

Appendix 3: Safety of Palbociclib Among Breast Cancer Patients in the United States: A retrospective cohort study
Final - February 14th, 2020

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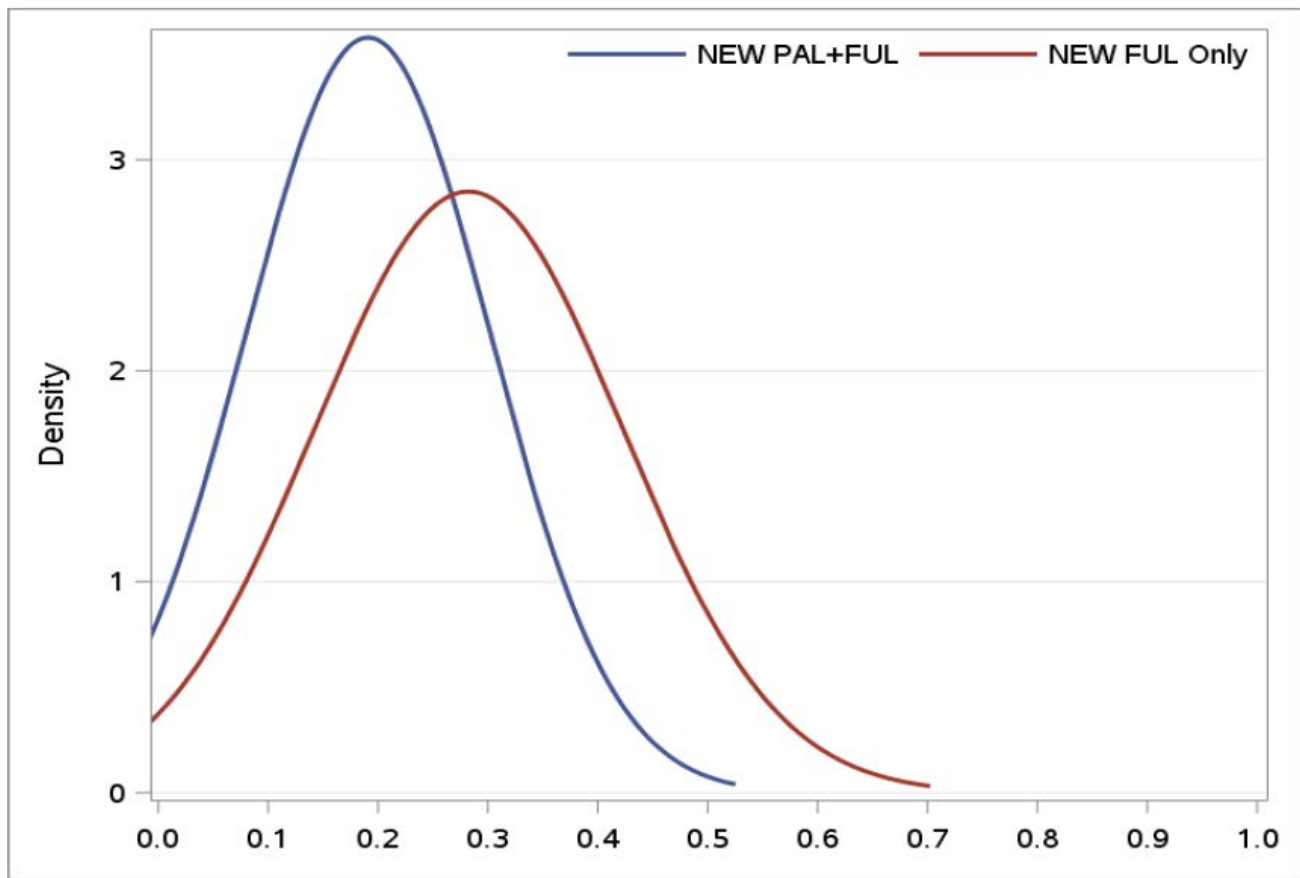
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Table 0. Formation of study cohorts

	Total		Total with advanced stage ER+/HER2- breast cancer*	
	N	%	N	%
Received palbociclib during the study period (01 Jan 2015 to 30 Sept 2017)	2,795	100.00%	2,600	100.00%
>=18 years of age	2,795	100.00%	2,600	100.00%
>=3 months of health plan coverage	2,445	87.48%	2,285	87.88%
>=3 months with no dispensing of palbociclib or CDK4/6 inhibitor before first dispensing of palbociclib	2,445	87.48%	2,285	87.88%
New users of palbociclib with fulvestrant	566	23.15%	548	23.98%
New users of palbociclib with letrozole	1,159	47.40%	1,083	47.40%
All other new users of palbociclib	720	29.65%	654	28.62%
Comparison group for Secondary Objective 3				
Received fulvestrant during the study period (01 Jan 2011 to 31 Jan 2015)	3,315	100.00%	2,983	100.00%
>=18 years of age	3,315	100.00%	2,983	100.00%
>=3 months of health plan coverage	2,773	83.65%	2,495	83.64%
>=3 months with no dispensing of fulvestrant before first dispensing of fulvestrant	2,316	69.86%	2,061	69.09%
All propensity score matched patients with fulvestrant	561	16.92%	544	18.24%
Abbreviations: N, number; ER+, Estrogen Receptor Positive; HER2-, Human Epidermal Growth Factor Negative; Jan, January; Sept, September; CDK, cyclin-dependent kinase.				
*Patients with advanced stage ER+/HER2- breast cancer (as defined by predictive model; this advanced stage ER+/HER2- breast cancer date must have occurred before or within three months of the first dispensing of study drug of interest (palbociclib or fulvestrant).				

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Figure 1. Propensity score distributions for palbociclib with fulvestrant new users and fulvestrant new users



Abbreviations: PAL, palbociclib; FUL, fulvestrant.

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Table 1.1. Characteristics of breast cancer patients utilizing palbociclib identified in the HIRD
[Primary Objective 1 and Secondary Objective 1]

Characteristics*	All new users of palbociclib		New users of palbociclib with fulvestrant		New users of palbociclib with letrozole		All other new users of palbociclib (no new use of fulvestrant or letrozole)	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD
Overall	2,445	100%	566	100%	1,159	100%	720	100%
Demographics								
Age at index date (in years)	59.8	11.6	59.5	11.4	59.2	11.3	61.0	12.3
Age (years)								
<45	226	9.2	51	9.0	117	10.1	58	8.1
45-64	1490	60.9	362	64.0	719	62.0	409	56.8
65+	729	29.8	153	27.0	323	27.9	253	35.1
Sex								
Male	53	2.2	≤10	n/a	14	1.2	30	4.2
Female	2392	97.8	557	98.4	1145	98.8	690	95.8
Calendar year of index date								
2015	791	32.4	99	17.5	456	39.3	236	32.8
2016	942	38.5	269	47.5	406	35.0	267	37.1
2017	712	29.1	198	35.0	297	25.6	217	30.1
Geographic region of residence								
Midwest	400	16.4	95	16.8	185	16.0	120	16.7
South	581	23.8	159	28.1	288	24.8	134	18.6
Northeast	696	28.5	166	29.3	340	29.3	190	26.4
West	768	31.4	146	25.8	346	29.9	276	38.3
Duration of health plan enrollment prior to index date (years)	3.45	2.1	3.46	2.1	3.2	2.0	3.8	2.0
Medical History								
Other primary cancer prior to first breast cancer diagnosis code	1055	43.1	223	39.4	532	45.9	300	41.7
Secondary malignancy (metastasis)	2137	87.4	496	87.6	1044	90.1	597	82.9
Lymph nodes of head, face, and neck	690	28.2	154	27.2	356	30.7	180	25.0
Respiratory and digestive systems	1058	43.3	257	45.4	490	42.3	311	43.2
Other specified sites	2017	82.5	463	81.8	978	84.4	576	80.0
Deyo-Charlson comorbidity index (DCI)	8.39	1.9	8.52	1.8	8.48	1.7	8.13	2.3
Secondary malignant neoplasm of breast	265	10.8	66	11.7	125	10.8	74	10.3
Breast cancer (female) diagnosis code	2365	96.7	558	98.6	1138	98.2	669	92.9
InSitu breast cancer	208	8.5	44	7.8	124	10.7	40	5.6
Advanced stage ER+/HER2- breast cancer	2,285	93.5	548	96.8	1,083	93.4	654	90.8
Cancer Therapy History								
Radiation therapy	483	19.8	112	19.8	233	20.1	138	19.2
External Beam	483	19.8	112	19.8	233	20.1	138	19.2
Surgery	88	3.6	11	1.9	59	5.1	18	2.5
Mastectomy in the last six months	36	1.47	≤10	n/a	28	2.42	≤10	n/a
Lumpectomy in the last six months	35	1.43	≤10	n/a	23	1.98	≤10	n/a
Radical Mastectomy in the last six months	40	1.64	≤10	n/a	25	2.16	≤10	n/a
Chemotherapy	472	19.30	100	17.67	218	18.81	154	21.39
Infusion based chemo (procedure)	14	0.57	≤10	n/a	≤10	n/a	≤10	n/a
Imaging	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
CT related imaging in the last six months	602	24.62	139	24.56	333	28.73	130	18.06
MRI for needle placement	≤10	n/a	0	0.00	≤10	n/a	0	0.00
Diagnostic imaging in the last six months	385	15.75	72	12.72	251	21.66	62	8.61
Mammography	55	2.25	≤10	n/a	37	3.19	≤10	n/a
MRI related imaging	168	6.87	25	4.42	116	10.01	27	3.75
Tomosynthesis (3D mammography)	62	2.54	18	3.18	35	3.02	≤10	n/a
Healthcare Utilization (six months prior to index date)								
Number of outpatient visits	39.7	25.2	38.6	23.6	39.5	23.8	40.8	28.4
Number of outpatient visits to an oncologist	0.0	0.2	0.0	0.2	0.0	0.3	0.0	0.1
Number of inpatient hospitalizations	0.3	0.7	0.3	0.7	0.3	0.6	0.4	0.8
Number of inpatient hospitalizations for breast cancer	0.1	0.3	0.0	0.2	0.1	0.4	0.1	0.4

Number of inpatient hospitalizations for any cancer	0.3	0.7	0.3	0.6	0.3	0.6	0.3	0.8
Number of emergency department visits	0.3	0.7	0.3	0.8	0.3	0.6	0.2	0.6
Medication Use (breast cancer related in past six months)								
Palbociclib	0	0.0	0	0.0	0	0.0	0	0.0
Aromatase Inhibitor	1527	62.5	326	57.6	815	70.3	386	53.6
Letrozole	1019	41.7	116	20.5	703	60.7	200	27.8
Anastrozole	391	16.0	136	24.0	142	12.3	113	15.7
Exemestane	286	11.7	86	15.2	94	8.1	106	14.7
HER2 positive Therapy	72	2.9	15	2.7	35	3.0	22	3.1
Trastuzumab	105	4.3	25	4.4	43	3.7	37	5.1
Lapatinib	≤10	n/a	≤10	n/a	0	0.00	≤10	n/a
Ado-trastuzumab	0	0.0	0	0.0	0	0.0	0	0.0
Pertuzumab	0	0.0	0	0.0	0	0.0	0	0.0
Tamoxifen	552	22.6	140	24.7	270	23.3	142	19.7
Fulvestrant	621	25.4	238	42.1	112	9.7	271	37.6
Denosumab or Pamidronate	836	34.2	206	36.4	359	31.0	271	37.6
Everolimus	150	6.1	40	7.1	52	4.5	58	8.1
Medication Use (not breast cancer related)								
Anticonvulsants	468	19.1	126	22.3	201	17.3	141	19.6
Antidepressants	746	30.5	178	31.4	348	30.0	220	30.6
Antidiabetics	292	11.9	67	11.8	134	11.6	91	12.6
Antifungals	125	5.1	28	4.9	64	5.5	33	4.6
Antihypertensives	653	26.7	173	30.6	293	25.3	187	26.0
Antimycobacterials	499	20.4	109	19.3	230	19.8	160	22.2
Antivirals	131	5.4	32	5.7	68	5.9	31	4.3
Corticosteroids	606	24.8	148	26.1	308	26.6	150	20.8
Oral contraceptive use (progestin)	≤10	n/a	≤10	n/a	≤10	n/a	0	0.00
Oral contraceptive use (combination)	≤10	n/a	≤10	n/a	≤10	n/a	≤10	n/a
Oral contraceptive use (unspecified)	26	1.06	≤10	n/a	13	1.12	≤10	n/a
Lipid lowering agent	528	21.60	132	23.32	251	21.66	145	20.14
Vaginal estrogen (local hormone treatment)	≤10	n/a	0	0.00	≤10	n/a	≤10	n/a
Macrolides	22	0.90	≤10	n/a	≤10	n/a	≤10	n/a
Sedatives/hypnotics	228	9.33	57	10.07	102	8.80	69	9.58
Selective estrogen receptor modulators	≤10	n/a	≤10	n/a	≤10	n/a	≤10	n/a
Unopposed estrogen hormone replacement therapy (HRT)	≤10	n/a	0	0.00	≤10	n/a	0	0.00
Co-morbidities (six months prior to index date)								
Pathologic fracture	211	8.6	46	8.1	110	9.5	55	7.6
Osteoporosis	196	8.0	56	9.9	79	6.8	61	8.5
Uterine malignancies	12	0.5	≤10	n/a	≤10	n/a	≤10	n/a
Pure hypercholesterolemia	215	8.8	48	8.48	105	9.06	62	8.61
Major adverse cardiac events (MACE)	57	2.3	20	3.53	24	2.07	13	1.81
Acute myocardial infarction (MI)	11	0.4	≤10	n/a	≤10	n/a	≤10	n/a
Cerebrovascular disease	1197	49.0	301	53.18	550	47.45	346	48.06
Stroke	48	2.0	16	2.83	21	1.81	11	1.53
Hyperglycemia	104	4.3	27	4.77	52	4.49	25	3.47
Deyo-Charlson Index (DCI)								
0-3	125	5.1	19	3.36	44	3.80	62	8.61
4-7	30	1.2	12	2.12	≤10	n/a	≤10	n/a
8-11	2214	90.6	512	90.5	1073	92.6	629	87.4
12 or more	76	3.1	23	4.1	32	2.8	21	2.9

Abbreviations: HIRD, HealthCore Integrated Research Database; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, number; SD, standard deviation; CT, computed tomography; MRI, magnetic resonance imaging.

*All characteristics are measured as presence within six months prior to the index date (new use of palbociclib), unless otherwise specified.

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Table 1.2. Incidence of the safety events of interest in all new users of palbociclib
[Primary Objective 1]

Event	All new users of palbociclib (N=2,445)				
	# Events	PT at risk	IR (per 100 person-years)		
			IR	95% Lower CI	95% Upper CI
Neutropenia (sensitive)	473	1,352	35.0	31.9	38.3
Neutropenia (specific)	313	1,417	22.1	19.7	24.7
Febrile neutropenia (sensitive)	44	1,530	2.9	2.1	3.9
Febrile neutropenia (specific)	11	1,538	0.7	0.4	1.3
Leukopenia (sensitive)	99	1,496	6.6	5.4	8.1
Leukopenia (specific)	98	1,496	6.6	5.3	8.0
Alopecia	12	1,535	0.8	0.4	1.4
Vomiting*	127	1,466	8.7	7.2	10.3
QT prolongation	80	1,514	5.3	4.2	6.6
Fatigue*	230	1,330	17.3	15.1	19.7
Serious infection	293	1,472	19.9	17.7	22.3
Brain/spinal infection	≤10	n/a	0.65	0.31	1.19
Pericardial/myocardial infection	0	1,540	0.00	0	0
Pulmonary infection	137	1,506	9.10	7.64	10.75
GI infection	12	1,539	0.78	0.40	1.36
Genitourinary/renal infection	140	1,496	9.36	7.87	11.04
Dental infection	≤10	n/a	0.06	0.00	0.36
Ear, nose, and throat infection	83	1,500	5.54	4.41	6.86
Skin, bones, and joint infection	82	1,512	5.42	4.31	6.73
Hepatitis B infection	≤10	n/a	0.20	0.04	0.57
Influenza infection	≤10	n/a	0.39	0.14	0.85
Other infection	284	1,445	19.66	17.44	22.08
Diarrhea*	61	1,496	4.08	3.12	5.24
Interstitial lung disease/pneumonitis	352	1,437	24.49	22.00	27.19
Anemia (sensitive)	536	1,358	39.47	36.20	42.96
Anemia (specific)	318	1,448	21.96	19.62	24.52
Nausea*	200	1,409	14.19	12.29	16.30
Thrombocytopenia	149	1,497	9.95	8.42	11.68
Pulmonary embolism*	45	1,505	2.99	2.18	4.00
No history	54	1,517	3.56	2.67	4.64
Other venous embolism and thrombosis*	64	1,489	4.30	3.31	5.49
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	45	1,509	2.98	2.18	3.99
No history of "other venous embolism and thrombosis"	94	1,509	6.23	5.03	7.62
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	61	1,520	4.01	3.07	5.16
Embolism and thrombosis of unspecified artery	≤10	n/a	0.19	0.04	0.57
Cataracts and other ocular disorders	94	1,498	6.28	5.07	7.68
Stomatitis and mucositis	35	1,529	2.29	1.59	3.18
Fever	152	1,499	10.14	8.59	11.89

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Anorexia	30	1,532	1.96	1.32	2.80
Peripheral neuropathy	109	1,497	7.28	5.98	8.78
Sudden cardiac death	≤10	n/a	0.26	0.07	0.67
Diabetes mellitus	176	1,464	12.02	10.31	13.93
Type 2 Diabetes mellitus	175	1,466	11.94	10.24	13.85
Hyperglycemia	31	1,526	2.03	1.38	2.88
Liver failure (Acute liver injury)	47	1,533	3.07	2.25	4.08
Abnormal ALT (incident)^	31	544	5.70	3.87	8.09
Abnormal ALT (incident or prevalent)^	74	684	10.83	8.50	13.59
Abnormal AST (incident)^	36	583	6.18	4.33	8.55
Abnormal AST (incident or prevalent)^	83	687	12.08	9.62	14.97
Abnormal ALP (incident)^	25	642	3.89	2.52	5.75
Abnormal ALP (incident or prevalent)^	66	704	9.38	7.25	11.93
Secondary malignancies (second primary cancers)	413	1,376	30.01	27.18	33.05
Non-melanoma skin cancer	37	1,517	2.44	1.72	3.36
Abbreviations: N, number; GI, gastrointestinal; PT, person-time; IR, incidence rate; CI, confidence interval; DVT, deep vein thrombosis; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase.					
*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date					
^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L; incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.					

