bjclub breast Journal club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

7-8 MARZO 2025
NAPOLI
Hotel Royal Continental
Via Partenope, 38

Breast Journal Club 2025

Napoli - 08 Marzo, 2025

La Sfida dell'Aderenza nelle Terapie Adiuvanti

Paolo Vigneri

Università di Catania
Humanitas Istituto Clinico Catanese

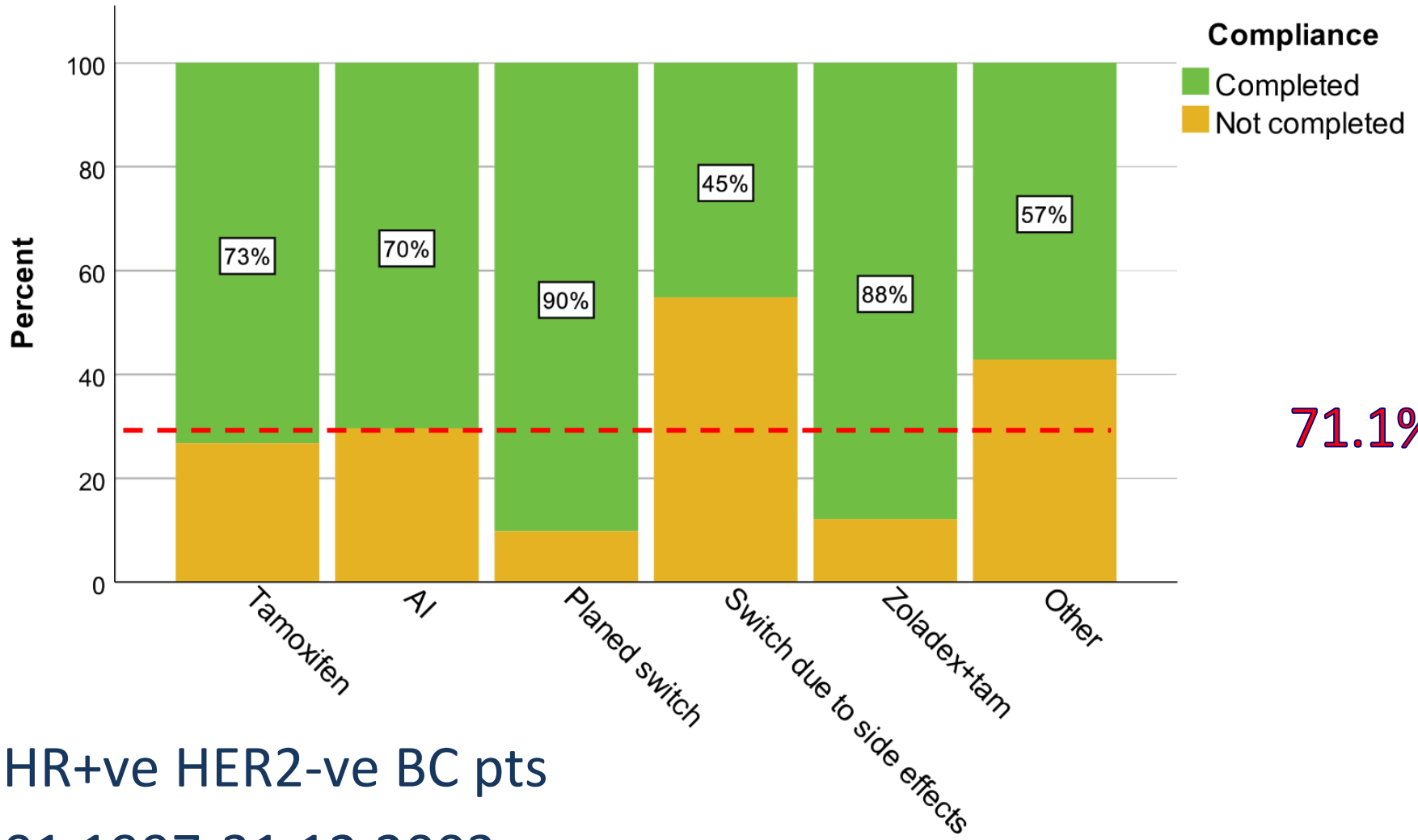
Conflicts of Interest

In the last 2 years

- Honoraria and Consultancy:

