# Pharmacokinetic Evaluation of MBQ-167, a dual Rac/Cdc42 Inhibitor, in Advanced Breast Cancer Patients

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## Abstract

MBQ-167 is a first-in-class dual inhibitor of Rac and Cdc42 GTPases with potent preclinical anti-metastatic activity and is currently under evaluation in a Phase 1 clinical trial (NCT06075810) in participants with advanced breast cancer. This study aimed to characterize the pharmacokinetic (PK) profile of MBQ-167 and its active metabolite M6 in participants treated with 20 mg, 40 mg, 80 mg, and 120 mg BID doses (cohorts 0, 1, 2, and 3 respectively). Plasma concentration-time data were analyzed from ten participants using non-compartmental analysis. MBQ-167 was rapidly absorbed with a median $T_{max}$ of 1–4 hours and a $C_{max}$ ranging from 139 to 573 ng/mL (20 mg BID), 520 to 843 ng/mL (40 mg BID) and 578 to 688 ng/mL (80 mg BID). The elimination half-life ($t_{½}$) of MBQ-167 was approximately 3–4.5 hours, and the mean residence time (MRT) was <7 hours. Dose-normalized systemic exposure (AUC/D) did not increase proportionally with dose, suggesting a possible reduction in bioavailability at higher doses, potentially due to enterohepatic recycling or saturation of absorption. Importantly, there was no evidence of systemic overexposure or meaningful accumulation (Rac < 2.0) of MBQ-167 or M6, indicating a favorable safety margin. Volume of distribution ($V_{dss}$) exceeded 30L for both compounds, reflecting extensive tissue distribution consistent with their lipophilicity. M6 demonstrated rapid formation and elimination with $t_{½}$ values ranging from 3.1 to 4.4 hours, further supporting efficient metabolic conversion. These findings confirm that MBQ-167 exhibits linear PK at clinically relevant doses with manageable exposure and clearance. The observed pharmacokinetics support continued clinical development and provided essential dosing guidance for Phase 2 trials. Further analyses with additional cohorts will be obtained up to 400 mg BIDM%.

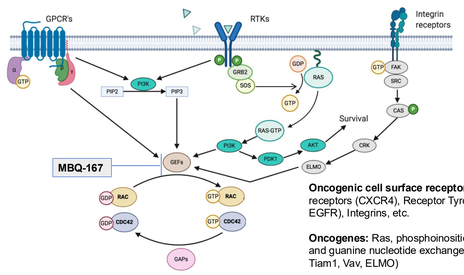
## Introduction

Metastasis remains a major challenge in cancer treatment due to the lack of effective targeted therapies. MBQ-167, a first-in-class dual Rac/Cdc42 inhibitor currently in a Phase 1 clinical trials in advanced breast cancer participants, has demonstrated promising activity in preclinical breast cancer models by reducing tumor burden and preventing metastasis. Rac and Cdc42 do not have to be mutated or overexpressed to regulate cancer progression because they relay signals from multiple oncogenic receptors such as G-protein coupled receptors (GPCR), receptor tyrosine kinases (RTK), and integrin receptors. Cell surface receptor signaling activates oncogenic signaling intermediates such as PI3K and Ras that converge upon guanine nucleotide exchange factors to activate the homologous GTPases Rac and Cdc42 by GTP exchange (**Fig.1**). Activated Rac and Cdc42 regulate cancer cell proliferation, survival, transformation, invasion, and evasion of immune surveillance, leading to metastasis[1].

We developed MBQ-167 as a potent dual Rac and Cdc42 inhibitor that is highly effective at targeting metastatic cancer cells[2]. It reduces both tumor burden and prevents liver and lung metastasis in a triple negative breast cancer (TNBC) mouse model[2,3]. To characterize its metabolism, we conducted a liver microsome assay and M6 was identified as the primary metabolite in dog plasma following oral administration. *In vivo* studies demonstrated that similar to MBQ-167, M6 is an active inhibitor of mammary tumor growth and metastasis in a mouse model (Grafals, et al., in review, Molecular Cancer Therapeutics).

**The objective in this part of the clinical trial is to characterize the pharmacokinetic (PK) profile of MBQ-167 and its metabolite M6 in participants in the ongoing Phase 1 clinical trial.**

**Figure 1**: **MBQ-167 is a first-in-class dual inhibitor of Rac and Cdc42 GTPases with potent preclinical anti-metastatic activity**

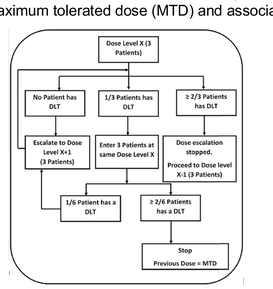



**Oncogenic cell surface receptors:** G protein coupled receptors (CXCR4), Receptor Tyrosine kinases (HER2, EGFR), Integrins, etc.

