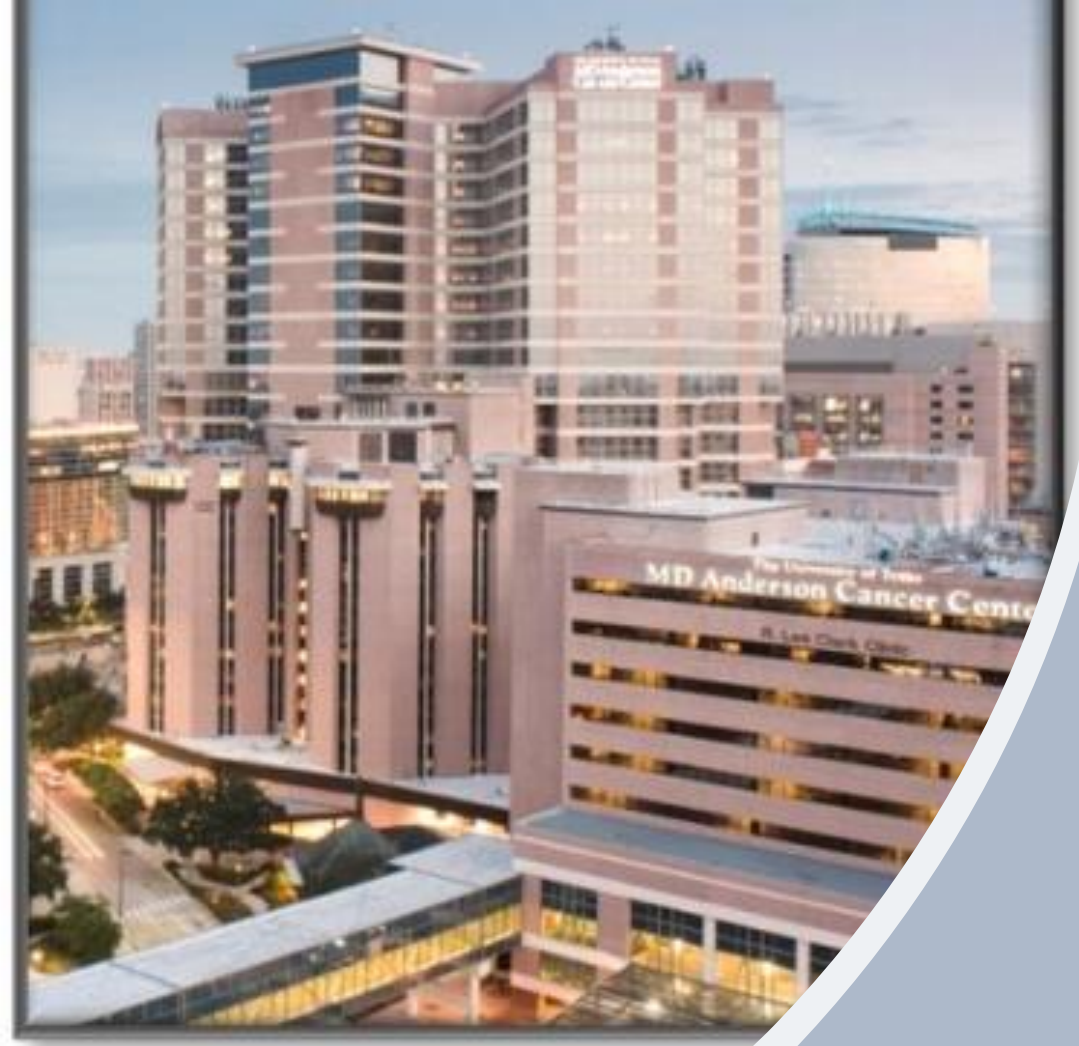


# “Pirtobrutinib in Mantle Cell Lymphoma”

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UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI MEDICINA SPECIALISTICA
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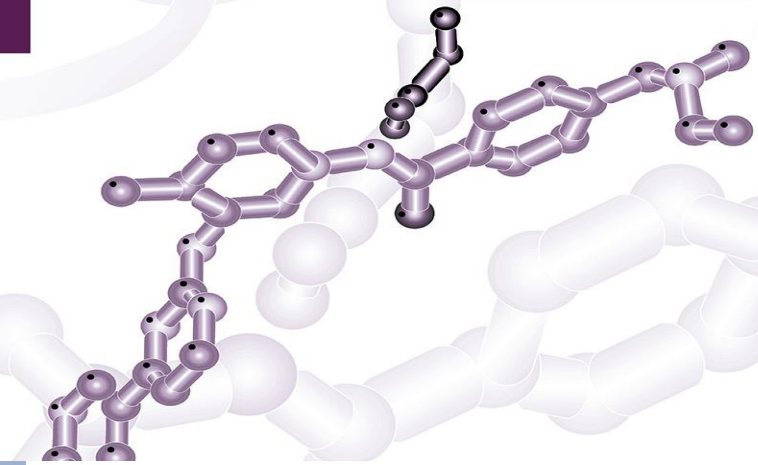

# New Drugs in Hematology

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## Disclosures of Michael Wang

Consultancy: AbbVie, AstraZeneca, BeiGene, BioInvent, CSTone, Deciphera, DTRM Biopharma (Cayman) Limited, Epizyme, Genentech, InnoCare, Janssen, Juno Therapeutics, Kite Pharma, Lilly, Loxo Oncology, Miltenyi Biomedicine GmbH, Oncternal, Pepromene Bio, Pharmacyclics, VelosBio

Research: Acerta Pharma, AstraZeneca, BeiGene, BioInvent, Celgene, Genmab, Genentech, Innocare, Janssen, Juno Therapeutics, Kite Pharma, Lilly, Loxo Oncology, Molecular Templates, Oncternal, Pharmacyclics, VelosBio, Vincerx

Honoraria: Acerta Pharma, Anticancer Association, AstraZeneca, BeiGene, BGICS, BioInvent, CAHON , Clinical Care Options, Dava Oncology, Eastern Virginia Medical School, Epizyme, Hebei Cancer Prevention Federation, Imedex, Janssen, Kite Pharma, Leukemia & Lymphoma Society, LLC TS Oncology, Medscape, Meeting Minds Experts, Miltenyi Biomedicine GmbH, First Hospital Zhejiang University, Moffit Cancer Center, Mumbai Hematology Group, OMI, OncLive, Pharmacyclics, Physicians Education Resources (PER), Practice Point Communications (PPC)

# Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Previously Treated Mantle Cell Lymphoma: Updated Results from the Phase 1/2 BRUIN Study

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# Outcomes in MCL are Extremely Poor Following Covalent BTK Inhibitor Progression

- Covalent BTK inhibitor resistance in MCL and other lymphomas is incompletely understood[1-10]
- BTK C481-mutations are uncommon; bypass alterations & epigenetic changes implicated in some patients[7]
- *Overall survival* following covalent BTK inhibitor therapy is poor[3,4,11]

