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Limited clinical activity of palbociclib and ribociclib monotherapy in advanced cancers with cyclin D-CDK4/6 pathway alterations in the Dutch DRUP and Australian MoST trials

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Abstract

The Dutch Drug Rediscovery Protocol (DRUP) and the Australian Cancer Molecular Screening and Therapeutic (MoST) Program are similar nonrandomized, multidrug, pan-cancer trial platforms that aim to identify signals of clinical activity of molecularly matched targeted therapies or immunotherapies outside their approved indications. Here, we report results for advanced or metastatic cancer patients with tumors harboring cyclin D-CDK4/6 pathway alterations treated with CDK4/6 inhibitors palbociclib or ribociclib. We included adult patients that had therapy-refractory solid malignancies with the following alterations: amplifications of *CDK4*, *CDK6*, *CCND1*, *CCND2 or CCND3*, or complete loss of *CDKN2A or SMARCA4*. Within MoST, all patients were treated with palbociclib, whereas in DRUP, palbociclib and ribociclib were assigned to different cohorts (defined by tumor type and alteration). The primary endpoint for this combined analysis was clinical benefit, defined as confirmed objective response or stable disease ≥16 weeks. We treated 139 patients with a broad variety of tumor types; 116 with palbociclib and 23 with ribociclib. In 112 evaluable patients, the objective response rate was 0% and clinical benefit rate at 16 weeks was 15%. Median progression-free survival was 4 months (95% CI:

Abbreviations: AE, adverse event; CB, clinical benefit; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; CTCAE, common terminology criteria for adverse events; Cyclin D-CDK4/6-pRB, cyclin D1-cyclin dependent kinase 4/6-retinoblastoma; DRUP, Drug Rediscovery Protocol; GBM, glioblastoma multiforme; IDSMC, independent data and safety monitoring committee; MEB, molecular expert board; MoST, Molecular Screening and Therapeutic program; MTB, molecular tumor board; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RANO, response assessment in neuro-oncology; RECIST, response evaluation criteria in solid tumors; SD, stable disease; TTP, time-to-progression; VUS, variant of unknown significance; WGS, whole genome sequencing.

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3-5 months), and median overall survival 5 months (95% CI: 4-6 months). In conclusion, only limited clinical activity of palbociclib and ribociclib monotherapy in patients with pretreated cancers harboring cyclin D-CDK4/6 pathway alterations was observed. Our findings indicate that monotherapy use of palbociclib or ribociclib is not recommended and that merging data of two similar precision oncology trials is feasible.

KEYWORDS
CDK4/6 inhibitors, drug rediscovery, monotherapy, precision oncology, targeted therapy

What's new?

Many advanced malignancies feature alterations in the cyclin D-CDK4/6 pathway, potentially rendering them sensitive to CDK4/6 inhibitor therapy. Here, clinical benefits of CDK4/6 inhibitor monotherapy with palbociclib or ribociclib were assessed in cancer patients from precision oncology trials in the Netherlands and Australia. In patients with advanced treatment-refractory tumors harboring cyclin D-CDK4/6 pathway alterations, no objective responses were observed following CDK4/6 inhibitor monotherapy. Palbociclib or ribociclib monotherapy further exhibited limited cytostatic potential for inducing tumor regression. The findings indicate that off-label use of either palbociclib or ribociclib alone is of limited clinical benefit against advanced tumors with cyclin D-CDK4/6 pathway alterations.

1 | INTRODUCTION

Driven by a wealth of novel targeted therapies, precision oncology offers innovative treatment options for patients with refractory cancers. The Dutch Drug Rediscovery Protocol (DRUP)[1] and Australian Cancer Molecular Screening and Therapeutic (MoST)[2] Program are national precision oncology platform studies in which parallel cohorts are opened for distinct molecular variants and targeted drug combinations, with the objective of detecting early signals of activity of FDA/EMA/TGA approved, commercially available targeted therapies used outside their indicated label. In small cohorts, it tests the hypothesis that tumor response to targeted therapy is dependent on molecular alterations in the pathway targeted by the drug. Structured data collection within the two protocols permitted the identification of patient subsets who may, or may not derive benefit from the off-label use of targeted drugs.

