Recent developments and translational aspects in targeted therapy for metastatic breast cancer

Maximilian Marhold, Rupert Bartsch, Christoph Zielinski

ABSTRACT
Biologically distinct subtypes of metastatic breast cancer (MBC) have been defined by multiple efforts in recent years, showing broad heterogeneity at the molecular level of disease. Throughout this endeavour, oncogenic drivers within MBC were identified as potential therapeutic targets. With recent results from clinical trials targeting these well-known cancer-promoting pathways, this review is trying to elucidate as well as summarise current new therapeutic aspects in MBC and shed light on translational aspects within this entity.

INTRODUCTION
The biological heterogeneity of breast cancer (BC) has been defined by various efforts in recent years, taking into account the distinct molecular and histopathological features of these tumours. Luminal-type and basal-like BCs have been shown to be completely different diseases at the molecular level, as well as in terms of the course of the disease, patient prognosis and survival.1 6 While the luminal subtype, characterised by the expression of estrogen and/or progesterone receptors (ER/PR), shows well-known characteristics of adenocarcinoma, basal-like phenotypes exhibit a wider and more continuous spectrum of genomic evolution and have been linked to biological features of other malignancies.3 With recent results from clinical trials targeting well-known cancer-promoting pathways, this review is seeking to elucidate and summarise current new therapeutic aspects in metastatic BC (MBC) and shed light on translational aspects within this entity.

METHODS
Articles from peer-reviewed journals as well as published abstracts were searched for using NCBIs ‘PubMed’ as well as ESMO, ASCO, AACR and SABCS online library databases as of 22 March 2016. Keywords used were ‘metastatic breast cancer’, ‘HER2’, ‘luminal breast cancer’, ‘triple-negative’, ‘translational’, ‘hormone’, ‘metastases’, ‘brain’, ‘bone’ and names of medications as well as gene and protein symbols of therapeutic targets dealt with in this manuscript.

HER2-overexpressing advanced BC
Targeted therapy in MBC consists of approaches where well-established or novel pathways are being targeted with the aim of prolonged disease control.2 8 Besides the ER, targeting HER2 is today regarded as the best established targeted treatment approach in MBC. HER2 is a transmembrane growth factor receptor of the ERBB family; HER2 protein overexpression and/or HER2/neu gene amplification result in an aggressive BC phenotype with high recurrence rates and poor outcome.9 Of note, before the availability of targeted treatment options, median overall survival (OS) in HER2-positive MBC was low at around 20 months.10 Addition of trastuzumab, a humanised monoclonal antibody targeting the extracellular domain of HER2, to chemotherapy significantly prolonged progression-free survival (PFS) and OS over chemotherapy alone.11 Still, secondary resistance to trastuzumab will eventually evolve and patients initially responding to HER2-targeted therapy will usually progress within 18 months,12 indicating the need for further alternative treatment approaches.

In the phase III trial CLEOPATRA, the classic first-line treatment standard of docetaxel plus trastuzumab was compared with a triple therapy of docetaxel, trastuzumab plus pertuzumab, a humanised monoclonal antibody targeting the dimerisation domain of HER2, thereby preventing receptor homodimerisation and heterodimerisation and consequently activation of HER2 signalling.13 At a median follow-up of 50 months, median OS in the pertuzumab group was 56.5 months.14 This number indicates the
impressive outcome improvements achievable in HER2-positive MBC with today’s therapeutic options.

Trastuzumab emtansine (TDM1) is another novel approach for targeting HER2. DM1 is a potent microtubule agent bound to trastuzumab via a molecular linker. When the antibody binds to HER2, the cell internalises the antigen-antibody complex; consequently, trastuzumab is degraded in the lysosome and DM1 is set free within the cancer cell. TDM1 was shown to be superior to lapatinib, a small molecule tyrosine kinase inhibitor (TKI) of HER2 and epidermal growth factor receptor (EGFR), plus capecitabine in terms of activity as well as tolerability in the phase III trial EMILIA with PFS 9.6 vs 6.4 months (HR 0.65; 95% CI 0.55 to 0.77). 16 Most patients received TDM1 as second-line therapy but 16% of patients had progressed on or within 6 months after the end of adjuvant trastuzumab; this lead to the approval of TDM1 as first-line treatment standard in earlier relapse. Another phase III study, TH3RESA, randomised pretreated patients to TDM1 or treatment by investigator’s choice. Since approximately 80% of patients in the control arm received trastuzumab-based therapy, TH3RESA is considered a comparison of TDM1 to trastuzumab treatment in multiple lines. In this study, TDM1 improved PFS from 3.3 to 6.2 months (HR 0.53; 95% CI 0.42 to 0.66). 17 In summary, these results suggest that despite considerable costs, TDM1 is indeed a valuable novel treatment option.

