CDK4/6 INHIBITORS: DOSING, SIDE EFFECTS, MONITORING

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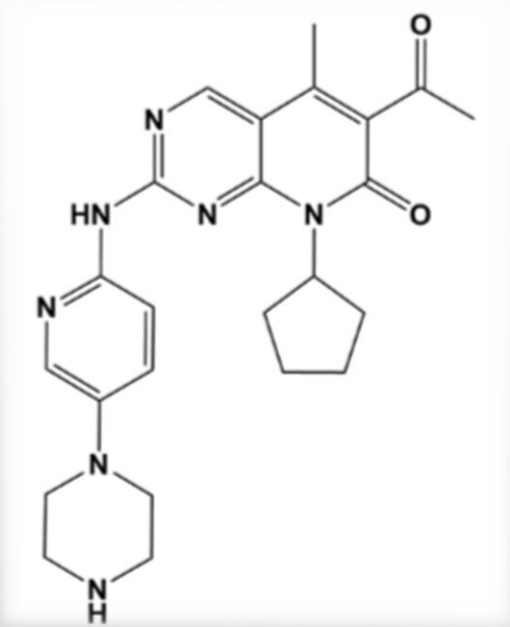
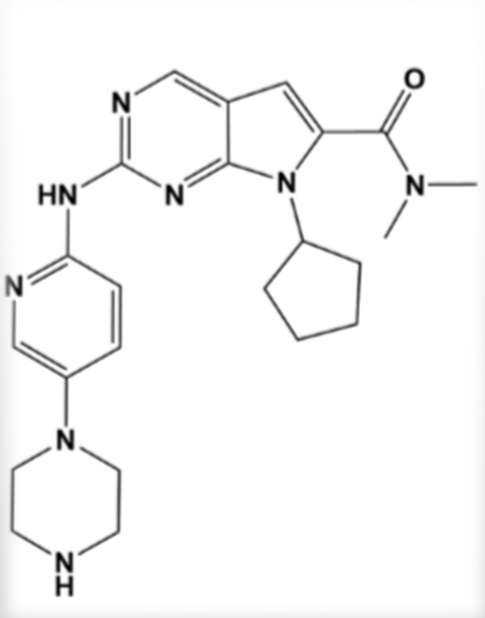
CONFLICT OF INTEREST

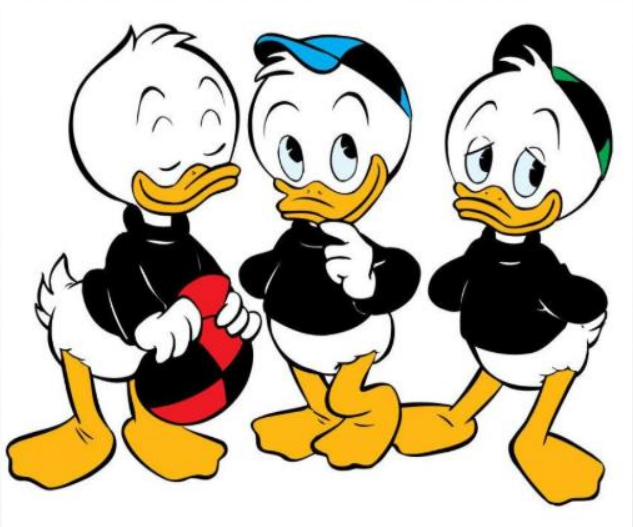
- SPEAKER, CONSULTING: LILLY, ROCHE, PFIZER, NOVARTIS, ASTRA ZENECA, DAIICHI
- TRAVEL GRANTS: ROCHE; PFIZER; ASTRO PHARMA, PIERRE FABRE