The DRUP and MoST studies both included cohorts testing a CDK4/6 inhibitor. Selective CDK4/6-inhibitors, such as palbociclib (PD-0332991) and ribociclib (LEE011), are approved for the treatment of hormone receptor positive advanced and/or metastatic breast cancers in combination with endocrine therapy.[3-5] CDK4 and CDK6 are part of the cyclin D1-cyclin dependent kinase 4/6-retinoblastoma (cyclin D-CDK4/6-pRB) signaling pathway. This pathway plays a critical role in the regulation of cell proliferation, by controlling the G1 checkpoint of the cell cycle.[6-8] Here, mitogenic signaling and signals of growth-inhibition regulate the activity of CDK4 and/or CDK6 complexes with cyclin D, ultimately controlling the activity of tumor suppressor pRb.[9-11]

Molecular alterations in the cyclin D1-CDK4/6-pRB pathway allowing cancer cells to bypass the pRb-dependent restriction point are common across a broad spectrum of cancers. They include amplifications of *CCND1*, *CDK4* and *CDK6*, or loss of negative regulators of the pathway, including deletions of *CDKN2A* or loss of *RB1*. While preclinical evidence suggests that CDK4/6 kinases are important therapeutic targets,[12-16] clinical activity as monotherapy has been disappointing to date.[9-11,17,18] The reasons for this are unclear and may relate to cytostatic rather than cytotoxic effects, drug-specific differences in activity or histotype context. Here, the clinical efficacy is reported for 139 patients with a wide range of advanced cancers harboring cyclin D-CDK4/6 pathway alterations treated with palbociclib or ribociclib monotherapy in a combined analysis of DRUP and MoST trials.

2 | METHODS

2.1 | Study design

2.1.1 | DRUP

DRUP is an ongoing, prospective, nonrandomized precision oncology trial for adult patients with advanced or metastatic solid tumors,

multiple myeloma or B-cell non-Hodgkin lymphoma. In this trial, actionable variants, as previously identified through molecular profiling tests performed during regular diagnostics, are matched with targeted- or immunotherapies that are available within the DRUP protocol. Parallel cohorts within the trial are designed for distinct combinations of histological tumor types, molecular variants and targeted therapies. A detailed version of study design and protocol has previously been published.[1]

2.1.2 | MoST

MoST is a precision medicine platform that assigns patients with solid tumors to therapeutic trials (substudies) on the basis of genomic alterations, agnostic to cancer histotype. Molecular alterations are identified through genomic profiling of an archival tumor sample. Substudies are designed as phase Ib/IIa open-label trials with the flexibility of individual trials to open and close while others continue accrual.[2]

2.2 | Participants

In both pan-cancer trials, adult patients were required to have exhausted or declined all standard lines of treatment, to have an acceptable performance score and organ function and measurable disease according to RECIST or RANO-criteria.[19,20] Furthermore, prior molecular profiling must have identified a potential target for targeted therapy within the trials: amplification of *CDK4*, *CDK6*, *CCND1*, *CCND2 or CCND3*, or complete loss of *CDKN2A or SMARCA4*. Alterations in RB1 itself were an exclusion criterion for both trials. An overview of main inclusion and exclusion criteria and specifics on molecular eligibility is provided in Table S1. Drug-specific inclusion criteria are described in Table S2.

2.3 | Procedures

2.3.1 | DRUP

DRUP is a national cross-institutional trial with 35 participating sites. Upon case submission based on previously performed tumor molecular profiling, the study team attempted to match patients to a suitable study treatment. If a patient was eligible for more than one study treatment, a decision was made based on evidence in literature and drug availability. The molecular expert board (MEB) was consulted for cases where pathogenicity of a molecular alteration was not evident, or for advice on matching tumor profile with study treatment. Palbociclib and ribociclib were randomly assigned to new cohorts, consisting of a tumor type and molecular alteration. An Independent Data and Safety Monitoring Committee (IDSMC) performed the assessment of safety and accrual data.

2.3.2 | MoST

A Molecular Tumor Board (MTB) reviewed molecular profiling results, including classification of variants. Molecular variant actionability was assessed based on available literature, therapies and patient history.[21] If several molecular targets were found, the MTB made a recommendation based on the clinical profile of the patient and expected pathogenicity of the genomic alterations. Assessments of patient safety and trial progress were provided by an IDSMC.

2.4 | Study agents

Palbociclib (PD-0332991; Ibrance), supplied by Pfizer and available in DRUP and MoST, 125 mg Q1D, was orally administered on 21 consecutive days followed by 7 days off treatment in 28-day cycles. Ribociclib (LEE011; Kisqali) supplied by Novartis and available only in DRUP, 600 mg Q1D, was orally administered on 21 consecutive days followed by 7 days off treatment in 28-day cycles. Patients were treated until radiological or clinical disease progression, unacceptable toxicity, death or withdrawal of consent.

