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Abemaciclib, A Recent Novel FDA-Approved Small Molecule Inhibiting Cyclin-Dependant Kinase 4/6 for the Treatment of Metastatic Breast Cancer: A mini-review.

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Abstract:

Abemaciclib (Verzenio[®]) is a cell cycle inhibitor of both CDK4 and CDK6. In 2017, abemaciclib was approved by the Food and Drug Administration (FDA) and, in 2018 by the European Medicines Agency (EMA) for the treatment of postmenopausal women with hormone receptor positive (HR⁺), human epidermal growth factor receptor 2 negative (HER2⁻) advanced breast cancer. In this mini-review, we provide a series of information for respectively their targets and its selectivity, results on preclinical trial, clinical phase I, II and III trials, and some perspectives. We also describe the batch and flow steps used for the synthesis of this cancer drug.

Keywords: approved drug, abemaciclib, FDA, EMA, CDK4/6, protein kinase inhibitor, metastatic breast cancer.

1. Introduction

Imatinib (1) (Figure 1; Gleevec[®] from Novartis, Basel, Switzerland) was the first approved protein kinase inhibitor [1-2] in May 2001 by the Food and Drug Administration for the treatment of myeloid leukemia [3]. To date, the number of protein kinase inhibitors (PKIs) approved worldwide continue to grow steadily between 2001 to January 2018 period: 39 drugs have been approved [4] by Food and Drug Administration, Chinese and European regulatory authorities for their respective markets.

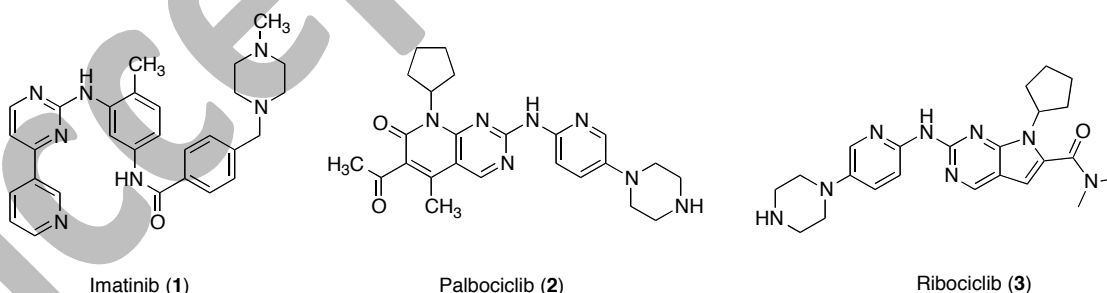


Figure 1: Chemical structure of Imatinib (1) and, the CDK4/6 inhibitor drugs palbociclib (2) and ribociclib (3)

In 2017, Food and Drug Administration approved the palbociclib (2) [5], a first-in-class inhibitor of CDK4/6 [6] developed by Pfizer for the treatment of postmenopausal women with hormone-receptor positive, HER-2 negative advanced breast cancer after initial endocrine-based therapy. During the Phase 2 PALOMA-1/TRIO 18 study, treatment with palbociclib (2) was associated to letrozole [7]. During the same period, ribociclib (3) owned by Novartis, the US Food and Drug Administration and the European Medicines Agency, also approved a

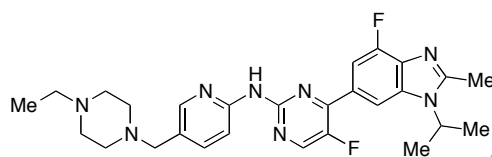
direct competitor of palbociclib (2), in March 2017 for the treatment of metastatic breast cancer [8-9].

Now the purpose of this mini-review is to provide information's on the third CDK4/6 inhibitor approved by Food and Drug Administration in 2017 named as abemaciclib (4) (LY2835219), for the treatment of certain breast cancer [10-11].