PALBOCICLIB

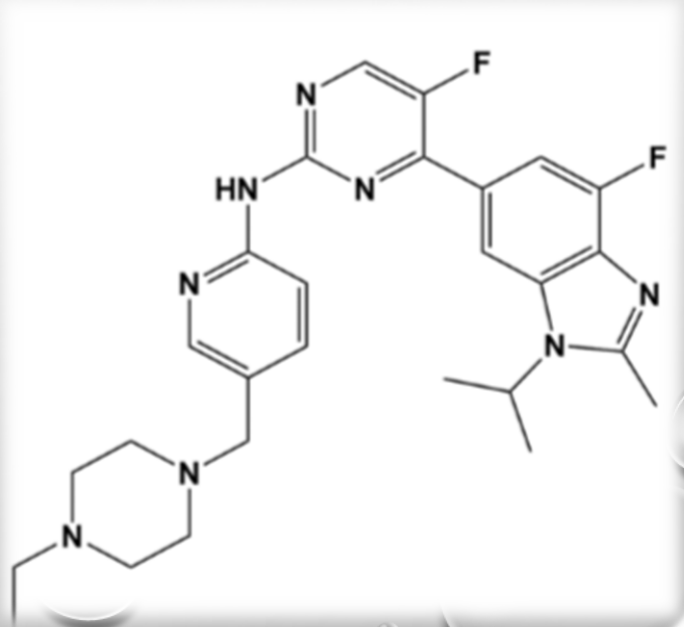


RIBOCICLIB





ABEMACICLIB



INTAKE

	PALBOCICLIB	RIBOCICLIB	ABEMACICLIB
How often	💊 – 0 – 0	💊💊💊 – 0 – 0	💊 – 0 – 💊
How	With food		?
When	?	Morning	Every 12 h
Schedule	21on/7 off	21 on/7 off	continuous

DOSE

	PALBOCICLIB	RIBOCICLIB	ABEMACICLIB
Start dose	125 mg x 1	200 mg x 3	150 mg x 2
Reduction Step 1	100 mg x 1	200 mg x 2	100 mg x 2
Reduction Step 2	75 mg x 1	200 mg x 1	50 mg x 2

METABOLISM

	PALBOCICLIB	RIBOCICLIB	ABEMACICLIB
Where	Leber		
Primary Enzyme	CYP3A		
Interactions	Avoid strong **CYP3A-Inhibitors** or reduce dose		
	Avoid moderate to strong **CYP3A-Inducers**		

CYP3A – INTERAKTIONS

STRONG INHIBITORS

- Antibiotics (Clarithromycin!)
- Antifungals (Itra, Ketoconazol, Voriconazol)

STRONG INDUCERS

- Rimfampin-class
- Anticonvulsives (Carbamazepin!)

CYP3A SUBTRATES

- Fentanyl!
- Midazolam

PALBOCICLIB TOXICITY

	>30% all Grades	>20% G 3/4
Monotherapy	Leukopenia (100%), neutropenia (92%), thrombocytopenia (76%), anemia (70%), lymphopenia (65%)	Neutropenia (54%), leukopenia (51%), lymphopenia (30%)
PALOMA-2	All causality AEs: Neutropenia (80%), leukopenia (39%), fatigue (37%), nausea (35%), arthralgia (33%), alopecia (33%)	Neutropenia (66%), leukopenia (25%)
PALOMA-3	All causality AEs: Neutropenia (81%), leukopenia (50%), infections (42%), fatigue (39%), nausea (32%)	Neutropenia (65%), leukopenia (28%)

RIBOCICLIB TOXICITY

	>30% all Grades	>20% G 3/4
Monotherapy	TEAEs: Neutropenia (46%), fatigue (45%), leukopenia (43%), nausea (42%), thrombocytopenia (30%)	Neutropenia (27%)
MONALEESA-2	All-causality AEs: neutropenia (74%), nausea (52%), infections (50%), fatigue (37%), diarrhea (35%), alopecia (33%), leukopenia (33%)	Neutropenia (59%), leukopenia (21%)