2.5 | Enrolment and drug assignment

The cut-off date for analysis was November 1, 2021. Enrolment for the MoST palbociclib substudy commenced in November 2016. Enrolment for palbociclib and ribociclib in DRUP commenced in July 2018 and October 2019, respectively. Within DRUP, 294 cases were submitted to the central study with an eligible molecular target for treatment with palbociclib or ribociclib. Out of these, 171 patients did not start treatment, for various reasons (Figure S1). Of the remaining eligible patients (n = 123), 100 were randomly assigned to palbociclib and 23 to ribociclib. In MoST, 16 patients were matched to palbociclib. Thus, 139 patients started treatment with palbociclib or ribociclib within the DRUP and MoST trials. In total, 37 palbociclib and ribociclib tumor-specific cohorts were opened for different actionable molecular variants in DRUP (Table S3). Within MoST, all patients were included in one histotype-agnostic cohort. At the time of analysis, one DRUP cohort had expanded to stage 2 (n > 8): palbociclib for glioblastomas with *CDKN2A* loss.

2.6 | Study endpoints and assessment

2.6.1 | Combined efficacy analysis

To evaluate the combined results of all patients treated in either study, the clinical benefit rate (CBR), defined as confirmed objective response (OR) or stable disease (SD) for at least 16 weeks, according to RECIST1.1[19] or RANO[20] criteria, was calculated. Safety was assessed for all patients that started treatment with palbociclib or ribociclib according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

2.6.2 | DRUP

The primary endpoint of DRUP was CBR, defined as confirmed OR or SD for at least 16 weeks, according to RECIST1.1[19] or RANO[20] criteria. Safety was assessed for all patients that started treatment with palbociclib or ribociclib according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. An overview of additional study endpoints and assessment is provided in Table S4.

2.6.3 | MoST

The primary endpoint of MoST was to evaluate clinical activity, using a composite endpoint of objective response rate (ORR) after trial registration and the time to progression (TTP) ratio. The TTP ratio was calculated as the time to progression on trial (TTP2), compared to the time to progression on the previous line of systemic therapy (TTP1). As time to progression generally decreases with each line of systemic therapy, a TTP ratio ≥1.3 assumes CB.[22-24] If TTP1 was not evaluable, TTP2 >6 months was prespecified to indicate clinical activity. An overview of study endpoints and assessment is provided in Table S4.

2.7 | Statistical considerations

2.7.1 | DRUP

A Simon-like two-stage design was used per cohort, with eight patients enrolled in stage 1.[25] If CB, defined as SD, partial or complete response (PR, CR) for at least 16 weeks, was observed in at least one patient, 16 more participants were included for stage 2. Stage 2 cohorts were considered potentially successful when ≥5 patients had CB. The study design has 85% power to reject a CBR of 10%, if the true percentage is 30%.

2.7.2 | MoST

A response rate of 40% supported the molecular hypothesis for this trial. Using the method of Mehta-Cain, boundaries for declaring similar activity were determined based on a one-sided 95% confidence interval (CI) for a hypothesized ORR of 40% at 6 months.[26] Thus, for a sample size of 16 patients, objective responses in ≥3 patients constitute sufficient activity to warrant further evaluation.

2.8 | Data collection and statistics

Statistical analysis was performed in R (version 4.0.3). Patient characteristics, tumor responses and adverse events were summarized with descriptive statistics. For the combined analysis, CB was summarized as a proportion with exact 95% CIs and Kaplan-Meier curves were generated to estimate the median progression-free survival (PFS) and overall survival (OS), both calculated from the first day of treatment administration for patients treated in DRUP and from the trial registration date in MoST. Waterfall plots were used to visualize the maximum tumor reduction of target lesions compared to baseline.

3 | RESULTS

3.1 | Baseline characteristics

Baseline characteristics of the 139 patients that commenced treatment with palbociclib or ribociclib in DRUP or MoST are provided in Table 1. Details on molecular eligibility per patient can be found in Data S1. Median age at consent was 60 (range 19-84) and 60% of patients were male. The median number of prior lines of systemic treatment was 3 (range 0-10). The most frequently included tumor types were glioblastoma multiforme (GBM) (18%), sarcoma (13%), non-small cell lung cancer (NSCLC) (9%) and pancreatic ductal adenocarcinoma (9%). Other rare cancer types treated on trial included a ceruminous gland carcinoma, a perivascular epithelioid cell tumor and an adrenocortical carcinoma.

3.2 | Treatment outcome

Of 139 patients who started study treatment in either DRUP or MoST, 27 were nonevaluable for the primary endpoint of this combined analysis, due to premature termination of treatment (ie, before completing one full treatment cycle of 28 days). Reasons for premature termination were clinical progression (n = 17), death (n = 5), adverse events (n = 4) or withdrawn consent (n = 1) (Figure S1), reflective of a heavily pretreated population. Accordingly, efficacy analysis was performed in 112 patients who were evaluable for trial endpoints.