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Table 1.3. Incidence of the safety events of interest in new users of palbociclib subgroups
[Secondary Objective 1]

Event	New users of palbociclib and fulvestrant (n=566)					New users of palbociclib and letrozole (n=1,159)					All other new users of palbociclib (no new use of fulvestrant or letrozole) (n=720)				
	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)		
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI
Neutropenia (sensitive)	107	285	37.54	30.77	45.37	240	709	33.87	29.72	38.44	126	359	35.11	29.25	41.81
Neutropenia (specific)	71	298	23.82	18.60	30.05	154	744	20.69	17.55	24.22	88	374	23.50	18.85	28.95
Febrile neutropenia (sensitive)	11	321	3.42	1.71	6.12	20	810	2.47	1.51	3.82	13	399	3.26	1.73	5.57
Febrile neutropenia (specific)	≤10	n/a	0.93	0.19	2.72	≤10	n/a	0.62	0.20	1.44	≤10	n/a	0.74	0.15	2.17
Leukopenia (sensitive)	17	318	5.34	3.11	8.56	56	785	7.13	5.39	9.26	26	393	6.62	4.33	9.70
Leukopenia (specific)	17	318	5.34	3.11	8.56	55	785	7.00	5.28	9.12	26	393	6.62	4.33	9.70
Alopecia	≤10	n/a	0.31	0.01	1.72	≤10	n/a	0.99	0.43	1.95	≤10	n/a	0.75	0.15	2.18
Vomiting*	32	309	10.36	7.09	14.63	47	771	6.10	4.48	8.11	48	387	12.40	9.15	16.44
QT prolongation	20	315	6.35	3.88	9.80	37	801	4.62	3.25	6.37	23	398	5.78	3.66	8.67
Fatigue*	53	284	18.69	14.00	24.45	98	692	14.17	11.50	17.27	79	355	22.27	17.63	27.75
Serious infection	79	309	25.56	20.24	31.86	135	773	17.46	14.64	20.67	79	389	20.28	16.06	25.28
Brain/spinal infection	≤10	n/a	1.24	0.34	3.17	≤10	n/a	0.74	0.27	1.61	0	404	0.00	0	0
Pericardial/myocardial infection	0	324	0.00	0	0	0	812	0.00	0	0	0	404	0.00	0	0
Pulmonary infection	34	318	10.69	7.40	14.94	70	791	8.85	6.90	11.18	33	397	8.32	5.73	11.68
GI infection	≤10	n/a	0.62	0.07	2.23	≤10	n/a	0.74	0.27	1.61	≤10	n/a	0.99	0.27	2.54
Genitourinary/Renal infection	35	314	11.16	7.78	15.53	73	785	9.30	7.29	11.69	32	397	8.06	5.51	11.38
Dental infection	0	324	0.00	0	0	≤10	n/a	0.12	0.00	0.69	0	404	0.00	0	0
Ear, nose, and throat infection	14	320	4.37	2.39	7.34	51	784	6.50	4.84	8.55	18	395	4.55	2.70	7.20
Skin, bones, and joint infection	17	319	5.33	3.10	8.53	46	793	5.80	4.25	7.73	19	399	4.76	2.86	7.43
Hepatitis B infection	0	324	0.00	0	0	≤10	n/a	0.25	0.03	0.89	≤10	n/a	0.25	0.01	1.38
Influenza infection	≤10	n/a	1.24	0.34	3.18	0	812	0.00	0	0	≤10	n/a	0.50	0.06	1.79
Other infection	65	306	21.22	16.38	27.05	146	756	19.30	16.30	22.70	73	382	19.11	14.98	24.03
Diarrhea*	14	316	4.42	2.42	7.42	27	788	3.43	2.26	4.99	20	392	5.10	3.12	7.88
Interstitial lung disease/pneumonitis	103	303	34.00	27.75	41.23	167	749	22.29	19.04	25.94	82	385	21.31	16.95	26.45
Anemia (sensitive)	134	283	47.38	39.69	56.11	276	706	39.11	34.63	44.01	126	369	34.11	28.41	40.61
Anemia (specific)	79	303	26.11	20.67	32.54	161	761	21.15	18.01	24.68	78	384	20.31	16.06	25.35
Nausea*	49	297	16.48	12.19	21.79	80	740	10.81	8.57	13.46	71	372	19.09	14.91	24.08
Thrombocytopenia	33	318	10.39	7.15	14.60	67	791	8.47	6.56	10.75	49	389	12.60	9.32	16.66
Pulmonary embolism*	14	318	4.41	2.41	7.40	16	791	2.02	1.16	3.29	15	397	3.78	2.12	6.24
No history	15	319	4.70	2.63	7.75	27	800	3.38	2.23	4.91	12	398	3.01	1.56	5.26
Other venous embolism and thrombosis*	11	309	3.56	1.78	6.37	28	782	3.58	2.38	5.17	25	398	6.28	4.07	9.27
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	≤10	n/a	2.24	0.90	4.62	17	796	2.14	1.24	3.42	21	400	5.25	3.25	8.02
No history of "other venous embolism and thrombosis"	23	315	7.30	4.63	10.96	50	794	6.30	4.67	8.30	21	400	5.24	3.25	8.02
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	16	316	5.06	2.89	8.21	28	802	3.49	2.32	5.05	17	401	4.24	2.47	6.79
Embolism and thrombosis of unspecified artery	≤10	n/a	0.31	0.01	1.72	0	812	0.00	0	0	≤10	n/a	0.50	0.06	1.79
Cataracts and other ocular disorders	19	316	6.01	3.62	9.38	54	787	6.86	5.16	8.96	21	395	5.32	3.29	8.13
Stomatitis and mucositis	≤10	n/a	2.80	1.28	5.31	11	807	1.36	0.68	2.44	15	401	3.74	2.10	6.17
Fever	37	318	11.65	8.20	16.05	77	787	9.78	7.72	12.23	38	394	9.64	6.82	13.23
Anorexia	≤10	n/a	3.10	1.49	5.70	14	807	1.74	0.95	2.91	≤10	n/a	1.49	0.55	3.24
Peripheral neuropathy	24	316	7.59	4.86	11.29	48	790	6.08	4.48	8.06	37	391	9.46	6.66	13.04
Sudden cardiac death	0	324	0.00	0	0	≤10	n/a	0.37	0.08	1.08	≤10	n/a	0.25	0.01	1.38
Diabetes mellitus	46	310	14.84	10.87	19.80	103	761	13.53	11.04	16.41	27	393	6.87	4.53	9.99
Type 2 Diabetes mellitus	46	310	14.83	10.86	19.78	103	761	13.53	11.04	16.41	26	394	6.60	4.31	9.67
Hyperglycemia	≤10	n/a	1.55	0.50	3.62	20	801	2.50	1.52	3.85	≤10	n/a	1.49	0.55	3.25
Liver failure (Acute liver injury)	13	323	4.03	2.14	6.89	22	807	2.73	1.71	4.13	12	403	2.98	1.54	5.20
Abnormal ALT (incident)^	≤10	n/a	7.37	3.37	13.99	≤10	n/a	3.38	1.55	6.41	13	155	8.37	4.46	14.32
Abnormal ALT (incident or prevalent)^	18	156	11.57	6.86	18.29	31	335	9.24	6.28	13.12	25	193	12.99	8.40	19.17
Abnormal AST (incident)^	≤10	n/a	7.02	3.21	13.33	13	295	4.41	2.35	7.53	14	160	8.77	4.79	14.71
Abnormal AST (incident or prevalent)^	21	152	13.77	8.53	21.06	31	342	9.06	6.16	12.86	31	193	16.10	10.94	22.85
Abnormal ALP (incident)^	≤10	n/a	5.04	2.02	10.38	≤10	n/a	2.15	0.86	4.43	11	177	6.20	3.09	11.09
Abnormal ALP (incident or prevalent)^	17	152	11.15	6.50	17.86	24	356	6.74	4.32	10.03	25	195	12.80	8.29	18.90
Secondary malignancies (second primary cancer)	106	290	36.49	29.88	44.14	205	715	28.66	24.87	32.87	102	371	27.52	22.44	33.40
Non-melanoma skin cancer	≤10	n/a	2.19	0.88	4.51	17	799	2.13	1.24	3.41	13	398	3.27	1.74	5.59

Abbreviations: n, number; GI, gastrointestinal; PT, person-time; IR, incidence rate; CI, confidence interval; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; DVT, deep vein thrombosis.

*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date

^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.

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Table 1.4A. Characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone (historical comparison group)

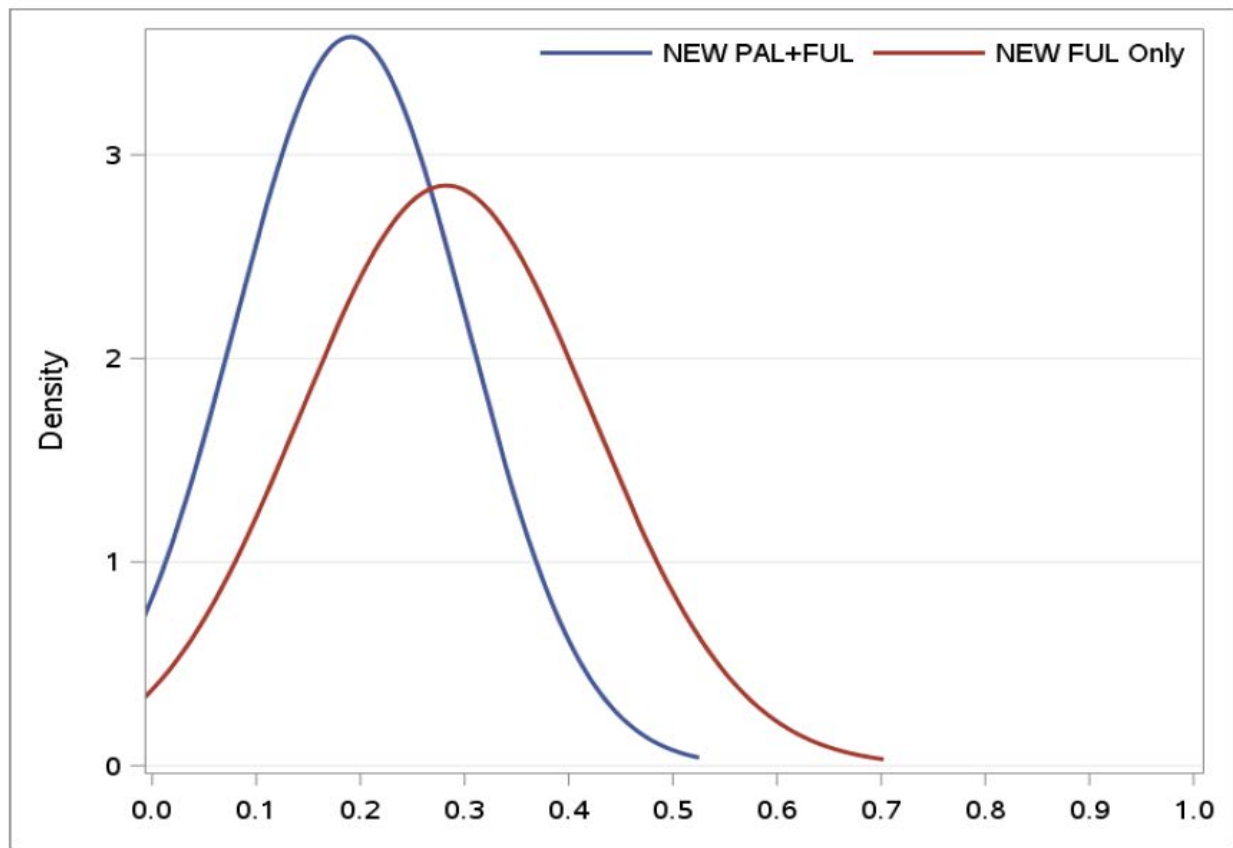
[Secondary Objective 3a]

Characteristics*	Before Propensity Score Matching					After Propensity Score Matching ^Δ				
	New users of palbociclib with fulvestrant		New users of fulvestrant alone (pre-2015)		Standardized difference	New users of palbociclib with fulvestrant		New users of fulvestrant alone (pre-2015)		Standardized difference
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Overall	566	100%	2,316	100%		561	100%	561	100%	
Demographics										
Age at index date (in years)	59.3	11.0	64.1	12.9	0.4	59.5	11.0	59.9	13.3	0.04
Age (years)										
<45	51.0	9.0	127.0	5.5	0.1	49.0	8.7	63.0	11.2	0.08
45-64	362.0	64.0	1121.0	48.4	0.3	360.0	64.2	306.0	54.5	0.20
65+	153.0	27.0	1068.0	46.1	0.4	152.0	27.1	192.0	34.2	0.16
Sex										
Male	≤10	n/a	30	1.30	0.0	≤10	n/a	≤10	n/a	0.10
Female	557	98.4	2286	98.7	0.0	552	98.4	558	99.5	0.10
Calendar year of index date										
2011	0	0.00	612	26.4	n/a	0	0.00	103	18.4	n/a
2012	0	0.00	507	21.9	n/a	0	0.00	138	24.6	n/a
2013	0	0.00	569	24.6	n/a	0	0.00	159	28.3	n/a
2014	0	0.00	628	27.1	n/a	0	0.00	161	28.7	n/a
2015	99	17.5	0	0.00	n/a	98	17.5	0	0.00	n/a
2016	269	47.5	0	0.00	n/a	267	47.6	0	0.00	n/a
2017	198	35.0	0	0.00	n/a	196	34.9	0	0.00	n/a
Geographic region of residence										
Midwest	95	16.8	422	18.2	0.04	95	16.9	93	16.6	0.01
South	159	28.1	690	29.8	0.04	157	28.0	165	29.4	0.03
Northeast	166	29.3	580	25.0	0.10	164	29.2	158	28.2	0.02
West	146	25.8	624	26.9	0.03	145	25.8	145	25.8	0.00
Medical History										
Other primary cancer prior to first breast cancer diagnosis code	223	39.4	1026	44.3	0.1	222	39.6	271	48.3	0.18
Secondary malignancy (metastasis)	496	87.6	1823	78.7	0.2	491	87.5	488	87.0	0.02
Lymph nodes of head, face, and neck	154	27.2	476	20.6	0.2	151	26.9	150	26.7	0.00
Respiratory and digestive systems	257	45.4	781	33.7	0.2	254	45.3	252	44.9	0.01
Other specified sites	463	81.8	1710	73.8	0.2	458	81.6	458	81.6	0.00
Deyo-Charlson comorbidity index (DCI) without cancer codes	8.5	1.8	7.85	2.3	0.3	8.5	1.8	8.56	1.6	0.03
Secondary malignant neoplasm of breast	66	11.7	204	8.8	0.1	65	11.6	67	11.9	0.01
Breast cancer (female) diagnosis code	558	98.6	2262	97.7	0.1	553	98.6	556	99.1	0.05
InSitu breast cancer	44	7.8	151	6.5	0.0	42	7.5	39	7.0	0.02
Cancer Therapy History										
Radiation therapy	112	19.8	386	16.7	0.1	112	20.0	117	20.9	0.02
External Beam	112	19.8	386	16.7	0.1	112	20.0	117	20.9	0.02
Surgery	11	1.9	68	2.9	0.1	11	2.0	13	2.3	0.02
Mastectomy in the last six months	≤10	n/a	32	1.38	0.09	≤10	n/a	≤10	n/a	0.06
Lumpectomy in the last six months	≤10	n/a	25	1.08	0.06	≤10	n/a	≤10	n/a	0.04
Radical mastectomy in the last six months	≤10	n/a	22	0.95	0.01	≤10	n/a	≤10	n/a	0.02
Chemotherapy	100	17.67	429	18.52	0.02	99	17.65	98	17.47	0.00
Infusion based chemo (procedure)	≤10	n/a	31	1.34	0.11	≤10	n/a	12	2.14	0.16
Imaging										
CT related imaging in the last six months	139	24.56	501	21.63	0.07	138	24.60	146	26.02	0.03
MR related imaging for needle placement	0	0.00	≤10	n/a	.	0	0.00	≤10	n/a	.
Diagnostic imaging in the last six months	72	12.72	461	19.91	0.20	72	12.83	79	14.08	0.04
Mammography	≤10	n/a	107	4.62	0.19	≤10	n/a	≤10	n/a	0.03
MRI related imaging	25	4.42	91	3.93	0.02	25	4.46	26	4.63	0.01
Tomosynthesis (3D mammography)	0	0.00	0	0.00	n/a	0	0.00	0	0.00	n/a
Healthcare Utilization (six months prior to index date)										
Number of outpatient visits	37.6	21.7	36.5	24.6	0.0	37.7	21.8	39.3	24.2	0.07
Number of outpatient visits to an oncologist	0.0	0.2	0.0	0.3	0.0	0.0	0.2	0.0	0.3	0.08
Number of inpatient hospitalizations	0.3	0.7	0.3	0.7	0.0	0.3	0.7	0.4	0.8	0.14
Number of inpatient hospitalizations for breast cancer	0.0	0.2	0.3	0.6	0.5	0.0	0.2	0.3	0.7	0.58
Number of inpatient hospitalizations for any cancer	0.3	0.6	0.3	0.7	0.1	0.3	0.6	0.4	0.7	0.15
Number of emergency department visits	0.3	0.8	0.2	0.6	0.1	0.3	0.8	0.3	0.7	0.03
Medication Use (breast cancer related)										
Palbociclib	0	0.00	0	0.00	n/a	0	0.00	0	0.00	n/a
Aromatase inhibitor	326	57.6	1285	55.5	0.04	321	57.2	303	54.0	0.06
Letrozole	116	20.5	429	18.5	0.05	113	20.1	116	20.7	0.01
Anastrozole	136	24.0	611	26.4	0.05	135	24.1	138	24.6	0.01
Exemestane	86	15.2	358	15.5	0.01	85	15.2	76	13.5	0.05
HER2 positive therapy	15	2.7	127	5.5	0.14	15	2.7	14	2.5	0.01
Trastuzumab	25	4.4	159	6.9	0.11	24	4.3	27	4.8	0.03
Lapatinib	≤10	n/a	16	0.69	0.05	≤10	n/a	≤10	n/a	n/a
Ado-trastuzumab	0	0.00	0	0.00	n/a	0	0.00	0	0.00	n/a
Pertuzumab	0	0.00	0	0.00	n/a	0	0.00	0	0.00	n/a
Tamoxifen	140	24.73	379	16.36	0.21	140	24.96	135	24.06	0.02
Fulvestrant	238	42.05	0	0.00	n/a	236	42.07	0	0.00	n/a

Denosumab or Pamidronate	206	36.40	424	18.31	0.41	201	35.83	197	35.12	0.01
Everolimus	40	7.07	84	3.63	0.15	39	6.95	37	6.60	0.01
Medication Use (not breast cancer related)										
Anticonvulsants	126	22.3	347	15.0	0.19	122	21.7	123	21.9	0.00
Antidepressants	178	31.4	631	27.2	0.09	175	31.2	184	32.8	0.03
Antidiabetics	67	11.8	252	10.9	0.03	66	11.8	75	13.4	0.05
Antifungals	28	4.9	119	5.1	0.01	28	5.0	35	6.2	0.05
Antihypertensives	173	30.6	623	26.9	0.08	171	30.5	135	24.1	0.14
Antimycobacterials	109	19.3	446	19.3	0.00	107	19.1	117	20.9	0.04
Antivirals	32	5.7	112	4.8	0.04	32	5.7	30	5.3	0.02
Corticosteroids	148	26.1	416	18.0	0.20	146	26.0	146	26.0	0.00
Oral contraceptive use (progestin)	0	0.00	≤10	n/a	n/a	0	0.00	0	0.00	n/a
Oral contraceptive use (combination)	≤10	n/a	≤10	n/a	0.02	≤10	n/a	≤10	n/a	n/a
Oral contraceptive use (unspecified)	≤10	n/a	23	0.99	0.02	≤10	n/a	≤10	n/a	n/a
Lipid lowering agent	132	23.32	556	24.01	0.02	130	23.17	121	n/a	0.04
Vaginal estrogen (local hormone treatment)	0	0.00	≤10	n/a	n/a	0	0.00	≤10	0.18	n/a
Macrolides	≤10	n/a	22	0.95	0.06	≤10	n/a	≤10	n/a	0.08
Sedatives/hypnotics	57	10.07	291	12.56	0.08	57	10.16	63	11.23	0.03
Selective estrogen receptor modulators	≤10	n/a	≤10	n/a	0.03	≤10	n/a	≤10	n/a	0.08
Unopposed estrogen hormone replacement therapy (HRT)	0	0.00	≤10	0.43	n/a	0	0.00	≤10	0.53	n/a
Co-morbidities (six months prior to index date)										
Pathologic fracture	46	8.13	173	7.47	0.02	46	8.20	51	9.09	0.03
Osteoporosis	56	9.89	225	9.72	0.01	55	9.80	52	9.27	0.02
Uterine malignancies	≤10	n/a	11	0.47	0.02	≤10	n/a	≤10	n/a	0.03
Pure hypercholesterolemia	48	8.48	237	10.23	0.06	48	8.56	54	9.63	0.04
Major adverse cardiac events (MACE)	20	3.53	83	3.58	0.00	20	3.57	23	4.10	0.03
Acute myocardial infarction (MI)	≤10	n/a	23	0.99	0.03	≤10	n/a	≤10	n/a	0.10
Cerebrovascular disease	301	53.18	1148	49.57	0.07	296	52.76	277	49.38	0.07
Stroke	16	2.83	63	2.72	0.01	16	2.85	15	2.67	0.01
Hyperglycemia	27	4.77	55	2.37	0.13	23	4.10	29	5.17	0.05
Devo-Charlson Index (DCI)										
0-3	19	3.36	259	11.18	0.30	19	3.39	17	3.03	0.02
4-7	12	2.12	57	2.46	0.02	12	2.14	≤10	n/a	0.12
8-11	512	90.46	1937	83.64	0.20	508	90.55	517	92.16	0.06
12 or more	23	4.06	63	2.72	0.07	22	3.92	23	4.10	0.01
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, number; SD, standard deviation; CT, computed tomography; MRI, magnetic resonance imaging.										
*All characteristics are measured as presence within six months prior to the index date, unless otherwise specified.										
^The following variables were included in the propensity score: age, region, Devo-Charlson Index, number of outpatient visits, number of emergency room visits, secondary malignancy to lymph nodes of head, face, and neck, secondary malignancy to other specified sites, secondary malignancy to respiratory sites, tamoxifen, everolimus, anastrozole, denosumab or pamidronate, exemestane, chemotherapy, corticosteroids, diagnostic imaging, breast cancer surgery, letrozole, HER2 positive therapy, radiation therapy, CT imaging, mammography, MRI imaging, anticonvulsants, antidepressants, sedatives/hypnotics, secondary malignancy to breast, breast cancer diagnosis code, in situ breast cancer diagnosis, hyperglycemia, and cerebrovascular disease.										

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Figure 2. Propensity score distributions for palbociclib with fulvestrant new users and fulvestrant new users (historical comparison group)



Abbreviations: PAL, palbociclib; FUL, fulvestrant.