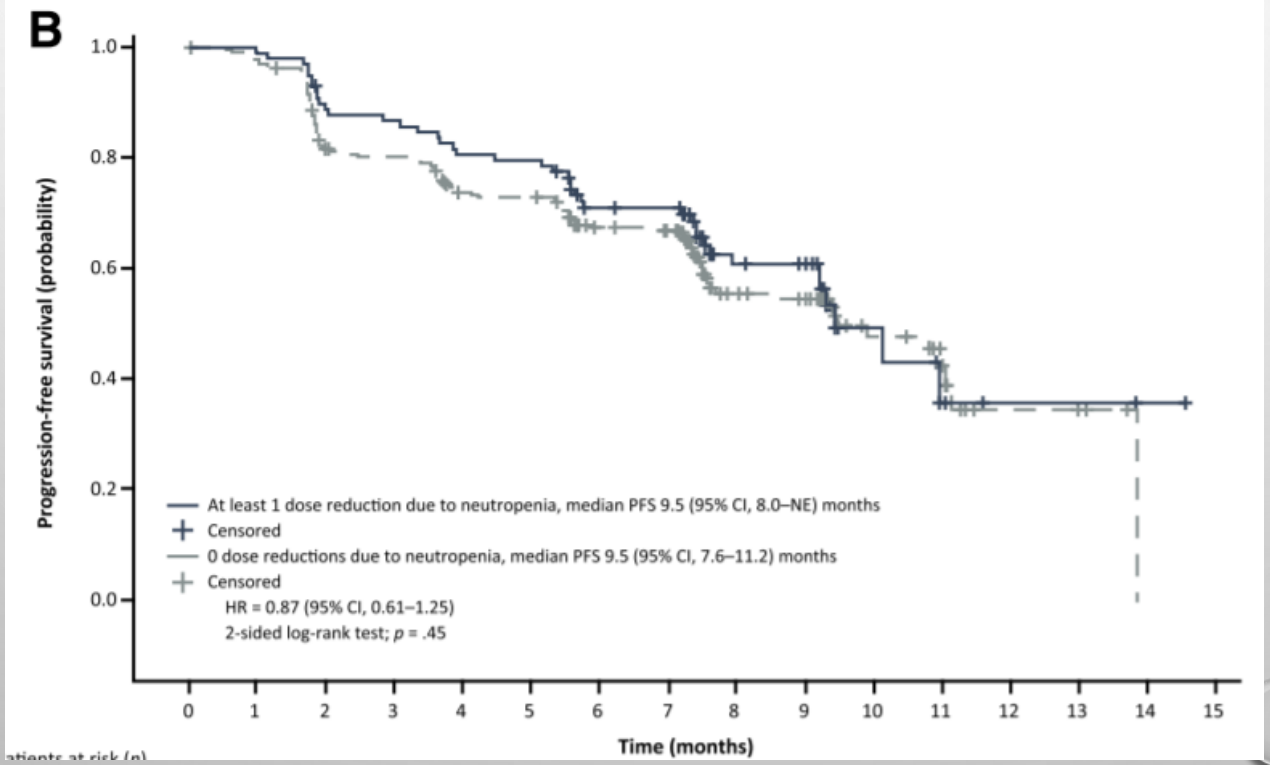
ABEMACICLIB TOXICITY

	>30% all Grades	>20% G 3/4
Monotherapy	TEAEs: Leukopenia (91%), diarrhea (90%), neutropenia (88%), anemia (69%), fatigue (65%), nausea (64%), decreased appetite (46%), thrombocytopenia (41%), abdominal pain (39%), vomiting (35%)	Leukopenia (28%), neutropenia (27%), diarrhea (20%)
MONARCH-2	TEAEs: Diarrhea (86%), neutropenia (46%), nausea (45%), fatigue (40%), abdominal pain (35%)	Neutropenia (23.6%),
MONARCH-3	TEAEs: Diarrhea (81.3%), neutropenia (41.3%), fatigue (40.1%), infections and infestations (39.1%), nausea (38.5%)	Neutropenia (21.1%)