3.2.1 | Combined efficacy analysis

Analysis within evaluable patients (n = 112) revealed no objective responses (CR or PR) within the first 16 weeks of treatment. SD at 16 weeks was observed in 16 patients across different histotypes, including chordoma (n = 1), GBM (n = 2), liposarcoma (n = 2), melanoma (n = 1), mesothelioma (n = 1), mucoepidermoid carcinoma (n = 1), neuroendocrine carcinoma (n = 1), NSCLC (n = 1), osteosarcoma (n = 1), perivascular epithelioid cell tumor (n = 1), prostate carcinoma (n = 1), salivary gland carcinoma (n = 1), solitary fibrous tumor (n = 1) and thymic carcinoma (n = 1). One additional patient with pancreatic adenocarcinoma with no target lesion at baseline had noncomplete response/nonprogressive disease maintaining ≥16 weeks by evaluation of the nontarget lesion (Table 2). This patient

TABLE 1 Baseline characteristics of 139 patients enrolled to treatment with palbociclib or ribociclib, including clinical benefits rates per tumor type.

	Clinical benefit ≥16 weeks			
	No (n = 122)	Yes (n = 17)	Total (n = 139)	*P*-value
Age at consent (IQR)	60 (51-66)	59 (56-68)	60 (51-66)	.46
Gender (%)				.8
Male	73 (60%)	11 (65%)	84 (60%)	
Female	49 (40%)	6 (35%)	55 (40%)	
WHO PS (%)				.58
WHO 0	36 (30%)	8 (47%)	44 (32%)	
WHO 1	73 (60%)	8 (47%)	81 (58%)	
WHO 2	7 (6%)	1 (6%)	8 (6%)	
Not available	6 (4%)	0 (0%)	6 (4%)	
Previous systemic therapy lines (range)	3 (0-10)	1 (0-7)	2 (0-10)	.015
Tumor type				**CBR**
Glioblastoma multiforme	23 (19%)	2 (12%)	25 (18%)	8.0%
Sarcoma	13 (11%)	5 (29%)	18 (13%)	27.8%
NSCLC	12 (10%)	1 (6%)	13 (9%)	7.7%
Pancreatic carcinoma	11 (9%)	1 (6%)	12 (9%)	8.3%
Cholangiocarcinoma	9 (7%)	0 (0%)	9 (7%)	0.0%
Esophageal carcinoma	7 (6%)	0 (0%)	7 (5%)	0.0%
(Uveal) melanoma	6 (5%)	1 (6%)	7 (5%)	14.3%
Prostate carcinoma	5 (4%)	1 (6%)	6 (4%)	16.7%
Ovarian carcinoma	6 (5%)	0 (0%)	6 (4%)	0.0%
Colorectal carcinoma	4 (3%)	0 (0%)	4 (3%)	0.0%
Urothelial cell carcinoma	4 (3%)	0 (0%)	4 (3%)	0.0%
HNSCC	3 (2%)	0 (0%)	3 (2%)	0.0%
Mesothelioma	2 (2%)	1 (6%)	3 (2%)	33.3%
Salivary gland carcinoma	2 (2%)	1 (6%)	3 (2%)	33.3%
Other	15 (12%)	4 (23%)	19 (14%)	21.0%

Note: Number of prior systemic therapies is the sum of prior lines of endocrine therapy, chemotherapy, immunotherapy and targeted therapy.
Abbreviations: CBR, clinical benefit rate; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; IQR, Interquartile range; WHO PS, World Health Organization Performance Status.

was therefore classified as having experienced CB, resulting in an overall CBR of 15% (95% CI: 9%-23%). Pooled analysis of all patients that started treatment regardless of evaluability (n = 139) demonstrated a CBR of 12% (95% CI: 7%-19%) at 16 weeks of treatment. Patients with CB received less systemic therapies prior to study enrolment compared to patients without CB (median of 1 vs 3; $P = .015$, Table 1). Kaplan-Meier estimates for median PFS and OS were 4 months (95% CI: 3-5 months) and 5 months (95% CI: 4-6 months), respectively (Figure 1). Best percentage change in the sum of target lesions is depicted in Figure 2. Clinical benefit rates per tumor type are reported in Table 1. Specific tumor types with a more notable CBR included sarcomas (5/18 = 28%, mainly consisting of well-/de-differentiated liposarcomas [n = 15]). Furthermore, in HNSCC and mesothelioma we found a CBR of 33%, but both groups had a limited sample size of three patients, and in each group only one patient experienced clinical benefit.

3.2.2 | Primary endpoint analysis for DRUP

In 96 patients from DRUP, no confirmed responses were observed but SD ≥16 weeks was demonstrated for 12 patients. Hence, CBR was 12.5% (95% CI: 7%-21%). At time of analysis, only the palbociclib cohort for *CDKN2A* loss cholangiocarcinoma had completed accrual as per protocol and was closed after stage 1 (CBR 0%).