Besides, other antibody-drug conjugates targeting HER2 are currently being tested in clinical trials and already showed favourable safety profiles, such as MM-302. Owing to the use of small amounts of its active agent doxorubicin, it caused only minor haematological toxicity when used as a monotherapy or in combination with trastuzumab, as well as with trastuzumab and cyclophosphamide in a phase I study. It is currently being evaluated in the randomised phase II HERMIONE trial in patients with anthracycline naïve HER2-positive locally advanced or MBC previously treated with trastuzumab, pertuzumab and TDM1. 18

Lapatinib was the second HER2-targeted drug to become available after trastuzumab. This first-generation, reversible TKI inhibits the tyrosine-kinase domains of HER2 as well as EGFR. In a prospective randomised phase III trial, addition of lapatinib to capecitabine improved PFS over chemotherapy alone in pretreated patients (median PFS 8.4 vs 4.4 months; HR 0.47; 95% CI 0.32 to 0.68; p<0.001) while OS was not changed. 19 This was the first phase III study to demonstrate that continuing anti-HER2 therapy in combination with chemotherapy in patients who had virtually all received prior trastuzumab was superior to chemotherapy alone. Owing to relevant side effects, however, lapatinib plus capecitabine was rarely used as second-line treatment. Often physicians continued their patients on trastuzumab in multiple treatment lines after a switch of the cytotoxic combination partner; indeed, several phase II trials suggested that this was a feasible treatment approach. 20 21 Before second-generation antibodies became available, this strategy was so common that the only prospective randomised phase III trial investigating trastuzumab treatment in multiple lines had to be closed early due to slow accrual after the inclusion of only 156 patients. 22 Similar to the lapatinib study, continuation of anti-HER2 treatment resulted in longer PFS (8.2 vs 5.6 months; HR 0.69; 95% CI 0.48 to 0.97; p=0.0338) while once again no difference in terms of OS was observed.

The concept of vertical dual blockade of HER2 with a combination of trastuzumab plus lapatinib has recently led to renewed interest in HER2 TKIs. In a heavily pretreated population, the combination of trastuzumab with lapatinib improved OS over lapatinib alone (14 vs 9.5 months; HR 0.74; 95% CI 0.57 to 0.97; p=0.026). 23 Of note, this effect was more pronounced in the HER2-positive/hormone receptor-negative subgroup, eventually leading to European Medicines Agency approval of vertical dual blockade in this subset.

Further, recent studies have focused on irreversible second-generation TKIs such as neratinib and afatinib with potentially improved activity. Afatinib yielded a partial response rate of 11% and stable disease rate of 37% in a phase II trial of 41 patients progressing on prior trastuzumab treatment (BIBW 2992 trial). 24 Median PFS was 15.1 weeks and a median OS of 61.0 weeks was reported. These results led to the initiation of the phase III LUX-Breast 1 trial comparing afatinib plus vinorelbine to trastuzumab plus vinorelbine in patients with HER2-positive MBC progressing on prior trastuzumab-based treatment. A similar outcome in terms of PFS was observed in both groups; OS, however, was shorter in the afatinib arm. 25 This effect was most likely caused by higher rates of dose reductions and treatment discontinuations in patients receiving afatinib. Indeed, toxicity issues—especially diarrhoea—remain a concern with first-generation and second-generation TKIs inhibiting EGFR and HER2, but may be less so with HER2-specific third-generation TKIs such as ONT-380. 26