DOSE REDUCTION AND EFFICACY

PALBOCICLIB

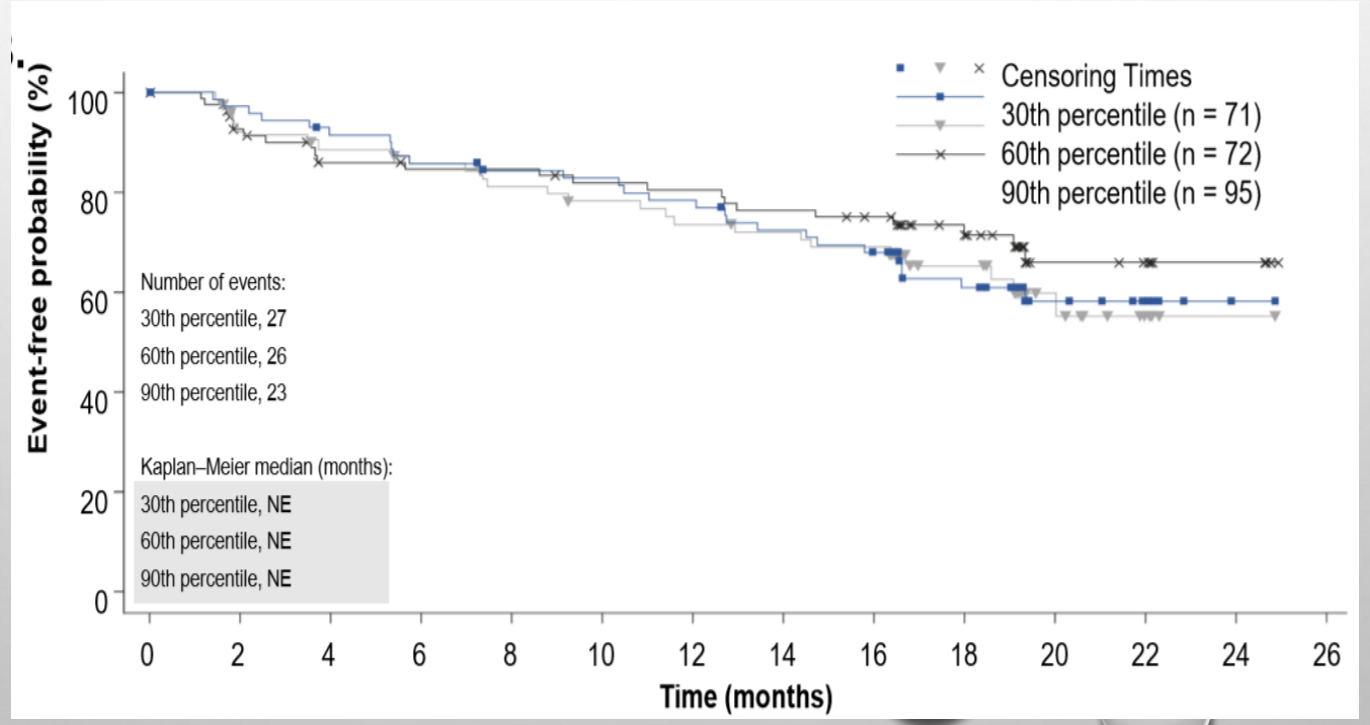
- PALOMA-3: n=345, FUL + Palbociclib
- Dose reduction in 34% of patients



Verma Oncology 2016

RIBOCICLIB

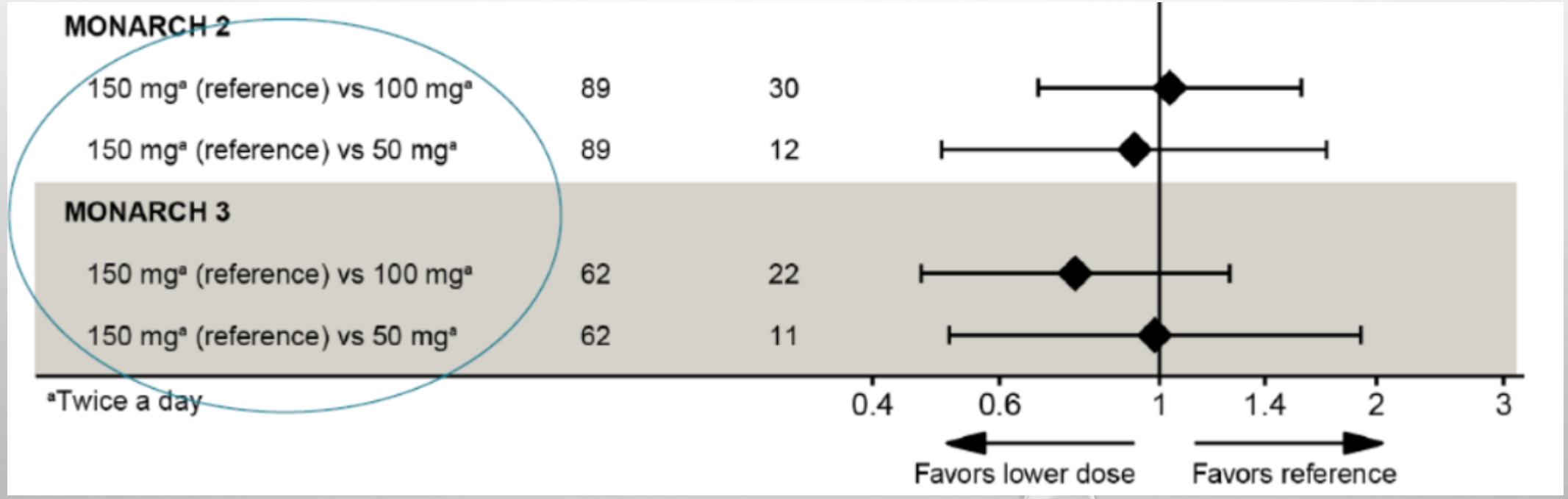
- MONALEESA-3 (1stL): n=238, FUL + Ribociclib
- Dose reduction in 48,7% of patients



