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Axitinib in first-line for patients with metastatic papillary renal cell carcinoma: results of the multicentre, open-label, single-arm phase II AXIPAP trial.

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Running Title: Axitinib in advanced or metastatic papillary renal cell carcinoma

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Pfizer provided the study drug axitinib and funding to Centre Léon Bérard to conduct the study. Pfizer had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Keywords: advanced renal cancer, papillary renal cell carcinoma, tyrosine kinase, vascular endothelial growth factor, VEGF inhibitor, targeted therapy.

Abbreviations: PRCC: Papillary renal cell carcinoma; VEGF: vascular endothelial growth factor; VEGFr: Vascular endothelial growth factor receptor; PD1: Programmed cell death 1; PDL1: Programmed death-ligand 1; RECIST: Response Evaluation Criteria in Solid Tumors; PFS: progression free survival; OS: overall survival; RR: response rates; 24w-PFR: progression free rate at 24 weeks; PR: partial response; SD: stable disease; PD: progression disease.

Abstract

Introduction: Papillary renal cell carcinoma (PRCC) represents 10-15% of renal carcinomas. No standard treatments exist for metastatic PRCC (mPRCC) patients. Axitinib is indicated as second-line treatment in metastatic clear cell renal carcinoma, and we aim to assess the efficacy of this VEGF receptor inhibitor in front line for metastatic PRCC.

Methods: This French multicenter phase II study AXIPAP enrolled untreated metastatic PRCC patients, with measurable disease, ECOG PS ≤ 1 , and adequate organ functions. PRCC had to be confirmed by histology expert central review (NRL). Axitinib was administered orally 5 mg twice daily. Primary endpoint was progression free rate at 24 weeks (24w-PFR) by central review.

Results: Fifty-six patients were screened, and 44 included (13 type 1, 30 type 2, and 1 non-specified). The median follow-up was 32.0 (13.1-39.9] months. The 24w-PFR was 45.2% [95%CI 32.6% - $+\infty$], the objective response rate was 28.6% (95%CI 15.7%-44.6%) (type 1: 7.7%; type 2: 35.7%). The overall median PFS was 6.6 (95%CI 5.5-9.2) months, 6.7 months [95%CI 5.5-9.2] and 6.2 months (95%CI 5.4-9.2) for type 1 and 2, respectively. Median overall survival was 18.9 months (95%CI 12.8-not reached). Adverse events were as expected, grade 3-4 treatment-related adverse events were rare except hypertension (27%).

Conclusions: Axitinib demonstrated encouraging efficacy in mPRCC patients, especially in type 2 PRCC. Toxicity was manageable. Axitinib appears as an interesting option for first line treatment and to be worth further investigation in combination with immunotherapy in these patients. Expert pathology review should be recommended in this setting.

Clinical Trial registration: ClinicalTrials.gov, NCT02489695.

Highlights:

- No standard treatments exist for metastatic PRCC patients.
- Axitinib showed encouraging results in mPRCC patients, especially in type 2 PRCC, and toxicity was manageable.
- Axitinib appears as an interesting agent to investigate in combination with immunotherapy in mPRCC patients.
- Expert pathology review to confirm PRCC should be recommended.

Introduction

Papillary renal cell carcinoma (PRCC) is the second most common subtype of renal carcinoma accounting for approximately 10-15% of all renal cancers. Different types of PRCC have been described on the basis of two histologic subtypes, type 1 and type 2, with a worse prognosis reported for type 2 metastatic disease (1). However, molecular analyses recently highlighted the need to refine classification to appropriately integrate newly identified molecular features.(2;3) Gene alterations including *MET* mutations or amplifications fostered the development of *MET*-driven therapeutic strategies (4). There is currently no standard of care specifically dedicated to metastatic PRCC (mPRCC) patients (2), and treatments developed for metastatic clear cell carcinomas are commonly used, therefore, mPRCC enrollment in clinical trials is encouraged (5). Clinical trials specifically investigated treatments such as sunitinib, or everolimus approved for advanced clear cell carcinoma, or the dual kinase inhibitor directed both towards VEGF receptors (VEGFr) and the *MET* pathway foretinib, or more recently, the selective MET inhibitor savolitinib (6-9). Response rates (RR) were disappointing because they were generally below 15%, except in a subset of patients with *MET* germline alterations (8). Axitinib is indicated as second-line treatment in advanced clear cell carcinoma. Based on its potent VEGFr inhibitory activity, we designed the AXIPAP trial to investigate its inhibitory effect in patients with mPRCC.