2. Abemaciclib

2.1. Names and structure

Abemaciclib (4) (Figure 2) is the active ingredient of Verzenio[®], commercialized by Eli Lilly and Co. Its IUPAC name is: *N*-[5-[(4-ethylpiperazin-1-yl)methyl]-pyridin-2-yl]-*N'*-[5-fluoro-4-(7-fluoro-2-methyl-3-methylethyl-3*H*-benzimidazol-5-yl)-pyrimidin-2-yl]-amine. CAS: 1231929-97-7.



Abemaciclib (4)

Figure 2: Abemaciclib chemical structure (4)

2.2. Uses

Abemaciclib (4) was designated as a breakthrough therapy for metastatic breast cancer after successful Phase I [12], and Phase II [13] trials realized respectively in May and December 2014. Food and Drug Administration approved it for use in USA in September 2017 [14] and the European Medicines Agency regulatory authorities in September 2018.

2.3. Targets and Selectivity

For regulating the cell cycle, the G1 restriction point is critical and is controlled by the retinoblastoma (Rb) pathway (CDK4/6-cyclin D1-Rb-p16/ink4a). The retinoblastoma protein is a tumor suppressor, which inhibits proliferation through binding to and suppressing the activity of the E2F family of transcription factors. The central role of the Rb pathway for controlling cellular proliferation has been demonstrated by its dysregulation in human cancer. Transition through the restriction point requires phosphorylation of Rb by CDK4/6, which validated cancer drug targets [15].

Eli Lilly and Company identified the 2-anilino-2,4-pyrimidine-[5-benzimidazole] scaffold as potent inhibitors of CDK4/cyclin D1 and CDK6/cyclin D1 by compound screening. Optimization of the scaffold has been realized by structure-activity relationship (SAR) studies associated to computing structure-based design and biochemical screening against a small panel of kinases to improve potency and selectivity, and with a colo-205-cell high content imaging monitoring inhibition of its phosphorylation. Compounds with good physicochemical and pharmacokinetic properties were then evaluated for *in vivo* tumor activity against xenograft tumors in immunodeficient mice. In this context, LY2835219 emerged as a good candidate for its potential biological activities and optimal pharmacological properties. In biochemical assays (Table 1), abemaciclib (4) (or LY2835219) inhibited respectively CDK4/cyclin D1 and CDK6/cyclin D1 with IC₅₀ 2 nM and 9.9 nM. K_i ATP constants were also determined through kinetic studies; for CDK4/cyclin D1, it showed K_i ATP = 0.6 nmol/l and 2.4 nmol/l for CDK6/cyclin D1. This means that abemaciclib (4) is a competitive ATP inhibitor [16].

On the other hand, in measured IC₅₀ for biochemical kinase selectivity against CDK1/cyclin B1, CDK2/cyclin E and CDK7/Mat1/cyclin H1, abemaciclib (4) showed a gain 2-3 orders of magnitude. Against PIM1, an activity was also seen (IC₅₀ 50 nM) and a lesser extent activity against PIM2 (IC₅₀ 3.4 μM) (Table 1).

Table 1: Abemaciclib (4) (LY2835219) biochemical profiling (issued from [17])

Biochemical profiling ^a	IC ₅₀ (nmol/l) ^b	K _i [ATP] (nmol/l) ^b
CDK4/cyclin D1	2.0 ± 0.4 (n = 5)	0.6 ± 0.3 (n = 2)
CDK6/cyclin D1	9.9 (n = 1)	2.4 ± 1.2 (n = 2)
CDK1/cyclin B1	1627 ± 666 (n = 5)	-
CDK2/cyclin E	504 ± 298 (n = 3)	-
CDK9/cyclin T1	57 ± 42 (n = 4)	-
CDK7/Mat1/cyclin H1	3910 ± 2410 (n = 4)	-
PIM1	50 (n = 1)	-
PIM2	3400 (n = 1)	-
ERK1	> 20000 (n = 1)	-

^a unless otherwise indicated, all data was generated internally at Eli Lilly and Co. All human kinases. ^b for n < 1, average of independent determinations ± standard deviation.

