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Short communication

Why upfront use of CDK inhibitors for the treatment of advanced breast cancer may be wasteful, and how we can increase their value

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ABSTRACT

Three Cyclin Dependent Kinase 4/6 (CDK) inhibitors have been approved by the United Stated Food and Drug Administration for front line treatment of advanced hormone receptor positive breast cancer based on improvements in progression free survival against endocrine monotherapy. Two clinical trials have so far reported results on overall survival but both are negative. CDK inhibitors are usually tolerated well but they do add to inconvenience and cost - for example, grade III-IV neutropenia occur at a frequency of over 60% requiring frequent blood work at least during the initial months of treatment. These drugs cost over $ 13,500 for a 4-week cycle in the United States, and are responsible for billions of dollars annually in drug cost alone. Importantly, many women with metastatic breast cancer do well for a long time with endocrine therapy alone and CDK inhibitors do not have a predictive marker. Selective use of these agents in later lines may improve substantially the convenience and cost without compromise in overall outcome. However, with results demonstrating impressive improvements in PFS published in major medical journals coupled with patients' natural desire for "best available" options, the trend among oncologists is to prescribe these drugs as the default front-line treatment. In this commentary I caution readers against over interpretation of results from the CDK inhibitor trials, describe adverse consequences of routine front-line use, and explain why selective use in later line may yield a higher value.

Combination of letrozole and palbociclib (Pfizer Inc., USA), the first Cyclin Dependent Kinase 4/6 (CDK) inhibitor received accelerated approval from the United States Food and Drug Administration (FDA) for first-line treatment of Hormone Receptor (HR) positive, Human Epidermal Growth Factor Receptor 2 (HER2) negative, Advanced Breast Cancer (ABC) in 2015 based on an impressive improvement in Progression Free Survival (PFS) compared to letrozole alone in a phase II Randomized Controlled Trial (RCT) [1]; the claimed PFS benefit was confirmed later in a phase III RCT leading to its regular approval in 2017 [2]. Subsequently, two more CDK inhibitors were also approved for the same indication [3,4]. All CDK inhibitors have surprisingly concordant efficacy results demonstrating improvement in PFS by around 10 months, compared to endocrine monotherapy. Overall Survival (OS) results are awaited from most CDK inhibitor trials but the first two trials that reported it are discouraging [5,6]. Nevertheless, academic and lay media have associated liberally terms like "blockbuster", "game changer", and "revolution" to describe CDK inhibitors [7–9]. With striking PFS results to accompany the news, natural inclination of oncologists and patients is to consider the combination treatment as default first line standard-of-care for advanced HR+, HER2- breast cancer.

Indisputable markers of benefit of an intervention in any disease at any stage is longer and/or better life of patients. Indeed, delaying progression of cancer is a highly desirable outcome but such pursuits should consider carefully tradeoffs like toxicity, inconvenience, and cost compared to the alternatives. If CDK inhibitor combination is to replace completely the well-established, relatively well tolerated, more convenient, inexpensive endocrine monotherapy as default treatment, it is wiser to wait until improvements in the ultimate clinical outcomes of duration and/or quality of life (QoL) are ascertained. Improvement in PFS accompanied by mere maintenance (but not improvement) in QoL without OS improvement is unacceptable for drug approvals – as this simply means that we are willing to accept any added cost and toxicity of new drugs in return of maintaining status-quo [10–12].

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1. Magnitude of benefits reported in RCTs evaluating CDK inhibitors may be inflated

First, improved PFS suggests higher biologic activity of the combination, but this does not prove ultimate benefits to the patients [13]. Validity of PFS as a surrogate for OS is promising is some tumor types but is less clear in HR + ABC [14,15]. Arguments for use of PFS as independent endpoint in ABC regardless of OS results include: (a) when the absolute PFS duration is large, (b) when effective post-progression treatments complicate measurement of OS due to long post-progression survival, (c) cross over. However, newer reports from multiple tumor types have confirmed that demonstration of OS benefit is possible despite post-treatment circumstances including cross-over provided the intervention is truly effective – recent examples include pertuzumab and eribulin in ABC, and pembrolizumab in PD-L1-positive non-small-cell lung cancer and advanced melanoma [16–19]. Unconditional reliance on PFS therefore may be an unnecessary compromise. Despite respectable PFS benefits observed consistently, negative OS results from the first two trials is sobering, [5,20] with results from larger trials keenly awaited.

Second, with toxicities as obvious as neutropenia and diarrhea, blinding of interventions in RCTs is difficult. This introduces bias in reporting of outcomes, and favors the experimental treatment. Furthermore, higher proportion of patients in the experimental arm withdrew from treatment in all RCTs because of toxicity, global deterioration of health, or other reasons not related to progression of disease. Most patients who withdraw prematurely are either not well enough, or are uninterested in the scheduled radiological assessments which biases outcomes in favor of the toxic treatment [21].

