Sponsor
Novartis Pharmaceuticals

Generic Drug Name
Ribociclib / Kisqali

Trial Indication(s)
Metastatic breast cancer

Protocol Number
CLEE011AUS64

Protocol Title
A real-world analysis of concomitant medication use among metastatic breast cancer patients treated with CDK4/6 inhibitors

Clinical Trial Phase
NA

Phase of Drug Development
NA

Study Start/End Dates
Study start date: 15 April 2020

Study Completion date: 15 June 2020

Reason for Termination
NA

Study Design/Methodology

This was a retrospective cohort study utilizing the US Optum research administrative claims database. Patients with HR+/HER2- mBC were identified and stratified into three cohorts based on the first CDK4/6i received (ribociclib, palbociclib, or abemaciclib). Health plan enrollment in the three months prior to the index treatment was included in the baseline period. Patients were followed up ≥3 months and until the end of study period or continuous enrollment or until the time when patients switched to another therapy including another CDK4/6i whichever came first.

Setting

Study analyses were conducted among adult women with HR+/HER2- mBC receiving ribociclib, palbociclib, or abemaciclib, regardless of the line of therapy. Patients were identified from the US Optum Claims Data.

Centers

NA

Objectives:

Primary objective(s)

This study aimed to:

- Describe concomitant medication use at baseline that can potentially lead to a DDI with a CDK4/6i during study follow-up among patients with HR+/HER2- mBC initiated on ribociclib, palbociclib, or abemaciclib

Secondary objective(s)

- To describe dosing and treatment patterns associated with ribociclib, palbociclib, and abemaciclib patients with respect to starting dose, dose reductions and uptitration, and duration of treatment among study patients
- To describe treatment discontinuation for each CDK4/6i (ribociclib, palbociclib, or abemaciclib) in the follow-up period stratified by use of concomitant medications at baseline and status of adherence to the concomitant medications

Test Product (s), Dose(s), and Mode(s) of Administration

≥1 ribociclib, palbociclib or abemaciclib medication

Statistical Methods

Patient demographics, clinical characteristics (comorbidities) and treatment in baseline period and at the index date were analyzed by frequency for categorical variables and by mean, median, and standard deviations (SD) for continuous variables. Adherence to concomitant medication at baseline was summarized using frequencies and proportions to describe the proportion of adherent (i.e., PDC >80%) and non-adherent (i.e., PDC ≤80%). Dosing patterns, dosing changes, and treatment discontinuation during follow-up was evaluated using frequencies and proportions. Duration of treatment was evaluated using medians and 95% confidence intervals (CI) and was visually represented using Kaplan-Meier curves. All secondary endpoints were evaluated in the overall population and among patients with ≥3, ≥6, and ≥12 months of follow-up, and ≥2 medication refills.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

Adult women meeting the inclusion criteria listed below were included:

- Treated with CDK4/6i from 2015-02-01 to 2019-06-30
- ≥2 claims with an mBC diagnosis, with a time interval between the first BC diagnosis date and the first mBC diagnosis date no longer than 30 days
- Female patients aged ≥18 years
- Continuous health plan enrollment for ≥3 months prior to the index date and ≥3 months post-index date

Exclusion criteria

None

Participant Flow

Overall, 6,870 patients received a CDK4/6i from 2015-02-01 to 2019-06-30. After applying all other selection criteria, 4,650 patients were selected, including 4,206 who were classified in the palbociclib cohort, 184 in the ribociclib cohort, and 260 in the abemaciclib cohort.

Baseline Characteristics

	All		RIBOCICLIB		PALBOCICLIB		ABEMACICLIB	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD
# Patients	4650		184		4206		260	
Age (Mean/SD)	66.00	12.10	66.43	12.31	66.03	12.12	65.25	11.54
Region (N/%)								
Midwest	988	21.25%	41	22.28%	898	21.35%	49	18.85%
Northeast	484	10.41%	10	5.43%	454	10.79%	20	7.69%
South	2032	43.70%	81	44.02%	1810	43.03%	141	54.23%
West	1128	24.26%	52	28.26%	1027	24.42%	49	18.85%
Unknown	18	0.39%	0	0.00%	17	0.40%	1	0.38%
Health Insurance (N/%)								
Commercial	1835	39.46%	60	32.61%	1668	39.66%	107	41.15%
Medicare	2815	60.54%	124	67.39%	2538	60.34%	153	58.85%
Calendar Year of Last mBC before CDK4/6i (N/%)								
Early than 2015	9	0.19%	0	0.00%	9	0.21%	0	0.00%
2015	682	14.67%	0	0.00%	682	16.21%	0	0.00%
2016	985	21.18%	0	0.00%	985	23.42%	0	0.00%