  Astra Zeneca; Daiichi-Sankyo; Eli Lilly; Gilead; Incyte; Istituto Gentili; Menarini; Novartis; Pfizer; Roche; Teva

Endocrine Therapy (lack of) Adherence



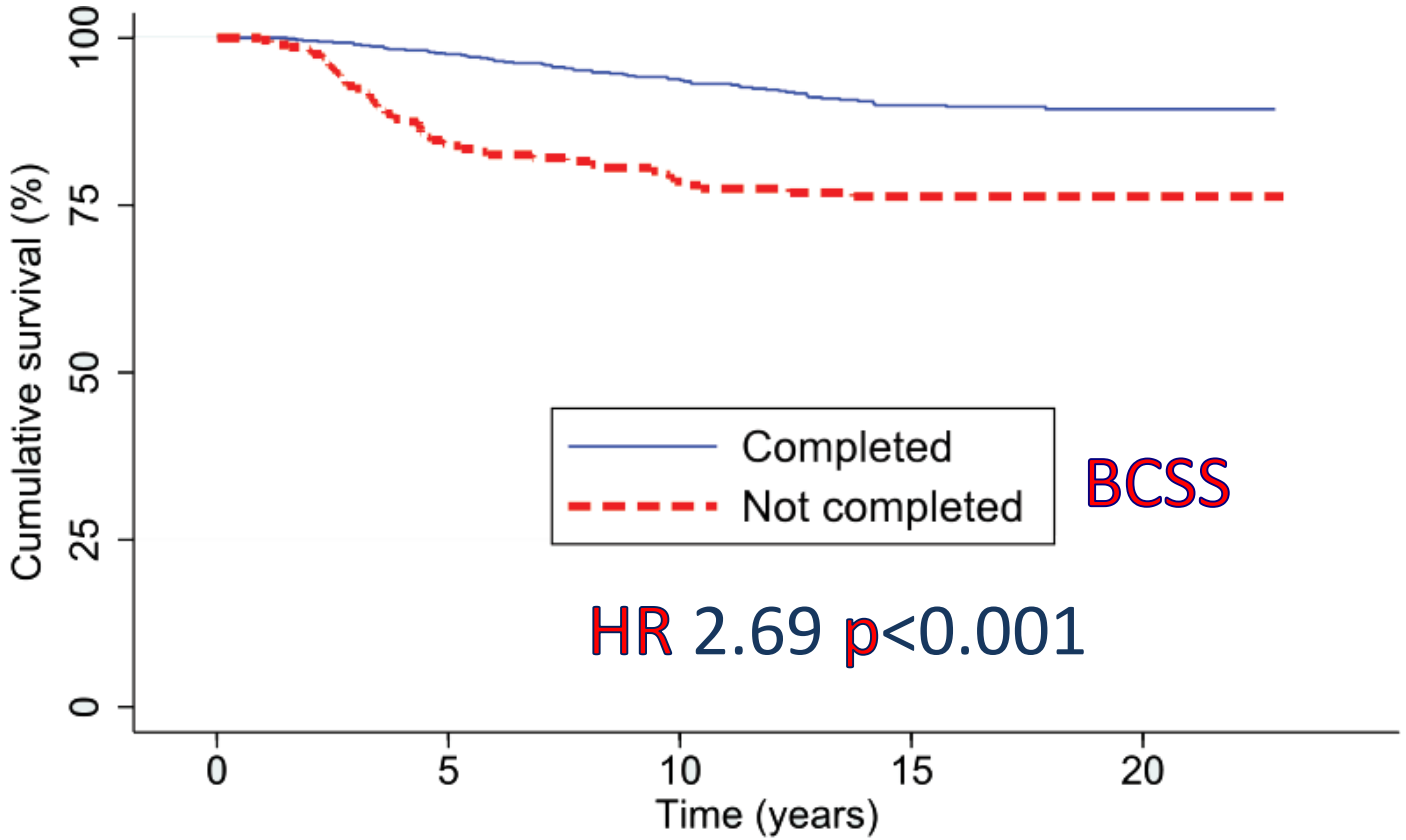
71.1%

1018 HR+ve HER2-ve BC pts

01.01.1997-31.12.2003

*Chamalidou C et al. Cancer Treat Res Commun **2023**; 100704*

Endocrine Therapy (lack of) Adherence



*Chamalidou C et al. Cancer Treat Res Commun **2023**; 100704*

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L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