2.4. Preclinical and Clinical Trials

In preclinical development [17], pharmacokinetic and pharmacodynamic properties of methane sulfonate salt of abemaciclib (4) (or LY2835219) were assessed in mice bearing colo-205-human xenografts 24 h after oral dosing for the observation of cell cycle effects. It significantly inhibited the growth of colo-205-xenografts with no loss of body weight or other signs of toxicity during or after treatment (dose up to 100 mg/kg) (Figure 3a). The long-term safety and antitumor activity of abemaciclib (4) (LY2835219) was also explored. Treatment of colo-205-xenograft bearing mice during 56 days with continuous and intermittent dosing schedules produced a similar efficient inhibition without loss of body weight (Figure 3b).

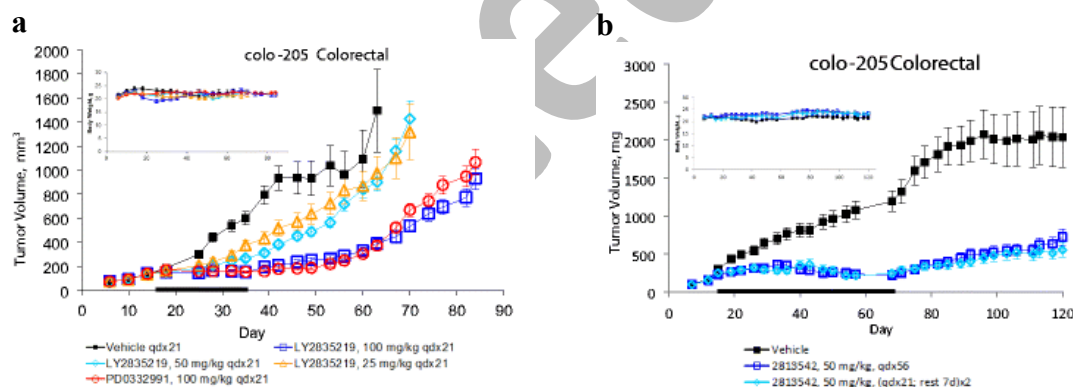


Figure 3: In vivo antitumor activity of abemaciclib (4) (LY2835219) in subcutaneous human xenografts [13]. Tumor have been implanted in the rear flank of athymic mice and randomized for treatment when the tumor volume reached 150 to 200 nm³. LY2835219 and PD0332991 (or palbociclib isethionate CAS 827022-33-3) were administered at the indicated dose and schedule. Treatment period is indicated by the horizontal black bar along the X-axis, body weight shown for each experiment is shown in the upper left corner. **a** (left): effect of 25, 50 or 100 mg/kg of LY2835219 and 100 mg/kg of PD0332991 on colo-205-xenografts. **b** (right): LY2835219 inhibits tumor growth and it is well tolerated in mice bearing colo-205-xenografts when dosed 56 days with 50 mg/kg continuously or intermittently.

In Phase I trial [18], effect of abemaciclib (4) has been explored in five different types ($n = 132$) with a cohort of 47 patients (median age: 55 years) with metastatic breast cancer who received a median of 7 prior-therapeutics. In the cohort of 47 patients, 74% had visceral metastases and 76% (36 patients) were hormone receptor-positive (HER⁺). Among this HER⁺ patient's group, 25% (9 patients) had confirmed partial responses and 56% (20 patients) had stable disease (including 2 patients with unconfirmed responses). The clinical benefit rate was

61% and disease central rate was 81%. The maximum tolerated dose was 200 mg every 12 hours (fatigue was the dose-limiting toxicity).