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Table 1.4B. Characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone (contemporaneous comparison group)

[Secondary Objective 4a]

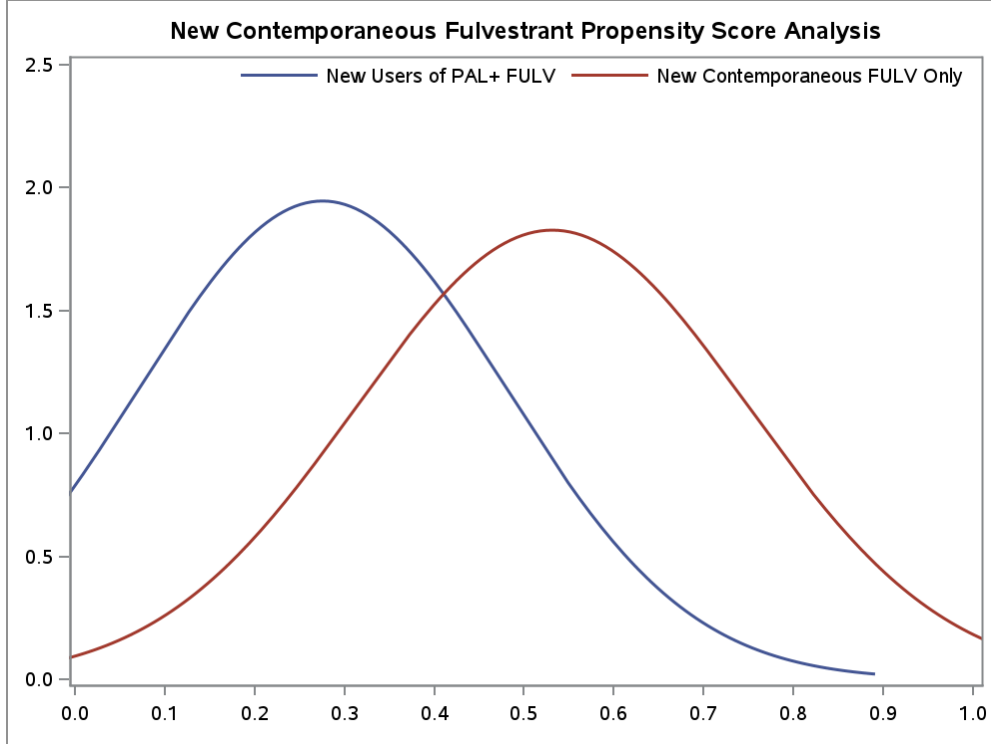
Characteristics*	Before Propensity Score Matching					After Propensity Score Matching^				
	New users of palbociclib with fulvestrant		New users of fulvestrant alone (Feb. 2015 or later)		Standardized difference	New users of palbociclib with fulvestrant		New users of fulvestrant alone (Feb. 2015 or later)		Standardized difference
	N/Mean	%/STD	N/Mean	%/STD		N/Mean	%/STD	N/Mean	%/STD	
Overall	566	100%	961	100%		292	100%	292	100%	
Demographics										
Age at index date (in years)	59.5	11.4	66	13.5	0.52	64.1	10.8	65.6	12.7	0.13
Age (years)										
<45	51	9.0	54	5.6	0.13	≤10	n/a	16	5.5	0.14
45-64	337	59.5	381	39.6	0.41	153	52.4	110	37.7	0.30
65+	178	31.4	526	54.7	0.48	131	44.9	166	56.8	0.24
Gender										
Male	≤10	n/a	15	1.6	0.00	≤10	n/a	≤10	n/a	0.07
Female	557	98.4	946	98.4	0.00	284	97.3	287	98.3	0.07
Calendar year of index date										
2015	99	17.5	444	46.2	0.65	91	31.2	97	33.2	0.04
2016	269	47.5	325	33.8	0.28	125	42.8	114	39.0	0.08
2017	198	35.0	192	20.0	0.34	76	26.0	81	27.7	0.04
Geographic region of residence										
Midwest	95	16.8	175	18.2	0.04	48	16.4	59	20.2	0.10
South	159	28.1	249	25.9	0.05	69	23.6	72	24.7	0.02
Northeast	166	29.3	264	27.5	0.04	84	28.8	87	29.8	0.02
West	146	25.8	273	28.4	0.06	91	31.2	74	25.3	0.13
Duration of health plan enrollment prior to index date (days)	1264	758.3	1322	721.5	0.08	1331	755.9	1406	751.2	0.10
Medical History										
Other primary cancer prior to first breast cancer diagnosis code	223	39.4	365	38.0	0.03	125	42.8	123	42.1	0.01
Secondary malignancy (metastasis)										
Lymph nodes of head, face, and neck	154	27.2	211	22.0	0.12	77	26.4	62	21.2	0.12
Respiratory and digestive systems	257	45.4	332	34.5	0.22	119	40.8	108	37.0	0.08
Other specified sites	463	81.8	662	68.9	0.30	216	74.0	217	74.3	0.01
Devo-Charlson comorbidity index (DCI)	8.52	1.8	7.94	2.7	0.26	8.31	2.0	8.24	2.4	0.03
Secondary malignant neoplasm of breast	66	11.7	90	9.4	0.07	35	12.0	36	12.3	0.01
Breast Cancer (Female) diagnosis code	558	98.6	924	96.1	0.15	284	97.3	282	96.6	0.04
InSitu Breast Cancer	44	7.8	63	6.6	0.05	15	5.1	16	5.5	0.02
History of Breast Cancer	327	57.8	358	37.3	0.42	147	50.3	132	45.2	0.10
Cancer Therapy History										
Radiation therapy	112	19.8	173	18.0	0.05	54	18.5	63	21.6	0.08
Implantation (Brachytherapy)	0	0.0	≤10	n/a	n/a	0	0.0	0	0.0	n/a
External Beam	112	19.8	173	18.0	0.05	54	18.5	63	21.6	0.08
Surgery	11	1.9	33	3.4	0.09	≤10	n/a	12	4.1	0.10
Mastectomy in the last six months	≤10	n/a	12	1.2	0.08	≤10	n/a	≤10	n/a	0.11
Lumpectomy in the last six months	≤10	n/a	17	1.8	0.12	≤10	n/a	≤10	n/a	0.12
Radical Mastectomy in the last six months	≤10	n/a	≤10	n/a	0.02	≤10	n/a	≤10	n/a	0.06
Chemotherapy	100	17.7	126	13.1	0.13	42	14.4	40	13.7	0.02
Infusion based chemo (procedure)	≤10	n/a	≤10	n/a	0.05	≤10	n/a	≤10	n/a	0.14
Imaging										
CT related imaging in the last six months	139	24.6	178	18.5	0.15	62	21.2	64	21.9	0.02
MR related imaging for needle placement	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Diagnostic imaging in the last six months	72	12.7	154	16.0	0.09	38	13.0	36	12.3	0.02
Mammography	≤10	n/a	21	2.2	0.06	≤10	n/a	≤10	n/a	0.05
MRI related imaging	25	4.4	47	4.9	0.02	13	4.5	13	4.5	0.00
Tomosynthesis (3D Mammography)	18	3.2	15	1.6	0.11	0	0.0	0	0.0	n/a
Healthcare Utilization (Six months prior to index date)										
Number of outpatient visits	38.6	23.6	36.8	25.8	0.07	38.7	26.4	37.6	22.8	0.05
Number of outpatient visits to an oncologist	0.0	0.2	0.0	0.3	0.04	0.0	0.2	0.0	0.3	0.04
Number of inpatient hospitalizations	0.3	0.7	0.4	0.7	0.04	0.3	0.7	0.4	0.8	0.10
Number of inpatient hospitalizations for breast cancer	0.0	0.2	0.1	0.4	0.25	0.1	0.3	0.1	0.4	0.11
Number of inpatient hospitalizations for any cancer	0.3	0.6	0.3	0.7	0.03	0.3	0.6	0.4	0.7	0.12
Number of emergency department visits	0.3	0.8	0.3	0.7	0.03	0.3	0.8	0.3	0.6	0.03
Medication Use (breast cancer related)										
Palbociclib	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Hormone Therapy	326	57.6	482	50.2	0.15	160	54.8	158	54.1	0.0
Letrozole	116	20.5	147	15.3	0.14	55	18.8	51	17.5	0.0
Anastrozole	136	24.0	240	25.0	0.02	67	22.9	72	24.7	0.0
Exemestane	86	15.2	122	12.7	0.07	42	14.4	49	16.8	0.1
HER2 positive Therapy	15	2.7	96	10.0	0.31	14	4.8	16	5.5	0.0
Trastuzumab	25	4.4	131	13.6	0.33	17	5.8	29	9.9	0.2
Lapatinib	≤10	n/a	≤10	n/a	0.01	≤10	n/a	≤10	n/a	0.0
Ado-trastuzumab	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Pertuzumab	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Tamoxifen	140	24.7	189	19.7	0.1	66	22.6	61	20.9	0.0
Fulvestrant	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Denosumab or Pamidronate	206	36.4	234	24.3	0.3	82	28.1	85	29.1	0.0
Everolimus	40	7.1	33	3.4	0.2	14	4.8	17	5.8	0.0
Medication Use (not breast cancer related)										
Anticonvulsants	126	22.3	146	15.2	0.18	49	16.8	45	15.4	0.04
Antidepressants	178	31.4	252	26.2	0.12	86	29.5	83	28.4	0.02
Antidiabetics	67	11.8	112	11.7	0.01	26	8.9	34	11.6	0.09
Antifungals	28	4.9	42	4.4	0.03	17	5.8	≤10	n/a	0.11
Antihypertensives	173	30.6	252	26.2	0.10	80	27.4	105	36.0	0.18
Antimycobacterials	109	19.3	196	20.4	0.03	56	19.2	70	24.0	0.12
Antivirals	32	5.7	30	3.1	0.12	17	5.8	13	4.5	0.06
Corticosteroids	148	26.1	200	20.8	0.13	65	22.3	76	26.0	0.09

Oral contraceptive use (progestin)	≤10	n/a	≤10	n/a	0.02	0	0.0	≤10	n/a	n/a
Oral contraceptive use (combination)	≤10	n/a	≤10	n/a	0.01	0	0.0	≤10	n/a	n/a
Oral contraceptive use (unspecified)	≤10	n/a	11	1.1	0.01	≤10	n/a	≤10	n/a	0.14
Lipid lowering agent	132	23.3	212	22.1	0.03	67	22.9	66	22.6	0.01
Vaginal estrogen (local hormone treatment)	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Macrolides	≤10	n/a	12	1.2	0.03	≤10	n/a	≤10	n/a	0.08
Sedatives/hypnotics	57	10.1	67	7.0	0.11	23	7.9	21	7.2	0.03
Selective estrogen receptor modulators	≤10	n/a	≤10	n/a	0.03	0	0.0	0	0.0	n/a
Unopposed estrogen hormone replacement therapy (HRT)	0	0.0	≤10	n/a	n/a	0	0.0	≤10	n/a	n/a
Co-morbidities (six months prior to index date)										
Pathologic fracture	46	8.1	62	6.5	0.06	20	6.8	20	6.8	0.00
Osteoporosis	56	9.9	116	12.1	0.07	33	11.3	36	12.3	0.03
Uterine malignancies	≤10	n/a	≤10	n/a	0.07	0	0.0	0	0.0	n/a
Pure hypercholesterolemia	48	8.5	99	10.3	0.06	32	11.0	29	9.9	0.03
Major adverse cardiac events (MACE)	20	3.5	42	4.4	0.04	14	4.8	12	4.1	0.03
Acute myocardial infarction (MI)	≤10	n/a	≤10	n/a	0.04	≤10	n/a	≤10	n/a	0.04
Cerebrovascular disease	19	3.4	47	4.9	0.08	13	4.5	11	3.8	0.03
Stroke	16	2.8	34	3.5	0.04	12	4.1	≤10	n/a	0.06
Diabetes	67	11.8	112	11.7	0.01	26	8.9	34	11.6	0.09
Hyperglycemia	27	4.8	42	4.4	0.02	11	3.8	≤10	n/a	0.02
Devo-Charlson Index (DCI)										
0-3	19	3.4	123	12.8	0.35	15	5.1	30	10.3	0.19
4-7	12	2.1	45	4.7	0.14	12	4.1	≤10	n/a	0.06
8-11	512	90.5	739	76.9	0.37	252	86.3	238	81.5	0.13
12 or more	23	4.1	54	5.6	0.07	13	4.5	15	5.1	0.03
ALI related risk factors										
Chronic liver disease or Alcoholism	74	13.1	98	10.2	0.09	34	11.6	32	11.0	0.02
Chronic or acute hepatitis	≤10	n/a	≤10	n/a	0.02	≤10	n/a	≤10	n/a	0.04
Chronic or acute disease of gallbladder or pancreas	36	6.4	86	8.9	0.10	25	8.6	29	9.9	0.05
Hepatic, Biliary or pancreatic cancer	160	28.3	190	19.8	0.20	69	23.6	71	24.3	0.02
Congestive heart failure	29	5.1	64	6.7	0.07	17	5.8	20	6.8	0.04
Medications association with liver injury										
Any medication (of list below)	467	82.5	689	71.7	0.26	220	75.3	226	77.4	0.05
Acarbose	0	0.0	0	0.0	0.00	0	0.0	0	0.0	n/a
Acetaminophen (prescription)	204	36.0	292	30.4	0.12	91	31.2	86	29.5	0.04
Allopurinol	≤10	n/a	13	1.4	0.03	≤10	n/a	≤10	n/a	0.03
Amiodarone	≤10	n/a	≤10	n/a	0.04	≤10	n/a	≤10	n/a	0.05
Amitriptyline	≤10	n/a	≤10	n/a	0.06	≤10	n/a	≤10	n/a	0.04
Amoxicillin + clavulanic acid	33	5.8	62	6.5	0.03	18	6.2	23	7.9	0.07
Anabolic steroids	0	0.0	≤10	n/a	n/a	0	0.0	0	0.0	n/a
Aripiprazole	≤10	n/a	≤10	n/a	0.07	0	0.0	0	0.0	n/a
Azathioprine	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Baclofen	≤10	n/a	≤10	n/a	0.04	≤10	n/a	≤10	n/a	0.08
Bupropion	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Captopril	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Carbamazepine	≤10	n/a	≤10	n/a	0.08	0	0.0	0	0.0	n/a
Chlorpromazine	≤10	n/a	≤10	n/a	0.02	0	0.0	0	0.0	n/a
Ciprofloxacin	46	8.1	87	9.1	0.03	25	8.6	28	9.6	0.04
Clindamycin	23	4.1	33	3.4	0.03	10	3.4	12	4.1	0.04
Clopidogrel	≤10	n/a	21	2.2	0.04	≤10	n/a	6	2.1	0.00
Cyproheptadine	≤10	n/a	≤10	n/a	0.03	≤10	n/a	≤10	n/a	0.00
Duloxetine	23	4.1	32	3.3	0.04	14	4.8	≤10	n/a	0.09
Enalapril	≤10	n/a	≤10	n/a	0.02	≤10	n/a	≤10	n/a	0.08
Erythromycins	0	0.0	≤10	n/a	n/a	0	0.0	0	0.0	n/a
Estrogens	63	11.1	99	10.3	0.03	34	11.6	31	10.6	0.03
Fluoxetine	12	2.1	14	1.5	0.05	≤10	n/a	≤10	n/a	0.00
Flutamide	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
HAART drugs	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Irbesartan	≤10	n/a	≤10	n/a	0.06	0	0.0	0	0.0	n/a
Isoniazid	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Ketoconazole	≤10	n/a	≤10	n/a	0.01	≤10	n/a	≤10	n/a	0.04
Lamotrigine	2	0.4	≤10	n/a	0.04	≤10	n/a	≤10	n/a	0.00
Lisinopril	76	13.4	87	9.1	0.14	29	9.9	33	11.3	0.04
Losartan	54	9.5	72	7.5	0.07	23	7.9	35	12.0	0.14
Methotrexate	≤10	n/a	≤10	n/a	0.06	≤10	n/a	≤10	n/a	0.00
Mirtazapine	≤10	n/a	≤10	n/a	0.02	≤10	n/a	≤10	n/a	0.06
Nitrofurantoin	≤10	n/a	31	3.2	0.09	≤10	n/a	≤10	n/a	0.02
NSAIDs	129	22.8	161	16.8	0.15	41	14.0	58	19.9	0.16
Omeprazole	76	13.4	125	13.0	0.01	34	11.6	35	12.0	0.01
Oral contraceptives	≤10	n/a	≤10	n/a	0.01	0	0.0	≤10	n/a	n/a
Paroxetine	≤10	n/a	22	2.3	0.05	≤10	n/a	≤10	n/a	0.04
Phenobarbital	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Phenothiazines	92	16.3	90	9.4	0.21	25	8.6	34	11.6	0.10
Phenytoin	0	0.0	≤10	n/a	n/a	0	0.0	0	0.0	n/a
Pyrazinamide	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Rifampicin	0	0.0	≤10	n/a	n/a	0	0.0	0	0.0	n/a
Risperidone	≤10	n/a	≤10	n/a	0.08	0	0.0	0	0.0	n/a
Sertraline	19	3.4	34	3.5	0.01	≤10	n/a	16	5.5	0.10
Statins	125	22.1	197	20.5	0.04	65	22.3	61	20.9	0.03
Sulfonamides	0	0.0	≤10	n/a	n/a	0	0.0	≤10	n/a	n/a
Terbinafine	≤10	n/a	≤10	n/a	0.02	0	0.0	0	0.0	n/a
Tetracyclines	31	5.5	44	4.6	0.04	14	4.8	16	5.5	0.03
Trazodone	15	2.7	24	2.5	0.01	11	3.8	13	4.5	0.03
Tricyclics	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Trimethoprim-sulfamethoxazole	28	4.9	58	6.0	0.05	13	4.5	19	6.5	0.09
Trovafoxacin	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Valproic acid	≤10	n/a	≤10	n/a	0.03	0	0.0	0	0.0	n/a
Verapamil	≤10	n/a	11	1.1	0.07	≤10	n/a	≤10	n/a	0.05
Abbreviations: Feb., February; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, number; STD, standard deviation; ALI, acute liver injury; HAART, highly active antiretroviral therapy; NSAIDs, nonsteroidal anti-inflammatory drugs.										
*All characteristics are measured as presence within six months prior to the index date, unless otherwise specified.										

^The following variables were included in the propensity score: age, calendar year of index date, region, Deyo-Charlson Index, number of outpatient visits, number of emergency room visits, secondary malignancy to lymph nodes of head, face, and neck, secondary malignancy to other specified sites, secondary malignancy to respiratory sites, tamoxifen, everolimus, anastrozole, denosumab or pamidronate, exemestane, chemotherapy, corticosteroids, diagnostic imaging, breast cancer surgery, letrozole, HER2 positive therapy, radiation therapy, CT imaging, mammography, MRI imaging, anticonvulsants, antidepressants, sedatives/hypnotics, secondary malignancy to breast, breast cancer diagnosis code, in situ breast cancer diagnosis, hyperglycemia, cerebrovascular disease, Chronic liver disease or Alcoholism, Chronic or acute disease of gallbladder or pancreas, Hepatic, Biliary or pancreatic cancer, Congestive heart failure, any medication associated with ALI- Acetaminophen, Allopurinol, Amiodarone, Amitriptyline, + clavulanic acid, Aripiprazole, Baclofen, Ciprofloxacin, Clindamycin, Clopidogrel, Duloxetine, Estrogens, Fluoxetine, Ketoconazole, Lisinopril, Losartan, Mirtazapine, Nitrofurantoin, NSAIDs, Omeprazole, Paroxetine, Phenothiazine, Sertraline, Statins, Tetracycline, Trazodone, and Trimethoprim

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Figure 3. Propensity score distributions for palbociclib with fulvestrant new users and fulvestrant new users (contemporaneous comparison group)



Abbreviations: FULV, Fulvestrant; PAL, palbociclib.

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Table 1.5. Incidence rates and unadjusted hazard ratios of the safety events of interest in new users of palbociclib and fulvestrant and new users of fulvestrant alone
[Secondary Objective 3a]

