The Aurora Kinase A Inhibitor Alisertib Alone or in Combination with Endocrine Therapy for Patients with Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer

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Background

- AURKA plays an integral role in the mitotic cell cycle, regulating spindle assembly, centrosome function, chromosome alignment, and mitotic entry.[1]
- In addition to its mitotic role, activated AURKA has been shown to induce epithelial–mesenchymal transition reprogramming and to contribute to endocrine resistance in ER+ breast cancer models.[2]
- Amplification/overexpression of AURKA is linked to poor prognosis across multiple tumor types, including ER+/HER2− breast cancer.[3–5]
- Alisertib is a selective, reversible, ATP-competitive AURKA inhibitor that has been shown to disrupt spindle formation, leading to mitotic defects and cell death.[6] In xenografts, alisertib administration led to antitumor activity across a variety of tumor types.[7]
- Preliminary clinical data with alisertib have shown promising antitumor activity and a manageable safety profile in patients with various cancers, including ER+/HER2– MBC.[8–11]

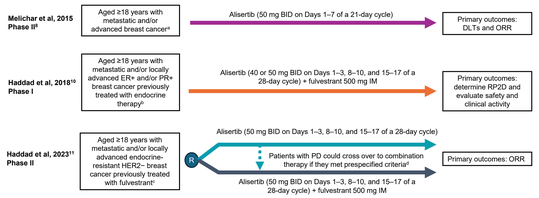
Objective

- To better characterize the role of alisertib in patients with advanced or metastatic ER+/HER2− breast cancer to provide a rationale for future clinical studies.

Methods

- Patient characteristics, efficacy, and safety data were reviewed for three completed studies of alisertib in patients with ER+/HER2– MBC (**Figure 1**):
  - a phase II alisertib monotherapy study (Melichar 2015)[8]
  - a phase I study of alisertib + fulvestrant (Haddad 2018)[10]
  - a phase II study of alisertib ± fulvestrant (TBCRC041; Haddad 2023)[11]
- Data were summarized using descriptive statistics; no formal statistical comparisons were conducted.

Figure 1. Designs of included studies



[a]Study included 249 patients in total, 29 of whom had ER+/HER2- breast cancer.[12]
[b]Study included 10 postmenopausal patients with endocrine-resistant, ER+/HER2- MBC who had been previously treated with endocrine therapy.
[c]Study included 91 postmenopausal women with endocrine-resistant, ER+/HER2− MBC who had been previously treated with fulvestrant.
[d]Arm 1 patients experiencing PD could cross over to arm 2 if (1) ER was 10% or greater positive in preregistration or PD tumor tissue; (2) recovery from toxic effects to grade 0 to 1; (3) adequate blood cell counts and chemistry results; and (4) treatment initiated within 35 days of PD.

Results

- A total of 129 patients with HR+/HER2- metastatic breast cancer were enrolled and evaluable for efficacy and/or safety in the three clinical studies (**Table 1**):
  - all patients had MBC and had received prior endocrine therapy and chemotherapy; all patients in TBCRC 041 also received a prior CDK4/6i.
- A summary of efficacy is shown in **Table 2** and **Figures 2, 3, and 4.**
- A summary of safety is shown in **Table 3**:
  - the most common grade 3/4 AEs across studies were hematologic AEs (neutropenia, leukopenia, and anemia), and fatigue.

Efficacy and safety outcomes

Table 1. Patient characteristics

	Phase II Alisertib monotherapy Melichar et al, 2015[8]	Phase I Alisertib + fulvestrant Haddad et al, 2018[10]	Phase II, TBCRC041 Alisertib ± fulvestrant Haddad et al, 2023[11]
No. of patients	26[a]	9	91
Regimen	Alisertib (50 mg BID on Days 1–7 of a 21-day cycle)	Alisertib (40 or 50 mg BID on Days 1–3, 8–10, and 15–17 of a 28-day cycle) + fulvestrant	**Arm1:** Alisertib 50 mg BID[b] **Arm 2:** Alisertib 50 mg BID[b] + fulvestrant
Allowable prior lines of therapy for MBC	Unlimited endocrine lines and ≤4 chemotherapy regimens	≥1 prior endocrine line and ≤2 chemotherapy regimens	Unlimited endocrine lines (fulvestrant required) and ≤2 chemotherapy regimens
Prior systemic therapy for MBC	100% had ≥3 prior systemic therapies	100% prior endocrine and 67% prior chemotherapy	100% prior endocrine; 48% and 69% prior chemotherapy in arms 1 and 2, respectively
Prior fulvestrant	62%	67%	**Arm 1:** 98% **Arm 2:** 100%
Prior CDK4/6i	0%[b]	0%	100%