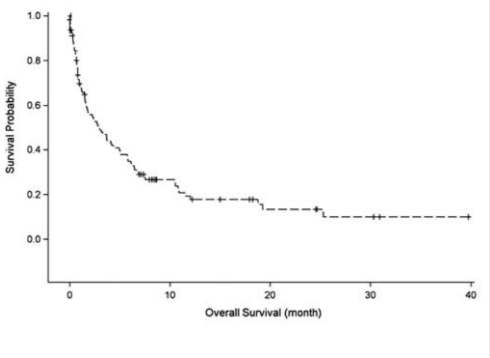



**Fig 1[4]**

Analysis of n = 114 global patients
Median OS = 2.9 months

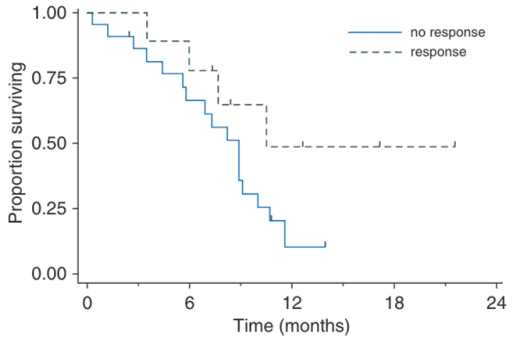



**Fig 2[3]**

Analysis of n = 31 US patients
Median OS = 8.4 months

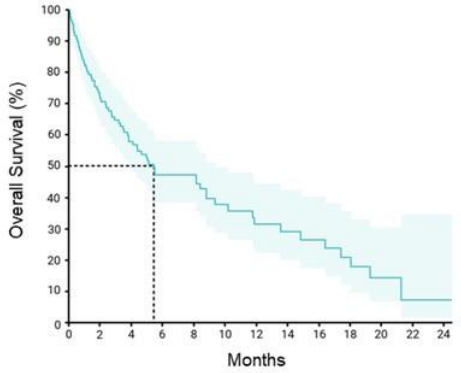



**Fig 3[11]**

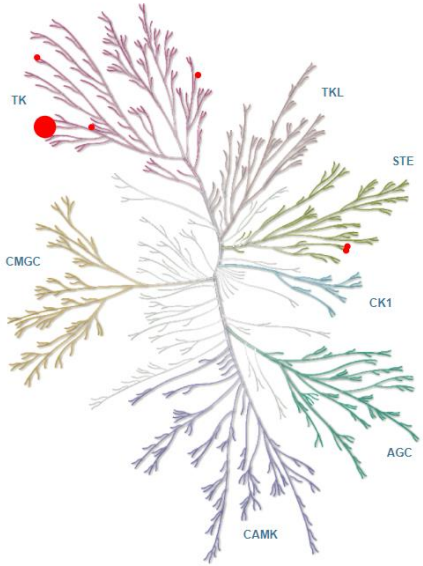
Analysis of n = 108 Japanese patients
Median OS = 5.46 months

[1]Hershkovitz-Rokah et al. *Br J. Haemtol.* 2018;181:306-19. [2]Wang et al. *N. Engl. J. Med.* 2013;369:507-16. [3]Cheah et al. *Ann. Oncol*. 2015;26:1175-79. [4]Martin et al. *Blood*. 2016;127:1559-63. [5]Dreyling et al. *Lancet*. 2016;387:770-8. [6]Epperla et al. *Hematol. Oncol.* 2017;35:528-35. [7]Ondrisova L and Mraz M, *Front. Oncol*. 2020;10. [8]O'Brien et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:648-57. [9]Byrd et al. *Blood*. 2019;130(Suppl 1):4326. [10]Tam et al. *Blood*. 2020;136:2038-50. [11]Rai et al. *Clin Lymphoma Myeloma Leuk*. 2021; 21(Suppl 1):S407-S408.

# Pirtobrutinib is a Highly Potent and Selective Non-Covalent (Reversible) BTK Inhibitor

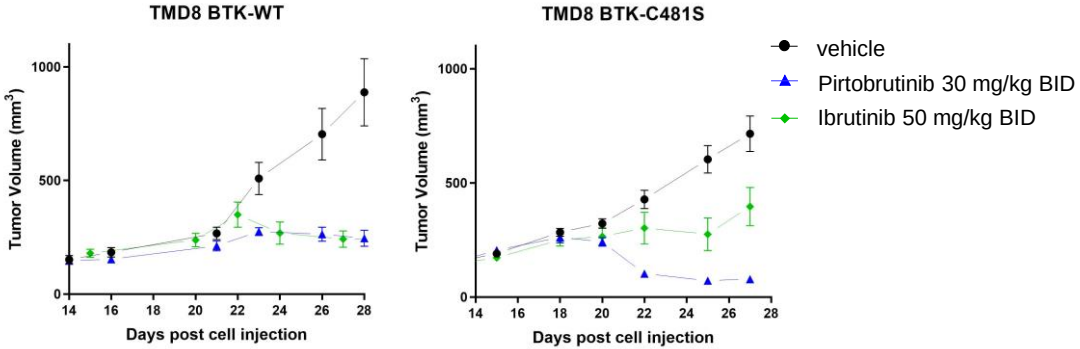
## Kinome selectivity[1]