Event	Before Propensity Score Matching [#]												
	All new users of palbociclib and fulvestrant (n=566)					All new users of fulvestrant alone (pre-2015) (n=2,316)					Unadjusted Hazard Ratios		
	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			HR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Neutropenia (sensitive)	107	285	37.5	30.77	45.37	95	1,661	5.7	4.63	6.99	6.0	4.5	7.9
Neutropenia (specific)	71	298	23.8	18.60	30.05	68	1,664	4.1	3.17	5.18	5.4	3.9	7.6
Febrile neutropenia (sensitive)	11	321	3.4	1.71	6.12	≤10	n/a	0.6	0.28	1.09	5.2	2.2	12.2
Febrile neutropenia (specific)	≤10	n/a	0.9	0.19	2.72	≤10	n/a	0.1	0.01	0.43	6.8	1.1	40.8
Leukopenia (sensitive)	17	318	5.3	3.11	8.56	13	1,682	0.8	0.41	1.32	6.3	3.1	12.9
Leukopenia (specific)	17	318	5.3	3.11	8.56	13	1,682	0.8	0.41	1.32	6.3	3.1	12.9
Alopecia	≤10	n/a	0.3	0.01	1.72	≤10	n/a	0.2	0.04	0.52	1.6	0.2	15.8
Vomiting*	32	309	10.4	7.09	14.63	209	1,627	12.8	11.17	14.71	0.8	0.5	1.1
QT prolongation	20	315	6.3	3.88	9.80	84	1,661	5.1	4.03	6.26	1.2	0.7	1.9
Fatigue*	53	284	18.7	14.00	24.45	297	1,566	19.0	16.87	21.25	0.9	0.7	1.2
Serious infection	79	309	25.6	20.24	31.86	342	1,616	21.2	18.98	23.53	1.1	0.9	1.5
Brain/spinal infection	≤10	n/a	1.2	0.34	3.17	≤10	n/a	0.1	0.01	0.43	9.6	1.8	52.5
Pericardial/myocardial infection	0	324	0.0	.	.	≤10	n/a	0.1	0.01	0.43	n/a	.	.
Pulmonary infection	34	318	10.7	7.40	14.94	130	1,659	7.8	6.55	9.30	1.3	0.9	1.9
GI infection	≤10	n/a	0.6	0.07	2.23	≤10	n/a	0.4	0.17	0.85	1.4	0.3	6.9
Genitourinary/Renal infection	35	314	11.2	7.78	15.53	180	1,630	11.0	9.49	12.78	0.9	0.7	1.4
Dental infection	0	324	0.0	.	.	≤10	n/a	0.1	0.01	0.43	0.0	0.0	.
Ear, nose, and throat infection	14	320	4.4	2.39	7.34	55	1,664	3.3	2.49	4.30	1.3	0.7	2.3
Skin, bones, and joint infection	17	319	5.3	3.10	8.53	71	1,659	4.3	3.34	5.40	1.2	0.7	2.0
Hepatitis B infection	0	324	0.0	.	.	38	1,661	2.3	1.62	3.14	n/a	.	.
Influenza infection	≤10	n/a	1.2	0.34	3.18	≤10	n/a	0.2	0.06	0.61	4.8	1.2	19.3
Other infection	65	306	21.2	16.38	27.05	557	1,463	38.1	34.99	41.38	0.5	0.4	0.7
Diarrhea*	14	316	4.4	2.42	7.42	90	1,655	5.4	4.37	6.69	0.8	0.4	1.3
Interstitial lung disease/pneumonitis	103	303	34.0	27.75	41.23	342	1,594	21.5	19.24	23.85	1.5	1.2	1.9
Anemia (sensitive)	134	283	47.4	39.69	56.11	372	1,564	23.8	21.43	26.33	1.8	1.5	2.2
Anemia (specific)	79	303	26.1	20.67	32.54	123	1,652	7.4	6.19	8.89	3.3	2.5	4.4
Nausea*	49	297	16.5	12.19	21.79	267	1,601	16.7	14.74	18.80	0.9	0.7	1.3
Thrombocytopenia	33	318	10.4	7.15	14.60	58	1,680	3.5	2.62	4.46	2.8	1.8	4.3
Pulmonary embolism*	14	318	4.4	2.41	7.40	46	1,668	2.8	2.02	3.68	1.5	0.8	2.7
No history	15	319	4.7	2.63	7.75	39	1,673	2.3	1.66	3.19	1.9	1.0	3.4
Other venous embolism and thrombosis*	11	309	3.6	1.78	6.37	104	1,635	6.4	5.20	7.71	0.5	0.3	1.0
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	≤10	n/a	2.2	0.90	4.62	69	1,658	4.2	3.24	5.27	0.5	0.2	1.1
No history of "Other venous embolism and thrombosis"	23	315	7.3	4.63	10.96	95	1,653	5.7	4.65	7.03	1.2	0.8	1.9
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	16	316	5.1	2.89	8.21	63	1,667	3.8	2.90	4.83	1.3	0.7	2.2
Embolism and thrombosis of unspecified artery	≤10	n/a	0.3	0.01	1.72	≤10	n/a	0.1	0.00	0.33	4.7	0.3	75.4
Cataracts and other ocular disorders	19	316	6.0	3.62	9.38	104	1,633	6.4	5.20	7.72	0.9	0.6	1.5
Stomatitis and mucositis	≤10	n/a	2.8	1.28	5.31	≤10	n/a	0.5	0.20	0.94	5.3	2.1	13.8
Fever	37	318	11.6	8.20	16.05	74	1,668	4.4	3.48	5.57	2.4	1.6	3.6
Anorexia	≤10	n/a	3.1	1.49	5.70	27	1,686	1.6	1.06	2.33	1.9	0.9	3.9
Peripheral neuropathy	24	316	7.6	4.86	11.29	53	1,668	3.2	2.38	4.16	2.2	1.4	3.6
Sudden cardiac death	0	324	0.0	.	.	≤10	n/a	0.2	0.06	0.61	n/a	.	.
Diabetes mellitus	46	310	14.8	10.87	19.80	215	1,608	13.4	11.64	15.28	1.0	0.7	1.4
Type 2 Diabetes mellitus	46	310	14.8	10.86	19.78	207	1,609	12.9	11.17	14.74	1.1	0.8	1.5
Hyperglycemia	≤10	n/a	1.5	0.50	3.62	14	1,685	0.8	0.45	1.39	1.9	0.7	5.3
Liver failure (Acute liver injury)	13	323	4.0	2.14	6.89	20	1,685	1.2	0.73	1.83	3.1	1.5	6.2
Abnormal ALT (incident) [^]	≤10	n/a	7.4	3.37	13.99	34	558	6.1	4.22	8.51	1.1	0.5	2.3
Abnormal ALT (incident or prevalent) [^]	18	156	11.6	6.86	18.29	81	634	12.8	10.14	15.87	0.8	0.5	1.4
Abnormal AST (incident) [^]	≤10	n/a	7.0	3.21	13.33	46	555	8.3	6.07	11.06	0.8	0.4	1.6
Abnormal AST (incident or prevalent) [^]	21	152	13.8	8.53	21.06	101	627	16.1	13.12	19.56	0.8	0.5	1.3
Abnormal ALP (incident) [^]	≤10	n/a	5.0	2.02	10.38	27	586	4.6	3.04	6.70	0.9	0.4	2.2
Abnormal ALP (incident or prevalent) [^]	17	152	11.2	6.50	17.86	90	637	14.1	11.36	17.36	0.7	0.4	1.2
Secondary malignancies (second primary cancer)	106	290	36.5	29.88	44.14	515	1,506	34.2	31.32	37.29	1.0	0.8	1.2
Non-melanoma skin cancer	≤10	n/a	2.2	0.88	4.51	63	1,647	3.8	2.94	4.89	0.5	0.2	1.2

Abbreviations: n, number; GI, gastrointestinal; PT, person-time; IR, incidence rate; CI, confidence interval; HR, hazard ratios, LCL, lower confidence limit; UCL, upper confidence limit; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; DVT, deep vein thrombosis.

*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date.

[^]Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.

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Table 1.6. Incidence rates and adjusted hazard ratios of the safety events of interest in propensity score matched new users of palbociclib and fulvestrant and new users of fulvestrant alone
[Secondary Objective 3a]

Event	After Propensity Score Matching												
	New users of palbociclib and fulvestrant (n=561)					New users of fulvestrant alone (pre-2015) (n=561)					Adjusted Hazard Ratios		
	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			aHR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Neutropenia (sensitive)	104	283	36.7	29.99	44.47	17	368	4.6	2.69	7.40	7.8	4.7	13.0
Neutropenia (specific)	71	296	24.0	18.73	30.25	14	368	3.8	2.08	6.38	6.3	3.6	11.2
Febrile neutropenia (sensitive)	≤10	n/a	3.1	1.50	5.76	≤10	n/a	0.3	0.01	1.50	11.1	1.4	87.1
Febrile neutropenia (specific)	≤10	n/a	0.9	0.19	2.73	0	373	0.0	.	0.99	n/a	.	.
Leukopenia (sensitive)	17	316	5.4	3.13	8.61	≤10	n/a	0.8	0.17	2.37	6.4	1.9	21.9
Leukopenia (specific)	17	316	5.4	3.13	8.61	≤10	n/a	0.8	0.17	2.37	6.4	1.9	21.9
Alopecia	≤10	n/a	0.3	0.01	1.73	0	373	0.0	.	0.99	n/a	0.0	.
Vomiting*	31	307	10.1	6.87	14.34	50	347	14.4	10.69	18.98	0.7	0.4	1.1
QT prolongation	20	313	6.4	3.90	9.87	13	368	3.5	1.88	6.04	1.8	0.9	3.5
Fatigue*	52	282	18.4	13.77	24.18	82	341	24.1	19.13	29.86	0.7	0.5	1.0
Serious infection	79	307	25.7	20.37	32.07	82	358	22.9	18.24	28.47	1.1	0.8	1.5
Brain/spinal infection	≤10	n/a	1.2	0.34	3.19	0	373	0.0	.	0.99	n/a	.	.
Pericardial/myocardial infection	0	322	0.0	.	.	0	373	0.0	.	0.99	n/a	.	.
Pulmonary infection	34	316	10.8	7.45	15.04	29	369	7.9	5.27	11.30	1.4	0.8	2.3
GI infection	≤10	n/a	0.6	0.08	2.25	≤10	n/a	0.5	0.07	1.94	1.1	0.2	8.1
Genitourinary/Renal infection	35	311	11.2	7.83	15.63	33	364	9.1	6.24	12.72	1.2	0.7	1.9
Dental infection	0	322	.	.	.	≤10	n/a	0.5	0.07	1.94	n/a	.	.
Ear, nose, and throat infection	14	318	4.4	2.41	7.38	18	367	4.9	2.91	7.75	0.8	0.4	1.7
Skin, bones, and joint infection	17	317	5.4	3.12	8.59	17	366	4.6	2.71	7.44	1.1	0.6	2.2
Hepatitis B infection	0	322	0.0	.	.	≤10	n/a	1.9	0.76	3.92	n/a	.	.
Influenza infection	≤10	n/a	1.2	0.34	3.20	≤10	n/a	0.5	0.07	1.94	2.3	0.4	12.9
Other infection	65	304	21.4	16.49	27.23	136	323	42.1	35.30	49.76	0.5	0.4	0.7
Diarrhea*	14	314	4.5	2.43	7.47	25	365	6.8	4.43	10.10	0.6	0.3	1.2
Interstitial lung disease/pneumonitis	103	301	34.2	27.93	41.51	85	353	24.1	19.22	29.75	1.4	1.1	1.9
Anemia (sensitive)	134	281	47.7	39.98	56.52	91	347	26.2	21.13	32.22	1.8	1.4	2.3
Anemia (specific)	79	301	26.3	20.81	32.75	33	366	9.0	6.21	12.68	2.9	1.9	4.3
Nausea*	49	296	16.6	12.26	21.92	71	339	21.0	16.38	26.45	0.8	0.5	1.1
Thrombocytopenia	33	315	10.5	7.20	14.69	17	370	4.6	2.67	7.35	2.3	1.3	4.1
Pulmonary embolism*	14	316	4.4	2.43	7.44	15	368	4.1	2.28	6.73	1.0	0.5	2.1
No history	15	317	4.7	2.65	7.80	12	369	3.2	1.68	5.67	1.4	0.7	3.0
Other venous embolism and thrombosis*	11	307	3.6	1.79	6.41	26	360	7.2	4.72	10.58	0.5	0.2	1.0
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	≤10	n/a	2.3	0.91	4.65	15	368	4.1	2.28	6.73	0.5	0.2	1.3
No history of "Other venous embolism and thrombosis"	22	313	7.0	4.40	10.64	25	362	6.9	4.47	10.20	1.0	0.6	1.8
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	15	315	4.8	2.67	7.87	15	369	4.1	2.28	6.71	1.2	0.6	2.4
Embolism and thrombosis of unspecified artery	≤10	n/a	0.3	0.01	1.73	≤10	n/a	0.3	0.01	1.50	1.1	0.1	17.4
Cataracts and other ocular disorders	19	314	6.0	3.64	9.45	27	363	7.4	4.91	10.83	0.8	0.4	1.4
Stomatitis and mucositis	≤10	n/a	2.8	1.29	5.34	≤10	n/a	0.5	0.07	1.94	5.0	1.1	23.1
Fever	36	316	11.4	7.99	15.79	22	368	6.0	3.75	9.06	1.9	1.1	3.2
Anorexia	≤10	n/a	3.1	1.50	5.74	≤10	n/a	1.3	0.44	3.13	2.3	0.8	6.6
Peripheral neuropathy	24	314	7.6	4.89	11.36	17	368	4.6	2.69	7.40	1.6	0.9	3.0
Sudden cardiac death	0	322	0.0	.	.	0	373	0.0	.	0.99	n/a	.	.
Diabetes mellitus	46	308	14.9	10.94	19.93	66	346	19.1	14.74	24.24	0.8	0.5	1.1
Type 2 Diabetes mellitus	46	308	14.9	10.93	19.91	65	347	18.7	14.47	23.89	0.8	0.5	1.2
Hyperglycemia	≤10	n/a	1.6	0.51	3.64	≤10	n/a	0.8	0.17	2.36	2.0	0.5	8.4
Liver failure (Acute liver injury)	13	321	4.1	2.16	6.93	≤10	n/a	0.8	0.17	2.35	4.8	1.4	16.9
Abnormal ALT (incident)^	≤10	n/a	6.6	2.84	12.98	≤10	n/a	5.7	2.29	11.75	1.0	0.4	2.8
Abnormal ALT (incident or prevalent)^	17	155	11.0	6.39	17.57	16	142	11.2	6.43	18.26	0.8	0.4	1.6
Abnormal AST (incident)^	≤10	n/a	7.1	3.23	13.42	≤10	n/a	4.9	1.78	10.58	1.3	0.5	3.6
Abnormal AST (incident or prevalent)^	20	152	13.2	8.06	20.38	19	144	13.2	7.94	20.59	0.9	0.5	1.7
Abnormal ALP (incident)^	≤10	n/a	5.1	2.04	10.43	≤10	n/a	2.2	0.46	6.55	2.0	0.5	7.6
Abnormal ALP (incident or prevalent)^	16	152	10.6	6.04	17.15	16	143	11.2	6.41	18.20	0.7	0.3	1.5
Secondary malignancies (second primary cancer)	105	289	36.4	29.76	44.04	133	340	39.2	32.78	46.40	0.9	0.7	1.2
Non-melanoma skin cancer	≤10	n/a	2.2	0.89	4.54	≤10	n/a	0.8	0.17	2.37	3.2	0.8	13.2
Abbreviations: GI, gastrointestinal; n, number; PT, person-time; IR, incidence rate; CI, confidence interval; aHR, adjusted hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; DVT, deep vein thrombosis.													
*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date.													
^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.													

Table 1.7. Characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone (historical comparison group - including ALI risk factors)

[Secondary Objective 3a]

Characteristics*	Before Propensity Score Matching					After Propensity Score Matching^				
	New users of palbociclib with fulvestrant		New users of fulvestrant alone (Pre-2015)		Standardized difference	New users of palbociclib with fulvestrant		New users of fulvestrant alone (Pre-2015)		Standardized difference
	N/Mean	%/STD	N/Mean	%/STD		N/Mean	%/STD	N/Mean	%/STD	
Overall	566	100%	2,316	100%		565	1.00	565	1.00	
Demographics										
Age at index date (in years)	59.5	11.4	64.1	12.9	0.40	59.5	11.4	60.0	12.9	0.04
Age (years)										
<45	51	9.0	127	5.5	0.14	51	9.0	53	9.4	0.01
45-64	337	59.5	1121	48.4	0.32	336	59.5	307	54.3	0.10
65+	178	31.4	1068	46.1	0.40	178	31.5	205	36.3	0.10
Gender										
Male	≤10	n/a	30	1.3	0.02	≤10	n/a	≤10	n/a	0.10
Female	557	98.4	2286	98.7	0.02	556	98.4	556	98.4	0.00
Calendar year of index date										
2011	0	0.0	612	26.4	n/a	0	0.0	118	20.9	n/a
2012	0	0.0	507	21.9	n/a	0	0.0	113	20.0	n/a
2013	0	0.0	569	24.6	n/a	0	0.0	151	26.7	n/a
2014	0	0.0	628	27.1	n/a	0	0.0	183	32.4	n/a
2015	99	17.5	0	0.0	n/a	99	17.5	0	0.0	n/a
2016	269	47.5	0	0.0	n/a	269	47.6	0	0.0	n/a
2017	198	35.0	0	0.0	n/a	197	34.9	0	0.0	n/a
Geographic region of residence										
Midwest	95	16.8	422	18.2	0.04	95	16.8	103	18.2	0.04
South	159	28.1	690	29.8	0.04	159	28.1	143	25.3	0.06
Northeast	166	29.3	580	25.0	0.10	165	29.2	154	27.3	0.04
West	146	25.8	624	26.9	0.03	146	25.8	165	29.2	0.08
Duration of health plan enrollment prior to index date (days)	1263.9	758.3	694.1	422.9	0.93	1264.2	759.0	744.6	444.5	0.84
Medical History										
Other primary cancer prior to first breast cancer diagnosis code	223	39.40	1026	44.30	0.10	223	39.47	265	46.90	0.15
Secondary malignancy (metastasis)										
Lymph nodes of head, face, and neck	154	27.2	476	20.6	0.16	153	27.1	160	28.3	0.03
Respiratory and digestive systems	257	45.4	781	33.7	0.24	257	45.5	244	43.2	0.05
Other specified sites	463	81.8	1710	73.8	0.19	462	81.8	458	81.1	0.02
Devo-Charlson comorbidity index (DCI)	8.52	1.8	7.85	2.3	0.31	≤10	n/a	8.44	1.7	0.05
Secondary malignant neoplasm of breast	66	11.7	204	8.8	0.09	66	11.7	64	11.3	0.01
Breast Cancer (Female) diagnosis code	558	98.6	2262	97.7	0.07	557	98.6	556	98.4	0.01
InSitu Breast Cancer	44	7.8	151	6.5	0.05	43	7.6	45	8.0	0.01
History of Breast Cancer	370	65.4	1338	57.8	0.16	349	61.8	370	65.5	0.08
Cancer Therapy History										
Radiation therapy	112	19.8	386	16.7	0.08	112	19.8	109	19.3	0.01
Implantation (Brachytherapy)	0	0.0	2	0.1	n/a	0	0.0	0	0.0	n/a
External Beam	112	19.8	386	16.7	0.08	112	19.8	109	19.3	0.01
Surgery	11	1.9	68	2.9	0.06	11	1.9	13	2.3	0.02
Mastectomy in the last six months	≤10	n/a	32	1.4	0.09	≤10	n/a	≤10	n/a	0.06
Lumpectomy in the last six months	≤10	n/a	25	1.1	0.06	≤10	n/a	≤10	n/a	0.04
Radical Mastectomy in the last six months	≤10	n/a	22	0.9	0.01	≤10	n/a	≤10	n/a	0.02
Chemotherapy	100	17.7	429	18.5	0.02	100	17.7	105	18.6	0.02
Infusion based chemo (procedure)	≤10	n/a	31	1.3	0.11	≤10	n/a	12	2.1	0.16
Imaging										
CT related imaging in the last six months	139	24.6	501	21.6	0.07	139	24.6	132	23.4	0.03
MR related imaging for needle placement	0	0.0	3	0.1	---	0	0.0	≤10	n/a	---
Diagnostic imaging in the last six months	72	12.7	461	19.9	0.20	72	12.7	80	14.2	0.04
Mammography	≤10	n/a	107	4.6	0.19	≤10	n/a	≤10	n/a	0.03
MRI related imaging	25	4.4	91	3.9	0.02	25	4.4	24	4.2	0.01
Tomosynthesis (3D Mammography)	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Healthcare Utilization (Six months prior to index date)										
Number of outpatient visits	38.58	23.6	36.5	24.6	0.05	39	23.7	39.2	25.0	0.02
Number of outpatient visits to an oncologist	0.02	0.2	0.0	0.3	0.04	0	0.2	0.0	0.2	0.00
Number of inpatient hospitalizations	0.33	0.7	0.3	0.7	0.04	0	0.7	0.4	0.8	0.08
Number of inpatient hospitalizations for breast cancer	0.03	0.2	0.3	0.6	0.51	0	0.2	0.3	0.7	0.55
Number of inpatient hospitalizations for any cancer	0.29	0.6	0.3	0.7	0.06	0	0.6	0.4	0.7	0.10
Number of emergency department visits	0.31	0.8	0.2	0.6	0.11	0	0.8	0.3	0.6	0.09
Medication Use (breast cancer related)										
Palbociclib	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Hormone Therapy	326	57.6	1285	55.5	0.04	325	57.5	293	51.9	0.11
Letrozole	116	20.5	429	18.5	0.05	115	20.4	121	21.4	0.03
Anastrozole	136	24.0	611	26.4	0.05	136	24.1	128	22.7	0.03
Exemestane	86	15.2	358	15.5	0.01	86	15.2	74	13.1	0.06
HER2 positive Therapy	15	2.7	127	5.5	0.14	15	2.7	19	3.4	0.04
Trastuzumab	25	4.4	159	6.9	0.11	25	4.4	33	5.8	0.06
Lapatinib	≤10	n/a	16	0.7	0.05	≤10	n/a	≤10	n/a	0.03
Ado-trastuzumab	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Pertuzumab	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Tamoxifen	140	24.7	379	16.4	0.21	140	24.8	125	22.1	0.06
Fulvestrant	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Denosumab or Pamidronate	206	36.4	424	18.3	0.41	205	36.3	178	31.5	0.10
Everolimus	40	7.1	84	3.6	0.15	40	7.1	33	5.8	0.05
Medication Use (not breast cancer related)										
Anticonvulsants	126	22.3	347	15.0	0.19	125	22.1	115	20.4	0.04
Antidepressants	178	31.4	631	27.2	0.09	177	31.3	176	31.2	0.00
Antidiabetics	67	11.8	252	10.9	0.03	67	11.9	75	13.3	0.04
Antifungals	28	4.9	119	5.1	0.01	28	5.0	35	6.2	0.05