Beck SABCS 2018

ABEMACICLIB

- MONARCH-2: n=446, FUL +/-Abemaciclib
- Dose reduction in 43% of patients



Sledge JCO 2017

MANAGEMENT OF TOXICITIES

MANAGEMENT OF TOXICITIES

1) NEUTROPENIA

CDK 4/6 INHIBITORS UND NEUTROPENIA

- CDK6 → proliferation of haemotopoetic stem cells
- CDK6 inhibition: hematologic quiescence
- No apoptosis observed under clinically relevant doses
- Duration until onset of neutropenia : ~14 days
- Recovery usually within 7 days → treatment pause
- Febrile neutropenias rare

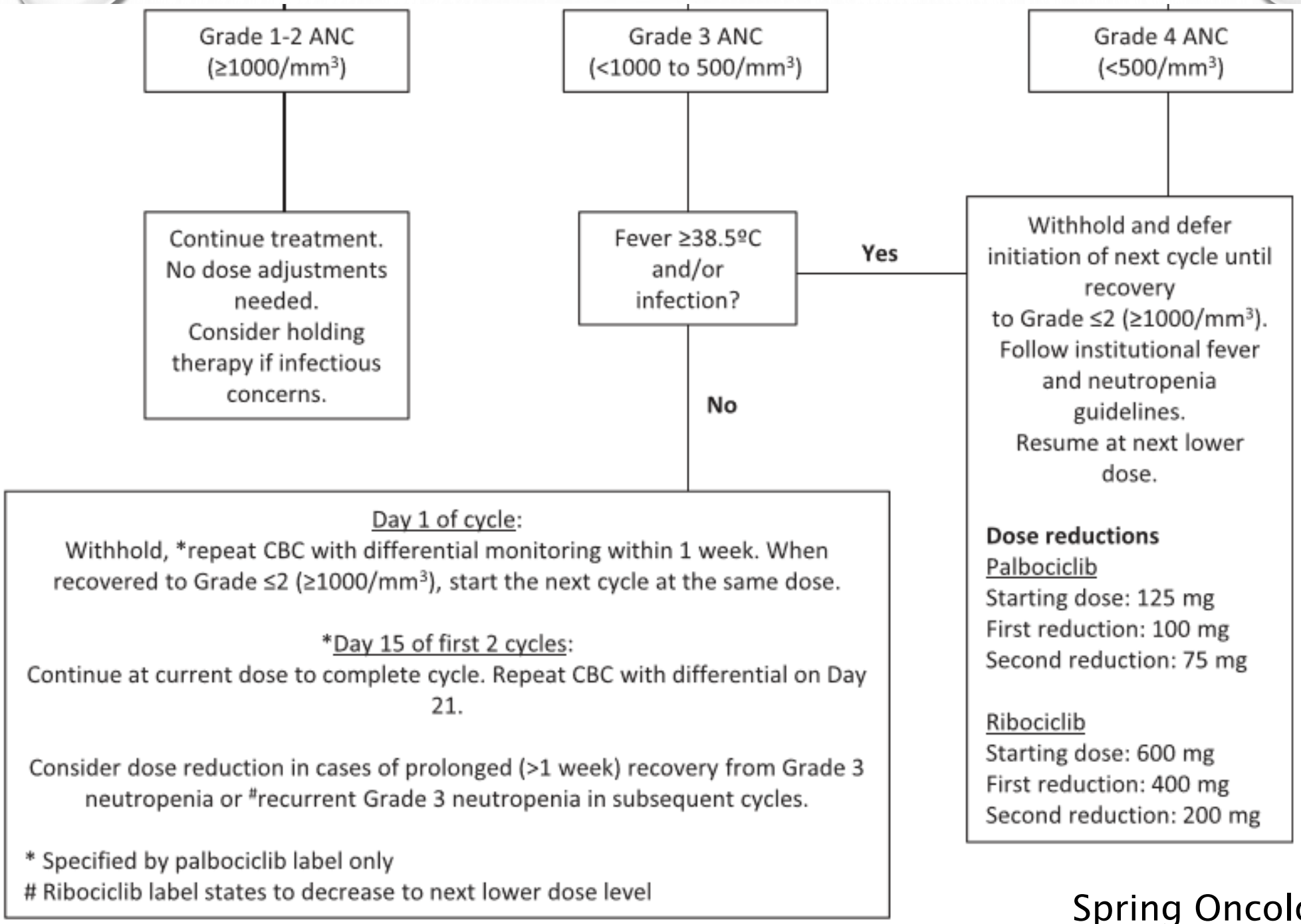
NEUTROPENIA – DOSE MODIFICATIONS

CDK4/6 inhibitor	Grade 1 or 2 (ANC 1000/mm³–<LLN)	Grade 3 (ANC 500–<10	Grade 3 (ANC 500–<1000/mm³) febrile neutropenia*	Grade 4 (ANC < 500/mm³)
Ribociclib				
Perform CBC before initiating treatment with ribociclib; monitor CBC every 2 weeks for the first two cycles, at the beginning each subsequent four cycles, clinically indicated	nt is d	Dose inter resume if toxic until ne ≤2; el; rruption lib at the	Dose interruption until recovery of neutropenia to grade ≤2; resume ribociclib at the next lower dose level	D e t
Palbociclib				