3.2.3 | Primary endpoints analysis for MoST

In 16 patients, no complete or partial response were achieved. Seven patients achieved SD as best response, with two patients maintaining SD for at least 6 months. One patient with no target lesions at baseline achieved a noncomplete response/nonprogressive disease by

TABLE 2 Overview of patients with stable disease ≥16 weeks as best response.

Tumor type	Molecular target	Weeks on treatment	Best change sum target lesions (%)[a]	Drug	Trial
GBM	*CDKN2A* loss	46	−17.6*	P	DRUP
GBM	*CDKN2A* loss	21	−45.5*	P	DRUP
Melanoma	*CDKN2A* loss	33	−4.2	P	DRUP
Mesothelioma	*CDKN2A* loss	20	−1.6	R	DRUP
Mucoepidermoid carcinoma	*CDK6* amplification	25	−3.0	R	DRUP
Neuroendocrine carcinoma	*CCND1* amplification	34	−11.8	P	DRUP
NSCLC	*CDKN2A* loss	47	−23.3	P	DRUP
PDAC	*CDKN2A* loss	96	N.A.$	P	MoST
PEComa	*CDKN2A* loss	30	−23.9	P	DRUP
Prostate carcinoma	*CDK6* amplification	23	−14.0	P	DRUP
Salivary gland carcinoma	*CDKN2A* loss	23	−5.4	R	DRUP
Sarcoma					
Chordoma	*CDKN2A* loss	20	+17.4	P	MoST
Liposarcoma	*CDK4* amplification	20	0.0	P	MoST
Liposarcoma	*CDK4* amplification	32	+2.5	P	MoST
Osteosarcoma	*CDK4* amplification	26	+16.7	P	DRUP
Solitary fibrous tumor	*CDKN2A* loss	24	+8.7	P	MoST
Thymic carcinoma	*CDKN2A* loss	49	−6.0	R	DRUP

[a]According to RECIST1.1 criteria, except for patients with GBM (for these patients, RANO criteria were followed and measurements are marked with "*"). For one patient marked with "$," no maximum change in target lesions was available as this patient had no target lesion at baseline; this patient achieved a noncomplete response/nonprogressive disease by evaluation of the nontarget lesion.

Abbreviations: GBM, glioblastoma multiforme; N.A., not applicable; NSCLC, non-small cell lung cancer; PDAC, pancreatic duct adenocarcinoma; PEComa, perivascular epithelioid cell tumor; P, palbociclib; R, ribociclib.