[a]Efficacy-evaluable patients; 3 patients included in the safety population were not evaluable for efficacy. [b]Dose schedule per prior phase I study (twice daily on Days 1–3, 8–10, and 15–17 of a 28-day cycle).

Table 2. Summary of efficacy

	Phase II Alisertib monotherapy Melichar et al, 2015[8]	Phase I Alisertib + fulvestrant Haddad et al, 2018[10]	Phase II, TBCRC041 Alisertib ± fulvestrant Haddad et al, 2023[11]	
No. of patients	26[a]	9	91	
Clinical efficacy	**ORR:** 23% **DOR:** 4.2 months **6-month CBR:**[b] 54% **mPFS:** 7.9 months (95% CI, 4.2–12.2)	2 of 3 patients with measurable disease had a **partial response** lasting 11.1 and 25.9 months, respectively **6-month CBR:**[b] 78% (95% CI, 40.0–87.2) **mPFS:** 12.4 months (95% CI, 5.3–not met)	**Arm 1** **ORR:** 20% (95% CI, 11–32) **DOR:** 15.1 months **24-week CBR:**[b] 41% (95% CI, 29–55) **mPFS:** 5.6 months (95% CI, 3.9–10.0)	**Arm 2** **ORR:** 20% (95% CI, 11–32%) **DOR:** 8.5 months **24-week CBR:**[a] 29% (95% CI, 18–42%) **mPFS:** 5.4 months (95% CI, 3.9–7.8)

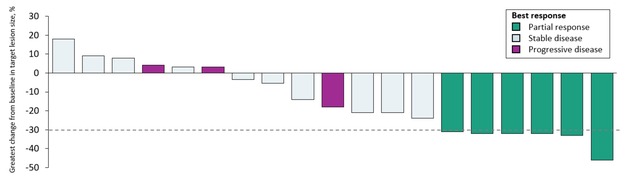
[a]Efficacy-evaluable patients. [b]CBR = complete response + partial response + stable disease for ≥6 months,[8,10] or percentage of patients who completed five treatment cycles without PD.[11]

Table 3. Summary of safety

	Phase II Alisertib monotherapy Melichar et al, 2015[8]	Phase I Alisertib + fulvestrant Haddad et al, 2018[12]	Phase II, TBCRC041 Alisertib ± fulvestrant Haddad et al, 2023[11]	
No. of patients	29[a]	9	91	
Most common grade 3/4 AEs	Neutropenia, 59% Leukopenia, 38% Stomatitis, 14% Fatigue, 10% Anemia, 10%	Neutropenia, 22% Leukopenia, 22% Lymphopenia, 11% Fatigue, 11%	**Arm 1** Neutropenia, 43% Anemia, 20% Leukopenia, 17%	**Arm 2** Neutropenia, 42% Leukopenia, 31% Lymphopenia, 16% Fatigue, 11%
Discontinuation due to AEs	n=1 (3%)	n=1 (11%)	**Arm 1:** n=2 (4%)	**Arm 2:** n=6 (13%)

[a]Safety-evaluable patients with HR+/HER2- breast cancer. Data on file.[12]

