PARP Inhibitors for Recurrent Ovarian Carcinoma: Current Treatment Options and Future Perspectives

PARP-Inhibitoren beim rezidivierenden Ovarialkarzinom, aktuelle Therapieoptionen und zukünftige Entwicklungen

Authors   J. Sehouli[1], E. I. Braicu[2], R. Chekerov[2]

Affiliations   [1] Universitätsklinikum Berlin Charité, Klinik für Gynäkologie, Charté Comprehensive Cancer Center (CCCC), Berlin
                   [2] Universitätsklinikum Berlin Charité, Campus Virchow-Klinikum, Klinik für Gynäkologie, Charté Comprehensive Cancer Center (CCCC), Berlin

Abstract
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More than simply a promising management option, PARP inhibitors can be regarded as a milestone in the development of personalised treatment of recurrent ovarian carcinoma. Their mechanism of action, known as "synthetic lethality", is dependent on functional differences of the DNA repair mechanisms of healthy cells and tumour cells; cells that repair DNA damage less efficiently are particularly sensitive to PARP inhibitors. Olaparib, licensed for use this year, is the best-studied PARP inhibitor used for treatment of high-grade serous ovarian carcinoma (HGSC). The efficacy of PARP inhibitors appears to be increased when used in combination with other treatments.

Zusammenfassung
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PARP-Inhibitoren stellen nicht nur eine sehr vielversprechende Behandlungsmöglichkeit dar, ihre Entwicklung kann zudem als Meilenstein bei der Einführung einer personalisierten Medizin in der Behandlung des rezidivierten Ovarialkarzinoms betrachtet werden. Ihre Wirkungsweise, auch als synthetische Letalität bezeichnet, beruht auf den unterschiedlichen Funktionalitäten der DNA-Reparaturmechanismen bei gesunden und Tumorzellen. Zellen, die eine verminderte Fähigkeit aufweisen, DNA-Schäden effizient zu reparieren, sind besonders sensitiv gegenüber PARP-Inhibitoren. Bei Olaparib handelt es sich um den beim High-grade, serösen Ovarialkarzinom (HGSC) inzwischen am besten untersuchten und seit diesem Jahr zugelassenen PARP-Inhibitor. Die Kombination von PARP-Inhibitoren mit anderen Therapieansätzen scheint die Effektivität der PARP-Inhibitoren zu steigern.

Correspondence
Dr. med. Radoslav Chekerov
Universitätsklinikum Berlin
Charité
Campus Virchow-Klinikum
Klinik für Gynäkologie
Charité Comprehensive Cancer
Center (CCCC)
Augustenburger Platz 1
13353 Berlin
radoslav.chekerov@charite.de

Introduction
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Ovarian carcinoma is the 5th most common cause of cancer related death in German women and has the highest mortality of all gynaecological cancers [1]. Treatment options have continued to improve in recent years due to both better operative techniques and systemic therapies, however a relative 5-year survival rate of 42% [1] is still disappointing; most patients have disease recurrence despite radical surgery and platinum/taxane-based chemotherapy [2].

Ovarian carcinoma is usually sporadic with 5 to 10% being hereditary, mostly with mutations of the *BRCA1* and/or *BRCA2* genes. Women with a *BRCA1* mutation have a 40–55% lifetime risk of ovarian carcinoma before the age of 70; for carriers of *BRCA2* mutations the risk is 11–17% [3]. The clinical course of ovarian carcinoma in the presence of *BRCA* mutations differs significantly from that with intact *BRCA*. Overall survival is significantly better for carriers of *BRCA1* and *BRCA2* mutations (for *BRCA1*: hazard ratio (HR), 0.73; 95% CI, 0.64–0.84; p < 0.001; for *BRCA2*: HR, 0.49; 95% CI, 0.39–0.61; p < 0.001) [4]. There is evidence that BRCA associated tumours are particularly sensitive to DNA alkylators and intercalating agents such as the platinum derivatives. Studies of tumour tissue from the TCGA project (the Cancer Genome Atlas http://cancergenome.nih.gov) have shown that mutations of genes involved with DNA repair mechanisms (HRR, homologous recombination repair) are present in about 50% of high-grade (G2–3) serous ovarian carcinomas (HGSC) [5].