**Oncogenes:** Ras, phosphoinositide 3-kinase (PI3K), and guanine nucleotide exchange factors (GEFs: Tiam1, Vav, ELMO)

**Figure 2: Open-Label, First-in-Human Trial of Oral MBQ-167, as Single Agent in Participants with Therapy Resistant Advanced Breast Cancer**

NCT06075810: To characterize the therapeutic window of MBQ-167 through identification of the maximum tolerated dose (MTD) and associated dose-limiting toxicities (DLTs).




**MBQ-167 administered for 21 days**

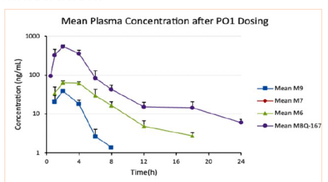
| |
|---|
| **MBQ-167 BID** |
| **Cohort 0: 20mg** |
| **Cohort 1: 40mg** |
| **Cohort 2: 80mg** |
| **Cohort 3: 120mg** |
| **Cohort 4: 180mg** |
| Cohort 5: 240mg |
| Cohort 6: 320mg |
| Cohort 7: 400mg |

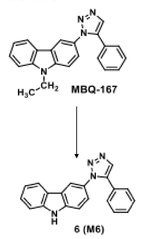
## Participants enrollment information

| Cohort | Participant No. | Participant History | Treatment dates | Outcome |
|---|---|---|---|---|
| **0 (20mg BID)** | 001-102 | 69 yr F, Invasive ductal BC+ DCIS (ER+, PR+, HER2-) Palbo/letrozole | 11/9/23-11/29/23 | no DLT |
| | 001-103 | 63 yr F, Invasive ductal BC+ DCIS (ER+, PR+, HER2-) Lumpectomy, Trodelvy | 11/30/23-12/21/23 | no DLT |
| | 001-107 | 32 yr F, Invasive lobular BC+ (ER-, PR-, HER2-) Brain mass resection, vinorelbine | 05/30/24-06/20/24 | no DLT |
| **Cohort** | **Participant No.** | **Participant History** | **Treatment dates** | **Outcome** |
| **1 (40mg BID)** | 001-109 | 74 yr F, Invasive ductal BC+ (ER+, PR+, HER2-) Local excision, Ibrance | 12/04/24-12/23/24 | no DLT |
| | 002-101 | 48 yr F, Invasive ductal BC+ (ER+, PR+, HER2-) Bilateral mastectomy, Palbociclib, letrozole | 01/08/25-01/28/25 | no DLT |
| | 003-101 | 53 yr F, Invasive lobular BC+ (ER+, PR+, HER2-) Breast resection, bilateral mastectomy, Adriamycin, Cyclophosphamide, Taxol, Letrozole, Fulvestrant, Abemaciclib, Palbociclib | 01/02/25-01/24/25 | no DLT |
| **Cohort** | **Participant No.** | **Participant History** | **Treatment dates** | **Outcome** |
| **2 (80mg BID)** | 003-102 | 76 yr F, Invasive ductal BC+ DCIS (ER 100%, PR 24%, HER2- Ki-67 17%) Lumpectomy with complete axillary lymphadenectomy Radiotherapy, Fulvestrant+ Anastrozole, + Abemaciclib, + Alpelisib, Exemestane + Everolimus | 02/11/25-03/04/25 | no DLT clinical disease progression |
| | 003-103 | 45 yr F, Invasive ductal BC, metastasis to bone, brain, liver, ER/PR +, HER2- Bilateral mastectomies, radiotherapy for brain, liver lesions Doxorubicin+ Cyclophosphamide followed by paclitaxel, Tamoxifen, Anastrozole, Abemaciclib + Fulvestrant, Elacestrant, Enhertu with SBRT | 03/05/25-03/26/25 | no DLT |
| | 003-104 | 72 yr F, Invasive Ductal Breast Cancer T2N0M0-Stage 2; (ER-pos, PR-neg, HER2-neg) metastatic Left breast partial mastectomy Anastrozole, Ribociclib+Fulvestrant, Abemaciclib+ Fulvestrant | 04/23/25-05/14/25 | no DLT |
| **Cohort** | **Participant No.** | **Participant History** | **Treatment dates** | **Outcome** |
| **3 (120mg BID)** | 004-101 | 47 yr F, Invasive Lobular BC (ER/PR+, HER2-), lumpectomy, Nex212, Fulvestrant, Methotrexate | 06/09/25-06/30/25 | no DLT |
| | 003-107 | 66 yr F Invasive Ductal BC (ER/PR+, HER2-), lumpectomy, therapy not reported | 07/02/25-07/23/25 | Fatigue, no DLT |
| | 002-103 | 54 yr F, Invasive Ductal BC ER+, PR-, HER2-, Mastectomy, PF-07248144 | 08/21/25-09/10/25 | no DLT |
| **Cohort** | **Participant No.** | **Participant History** | **Treatment dates** | **Outcome** |
| **4 (180mg BID)** | 003-108 | 64 yr F, Invasive ductal BC+ (ER+, PR+, HER2+) Adjuvant radiation therapy (L) | 09/29/25-10/17/25 | no DLT |
| | 003-109 | 71 yr F, DCIS (ER+, PR+, HER2-) R axillary LND/lumpectomy, bilateral mastectomy, famtraztuzumab | 10/01/25-10/21/25 | no DLT |
| | 003-010 | 73yr, F, Invasive Ductal Breast Cancer (ER+, PR+, HER2-) Neoadjuvant Doxorubicin + Cytoxan, Paclitaxel, R MRM, R axillary LND, XRT, Anastrozole, Imlunestrant, Abemaciclib + Exemestane, Elacestrant | 11/12/25-12/3/25 | On treatment |