2017	1226	26.37%	70	38.04%	1135	26.99%	21	8.08%
2018	1123	24.15%	77	41.85%	900	21.40%	146	56.15%
2019	625	13.44%	37	20.11%	495	11.77%	93	35.77%
Calendar Year of Initiation of CDK4/6i (N/%)								
2015	670	14.41%	0	0.00%	670	15.93%	0	0.00%
2016	986	21.20%	0	0.00%	986	23.44%	0	0.00%
2017	1227	26.39%	70	38.04%	1137	27.03%	20	7.69%
2018	1110	23.87%	75	40.76%	890	21.16%	145	55.77%
2019	657	14.13%	39	21.20%	523	12.43%	95	36.54%
NCI Comorbidity Index Score (Mean/SD)	1.11	1.63	1.20	1.63	1.11	1.63	1.14	1.64
Menopausal Status (N/%)								
Premenopausal	339	7.29%	20	10.87%	293	6.97%	26	10.00%
Postmenopausal	4311	92.71%	164	89.13%	3913	93.03%	234	90.00%
Prior treatment Before Index Date (N/%)								
CDK4/6i as first line treatment	538	11.57%	34	18.48%	475	11.29%	29	11.15%
CDK4/6i as second or above line treatment	4112	88.43%	150	81.52%	3731	88.71%	231	88.85%

Abbreviations: CDK4/6i = CDK4/6 inhibitor; mBC = metastatic breast cancer; NCI = National Cancer Institute; SD = standard deviation

Primary Outcome Result(s)

Analysis of Index Regimens (all medications used in the ±7-day period around the index date)

Index_drug	Other treatment along with index drug	COUNT	PERCENT
RIBOCICLIB	Endocrine	77	41.85%
	Endocrine + Other_Tx	46	25.00%
	RIBOCICLIB Only	30	16.30%
	Endocrine + GnRH + Other_Tx	7	3.80%
	Chemo + Endocrine	6	3.26%
	Endocrine + GnRH	6	3.26%
	Other_Tx	6	3.26%
	Chemo + Endocrine + Other_Tx	2	1.09%
	GnRH	2	1.09%
	GnRH + Other_Tx	2	1.09%
PALBOCICLIB	Endocrine	2366	56.25%
	Endocrine + Other_Tx	1023	24.32%
	PALBOCICLIB Only	195	4.64%
	Chemo + Endocrine	186	4.42%
	Chemo + Endocrine + Other_Tx	147	3.50%
	Endocrine + GnRH	114	2.71%
	Endocrine + GnRH + Other_Tx	76	1.81%
	Other_Tx	38	0.90%
	Chemo	29	0.69%
	Chemo + Other_Tx	9	0.21%
	GnRH	7	0.17%
	Chemo + Endocrine + GnRH	6	0.14%
	Chemo + Endocrine + GnRH + Other_Tx	5	0.12%
	GnRH + Other_Tx	5	0.12%
ABEMACICLIB	Endocrine	124	47.69%
	Endocrine + Other_Tx	60	23.08%
	ABEMACICLIB Only	32	12.31%
	Other_Tx	11	4.23%
	Endocrine + GnRH	10	3.85%
	Chemo + Endocrine + Other_Tx	7	2.69%
	Chemo	4	1.54%
	Endocrine + GnRH + Other_Tx	4	1.54%
	Chemo + Endocrine	3	1.15%
	Chemo + Other_Tx	2	0.77%
	GnRH	2	0.77%
	Chemo + Endocrine + GnRH	1	0.38%

Abbreviations: chemo = chemotherapy; GnRH = gonadotropin-releasing hormone; Tx = treatment

Descriptive Analysis of Concomitant Medication Use During the Baseline Period

	All		RIBOCICLIB		PALBOCICLIB		ABEMACICLIB	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD
# Patients	4650		184		4206		260	
Number of patients with at least one concomitant medications	2962	63.70%	111	60.33%	2680	63.72%	171	65.77%
PDC rate based on patients with at least one concomitant medications	0.65	0.31	0.63	0.31	0.65	0.31	0.69	0.30
Categorized patients based on PDC rate								
0 (without any concomitant drugs in baseline)	1688	36.30%	73	39.67%	1526	36.28%	89	34.23%
<=0.2	361	7.76%	16	8.70%	329	7.82%	16	6.15%
0.2-0.4	437	9.40%	15	8.15%	399	9.49%	23	8.85%
0.4-0.6	447	9.61%	20	10.87%	407	9.68%	20	7.69%
0.6-0.8	459	9.87%	16	8.70%	412	9.80%	31	11.92%
0.8-1.0	1258	27.05%	44	23.91%	1133	26.94%	81	31.15%
Number of patients with CYP3A Inhibitor	680	14.62%	28	15.22%	612	14.55%	40	15.38%
PDC rate based on patients with CYP3A Inhibtor	0.47	0.39	0.39	0.38	0.47	0.39	0.53	0.41
Categorized patients based on PDC rate								
0 (without CYP3A Inhibitor in baseline)	3970	85.38%	156	84.78%	3594	85.45%	220	84.62%
<=0.2	286	6.15%	16	8.70%	254	6.04%	16	6.15%
0.2-0.4	93	2.00%	1	0.54%	88	2.09%	4	1.54%
0.4-0.6	42	0.90%	3	1.63%	39	0.93%	0	0.00%
0.6-0.8	34	0.73%	2	1.09%	27	0.64%	5	1.92%
0.8-1.0	225	4.84%	6	3.26%	204	4.85%	15	5.77%
Number of patients with CPY3A Inductor	3	0.06%	0	0.00%	2	0.05%	1	0.38%