The lack of benefit of afatinib over standard treatment options was further substantiated by results of a randomised phase II trial of afatinib versus afatinib plus vinorelbine versus treatment by investigators’ choice in patients with progressive brain metastases after trastuzumab-based and/or lapatinib-based therapy (LUX-Breast 3 trial). In this study including 121 patients, both regimen containing afatinib did not yield gains in terms of clinical benefit rate at 12 weeks (which was defined as primary study end point) as well as PFS or OS. Further, afatinib-containing treatments were less well tolerated. 27

Another irreversible TKI, neratinib, has shown promising objective response rates (ORR) of up to 56% as single agent in patients with HER2-overexpressing advanced BC in an open-label phase II trial; PFS in this study was 39.6 weeks. 28 However, the benefit was more substantial in patients without prior trastuzumab treatment compared with those with prior treatment (ORR
observed as well. A subsequent phase I/II trial of neratinib in the continuum of anti-HER2 therapy awaits further clarification. A phase I basket study of 60 patients with HER2-overexpressing carcinomas was able to shed light on a potential future avenue for the development of neratinib; in this trial, neratinib was combined with temsirolimus in order to achieve inhibition of HER2-signalling by the additional abolishment of one of its major downstream effector kinases, mammalian target of rapamycin (mTOR). This combination produced responses in 2 of the 15 patients (13.3%) with HER2-positive MBC; in this trial, neratinib was directly compared with the former second-line standard of lapatinib plus capecitabine, single-agent activity of neratinib was confirmed; still, the exact future place of neratinib in the continuum of anti-HER2 therapy awaits further clarification. A phase I trial, 52 patients with different HER2-positive malignancies without any further standard therapy available were included. In the BC subset consisting of 19 participants, a reduction in tumour size was observed in 57.9% of patients. Treatment was generally well tolerated, with grade I/II fever and nausea as well as diarrhoea and fatigue being the main toxicities.

Heterodimers of HER2 and HER3 are known to be the most potent inducers of HER2 signalling. Furthermore, upregulation of HER3 was also described as a relevant mechanism of resistance to treatment with trastuzumab and lapatinib. Recently, it was shown that co-expression of HER2 and HER3 was associated with shorter OS in patients with HER2-positive MBC treated with trastuzumab in multiple lines. Therefore, it appears reasonable to examine strategies of targeting HER3 in combination with HER2. In a phase I trial, patritumab was added to trastuzumab plus paclitaxel in 18 patients with HER2-positive MBC who had received at least one prior treatment line for MBC; this fully human monoclonal antibody targets HER3, blocks receptor–ligand interaction and receptor activation and induces HER3 downregulation. Tolerability of this approach was excellent and no DLTs were observed with diarrhoea being the main side effect; the authors reported a relatively high response rate of 38.9%, suggesting that this approach should be investigated further in future clinical trials.

Luminal BC

Luminal BC is defined by the expression of the ER and progesterone receptor; the vast majority of all BC cases belong to this subtype. Hormone-dependent cancer growth allows for targeted therapy with antihormonal agents. In this context, surgical oophorectomy, first described by Beatson, is regarded as the first systemic anticancer therapy and the prototype of the concept of biologically targeted treatment. The former adjuvant treatment standard of tamoxifen administered for 5 years reduces recurrence risk by half and BC mortality by one-third. In the metastatic setting, sequential administration of different non-cross resistant classes of antihormonal therapy allows for delaying initiation of cytotoxic chemotherapy. Still, even in highly hormone expressing tumours, resistance to endocrine therapy will eventually arise. Several factors add to secondary resistance: CCND1 amplification, ESR1 mutation and...
activation of growth factor signalling pathways.\textsuperscript{44–47} The latter results in ER activation even in the absence of estrogen via the activation of signalling molecules downstream of receptor tyrosine kinases (RTKs); phosphatidylinositol-3-kinase (PI3K) and mTOR have been identified as central downstream molecules in this cross-talk leading to the testing of mTOR inhibitors such as everolimus in combination with endocrine therapy in clinical trials.