TAVOLA ROTONDA INTERDISCIPLINARE

La sfida dell'aderenza nelle terapie adiuvanti

Romano Danesi

Università degli Studi di Milano

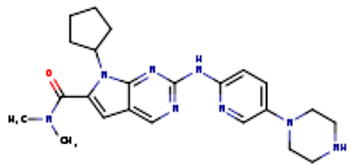
Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
MSD			X		X		
Eisai			X		X	X	
AstraZeneca	X		X		X	X	
BeiGene					X		
Janssen	X		X		X		
Novartis			X		X		
Lilly			X		X		
Incyte			X		X		
AB Science			X				
Sanofi			X		X	X	
Abbvie			X		X		
Gilead					X	X	

Pharmacodynamics (target prediction) of ribociclib and abemaciclib

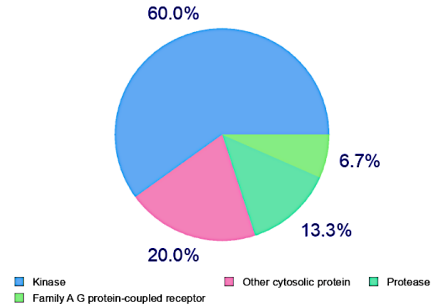
Query Molecule

Ribociclib



Target Classes

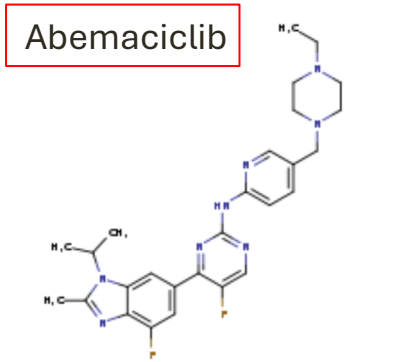
Top 15
Top 25
Top 50
All



Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*
Cyclin-dependent kinase 6	CDK6	Q00534	CHEMBL2508	Kinase	
Cyclin-dependent kinase 4	CDK4	P11802	CHEMBL331	Kinase	
Cyclin-dependent kinase 1	CDK1	P06493	CHEMBL308	Kinase	
Cyclin-dependent kinase 2	CDK2	P24941	CHEMBL301	Kinase	
Serine/threonine-protein kinase Aurora-B	AURKB	Q96GD4	CHEMBL2185	Kinase	
Serine/threonine-protein kinase Aurora-A	AURKA	O14965	CHEMBL4722	Kinase	