The introduction of PARP inhibitors as a new, targeted intervention has shown clinical benefit in numerous studies of recurrent platinum-sensitive ovarian carcinoma, the greatest benefits ap-

plying to carriers of BRCA mutations [6]. This article will detail the current status of the PARP inhibitors that have been subjected to clinical trials, and describe their importance in the treatment of recurrent ovarian carcinoma.

Among tumour therapies Poly (ADP-ribose) polymerase (PARP) inhibitors are a drug class known to provide impressive results. Their mechanism of action has largely been described in preclinical studies [7,8]. The addition of a PARP inhibitor to treatment regimes for recurrent ovarian carcinoma, consisting of established systemic therapies, appears to provide a definite improvement in disease response. The molecular biological characterisation of tumour tissue as precisely as possible is decisive for treatment success with PARP inhibitors as it enables an individualised treatment strategy.

Background Information on Mechanism of Action and a Description of the Substance Class
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Poly (ADP-ribose) polymerases (PARP) are a family of numerous individual enzymes of which at least 2 (PARP-1 und PARP-2) are involved in repairing damaged DNA [7,9]. DNA repair mechanisms play an important roll in the maintenance of genomic integrity and consequently in cell survival. Numerous factors, e.g. metabolic byproducts such as reactive oxygen species, can damage DNA through causing single-strand breaks. Repair of these single-strand breaks usually occurs through base excision repair (BER), a mechanism in which members of the PARP family of enzymes are involved. If repair does not occur or is incomplete, double-strand breaks arise during the next DNA replication. In healthy cells these are repaired by homologous recombination repair (HRR) and the error-prone non-homologous end joining (NHEJ). PARP inhibitors initially prevent the repair of single-strand breaks by inhibiting BER. In HRR deficient cells, which are characterised by mutations in the *BRCA1* and/or *BRCA2* genes, effective repair of double-strand breaks is not possible either. It is now known that there are also other genetic/epigenetic errors that can restrict the cell's ability to repair DNA damage efficiently. Repair is then carried out more often by the error-prone NHEJ mechanism resulting in the accumulation of DNA damage that leads to cell death. In addition to inhibiting the BER pathway PARP inhibitors stimulate the NHEJ pathway promoting cell death of HRR deficient cells [10]. The mechanism of action of PARP inhibitors is known as "synthetic lethality"; schematic representation in ● **Fig. 1**.
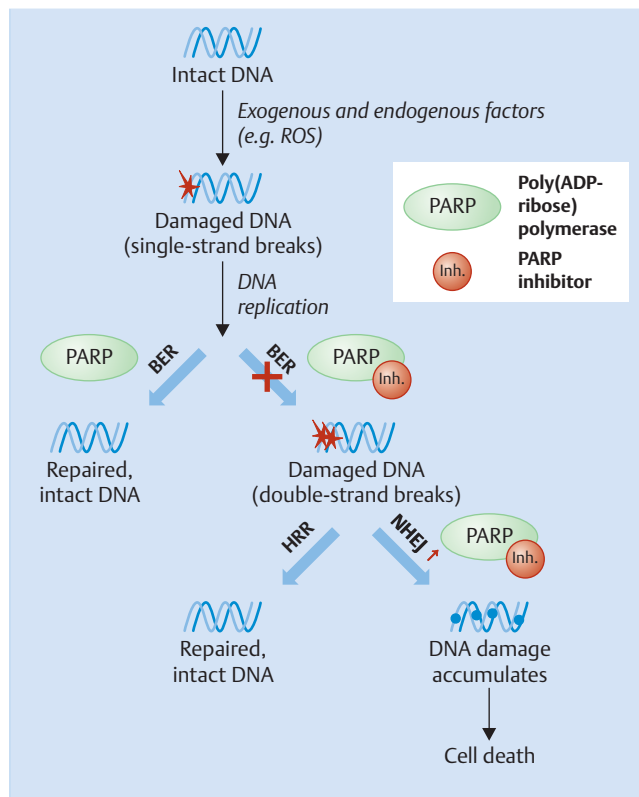