CBC should be moni the start of palbociclib at the beginning of ea as well as on irst 2 cycles, and dicated	No dose adjustment is required	palbociclib, repeat n 1 week; when ≤2, start the next cycle at cycles: continue palbociclib at to complete cycle; repeat CBC consider dose reduction in cases of ed (>1 week) recovery from grade 3 penia or recurrent grade 3 neutropeni ubsequent cycles	Withhold pa until reco ≤2 (≥1 resum dos	palbociclib ecovery to grade resume at next wer dose
b				
CBC prior to starting ab aciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated	No modifica required	Suspend dose until toxicity resolves to ≤grade 2; dose reduction is not required	ct mendation in the cribing information	Suspend dose until toxicity resolves to ≤grade 2; resume at *next lower dose*

BC every 2 weeks, then at the beginning of each cycle, then acoording to clinical course

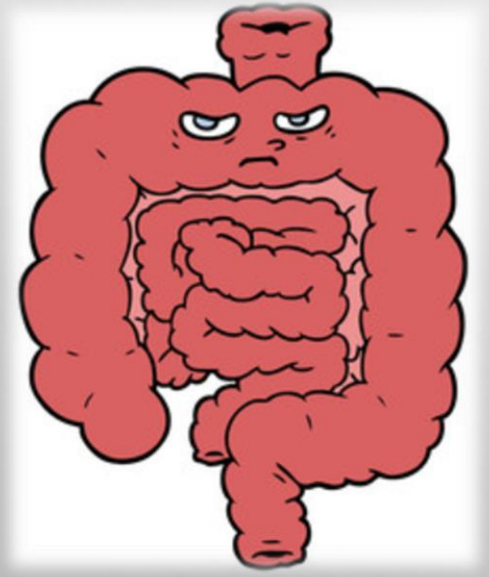
Grade 3 neutropenia without fever:
1st time: wait until G2, continue on same dose level
2nd time: wait until G2, reduce dose
3rd time: wait until G2, reduce dose again
4th time: stop treatment

Grade 4 neutropenia oder grade 3 with fever:
1st time: wait until recovery and reduce dose
2nd time: wait until recovery and reduce dose
3rd time: stop treatment



