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# Camonsertib (cam) monotherapy in patients (pts) with advanced cancers harboring ATM loss-of-function (LoF)

**Benedito A. Carneiro**

Legorreta Cancer Center, Division of Hematology/Oncology, The Warren Alpert Medical School, Brown University, Providence, RI, USA

Benedito A. Carneiro, Ezra Rosen, Elisa Fontana, Elizabeth K. Lee, Niharika B. Mettu, Stephanie Lheureux, Ruth Plummer, Ian M. Silverman, Joseph D. Schonhoft, Julia Yang, Gabriela Gomez, Kezhen Fei, Danielle Ulanet, Paul Basciano, Timothy A. Yap, Martin Højgaard

*[1]Legorreta Cancer Center at Brown University and Lifespan Cancer Institute, Division of Hematology/Oncology, The Warren Alpert Medical School, Brown University, Providence, RI, USA; [2]Early Drug Development and Breast Medicine Services, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Sarah Cannon Research Institute UK, London, UK; [4]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [5]Duke University, Medical Oncology, Durham, NC, USA; [6]Princess Margaret Cancer Centre, Toronto, ON, Canada;[7]Sir Bobby Robson Cancer Trials Research Centre, Freeman Hospital, Newcastle upon Tyne, UK [8]Repare Therapeutics, Cambridge, MA, USA; [9]Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [10]Rigshospitalet, Department of Oncology, Copenhagen, Denmark*

# DECLARATION OF INTERESTS

**Benedito A. Carneiro**

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# Camonsertib (cam) ATRi evaluation in TRESR study: ATM subset

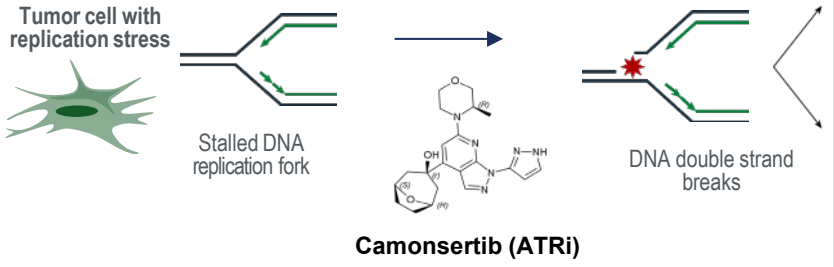
**Cam is a highly selective ATRi synthetically lethal with ATM kinase loss-of-function (LoF)**

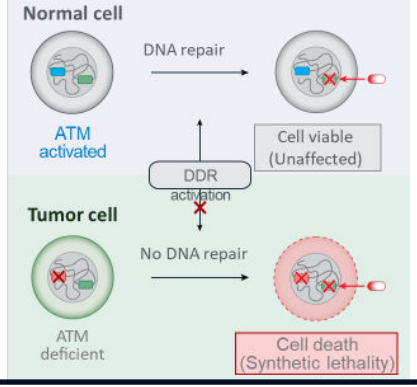
**Safety, efficacy, and dose optimization of cam was previously reported [1,2]**

- Cam monotherapy (>100 mg/day) resulted in durable clinical benefit across multiple tumor types and genomic alterations [1]
- 160 mg QD 3d on/4d off (3/4), 2w on/1w off (2/1w) selected as optimized regimen [2]
  - the dominant Gr3+ toxicities were hematologic: Gr3/4 anemia 11/0%, Gr3/4 neutropenia 11/3.7% [2]

**Here we characterize the efficacy of cam monotherapy in patients with tumors harboring ATM LoF**

**Mechanism of ATM-ATR synthetic lethality**




**Inhibition of ATR:**

- Compromises the stabilization of DNA replication forks
- Leads to formation of double stranded DNA breaks
- In synthetic lethal screens is synthetic lethal with ATM loss

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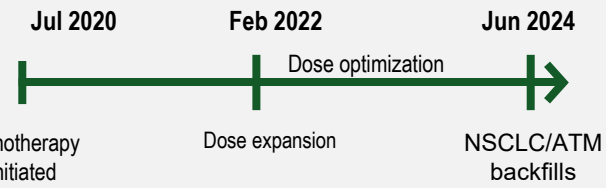
*1. Yap et al. Nat Med. 2023;29(6):1400-11. 2. Fontana et al. JNCI 2024;116(9):1439-49.*