PDC rate based on patients with CYP3A Inductor	0.23	0.10	0.00	0.00	0.29	0.05	0.12	0.00
Categorized patients based on PDC rate								
0 (without CPY3A Inductor in baseline)	4647	99.94%	184	100.00%	4204	99.95%	259	99.62%
<=0.2	1	0.02%	0	0.00%	0	0.00%	1	0.38%
0.2-0.4	2	0.04%	0	0.00%	2	0.05%	0	0.00%
0.4-0.6	0	0.00%	0	0.00%	0	0.00%	0	0.00%
0.6-0.8	0	0.00%	0	0.00%	0	0.00%	0	0.00%
0.8-1.0	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Number of patients with medications with potentially torsade risk	2741	58.95%	105	57.07%	2475	58.84%	161	61.92%
PDC rate based on patients with potentially torsade risk	0.66	0.31	0.65	0.31	0.66	0.31	0.69	0.30
Categorized patients based on PDC rate								
0 (without torsade risk drugs in baseline)	1909	41.05%	79	42.93%	1731	41.16%	99	38.08%
<=0.2	295	6.34%	15	8.15%	268	6.37%	12	4.62%
0.2-0.4	420	9.03%	11	5.98%	384	9.13%	25	9.62%
0.4-0.6	413	8.88%	22	11.96%	373	8.87%	18	6.92%
0.6-0.8	434	9.33%	13	7.07%	391	9.30%	30	11.54%
0.8-1.0	1179	25.35%	44	23.91%	1059	25.18%	76	29.23%
Multiple concomitant medications	460	9.89%	22	11.96%	408	9.70%	30	11.54%

Abbreviations: PDC = proportion of days covered; SD = standard deviation

Descriptive Analysis on mBC Treatment in Baseline Period

	All		RIBOCICLIB		PALBOCICLIB		ABEMACICLIB	
	N	%	N	%	N	%	N	%
# Patients	4650		184		4206		260	
Patients with following prior treatment of mBC								
Chemotherapy	757	16.28%	22	11.96%	684	16.26%	51	19.62%
Endocrine Therapy	3727	80.15%	136	73.91%	3391	80.62%	200	76.92%
Aromatase Inhibitor	2918	62.75%	109	59.24%	2663	63.31%	146	56.15%
SERD-SERM	1449	31.16%	45	24.46%	1310	31.15%	94	36.15%
Other ET	37	0.80%	3	1.63%	30	0.71%	4	1.54%
GnRH	233	5.01%	18	9.78%	203	4.83%	12	4.62%
Other Treatment	1365	29.35%	59	32.07%	1221	29.03%	85	32.69%
Multiple Treatment	1668	35.87%	70	38.04%	1499	35.64%	99	38.08%
No Prior Treatment	538	11.57%	34	18.48%	475	11.29%	29	11.15%
Detailed prior treatment pattern of mBC								
No Prior Treatment	538	11.57%	34	18.48%	475	11.29%	29	11.15%
Chemo	187	4.02%	3	1.63%	171	4.07%	13	5.00%
Chemo + Endocrine	254	5.46%	8	4.35%	231	5.49%	15	5.77%
Chemo + Endocrine + GnRH	20	0.43%	2	1.09%	16	0.38%	2	0.77%
Chemo + Endocrine + GnRH + Other_Tx	12	0.26%	1	0.54%	11	0.26%	0	0.00%
Chemo + Endocrine + Other_Tx	176	3.78%	4	2.17%	160	3.80%	12	4.62%
Chemo + GnRH	2	0.04%	0	0.00%	2	0.05%	0	0.00%
Chemo + Other_Tx	106	2.28%	4	2.17%	93	2.21%	9	3.46%
Endocrine	2173	46.73%	72	39.13%	1990	47.31%	111	42.69%
Endocrine + GnRH	103	2.22%	5	2.72%	94	2.23%	4	1.54%

Endocrine + GnRH + Other_Tx	82	1.76%	7	3.80%	71	1.69%	4	1.54%
Endocrine + Other_Tx	907	19.51%	37	20.11%	818	19.45%	52	20.00%
GnRH	8	0.17%	1	0.54%	6	0.14%	1	0.38%
GnRH + Other_Tx	6	0.13%	2	1.09%	3	0.07%	1	0.38%
Other_Tx	76	1.63%	4	2.17%	65	1.55%	7	2.69%

Abbreviations: chemo = chemotherapy; ET = endocrine therapy; GnRH = gonadotropin-releasing hormone; mBC = metastatic breast cancer; SERD-SERM = selective estrogen degrader-selective estrogen receptor modulator; Tx = treatment

Secondary Outcome Result(s)