Patients and methods

Study design

This multicenter single-arm, phase II trial enrolled patients with locally advanced or metastatic confirmed PRCC in first-line treatment. The study was conducted according to the declaration of Helsinki and the International Conference of Good Clinical Practices after local approval of the Ethic Committee of Lyon Sud-Est IV and all patients provided written informed consent before enrolment. The study was registered on ClinicalTrials.gov, number NCT02489695.

Patients

Eligible patients had histologically proven advanced or metastatic PRCC (pure type 1, or 2, or mixed, whatever the percentage) confirmed by expert central pathology review. Other inclusion criteria were Eastern Cooperative Oncology Group performance status 0 or 1, age above 18, adequate hematologic, renal and liver functions, at least one measurable lesion by CT-scan as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, no active cardiac disease nor history of grade 3 vascular or cardiac disease, no prior systemic treatment for metastatic renal cancer and no brain metastases.

Treatment and study assessments

Patients received axitinib (Pfizer, France) orally twice a day until progression or unacceptable toxicity; the starting dose was 5 mg twice daily, with possible dose adaptation according to the label recommendations.

Screening and baseline assessments were performed within 28 days prior axitinib initiation; Radiological response was assessed every 8 to 10 weeks and tumor assessment was classified as partial response (PR), stable disease (SD), or progression by the investigators according to RECIST 1.1 (10). A central radiology review was performed for all patients who received at least 4 weeks of treatment to confirm the progression of the

disease or not (RECIST 1.1) at 24 weeks or earlier in case of treatment discontinuation. All patients were assessed clinically every 4 weeks, routine blood and urine samples were also verified every 4 weeks. Adverse events were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Outcomes

The primary endpoint was the 24-week progression-free rate (24w-PFR), defined as the proportion of patients with a complete response (CR), or a partial response (PR), or a stable disease (SD) at 24 weeks according to RECIST 1.1, validated by the central review committee. According to results obtained in two previous trials (6,7), the 24w-PFR appeared as an appropriate and rapidly available endpoint.

The secondary endpoints included safety assessed through adverse events grading according to the CTCAE version 4.0, Progression free survival (PFS) in each PRCC subtypes, Overall Survival (OS), Objective Response rate (ORR), and duration of responses.

Statistics and data analysis

We calculated the sample size using A'Hern's single-stage design for phase II trials with the assumption that axitinib should result in a non-progression rate at 24 weeks (24w-PFR) of at least 45% to be judged appropriate for further investigation. This threshold used the 24w-PFR of 45% observed in type 1 and 2 PRCC patients treated by sunitinib in the SUPAP first-line study (6). A 65% cut-off was defined as the expected minimum efficacy threshold in our study, close to 57% defined as the upper bound of the 95% CI for 24w-PFR reported in former trials. A sample size of 42 patients provided 80% power to reject the null hypothesis with a one-sided, type 1 error of 5%, 25 patients being the lower cutoff point of decision making. To account for a non-assessable patient rate of 15%, eight patients were added to reach a total sample size of 50 patients.

The primary endpoint was assessed in terms of success and failure, with success defined as being progression free at 24 weeks, and failure defined as disease progression, or death from any cause within the 24 weeks following treatment initiation, or axitinib permanent discontinuation for toxicity before 24 weeks. The 24-week progression free rate is presented as a proportion with its unilateral 95% confidence interval (CI).

Progression free survival (PFS) was defined as the time from axitinib initiation to the date of first documented event of disease progression according to RECIST version 1.1 or death from any cause, whichever occurred first. Patients with no event at the time of analysis were censored at the date of last adequate tumour assessment. Overall survival (OS) was defined as the time from axitinib initiation until death from any cause. Patients alive at the time of analysis were censored at the date of last contact.