Antihypertensives	173	30.6	623	26.9	0.08	173	30.6	179	31.7	0.02
Antimycobacterials	109	19.3	446	19.3	0.00	109	19.3	120	21.2	0.05
Antivirals	32	5.7	112	4.8	0.04	32	5.7	33	5.8	0.01
Corticosteroids	148	26.1	416	18.0	0.20	147	26.0	142	25.1	0.02
Oral contraceptive use (progestin)	0	0.0	≤10	n/a	n/a	0	0.0	0	0.0	n/a
Oral contraceptive use (combination)	≤10	n/a	≤10	n/a	0.02	≤10	n/a	≤10	n/a	0.00
Oral contraceptive use (unspecified)	≤10	n/a	23	1.0	0.02	≤10	n/a	≤10	n/a	0.02
Lipid lowering agent	132	23.3	556	24.0	0.02	131	23.2	137	24.2	0.02
Vaginal estrogen (local hormone treatment)	0	0.0	≤10	n/a	n/a	0	0.0	≤10	n/a	n/a
Macrolides	≤10	n/a	22	0.9	0.06	≤10	n/a	≤10	n/a	0.08
Sedatives/hypnotics	57	10.1	291	12.6	0.08	57	10.2	63	11.2	0.03
Selective estrogen receptor modulators	≤10	n/a	≤10	n/a	0.03	≤10	n/a	≤10	n/a	0.08
Unopposed estrogen hormone replacement therapy (HRT)	0	0.0	≤10	n/a	n/a	0	0.0	≤10	n/a	n/a
Co-morbidities (six months prior to index date)										
Pathologic fracture	46	8.1	173	7.5	0.02	46	8.1	43	7.6	0.02
Osteoporosis	56	9.9	225	9.7	0.01	56	9.9	41	7.3	0.09
Uterine malignancies	≤10	n/a	11	0.5	0.02	≤10	n/a	≤10	n/a	0.03
Pure hypercholesterolemia	48	8.5	237	10.2	0.06	48	8.5	65	11.5	0.10
Major adverse cardiac events (MACE)	20	3.5	83	3.6	0.00	20	3.5	21	3.7	0.01
Acute myocardial infarction (MI)	≤10	n/a	23	1.0	0.03	≤10	n/a	≤10	n/a	0.10
Cerebrovascular disease	19	3.4	104	4.5	0.05	19	3.4	21	3.7	0.02
Stroke	16	2.8	63	2.7	0.01	16	2.8	16	2.8	0.00
Diabetes	67	11.8	252	10.9	0.03	67	11.9	75	13.3	0.04
Hyperglycemia	27	4.8	55	2.4	0.13	26	4.6	19	3.4	0.06
Devo-Charlson Index (DCI)										
0-3	19	3.4	259	11.2	0.30	19	3.4	23	4.1	0.04
4-7	12	2.1	57	2.5	0.02	12	2.1	≤10	n/a	0.12
8-11	512	90.5	1937	83.6	0.20	511	90.4	517	91.5	0.04
12 or more	23	4.1	63	2.7	0.07	23	4.1	20	3.5	0.03
ALI related risk factors										
Chronic liver disease or Alcoholism	74	13.1	246	10.6	0.09	74	13.1	69	12.2	0.03
Chronic or acute hepatitis	≤10	n/a	≤10	n/a	0.04	≤10	n/a	≤10	n/a	0.00
Chronic or acute disease of gallbladder or pancreas	36	6.4	145	6.3	0.01	36	6.4	34	6.0	0.01
Hepatic, Biliary or pancreatic cancer	160	28.3	458	19.8	0.18	160	28.3	143	25.3	0.07
Congestive heart failure	29	5.1	159	6.9	0.07	29	5.1	29	5.1	0.00
Medications association with liver injury										
Any medication (of list below)	467	82.51	1749	75.52	0.17	466	82.48	466	82.48	0.00
Acarbose	0	0.00	0	0.00	n/a	0	0.00	0	0.00	n/a
Acetaminophen (prescription)	204	36.04	899	38.82	0.06	204	36.11	202	35.75	0.01
Allopurinol	≤10	n/a	19	0.82	0.02	≤10	n/a	≤10	n/a	0.02
Amiodarone	≤10	n/a	14	0.60	0.01	≤10	n/a	≤10	n/a	0.02
Amitriptyline	≤10	n/a	35	1.51	0.01	≤10	n/a	≤10	n/a	0.03
Amoxicillin + clavulanic acid	33	5.83	116	5.01	0.04	33	5.84	28	4.96	0.04
Anabolic steroids	0	0.00	0	0.00	n/a	0	0.00	0	0.00	n/a
Aripiprazole	≤10	n/a	≤10	n/a	0.07	≤10	n/a	≤10	n/a	0.04
Azathioprine	≤10	n/a	≤10	n/a	0.01	≤10	n/a	≤10	n/a	0.03
Baclofen	≤10	n/a	16	0.69	0.04	≤10	n/a	≤10	n/a	0.03
Bupropion	0	0.00	0	0.00	n/a	0	0.00	0	0.00	n/a
Captopril	0	0.00	≤10	n/a	n/a	0	0.00	0	0.00	n/a
Carbamazepine	≤10	n/a	≤10	n/a	0.04	≤10	n/a	≤10	n/a	0.00
Chlorpromazine	≤10	n/a	≤10	n/a	0.04	0	0.00	0	0.00	n/a
Ciprofloxacin	46	8.13	238	10.28	0.07	46	8.14	39	6.90	0.05
Clindamycin	23	4.06	74	3.20	0.06	23	4.07	25	4.42	0.02
Clopidogrel	≤10	n/a	57	2.46	0.06	≤10	n/a	≤10	n/a	0.01
Cyproheptadine	≤10	n/a	≤10	n/a	0.05	0	0.00	0	0.00	n/a
Duloxetine	23	4.06	66	2.85	0.06	23	4.07	24	4.25	0.01
Enalapril	≤10	n/a	33	1.42	0.07	≤10	n/a	≤10	n/a	0.07
Erythromycins	0	0.00	≤10	n/a	n/a	0	0.00	0	0.00	n/a
Estrogens	63	11.13	265	11.44	0.01	63	11.15	63	11.15	0.00
Fluoxetine	12	2.12	47	2.03	0.01	12	2.12	11	1.95	0.01
Flutamide	0	0.00	0	0.00	n/a	0	0.00	0	0.00	n/a
HAART drugs	0	0.00	≤10	n/a	n/a	0	0.00	0	0.00	n/a
Irbesartan	≤10	n/a	≤10	n/a	0.03	≤10	n/a	≤10	n/a	0.03
Isoniazid	0	0.00	0	0.00	n/a	0	0.00	0	0.00	n/a
Ketoconazole	≤10	n/a	≤10	n/a	0.07	≤10	n/a	≤10	n/a	0.02
Lamotrigine	≤10	n/a	17	0.73	0.05	≤10	n/a	≤10	n/a	0.11
Lisinopril	76	13.43	237	10.23	0.10	76	13.45	80	14.16	0.02
Losartan	54	9.54	121	5.22	0.17	54	9.56	48	8.50	0.04
Methotrexate	≤10	n/a	14	0.60	0.07	≤10	n/a	≤10	n/a	0.06
Mirtazapine	≤10	n/a	34	1.47	0.04	≤10	n/a	≤10	n/a	0.03
Nitrofurantoin	10	1.77	71	3.07	0.08	≤10	n/a	13	2.30	0.04
NSAIDs	129	22.79	398	17.18	0.13	128	22.65	124	21.95	0.02
Omeprazole	76	13.43	305	13.17	0.01	76	13.45	81	14.34	0.03
Oral contraceptives	≤10	n/a	≤10	n/a	0.02	0	0.00	0	0.00	n/a
Paroxetine	≤10	n/a	30	1.30	0.02	≤10	n/a	≤10	n/a	0.03
Phenobarbital	0	0.00	≤10	n/a	n/a	0	0.00	0	0.00	n/a
Phenothiazines	92	16.25	276	11.92	0.12	92	16.28	84	14.87	0.04
Phenytoin	0	0.00	≤10	n/a	n/a	0	0.00	≤10	n/a	n/a
Pyrazinamide	0	0.00	0	0.00	n/a	0	0.00	0	0.00	n/a
Rifampicin	0	0.00	≤10	n/a	n/a	0	0.00	≤10	n/a	n/a
Risperidone	≤10	n/a	≤10	n/a	0.02	≤10	n/a	≤10	n/a	0.03
Sertraline	19	3.36	72	3.11	0.01	19	3.36	23	4.07	0.04
Statins	125	22.08	502	21.68	0.01	124	21.95	121	21.42	0.01
Sulfonamides	0	0.00	≤10	n/a	n/a	0	0.00	≤10	n/a	n/a
Terbinafine	≤10	n/a	≤10	n/a	0.01	≤10	n/a	≤10	n/a	0.06
Tetracyclines	31	5.48	69	2.98	0.12	31	5.49	33	5.84	0.02
Trazodone	15	2.65	60	2.59	0.01	15	2.65	20	3.54	0.05
Tricyclics	0	0.00	≤10	n/a	n/a	0	0.00	0	0.00	n/a
Trimethoprim-sulfamethoxazole	28	4.95	123	5.31	0.00	28	4.96	30	5.31	0.02
Trovaflaxacin	0	0.00	0	0.00	n/a	0	0.00	0	0.00	n/a
Valproic acid	≤10	n/a	≤10	n/a	0.04	≤10	n/a	≤10	n/a	0.08

Verapamil	≤10	n/a	22	0.95	0.05	≤10	n/a	≤10	n/a	0.00
Abbreviations: Feb., February; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, number; STD, standard deviation; ALI, acute liver injury; HAART, highly active antiretroviral therapy; NSAIDs, nonsteroidal anti-inflammatory drugs.										
*All characteristics are measured as presence within six months prior to the index date, unless otherwise specified.										
^The following variables were included in the propensity score: age, region, Deyo-Charlson Index, number of outpatient visits, number of emergency room visits, secondary malignancy to lymph nodes of head, face, and neck, secondary malignancy to other specified sites, secondary malignancy to respiratory sites, tamoxifen, everolimus, anastrozole, denosumab or pamidronate, exemestane, chemotherapy, corticosteroids, diagnostic imaging, breast cancer surgery, letrozole, HER2 positive therapy, radiation therapy, CT imaging, mammography, MRI imaging, anticonvulsants, antidepressants, sedatives/hypnotics, secondary malignancy to breast, breast cancer diagnosis code, in situ breast cancer diagnosis, hyperglycemia, cerebrovascular disease, Chronic liver disease or Alcoholism, Chronic or acute disease of gallbladder or pancreas, Hepatic, Biliary or pancreatic cancer, Congestive heart failure, any medication associated with ALI- Acetaminophen, Allopurinol, Amiodarone, Amitriptyline, + clavulanic acid, Aripiprazole, Baclofen, Ciprofloxacin, Clindamycin, Clopidogrel, Duloxetine, Estrogens, Fluoxetine, Ketoconazole, Lisinopril, Losartan, Mirtazapine, Nitrofurantoin, NSAIDs, Omeprazole, Paroxetine, Phenothiazine, Sertraline, Statins, Tetracycline, Trazodone, and Trimethoprim.										

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Table 1-8A. Incidence rates and unadjusted hazard ratios of the acute liver injury in new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparison group)

			Before Propensity Score Matching										
			All new users of palbociclib and fulvestrant (N=566)			All new users of fulvestrant alone (pre-2015) (N=2,316)					Unadjusted Hazard Ratios		
Event	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			HR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Overall													
Acute liver injury (primary algorithm)	13	323	4.0	2.1	6.9	22	1,686	1.3	0.8	2.0	2.8	1.4	5.6
Acute liver injury (original with labs algorithm)	13	323	4.0	2.1	6.9	20	1,685	1.2	0.7	1.8	3.1	1.5	6.2
Acute liver injury (sensitive algorithm)	39	317	12.3	8.7	16.8	35	1,682	2.1	1.5	2.9	5.4	3.4	8.5
Acute liver injury (specific algorithm)	0	324	0	.	1.1	0	1,689	0	.	0.2	--	--	--
Among patients with a risk factor for ALI*													
Acute liver injury (primary algorithm)	11	188	5.8	2.9	10.5	19	912	2.1	1.3	3.3	2.6	1.2	5.5
Among patients without a risk factor for ALI*													
Acute liver injury (primary algorithm)	≤10	n/a	1.5	0.2	5.4	≤10	n/a	0.4	0.1	1.1	3.5	0.6	20.9
Stratified by amount of follow-up-time (primary algorithm)													
Acute liver injury - ≤5.9 months of follow-up	≤10	n/a	4.8	2.3	8.8	17	n/a	2.0	1.2	3.2	2.4	1.1	5.3
Acute liver injury - 6 to 11.9 months of follow-up	≤10	n/a	3.9	0.8	11.2	≤10	n/a	0.8	0.2	2.3	4.7	0.9	23.2
Acute liver injury - ≥12 months of follow-up	0	35	0	0.0	.	≤10	n/a	0.4	0.1	1.6	--	--	---
Restricting to confirmed cases													
Acute liver injury (primary algorithm)	≤10	n/a	0.9	0.2	2.7	≤10	n/a	0.4	0.2	0.7	2.6	0.4	12.2
Acute liver injury (original with labs algorithm)	≤10	n/a	0.9	0.2	2.7	≤10	n/a	0.3	0.1	0.7	3.1	0.5	16.1
Acute liver injury (sensitive algorithm)	≤10	n/a	1.6	0.5	3.6	≤10	n/a	0.4	0.2	0.8	3.0	0.6	11.7
Acute liver injury (specific algorithm)	0	324	0.0	.	1.1	0	1,689	0.0	.	0.2	--	--	--
Confirmed cases and PPV adjusted results^													
Acute liver injury (primary algorithm)^	≤10	n/a	3.0	1.5	5.4	16.5	1,686	1.0	0.6	1.5	2.8	1.4	5.6
Acute liver injury (original with labs algorithm)^	12.0	323	3.7	2.0	6.3	11.4	1,685	0.7	0.4	1.2	1.8	0.9	3.6
Acute liver injury (sensitive algorithm)^	27.7	322	8.6	5.8	12.3	22.4	1,682	1.3	0.9	2.0	4.9	3.1	7.7
Acute liver injury (specific algorithm)^	0	324	0	.	1.1	0	1,689	0	.	0.2	--	--	--

*Risk factors for ALI defined as chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart failure, or prescription acetaminophen use.

^Assuming 100% sensitivity for each algorithm

Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; HR, hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALI, acute liver injury

Table 1-8B. Incidence rates and adjusted hazard ratios of the safety events of interest in propensity score matched new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparison group)

Event	After Propensity Score Matching										Adjusted Hazard Ratios ^Δ		
	New users of palbociclib and fulvestrant (N=565)					New users of fulvestrant alone (pre-2015) (N=565)							
	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			aHR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Overall													
Acute liver injury (primary algorithm)	13	322	4.0	2.2	6.9	≤10	n/a	1.2	0.4	2.9	3.0	1.1	8.4
Acute liver injury (original with labs algorithm)	13	322	4.0	2.2	6.9	≤10	n/a	1.7	0.7	3.6	2.2	0.9	5.4
Acute liver injury (sensitive algorithm)	39	317	12.3	8.8	16.8	≤10	n/a	2.5	1.2	4.6	4.6	2.3	9.1
Acute liver injury (specific algorithm)	0	323	0	.	1.1	0	402	0	.	0.9	--	--	--
Among patients with a risk factor for ALI*													
Acute liver injury (primary algorithm)	11	188	5.8	2.9	10.5	≤10	n/a	2.5	0.8	5.8	2.3	0.8	6.5
Among patients without a risk factor for ALI*													
Acute liver injury (primary algorithm)	≤10	n/a	1.5	0.2	5.4	0	n/a	0	.	1.9	--	--	--
Stratified by amount of follow-up-time (primary algorithm)													
Acute liver injury - ≤5.9 months of follow-up	≤10	n/a	4.8	2.3	8.8	≤10	n/a	2.4	0.8	5.5	2.0	0.7	5.8
Acute liver injury - 6 to 11.9 months of follow-up	≤10	n/a	3.8	0.8	11.2	0	90	0.0	0.0	4.1	--	--	--
Acute liver injury - ≥12 months of follow-up	0	35	0.0	0.0	.	0	100	0.0	0.0	3.7	---	---	---
Restricting to confirmed cases													
Acute liver injury (primary algorithm)	≤10	n/a	0.9	0.2	2.7	≤10	n/a	0.2	0.0	1.2	3.7	0.3	196.1
Acute liver injury (original with labs algorithm)	≤10	n/a	0.9	0.2	2.7	≤10	n/a	0.2	0.0	1.2	3.7	0.3	196.1
Acute liver injury (sensitive algorithm)	≤10	n/a	1.6	0.5	3.6	≤10	n/a	0.3	0.0	1.2	6.2	0.7	294.0
Acute liver injury (specific algorithm)	0	323	0	0	0	0	402	0.0	0.0	0.9	0	0	0
Confirmed cases and PPV adjusted results													
Acute liver injury (primary algorithm) ^Δ	≤10	n/a	3.0	1.5	5.4	≤10	n/a	1.2	0.5	2.7	4.0	1.4	11.2
Acute liver injury (original with labs algorithm) ^Δ	12.0	322	3.7	2.0	6.3	≤10	n/a	0.6	0.1	1.7	0.7	0.3	1.8
Acute liver injury (sensitive algorithm) ^Δ	27.7	321	8.6	5.9	12.3	≤10	n/a	0.8	0.3	2.1	2.1	1.1	4.3
Acute liver injury (specific algorithm) ^Δ	0	323	0	.	1.1	0	402	0	0	0.6	--	--	--

*Risk factors for ALI defined as chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart failure, or prescription acetaminophen use.

^ΔAssuming 100% sensitivity for each algorithm

^ΔThe following variables were included in the propensity score: age, region, Deyo-Charlson Index, number of outpatient visits, number of emergency room visits, secondary malignancy to lymph nodes of head, face, and neck, secondary malignancy to other specified sites, secondary malignancy to respiratory sites, tamoxifen, everolimus, anastrozole, denosumab or pamidronate, exemestane, chemotherapy, corticosteroids, diagnostic imaging, breast cancer surgery, letrozole, HER2 positive therapy, radiation therapy, CT imaging, mammography, MRI imaging, anticonvulsants, antidepressants, sedatives/hypnotics, secondary malignancy to breast, breast cancer diagnosis code, in situ breast cancer diagnosis, hyperglycemia, cerebrovascular disease, Chronic liver disease or Alcoholism, Chronic or acute disease of gallbladder or pancreas, Hepatic, Biliary or pancreatic cancer, Congestive heart failure, any medication associated with ALI- Acetaminophen, Allopurinol, Amiodarone, Amitriptyline, + clavulanic acid, Aripiprazole, Baclofen, Ciprofloxacin, Clindamycin, Clopidogrel, Duloxetine, Estrogens, Fluoxetine, Ketoconazole, Lisinopril, Losartan, Mirtazapine, Nitrofurantoin, NSAIDs, Omeprazole, Paroxetine, Phenothiazine, Sertraline, Statins, Tetracycline, Trazodone, and Trimethoprim.

Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; aHR, adjusted hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALI, acute liver injury; PPV, positive predictive value

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Table 1-8C Incidence rates and unadjusted hazard ratios of the acute liver injury in new users of palbociclib and fulvestrant and new users of fulvestrant alone (contemporaneous comparison)

	Before Propensity Score Matching												
	All new users of palbociclib and fulvestrant (N=566)					All new users of fulvestrant alone (2015 or later) (N=961)					Unadjusted Hazard Ratios		
Event	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			HR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Overall													
Acute liver injury (primary algorithm)	13	323	4.0	2.1	6.9	11	553	2.0	1.0	3.6	2.1	0.9	4.7
Acute liver injury (original with labs algorithm)	13	323	4.0	2.1	6.9	16	550	2.9	1.7	4.7	1.5	0.7	3.0
Acute liver injury (sensitive algorithm)	39	317	12.3	8.7	16.8	29	549	5.3	3.5	7.6	2.3	1.4	3.8
Acute liver injury (specific algorithm)	0	324	0	.	1.1	0	553	0	.	0.7	--	--	--
Among patients with a risk factor for ALI*													
Acute liver injury (primary)	11	188	5.8	2.9	10.5	≤10	n/a	3.2	1.5	6.1	1.9	0.8	4.6
n													
Acute liver injury (primary)	≤10	n/a	1.5	0.2	5.4	≤10	n/a	0.7	0.1	2.7	2.2	0.3	15.4
Stratified by amount of follow-up-time (primary algorithm)													
Acute liver injury - ≤5.9 months of follow-up	≤10	n/a	4.8	2.3	8.8	≤10	n/a	3.1	1.5	5.6	1.6	0.7	3.9
Acute liver injury - 6 to 11.9 months of follow-up	≤10	n/a	3.9	0.8	11.2	≤10	n/a	0.8	0.0	4.3	4.9	0.5	47.0
Acute liver injury - ≥12 months of follow-up	0	35	0.0	0.0	.	0	96	0.0	0.0	.	---	---	---
Restricting to confirmed cases													
Acute liver injury (primary algorithm)	≤10	n/a	0.9	0.2	2.7	≤10	n/a	0.7	0.2	1.9	1.3	0.3	5.7
Acute liver injury (original with labs algorithm)	≤10	n/a	0.9	0.2	2.7	≤10	n/a	0.9	0.3	2.1	1.0	0.2	4.3
Acute liver injury (sensitive algorithm)	≤10	n/a	1.6	0.5	3.6	≤10	n/a	0.9	0.3	2.1	1.7	0.5	5.9
Acute liver injury (specific algorithm)	0	324	0	0	0	0	554	0	.	0.7	--	--	--
Confirmed cases and PPV adjusted results													
Acute liver injury (primary algorithm)^	≤10	n/a	3.0	1.5	5.4	11	554	2.0	1.1	3.4	2.8	1.3	6.3
Acute liver injury (original with labs algorithm)^	12.0	323	3.7	2.0	6.3	16	553	2.9	1.7	5	1.5	0.7	3.0
Acute liver injury (sensitive algorithm)^	27.7	322	8.6	5.8	12.3	29	553	5.2	3.6	7.4	3.3	2.0	5.3
Acute liver injury (specific algorithm)^	0	324	0	.	1.1	0	553	0	.	0.7	--	--	--
*Risk factors for ALI defined as chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart failure, or prescription acetaminophen use													
^Assuming 100% sensitivity													
Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; HR, hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALI, acute liver injury.													