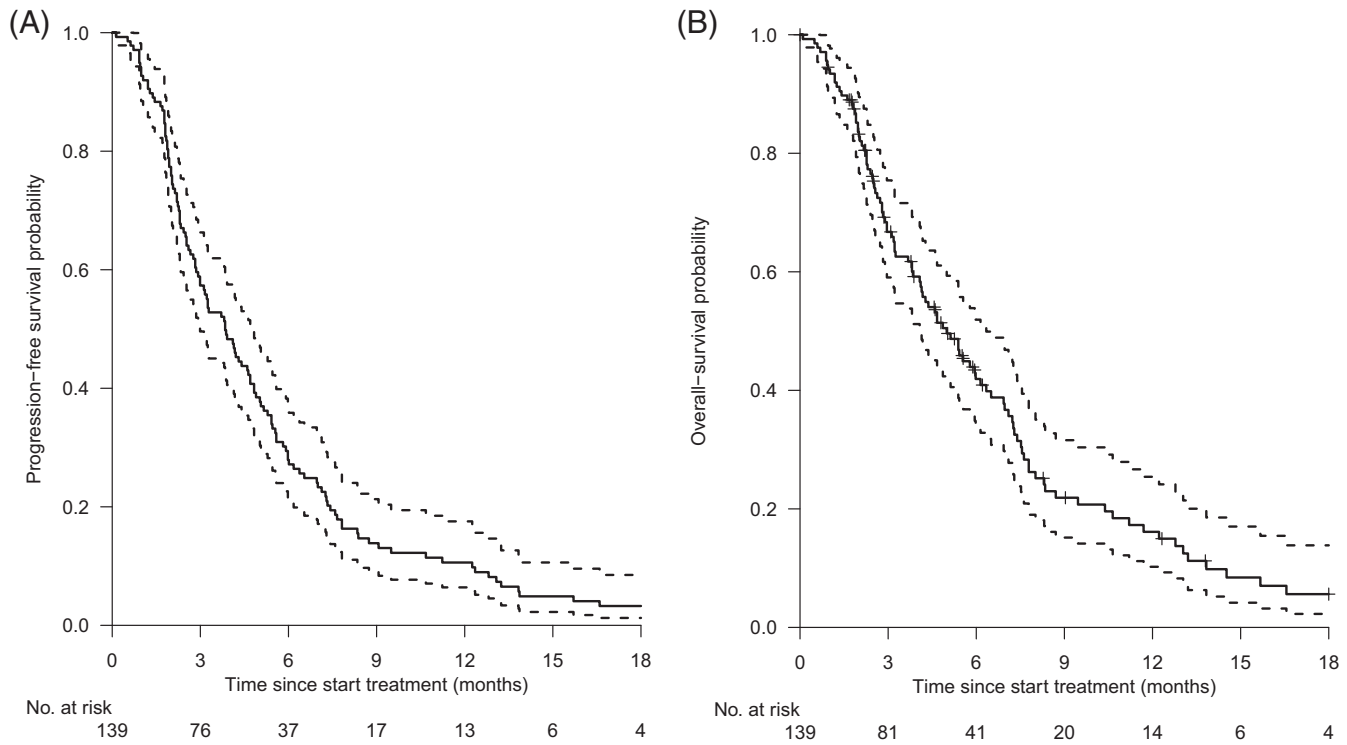

FIGURE 1 Evaluation of response. (A) Kaplan-Meier curve for estimated progression-free survival. (B) Kaplan-Meier curve for estimated overall survival.

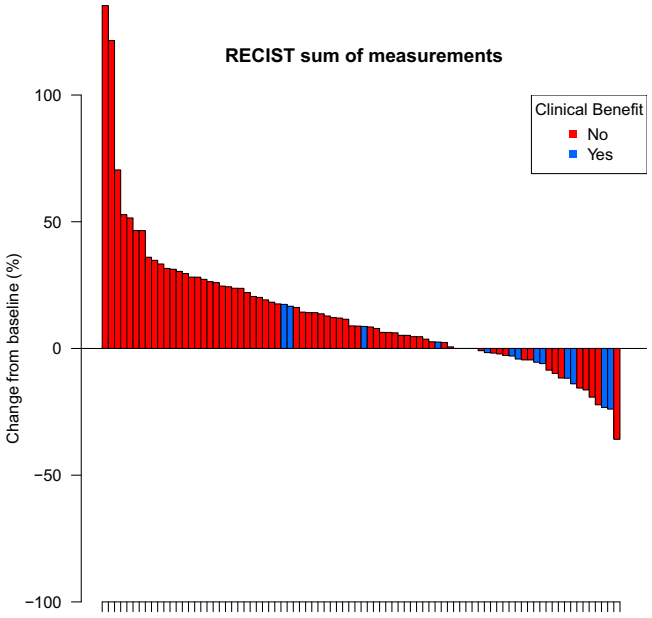

FIGURE 2 Waterfall plot representing the best percentage change from baseline to sum of target lesions according to RECIST (n = 84; 73 DRUP patients and 11 MoST patients). Patients are depicted in order of percentage change. Patients that did not finish one full cycle of treatment and were thus not evaluable for the primary endpoint (n = 27), patients for whom disease was evaluated according to RANO criteria (n = 23) and patients for whom no measurement data were available (n = 5) were not included in the graph. Only 12 of 17 patients with CB can be identified from this figure; two had measurements according to RANO criteria, two had best percentage changes too small to depict (−1.6% and 0%) and one had no target lesions and was assessed according to nontarget lesions. [Color figure can be viewed at wileyonlinelibrary.com]

evaluation of nontarget lesions, which was maintained for over 6 months. Post hoc analysis of TTP1 from a previous line of systemic therapy was possible for only five patients. Two of these five patients demonstrated a ratio of ≥1.3 for TTP on study treatment compared to therapy before study enrolment. Taken together, this indicated a CBR of 25% (95% CI: 7%-52%), comprised of two patients that remained progression-free at 6 months and two additional patients that achieved a TTP ratio ≥1.3.

3.3 | Safety

Of all patients that started treatment, 28% (n = 39) experienced at least one grade ≥3 adverse event (AE) that was deemed at least possibly related to treatment (Table S5). One fatal case of pneumonia was reported for a patient with NSCLC treated with palbociclib, this event was assessed as possibly related to treatment. The most commonly reported related AEs were a decrease in white blood cell count (n = 16), anemia (n = 6) and vomiting (n = 4). No suspected unexpected serious adverse reactions occurred.

4 | DISCUSSION

By combining results of the DRUP and MoST trials, we show very limited clinical activity of treatment with either palbociclib or ribociclib monotherapy in one of the largest cohorts to date of patients with a broad spectrum of advanced cancers with CDK4/6 pathway alterations. Results of our analysis, with a CBR of 15%, are in line with previously reported work on a similar, heterogeneous patient group treated with ribociclib.[27] We, therefore, conclude that monotherapy use of these agents has little role in cancer treatment.