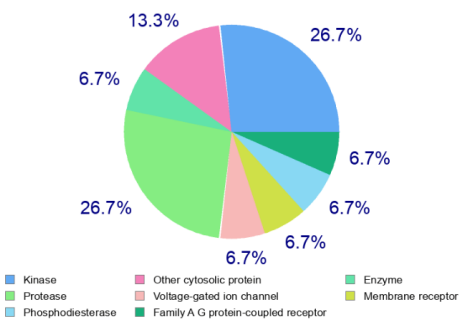
Query Molecule

Abemaciclib



Target Classes

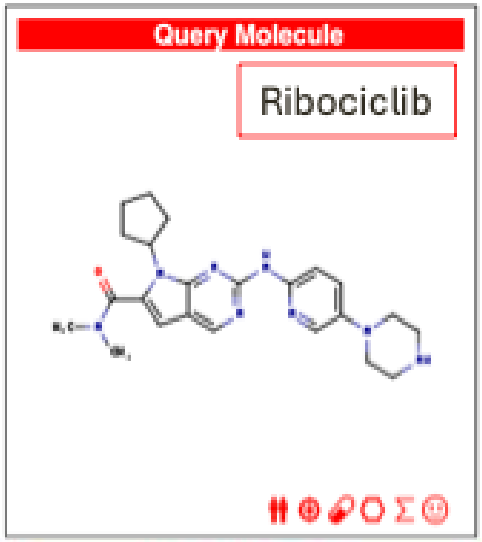
Top 15
Top 25
Top 50
All



Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*
Cyclin-dependent kinase 5/CDK5 activator 1	CDK5R1 CDK5	Q15078 Q00535	CHEMBL1907600	Kinase	
Cyclin-dependent kinase 4/cyclin D1	CCND1 CDK4	P24385 P11802	CHEMBL1907601	Kinase	
Cyclin-dependent kinase 1/cyclin B1	CDK1 CCNB1	P06493 P14635	CHEMBL1907602	Other cytosolic protein	
CDK6/cyclin D3	CCND3 CDK6	P30281 Q00534	CHEMBL2111448	Kinase	
Gamma-secretase	PSEN2 PSENEN NCSTN APH1A PSEN1 APH1B	P49810 Q9NZ42 Q92542 Q96BI3 P49768 Q8WW43	CHEMBL2094135	Protease	
Cathepsin K	CTSK	P43235	CHEMBL268	Protease	

Simulation by Molecular Modelling Group of the University of Lausanne and the SIB Swiss Institute of Bioinformatics, 2025

Pharmacokinetics of ribociclib and abemaciclib



	Pharmacokinetics
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes

	Pharmacokinetics
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No

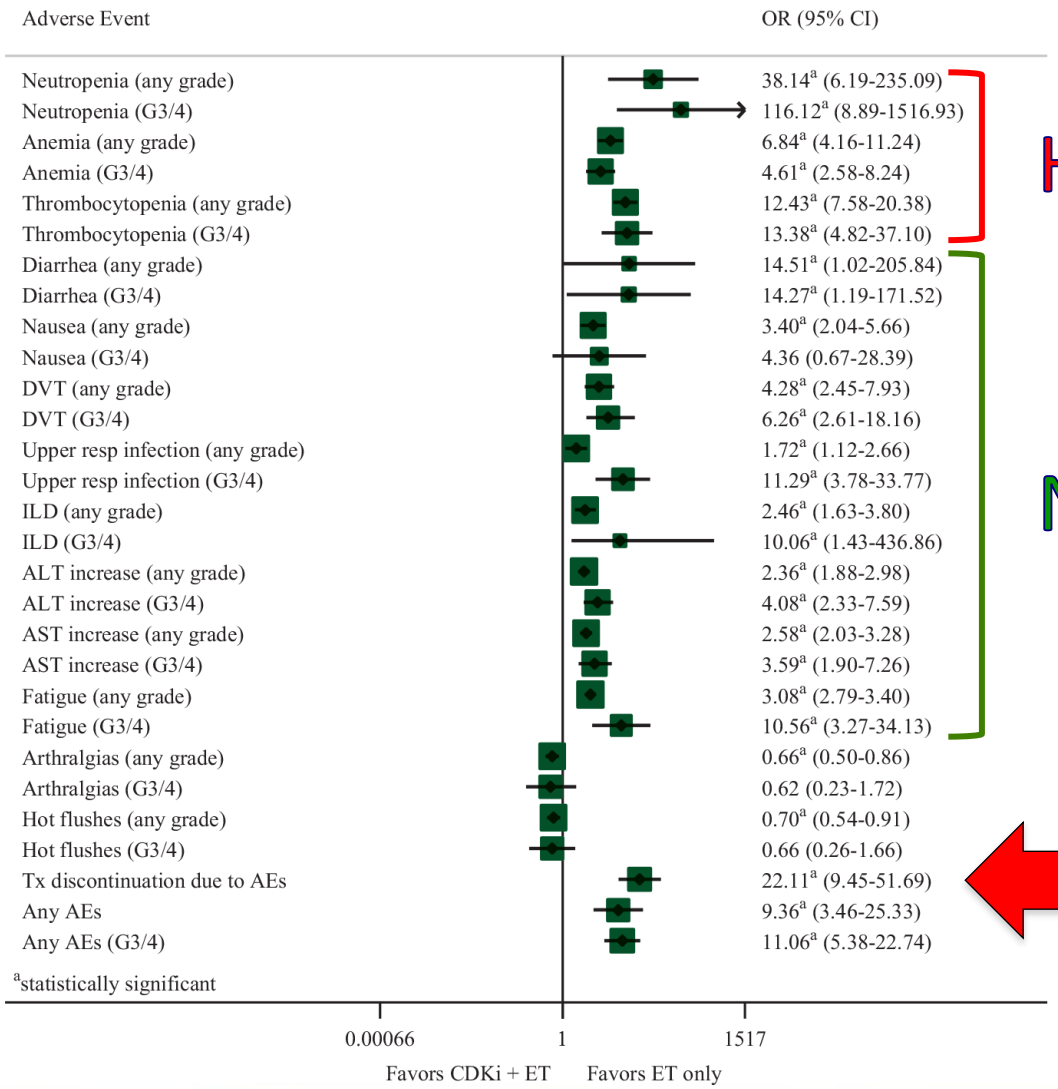
Despite the differences between ribociclib and abemaciclib as perpetrators, they are very similar as victim drugs because are extensively metabolized by CYP3A4. Therefore, considering the frequent and numerous concomitant drug treatments, the risk of DDI is the same for both drugs and potentially relevant.