Third, with appropriate caution we can make some inferences based on available PFS data from first and second line use of CDK inhibitors (Table 1): upfront CDK combination has led to a median PFS of close to 25 months in all studies consistently compared to around 15 months in endocrine monotherapy control arms. This duration of PFS in control arm coincides with that of around 15–16 months observed in RCTs evaluating upfront endocrine monotherapy [22]. And, studies evaluating second line endocrine monotherapy generally show a PFS ranging from 3 to 7 months [23–25]. A study evaluating the combination of CDK inhibitor in second line has resulted in a median PFS of 16 months [26]. One can reasonably infer from these data, in the absence of direct comparison, that use of CDK combination in first line or in second line with a different endocrine partner is likely to yield a total PFS after 2 lines of treatment (PFS1+PFS2) in the range of 30 months. It should be recognized however that eligibility criteria of each trials were different and direct cross-trial comparisons are not without their dangers. However, despite adverse financial risk to the manufacturers, this provides a strong case for conduction of cross-over trials of first versus later line CDK inhibitors against endocrine monotherapy. Findings of such cross over trials can be highly consequential in terms of societal resources and convenience.

Fourth, there is limited data regarding mechanism of resistance to CDK inhibitors and optimal sequence post progression on CDK inhibitors. This makes it prudent to utilize established treatment whenever such treatments are likely to offer a long progression free time before introducing CDK inhibitors. Furthermore, due to unique mechanistic property of CDK inhibitors, whether the otherwise highly effective breast cancer chemotherapy such as anthracyclines and taxanes maintain their sensitivity in CDK inhibitor-refractory tumors still remains to be clear.

Fifth, CDK inhibition appears to retain synergy with endocrine therapy regardless of prior use of endocrine therapy, as evidenced by comparable relative benefits observed in previously treated versus untreated patients [27]. Continued efficacy of CDK inhibitors with an alternate endocrine partner further late in disease course is plausible, although this strategy is unlikely to be tested in a clinical trial.

2. Toxicity

Dose-reductions and interruptions due to toxicities were consistently high in the combination treatment compared to endocrine monotherapy in all studies. Treatment discontinuation due to toxicity occurred in up to 1 in 5 participants in the combination arm, which was over 3 times the discontinuation rate in endocrine monotherapy arms. A high degree of differential discontinuation is likely to compromise validity of results, biasing in favor of experimental arm [28]. Similarly, frequency of occurrence of toxicities regarded as 'serious adverse events' attributed to study drug (such as pulmonary embolism and QTc prolongation) was also consistently higher in the combination arm. In addition to requiring high caution this also leads to the same bias favoring experimental arm. Formal assessment of health related quality of life have been presented in a few reports suggesting that such benefits are observed in patients that achieved objective response versus those that didn't respond [12,29].

3. Financial toxicity

Monthly wholesale price of all three CDK inhibitors in the US is over US $13,500 compared to less than $50 for endocrine monotherapy, although Canada and some European countries that

Table 1
Characteristics of pivotal clinical trials of CDK inhibitors in advanced breast cancer.

Study	Expr Arm	Ctrl Arm	N expt	N Ctrl	Line	△ PFS (months)	PFS events Expt	PFS events Ctrl	cost to prevent 1 PFS event (USD)	Grade III-IV neutropenia (%)
PALOMA-1 [1]	Palbociclib + Letrozole	Letrozole	84	81	1	10	41	59	1,272,600	45 Vs 1
PALOMA-2 [38]	Palbociclib + Letrozole	Letrozole	444	222	1	10.3	331	388	2,607,916	66 VS 1
PALOMA-3 [39]	Palbociclib + Fulvestrant	Fulvestrant	347	174	2	4.9	145	228	536,178	65 Vs 1
MONALEESA-2 [3,40]	Ribociclib + Letrozole	Letrozole	334	334	1	9.3	140	205	1,755,042	62 Vs 1
MONALEESA-3 [27]	Ribociclib + Fulvestrtant	Placebo	484	242	1/2	7.7	210	302	1,455,946	54 Vs 1
MONALEESA-7 [41]	Ribociclib + OFS + oral anti-hormone	OFS + oral anti-hormone	335	337	1	10.8	131	187	1,922,063	60 Vs 1
MONARCH-2 [26]	Abemaciclib + Fulvestrant	Fulvestrant	446	223	2	7.1	222	314	1,073,309	26 Vs 1 (Diarrhea: 13 Vs 0.4)
MONARCH-3 [4]	Abemaciclib + NSAI	NSAI	328	165	1	not reached	108	172	not estimable	21 Vs 1 (Diarrhea 10 Vs 1)

N = sample size; Exp: Experimental arm; Ctr: Control Arm, PFS = Progression-free survival; △ = difference; NSAI = Non-steroidal Aromatase Inhibitor.