*ATM, ataxia telangiectasia-mutated; ATRi, ataxia telangiectasia and Rad3-related kinase inhibitor; cam, camonsertib; DDR, DNA damage response; gr, grade; LoF, loss-of-function; QD, once daily.*

# TRESR: Study design and ATM analysis cohort

## Design and objectives

### Camonsertib monotherapy




Tumors with deleterious somatic or germline gene alterations

*ATM, ATRIP, BRCA1/2, CDK12, CHTF8, FZR1, MRE11, NBN, PALB2, RAD51B/C/D, RNASEH2A/B, RAD17, REV3L, RAD50, SETD2*

**Efficacy Endpoints:**

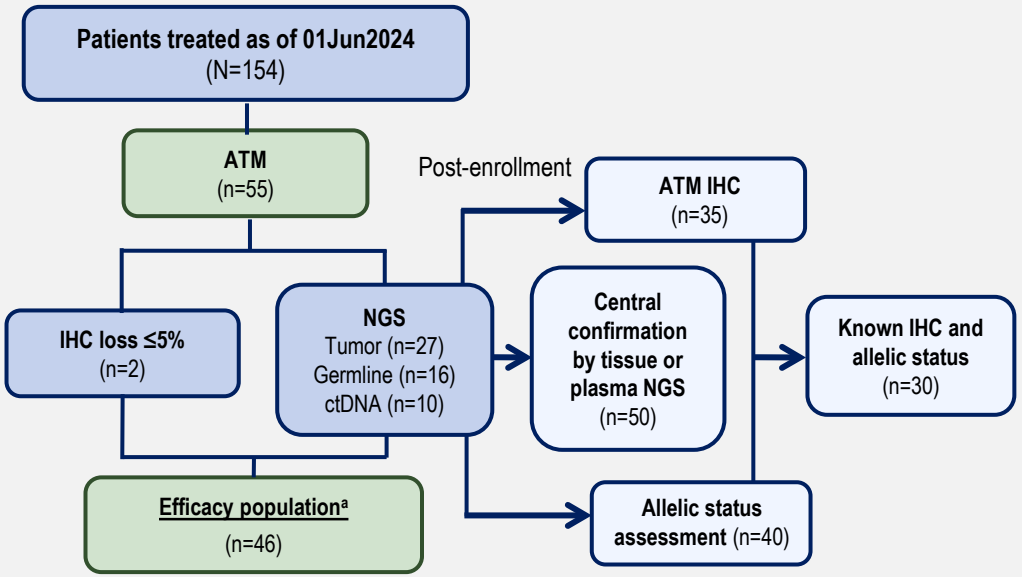
**Overall response:** RECIST v1.1, PSA, or CA-125 response

**Clinical benefit**: Response or treatment duration of ≥16 weeks without progression

**Progression Free Survival (PFS)**; Investigator assessed

**Molecular response rate (MRR):** ≥ 50% decline in mVAF

## ATM subset (n=55)




[a]*Patients that received cam doses >100 mg/day with ≥1 post-baseline tumor assessment.*

*ATM, ataxia telangiectasia-mutated; CA-125, cancer antigen-125; cam, camonsertib; ctDNA, circulating tumor DNA; IHC, immunohistochemistry; MRR, molecular response rate; mVAF, mean variant allele frequency; NSCLC, non-small cell lung cancer; NGS, next-generation sequencing; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression free survival; prelim, preliminary; PSA, prostate specific antigen; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose.*