PFS and OS were estimated using the Kaplan-Meier method, and described in terms of median survival, along with the associated 2-sided 95% CIs for the estimates. PFS distributions were compared between the two PRCC subtypes using the Log-Rank test. Median follow-up (min-max) was calculated by a reverse Kaplan-Meier estimate. Qualitative variables are described using frequency and percentage. Quantitative data are described using median, minimum and maximum values. All analyses were done with SAS (version 9.4).

Data cut-off was May 6, 2019 for the final analysis.

Review of the literature: Medline database was searched using the following keywords: advanced or metastatic papillary renal carcinoma or non-clear cell renal carcinoma and treatment and trial. We exclusively considered prospective trials with at least 12 patients with papillary carcinoma.

Results

Patients

Between October 2015 and January 2018, 56 patients from 7 centers were screened for eligibility (Table S1). Histologic pathology central review was performed and confirmed PRCC diagnosis in 44 patients; five patients had other renal carcinoma subtypes. Seven patients did not meet other inclusion/exclusion criteria (Figure 1). Table 1 shows patient demographics and baseline characteristics.

Characteristic	Patients with confirmed PRCC (N=44)
Median age at inclusion (years)	65.0 (27.5–82.7)
ECOG performance status	
0	22 (50.0%)
1	22 (50.0%)
Gender	
Male	37 (84.1%)
Female	7 (15.9%)
PRCC type	
Type 1	13 (30.2%)
Type 2	30 (69.8%)
Not specified	1
Disease status at diagnosis	
Synchronous metastases	19 (43.2%)
Metachronous metastases	25 (56.8%)
Number of metastatic sites at inclusion	
1	4 (16.0%)
2	12 (48.0%)
Greater than 2 sites	9 (36.0%)
Previous treatment	
Nephrectomy	37 (84.1%)
Metastasectomy	6 (13.6%)
Radiotherapy	7 (15.9%)
Other	7 (15.9%)
MSKCC risk score (11)	
Favourable	9 (23.1%)
Intermediate	24 (61.5%)
High	6 (15.4%)
Missing data	5
IMDC score (12;13)	
Favourable	10 (23.8%)
Intermediate	19 (45.2%)
High	13 (31.0%)

Table 1. Patient demographics and baseline characteristics. Data are median (range) or n (%) unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group.

The majority ($N=30$, 69.8%) of patients had type 2 PRCC. Most patients underwent a prior nephrectomy ($N=37$, 84%) and were classified in the intermediate or poor prognosis groups according to the Memorial Sloan Kettering Cancer Center (MSKCC) score ($N=30$, 76.9%) or International Metastatic RCC Database Consortium (IMDC) score ($N=32$, 76.2%).

Treatment exposure

At the time of the analysis, the median follow-up was 32.0 (13.1–39.9) months and 4 patients were still on treatment (total administration duration from 14 to 22 months). The average daily dose of axitinib was 10 mg. The median duration of exposure to axitinib was 8.0 (0.3–31.3) months, 36 (81.8%) patients had at least one dose modification for toxicity including 7 (15.9%) patients who prematurely discontinued treatment due to adverse events (transient ischemic attacks ($n=1$); myocardial infarction ($n=1$); acute renal insufficiency ($n=1$); masticatory muscles cramps ($n=1$), peritonitis and septic shock ($n=1$), peritoneal bleeding ($n=1$), general physical deterioration ($n=1$)). The daily dose was adapted according to manufacturer recommendations and 21 (48%) patients received more than 10 mg axitinib, including 14 (32%) patients who received more than 14 mg per day.

25 of 36 patients discontinued treatment before 18 months and initiated another treatment: nivolumab ($n=8$), cabozantinib ($n=8$), everolimus ($n=5$), sunitinib ($n=3$) and temsirolimus ($n=1$).

Efficacy

The 24w-PFR was 45.2% (95% CI 32.6% to $+\infty$) in 42 evaluable patients according to the review committee, 46.2 (95% CI 23.4 to $+\infty$) in type 1 and 42.9 (95% CI 27.5 to $+\infty$) in type 2. The objective response rate (ORR) assessed by the investigators was 28.6% (95% CI 15.7–44.6) in the global population, and 7.7% and 35.7% in type 1 and 2, respectively (Table 2). The median duration of response in the 12 patients who have achieved PR was 7.9 months (3.7–18.3), and reached 15.7 (13.0–18.3) in the 2 patients with favorable risk according to IMDC risk criteria (13). Figure 2 shows the change in tumor measurements in both subtypes.