## MBQ-167 & M6 metabolite in dogs

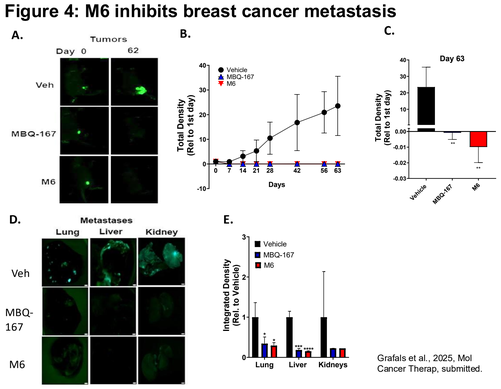
**Figure 3. M6 was identified from dog plasma as the major metabolite of MBQ-167 following oral administration.**




## M6 is an active metabolite of MBQ-167

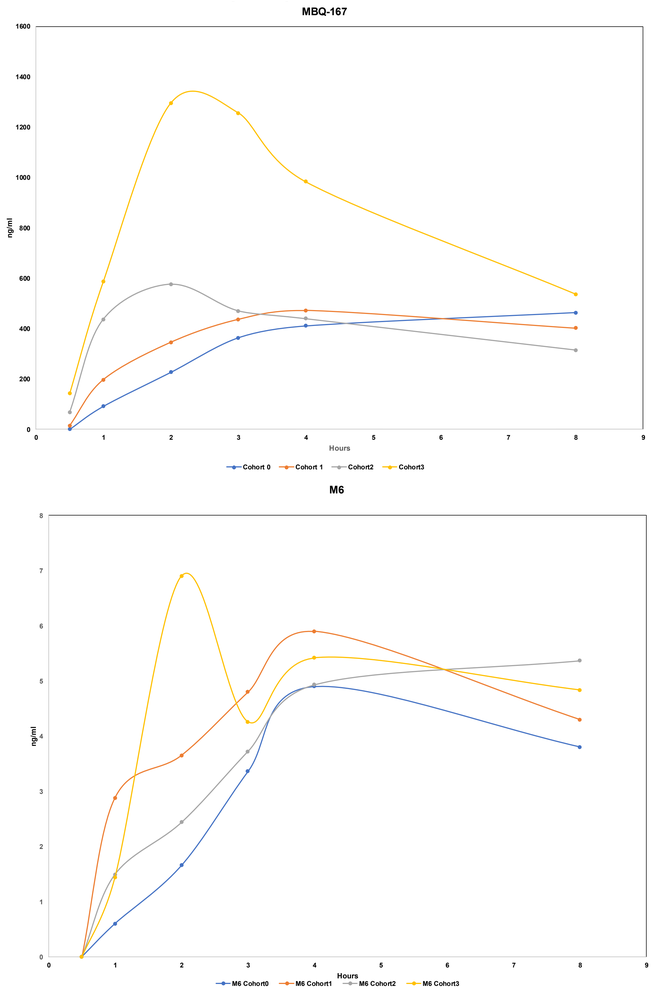
**Figure 4: M6 inhibits breast cancer metastasis**




Grafals et al., 2025, Mol Cancer Therap, submitted.