Table 1-8D Incidence rates and adjusted hazard ratios of the safety events of interest in propensity score matched new users of palbociclib and fulvestrant and new users of fulvestrant alone (contemporaneous comparison)

		After Propensity Score Matching												
		New users of palbociclib and fulvestrant (N=292)					New users of fulvestrant alone (2015 or later) (N=292)					Adjusted Hazard Ratios [*]		
Event	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			aHR	95% LCL	95%UCL	
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI				
Overall														
Acute liver injury (primary algorithm)	≤10	n/a	1.6	0.3	4.7	≤10	n/a	3.6	1.2	8.4	0.5	0.1	2.2	
Acute liver injury (original with labs algorithm)	≤10	n/a	2.7	0.9	6.3	≤10	n/a	4.3	1.6	9.5	0.7	0.2	2.4	
Acute liver injury (sensitive algorithm)	18	183	9.8	5.8	15.5	12	n/a	8.7	4.5	15.2	1.2	0.6	2.5	
Acute liver injury (specific algorithm)	0	186	0.0	.	2.0	0	139	0	.	2.7	--	--	--	
Among patients with a risk factor for ALI*														
Acute liver injury (primary algorithm)	≤10	n/a	2.1	0.3	7.5	≤10	n/a	5.3	1.5	13.6	0.5	0.1	2.5	
Among patients without a risk factor for ALI*														
Acute liver injury (primary algorithm)	≤10	n/a	1.1	0	6.2	≤10	n/a	1.6	0	8.8	0.8	0	13.4	
Stratified by amount of follow-up-time (primary algorithm)														
Acute liver injury - ≤5.9 months of follow-up	≤10	n/a	1.8	0.2	6.4	≤10	n/a	4.5	1.2	11.4	0.4	0.1	2.3	
Acute liver injury - 6 to 11.9 months of follow-up	≤10	n/a	2.1	0.1	11.6	≤10	n/a	3.5	0.1	19.4	0.7	0.0	10.8	
Acute liver injury - ≥12 months of follow-up	0	26	0.0	0.0	0.0	0	20	0.0	0.0	0.0	0.0	0.0	0.0	
Restricting to confirmed cases														
Acute liver injury (primary algorithm)	≤10	n/a	0.5	0.0	3.0	≤10	n/a	0.7	0	4.0	0.8	0.1	58.7	
Acute liver injury (original with labs algorithm)	≤10	n/a	0.5	0.0	3.0	≤10	n/a	1.4	0.2	5.2	0.4	0	7.1	
Acute liver injury (sensitive algorithm)	≤10	n/a	1.1	0.1	3.9	≤10	n/a	1.4	0.2	5.2	0.7	0.1	10.2	
Acute liver injury (specific algorithm)	0	186	0	.	2.0	0	139	0	.	2.7	--	--	--	
Confirmed cases and PPV adjusted results														
Acute liver injury (primary algorithm) ^Δ	≤10	n/a	3.0	1.5	5.4	≤10	n/a	3.6	1.2	8.4	0.5	0.1	2.2	
Acute liver injury (original with labs algorithm) ^Δ	≤10	n/a	3.7	2.0	6.3	≤10	n/a	4.3	1.6	9.5	0.7	0.2	2.4	
Acute liver injury (sensitive algorithm) ^Δ	18	322	8.6	5.8	12.3	12	138	8.7	4.5	15.2	1.2	0.6	2.5	
Acute liver injury (specific algorithm) ^Δ	0	324	0	.	1.1	0	139	0	.	2.7	--	--	--	
*Risk factors for ALI defined as chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart failure, or prescription acetaminophen use														
^Δ Assuming 100% sensitivity														
[*] The following variables were included in the propensity score: age, calendar year of index date, region, Deyo-Charlson Index, number of outpatient visits, number of emergency room visits, secondary malignancy to lymph nodes of head, face, and neck, secondary malignancy to other specified sites, secondary malignancy to respiratory sites, tamoxifen, everolimus, anastrozole, denosumab or pamidronate, exemestane, chemotherapy, corticosteroids, diagnostic imaging, breast cancer surgery, letrozole, HER2 positive therapy, radiation therapy, CT imaging, mammography, MRI imaging, anticonvulsants, antidepressants, sedatives/hypnotics, secondary malignancy to breast, breast cancer diagnosis code, in situ breast cancer diagnosis, hyperglycemia, cerebrovascular disease, Chronic liver disease or Alcoholism, Chronic or acute disease of gallbladder or pancreas, Hepatic, Biliary or pancreatic cancer, Congestive heart failure, any medication associated with ALI- Acetaminophen, Allopurinol, Amiodarone, Amitriptyline, + clavulanic acid, Aripiprazole, Baclofen, Ciprofloxacin, Clindamycin, Clopidogrel, Duloxetine, Estrogens, Fluoxetine, Ketoconazole, Lisinopril, Losartan, Mirtazapine, Nitrofurantoin, NSAIDs, Omeprazole, Paroxetine, Phenothiazine, Sertraline, Statins, Tetracycline, Trazodone, and Trimethoprim														
Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; aHR, adjusted hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALI, acute liver injury; PPV, positive predictive value.														

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Table 1-9 Positive Predictive Values of All Diagnosis Codes and Combinations of Codes for Adjudicated Cases of ALI

Code or Combination of Codes	Number of provisional cases identified by algorithm	Number of provisional case with collected medical record	Number of Confirmed Cases and Non-cases	Number of Confirmed Cases	PPV (95% CI)	95% CI	
Acute Liver Injury - All adjudication results							
Algorithm 1 (primary algorithm)	----	29	25	21	0.84	0.64	0.95
Algorithm 2 (original with labs algorithm)	----	29	25	18	0.72	0.51	0.88
Algorithm 3 (sensitive algorithm)	----	52	40	29	0.73	0.56	0.85
Algorithm 4 (specific algorithm)	----	≤10	0	0	0.00	0.00	---
Algorithm 1 (primary algorithm)	70	20	17	14	0.84	0.64	0.95
Subsets of codes (Individual codes with counts >10)							
Most common code - K76.89 (Other specified diseases of liver)	59	---	≤10	≤10	1.00	0.29	1.00
Second most common code - K72.90 (Hepatic failure, unspecified without coma)	59	---	19	19	1.00	0.82	1.00
Algorithm 1 (Palbociclib index use)	37	≤10	≤10	≤10	0.80	0.28	0.99
Algorithm 1 (Palbociclib with fulvestrant)	13	≤10	≤10	≤10	0.75	0.19	0.99
Algorithm 1 (Palbociclib with letrozole)	14	≤10	≤10	≤10	1.00	0.03	1.00
Algorithm 1 (Other palbociclib)	≤10	0	0	0	---	0.00	0.00
Algorithm 1 (Fulvestrant index use)	33	13	12	≤10	0.83	0.52	0.98
Algorithm 1 (Fulvestrant - historical)	22	≤10	≤10	≤10	0.75	0.35	0.97
Algorithm 1 (Fulvestrant - contemporaneous)	11	≤10	≤10	≤10	1.00	0.40	1.00
Algorithm 1 - assuming all provisional cases after palbociclib are negative	37	≤10	≤10	≤10	0.57	0.18	0.90
Algorithm 1 - assuming all provisional cases after palbociclib are positive	37	≤10	≤10	≤10	0.86	0.42	1.00
Algorithm 2 (original with labs algorithm)	83	20	17	12	0.71	0.44	0.90
Algorithm 2 (Palbociclib index use)	47	≤10	≤10	≤10	0.60	0.15	0.95
Algorithm 2 (Palbociclib with fulvestrant)	13	≤10	≤10	≤10	1.00	0.29	1.00
Algorithm 2 (Palbociclib with letrozole)	22	≤10	≤10	0	0.00	0.00	0.98
Algorithm 2 (Other palbociclib)	12	≤10	≤10	0	0.00	0.00	0.98
Algorithm 2 (Fulvestrant index use)	36	12	12	≤10	0.75	0.43	0.95
Algorithm 2 (Fulvestrant - historical)	20	≤10	≤10	≤10	0.57	0.18	0.90
Algorithm 2 (Fulvestrant - contemporaneous)	16	≤10	≤10	≤10	1.00	0.48	1.00
Algorithm 2 - assuming all provisional cases after palbociclib are negative	47	≤10	≤10	≤10	0.38	0.09	0.76
Algorithm 2 - assuming all provisional cases after palbociclib are positive	47	≤10	≤10	≤10	0.75	0.35	0.97
Algorithm 3 (sensitive algorithm)	185	39	28	20	0.71	0.51	0.87
Algorithm 3 (Palbociclib index use)	121	21	12	≤10	0.67	0.35	0.90
Algorithm 3 (Palbociclib with fulvestrant)	39	14	≤10	≤10	0.71	0.29	0.96
Algorithm 3 (Palbociclib with letrozole)	54	≤10	≤10	≤10	0.67	0.09	0.99
Algorithm 3 (Other palbociclib)	28	≤10	≤10	≤10	0.50	0.01	0.99
Algorithm 3 (Fulvestrant index use)	64	18	16	12	0.75	0.48	0.93
Algorithm 3 (Fulvestrant - historical)	35	12	11	≤10	0.64	0.31	0.89
Algorithm 3 (Fulvestrant - contemporaneous)	29	≤10	≤10	≤10	1.00	0.48	1.00
Algorithm 3 - assuming all provisional cases after palbociclib are negative	121	≤10	21	≤10	0.38	0.18	0.62
Algorithm 3 - assuming all provisional cases after palbociclib are positive	121	21	21	17	0.81	0.58	0.95
Algorithm 4 (specific algorithm)	0	0	0	0	----	----	----
Algorithm 4 (Palbociclib index use)	0	0	0	0	----	----	----
Algorithm 4 (Palbociclib with fulvestrant)	0	0	0	0	----	----	----
Algorithm 4 (Palbociclib with letrozole)	0	0	0	0	----	----	----
Algorithm 4 (Other palbociclib)	0	0	0	0	----	----	----
Algorithm 4 (Fulvestrant index use)	0	0	0	0	----	----	----
Algorithm 4 (Fulvestrant - historical)	0	0	0	0	----	----	----
Algorithm 4 (Fulvestrant - contemporaneous)	0	0	0	0	----	----	----
Algorithm 4 - assuming all provisional cases after palbociclib are negative	0	0	0	0	----	----	----
Algorithm 4 - assuming all provisional cases after palbociclib are positive	0	0	0	0	----	----	----
Abbreviations: ALI, acute liver injury; PPV, positive predictive value; CI, confidence interval.							

Abbreviations: ALI, acute liver injury; PPV, positive predictive value; CI, confidence interval.

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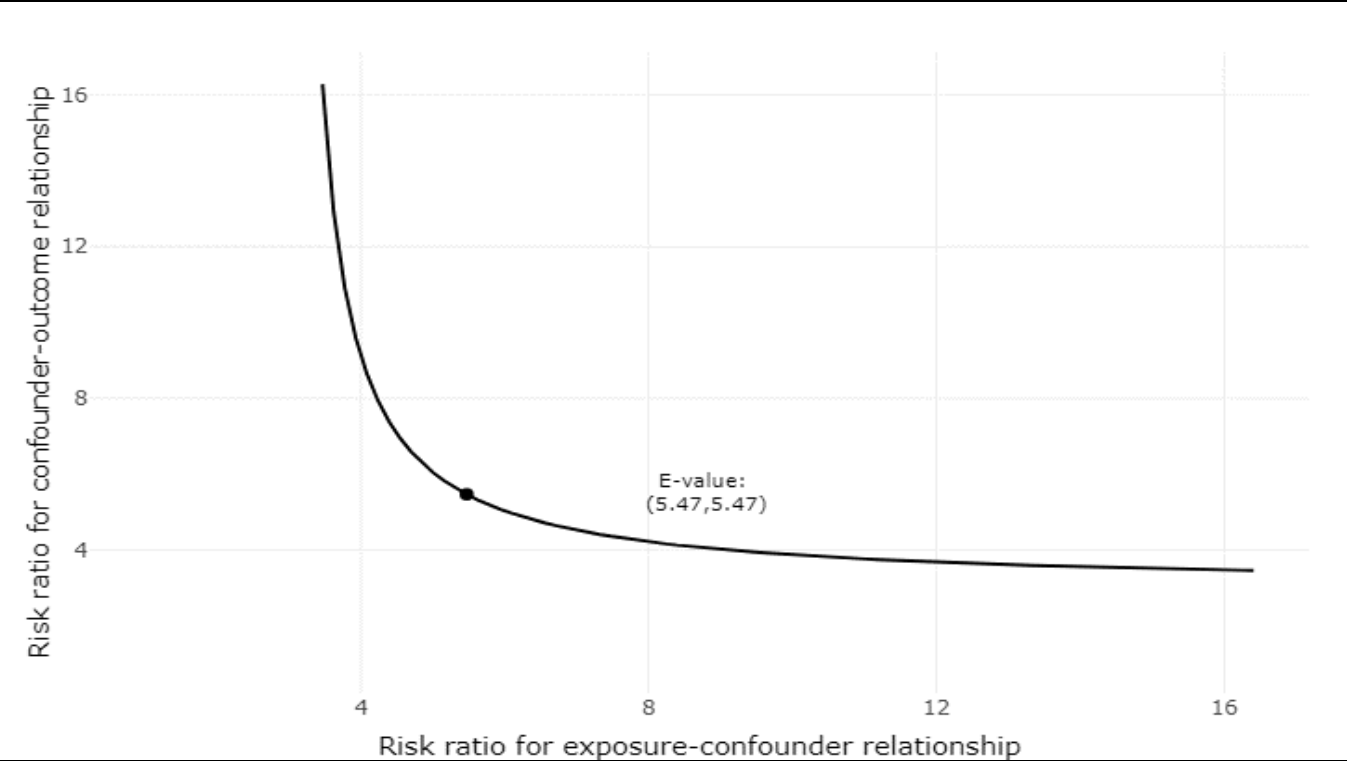
Table 1-10 Incidence of ALI between April 2014 and March 2017

Event	April 2014 to December 2014			January 2015 to September 2015			October 2015 to June 2016			July 2016 to March 2017		
	IR (per 100 person-years)			IR (per 100 person-years)			IR (per 100 person-years)			IR (per 100 person-years)		
	IR	95% Lower CI	95% Upper CI	IR	95% Lower CI	95% Upper CI	IR	95% Lower CI	95% Upper CI	IR	95% Lower CI	95% Upper CI
Overall - All HIRD												
Acute liver injury (primary)	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Palbociclib users												
Acute liver injury (primary)	.	.	.	0	0	31.1	28.4	3.4	102.5	37.9	12.3	88.5
Fulvestrant only users												
Acute liver injury (primary)	10.8	2.2	31.5	32.09	10.73	76.29	27.7	9.0	64.7	10.7	1.3	38.5

Abbreviations: ALI, acute liver injury; IR, incidence rate; CI, confidence interval; HIRD, HealthCore Integrated Research Database.

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Figure 4. E-value to explain away the association between palbociclib and the primary ALI algorithm*



*Minimum strength required for both the palbociclib-confounder and confounder-ALI relationships to explain away the estimated relationship between palbociclib and ALI. The E-value for the 95% CI to remain significant is 1.34
Abbreviations: ALI, acute liver injury; CI, confidence interval.

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Table 2.1. Characteristics of advanced stage ER+/HER2- breast cancer patients utilizing palbociclib identified in the HIRD
[Secondary Objective 2]

Characteristics	All new users of Palbociclib		New users of palbociclib with fulvestrant		New users of palbociclib with letrozole		All other new users of palbociclib (no new use of fulvestrant or letrozole)	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD
Overall	2,285	1.0	548	1.0	1,083	1.0	654	1.0
Demographics								
Age at index date (in years)	59.9	11.6	59.6	11.3	59.2	11.3	61.2	12.3
Age (years)								
<45	207	9.1	47	8.6	110	10.2	50	7.6
45-64	1391	60.9	352	64.2	671	62.0	368	56.3
65+	687	30.1	149	27.2	302	27.9	236	36.1
Gender								
Male	44	1.9	≤10	n/a	12	1.1	23	3.5
Female	2241	98.1	539	98.4	1071	98.9	631	96.5
Calendar year of index date								
2015	746	32.6	97	17.7	425	39.2	224	34.3
2016	881	38.6	260	47.4	381	35.2	240	36.7
2017	658	28.8	191	34.9	277	25.6	190	29.1
Geographic region of residence								
Midwest	378	16.5	93	17.0	175	16.2	110	16.8
South	545	23.9	154	28.1	267	24.7	124	19.0
Northeast	654	28.6	159	29.0	318	29.4	177	27.1
West	708	31.0	142	25.9	323	29.8	243	37.2
Duration of health plan enrollment prior to index date (years)	3.43	2.1	3.43	2.1	3.22	2.0	3.77	2.0
Medical History								
Other primary cancer prior to first breast cancer diagnosis code	985	43.1	216	39.4	498	46.0	271	41.4
Secondary malignancy (metastasis)	2032	88.9	481	87.8	990	91.4	561	85.8
Lymph nodes of head, face, and neck	634	27.7	149	27.2	324	29.9	161	24.6
Respiratory and digestive systems	1007	44.1	251	45.8	465	42.9	291	44.5
Other specified sites	1943	85.0	448	81.8	947	87.4	548	83.8
Deyo-Charlson comorbidity index (DCI) without cancer codes	8.45	1.8	8.52	1.8	8.53	1.6	8.26	2.1
Secondary malignant neoplasm of breast	255	11.2	64	11.7	121	11.2	70	10.7
Breast cancer (female) diagnosis code	2225	97.4	540	98.5	1065	98.3	620	94.8
InSitu breast cancer	193	8.4	44	8.0	112	10.3	37	5.7
Cancer Therapy History								
Radiation therapy	455	19.9	108	19.7	224	20.7	123	18.8
External Beam	455	19.9	108	19.7	224	20.7	123	18.8
Surgery	78	3.4	11	2.0	52	4.8	15	2.3
Mastectomy in the last six months	28	1.2	≤10	n/a	22	2.0	≤10	n/a
Lumpectomy in the last six months	31	1.4	≤10	n/a	21	1.9	≤10	n/a
Radical mastectomy in the last six months	37	1.6	≤10	n/a	23	2.1	≤10	n/a
Chemotherapy	437	19.1	95	17.3	201	18.6	141	21.6
Infusion based chemo (procedure)	12	0.5	≤10	n/a	≤10	n/a	≤10	n/a
Imaging								
CT related imaging in the last six months	563	24.6	131	23.9	316	29.2	116	17.7
MR related imaging for needle placement	≤10	n/a	0	0.0	≤10	0.1	n/a	.
Diagnostic imaging in the last six months	358	15.7	70	12.8	230	21.2	58	8.9
Mammography	48	2.1	≤10	n/a	33	3.0	≤10	n/a
MRI related imaging	148	6.5	24	4.4	102	9.4	22	3.4
Tomosynthesis (3D mammography)	58	2.5	18	3.3	31	2.9	≤10	n/a
Healthcare Utilization								
Number of outpatient visits	39.6	25.3	38.3	23.8	39.5	23.8	41.0	28.4
Number of outpatient visits to an oncologist	0.0	0.2	0.02	0.2	0.0	0.3	0.0	0.1
Number of inpatient hospitalizations	0.3	0.7	0.33	0.7	0.3	0.6	0.3	0.8
Number of inpatient hospitalizations for breast cancer	0.1	0.3	0.03	0.2	0.1	0.4	0.1	0.4

Number of inpatient hospitalizations for any cancer	0.3	0.7	0.29	0.6	0.3	0.6	0.3	0.8
Number of emergency department visits	0.3	0.7	0.31	0.8	0.3	0.6	0.2	0.6
Medication Use (breast cancer related)								
Palbociclib	0	0.0	0	0.0	0	0.0	0	0.0
Aromatase inhibitor	1440	63.0	316	57.7	772	71.3	352	53.8
Letrozole	964	42.2	112	20.4	663	61.2	189	28.9
Anastrozole	368	16.1	133	24.3	137	12.7	98	15.0
Exemestane	270	11.8	82	15.0	92	8.5	96	14.7
HER2 positive therapy	24	1.1	≤10	n/a	12	1.1	≤10	n/a
Trastuzumab	24	1.1	≤10	n/a	11	1.0	≤10	n/a
Lapatinib	≤10	n/a	≤10	n/a	0	0.0	0	0.0
Ado-trastuzumab	0	0.0	0	0.0	0	0.0	0	0.0
Pertuzumab	0	0.0	0	0.0	0	0.0	0	0.0
Tamoxifen	531	23.2	137	25.0	262	24.2	132	20.2
Fulvestrant	601	26.3	234	42.7	109	10.1	258	39.4
Denosumab or Pamidronate	806	35.3	196	35.8	348	32.1	262	40.1
Everolimus	144	6.3	39	7.1	51	4.7	54	8.3
Medication Use (not breast cancer related)								
Anticonvulsants	431	18.9	120	21.9	184	17.0	127	19.4
Antidepressants	696	30.5	169	30.8	328	30.3	199	30.4
Antidiabetics	269	11.8	64	11.7	126	11.6	79	12.1
Antifungals	116	5.1	27	4.9	61	5.6	28	4.3
Antihypertensives	606	26.5	168	30.7	273	25.2	165	25.2
Antimycobacterials	460	20.1	104	19.0	213	19.7	143	21.9
Antivirals	121	5.3	29	5.3	63	5.8	29	4.4
Corticosteroids	563	24.6	137	25.0	288	26.6	138	21.1
Oral contraceptive use (progestin)	≤10	n/a	≤10	n/a	≤10	n/a	0	0.0
Oral contraceptive use (combination)	≤10	n/a	≤10	0.2	≤10	n/a	≤10	n/a
Oral contraceptive use (unspecified)	24	1.1	≤10	1.3	13	1.2	≤10	n/a
Lipid lowering agent	489	21.4	129	23.5	231	21.3	129	19.7
Vaginal estrogen (local hormone treatment)	≤10	n/a	0	0.0	≤10	n/a	≤10	n/a
Macrolides	21	0.9	≤10	1.6	≤10	n/a	≤10	n/a
Sedatives/hypnotics	213	9.3	52	9.5	94	8.7	67	10.2
Selective estrogen receptor modulators	≤10	n/a	≤10	n/a	≤10	n/a	≤10	n/a
Unopposed estrogen hormone replacement therapy (HRT)	≤10	n/a	0	0.0	≤10	n/a	0	0.0
Co-morbidities (six months prior to index date)								
Pathologic fracture	204	8.9	45	8.2	106	9.8	53	8.1
Osteoporosis	185	8.1	52	9.5	75	6.9	58	8.9
Uterine malignancies	≤10	n/a	≤10	n/a	≤10	n/a	≤10	n/a
Pure hypercholesterolemia	204	8.9	47	8.6	101	9.3	56	8.6
Major adverse cardiac events (MACE)	55	2.4	20	3.6	22	2.0	13	2.0
Acute myocardial infarction (MI)	11	0.5	≤10	n/a	≤10	n/a	≤10	n/a
Cerebrovascular disease	1116	48.8	292	53.3	514	47.5	310	47.4
Stroke	46	2.0	16	2.9	19	1.8	11	1.7
Hyperglycemia	97	4.2	26	4.7	50	4.6	21	3.2
Deyo-Charlson Index (DCI)								
0-3	93	4.1	19	3.5	31	2.9	43	6.6
4-7	28	1.2	12	2.2	≤10	n/a	≤10	n/a
8-11	2090	91.5	494	90.1	1012	93.4	584	89.3
12 or more	74	3.2	23	4.2	31	2.9	20	3.1
Abbreviations: GI, gastrointestinal; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, number; SD, standard deviation; CT, computed tomography; MRI, magnetic resonance imaging.								