Descriptive analysis of CDK4/6i dosing patterns, treatment discontinuation, and dosing changes during follow-up in the overall population (i.e., patients with ≥3 months of follow-up)

	All		RIBOCICLIB		PALBOCICLIB		ABEMACICLIB	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N	%/SD
# Patients	4650		184		4206		260	
Follow up Period in months (Mean/SD)	17.77	12.00	14.13	7.40	18.39	12.27	10.37	5.33
Follow up Period in months (Median/IQR)	14.89	16.80	13.71	11.75	15.61	17.98	9.32	9.17
Starting Dose (Mean/SD)	133.84	99.89	491.70	197.95	117.44	57.60	145.89	45.46
Starting Dose (Median/IQR)	125.00	48.61	541.94	268.50	121.74	44.55	150.00	65.94
Dose Change (N/%)								
No change	631	13.57%	35	19.02%	546	12.98%	50	19.23%
Any change	4019	86.43%	149	80.98%	3660	87.02%	210	80.77%
Dose reductions	2318	49.85%	72	39.13%	2103	50.00%	143	55.00%
decrease 10%-20%	834	17.94%	24	13.04%	758	18.02%	52	20.00%
decrease 20%-30%	590	12.69%	14	7.61%	546	12.98%	30	11.54%
decrease 30%-50%	629	13.53%	25	13.59%	567	13.48%	37	14.23%
decrease more than 50%	265	5.70%	9	4.89%	232	5.52%	24	9.23%
Dose increase	1701	36.58%	77	41.85%	1557	37.02%	67	25.77%
increase 10%-20%	448	9.63%	16	8.70%	417	9.91%	15	5.77%
increase 20%-30%	305	6.56%	10	5.43%	284	6.75%	11	4.23%
increase 30%-50%	332	7.14%	15	8.15%	301	7.16%	16	6.15%
increase more than 50%	616	13.25%	36	19.57%	555	13.20%	25	9.62%

Discontinuation* of Index Treatment (N/%)	2614	56.22%	96	52.17%	2395	56.94%	123	47.31%
Discontinuation within 1st month	380	8.17%	26	14.13%	316	7.51%	38	14.62%
Patients Switched to another CDK4/6i	305	6.56%	26	14.13%	246	5.85%	33	12.69%
Modified PDC rate in all patients (Mean/SD)**	0.87	0.15	0.85	0.15	0.87	0.15	0.87	0.15
Modified PDC rate in all patients (Median/SD)	0.91	0.19	0.88	0.20	0.91	0.18	0.92	0.19
Categorize patients based on PDC rate (N/%)								
greater than 80%	3479	74.82%	134	72.83%	3145	74.77%	200	76.92%
less or equal to 80%	1171	25.18%	50	27.17%	1061	25.23%	60	23.08%

Abbreviations: CDK4/6i = CDK4/6 inhibitor; IQR = interquartile range; PDC = proportion of days covered; SD = standard deviation

Notes:

*Discontinuation was defined as an interruption of ≥ 90 consecutive days of ribociclib between the last day of supply of ribociclib and the next prescription fill for ribociclib or end of continuous enrollment or disruption of other CDK inhibitor

**Modified PDC is computed with the following formula total days_supply/(last_drug_dt-first_drug_dt)

Descriptive analysis of CDK4/6i dosing patterns, treatment discontinuation, and dosing changes during follow-up in patients with ≥2 medication refills

	All		RIBOCICLIB		PALBOCICLIB		ABEMACICLIB	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N	%/SD
# Patients	4304		160		3919		225	
Follow up Period in months (Mean/SD)	18.04	12.00	13.89	7.26	18.64	12.24	10.49	5.36
Follow up Period in months (Median/IQR)	15.32	17.09	13.41	11.49	15.98	18.01	9.40	9.40
Starting Dose(Mean/SD)	132.59	98.90	486.70	204.89	117.38	59.54	145.70	47.73
Starting Dose(Median/IQR)	125.00	50.38	517.05	275.79	120.69	46.25	155.17	65.94
Dose Change (N/%)								
No change	285	6.62%	11	6.88%	259	6.61%	15	6.67%
Any change	4019	93.38%	149	93.13%	3660	93.39%	210	93.33%
Dose reductions	2318	53.86%	72	45.00%	2103	53.66%	143	63.56%
decrease 10%-20%	834	19.38%	24	15.00%	758	19.34%	52	23.11%
decrease 20%-30%	590	13.71%	14	8.75%	546	13.93%	30	13.33%
decrease 30%-50%	629	14.61%	25	15.63%	567	14.47%	37	16.44%
decrease more than 50%	265	6.16%	9	5.63%	232	5.92%	24	10.67%
Dose increase	1701	39.52%	77	48.13%	1557	39.73%	67	29.78%
increase 10%-20%	448	10.41%	16	10.00%	417	10.64%	15	6.67%
increase 20%-30%	305	7.09%	10	6.25%	284	7.25%	11	4.89%
increase 30%-50%	332	7.71%	15	9.38%	301	7.68%	16	7.11%
increase more than 50%	616	14.31%	36	22.50%	555	14.16%	25	11.11%
Discontinuation* of Index Treatment (N/%)	2305	53.55%	72	45.00%	2144	54.71%	89	39.56%