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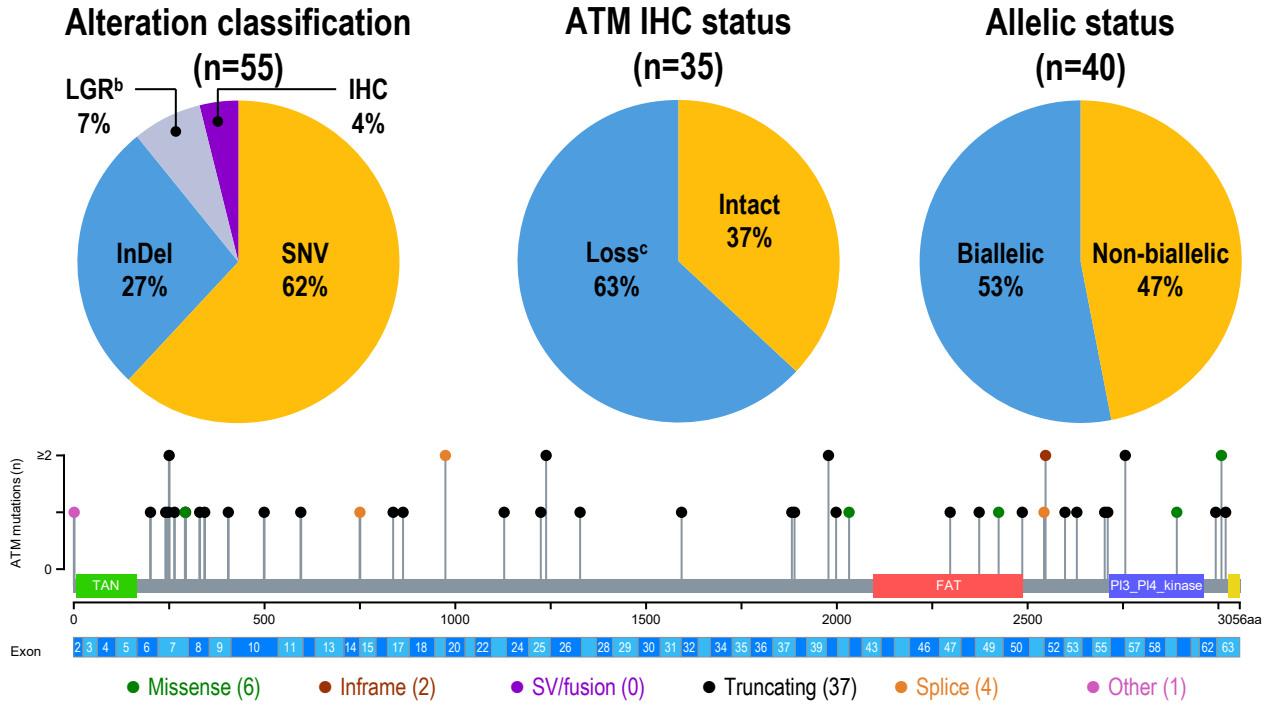
# ATM cohort: Heavily pretreated and heterogenous

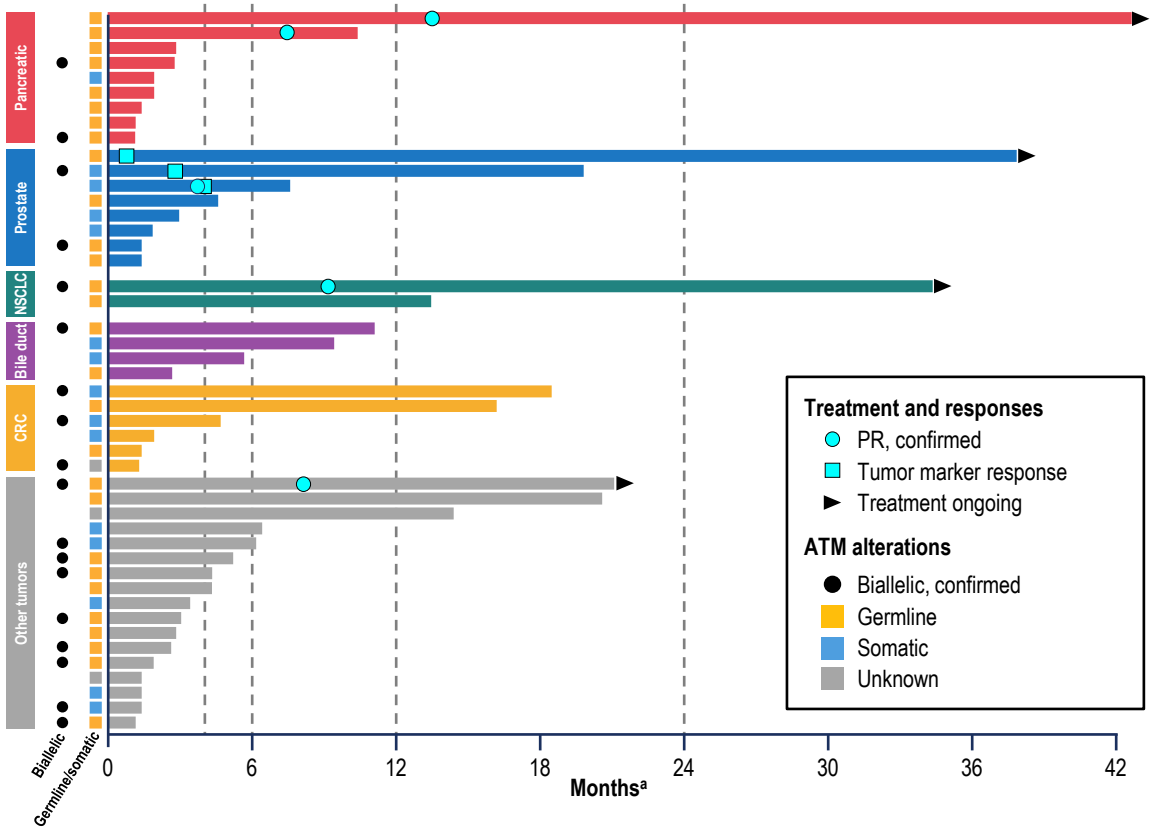
| Parameter | 55 patients |
|---|---|
| **Age (years)** median (IQR) | 66 (57–71) |
| **Sex, n (%)** | |
| Female | 27 (49) |
| **ECOG PS, n (%)** | |
| 0 | 28 (51) |
| 1 | 27 (49) |
| **Prior system therapies** | |
| ≥ 3, n (%) | 33 (60) |
| PARPi, n (%) | 6 (11) |
| Platinum, n (%) | 39 (71) |
| **Tumor types, n (%)** | |
| Pancreatic | 10 (18) |
| Prostate | 10 (18) |
| Colorectal | 7 (13) |
| Bile duct | 6 (11) |
| Other[a] | 22 (40) |
| **Mutation origin, n (%)** | |
| Germline | 32 (58) |
| Somatic | 19 (35) |
| Unknown | 4 (7) |
| **Central confirmation, n/N (%)** | |
| Either tissue or ctDNA | 48/50 (96) |
| Tissue only | 42/48 (88) |
| ctDNA only | 31/37 (84) |
| **Study follow-up**, months | 20+ |