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Table 2.2. Incidence of the safety events of interest in all new users of palbociclib with advanced stage ER+/HER2- breast cancer [Secondary Objective 2]

Event	All new users of palbociclib with advanced stage ER+/HER2- breast cancer (n=2,285)				
	# Events	PT at risk	IR (per 100 person-years)		
			IR	95% Lower CI	95% Upper CI
Neutropenia (sensitive)	447	1,259	35.5	32.29	38.96
Neutropenia (specific)	293	1,319	22.2	19.74	24.90
Febrile neutropenia (sensitive)	43	1,422	3.0	2.19	4.07
Febrile neutropenia (specific)	≤10	n/a	0.7	0.34	1.29
Leukopenia (sensitive)	91	1,390	6.5	5.27	8.04
Leukopenia (specific)	91	1,390	6.5	5.27	8.04
Alopecia	11	1,427	0.8	0.38	1.38
Vomiting*	119	1,361	8.7	7.24	10.46
QT prolongation	73	1,409	5.2	4.06	6.52
Fatigue*	218	1,232	17.7	15.43	20.21
Serious infection	278	1,365	20.4	18.04	22.91
Brain/spinal infection	≤10	n/a	0.7	0.34	1.29
Pericardial/myocardial infection	0	1,431	0.0	.	.
Pulmonary infection	127	1,400	9.1	7.56	10.79
GI infection	≤10	n/a	0.7	0.34	1.29
Genitourinary/renal infection	131	1,388	9.4	7.89	11.20
Dental infection	≤10	n/a	0.1	0.00	0.39
Ear, nose, and throat infection	77	1,394	5.5	4.36	6.90
Skin, bones, and joint infection	78	1,405	5.5	4.39	6.93
Hepatitis B infection	≤10	n/a	0.1	0.02	0.51
Influenza infection	≤10	n/a	0.4	0.15	0.91
Other infection	264	1,343	19.7	17.36	22.18
Diarrhea*	57	1,389	4.1	3.11	5.32
Interstitial lung disease/pneumonitis	329	1,337	24.6	22.01	27.41
Anemia (sensitive)	510	1,264	40.3	36.92	44.00
Anemia (specific)	302	1,346	22.4	19.97	25.11
Nausea*	189	1,306	14.5	12.49	16.69
Thrombocytopenia	146	1,389	10.5	8.87	12.36
Pulmonary embolism*	43	1,399	3.1	2.22	4.14
No history	52	1,411	3.7	2.75	4.83
Other venous embolism and thrombosis*	60	1,384	4.3	3.31	5.58
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	41	1,402	2.9	2.10	3.97
No history of "Other venous embolism and thrombosis"	89	1,404	6.3	5.09	7.80
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	57	1,413	4.0	3.06	5.23
Embolism and thrombosis of unspecified artery	≤10	n/a	0.1	0.02	0.51
Cataracts and other ocular disorders	89	1,393	6.4	5.13	7.86
Stomatitis and mucositis	34	1,421	2.4	1.66	3.34
Fever	144	1,392	10.3	8.72	12.18
Anorexia	28	1,424	2.0	1.31	2.84
Peripheral neuropathy	100	1,391	7.2	5.85	8.74
Sudden cardiac death	≤10	n/a	0.3	0.08	0.72
Diabetes mellitus	164	1,363	12.0	10.26	14.02
Type 2 Diabetes mellitus	163	1,364	11.9	10.18	13.93
Hyperglycemia	31	1,417	2.2	1.49	3.11

Liver failure (Acute liver injury)	46	1,424	3.2	2.36	4.31
Abnormal ALT (incident)^	28	504	5.6	3.69	8.04
Abnormal ALT (incident or prevalent)^	69	636	10.8	8.44	13.72
Abnormal AST (incident)^	33	541	6.1	4.20	8.57
Abnormal AST (incident or prevalent)^	77	639	12.0	9.51	15.06
Abnormal ALP (incident)^	23	594	3.9	2.45	5.81
Abnormal ALP (incident or prevalent)^	63	655	9.6	7.39	12.30
Secondary malignancies (second primary cancer)	378	1,279	29.6	26.65	32.69
Non-melanoma skin cancer	35	1,409	2.5	1.73	3.45
Abbreviations: GI, gastrointestinal; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PT, person-time; IR, incidence rate; CI, confidence interval; DVT, deep vein thrombosis; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase.					
*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date					
^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.					

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Table 2.3. Incidence of the safety events of interest in new users of palbociclib subgroups with advanced stage ER+/HER2- breast cancer [Secondary Objective 2]

Event	New users of palbociclib and fulvestrant (n=548)					New users of palbociclib and letrozole (n=1,083)					All other new users of palbociclib (no new use of fulvestrant or letrozole) (n=654)				
	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)		
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI
Neutropenia (sensitive)	104	278	37.4	30.58	45.35	228	653	34.91	30.53	39.75	115	328	35.08	28.96	42.10
Neutropenia (specific)	70	289	24.2	18.85	30.56	144	687	20.97	17.69	24.69	79	343	23.01	18.22	28.68
Febrile neutropenia (sensitive)	11	312	3.5	1.76	6.30	20	744	2.69	1.64	4.15	12	365	3.28	1.70	5.74
Febrile neutropenia (specific)	≤10	n/a	1.0	0.20	2.80	≤10	n/a	0.67	0.22	1.56	≤10	n/a	0.54	0.07	1.95
Leukopenia (sensitive)	17	309	5.5	3.21	8.81	52	721	7.21	5.39	9.46	22	361	6.10	3.82	9.24
Leukopenia (specific)	17	309	5.5	3.21	8.81	52	721	7.21	5.39	9.46	22	361	6.10	3.82	9.24
Alopecia	≤10	n/a	0.3	0.01	1.77	≤10	n/a	1.08	0.46	2.12	≤10	n/a	0.54	0.07	1.96
Vomiting*	30	301	10.0	6.73	14.25	46	707	6.51	4.77	8.68	43	354	12.16	8.80	16.37
QT prolongation	19	306	6.2	3.74	9.69	33	738	4.47	3.08	6.28	21	364	5.76	3.57	8.81
Fatigue*	51	276	18.5	13.78	24.33	94	634	14.83	11.98	18.15	73	322	22.66	17.76	28.50
Serious infection	77	300	25.7	20.25	32.06	129	709	18.20	15.20	21.63	72	356	20.22	15.82	25.46
Brain/spinal infection	≤10	314	1.3	0.35	3.26	≤10	n/a	0.80	0.30	1.75	0	370	0.00	.	.
Pericardial/myocardial infection	0	315	0.0	.	.	0	747	0.00	.	.	0	370	0.00	.	.
Pulmonary infection	33	309	10.7	7.35	15.00	64	728	8.79	6.77	11.23	30	363	8.26	5.57	11.80
GI infection	≤10	314	0.6	0.08	2.30	≤10	746	0.80	0.29	1.75	≤10	n/a	0.54	0.07	1.95
Genitourinary/Renal infection	34	304	11.2	7.74	15.61	69	721	9.57	7.45	12.12	28	363	7.71	5.12	11.14
Dental infection	0	315	0.0	.	.	≤10	n/a	0.13	0.00	0.75	0	370	0.00	.	.
Ear, nose, and throat infection	14	311	4.5	2.46	7.55	46	721	6.38	4.67	8.50	17	362	4.70	2.74	7.52
Skin, bones, and joint infection	16	310	5.2	2.95	8.38	45	730	6.17	4.50	8.25	17	366	4.65	2.71	7.44
Hepatitis B infection	0	315	0.0	.	.	≤10	n/a	0.13	0.00	0.75	≤10	n/a	0.27	0.01	1.51
Influenza infection	≤10	n/a	1.3	0.35	3.27	0	747	0.00	.	.	≤10	n/a	0.54	0.07	1.96
Other infection	64	297	21.5	16.58	27.50	135	697	19.38	16.25	22.94	65	349	18.62	14.37	23.73
Diarrhea*	14	308	4.6	2.49	7.64	26	723	3.60	2.35	5.27	17	359	4.73	2.76	7.58
Interstitial lung disease/pneumonitis	100	294	34.0	27.66	41.35	156	689	22.63	19.22	26.48	73	354	20.61	16.16	25.92
Anemia (sensitive)	133	274	48.6	40.67	57.57	261	651	40.07	35.36	45.24	116	339	34.22	28.28	41.04
Anemia (specific)	78	294	26.6	21.00	33.16	152	701	21.70	18.38	25.43	72	352	20.45	16.00	25.76
Nausea*	47	289	16.3	11.94	21.61	79	677	11.67	9.24	14.55	63	340	18.55	14.26	23.74
Thrombocytopenia	33	308	10.7	7.37	15.03	66	726	9.09	7.03	11.57	47	355	13.24	9.73	17.60
Pulmonary embolism*	14	308	4.5	2.48	7.62	15	727	2.06	1.16	3.40	14	364	3.85	2.10	6.46
No history	15	310	4.8	2.71	7.98	26	735	3.54	2.31	5.18	11	366	3.01	1.50	5.38
Other venous embolism and thrombosis*	11	300	3.7	1.83	6.57	27	720	3.75	2.47	5.46	22	364	6.04	3.78	9.14
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	≤10	n/a	2.3	0.93	4.76	16	733	2.18	1.25	3.55	18	367	4.91	2.91	7.76
No history of "Other venous embolism and thrombosis"	23	306	7.5	4.77	11.28	48	731	6.56	4.84	8.70	18	367	4.91	2.91	7.76
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	16	307	5.2	2.98	8.46	27	738	3.66	2.41	5.32	14	367	3.81	2.08	6.39
Embolism and thrombosis of unspecified artery	0	315	0.0	.	.	0	747	0.00	.	.	≤10	n/a	0.54	0.07	1.96
Cataracts and other ocular disorders	18	308	5.8	3.46	9.24	50	723	6.91	5.13	9.11	21	361	5.81	3.60	8.89
Stomatitis and mucositis	≤10	n/a	2.9	1.32	5.46	11	741	1.48	0.74	2.66	14	367	3.81	2.08	6.40
Fever	34	309	11.0	7.62	15.38	75	723	10.38	8.16	13.01	35	361	9.70	6.76	13.49
Anorexia	≤10	n/a	2.9	1.31	5.45	13	741	1.75	0.93	3.00	≤10	n/a	1.63	0.60	3.54
Peripheral neuropathy	22	308	7.1	4.47	10.80	46	724	6.35	4.65	8.47	32	358	8.93	6.11	12.61
Sudden cardiac death	0	315	0.0	.	.	≤10	n/a	0.40	0.08	1.17	≤10	n/a	0.27	0.01	1.51
Diabetes mellitus	44	301	14.6	10.62	19.63	95	701	13.54	10.96	16.56	25	361	6.93	4.49	10.23
Type 2 Diabetes mellitus	44	301	14.6	10.61	19.61	95	702	13.54	10.95	16.55	24	361	6.64	4.25	9.88
Hyperglycemia	≤10	313	1.6	0.52	3.72	20	736	2.72	1.66	4.20	≤10	n/a	1.63	0.60	3.55
Liver failure (Acute liver injury)	13	314	4.1	2.21	7.09	22	742	2.97	1.86	4.49	11	369	2.98	1.49	5.33
Abnormal ALT (incident)^	≤10	n/a	7.6	3.47	14.39	≤10	n/a	2.86	1.15	5.89	12	140	8.57	4.43	14.97
Abnormal ALT (incident or prevalent)^	17	151	11.3	6.55	18.02	28	312	8.99	5.97	12.99	24	174	13.82	8.86	20.56
Abnormal AST (incident)^	≤10	n/a	7.1	3.25	13.51	11	272	4.04	2.02	7.23	13	142	9.13	4.86	15.61
Abnormal AST (incident or prevalent)^	20	148	13.5	8.23	20.80	28	317	8.83	5.87	12.77	29	174	16.69	11.18	23.98
Abnormal ALP (incident)^	≤10	n/a	4.4	1.63	9.65	≤10	300	2.34	0.94	4.81	≤10	159	6.27	3.01	11.54
Abnormal ALP (incident or prevalent)^	16	148	10.8	6.16	17.50	24	330	7.27	4.66	10.82	23	177	13.01	8.24	19.51
Secondary malignancies (second primary cancer)	102	282	36.2	29.53	43.96	194	654	29.68	25.65	34.17	82	344	23.86	18.97	29.61
Non-melanoma skin cancer	≤10	n/a	2.3	0.91	4.65	17	734	2.32	1.35	3.71	11	365	3.01	1.50	5.39
Abbreviations: GI, gastrointestinal; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PT, person-time; IR, incidence rate; CI, confidence interval; DVT, deep vein thrombosis; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase.															
*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date.															
^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.															

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Table 2.4. Characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone with algorithm-defined advanced stage ER+/HER2- breast cancer [Secondary Objective 3b]

Characteristics of patients with advanced stage ER+/HER2- Breast Cancer	Before Propensity Score Matching					After Propensity Score Matching^				
	New users of palbociclib with fulvestrant		New users of fulvestrant alone (pre-2015)		Standardized difference	New users of palbociclib with fulvestrant		New users of fulvestrant alone (pre-2015)		Standardized difference
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Overall	548	1.0	2,061	1.0		544	1.0	544	1.0	
Demographics										
Age at index date (in years)	59.7	10.9	64.0	12.8	0.37	59.8	10.9	60.2	12.2	0.04
Age (years)										
<45	47	8.6	107	5.2	0.13	45	8.3	41	7.5	0.03
45-64	352	64.2	1010	49.0	0.31	351	64.5	327	60.1	0.09
65+	149	27.2	944	45.8	0.39	148	27.2	176	32.4	0.11
Gender										
Male	≤10	n/a	≤10	n/a	0.04	≤10	n/a	≤10	n/a	0.07
Female	539	98.4	2036	98.8	0.04	535	98.3	539	99.1	0.07
Calendar year of index date										
2011	0	0.0	541	26.2	n/a	0	0.0	119	21.9	n/a
2012	0	0.0	453	22.0	n/a	0	0.0	102	18.8	n/a
2013	0	0.0	509	24.7	n/a	0	0.0	144	26.5	n/a
2014	0	0.0	558	27.1	n/a	0	0.0	179	32.9	n/a
2015	97	17.7	0	0.0	n/a	96	17.6	0	0.0	n/a
2016	260	47.4	0	0.0	n/a	259	47.6	0	0.0	n/a
2017	191	34.9	0	0.0	n/a	189	34.7	0	0.0	n/a
Geographic region of residence										
Midwest	93	17.0	370	18.0	0.03	93	17.1	92	16.9	0.00
South	154	28.1	603	29.3	0.03	152	27.9	155	28.5	0.01
Northeast	159	29.0	519	25.2	0.09	158	29.0	160	29.4	0.01
West	142	25.9	569	27.6	0.04	141	25.9	137	25.2	0.02
Medical History										
Other primary cancer prior to first breast cancer diagnosis code	216	39.4	927	45.0	0.11	216	39.7	252	46.3	0.13
Secondary malignancy (metastasis)	481	87.8	1696	82.3	0.15	477	87.7	458	84.2	0.10
Lymph nodes of head, face, and neck	149	27.2	428	20.8	0.15	146	26.8	143	26.3	0.01
Respiratory and digestive systems	251	45.8	740	35.9	0.20	248	45.6	252	46.3	0.01
Other specified sites	448	81.8	1612	78.2	0.09	444	81.6	427	78.5	0.08
Deyo-Charlson comorbidity index (DCI) without cancer codes	8.49	1.9	8.07	2.1	0.21	8.49	1.9	8.48	1.8	0.01
Secondary malignant neoplasm of breast	64	11.7	190	9.2	0.08	63	11.6	73	13.4	0.06
Breast cancer (female) diagnosis code	540	98.5	2016	97.8	0.05	536	98.5	537	98.7	0.02
InSitu breast cancer	44	8.0	128	6.2	0.07	42	7.7	48	8.8	0.04
Cancer Therapy History										
Radiation therapy	108	19.7	348	16.9	0.07	108	19.9	102	18.8	0.03
External Beam	108	19.7	348	16.9	0.07	108	19.9	102	18.8	0.03
Surgery	11	2.0	52	2.5	0.03	11	2.0	11	2.0	0.00
Mastectomy in the last six months	≤10	n/a	21	1.0	0.05	≤10	n/a	≤10	n/a	0.02
Lumpectomy in the last six months	≤10	n/a	19	0.9	0.04	≤10	n/a	≤10	n/a	0.03
Radical Mastectomy in the last six months	≤10	n/a	20	1.0	0.01	≤10	n/a	≤10	n/a	0.02
Chemotherapy	95	17.3	369	17.9	0.01	94	17.3	100	18.4	0.03
Infusion based chemo (procedure)	≤10	n/a	25	1.2	0.10	≤10	n/a	11	2.0	0.15
Imaging										
CT related imaging in the last six months	131	23.9	465	22.6	0.03	130	23.9	126	23.2	0.02
MR related imaging for needle placement	0	0.0	≤10	n/a	n/a	0	0.0	≤10	n/a	n/a
Diagnostic imaging in the last six months	70	12.8	384	18.6	0.16	70	12.9	70	12.9	0.00
Mammography	≤10	n/a	90	4.4	0.19	≤10	n/a	≤10	n/a	0.00
MRI related imaging	24	4.4	77	3.7	0.03	24	4.4	27	5.0	0.03
Tomosynthesis (3D Mammography)	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Healthcare Utilization (six months prior to index date)										
Number of outpatient visits	37.2	21.9	36.13	24.3	0.05	37.21	21.9	37.56	23.4	0.02
Number of outpatient visits to an oncologist	0.02	0.2	0.03	0.4	0.03	0.02	0.2	0.03	0.3	0.05
Number of inpatient hospitalizations	0.29	0.7	0.34	0.7	0.07	0.29	0.7	0.4	0.7	0.16
Number of inpatient hospitalizations for breast cancer	0.03	0.2	0.26	0.6	0.51	0.03	0.2	0.34	0.7	0.61
Number of inpatient hospitalizations for any cancer	0.25	0.6	0.3	0.7	0.08	0.25	0.6	0.38	0.7	0.20
Number of emergency department visits	0.3	0.8	0.23	0.6	0.10	0.3	0.8	0.3	0.7	0.00
Medication Use (breast cancer related)										
Palbociclib										
Aromatase inhibitor	316	57.7	1161	56.3	0.03	312	57.4	295	54.2	0.06
Letrozole	112	20.4	400	19.4	0.03	109	20.0	114	21.0	0.02
Anastrozole	133	24.3	544	26.4	0.05	132	24.3	132	24.3	0.00
Exemestane	82	15.0	327	15.9	0.02	82	15.1	79	14.5	0.02
HER2 positive therapy	≤10	n/a	27	1.3	0.00	≤10	n/a	≤10	n/a	0.02
Trastuzumab	≤10	n/a	33	1.6	0.03	≤10	n/a	≤10	n/a	0.00
Lapatinib	≤10	n/a	≤10	n/a	0.03	≤10	n/a	≤10	n/a	0.04
Ado-trastuzumab	0	0.0	0	0.0	0.00	0	0.0	0	0.0	n/a
Pertuzumab	0	0.0	0	0.0	0.00	0	0.0	0	0.0	n/a
Tamoxifen	137	25.0	357	17.3	0.19	137	25.2	135	24.8	0.01
Fulvestrant	234	42.7	0	0.0	n/a	232	42.6	0	0.0	n/a
Denosumab or Pamidronate	196	35.8	391	19.0	0.38	192	35.3	187	34.4	0.02

Everolimus	39	7.1	84	4.1	0.13	38	7.0	31	5.7	0.05
Medication Use (not breast cancer related)										
Anticonvulsants	120	21.9	300	14.6	0.19	117	21.5	111	20.4	0.03
Antidepressants	169	30.8	558	27.1	0.08	167	30.7	166	30.5	0.00
Antidiabetics	64	11.7	227	11.0	0.02	63	11.6	69	12.7	0.03
Antifungals	27	4.9	99	4.8	0.01	27	5.0	40	7.4	0.10
Antihypertensives	168	30.7	551	26.7	0.09	167	30.7	135	24.8	0.13
Antimycobacterials	104	19.0	385	18.7	0.01	103	18.9	113	20.8	0.05
Antivirals	29	5.3	97	4.7	0.03	29	5.3	34	6.3	0.04
Corticosteroids	137	25.0	370	18.0	0.17	136	25.0	148	27.2	0.05
Oral contraceptive use (progestin)	0	0.0	0	0.0	n/a	0	0.0	0	0.0	n/a
Oral contraceptive use (combination)	≤10	n/a	≤10	n/a	0.02	0	0.0	0	0.0	n/a
Oral contraceptive use (unspecified)	≤10	n/a	20	1.0	0.03	≤10	n/a	≤10	n/a	0.08
Lipid lowering agent	129	23.5	499	24.2	0.02	127	23.3	119	21.9	0.04
Vaginal estrogen (local hormone treatment)	0	0.0	≤10	n/a	n/a	0	0.0	≤10	0.2	n/a
Macrolides	≤10	n/a	20	1.0	0.06	≤10	n/a	≤10	0.7	0.08
Sedatives/hypnotics	52	9.5	251	12.2	0.09	52	9.6	52	9.6	0.00
Selective estrogen receptor modulators	≤10	n/a	≤10	n/a	0.04	≤10	0.2	≤10	0.7	0.08
Unopposed estrogen hormone replacement therapy (HRT)	0	0.0	≤10	n/a	n/a	0	0.0	≤10	0.4	n/a
Co-morbidities (six months prior to index date)										
Pathologic fracture	45	8.2	161	7.8	0.01	45	8.3	50	9.2	0.03
Osteoporosis	52	9.5	196	9.5	0.00	51	9.4	45	8.3	0.04
Uterine malignancies	≤10	n/a	11	0.5	0.03	≤10	n/a	≤10	n/a	0.07
Pure hypercholesterolemia	47	8.6	215	10.4	0.06	47	8.6	58	10.7	0.07
Major adverse cardiac events (MACE)	20	3.6	73	3.5	0.01	20	3.7	15	2.8	0.05
Acute Myocardial Infarction (MI)	≤10	n/a	22	1.1	0.04	≤10	n/a	≤10	n/a	0.04
Cerebrovascular disease	292	53.3	995	48.3	0.10	288	52.9	250	46.0	0.14
Stroke	16	2.9	54	2.6	0.02	16	2.9	≤10	n/a	0.07
Hyperglycemia	26	4.7	49	2.4	0.13	23	4.2	24	4.4	0.01
Deyo-Charlson Index (DCI)										
0-3	19	3.5	177	8.6	0.22	19	3.5	21	3.9	0.02
4-7	12	2.2	27	1.3	0.07	12	2.2	≤10	n/a	0.07
8-11	494	90.1	1798	87.2	0.09	491	90.3	493	90.6	0.01
12 or more	23	4.2	59	2.9	0.07	22	4.0	23	4.2	0.01
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, number; STD, standard deviation; DVT, deep vein thrombosis; CT, computed tomography; MRI, magnetic resonance imaging.										
^The following variables were included in the propensity score: age, region, Deyo-Charlson Index, Number of outpatient visits, Number of emergency room visits, secondary malignancy to lymph nodes of head, face, and neck, secondary malignancy to other specified sites, secondary malignancy to respiratory sites, tamoxifen, everolimus, anastrozole, Denosumab or Pamidronate, exemestane, chemotherapy, corticosteroids, diagnostic imaging, breast cancer surgery, letrozole, HER2 positive therapy, radiation therapy, CT imaging, mammography, MRI imaging, anticonvulsants, antidepressants, sedatives/hypnotics, secondary malignancy to breast, breast cancer diagnosis code, in situ breast cancer diagnosis, hyperglycemia, and cerebrovascular disease.										