Fig. 1 Action of the PARP inhibitors on DNA repair mechanisms (modified according to [8, 11]). DNA single-strand breaks, caused by exogenous and endogenous factors (e.g. reactive oxygen species [ROS], byproducts of metabolism), are repaired by physiological base excision repair (BER). The BER pathway is inhibited in the presence of PARP inhibitors; this results in double-strand breaks during DNA replication. In healthy cells these breaks are corrected faultlessly by homologous recombinant repair (HRR). Cells that have a dysfunctional HRR pathway (see box BRCA and "*BRCA*ness") must use non-homologous end joining (NHEJ) that is error-prone and whose activity is increased in the presence of PARP inhibitors. Through this process DNA damage accumulates in HRR deficient cells destabilising genomic integrity and leading to cell death.

BRCA and "BRCAness"

BRCA1 and *BRCA2* are classified as tumour suppressor genes. Their gene products are involved in homologous recombination (HR) mediated DNA repair. Patients with *BRCA1/2* mutations are at increased risk of various forms of cancer; for ovarian carcinoma the risk is 10–55%. The term "*BRCA*ness" describes characteristics of a sporadic tumour that are usually found in tumours among *BRCA1/2* germ line mutation carriers; genetic or epigenetic errors are usually present leading to loss of HR associated DNA repair. Tumour cells that do not have efficient DNA repair mechanisms are particularly sensitive to DNA damaging drugs such as platinum-based chemotherapies. PARP inhibitors are promising for tumour treatment not only in the presence of *BRCA* mutations but possibly also where there is "*BRCA*ness".

PARP inhibitors block the enzymatic activity of PARP by attaching to the enzyme's active centre and competing with its natural substrate. In addition to their pure enzyme blocking action some PARP inhibitors appear to induce the formation of a PARP-DNA complex that further impairs DNA repair [11].

Clinical Studies in Recurrent Ovarian Carcinoma
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The PARP inhibitors available for tumour treatment today have high potency and specificity. Their efficacy and tolerability in patients with ovarian carcinoma, most often with *BRCA1* and/or *BRCA2* gene mutations, have been studied in numerous clinical trials. Data from the clinical development of the most promising of the PARP inhibitors will now be detailed. Since its antitumour action is no longer ascribed to PARP inhibition [12], iniparib will not be considered further here.

Olaparib

Olaparib is currently the best-studied oral PARP inhibitor (PARP-1 and PARP-2 blockade) for use in ovarian carcinoma. Numerous phase I and phase II trials have shown its efficacy for BRCA asso-

Table 1 Pivotal trials on the efficacy olaparib monotherapy.

Study	Requirements (inclusion criteria) with respect to previous treatment	BRCA status and patient number in olaparib group	Dose	Clinical	
Phase I [13]	No requirement, categorisation according to platinum resistance or sensitivity	BRCAm+ n = 50	40 mg daily up to max. 600 mg BID Dose escalation	CBR Plat-sens: 69% Plat-res: 45% Plat-refr: 23%	RD: 28 weeks
Phase II [14]	At least one previous unsuccessful chemotherapy	BRCAm+ n = 33	400 mg BID	ORR 33%	RD: 41 weeks
		BRCAm+ n = 24	100 mg BID	ORR 13%	RD: 38 weeks
Phase II [15]	No requirement	BRCAm+ n = 17 BRCAwt n = 46	400 mg BID	ORR BRCAm+: 41% BRCAwt: 24%	PFS BRCAm+: 7.3 months BRCAwt: 6.3 months
Phase II [16]	Recurrence/progression within 12 months of previous platinum-based therapy	BRCAm+ n = 32	400 mg BID	ORR: 31%	PFS: 8.8 months
		BRCAm+ n = 32	200 mg BID	ORR: 25%	PFS: 6.5 months
Phase II [6]	At least 2 previous platinum-based agents, platinum sensitivity	BRCAm+ n = 74 BRCAwt n = 57	400 mg BID		PFS BRCAm+: 11.2 months BRCAwt: 7.4 months