Simulation by Molecular Modelling Group of the University of Lausanne and the SIB Swiss Institute of Bioinformatics, 2025, modified on the basis of current literature.

Conclusions

- CDK4/6 inhibitors ribociclib and abemaciclib have a different target engagement and metabolic profiles.
- Drug pharmacokinetics and pharmacodynamics may influence clinical efficacy, tolerability and number of DDIs.
- It should be pointed out that, in most cases, DDIs are preventable and manageable by clinical monitoring of adverse events.

CDK4/6Is AEs in the Adjuvant Setting



Hematologic

Non Hematologic

*Agostinetto E et al. ESMO Open **2021**; 6:100091*

Neutropenia

Grade	Description
1/2	**No** dose adjustment
3	Discontinue drug until toxicity not ≤G2 **No** dose adjustment
3R or FN Ribo	Discontinue drug until toxicity ≤G2 Resume drug at **lower dose**
4	Discontinue drug until toxicity ≤G2 Resume drug at **lower dose**

Abemaciclib e Ribociclib: Riassunto delle Caratteristiche del Prodotto

Gastrointestinal Toxicities: diarrhea Abema

Grade	Description
1	**No** dose adjustment
2	Discontinue drug if toxicity not ≤G1 within 24 hours **No** dose adjustment
2R	Discontinue drug until toxicity ≤G1 Resume drug at **lower dose**
3/4	Discontinue drug until toxicity ≤G1 Resume drug at **lower dose**

Abemaciclib e Ribociclib: Riassunto delle Caratteristiche del Prodotto

Gastrointestinal Toxicities: ALT/AST increase Abema

Grade	Description
1 [up to 3 x ULN]	**No** dose adjustment
2 [>3 up to 5 x ULN]	**No** dose adjustment
2R/3 [>5 up to 20 x ULN]	Discontinue drug until toxicity ≤G1 Resume drug at **lower dose**
4 [>20 x ULN]	**Discontinue** drug

Abemaciclib e Ribociclib: Riassunto delle Caratteristiche del Prodotto

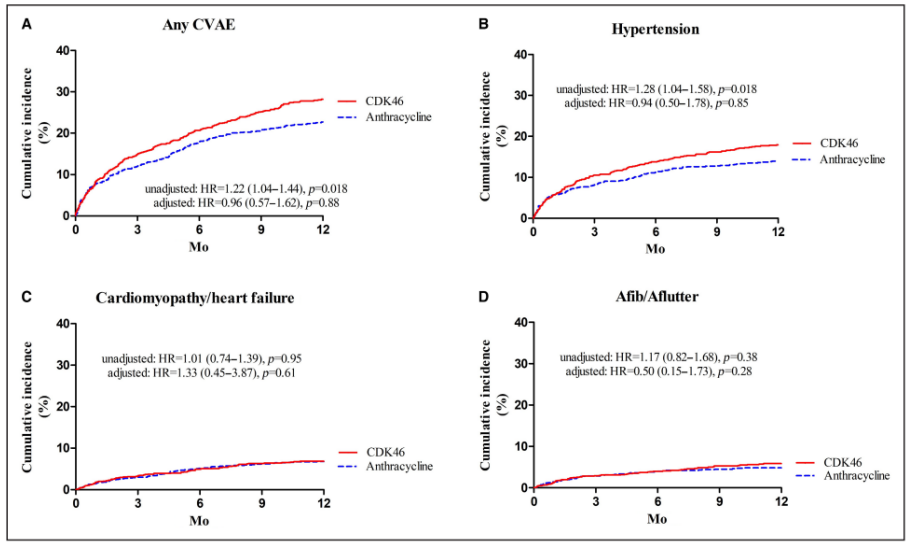
Gastrointestinal Toxicities: ALT/AST increase Ribo