- Complex genomic alteration landscape in the ATM cohort

[a]*Ampullary (n=4), breast (n=4), NSCLC (n=3), soft tissue sarcoma (n=2), endometrial (n=1), esophageal (n=1), gastrointestinal (n=1), head and neck (n=1), liver (n=1), melanoma (n=1), appendiceal (n=1), malignant pleural mesothelioma (n=1), stomach (n=1).* [b]*LGRs include deletions and structural variants.* [c]*ATM IHC loss defined as ≤5% of positive tumor cells. ATM, ataxia telangiectasia-mutated; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IHC, immunohistochemistry; IQR, interquartile range; LGR, large genomic rearrangement; PARPi, poly (ADP-ribose) polymerase inhibitor; SNV, single nucleotide variant; SV, structural variant.*

# Durable, often late, responses in tumors with ATM LoF




**Responses in efficacy evaluable patients[b] (n=46):**

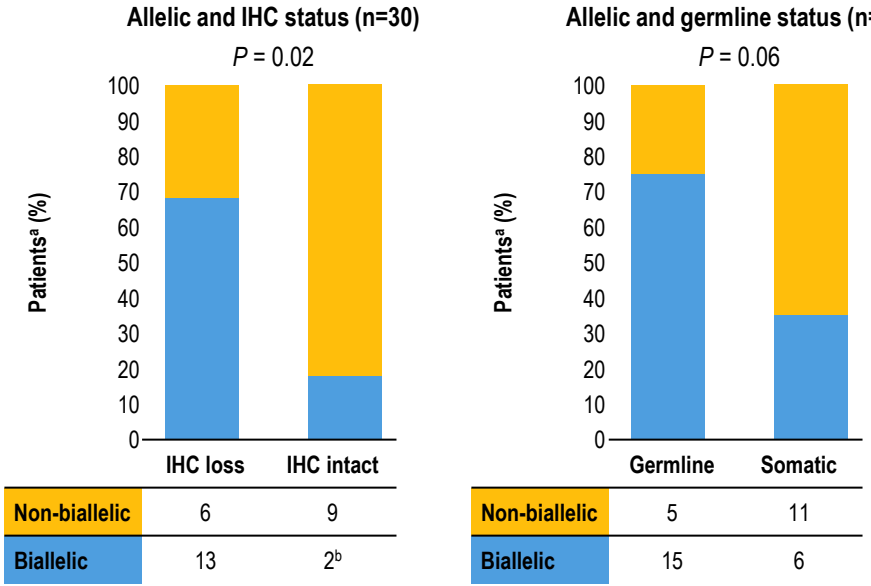
- Response Rate[c]: 15%
- Median time to response: 8.3 mo
- Response durations: up to 23+ mo
  - 4 patients remain on treatment