BID: twice daily; BRCAm+: Mutation in BRCA1/BRCA2; BRCAwt: BRCA Wildtype; CBR: Clinical Benefit Rate; ORR: Overall Response Rate; PFS: Progression-free Survival; RD: Response Duration

ciated ovarian carcinoma and recurrent somatic mutation high-grade serous ovarian carcinoma (data summarised in ◯ **Table 1**) [6, 13–16]. In a phase I trial, Fong et al. [13] showed that the clinical benefits of olaparib (200 mg twice daily) for BRCA associated malignant epithelial tumours of the ovary, salpinges (fallopian tubes) and peritoneum was significantly greater in platinum-sensitive disease (clinical benefit rate [CBR] 69.2%) compared to platinum-resistant and refractory disease (CBR 45.6% and 23.1% respectively). A course of olaparib (400 mg twice daily) [17] increased progression-free survival (PFS) in platinum-sensitive recurrent HGSC measurably. This effect was particularly impressive among women with *BRCA*-mutation associated tumours (PFS in olaparib group 11.2 months vs. 4.3 months in placebo group) [6]. With data collection still incomplete (58% of events) a statistical difference in overall survival has not yet been shown for olaparib, though a numeric effect is already evident (total study population: HR 0.99 [95% CI 0.64–1.21]; patients with BRCA mutations: HR 0.73 [95% CI 0.45–1.17]) [6].

Olaparib monotherapy is generally well tolerated (maximum tolerable dose 400 mg twice daily) [18]. Side effects included gastrointestinal symptoms such as nausea and vomiting, fatigue and mild haematotoxicity. A complete representation of all adverse events therapy is shown in ◯ **Table 2**. Myelodysplastic syndrome and acute myeloid leukaemia occurred in a few cases during olaparib monotherapy, however since these patients had all undergone intensive tumour treatment previously (notably with chemotherapy) there is a degree of doubt as to whether these events were a direct effect of olaparib. The safety and efficacy of olaparib is being tested further in numerous phase III trials both in primary advanced *BRCA*-associated ovarian carcinoma after platinum-based chemotherapy (SOLO1) and in platinum-sensitive *BRCA*-associated recurrent ovarian carcinoma after a response to platinum-based chemotherapy (SOLO2, SOLO3).

Olaparib (Lynparza®) is now available on the market as the first officially licensed PARP inhibitor. After its fast-track licensing by the FDA (1/2015) it was subsequently licensed by the EMA (4/2015) as monotherapy for maintenance treatment of platinum-sensitive recurrent *BRCA*-mutation (germ line and/or somatic) high-grade serous epithelial ovarian carcinoma, carcinoma of the salpinges or primary peritoneal carcinoma with clinical response to platinum-based chemotherapy.

Veliparib

Veliparib (ABT-888) was initially researched in numerous preclinical and pharmacokinetic trials. A pharmacokinetic trial of diverse tumour entities showed an inhibitory effect (veliparib dose 25 mg and 50 mg) on PARP in tumour tissue and blood samples [19]. Since then numerous phase I trials of veliparib as a drug combination partner for various tumour entities have been conducted (cyclophosphamide [20]; temolozomide [21]; topotecan [22]). Published in March 2014, the provisional findings of a phase II trial involving 52 patients with recurrent or persistent *BRCA*-associated ovarian carcinoma suggest veliparib is potentially effective used as monotherapy [23]. At a veliparib dose of 400 mg twice daily the overall response rate was 26% with a better response rate for platinum-sensitive disease than platinum-resistant disease (35 vs. 20%). Toxicity of veliparib monotherapy was described as acceptable. Side effects included gastrointestinal symptoms, fatigue and haematological toxicity with a need for dose reduction because of toxicity in 48% of patients. The efficacy of veliparib for recurrent ovarian carcinoma is currently being tested in numerous phase II trials. Most current phase III trials are focused on combination strategies using veliparib and other chemotherapeutic agents for various solid tumours (breast carcinoma, non-small cell bronchial carcinoma, glioblastoma).

Table 2 Pivotal trials on the safety of olaparib monotherapy in ovarian carcinoma.