These findings, with several cases of SD as best result, could potentially be explained by the cytostatic nature of CDK4/6 inhibitors, with limited potential to induce tumor regression when administered as monotherapy.[28] The approved indications for palbociclib or ribociclib are in combination with endocrine therapy and have demonstrated significant improvements in PFS for patients with hormone receptor positive advanced breast cancer.[3-5] Amongst these patients, *CDK4* and *CDK6* amplification is associated with endocrine resistance, suggesting these cancers are dependent on cyclin D1-CDK4/6-pRB signaling.[29,30] The pivotal PALOMA-1 trial, however, demonstrated similar clinical efficacy of palbociclib in breast cancer patients with *CDKN2A* loss or *CCND1* amplification compared to otherwise molecularly unselected patients,[31] leaving the value of biomarker selection unclear.

This analysis merges data from two precision oncology trials with minor differences in study design. A key difference between DRUP and MoST is an assessment of treatment efficacy in the context of cancer histotype for DRUP, while MoST substudies were tumor-agnostic and defined by molecular alterations alone. For this reason, 37 separate cohorts were created in DRUP. By design, this would allow the study team to determine whether responses also vary by histotype. However, due to perceived futility (no objective responses observed after >100 patients that started study treatment in DRUP), the IDSMC was consulted. Based on their advice and after consultation of both pharmaceutical companies, it was decided to discontinue accrual and merge trial data. Supported by the emerging concept of tissue-agnostic evaluation of targeted anticancer agents and the subsequent recent approvals of pembrolizumab for microsatellite instable tumors and TRK-inhibitors for tumors harboring *NTRK* gene fusions, tissue-agnostic analysis of study endpoints of all included patients was performed.[32] By analyzing results tumor-agnostically, however, we cannot exclude CB in specific patient subsets, although we felt this was outweighed by the overall lack of CB in this large cohort of patients with various histotypes. For instance, even two histotype-specific single arm studies in patients with soft tissue sarcomas harboring cyclin D-CDK4/6 pathway alterations treated with palbociclib (total n = 59) could not draw any definitive conclusions; while the studies reported a 12-week PFS rate of 57.2%[33] and a disease control rate of 48%,[34] the possibility of an indolent natural disease trajectory of well-/de-differentiated liposarcomas inflating disease control rates cannot be excluded from single arm studies. Within our combined analysis these outcomes could not be reproduced, with only 3 of

15 (20%) soft tissue sarcoma patients demonstrating SD at 16 weeks. While an indolent natural disease trajectory cannot explain the *positive* results of the TAPUR NSCLC[35] or HNSCC[36] cohorts based on a CBR of 31% and 37%, optimal sequencing of therapies (EGFR, or checkpoint inhibitors) in these cancers, synergizing with the cytostatic, or immune potentiating effects of CDK4/6 inhibition, may be considered.[37] This provides rationale for a combined therapy approach to induce tumor regression, and a MoST trial of palbociclib and avelumab (ACTRN12620000568910) is currently underway.

In 2017, a third CDK4/6 inhibitor, abemaciclib, received FDA approval in hormone receptor positive advanced breast cancer after demonstrating superior efficacy when combined with endocrine therapy compared to endocrine therapy and placebo.[38] Abemaciclib is unique amongst the CDK4/6 inhibitors in that it has also demonstrated efficacy as monotherapy in advanced breast cancer patients having progressed on endocrine therapy and chemotherapy.[39] Preclinically, abemaciclib demonstrates the ability to induce cell cycle arrest, tumor cell regression and death.[40] The efficacy of abemaciclib as monotherapy beyond the breast cancer setting remains to be further established but appears more promising than palbociclib and ribociclib monotherapy.[39,41] Further characterization of this is currently underway in several precision oncology trials including the TAPUR (NCT02693535) and DRUP (NCT02925234) studies.

Due to the absence of objective responses, no comparative exploratory biomarker analyses could be performed. Nevertheless, additional potential drivers were identified in the majority of the study population and may have contributed to resistance to single-agent targeted therapy.[42] Combinatorial regimens, enabling simultaneous targeting of oncogenic events that promote tumor proliferation, may lead to improved therapy responses for these patients. Recently, the I-PREDICT precision oncology trial demonstrated the feasibility of such an approach.[24] Also, development of N-of-one-strategies for combination therapies based on the unique molecular alterations of individuals has shown promise in improving clinical outcomes in cancer patients, compared to unmatched treatment regimens.[43] Both protocols incorporated CDK4/6 inhibitors into their treatments, suggesting a role for these compounds in a setting other than monotherapy.