## Parallel pharmacokinetic profiles of MBQ-167 and M6

**Figure 5. Pharmacokinetic assessment of MBQ-167 and its metabolite M6 after oral administration of MBQ-167 (20mg, 40 mg, 80 mg, and 120 mg BID) in advanced breast cancer participants**

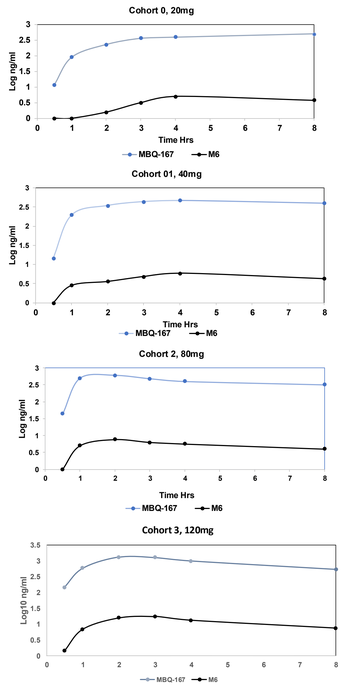



The pharmacokinetics of orally administered MBQ-167 and its active M6 metabolite were evaluated in 10 advanced breast cancer participants from four cohorts (i.e., 20, 40, 80 and 120 mg BID) using the non-compartmental analysis (NCA) approach in Phoenix WinNonlin™ v8.4 (Certara, Pharsight).

**Table 2: Plasma concentration-time data from non-compartmental analysis after oral administration of MBQ-167. M6 is the metabolite.**

| PK Parameters | MBQ-167 40mg | M6 40mg | MBQ-167 80mg | M6 80mg | MBQ-167 120mg | M6 120mg |
|---|---|---|---|---|---|---|
| **$C_{max}$ (ng/ml)** | 670.7 | 12.5 | 633 | 7.5 | 1295 | 17.3 |
| **$T_{max}$ (hr)** | 4.3 | 3.0 | 1.5 | 1.5 | 2.0 | 3.0 |
| **T1/2 (hr)** | 3.7 | 3.1 | 3.8 | 4.2 | 4.6 | 4.7 |
| **AUC all (h*ng/ml)** | 3140.75 | 55.8 | 3665 | 50.73 | 6590.25 | 86.95 |
| **MRT last (h)** | 5.1 | 4.9 | 4.7 | 5 | 7.25 | 8.2 |

**Figure 6: Pharmacokinetics of M6 which parallels MBQ-167 profiles in participants' plasma**




## Conclusions

- MBQ-167 is well tolerated in advanced breast cancer participants without any major adverse event in the dose range between 20 mg BID to 180 mg BID.
- MBQ-167 is steadily absorbed, with peak plasma levels ($T_{max}$) reached between 1-4 hrs. post-dose in cohorts 0-3, as compared to the delayed absorption observed in participants from cohort 0 (20 mg BID), who reached peak levels at 3–4 hrs. post-dose.
- A slightly rapid elimination phase was also noted (elimination half-lives lambda z of approx. 3-5 hours and MRT of 4-8 hrs., except in participant #003-104), which were faster than anticipated when compared to previous results.
- There was no evidence of systemic overexposure to MBQ-167 ($AUC_{0-\infty}$/D between 49 and 173 hr·ng/mL; $AUC_0$-last ranging from 2,105 to 7,372 ng·h/mL), nor any indication of notable drug or metabolite accumulation (Rac < 2), suggesting a low risk of adverse events associated with systemic exposure.
- MBQ-167 is predicted to be effective at higher doses, given its relatively short elimination half-life. At the highest dose level analyzed (120 mg BID), PK profiling demonstrated an increase in $C_{max}$ (1,250-1,340 ng/mL) without a corresponding rise in other exposure parameters ($C_{max}$/D: 6.46–11.16 ng/mL/mg; $AUC_{0-last}$/D: 43.15-61.44 ng·h/mL/mg), which were comparable to or lower than those observed in the lower-dose cohorts.
- MBQ-167 exhibits rapid yet dose-dependent systemic clearance (CL/F), unadjusted for bioavailability, nearly doubling from 7.62-9.94 L/hr in the lower-dose cohort to 13.01-20.42 L/hr in the higher-dose cohorts following a two and three-fold increases in dose.
- Both MBQ-167 and its metabolite M6 demonstrated significant distribution beyond the plasma compartment into total body water ($V_{dss}$ >30 L), particularly in the case of M6, indicating substantial tissue uptake.

## References

1. Maldonado, et al. 2020, Targeting Rac and Cdc42 GEFs in metastatic cancer. Front Cell Dev Biol. 8:201.
2. Humphries-Bickley, T. et al. 2017. Characterization of a dual Rac/Cdc42 inhibitor MBQ-167 in metastatic cancer. *Mol Cancer Ther.* 16, 805-818.
3. Cruz-Collazo et al. 2021. Efficacy of Rac and Cdc42 Inhibitor MBQ-167 in Triple-negative Breast Cancer. *Mol Cancer Ther.* 20(12): 2420–2432.

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