negotiate drug prices actively are frequently able to lower prices to less than half of the US prices [9]. On rough estimate based on sample sizes, PFS events, and absolute PFS durations reported in each arms of available RCTs, dollar amount necessary to prevent one recurrence event with the combination approaches approximately US $2.6 million when used in first line and up to US $1.07 million in second line. (Table 1). To further put this in context, in 2016 there were about 20,000 new de-novo metastatic breast cancer and approximately 70,000 metastatic recurrences in the United States alone [30–32]. If 70% of this number, which would represent hormone receptor positive cancers, were to be treated with the combination frontline, this would lead to an increase in drug cost of $21.2 billion in that year alone. Using the combination in second line will cut down the total drug cost by up to two-thirds. (Table 1). Presented costs here are underestimates of total cost to healthcare system because only the drug prices were considered. Cost of toxicities and utilization of healthcare resource (e.g., for frequent bloodwork and clinic visits) can add substantially to the total expenditure. Of note, none of the CDK inhibitors have yet shown improvements in OS, and hence current estimate for cost of preventing one death would be infinity. With such price tag, CDK inhibitors are unlikely to be cost-effective by any measure, even with high purchasing capacity. With multiple effective, well-tolerated chemotherapeutic options available, a switch to chemotherapy will remain as the only financially viable option in developing countries, and resource deprived setting of developed countries.

4. Inconvenience

Absence of OS benefits aside, major attraction of early introduction of CDK inhibitors is to delay time to initiation of cytotoxic chemotherapy and hence its nuisances. Due to their mechanism of action, CDK inhibitors share some of their side effects with conventional chemotherapy such as neutropenia, fatigue, or even alopecia, and require biweekly blood draws at least in the initial few months. These complexities may keep patients from regarding CDK inhibitors as advantageous against the relatively well tolerated chemotherapeutic alternatives used in this situation such as vinorelbine or capecitabine. Mechanism of action of CDK inhibitors is credited for low febrile neutropenia rates despite relatively high neutropenia rates based on data from RCTs. However, unselected patient population in the community may experience more frequent toxicity events– such outcomes need to be collected rigorously, and reported well in post-approval studies. Additionally, two of the three CDK inhibitors are taken on a 3 weeks on and one week off cycles which adds complexity and can affect compliance.

5. Biomarkers

When cost and/or toxicities become prohibitive, availability of predictive biomarker can be valuable. Preclinical studies have shown that intact, functional retinoblastoma (Rb) protein is necessary (but not sufficient) for efficacy of CDK inhibitors [33]. Loss of Rb can occur in about a quarter of breast cancers but is most frequent in triple negative disease, with more than 90% of HR + tumors having intact Rb [34]. Preclinical studies have also suggested improved response with increased expression of Cyclin D, Rb1, CCND1, and decreased expression of p16 and CCND2 [35,36]. A recent attempt to assess correlation between gene expression levels and PFS suggested consistent benefits across patient subgroups [37]. Unfortunately, preclinical signals mentioned above have not been reproduced in clinical trials leaving the search of biomarkers predicting benefits from CDK inhibitors to be an elusive task, like most of our search for biomarkers in oncology overall.

6. The way forward

Great leaps in medical science have mostly been aggregation of small incremental gains. In that, CDK inhibitors have been important additions to ABC drug armamentarium. However rushing to default frontline use of these agents may deprive us of evidence required to strategize their use for maximal value. Until overall survival results are available for the remaining studies – and most trials were in fact followed up in a double blinded fashion to maintain integrity of the OS analysis – current evidence only allows us to deduce that: (1) combination of CDK inhibitors and endocrine therapy has an encouraging biologic activity in ABC, but adds significantly to cost, toxicity, and inconvenience, (2) front-line treatment provides respectable PFS benefits without compromise in quality of life compared to endocrine monotherapy but overall outcomes may be comparable, costs reduced by almost two-thirds, and harms minimized by selectively reserving the combination strategy after progression on endocrine monotherapy, (3) cross over trial of CDK inhibitor combination and endocrine monotherapy in first versus second line and vice-versa should be considered, (4) outside of such trial, patients with limited volume disease, asymptomatic bone-only metastasis, elderly, lower grade disease (which together constitutes majority of ABC) should be spared of the up-front combination, (5) in contrary to the basic principles of free market economy, increased competition has not led to a better price – this trend threatens sustainability and necessitates more rigorous regulatory strategies to maximize drug value, (6) room for improvement is large throughout the life cycle of a new drug - from evidence generation, to regulatory approvals, to drug utilization in real life. With multiple lines of effective options available, our expectation from a new treatment strategy in ABC should be nothing less than longer and/or better life for our patients.

Ethical statements

Conflict of interest

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Research involving human participants and/or animals

Not applicable.

Informed consent

Not applicable.

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