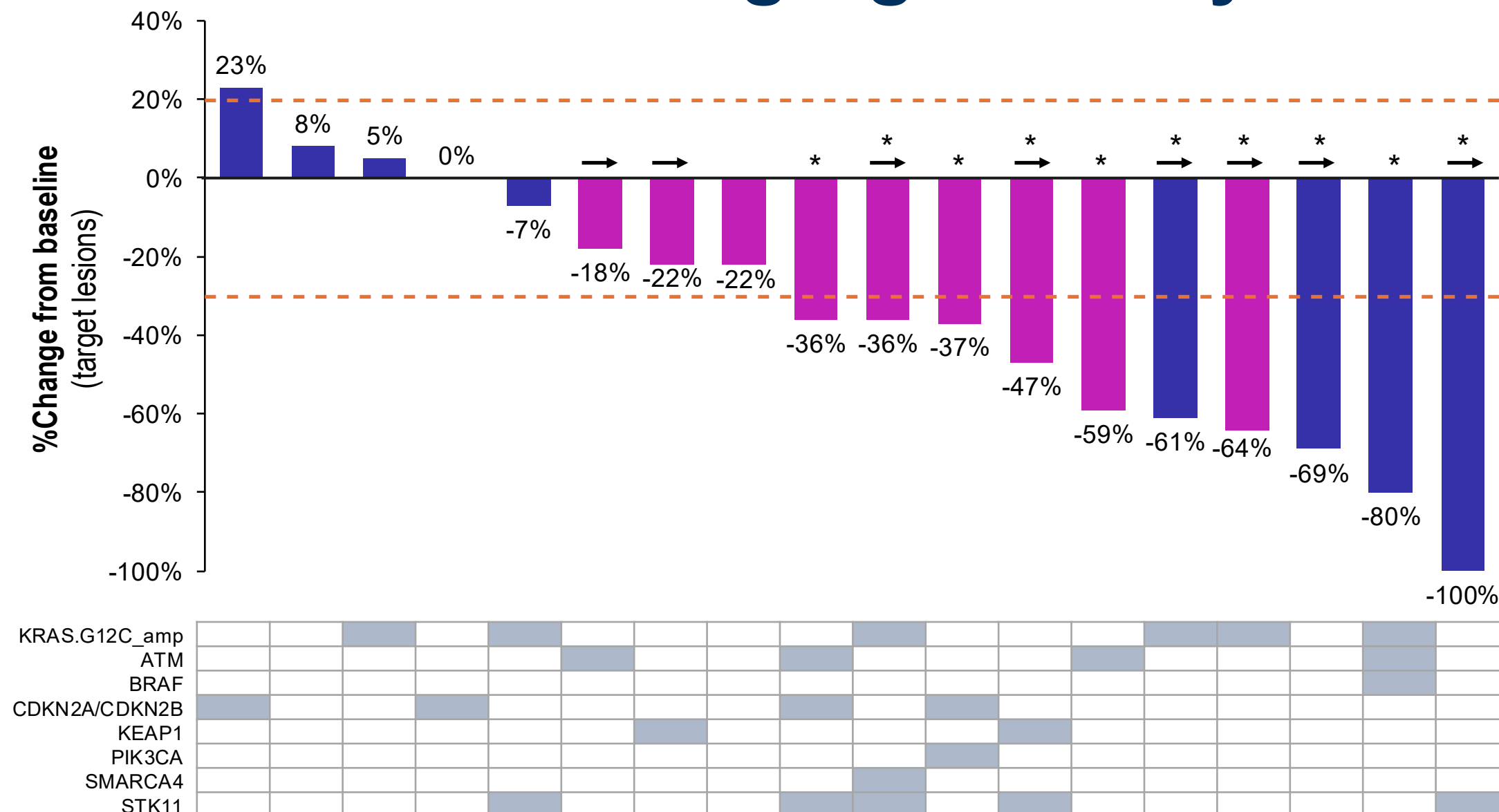
Grade 3/4 CPK events at 500 mg BID occurred early and are manageable (n=10)



- Majority of CPK events occur early
- Largely asymptomatic
- Monitorable and rapidly reversible
- Successfully managed with brief interruption and dose reduction
- No discontinuations due to CPK events

*CPK event occurred after stopping FMC-376
Discontinued due to PD

Preliminary FMC-376 data demonstrated encouraging efficacy in NSCLC



- Confirmed ORR: 56% (10/18); G12Ci pre-treated: 44% (4/9); G12Ci naïve: 67% (6/9)
- Median DOR (Range): 7.5 months (2.7+, 13.7+); 6/10 patients still on treatment

- DCR: 89% (16/18); G12Ci-pretreated: 78% (7/9); G12Ci naïve: 100% (9/9)
- 9 of 10 responders carried ≥ 1 co-alterations associated with clinical resistance to KRAS inhibitors including KRAS G12C amplifications

Conclusions

FMC-376 showed promising efficacy in NSCLC patients – confirmed ORR 56%

- G12Ci-pretreated: ORR 44% / G12Ci-naïve: ORR 67%

FMC-376 was well tolerated with a favorable safety profile

- Low rates of GI and hepatic toxicity
- CPK increase is predictable, monitorable, and reversible with no treatment discontinuations

Clinical development of FMC-376 is ongoing

- Dose escalation cohort of combination with pembrolizumab in NSCLC - no hepatic AEs to date*
- Randomized Phase 1b dose ranging cohort in OFF-state G12Ci naïve and pre-treated NSCLC
- First-line NSCLC monotherapy cohort

**Thank you to the patients and their caregivers, site investigators,
and site staff who made this study possible**

PROSPER is sponsored by Frontier Medicines Corporation