In the prospective randomised placebo-controlled trial BOLERO-2, postmenopausal patients with ER-positive advanced BC progressing on or after prior therapy with a non-steroidal aromatase inhibitor (AI) were randomised to receive everolimus or placebo in combination with the steroidal AI exemestane. BOLERO-2 was able to show a clear-cut benefit in terms of PFS (7.4 vs 3.2 months; HR 0.34; 95% CI 0.36 to 0.53)\textsuperscript{48} for patients showing a clinical trial. The BOLERO-2 trial was randomised to receive everolimus or placebo in combination with the steroidal AI exemestane. BOLERO-2 was able to show a clear-cut benefit in terms of PFS (7.4 vs 3.2 months; HR 0.34; 95% CI 0.36 to 0.53)\textsuperscript{48} for patients in the everolimus group. This supported findings from the randomised phase II trial TAMRAD\textsuperscript{49} and the HORIZON\textsuperscript{50} trials; on the downside, a significant OS advantage could not be shown (BOLERO-2: OS HR 0.89; 31.0 vs 26.6 months, p=0.14) and a relevant increase in toxicity was observed as well.

PIK3CA, a gene coding for the catalytic p110α subunit of PI3K, is among the most commonly mutated genes in BC\textsuperscript{51}, mutations have been linked to endocrine resistance by activating the aforementioned crosstalk between ER and RTKs, thus suggesting to serve as a predictive marker for response of drugs targeting the PI3K/mTOR pathway. Indeed, activity of mTOR inhibitors might be restricted to patients harbouring alterations in the PI3K/AKT/mTOR pathway, such as PIK3CA mutations or PTEN deletions.\textsuperscript{52} While this notion is supported by preclinical data,\textsuperscript{53} biological subprotocols of BOLERO-2 and TAMRAD suggested that, in contrast to expectation, patients without activating alterations in the PI3K/mTOR pathway derived the greatest benefit from treatment.\textsuperscript{54,55}

The quest for predictive markers for novel targeted therapies in luminal BC is therefore ongoing and interest in this field has recently focused on PI3K-inhibitors. While it appears reasonable to assume that PI3K-inhibitors may be most active in tumours harbouring activating PIK3CA mutations, no such clinical correlation was proven henceforth. While the addition of BKM120 (buparlisib, a pan-class PI3K inhibitor) increased activity of endocrine therapy over endocrine therapy alone in the BELLE-2 trial, this effect was overall modest (HR 0.78, PFS 6.9 vs 5.0 months, p<0.001) and considerable toxicity was observed as well. Of note, in a prospective substudy within BELLE-2, it was shown that PIK3CA mutations in cell-free tumour DNA (cfDNA) predicted further activity of buparlisib in this subset of patients (HR 0.56, PFS 7.0 vs 3.2 months, p<0.001).\textsuperscript{56} One hypothesis suggests that PIK3CA mutations may predict especially for activity of α-specific inhibitors of the p110α catalytic subunit of class I PI3K, but clinical proof of this concept is still awaited. If these data can be verified, however, a predictive biomarker beyond the ER will be available in luminal BC for the first time.

Cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors are a novel and promising treatment approach as dysregulation of cell cycle control may cause resistance to antihormonal treatment as well. Palbociclib, an irreversible inhibitor of CDK 4/6, when added to letrozole, has been shown to prolong progression-free interval over letrozole alone to a significant and clinically relevant extent. In the prospective, randomised phase II trial PALOMA-1/TRIO-18,\textsuperscript{57} median PFS at 29.6 months median follow-up was prolonged from 10.2 to 20.1 months (HR 0.488; 95% CI 0.319 to 0.748; one-sided p=0.0004) with the addition of palbociclib while the tolerability profile was generally favourable. The main toxicity consisted of neutropenia and was easily manageable with dose delays and modifications. Again, PALOMA-1 also aimed at identifying markers predictive for treatment response. Patients were enrolled into two separate sequential cohorts: cohort 1 (n=66) included unselected patients with ER-positive, HER2-negative tumours; cohort 2 (n=99) enrolled patients with luminal cancers and CCND1 amplification or p16 loss. Disappointingly, however, results demonstrated that no reliable response prediction is possible on the basis of these markers.