**Impressive disease control in this Ph1 population:**

- CBR[d]: 48%
- PFS 6 mo: 46%
- DOT **>12 mo: 22%**
- Tumor types with responses or DOT >6 mo
  - Bile duct (2/4), GI[e] (5/10), NSCLC (2/2), pancreatic (2/9), and prostate cancers (3/8)

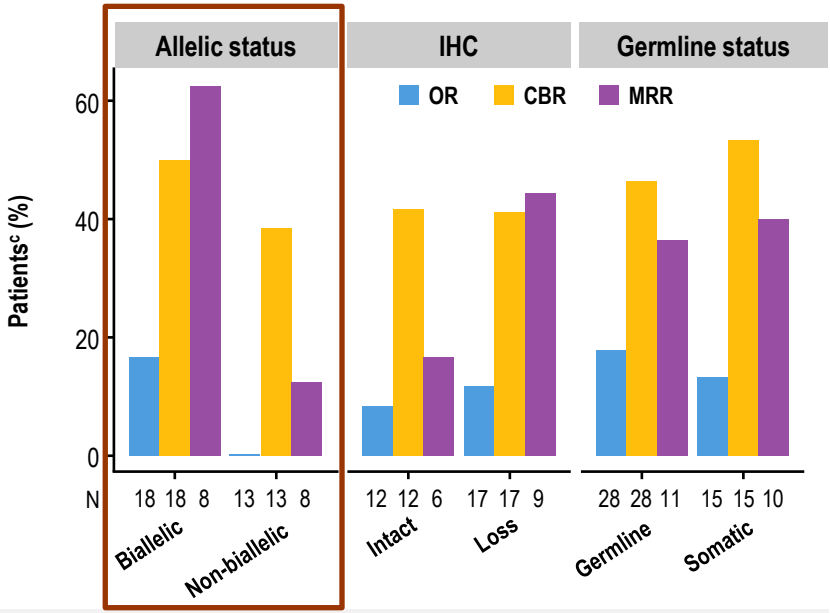
*[a]1 month = 4 weeks. [b]Efficacy evaluable patients (n=46) received cam doses >100 mg/day with ≥1 post-baseline tumor assessment as of 12 June 2024. [c]OR was defined as RECIST v1.1, PSA, or CA-125 response. [d]CBR was defined as response or treatment duration of ≥16w w/o progression. [e]GI cancers were colorectal (n=6), esophageal (n=1), gastrointestinal (n=1), appendiceal (n=1), and stomach (n=1). ATM, ataxia telangiectasia-mutated; CA-125, cancer antigen-125; CBR, clinical benefit rate; CRC, colorectal cancer; DOT, duration of treatment; LoF, loss-of-function; mo, months; NSCLC, non-small cell lung cancer; OR, overall response; PFS, progression free survival; PR, partial response; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.*

# ATM molecular status and correlation with clinical activity










Tumors with ATM IHC loss or germline alterations are enriched for biallelic LoF

No responses observed in patients (n=13) with tumors with confirmed non-biallelic ATM LoF

Selection for patients most likely to respond is critical to optimize benefit

*[a]All patients harboring tumors with ATM alterations (n=55). [b]1 patient with advanced CRPC had a pathogenic missense mutation in ATM (p.R3008H), which is not expected to result in loss of ATM protein expression and 1 patient had borderline ATM IHC H-score of 10 (loss defined as ≤ 5). [c]Efficacy evaluable patients (n=46) received cam doses >100mg/day with ≥1 post-baseline tumor assessment. CBR was defined as response or treatment duration of ≥16w w/o progression. OR was defined as RECIST v1.1, PSA, or CA-125 response. MRR was defined as ≥ 50% decline in mVAF. ATM, ataxia telangiectasia-mutated; cam, camonsertib; CA-125, cancer antigen-125; CBR, clinical benefit rate; CRPC, castrate resistant prostate cancer; LoF, loss of function; mVAF, mean variant allele frequency. OR, overall response; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumours.*