Highly selective for BTK




## Xenograft models

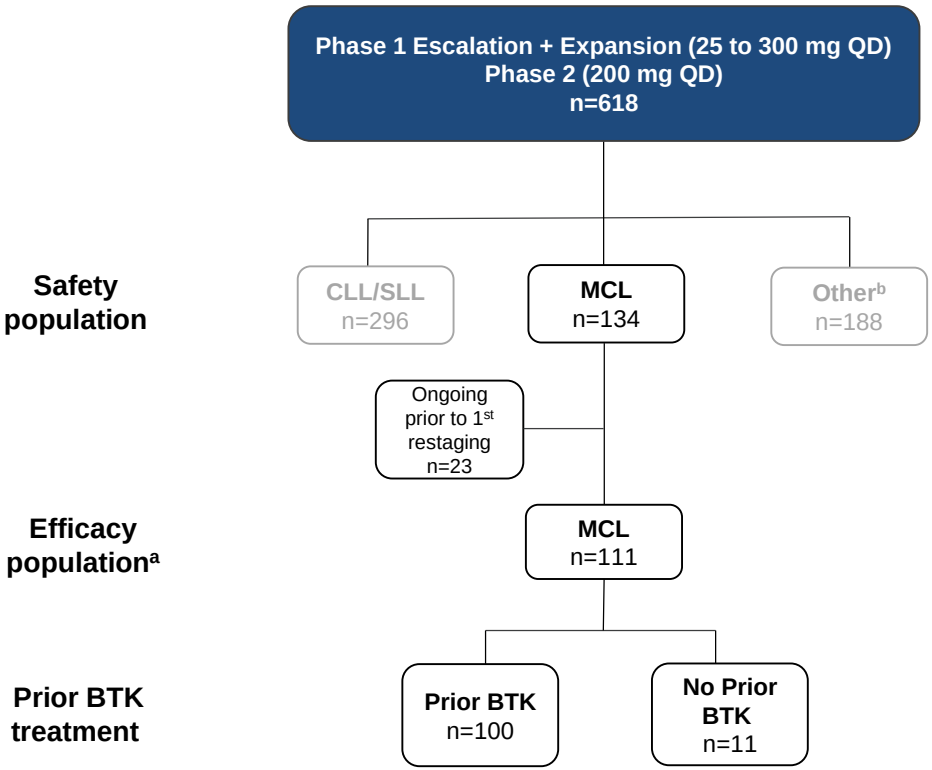
*In vivo* activity similarly efficacious as ibrutinib in WT; superior in C481S




- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays[2]
- >300-fold selectivity for BTK vs 370 other kinases[2]
- Due to reversible binding mode, BTK inhibition not impacted by intrinsic rate of BTK turnover[2]
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[2]

BID, twice-daily; BTK, Bruton tyrosine kinase. [1]Mato et al, *Lancet*, 2021:397:892-901. [2]Brandhuber BJ, et al. *Clin. Lymphoma Myeloma Leuk*. 2018.18:S216. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

# Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment




**Phase 1 3+3 design**

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

**Eligibility**

- Age ≥18
- ECOG 0-2
- CLL or other B-cell NHL
- Active disease and in need of treatment
- Previously treated

**Key endpoints**

- Safety/tolerability
- Determine MTD & recommended phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR & DoR based on disease criteria (Lugano, iwCLL, IWWM)

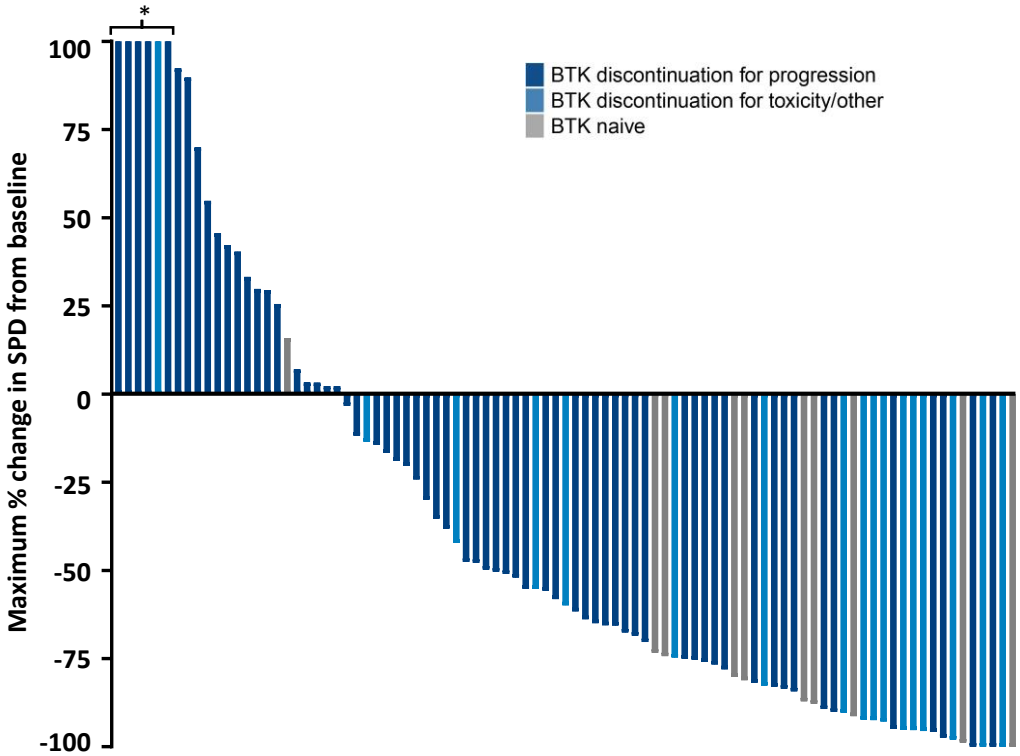
Data cutoff date of 16 July 2021. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]Other includes DLBCL, WM, FL, MZL, Richter's transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