The MONARCH 2 clinical Phase III study (Clinical Trials.gov: NTC 02107703) of women with HER⁺ and human epidermal growth factor-receptor 2-negative ABC was realized between August 2014 and December 2015 with 669 patients [19]. This Phase III, randomized, double-blind, placebo-controlled study of fulvestrant with abemaciclib (4) (*n* = 446) or without (*n* = 223) was conducted in 142 centers and in 19 countries. Treatment of patients randomly assigned 2:1 to receive abemaciclib (4) or placebo (150 mg twice daily) on a continuous schedule and fulvestrant (500 mg, per label), improved significantly the progression-free survival (PFS) versus fulvestrant alone (median, 16.4 v 9.3 months, hazard ratio, 0.553; 95% CI, 0.449 to 0.681; *P* < .001). During treatment, the common adverse events in the abemaciclib (4) *versus* placebo arms were: diarrhea (86.4% v 24.7%), neutropenia (46% v 4.0%), nausea (45.1% v 22.9) and fatigue (39.9% v 26.9%).

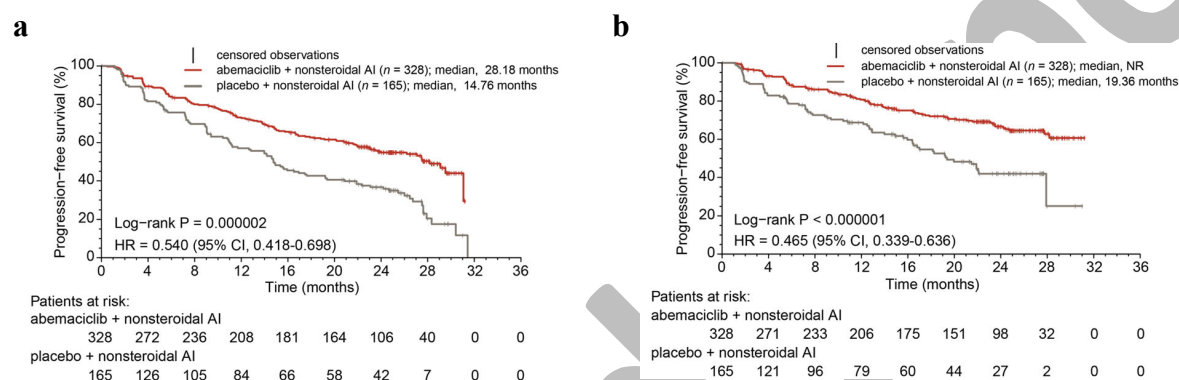


Figure 4: Progression-free survival. **a** (left) Investigator-assessed and **b** (right) Independent central review in the intent-to-treat population. NR, not reached [20].

During MONARCH 3 Clinical Phase III [20] conducted between November 18, 2014 and November 11, 2015 with 493 women patients (HR⁺ and HER2⁺ advanced breast cancers) in 158 sites and in 22 countries, abemaciclib (4) dosed in combination with a nonsteroidal A1 (anastrozole or letrozole) improved progression-free survival and the clinical benefit rate (79.4% v 69.2% with placebo plus nonsteroidal A1).

In MONARCH 3 Final PFS (Progression Free Survival) study [21], a total of 125 women patients (38.1%) in the abemaciclib arm and 35 patients (21.2%) in the placebo arm remained in treatment. Following 24 cycles of treatments, the mean decrease in tumor size was 76.1% in the abemaciclib arm and 50% in the placebo arm. For patients responded to abemaciclib (4), the response typically occurred within the first 8 months of treatment (Figure 4a) Results of this clinical Phase III trial come in light for CD4/6 cyclin D in the regulation of cancer immune surveillance [22-23].

2.5. Syntheses

As depicted in the retrosynthetic approach (Figure 5), abemaciclib (4) [24] involved a carbon-carbon Suzuki coupling as key step between boronic ester (5) and 2,4-dichloro-5-fluoro pyrimidine (6) as readily available commercial building blocks [25]. For this, the authors used PdCl₂(PPh₃)₂ with Na₂CO₃ in DME at 80°C and they obtained the biaryl compound (9) after 4 h in 66% isolated yield (Scheme 1).