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Table 2.5. Incidence rates and unadjusted hazard ratios of the safety events of interest in new users of palbociclib and fulvestrant and new users of fulvestrant alone with advanced stage ER+/HER2- breast cancer [Secondary Objective 3b]

Event	Before Propensity Score Matching												
	New users of palbociclib and fulvestrant with advanced stage ER+/HER2- breast cancer (n=548)					New users of fulvestrant alone (pre-2015) with advanced stage ER+/HER2- breast cancer (n=2,061)					Unadjusted Hazard Ratios		
	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			HR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Neutropenia (sensitive)	104	278	37.4	30.58	45.35	83	1,432	5.8	4.62	7.19	6.0	4.5	8.0
Neutropenia (specific)	70	289	24.2	18.85	30.56	57	1,435	4.0	3.01	5.15	5.7	4.0	8.2
Febrile neutropenia (sensitive)	11	312	3.5	1.76	6.30	≤10	n/a	0.6	0.28	1.17	5.1	2.1	12.4
Febrile neutropenia (specific)	≤10	n/a	1.0	0.20	2.80	≤10	n/a	0.1	0.00	0.38	11.7	1.2	113.0
Leukopenia (sensitive)	17	309	5.5	3.21	8.81	13	1,451	0.9	0.48	1.53	5.7	2.7	11.7
Leukopenia (specific)	17	309	5.5	3.21	8.81	13	1,451	0.9	0.48	1.53	5.7	2.7	11.7
Alopecia	≤10	n/a	0.3	0.01	1.77	≤10	n/a	0.2	0.04	0.60	1.5	0.2	14.1
Vomiting*	30	301	10.0	6.73	14.25	190	1,405	13.5	11.67	15.59	0.7	0.5	1.0
QT prolongation	19	306	6.2	3.74	9.69	76	1,432	5.3	4.18	6.64	1.1	0.7	1.8
Fatigue*	51	276	18.5	13.78	24.33	263	1,349	19.5	17.22	22.01	0.9	0.7	1.2
Serious infection	77	300	25.7	20.25	32.06	308	1,395	22.1	19.69	24.70	1.1	0.9	1.4
Brain/spinal infection	≤10	n/a	1.3	0.35	3.26	≤10	n/a	0.1	0.02	0.50	8.6	1.6	47.2
Pericardial/myocardial infection	0	315	0.0	.	.	≤10	n/a	0.1	0.02	0.50	n/a	0.0	.
Pulmonary infection	33	309	10.7	7.35	15.00	119	1,432	8.3	6.88	9.94	1.2	0.8	1.8
GI infection	≤10	n/a	0.6	0.08	2.30	≤10	n/a	0.4	0.15	0.90	1.5	0.3	7.4
Genitourinary/Renal infection	34	304	11.2	7.74	15.61	161	1,412	11.4	9.71	13.31	0.9	0.6	1.3
Dental infection	0	315	0.0	.	.	≤10	n/a	0.1	0.02	0.50	n/a	0.0	.
Ear, nose, and throat infection	14	311	4.5	2.46	7.55	47	1,437	3.3	2.40	4.35	1.3	0.7	2.4
Skin, bones, and joint infection	16	310	5.2	2.95	8.38	61	1,432	4.3	3.26	5.47	1.2	0.7	2.0
Hepatitis B infection	0	315	0.0	.	.	33	1,434	2.3	1.58	3.23	n/a	0.0	.
Influenza infection	≤10	n/a	1.3	0.35	3.27	≤10	n/a	0.2	0.04	0.60	5.7	1.3	25.5
Other infection	64	297	21.5	16.58	27.50	486	1,270	38.3	34.93	41.81	0.6	0.4	0.7
Diarrhea*	14	308	4.6	2.49	7.64	86	1,425	6.0	4.83	7.45	0.7	0.4	1.2
Interstitial lung disease/pneumonitis	100	294	34.0	27.66	41.35	311	1,372	22.7	20.22	25.33	1.4	1.2	1.8
Anemia (sensitive)	133	274	48.6	40.67	57.57	327	1,348	24.3	21.69	27.03	1.9	1.5	2.3
Anemia (specific)	78	294	26.6	21.00	33.16	108	1,423	7.6	6.22	9.16	3.3	2.5	4.5
Nausea*	47	289	16.3	11.94	21.61	241	1,382	17.4	15.30	19.78	0.9	0.7	1.2
Thrombocytopenia	33	308	10.7	7.37	15.03	57	1,449	3.9	2.98	5.10	2.6	1.7	3.9
Pulmonary embolism*	14	308	4.5	2.48	7.62	43	1,438	3.0	2.16	4.03	1.4	0.8	2.6
No history	15	310	4.8	2.71	7.98	37	1,443	2.6	1.81	3.54	1.8	1.0	3.2
Other venous embolism and thrombosis*	11	300	3.7	1.83	6.57	93	1,411	6.6	5.32	8.07	0.5	0.3	1.0
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	≤10	n/a	2.3	0.93	4.76	60	1,430	4.2	3.20	5.40	0.5	0.2	1.2
No history of "Other venous embolism and thrombosis"	23	306	7.5	4.77	11.28	85	1,427	6.0	4.76	7.36	1.2	0.8	1.9
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	16	307	5.2	2.98	8.46	55	1,439	3.8	2.88	4.98	1.3	0.8	2.3
Embolism and thrombosis of unspecified artery	0	315	0.0	.	.	≤10	n/a	0.1	0.00	0.38	n/a	0.0	.
Cataracts and other ocular disorders	18	308	5.8	3.46	9.24	88	1,413	6.2	5.00	7.67	0.9	0.5	1.5
Stomatitis and mucositis	≤10	n/a	2.9	1.32	5.46	≤10	n/a	0.6	0.24	1.08	4.8	1.8	12.4
Fever	34	309	11.0	7.62	15.38	68	1,438	4.7	3.67	6.00	2.2	1.4	3.3
Anorexia	≤10	n/a	2.9	1.31	5.45	27	1,455	1.9	1.22	2.70	1.5	0.7	3.3
Peripheral neuropathy	22	308	7.1	4.47	10.80	46	1,440	3.2	2.34	4.26	2.1	1.2	3.5
Sudden cardiac death	0	315	0.0	.	.	≤10	n/a	0.1	0.02	0.50	n/a	0.0	.
Diabetes mellitus	44	301	14.6	10.62	19.63	194	1,388	14.0	12.08	16.09	1.0	0.7	1.4
Type 2 Diabetes mellitus	44	301	14.6	10.61	19.61	189	1,389	13.6	11.73	15.69	1.0	0.7	1.4
Hyperglycemia	≤10	n/a	1.6	0.52	3.72	11	1,454	0.8	0.38	1.35	2.1	0.7	6.0
Liver failure (Acute liver injury)	13	314	4.1	2.21	7.09	18	1,454	1.2	0.73	1.96	3.1	1.5	6.3
Abnormal ALT (incident)^	≤10	n/a	7.6	3.47	14.39	34	465	7.3	5.07	10.22	0.9	0.5	2.0
Abnormal ALT (incident or prevalent)^	17	151	11.3	6.55	18.02	78	530	14.7	11.63	18.36	0.7	0.4	1.2
Abnormal AST (incident)^	≤10	n/a	7.1	3.25	13.51	45	467	9.6	7.03	12.89	0.7	0.3	1.4
Abnormal AST (incident or prevalent)^	20	148	13.5	8.23	20.80	96	525	18.3	14.81	22.33	0.7	0.4	1.1
Abnormal ALP (incident)^	≤10	n/a	4.4	1.63	9.65	25	490	5.1	3.30	7.53	0.8	0.3	1.9
Abnormal ALP (incident or prevalent)^	16	148	10.8	6.16	17.50	82	535	15.3	12.20	19.03	0.6	0.4	1.1
Secondary malignancies (second primary cancer)	102	282	36.2	29.53	43.96	468	1,293	36.2	32.99	39.62	1.0	0.8	1.2
Non-melanoma skin cancer	≤10	n/a	2.3	0.91	4.65	57	1,421	4.0	3.04	5.20	0.5	0.2	1.2

Abbreviations: GI, gastrointestinal; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PT, person-time; IR, incidence rate; CI, confidence interval; HR, hazard ratio; LCL, lower confidence limit; UCL, upper confidence limit; DVT, deep vein thrombosis; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase.

*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date.

^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.

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Table 2.6. Incidence rates and adjusted hazard ratios of the safety events of interest in new users of palbociclib and fulvestrant and new users of fulvestrant alone with advanced stage ER+/HER2- breast cancer [Secondary Objective 3b]

Event	After Propensity Score Matching												
	New users of palbociclib and fulvestrant with advanced stage ER+/HER2- breast cancer (n=544)					New users of fulvestrant alone (pre-2015) with advanced stage ER+/HER2- breast cancer (n=544)					Adjusted Hazard Ratios		
	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			aHR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Neutropenia (sensitive)	101	277	36.5	29.74	44.36	16	351	4.6	2.61	7.41	7.6	4.5	12.9
Neutropenia (specific)	70	288	24.3	18.96	30.73	11	351	3.1	1.56	5.60	7.5	4.0	14.1
Febrile neutropenia (sensitive)	≤10	n/a	3.2	1.54	5.92	≤10	n/a	0.3	0.01	1.56	10.8	1.4	84.4
Febrile neutropenia (specific)	≤10	n/a	1.0	0.20	2.81	0	357	0.0	.	1.03	n/a	.	.
Leukopenia (sensitive)	17	307	5.5	3.22	8.86	≤10	n/a	0.3	0.01	1.56	18.6	2.5	139.6
Leukopenia (specific)	17	307	5.5	3.22	8.86	≤10	n/a	0.3	0.01	1.56	18.6	2.5	139.6
Alopecia	≤10	n/a	0.3	0.01	1.78	≤10	n/a	0.3	0.01	1.56	1.1	0.1	17.4
Vomiting*	28	299	9.4	6.23	13.55	52	340	15.3	11.42	20.06	0.6	0.4	1.0
QT prolongation	19	304	6.2	3.76	9.75	19	346	5.5	3.31	8.57	1.1	0.6	2.1
Fatigue*	49	274	17.9	13.24	23.66	68	334	20.4	15.82	25.83	0.8	0.6	1.2
Serious infection	77	299	25.8	20.36	32.24	78	344	22.7	17.91	28.28	1.1	0.8	1.5
Brain/spinal infection	≤10	n/a	1.3	0.35	3.28	≤10	n/a	0.6	0.07	2.02	2.2	0.4	11.8
Pericardial/myocardial infection	0	313	0.0	.	1.18	0	357	0.0	.	1.03	n/a	.	.
Pulmonary infection	33	307	10.7	7.39	15.08	26	352	7.4	4.82	10.81	1.4	0.8	2.3
GI infection	≤10	n/a	0.6	0.08	2.31	≤10	n/a	0.3	0.01	1.56	2.4	0.2	26.0
Genitourinary/Renal infection	34	303	11.2	7.78	15.69	42	347	12.1	8.72	16.36	0.9	0.6	1.4
Dental infection	0	313	0.0	.	1.18	≤10	n/a	0.3	0.01	1.56	0.0	0.0	.
Ear, nose, and throat infection	14	309	4.5	2.47	7.59	≤10	n/a	2.0	0.79	4.06	2.1	0.8	5.2
Skin, bones, and joint infection	16	308	5.2	2.97	8.43	13	353	3.7	1.96	6.29	1.3	0.6	2.8
Hepatitis B infection	0	313	0.0	.	1.18	≤10	n/a	1.4	0.46	3.28	n/a	.	.
Influenza infection	≤10	n/a	1.3	0.35	3.29	0	357	0.0	.	1.03	n/a	.	.
Other infection	64	296	21.7	16.68	27.65	124	309	40.1	33.38	47.84	0.5	0.4	0.7
Diarrhea*	14	306	4.6	2.50	7.68	24	347	6.9	4.44	10.30	0.6	0.3	1.2
Interstitial lung disease/pneumonitis	100	292	34.2	27.82	41.58	92	333	27.6	22.24	33.83	1.2	0.9	1.6
Anemia (sensitive)	133	272	48.9	40.92	57.91	82	331	24.8	19.70	30.74	1.9	1.4	2.5
Anemia (specific)	78	292	26.7	21.12	33.35	37	345	10.7	7.55	14.79	2.4	1.6	3.5
Nausea*	46	288	16.0	11.71	21.34	72	329	21.9	17.14	27.58	0.7	0.5	1.0
Thrombocytopenia	33	307	10.8	7.41	15.11	15	356	4.2	2.36	6.95	2.4	1.3	4.5
Pulmonary embolism*	14	307	4.6	2.50	7.66	12	351	3.4	1.77	5.98	1.2	0.5	2.6
No history	15	308	4.9	2.72	8.02	≤10	n/a	2.8	1.36	5.20	1.6	0.7	3.6
Other venous embolism and thrombosis*	11	298	3.7	1.84	6.60	33	337	9.8	6.74	13.75	0.4	0.2	0.7
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	≤10	n/a	2.3	0.93	4.78	22	342	6.4	4.03	9.73	0.4	0.2	0.9
No history of "Other venous embolism and thrombosis"	22	304	7.2	4.53	10.95	29	342	8.5	5.68	12.19	0.8	0.5	1.4
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)	15	306	4.9	2.75	8.09	19	347	5.5	3.30	8.56	0.9	0.5	1.7
Embolism and thrombosis of unspecified artery	0	313	0.0	.	1.18	≤10	n/a	0.3	0.01	1.56	n/a	.	.
Cataracts and other ocular disorders	18	306	5.9	3.48	9.29	20	349	5.7	3.50	8.86	1.0	0.5	1.8
Stomatitis and mucositis	≤10	n/a	2.9	1.32	5.49	≤10	n/a	0.3	0.01	1.56	9.4	1.2	74.1
Fever	33	307	10.7	7.39	15.07	18	350	5.1	3.05	8.13	2.0	1.1	3.5
Anorexia	≤10	n/a	2.9	1.32	5.48	≤10	n/a	2.5	1.16	4.80	1.1	0.4	2.8
Peripheral neuropathy	22	307	7.2	4.49	10.86	≤10	n/a	2.5	1.16	4.81	2.6	1.2	5.7
Sudden cardiac death	0	313	0.0	.	1.18	≤10	n/a	0.3	0.01	1.56	0.0	0.0	.
Diabetes mellitus	44	299	14.7	10.68	19.73	60	337	17.8	13.59	22.92	0.8	0.5	1.2
Type 2 Diabetes mellitus	44	300	14.7	10.67	19.71	59	337	17.5	13.32	22.57	0.8	0.5	1.2
Hyperglycemia	≤10	n/a	1.6	0.52	3.74	≤10	n/a	0.8	0.17	2.46	2.0	0.5	8.8
Liver failure (Acute liver injury)	13	312	4.2	2.22	7.13	≤10	n/a	2.0	0.79	4.06	1.9	0.8	4.8
Abnormal ALT (incident)^	≤10	n/a	6.8	2.92	13.35	11	113	9.8	4.87	17.46	0.6	0.3	1.6
Abnormal ALT (incident or prevalent)^	16	150	10.6	6.08	17.28	20	134	14.9	9.12	23.05	0.6	0.3	1.2
Abnormal AST (incident)^	≤10	n/a	7.2	3.28	13.61	12	117	10.2	5.30	17.90	0.7	0.3	1.6
Abnormal AST (incident or prevalent)^	19	148	12.9	7.75	20.11	31	134	23.2	15.76	32.91	0.5	0.3	0.9
Abnormal ALP (incident)^	≤10	n/a	4.5	1.64	9.71	≤10	n/a	4.1	1.33	9.56	1.0	0.3	3.2
Abnormal ALP (incident or prevalent)^	15	148	10.2	5.69	16.77	28	133	21.0	13.96	30.35	0.4	0.2	0.7
Secondary malignancies (second primary cancer)	101	280	36.0	29.36	43.80	139	371	37.5	31.54	44.30	0.9	0.7	1.2
Non-melanoma skin cancer	≤10	n/a	2.3	0.91	4.67	≤10	n/a	1.7	0.70	3.56	1.8	0.6	6.0
Abbreviations: GI, gastrointestinal; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PT, person-time; IR, incidence rate; CI, confidence interval; aHR, adjusted hazard ratios; LCL, lower confidence limit; UCL, upper confidence limit; DVT, deep vein thrombosis; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase.													
*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date													
^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.													

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Table 2-7A Incidence rates and unadjusted hazard ratios of the acute liver injury in new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparison group) with algorithm-defined advanced stage ER+/HER2- Breast cancer

Event		Before Propensity Score Matching												
		All new users of palbociclib and fulvestrant (n=548)					All new users of fulvestrant alone (pre-2015) (n=2,061)					Unadjusted Hazard Ratios		
		# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			HR	95% LCL	95% UCL
IR	95% Lower CI			95% Upper CI	IR	95% Lower CI			95% Upper CI					
Overall														
Acute liver injury (primary)		13	314	4.1	2.2	7.1	22	1,455	1.5	1.0	2.3	2.6	1.3	5.1
Acute liver injury (original with labs)		13	314	4.1	2.2	7.1	18	1,454	1.2	0.7	2.0	3.1	1.5	6.3
Acute liver injury (sensitive)		37	308	12.0	8.5	16.5	33	1,451	2.3	1.6	3.2	4.9	3.0	7.8
Acute liver injury (specific)		0	315	0.0	.	1.2	0	1,457	0.0	.	0.3			
Among patients with a risk factor for ALI*														
Acute liver injury (primary)		11	184	6	3.0	10.7	19	797	2	1.4	3.7	2.4	1.1	5.0
Among patients without a risk factor for ALI*														
Acute liver injury (primary)		≤10	n/a	2	0.2	5.6	≤10	n/a	0	0.1	1.3	3.1	0.5	18.4
*Risk factors for ALI defined as chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; HR, hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALI, acute liver injury.														

*Risk factors for ALI defined as chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart
Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; HR, hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALI, acute liver injury.

Table 2-7B Incidence rates and adjusted hazard ratios of the safety events of interest in propensity score matched new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparison group) with algorithm-defined advanced stage ER+/HER2- Breast cancer

Event		After Propensity Score Matching												
		New users of palbociclib and fulvestrant (n=544)					New users of fulvestrant alone (pre-2015) (n=544)					Adjusted Hazard Ratios		
		# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			aHR	95% LCL	95%UCL
IR	95% Lower CI			95% Upper CI	IR	95% Lower CI			95% Upper CI					
Overall														
Acute liver injury (primary)		13	312	4.2	2.2	7.1	≤10	n/a	1.5	0.5	3.2	2.8	1.0	7.8
Acute liver injury (original with labs)		13	312	4.2	2.2	7.1	≤10	n/a	2.2	1.0	4.2	1.9	0.8	4.8
Acute liver injury (sensitive)		37	307	12.1	8.5	16.6	15	411	3.7	2.0	6.0	3.6	1.8	7.0
Acute liver injury (specific)		0	313	0.0	.	1.2	0	413	0.0	.	0.9	--	--	--
Among patients with a risk factor for ALI*														
Acute liver injury (primary)		11	183	6.0	3	10.8	≤10	258	1.9	0.6	4.5	3.1	1.0	9.7
Among patients without a risk factor for ALI*														
Acute liver injury (primary)		≤10	n/a	1.5	0.2	5.6	≤10	n/a	0.6	0.0	3.6	1.9	0.2	21.0
*Risk factors for ALI defined as chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; aHR, adjusted hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALI, acute liver injury.														

*Risk factors for ALI defined as chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart
Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; aHR, adjusted hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALI, acute liver injury.