# Patient Characteristics

| Characteristics | MCL (n=134) |
|---|---|
| Median age (range), years | 70 (46, 88) |
| Female / Male, n (%) | 30 (22) / 104 (78) |
| Histology | |
| Classic | 108 (81) |
| Pleomorphic/Blastoid | 26 (19) |
| ECOG PS, n (%) | |
| 0 | 82 (61) |
| 1 | 50 (37) |
| 2 | 2 (2) |
| Median number prior lines of systemic therapy (range) | 3 (1, 9) |
| Prior therapy, n (%) | |
| BTK inhibitor | 120 (90) |
| Anti-CD20 antibody | 130 (97) |
| Chemotherapy | 122 (91) |
| Stem cell transplant[b] | 30 (22) |
| IMiD | 23 (17) |
| BCL2 inhibitor | 20 (15) |
| Proteasome inhibitor | 17 (13) |
| CAR-T | 7 (5) |
| PI3K inhibitor | 5 (4) |
| Reason discontinued prior BTKi[a] | |
| Progressive disease | 100 (83) |
| Toxicity/Other | 20 (17) |

Data cutoff date of 16 July 2021. Total % may be different than the sum of the individual components due to rounding. [a]Calculated as percent of patients who received prior BTK inhibitor. [b]3 patients had both auto and allo stem cell transplants.