Trial	Dose/Patient number	Toxicity	Grade 1–2	Grade 3–4
Phase II [14]	400 mg BID n = 33	nausea	42%	6%
		fatigue	30%	3%
		anaemia	15%	3%
	100 mg BID n = 24	nausea	29%	8%
		fatigue	38%	0%
Phase II [15]	400 mg BID n = 64 (OvCa) n = 26 (BCa)	nausea	64%	2%
		fatigue	59%	11%
		loss of appetite	34%	2%
		diarrhoea	19%	5%
Phase II [16]	400 mg BID n = 32	nausea	72%	6%
		fatigue	56%	9%
		abdominal pain	25%	0%
		vomiting	47%	3%
		constipation	16%	0%
		diarrhoea	38%	0%
		asthenia (muscle weakness)	34%	0%
		urinary tract infection	34%	0%
		anaemia	19%	13%
	200 mg BID n = 32	nausea	56%	3%
		fatigue	38%	3%
		abdominal pain	31%	6%
		vomiting	34%	0%
		constipation	22%	6%
		diarrhoea	19%	0%
		asthenia	16%	3%
		urinary tract infection	16%	0%
		anaemia	6%	6%
Phase II [17]	400 mg BID n = 136	nausea	66%	2%
		fatigue	42%	7%
		vomiting	29%	2%
		diarrhoea	21%	2%
		abdominal pain	16%	1%
		anaemia	12%	5%
		asthenia	11%	1%
		back pain	9%	2%

BID: twice daily; OvCa: ovarian carcinoma; BCa: breast carcinoma

Niraparib

Niraparib (MK4827) is a selective PARP1 and PARP2 inhibitor whose antiproliferative effect was first shown in in-vitro trials on *BRCA1* and *BRCA2* deficient cancer cells. Its efficacy was also shown in an animal model on artificial *BRCA1*-deficient tumours [24]. A phase I dose-finding trial found a maximum tolerable dose of 300 mg daily. Toxic effects such as gastrointestinal symptoms, fatigue, anaemia, thrombocytopenia and neutropenia occurred frequently but severity was mostly low. Of patients with *BRCA*-associated ovarian carcinoma 40% (8 out of 20) showed partial response (RECIST) [25]. The efficacy and tolerability of niraparib monotherapy for platinum-sensitive recurrent ovarian carcinoma are currently being tested in an international phase III trial (NOVA). Results of phase II and phase III trials on the clinical use of niraparib have not yet been published.

Rucaparib

Ihnen et al. [26] studied the effect of the PARP inhibitor rucaparib (CO-338, AG014699, PF-01367338) on 39 different ovarian carcinoma cell lines in-vitro. The antitumour action of rucaparib was not limited to *BRCA*-mutated cells alone but also shown in cells with low-level expression of HRR-associated genes. The most obvious synergistic effects were shown for the combination of rucaparib plus topotecan. The efficacy and tolerability of oral rucaparib monotherapy have been tested in clinical studies. In addition to good tolerability [27], antitumour effect has been shown among patients with ovarian and peritoneal carcinoma both in platinum-sensitive and platinum-resistant disease (total tumour follow-up rate 86%) with doses between 40 to 500 mg rucaparib daily and 240 mg rucaparib twice daily respectively [28]. There is also published data on rucaparib in combination with cytostatic drugs. The efficacy of rucaparib as maintenance therapy for platinum-sensitive recurrent ovarian carcinoma is the focus of two current international trials (ARIEL2 und ARIEL3).

Talazoparib (BMN 673)

BMN 673 is a PARP inhibitor whose antitumour action – according to findings of in-vitro studies on HRR-deficient cells (*BRCA1, BRCA2, PTEN* gene defects) – is assumed to be 20 to 200 times stronger than the other PARP inhibitors (olaparib, rucaparib, veliparib) [29]. The first clinical data on the use of talazoparib as monotherapy support these findings: tumour response (RECIST and/or CA-125) was shown at BMN 673 doses of 100 to 1100 µg daily in 11 out of 17 patients with *BRCA*-associated ovarian and peritoneal carcinoma [30]. The occurrence of thrombocytopenia was however dose limiting so that the maximum tolerated dose of BMN 673 (1000 µg) was significantly lower than that of other PARP inhibitors. Further phase II clinical trials of talazoparib's efficacy in ovarian carcinoma as well as phase II and phase III trials of talazoparib for *BRCA*-associated breast carcinoma (ABRAZO, EMBRACA) are still at recruiting stage.