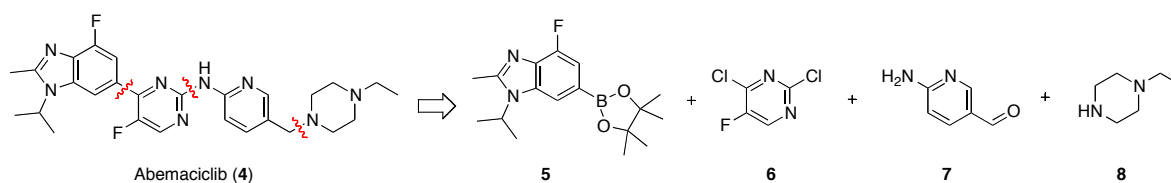
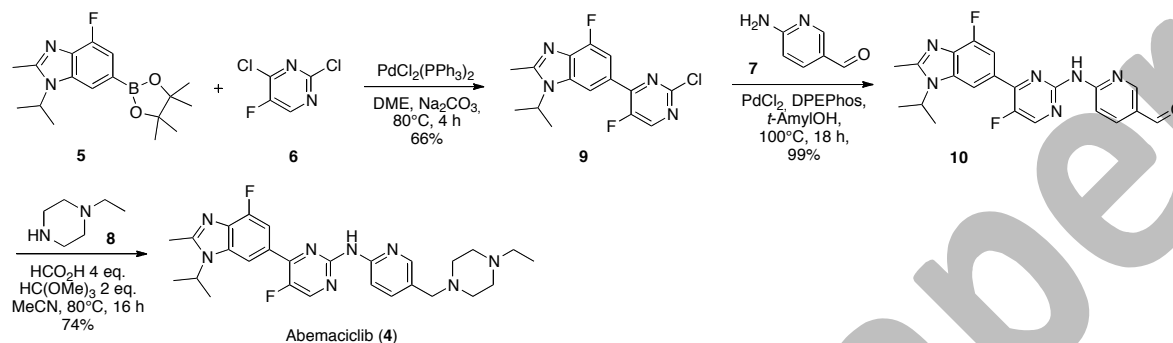


Figure 5: Retrosynthetic strategy for the preparation of abemaciclib (4) [25]

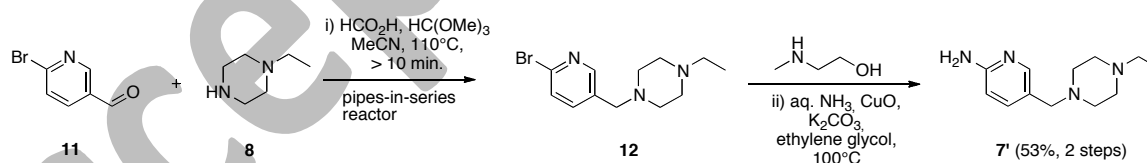
For the second step, they investigated a carbon-nitrogen coupling *via* Buchwarld-Hartwing amidation. For optimization of this N,C-coupling, they explored successively the choice of appropriate solvent (MeOH, EtOH, *t*-AmylOH) due to solubility limitations of the starting reagents (**9**) and (**7**), the ligand and reaction temperature. Using the more hindered *t*-AmylOH (no undesired *t*-Amyl ether by-product was observed), DPEPhos (as sufficient active catalyst), they obtained successful carbon-nitrogen coupling after 18 h at 100°C and the aldehyde intermediate (**10**) was prepared quantitatively.



Scheme 1: Initial route used for the three-step synthesis of abemaciclib (**4**).

The third and last step in the synthesis of abemaciclib (**4**) is a classical reductive amination involving the aldehyde (**10**) and *N*-ethylpiperazine (**8**). After a few set of exploring experiences with NaBH(OAc)₃ as reductant, they observed a 97:3 distribution of (**4**) and reduced aldehyde (**10**) which, increased difficulties of separation and purification through crystallization. In this context, they dropped out these classical reductive reaction conditions and these setbacks led to the exploration of Leuckart-Wallach conditions without catalyst. Starting from 4 equivalents of formic acid as source of reducing reagent associated to trimethyl orthoester for removal of water, reductive amination of aldehyde (**10**) in the presence of 2 equivalents of *N*-ethylpiperazine afforded quantitatively after 16 h abemaciclib (**4**) in 74% isolated yield.