Spring Oncologist 2017

MANAGEMENT OF TOXICITIES

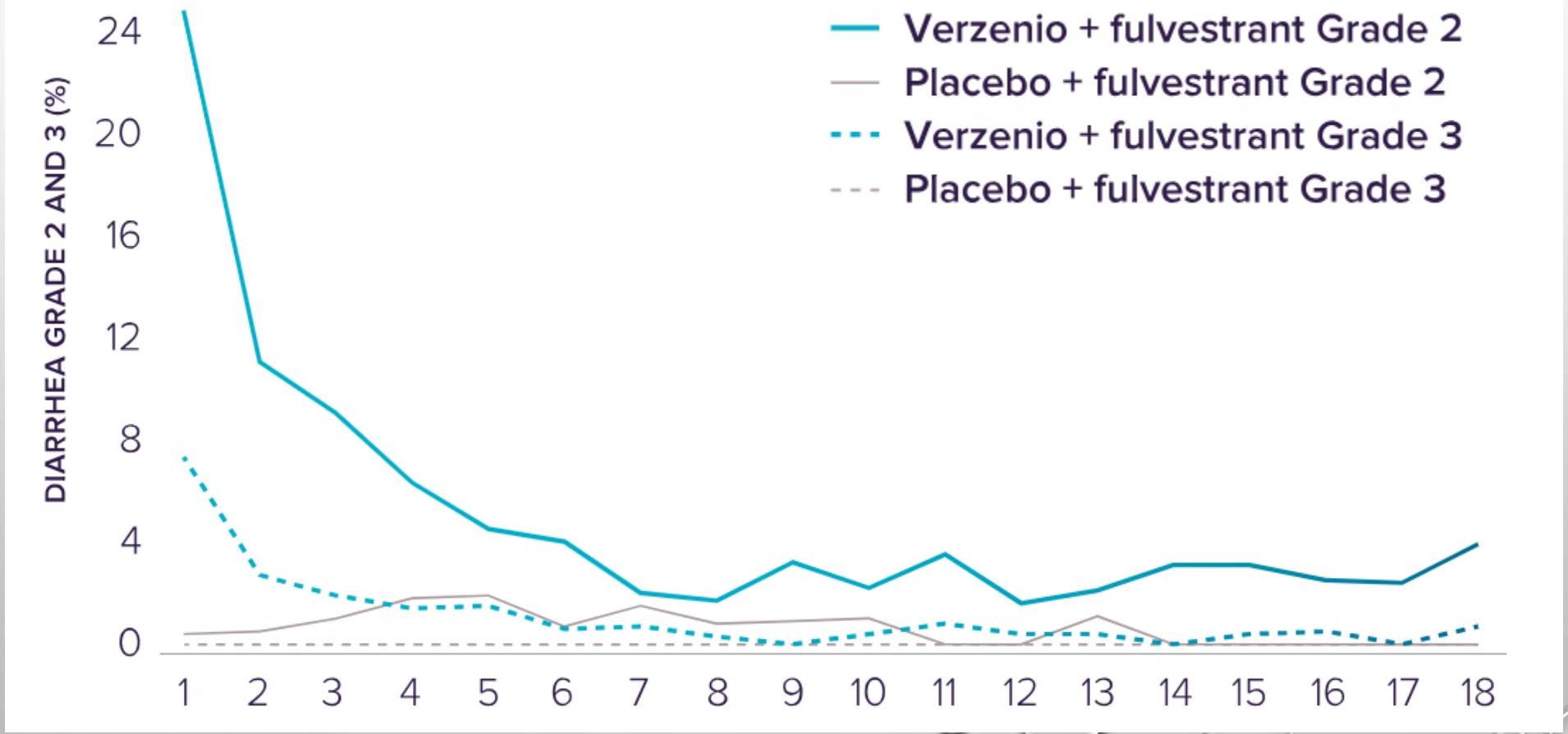


2) GI SIDE EFFECTS

ABEMACICLIB & DIARRHEA

- Incidence ~85%; grade 3: 9–13%
- Dose reductions ~20%
- Onset after a median of 6–8 days
- Median duration: G2 → 9–12 days; G3 → 6–8 days
- Dehydration!
- Loperamide if necessary
- Dose reductions if G3 or persistent G2 diarrhea

COURSE OF DIARRHEA



MANAGEMENT OF TOXICITIES

3) PROLONGED QT-TIME (RIBOCICLIB)