Recently, the favourable results of PALOMA-1 were duplicated in the prospective randomised phase III trial PALOMA-3 where palbociclib was added to the pure anti-oestrogen fulvestrant in pretreated patients. Again, addition of palbociclib resulted in a clinically meaningful improvement of median PFS from 3.8 to 9.2 months (HR 0.422; 95% CI 0.318 to 0.560; p<0.00001); of note, this study included premenopausal women as well and results were consistent in this population. No new safety signals were observed and main toxicity again consisted of neutropenia (78.8% vs 3.5%), leucopenia (45.5% vs 1.5%), and fatigue (38.0% vs 26.7%). Still, febrile neutropenia was rare and comparable in between both groups; cohort 1 (n=66) included unselected patients with ER-positive, HER2-negative tumours; cohort 2 (n=99) enrolled patients with luminal cancers and CCND1 amplification or p16 loss. Disappointingly, however, results demonstrated that no reliable response prediction is possible on the basis of these markers.

The role of immunotherapy and immune checkpoint modulators in luminal BC has not been fully characterised, although safety and comparably good response rates have been reported after multiple lines of therapy for patients suffering from programmed death ligand 1 (PD-L1)-overexpressing tumours in the KEYNOTE-028 trial.\textsuperscript{60} Further investigation in this field is greatly needed to objectify biological activity and to find biomarkers aside from PD-L1 that would point to responsiveness towards immune checkpoint inhibition in this setting.
Triple-negative BC (TNBC)
As indicated by the negative definition of being a BC subtype without expression of the ER and progesterone receptor as well as by the lack of HER2 protein overexpression or HER2/neu gene amplification, TNBC is the disease subtype with the least clinically relevant attributes. This lack of potential targets is clinically reflected by the poor prognosis of patients with TNBC.

Chemotherapy remains the mainstay of TNBC therapy and patients with pathological complete remission to neoadjuvant chemotherapy are known to have a favourable prognosis despite the inherent aggressiveness of this disease subtype. Patients with a less chemotherapy-sensitive disease, on the other hand, have a markedly poor prognosis with high recurrence rates and mortality. This warrants the search for novel targets in TNBC.

Around 10% of all BC cases can be attributed to BRCA-1/2 germline mutations with considerably higher rates of BRCA-1 mutations in women with TNBC. Further, women with early-onset BC are at a higher risk of carrying BRCA-1/2 mutations, with BRCA-1 being the more frequently altered gene. Owing to consecutive defects in genetic repair mechanisms such as homologous repair, BRCA-deficient cells must resort to other error-prone options of double-strand break repair such as non-homologous end-joining (NHEJ) and base excision repair (BER). Both repair mechanisms depend on PARP (poly-(ADP-ribose)-polymerases) as molecular scaffolds for repairing double-strand breaks, making PARP inhibitors either alone or in combination with DNA-damaging agents a promising treatment option, inducing synthetic lethality due to loss of PARP and BRCA-1/2 functions.

A single-arm multicentre phase II trial of olaparib as a single agent was conducted in patients with different malignancies harbouring BRCA-1/2 germline mutations; 62 patients with BC who had received at least three prior treatment lines for MBC were included. In this subset, there was an overall response rate of 12.9% (95% CI 5.7% to 23.9%) with an additional 47% (95% CI 34.0% to 59.9%) of patients experiencing disease stabilisation for a minimum of 8 weeks. On the other hand, activity of olaparib in an unselected TNBC population was disappointing. Several trials of PARP inhibitors in BC are currently ongoing; of special interest, the randomised phase III trial OLYMPIA (NCT02032823) focuses on the potential role of olaparib as adjuvant therapy in patients with high-risk HER2-negative primary BC harbouring BRCA germline mutations. In this context, it needs to be mentioned that, in contrast to germline BRCA mutations, the predictive role of the more abundant somatic BRCA mutations in BC remains elusive.

The quest for novel therapeutic approaches has brought to light various potential targets including RTKs such as MET and FGF. MET and its ligand hepatocyte growth factor are considered especially promising targets, being overexpressed in up to 45% of BCs and associated with poor clinical outcome, increased propensity to metastatic spread, increased tumour cell proliferation, high grading and a triple-negative phenotype. Of note, the MET-inhibitor cabozantinib has recently shown activity in humanised patient-derived xenograft models of TNBC. Furthermore, phase I clinical trials have also suggested promising activity and relative safety of MET inhibitors such as cabozantinib and foretinib, and results of later-phase clinical trials are therefore awaited with great interest. On the other side, targeting the extracellular domain of MET by means of the monoclonal humanised antibody onartuzumab has currently shown no benefit when added to paclitaxel/bevacizumab; in this context, it needs to be stated that most patients included in this study (88%) had only weak MET expression as defined by immunohistochemistry, raising the question whether this study was indeed conducted in the right population.