Discontinuation within 1st month	75	1.74%	2	1.25%	67	1.71%	6	2.67%
Patients Switched to another CDK4/6	269	6.25%	16	10.00%	230	5.87%	23	10.22%
Modified PDC rate in all patients (Mean/SD)**	0.85	0.15	0.83	0.15	0.86	0.15	0.85	0.15
Modified PDC rate in all patients (Median/SD)	0.90	0.18	0.87	0.18	0.90	0.18	0.88	0.18
Categorize patients based on PDC rate (N/%)								
greater than 80%	3133	72.79%	110	68.75%	2858	72.93%	165	73.33%
less or equal to 80%	1171	27.21%	50	31.25%	1061	27.07%	60	26.67%

Abbreviations: CDK4/6i = CDK4/6 inhibitor; IQR = interquartile range; PDC = proportion of days covered; SD = standard deviation

Notes:

*Discontinuation was defined as an interruption of ≥ 90 consecutive days of ribociclib between the last day of supply of ribociclib and the next prescription fill for ribociclib or end of continuous enrollment or disruption of other CDK inhibitor

**Modified PDC is computed with the following formula total days_supply/(last_drug_dt-first_drug_dt)

Descriptive analysis of CDK4/6i dosing patterns, treatment discontinuation, and dosing changes during follow-up in patients with ≥6 months of follow-up

	All		RIBOCICLIB		PALBOCICLIB		ABEMACICLIB	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N	%/SD
# Patients	3897		151		3557		189	
Follow up Period in months (Mean/SD)	20.33	11.45	16.24	6.43	20.91	11.69	12.62	4.52
Follow up Period in months (Median/IQR)	17.85	16.34	15.61	10.42	18.57	17.03	11.83	7.63
Starting Dose (Mean/SD)	132.61	92.90	498.84	192.79	116.45	42.61	144.00	45.37
Starting Dose (Median/IQR)	125.00	48.61	541.94	248.89	121.74	45.41	150.00	58.33
Dose Change (N/%)								
No change	464	11.91%	26	17.22%	403	11.33%	35	18.52%
Any change	3433	88.09%	125	82.78%	3154	88.67%	154	81.48%
Dose reductions	1977	50.73%	63	41.72%	1814	51.00%	100	52.91%
decrease 10%-20%	706	18.12%	20	13.25%	650	18.27%	36	19.05%
decrease 20%-30%	502	12.88%	11	7.28%	471	13.24%	20	10.58%
decrease 30%-50%	536	13.75%	23	15.23%	486	13.66%	27	14.29%
decrease more than 50%	233	5.98%	9	5.96%	207	5.82%	17	8.99%
Dose increase	1456	37.36%	62	41.06%	1340	37.67%	54	28.57%
increase 10%-20%	389	9.98%	14	9.27%	362	10.18%	13	6.88%
increase 20%-30%	258	6.62%	9	5.96%	241	6.78%	8	4.23%
increase 30%-50%	284	7.29%	13	8.61%	257	7.23%	14	7.41%
increase more than 50%	525	13.47%	26	17.22%	480	13.49%	19	10.05%
Discontinuation* of Index Treatment (N/%)	2502	64.20%	89	58.94%	2306	64.83%	107	56.61%

Discontinuation within 1st month	314	8.06%	20	13.25%	266	7.48%	28	14.81%
Patients Switched to another CDK4/6	278	7.13%	21	13.91%	231	6.49%	26	13.76%
Modified PDC rate in all patients (Mean/SD)**	0.86	0.16	0.86	0.15	0.86	0.16	0.87	0.16
Modified PDC rate in all patients (Median/SD)	0.91	0.18	0.89	0.18	0.91	0.18	0.92	0.18
Categorize patients based on PDC rate (N/%)								
greater than 80%	2918	74.88%	114	75.50%	2656	74.67%	148	78.31%
less or equal to 80%	979	25.12%	37	24.50%	901	25.33%	41	21.69%

Abbreviations: CDK4/6i = CDK4/6 inhibitor; IQR = interquartile range; PDC = proportion of days covered; SD = standard deviation

Notes:

*Discontinuation was defined as an interruption of ≥ 90 consecutive days of ribociclib between the last day of supply of ribociclib and the next prescription fill for ribociclib or end of continuous enrollment or disruption of other CDK inhibitor

**Modified PDC is computed with the following formula total days supply/(last drug dt-first drug dt)

Descriptive analysis of CDK4/6i dosing patterns, treatment discontinuation, and dosing changes during follow-up in patients with ≥12 months of follow-up