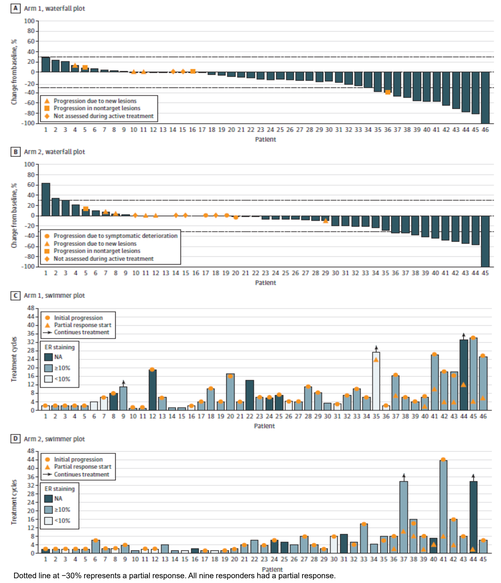
Figure 2. Efficacy outcomes with alisertib monotherapy: change in target lesion size and best response in evaluable patients with HR+/HER2− breast cancer (n=19/26; Melichar et al, 2015)[8]



Dotted line at −30% represents a partial response.

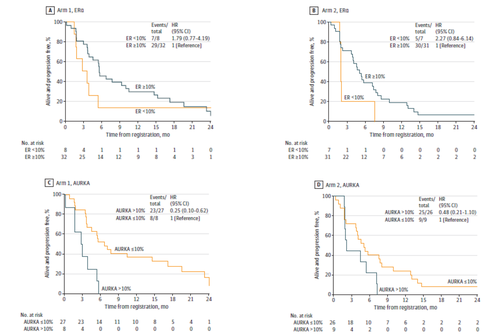
Figure 3. Efficacy outcomes with alisertib ± fulvestrant[11]

A. Best tumor response in arms 1 (a, c) and 2 (b, d)



Dotted line at ~30% represents a partial response. All nine responders had a partial response.

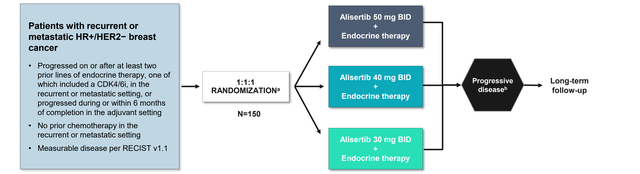
B. PFS by expression of ERα (a, b) and AURKA (c, d) in arms 1 (a, c) and 2 (b, d)



Conclusions

- Alisertib has shown efficacy and safety across multiple clinical studies in patients with ER+/HER2− MBC and could provide a novel option for treating patients following progression on endocrine therapy and a CDK4/6i. These findings provide a strong rationale for further development of alisertib in this patient population. Additionally, biomarker analyses are ongoing.
- The ongoing phase II ALISCA-Breast1 study (NCT06369285) is investigating the optimal dose of alisertib in combination with standard endocrine therapies in this setting (**Figure 4**). A secondary endpoint is to evaluate whether any biomarkers correlate with efficacy.

Figure 4. ALISCA-Breast1 study design



Alisertib BID orally on Days 1–3, 8–10, and 15–17 of every 28-day cycle[c]

Investigator-selected endocrine therapy choices: anastrozole, exemestane, fulvestrant, letrozole, or tamoxifen

[a]Stratified by TTP after initiating CDK4/6i therapy in any setting (<12 months or ≥12 months); presence of visceral disease (defined as liver, lung, brain, kidney, or adrenal metastasis: yes/no).
[b]Other reasons for discontinuation: unacceptable toxicity; withdrawal of consent.
[c]Patients who experienced grade 4 neutropenia (ANC <500/mm^3) or any grade febrile neutropenia during previous treatments in the metastatic setting must receive G-CSF after the Day 17 dose of alisertib of each cycle. Schedule and duration of G-CSF will be per institutional practice.

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Abbreviations

AE, adverse event
ANC, absolute neutrophil count
ATP, adenosine triphosphate
AURKA, Aurora kinase A
BID, twice daily
CBR, clinical benefit rate
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor
CI, confidence interval
DLTs, dose-limiting toxicities
DOR, duration of response
ER+, estrogen receptor-positive
ERα, estrogen receptor alpha
G-CSF, granulocyte colony-stimulating factor
HER2−, human epidermal growth factor receptor 2-negative
HR+, hormone receptor-positive
IM, intramuscularly
MBC, metastatic breast cancer
mo, month
mPFS, median progression-free survival
NA, not available
ORR, objective response rate
PD, progressive disease
PR+, progesterone receptor-positive
RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1
RP2D, recommended phase 2 dose
TTP, time to progression

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