Other PARP inhibitors

In addition to those mentioned above numerous other well-known PARP inhibitors have been tested in clinical trials or are currently being tested (e.g. AZD2461, CEP9722, A7016, E7449, INO-1001). The efficacy of these substances has not yet been tested for ovarian carcinoma or data is yet to be published.

Combination Strategies
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In addition to use as monotherapy, PARP inhibitors have shown promise when used in combination with other treatments. The following is a selection of possible therapeutic approaches:

▶ **In combination with chemotherapy:** The DNA repair blocking effects of PARP inhibitors cause cells to be more sensitive to DNA damaging substances and can also delay the development of resistance to chemotherapy. [31]. Oza et al. [32] studied the combination of olaparib wtih carboplatin/paclitaxel followed by olaparib maintenance therapy in patients with platinum-sensitive recurrent serous ovarian carcinoma. The addition of olaparib to carboplatin/paclitaxel chemotherapy and as maintenance thereafter resulted in a significant increase in progression-free interval from 9.6 (arm B) to 12.2 months (arm A) (arm A: olaparib 2 × 200 mg daily, day 1–10 with paclitaxel 175 mg/m^2 and carboplatin AUC6 on day 1, for 6 cycles at intervals of 21 days followed by olaparib maintenance therapy

2×400 mg/d until tumour progression; arm B: paclitaxel 175 mg/m² and carboplatin AUC6 on day 1, for 6 cycles at intervals of 21 days without maintenance therapy). Toxicity profiles of the two regimes were similar.

▶ **In combination with PI3-kinase inhibitors:** The PI3K/AKT/mTOR signal pathway is critical for many cell functions such as growth, metabolism and the initiation of DNA translation. The inhibition of PI3-kinase with PI3K inhibitors is a particularly interesting potential treatment strategy for ovarian carcinoma, since up to 70% of these tumours show overactivity of this pathway. Promising preclinical data have been published for the combination of PARP inhibitors with PI3K inhibitors [33]. The combination of olaparib and the PI3K inhibitor BKM120 for triple negative breast carcinoma and high-grade serous ovarian carcinoma (NCT01623349) is the subject of a current phase I trial that is still in the recruiting phase.

▶ **In combination with angiogenesis inhibitors:** Preclinical trials have provided evidence of hypoxia-mediated, reduced expression of proteins involved in DNA repair via the HRR pathway. A hypoxic environment is also known to increase the sensitivity of cells to PARP inhibitors [34–36]. Combinations of olaparib with bevacizumab [37] and cediranib [38] have been studied in clinical trials. In a phase II trial Liu et al. [39] showed that the "chemotherapy-free" combination of olaparib with cediranib clearly improved progression-free survival rate in platinum-sensitive recurrent ovarian carcinoma compared to olaparib monotherapy (PFS 17.7 months vs. 9.0 months respectively), although from the outset patients in both groups received no chemotherapy during recurrence. A phase III trial of the same combination strategy is planned [40].

Future Prospects
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The treatment of recurrent ovarian carcinoma remains a major challenge to clinicians. Since the disease in this form is incurable treatment is aimed at achieving a compromise between antitumour effect and a reasonable degree of reduced bodily reserves and quality of life. The fundamental treatment strategies target the platinum-free interval and are governed by differing tumour sensitivities to previous platinum-based chemotherapy. Results of all trials to date allow the conclusion that the various members of the PARP inhibitor drug class have clinically meaningful antitumour effects especially in high-grade serous platinum-sensitive ovarian carcinoma. With its licensing for treatment of platinum-sensitive *BRCA*-mutated ovarian carcinoma, olaparib is the first PARP inhibitor to become part of the gynaecological-oncological treatment spectrum. This innovative treatment approach is a further step towards improved individualisation and the establishment of personalised, goal-directed therapy in clinical practice. This is conditional on a new level of clinical understanding of tumour complexity as well as molecular genetic evidence of disturbed DNA repair caused by BRCA mutations, both somatic and germ line. An exact genetic characterisation of tumours should thus be performed early on in tumour management. To achieve this prompt analysis of somatic and germ line mutations in patients with ovarian carcinoma the promotion of efficient organisational structures is necessary.

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