	All		RIBOCICLIB		PALBOCICLIB		ABEMACICLIB	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N	%/SD
# Patients	2762		106		2562		94	
Follow up Period in months (Mean/SD)	25.09	10.29	19.36	5.01	25.64	10.42	16.56	2.65
Follow up Period in months (Median/IQR)	22.47	14.27	18.72	8.61	23.18	14.53	16.32	4.17
Starting Dose (Mean/SD)	133.60	95.47	516.03	183.28	117.25	45.41	148.22	40.29
Starting Dose (Median/IQR)	125.00	48.61	600.00	222.22	121.74	44.55	150.00	51.47
Dose Change (N/%)								
No change	309	11.19%	21	19.81%	272	10.62%	16	17.02%
Any change	2453	88.81%	85	80.19%	2290	89.38%	78	82.98%
Dose reductions	1430	51.77%	42	39.62%	1334	52.07%	54	57.45%
decrease 10%-20%	499	18.07%	14	13.21%	466	18.19%	19	20.21%
decrease 20%-30%	365	13.22%	8	7.55%	348	13.58%	9	9.57%
decrease 30%-50%	394	14.27%	14	13.21%	364	14.21%	16	17.02%
decrease more than 50%	172	6.23%	6	5.66%	156	6.09%	10	10.64%
Dose increase	1023	37.04%	43	40.57%	956	37.31%	24	25.53%
increase 10%-20%	274	9.92%	7	6.60%	261	10.19%	6	6.38%
increase 20%-30%	186	6.73%	8	7.55%	172	6.71%	6	6.38%
increase 30%-50%	200	7.24%	10	9.43%	185	7.22%	5	5.32%
increase more than 50%	363	13.14%	18	16.98%	338	13.19%	7	7.45%
Discontinuation* of Index Treatment (N/%)	2016	72.99%	71	66.98%	1890	73.77%	55	58.51%

Discontinuation within 1st month	210	7.60%	17	16.04%	179	6.99%	14	14.89%
Patients Switched to another CDK4/6i	236	8.54%	18	16.98%	200	7.81%	18	19.15%
Modified PDC rate in all patients (Mean/SD)**	0.86	0.16	0.87	0.15	0.86	0.16	0.87	0.17
Modified PDC rate in all patients (Median/SD)	0.92	0.18	0.91	0.21	0.92	0.18	0.92	0.19
Categorize patients based on PDC rate (N/%)								
greater than 80%	2061	74.62%	79	74.53%	1910	74.55%	72	76.60%
less or equal to 80%	701	25.38%	27	25.47%	652	25.45%	22	23.40%

Abbreviations: CDK4/6i = CDK4/6 inhibitor; IQR = interquartile range; PDC = proportion of days covered; SD = standard deviation

Notes:

*Discontinuation was defined as an interruption of ≥ 90 consecutive days of ribociclib between the last day of supply of ribociclib and the next prescription fill for ribociclib or end of continuous enrollment or disruption of other CDK inhibitor

**Modified PDC is computed with the following formula total days_supply/(last_drug_dt-first_drug_dt)

Descriptive analysis of characteristics during follow-up by PDC of concomitant medication for patients treated with ribociclib

	All		No Concomitant		PDC<=80%		PDC>80%	
	N/Mean/Median	%/SD/IQR	N/Mean/Median	%/SD/IQR	N/Mean/Median	%/SD/IQR	N/Mean/Median	%/SD/IQR
# Patients	184		73		67		44	
Follow up Period in months (Mean/SD)	14.13	7.40	14.13	8.05	13.65	7.10	14.84	6.80
Follow up Period in months (Median/IQR)	13.71	11.75	13.31	12.39	13.71	12.43	14.73	10.34
Starting Dose(Mean/SD)	491.70	197.95	496.46	200.69	481.53	197.61	499.29	197.80
Starting Dose(Median/IQR)	541.94	268.50	579.31	257.00	480.00	305.24	569.66	234.61
Dose Change (N/%)								
No change	35	19.02%	14	19.18%	9	13.43%	12	27.27%
Any change	149	80.98%	59	80.82%	58	86.57%	32	72.73%
Dose reductions	72	39.13%	32	43.84%	23	34.33%	17	38.64%
decrease 10%-20%	24	13.04%	12	16.44%	11	16.42%	1	2.27%
decrease 20%-30%	14	7.61%	7	9.59%	3	4.48%	4	9.09%
decrease 30%-50%	25	13.59%	10	13.70%	7	10.45%	8	18.18%
decrease more than 50%	9	4.89%	3	4.11%	2	2.99%	4	9.09%
Dose increase	77	41.85%	27	36.99%	35	52.24%	15	34.09%
increase 10%-20%	16	8.70%	7	9.59%	6	8.96%	3	6.82%
increase 20%-30%	10	5.43%	2	2.74%	6	8.96%	2	4.55%
increase 30%-50%	15	8.15%	4	5.48%	10	14.93%	1	2.27%
increase more than 50%	36	19.57%	14	19.18%	13	19.40%	9	20.45%