	Global PRCC population (N=42) [±]	Type 1 subgroup (N=13)	Type 2 subgroup (N=28)*
Best response			
PR [±]	12 (28.6%) [±]	1 (7.7%)	10 (35.7%)
SD	26 (61.9%)	10 (76.9%)	16 (57.1%)
PD	4 (9.5%)	2 (15.4%)	2 (7.1%)
Median PFS (months)	6.6 (95%CI 5.5–9.2)	6.7 (95%CI 2.9–14.0)	6.2 (95%CI 5.4–9.2)
24w-PFR	45.2 (95%CI 32.6 - $+\infty$)	46.2 (95%CI 23.4 - $+\infty$)	42.9 (95%CI 27.5 - $+\infty$)
Median OS (months)	18.9 (95%CI 12.8 – NR)	NR	17.4 (95%CI 11.4 – NR)

Table 2. Efficacy endpoints in the global PRCC population, and type 1 or type 2 subgroups. [±]To note, the type subgroup was not specified for one patient in PR. *2 patients in the type 2 subgroup received less than 4 weeks treatment duration and were subsequently excluded from the efficacy analysis. Data are n (%). Best responses were investigator-assessed. PR: Partial response; SD: stable disease; PD: progression disease. PFS: Progression free survival. 24w-PFR: centrally-assessed progression free rate at 24 weeks. OS: Overall survival. [±] Subgroup type was not specified for one patient. NR: Not reached.

The median PFS was 6.6 months (95% CI 5.5–9.2) in the whole population. The median PFS according to the papillary subtypes (Figure 3) was 6.7 months (95% CI 2.9–14.0) and 6.2 months (95%CI 5.4–9.2) for type 1 and 2, respectively. At the time of the analysis, 23 patients have died with median overall survival (OS) of 18.9 (95% CI 12.8–not reached) months, not yet reached in type 1, and 17.4 months (11.4–not reached) in type 2 papillary

carcinoma. There was no difference in response rate or PFS according to the dose delivered.

Safety

Adverse events were as expected and are detailed in Table 3.

Treatment-related adverse events	All grade	Grade 3 or 4
Fatigue	34 (77.3%)	2 (4.5%)
Hypertension	28 (63.6%)	12 (27.3%)
Dysphonia	26 (59.1%)	0 (0.0%)
Diarrhea	25 (56.8%)	3 (6.8%)
Anorexia	16 (36.4%)	3 (7%)
Nausea	17 (38.6%)	0 (0.0%)
Loss Weight	11 (25.0%)	1 (2.3%)
Stomatitis	12 (27.3%)	0 (0.0%)
Vomiting	8 (18.2%)	0 (0.0%)
Constipation	8 (18.2%)	0 (0.0%)
Hand & Foot	15 (34.1%)	1 (2.3%)
Hypothyroidism	9 (20.5%)	0 (0.0%)
Abdominal pain	6 (13.6%)	1 (2.3%)
Mucosal inflammation	5 (11.4%)	1 (2.3%)
Pruritus	5 (11.4%)	0 (0.0%)

Table 3. Treatment-related adverse events in the safety population (N=44).

Treatment-related adverse events of any grade that occurred during the treatment in at least 10% of patients, or treatment-related adverse events of grade 3 or 4 that occurred during the treatment in at least 5% of patients. Data are n (%).

43 (97.7%) out of the 44 patients analysed in the safety population experienced at least one treatment-related adverse event including 24 (54.5%) patients with at least one grade ≥ 3 treatment-related adverse event and grade ≥ 3 hypertension represents half of the cases. No toxic death occurred. Side effects were those generally observed with axitinib. Most common AEs were related to vascular effects, that is, hypertension, dysphonia, and diarrhea.