FGF was shown to play a significant role in up to 10% of patients with BC, facilitating epithelial to mesenchymal transition and hence metastatic spread. Subsequently, clinical trials of TKIs targeting selected (AZD4547) or multiple subforms of fibroblast growth factor receptor (FGFR) (dovitinib, lucitanib or nintedanib) were initiated; of note, the latter showed promising activity when combined with paclitaxel in a neoadjuvant setting. The rationale for the approach of FGFR-targeted therapy is to delay mesenchymal dedifferentiation and hence resistance to chemotherapy and targeted therapy that had originally been tailored for epithelial tumours. Although activity was also seen in luminal tumours, recent trials using FGFR inhibitors were focusing on the triple-negative setting because of inherent toxicity and missing alternative treatments in TNBC.

As with other malignancies, immune checkpoint modulators are currently being investigated in TNBC, although clinical development started with considerable delay as compared with melanoma or lung cancer. TNBC is characterised by high mutational load, which again is apparently associated with high immunogenicity. This makes TNBC an attractive field for developing immunotherapy in BC. First data on immunotherapy with immune checkpoint modulators in TNBC were presented at the 2014 San Antonio Breast Cancer Symposium. Thirty-two patients with pretreated MBC received pembrolizumab (MK-3475), a humanised IgG4 monoclonal antibody targeting PD-1 within the BC cohort of the phase 1b trial KEYNOTE-012. Of note, approximately 45% had already received at least three prior treatment lines for metastatic disease. While the overall response rate was relatively low at 18.5%, it is worth mentioning that responses were observed even in heavily pretreated participants and some patients seemed to experience prolonged disease stabilisation. Another phase I trial tested MDPL3280A, an anti-PD-L1 antibody, in 54 patients with TNBC. Again, 85% of all patients had at least four prior systemic therapy lines. In 21 evaluable patients, the

authors observed a response rate of 19%, with two complete responses and two partial responses; although it is too early to draw any firm conclusions, it must be mentioned that these four patients had high expression of pretreatment PD-L1. Recently, the phase Ib JAVELIN study reported first results from the BC cohort. 81 The anti-PD-L1 antibody avelumab (MSB0010718C) yielded an overall relative response (RR) of 4.8% in 168 unselected patients with pretreated MBC. In patients with TNBC (34.5%), RR was somewhat higher (8.6%) but responses were seen across all subtypes with a median duration of response of 28.7 weeks. When analysing patients with tumours harbouring ≥10% PD-L1 expression, a response rate of 33% in the overall population was observed; RR in patients with TNBC was a striking 44%. In summary, these data suggest that immunotherapy is indeed a valuable addition to the therapeutic armamentarium in TNBC (table 1).

### Table 1 Selected drugs and their molecular targets undergoing clinical evaluation in MBC

<table>
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<th>HER2-overexpressing MBC</th>
<th>Luminal MBC</th>
<th>Metastatic triple-negative breast cancer</th>
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<td>▶ Everolimus (mTORC1)</td>
<td>▶ Palbociclib (CDK 4/6)</td>
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CDK 4/6, cyclin-dependent kinase 4 and 6; FGFR, fibroblast growth factor receptor; MBC, metastatic breast cancer; mTORC1, mammalian target of rapamycin complex 1; PD-L1, programmed death ligand 1.

### CONCLUSION
Following the discovery of crucial molecular signalling mechanisms, targeted drugs have been developed for MBC. Although generally applicable as a concept, the identification of a true driver pathway, the identification of biomarkers for patient selection and, finally and most importantly, the therapeutic efficacy of a specific targeted approach has to be proven for each BC subtype and each setting separately. An abundance of drugs is in development which will challenge the scientific community to develop appropriate models for preclinical as well as clinical testing of these compounds but may eventually help in further improving patient outcomes.

### Contributors
MM contributed to the literature search; and writing, submission and editing of the manuscript. RB contributed to the literature search; and writing and editing of the manuscript. CZ contributed to the planning of the study; and editing of the manuscript, and also gave approval for its final version.

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None declared.

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