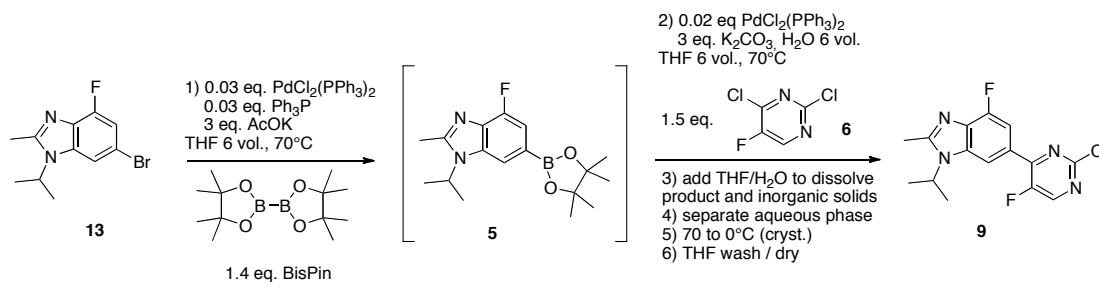
The authors continued to develop efforts on Leuckart-Wallach reductive amination conditions for a robust batch process and a more convergent approach for the kilogram scale preparation of abemaciclib (**4**) [26]. Briefly, they opted for modifications on the 6-aminopyridine-3-carbaldehyde (**7**) used in the carbon-nitrogen coupling of Buchwarld-Hartwing amidation.



Scheme 2: Process for preparation of 2-amino pyridine (**7'**) used for carbon-nitrogen coupling of Buchwarld-Hartwing with the biaryl compound (**9**) [26].

In fact, a robust process (Scheme 2) was fully realized to make directly the 2-amino pyridine (**7'**) through two telescoped steps: i) the first was the Leuckart-Wallach reductive amination using pipe-in-series reactors with near instantaneous heat-up times to maximize conversion and to reduce by-products, ii) and the second was an Ullmann coupling with aqueous ammonia. Fortunately, the use of 2-methylaminoethanol at 100°C provided high conversion (99%).

For the intermediate (**9**) issued from the carbon-carbon Suzuki coupling (Scheme 1), the Eli Lilly's chemists, finally, developed also a telescoped Miyaura borylation and Suzuki coupling (Scheme 3) to maintain its high quality [27].



Scheme 3: Telescoped Borylation Suzuki coupling for the preparation of intermediate (**9**) [26].

The use of *bis*(pinacolato)diboron (BisPin) and the aid of a Quality by Design (QbD) approach was the key point of success to control the risk of pinacol precipitation in THF and to provide a maximally flexible process for manufacturing in large scale.

2.6. Perspectives

Abemaciclib pharmacological profile as novel CDK4/6 inhibitor represented an optimal first line treatment for hormone receptor (HR) positive, human epidermal growth-factor receptor 2 (HER2) non-amplified metastatic breast cancer (MBC) in combination with endocrine therapy. Its indication can be extended for treatments of patients (clinical phase II) with brain metastases secondary to ER⁺ breast cancer, non-small lung cancer, or melanoma (ClinicalTrials.gov: NCT 02308020). Given the observed benefits of CDK4/6 inhibitors in combination with endocrine therapy for patients with HR⁺, HER2-non amplified MBC, adjuvant studies are now underway to investigate the combination in HR⁺, HER2-non amplified early breast cancer [28].

3. Conclusion

For the treatment of advanced or metastatic HR⁺ breast cancer, CDK4/6 inhibitors are an effective option. Their oral administration and their toxicity profile [29] are convenient and manageable. In this context, abemaciclib appears to possess unique pharmacological properties and seems to obtain the best results in heavily pretreated with visceral disease and worse prognosis. The approval of abemaciclib by Food and Drug Administration adds another option to the armamentarium of effective CDK4/6 inhibitors [30-31] currently available.

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