Discontinuation* of Index Treatment (N/%)	96	52.17%	41	56.16%	33	49.25%	22	50.00%
Discontinuation within 1st month	26	14.13%	9	12.33%	7	10.45%	10	22.73%
Patients Switched to another CDK4/6i	26	14.13%	8	10.96%	10	14.93%	8	18.18%
Modified PDC rate in all patients (Mean/SD)**	0.85	0.15	0.82	0.18	0.87	0.13	0.89	0.12
Modified PDC rate in all patients (Median/SD)	0.88	0.20	0.88	0.22	0.88	0.18	0.93	0.21
Categorize patients based on PDC rate (N/%)								
greater than 80%	134	72.83%	49	67.12%	52	77.61%	33	75.00%
less or equal to 80%	50	27.17%	24	32.88%	15	22.39%	11	25.00%

Abbreviations: CDK4/6i = CDK4/6 inhibitor; IQR = interquartile range; PDC = proportion of days covered; SD = standard deviation

Notes:

*Discontinuation was defined as an interruption of ≥ 90 consecutive days of ribociclib between the last day of supply of ribociclib and the next prescription fill for ribociclib or end of continuous enrollment or disruption of other CDK inhibitor

**Modified PDC is computed with the following formula total days_supply/(last_drug_dt-first_drug_dt)

Descriptive analysis of characteristics during follow-up by PDC of concomitant medication for patients treated with Palbociclib

	All		No Concomitant		PDC<=80%		PDC>80%	
	N/Mean/Median	%/SD/IQR	N/Mean/Median	%/SD/IQR	N/Mean/Median	%/SD/IQR	N/Mean/Median	%/SD/IQR
# Patients	4206		1526		1547		1133	
Follow up Period in months (Mean/SD)	18.39	12.27	19.25	12.50	17.99	12.29	17.76	11.87
Follow up Period in months (Median/IQR)	15.61	17.98	17.04	19.03	15.12	17.75	14.46	16.93
Starting Dose(Mean/SD)	117.44	57.60	118.94	73.96	115.46	34.16	118.13	57.92
Starting Dose(Median/IQR)	121.74	44.55	125.00	45.41	120.69	38.06	120.69	44.55
Dose Change(N/%)								
No change	546	12.98%	187	12.25%	202	13.06%	157	13.86%
Any change	3660	87.02%	1339	87.75%	1345	86.94%	976	86.14%
Dose reductions	2103	50.00%	778	50.98%	782	50.55%	543	47.93%
decrease 10%-20%	758	18.02%	274	17.96%	299	19.33%	185	16.33%
decrease 20%-30%	546	12.98%	208	13.63%	207	13.38%	131	11.56%
decrease 30%-50%	567	13.48%	200	13.11%	203	13.12%	164	14.47%
decrease more than 50%	232	5.52%	96	6.29%	73	4.72%	63	5.56%
Dose increase	1557	37.02%	561	36.76%	563	36.39%	433	38.22%
increase 10%-20%	417	9.91%	156	10.22%	150	9.70%	111	9.80%
increase 20%-30%	284	6.75%	105	6.88%	100	6.46%	79	6.97%
increase 30%-50%	301	7.16%	100	6.55%	119	7.69%	82	7.24%
increase more than 50%	555	13.20%	200	13.11%	194	12.54%	161	14.21%
Discontinuation* of Index Treatment (N/%)	2395	56.94%	883	57.86%	866	55.98%	646	57.02%

Discontinuation within 1st month	316	7.51%	110	7.21%	115	7.43%	91	8.03%
Patients Switched to another CDK4/6	246	5.85%	84	5.50%	85	5.49%	77	6.80%
Modified PDC rate in all patients (Mean/SD)**	0.87	0.15	0.86	0.15	0.86	0.16	0.87	0.15
Modified PDC rate in all patients (Median/SD)	0.91	0.18	0.91	0.18	0.91	0.19	0.92	0.18
Categorize patients based on PDC rate (N/%)								
greater than 80%	3145	74.77%	1134	74.31%	1152	74.47%	859	75.82%
less or equal to 80%	1061	25.23%	392	25.69%	395	25.53%	274	24.18%

Abbreviations: CDK4/6i = CDK4/6 inhibitor; IQR = interquartile range; PDC = proportion of days covered; SD = standard deviation

Notes:

*Discontinuation was defined as an interruption of ≥ 90 consecutive days of ribociclib between the last day of supply of ribociclib and the next prescription fill for ribociclib or end of continuous enrollment or disruption of other CDK inhibitor

**Modified PDC is computed with the following formula total days_supply/(last_drug_dt-first_drug_dt)

Descriptive analysis of characteristics during follow-up by PDC of concomitant medication for patients treated with Abemaciclib