# Case study: Prolonged response in patient with NSCLC and g*ATM* mutation

**Case description:** 68-yo female, NSCLC, germline *ATM* p.R2598*, biallelic ATM LoF (and IHC loss), *KRAS* G12V and *TP53* WT

**Disease History:**

- Metastatic disease diagnosed June 2015
- Prior therapies:
  - 1) pemetrexed + carboplatin, 2) nivolumab, 3) docetaxel, and 4) gemcitabine
  - Multiple courses of radiotherapy

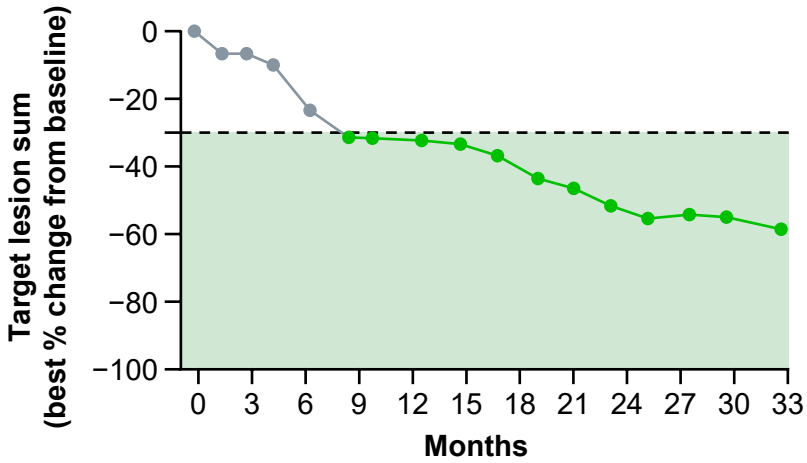
**Camonsertib initiated Oct 2021:** 160mg QD 3/4, 2/1w

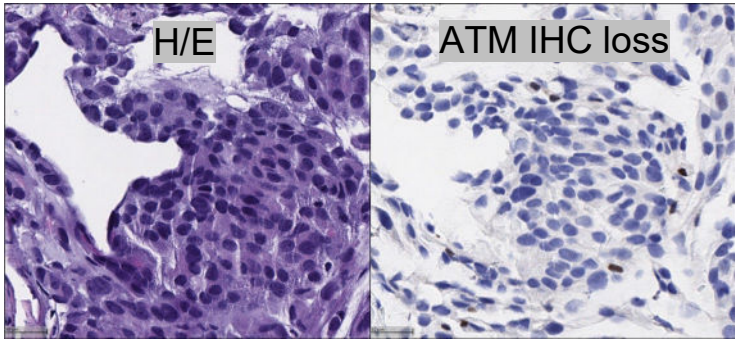
- 2 early dose reductions due to neutropenia/anemia: on 100 mg QD 3/4, 2/1w since 4mo. with excellent tolerability

**Duration of treatment:** 2.7 years, on-going

**Response:**

- Confirmed PR at 8.5 months, with continued TL decline (best % change from baseline: –55%)
  - Target lesions: right iliac lymph node, lungs, and pelvic bone
- ctDNA: KRAS G12V at baseline; undetectable Day 35

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*Data as of 12 July 2024.*
*2/1w, 2 weeks on/1 week off; 3/4, 3 days on/4 days off; ATM, ataxia telangiectasia-mutated; gATM, germline ATM; H/E, hematoxylin and eosin; IHC, immunohistochemistry; LN, lymph node; MR, molecular response; NSCLC, non-small cell lung cancer; PR, partial response; QD, once daily; TL, target lesion; yo, year old.*

# Conclusions

- Camonsertib monotherapy resulted in durable, often late (median 8.5 mo), responses and notable stable disease in multiple ATM-altered advanced cancers
  - Patients with GI cancers (n=10) had prolonged treatment durations (>6 mo: 50%, >12 mo: 40%)
  - Durable response and long treatment duration (>1 yr and almost 3 yrs) in patients with ATM NSCLC supports the ongoing evaluation of camonsertib in ATM LoF NSCLC
- Molecular selection for *ATM* biallelic LoF, enriched in germline and ATM IHC loss, represents a promising approach to identify patients most likely to benefit from ATRi monotherapy

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