Discussion

The AXIPAP trial is the first prospective trial reporting the use of axitinib in previously untreated mPRCC. Classification of this rare histologic subtype of renal carcinoma is difficult to achieve. Misclassification rate exceeds 9% in the present trial. The centralised pathology review of the international trial RAPTOR investigating the use of everolimus in this subpopulation reported a re-classification rate of 21.7%.⁽⁷⁾ Therefore, a central pathology review should be mandatory in all future trials investigating papillary renal carcinomas.

Patients with mPRCC receiving axitinib in the AXIPAP trial achieved a 24-week PFR (24w-PFR) of 45.2%. The trial showed 19 non progressive patients at 24 weeks according to central review assessment. Nevertheless, median PFS was 6.6 months, median OS 18.9 months and, interestingly, the objective response rate was 28.6%. Results from different clinical trials in patients with mPRCC vary according to the population and selection methods used, and especially the use of pathology central review or not, to confirm PRCC. In our trial, patients had PRCC confirmed with histology central review. The magnitude of disease control rate achieved with axitinib is similar to that reached in naïve patients with sunitinib in a specific phase 2 trial, or in stratified subgroup analyses of randomised trials enrolling different non clear cell renal carcinomas (Table 4).

	Targeted therapy (trial name)	Patients (N)	Response Rate	Median PFS (Months)	Median OS (Months)
VEGFR TKI					
VEGFR TKI	Axitinib (AXIPAP)	44	28.6%	6.6	18.9
				6.7 type 1	NR type 1
				6.2 type 2	17.4 type 2
VEGFR TKI	Sunitinib (SUPAP) (6)	15 type 1	12%	6.6 type 1	17.8 type 1
		46 type 2		5.5 type 2	12.4 type 2
VEGFR TKI	Sunitinib (14) ^a	22 type 1	23.5%	6.4	NR
VEGFR TKI	Sunitinib (15) ^b	27 type 2	0%	1.6	12.6
EGFR TKI					

EGFR TKI	Erlotinib (16)	45	11%	NR	NR
mTOR Inhibition					
mTOR Inhibition	Everolimus (RAPTOR) (7)	23 type 1 46 type 2	1%	5 type 1 4 type 2	17.8 type 1 20.5 type 2
VEGFR mTOR Combined therapy					
VEGFR TKI vs mTOR Inhibition	Sunitinib vs Everolimus (ASPEN) (17)	51 vs 57	24%-5%	8.1-5.5	31.5-13.2 ++
VEGFR TKI vs mTOR Inhibition	Sunitinib vs Everolimus (ESPN) (18)	51 vs 57	7%-0%	5.7-4.1	16.6-14.9
cMET Inhibition					
cMET Inhibition	Savolitinib	109 ^c	7%	1.4	NR
	In <i>MET</i> driven tumors (9)	44	18%	6.2	
cMET Inhibition and VEGFR Inhibition	Foretinib	74 ^d	13.5%	9.3	NR
	in <i>MET</i> germline mutation (8)	10	50%		
cMET Inhibition vs cMET & EGFR Inhibition	Tivantinib vs Tivantinib & Erlotinib (19) ^e	25 vs 25	0%-0%	2-3.9	10-11.3
cMET kinase activity Inhibition	Crizotinib (CREATE) (20)	23***	17%	NR	NR
Immune checkpoint inhibition					
Anti-PD1 Ab	Pembrolizumab (21)	118	25.4% at 12w	4.1#	72% at 1 year#
Anti-PDL1 Ab + anti VEGF Ab	Atezolizumab+Bevacizumab (22) ^f	12	25%	NR##	NR##
Inhibition cMET and PDL-1	Savolitinib+Durvalumab (CALYPSO) (23) ^g	41	27%	NR	6.9 (immature)

Table 4 - Response rate (RR), median progression free survival (PFS) and median overall

survival (OS) of targeted therapies or immunotherapy in mPRCC patients. NR: Not reached;

Ab: Antibody (monoclonal antibody). Patients (%) who had received previous therapy(ies) ^a36%; ^b14% (less than 2 previous treatments); ^c45% (up to ≥3 previous treatment); ^d19%; ^e34%; ^f48%; ^g32% ; ***mPRCC type 1 -eligible and evaluable patients only; ++ Median OS obtained in all non-clear cell carcinomas; # in the global population of 165 patients including 118 (71%) patients with mPRCC; ## in the global population of 65 patients including 12 mPRCC.