# Pirtobrutinib Efficacy in Mantle Cell Lymphoma



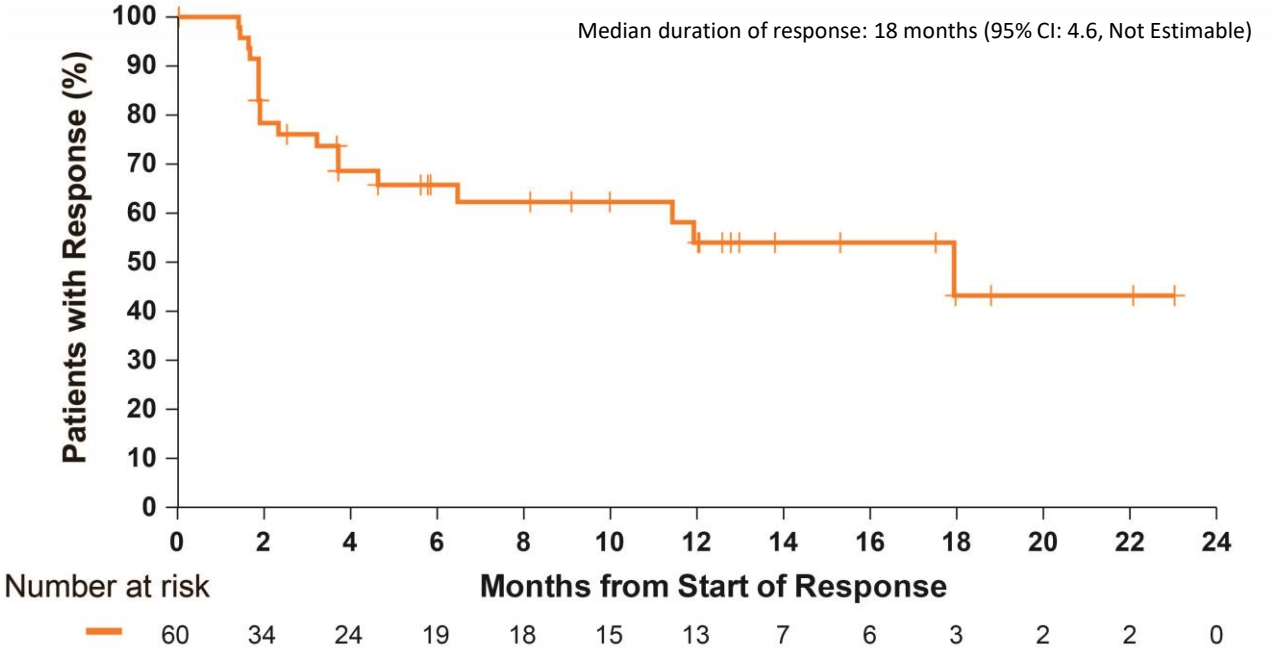

| BTK Pre-Treated MCL Patients[a] | n=100 |
|---|---|
| **Overall Response Rate[b], % (95% CI)** | **51% (41-61)** |
| **Best Response** | |
| CR, n (%) | 25 (25) |
| PR, n (%) | 26 (26) |
| SD, n (%) | 16 (16) |
| **BTK Naive MCL Patients[a]** | **n=11** |
| **Overall Response Rate[b], % (95% CI)** | **82% (48-98)** |
| **Best Response** | |
| CR, n (%) | 2 (18) |
| PR, n (%) | 7 (64) |
| SD, n (%) | 1 (9) |

Efficacy also seen in patients with prior:

- Stem cell transplant (n=28): ORR 64% (95% CI: 44-81)
- CAR-T therapy (n=6): ORR 50% (95% CI: 12-88)

Data cutoff date of 16 July 2021. Data for 20 MCL patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. *Indicates patients with >100% increase in SPD. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR and PR. Response status per Lugano 2014 criteria based on investigator assessment. Total % may be different than the sum of the individual components due to rounding.

# Pirtobrutinib Duration of Response in Mantle Cell Lymphoma




- Median follow-up of 8.2 months (range, 1.0 - 27.9 months) for responding patients
- 60% (36 of 60) of responses are ongoing

# Pirtobrutinib Safety Profile

| | All doses and patients (n=618) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Treatment-emergent AEs, (≥15%), % | | | | | Treatment-related AEs, % | |
| Adverse Event | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Any Grade | Grades 3/4 | Any Grade |
| Fatigue | 13% | 8% | 1% | - | 23% | 1% | 9% |
| Diarrhea | 15% | 4% | <1% | <1% | 19% | <1% | 8% |
| Neutropenia[a] | 1% | 2% | 8% | 6% | 18% | 8% | 10% |
| Contusion | 15% | 2% | - | - | 17% | - | 12% |
| AEs of special interest[b] | | | | | | | |
| Bruising[c] | 20% | 2% | - | - | 22% | - | 15% |
| Rash[d] | 9% | 2% | <1% | - | 11% | <1% | 5% |
| Arthralgia | 8% | 3% | <1% | - | 11% | - | 3% |
| Hemorrhage[e] | 5% | 2% | 1%[g] | - | 8% | <1% | 2% |
| Hypertension | 1% | 4% | 2% | - | 7% | <1% | 2% |
| Atrial fibrillation/flutter[f] | - | 1% | <1% | <1% | 2%[h] | - | <1% |

**No DLTs reported and MTD not reached**

**96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily**

**1% (n=6) of patients permanently discontinued due to treatment-related AEs**

# Conclusions

- Pirtobrutinib demonstrates promising efficacy in MCL patients previously treated with BTK inhibitors, a population with extremely poor outcomes
- Favorable safety and tolerability are consistent with the design of pirtobrutinib as a highly selective and non-covalent (reversible) BTK inhibitor
- A randomized, global, phase 3 trial comparing pirtobrutinib with investigator's choice of covalent BTK inhibitors in BTK naïve relapsed MCL is ongoing (BRUIN MCL-321; NCT04662255)