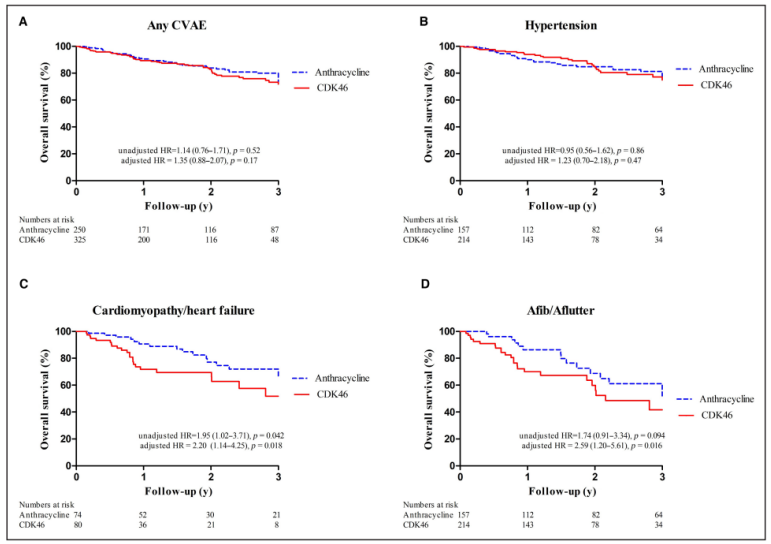
Grade	Description
1 [up to 3 x ULN]	**No** dose adjustment
2 [>3 up to 5 x ULN]	Discontinue drug until toxicity = basal level **No** dose adjustment
2R/3 [>5 up to 20 x ULN]	Discontinue drug until toxicity = basal level Resume drug at **lower dose**
3R/4 [>20 x ULN]	**Discontinue** drug

Abemaciclib e Ribociclib: Riassunto delle Caratteristiche del Prodotto

OneFlorida Data Trust, 1376 adult patients without prior CVD
who received at least 1 CDK4/6 inhibitor, without exposure to either anthracyclines or HER2i

Cardiovascular events, n (%)	CDK4/6 inhibitors, N=1376		Anthracyclines, N=1215		
	Event, n (%)	Rate (per 100 person-years)	Event, n (%)	Rate (per 100 person-years)	*P* value*
Cardiomyopathy/heart failure	80 (5.8)	7.8	74 (6.1)	7.5	0.77
Atrial fibrillation/flutter	68 (4.9)	6.5	54 (4.4)	5.4	0.55
Pericardial disease	28 (2.0)	2.6	22 (1.8)	2.2	0.68
Hypertension	214 (16)	22.7	157 (13)	17	0.056
Ischemic heart disease	48 (3.5)	4.6	29 (2.4)	2.9	0.10
Any cardiotoxicity†	325 (24)	35.9	250 (21)	28.5	0.063





Cardiotoxicities events by CDK 4/6 inhibitor, n (%)	Overall n = 1,376*	Palbociclib n= 1,049	Ribociclib n = 156	Abemaciclib n = 74	p-value
Cardiomyopathy/Heart Failure	80 (5.8%)	64 (6.1%)	9 (5.8%)	4 (5.4%)	0.89
Atrial Fibrillation/Flutter	68 (4.9%)	53 (5.1%)	7 (4.5%)	4 (5.4%)	>0.99
Pericardial	28 (2.0%)	22 (2.1%)	2 (1.3%)	2 (2.7%)	0.85
Hypertension	214 (16%)	174 (17%)	22 (14%)	6 (8.1%)	0.27
Ischemic heart disease	48 (3.5%)	35 (3.3%)	6 (3.8%)	4 (5.4%)	0.32
Any CVAE	325 (24%)	258 (25%)	34 (22%)	13 (18%)	0.54

Fradley MG, et al. J Am Heart Assoc. 2023;12:e029361