PFS and OS appeared shorter in the phase 2 trial investigating axitinib after failure of first line temsirolimus treatment, that is, 3.5 and 8.3 months, respectively; however no central review for pathology or radiology had been performed in this trial (24).

This study has some limitations. The overall response rate was exclusively based on investigator assessment; correlative genomic studies such as MET status determination are lacking and deserve to be further explored.

The AXIPAP trial showed 24w-PFR based on central review assessment to be slightly more favourable and overall survival is longer in type 1 compared with type 2 subgroup. Longer

survivals were previously reported in type 1 mPRCC patients potentially reflecting a rather slow tumor growth (1;3;6). Notably, all but one responders in the AXIPAP trial had a type 2 mPRCC. Trials investigating different VEGFr inhibitors reported higher response rates in type 2 than in type 1 mPRCC patients (6;24). These results indicate that type 2 papillary renal carcinoma, regardless of their recently demonstrated molecular heterogeneity, seems to be more dependent on the VEGF pathway than the type 1 subgroup (1;3;25).

MET alterations have been quite often reported especially in the type 1 subgroup (1-4). Therapies targeting the *MET* pathway were thus developed with some degrees of efficacy especially in patients with *MET* germline mutations (8;9;20). However, recent results in patients with tumors harboring non-germline *MET* alterations did not support the development of savolitinib, a *MET*-directed agent alone in phase 3 trials (9). The randomized phase 2 trial PAPMET (NCT02761057) investigates the efficacy of cabozantinib which seems to have some activity in retrospectives series of mRCC (26;27). As previously reported in clear cell renal carcinoma, the tumor heterogeneity in papillary renal carcinoma has to be considered. Some tumors may mostly depend on the VEGF pathway while others may be driven by other genes or pathways (3;25;28). Preliminary results from prospective trials using immune check point inhibitors such as PD1 or PDL1 directed antibodies in mPRCC recently reported interesting response rates, although confirmation of efficacy is still expected (21-23).

Axitinib combined with PD1- or PDL1-directed antibodies showed efficacy with manageable toxicity in patients with metastatic clear cell carcinoma and is now registered for use in the USA. This combination should be further investigated in patients with mPRCC (29;30).

Conclusions

Expert pathology review to confirm PRCC should be recommended. Axitinib showed encouraging results in mPRCC patients, especially in type 2 PRCC, and toxicity was manageable. Axitinib appears as an interesting agent to investigate in combination with immunotherapy in mPRCC patients.

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The funder of the study, Centre Leon Berard, was responsible for trial conception and coordination, data analysis, and writing of the report. All authors were involved in writing and reviewing the report and in making the decision to submit for publication. SN, EB, CSF, and DP had full access to all study data and full responsibility to submit for publication. Pfizer provided the study drug axitinib and funding to Centre Leon Berard to conduct the study. Pfizer had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Disclosure of potential conflicts of interest:

Dr. Negrier reports grants, personal fees, non-financial support and other from PFIZER, grants, personal fees and other from IPSEN, during the conduct of the study; personal fees and other from BMS, personal fees from EUSAPHARMA, personal fees from NOVARTIS, personal fees from MSD, outside the submitted work; Dr. Rioux-Leclercq reports personal fees from PFIZER and BMS, outside the submitted work; for conferences on non-clear cell RCC and molecular pathways in RCC. Dr. Gross-Goupil reports personal fees and non-financial support from IPSEN, personal fees and non-financial support from ROCHE, personal fees and non-financial support from MSD,

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Figure legends

Figure 1. Trial profile. **2 patients with type 2 PRCC received less than 4 weeks treatment duration and were subsequently excluded for the efficacy analysis (N=42).

Figure 2. Maximum change from baseline in target lesions. One patient clinically progressive according to the investigator had no lesion measurement.

Figure 3. Progression-free survival (PFS) A) in the global population, B) according to histological subtypes of PRCC. Kaplan-Meier plots for progression-free survival. Data cut-off was May 6, 2019.

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