To our knowledge, this is the first effort to merge data from two separate precision oncology trials. By presenting efficacy data together, we demonstrate how results from independent, yet similar precision oncology protocols can be pooled to provide relevant insights and guidance for international data sharing. Sharing data among precision oncology studies will be particularly important in generating sufficient patient numbers for rare cancer types and/or molecular alterations.

To conclude, palbociclib and ribociclib monotherapy had only limited clinical activity in a large cohort of 139 cancer patients derived from two precision oncology trials. Findings of our study indicate that off-label use of these two CDK4/6 inhibitors as monotherapy is not advisable. International data sharing of study results with comparable design has significant benefit in strengthening clinical guidance, which is especially relevant in the context of precision oncology with rare molecular subsets and/or cancer histologies.

AUTHOR CONTRIBUTIONS

Laurien J. Zeverijn: Conception and design; Provision of study materials or patients; Collection and assembly of data; Data analysis and interpretation; Article writing; Final approval of article. **Eleonora J. Looze:** Conception and design; Provision of study materials or patients; Collection and assembly of data; Data analysis and interpretation; Article writing; Final approval of article. **Subotheni Thavaneswaran:** Conception and design; Provision of study materials or patients; Collection and assembly of data; Data analysis and interpretation; Article writing; Final approval of article. **J. Maxime van Berge Henegouwen:** Provision of study materials or patients; Collection and assembly of data; Article writing; Final approval of article. **Robert J. Simes:** Conception and design; Article writing; Final approval of article. **Louisa R. Hoes:** Provision of study materials or patients; Collection and assembly of data; Article writing; Final approval of article. **Katrin M. Sjoquist:** Provision of study materials or patients; Article writing; Final approval of article. **Hanneke van der Wijngaart:** Provision of study materials or patients; Collection and assembly of data; Article writing; Final approval of article. **Lucille Sebastian:** Provision of study materials or patients; Article writing; Final approval of article. **Birgit S. Geurts:** Provision of study materials or patients; Collection and assembly of data; Article writing; Final approval of article. **Chee K. Lee:** Provision of study materials or patients; Article writing; Final approval of article. **Gijsbrecht F. de Wit:** Provision of study materials or patients; Collection and assembly of data; Article writing; Final approval of article. **David Espinoza:** Collection and assembly of data; Data analysis and interpretation; Article writing; Final approval of article. **Paul Roepman:** Provision of study materials or patients; Article writing; Final approval of article. **Frank P. Lin:** Provision of study materials or patients; Article writing; Final approval of article. **Anne M. L. Jansen:** Provision of study materials or patients; Article writing; Final approval of article. **Wendy W. J. de Leng:** Provision of study materials or patients; Article writing; Final approval of article. **Vincent van der Noort:** Collection and assembly of data; Data analysis and interpretation; Article writing; Final approval of article. **Lindsay V. M. Leek:** Data analysis and interpretation; Article writing; Final approval of article. **Filip Y. F. L. de Vos:** Provision of study materials or patients; Article writing; Final approval of article. **Carla M. L. van Herpen:** Provision of study materials or patients; Article writing; Final approval of article. **Hans Gelderblom:** Conception and design; Article writing; Final approval of article. **Henk M. W. Verheul:** Conception and design; Article writing; Final approval of article. **David M. Thomas:** Conception and design; Article writing; Final approval of article. **Emile E. Voest:** Conception and design; Article writing; Final approval of article. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

Emile E. Voest has, through DRUP, received support from pharmaceutical companies that are participating in the DRUP (Novartis and Pfizer), paid to the Netherlands Cancer Institute. David M. Thomas and Robert J. Simes have, through MoST, received support from Pfizer, paid to the University of Sydney. Katrin M. Sjoquist received honoraria for education events and advisory boards from BMS, Merck, MSD and Servier (all <5000 AUD), within the last 36 months, and reports participation on a Data Safety Monitoring Board for Novotech (2022-ongoing). Chee K. Lee has participated on the advisory board for AstraZeneca, Roche, Amgen, Janssen, Pfizer, Takeda, MSD, Novartis and GSK, and received funding for clinical trials from Roche, AstraZeneca, Amgen and Merck KGaA. The other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

DRUP (trial registration number: NCT02925234) was approved by the Netherlands Cancer Institute independent ethics committee (Amsterdam, the Netherlands) and by the institutional review boards in every participating hospital. MoST (trial registration number: ACTRN12616000931471) was approved by the St Vincent's Hospital Sydney Human Research Ethics Committee (Sydney, Australia). The studies are conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki's ethical principles for medical research. Written informed consent was obtained from all study subjects.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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