	All		No Concomitant		PDC<=80%		PDC>80%	
	N/Mean/Median	%/SD/IQR	N/Mean/Median	%/SD/IQR	N/Mean/Median	%/SD/IQR	N/Mean/Median	%/SD/IQR
# Patients	260		89		90		81	
Follow up Period in months (Mean/SD)	10.37	5.33	10.58	5.07	10.20	5.53	10.33	5.46
Follow up Period in months (Median/IQR)	9.32	9.17	9.93	8.65	8.78	9.47	9.37	9.11
Starting Dose(Mean/SD)	145.89	45.46	141.73	46.12	148.89	46.08	147.12	44.24
Starting Dose(Median/IQR)	150.00	65.94	150.00	48.00	150.00	80.38	150.00	65.94
Dose Change(N/%)								
No change	50	19.23%	15	16.85%	16	17.78%	19	23.46%
Any change	210	80.77%	74	83.15%	74	82.22%	62	76.54%
Dose reductions	143	55.00%	55	61.80%	52	57.78%	36	44.44%
decrease 10%-20%	52	20.00%	19	21.35%	16	17.78%	17	20.99%
decrease 20%-30%	30	11.54%	15	16.85%	8	8.89%	7	8.64%
decrease 30%-50%	37	14.23%	10	11.24%	19	21.11%	8	9.88%
decrease more than 50%	24	9.23%	11	12.36%	9	10.00%	4	4.94%
Dose increase	67	25.77%	19	21.35%	22	24.44%	26	32.10%
increase 10%-20%	15	5.77%	3	3.37%	4	4.44%	8	9.88%
increase 20%-30%	11	4.23%	3	3.37%	3	3.33%	5	6.17%
increase 30%-50%	16	6.15%	4	4.49%	8	8.89%	4	4.94%
increase more than 50%	25	9.62%	9	10.11%	7	7.78%	9	11.11%
Discontinuation* of Index Treatment (N/%)	123	47.31%	38	42.70%	45	50.00%	40	49.38%

Discontinuation within 1st month	38	14.62%	12	13.48%	14	15.56%	12	14.81%
Patients Switched to another CDK4/6	33	12.69%	9	10.11%	12	13.33%	12	14.81%
Modified PDC rate in all patients (Mean/SD)**	0.87	0.15	0.86	0.16	0.89	0.13	0.86	0.17
Modified PDC rate in all patients (Median/SD)	0.92	0.19	0.91	0.20	0.93	0.16	0.90	0.20
Categorize patients based on PDC rate (N/%)								
greater than 80%	200	76.92%	67	75.28%	73	81.11%	60	74.07%
less or equal to 80%	60	23.08%	22	24.72%	17	18.89%	21	25.93%

Abbreviations: CDK4/6i = CDK4/6 inhibitor; IQR = interquartile range; PDC = proportion of days covered; SD = standard deviation

Notes:

*Discontinuation was defined as an interruption of ≥ 90 consecutive days of ribociclib between the last day of supply of ribociclib and the next prescription fill for ribociclib or end of continuous enrollment or disruption of other CDK inhibitor

**Modified PDC is computed with the following formula total days_supply/(last_drug_dt-first_drug_dt)

Duration of treatment: Median treatment duration (in months) 95% Confidence Interval

	Ribociclib	Palbociclib	Abemaciclib
Overall study population (i.e., ≥3 months of follow-up)	9.4 (6.5-16.2) months	10.8 (10.1-11.4) months	8.3 (5.5-14.3) months
Patients with ≥2 medication refills	12.0 (9.1-23.2) months	12.0 (11.3-12.6) months	14.3 (8.2-not reached) months
patients with ≥6 months of follow-up	8.7 (5.6-12.2) months	10.3 (9.7-11.0) months	7.0 (4.9-12.0) months
≥12 months of follow-up	7.9 (5.3-11.5) months	10.2 (9.5-11.0) months	8.3 (5.4-16.5) months

Safety Results

As this is a study based on secondary use of data, safety monitoring and safety reporting, where there is a safety relevant result, were provided on an aggregate level only; no reporting on an individual case level was required. In studies based on secondary use of data with a safety relevant result, reports of adverse events/adverse reactions were summarized in the study report, i.e. the overall association between an exposure and an outcome. Relevant findings from the study report were included in the periodic aggregated regulatory reports submitted to Health Authorities.

Other Relevant Findings

None

Conclusion

In this retrospective cohort study, 4.0% of patients with HR+/HER2- mBC who initiated CDK4/6i therapy received ribociclib, 90.4% received palbociclib, and 5.6% received abemaciclib. CDK4/6i was used as second-line therapy in 88.4% of patients. Overall, 63.7% of patients received ≥1 concomitant medication at baseline that could potentially lead to a DDI with subsequent CDK4/6i therapy, and 42.5% of patients with concomitant medication use were adherent to their concomitant medication based on a PDC threshold of >80%. On average, patients were initiated on a starting dose of 491.7 mg for ribociclib, 117.4 mg for palbociclib, and 145.9 mg for abemaciclib. Over a median follow-up period of 14.9 months in the overall study population, 56.2% of patients discontinued the index CDK4/6i. Median treatment duration was 9.4 months in the ribociclib cohort, 10.8 months in the palbociclib cohort, and 8.3 months in the abemaciclib cohort. Lastly, 86.4% of patients had a dose modification during follow-up; of these changes, 57.7% were dose reductions and 42.3% were dose increases. These results remained largely consistent across the different CDK4/6i cohorts.

Date of Clinical Study Report:

30 March 2021