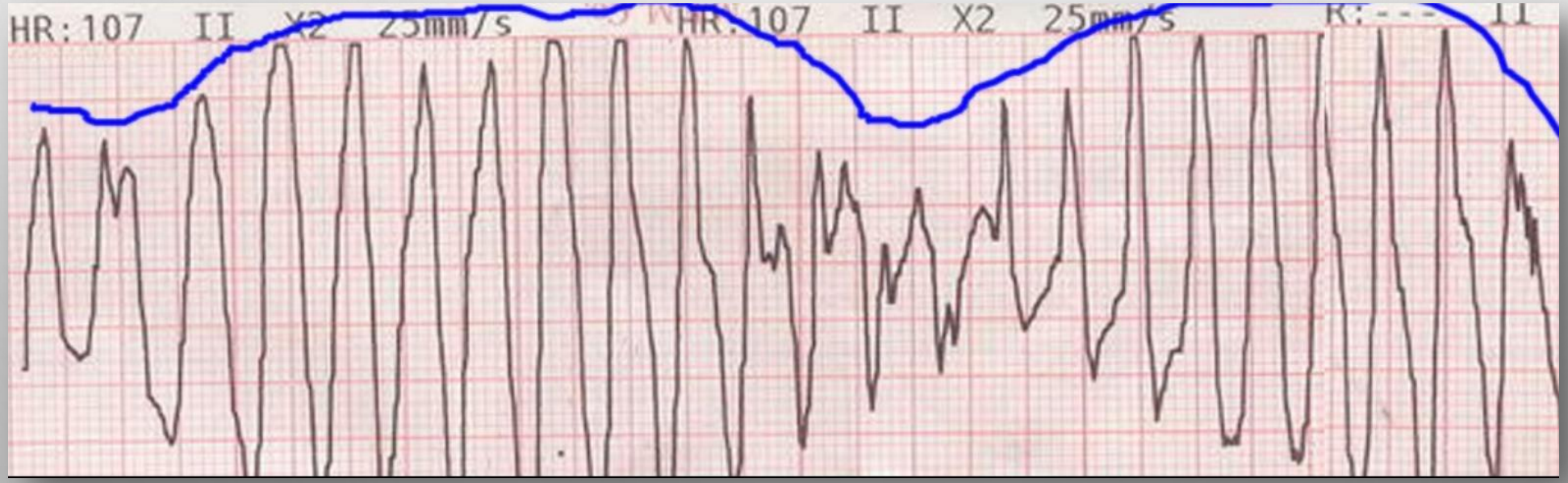
PROLONGED QT-TIME IN MONALEESA-2

- 3,3% (11/334) in experimental arm (Ribociclib + Letrozol)
- ≥ 60 msec. above baseline: 2,7%
- 0,3% (1/330) in letrozole arm
- Dose dependent
- Median time to onset: 15 days
- Reversible if dose reduced or treatment paused
- No documented Torsade-de-Pointes

QT-TIME

Prolonged QT-time = delayed repolarisation

Increases risk of ventricular extra beats during vulnerable phase of repolarisation → risk of Torsade-de-Pointes



PROLONGED QT-TIME CAUSED BY…

- Drugs (in particular class 1a or class 3-antiarrhythmics)
- Electrical accidents
- Congenital ’Long QT-Syndrome’
- Bradycardia (physiological prolongation of QT time)
- Elektrolyte disorders (Hypomagnesemia oder Hypokalemia)
- Cardiac insufficiency
- Cardiac hypertrophy
- Hypoxaemia

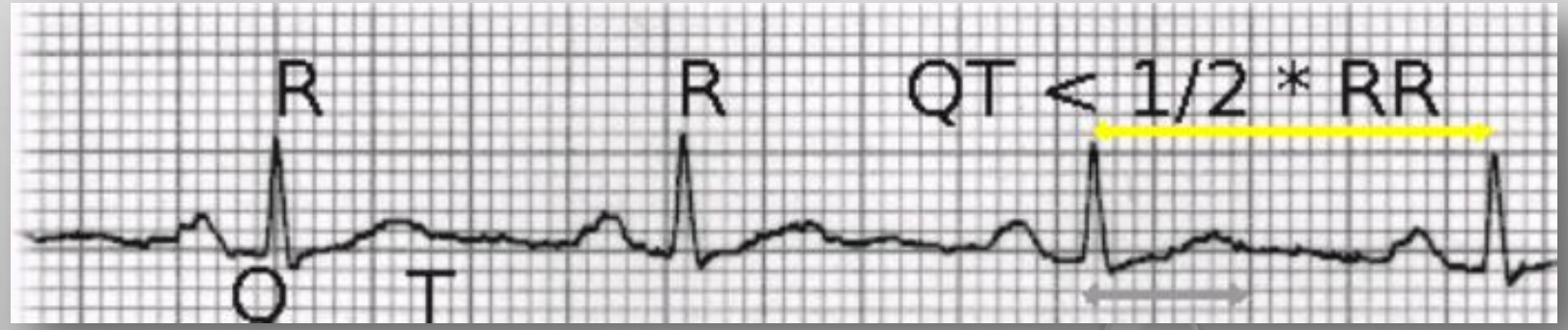
MEASUREMENT OF QT TIME?

Start of QRS-complex until end of T-wave

Normal: < ~400 ms

BUT: varies with age, gender and heart rate

Heart rate 60-100 and QT > half of RR-interval → QT-time prolonged



CORRECTED QT–TIME(QTc)

QTc Bazett:[1]

$$QTc = \frac{QT}{\sqrt{RR}}$$

QTc Fridericia:[2]

$$QTc = \frac{QT}{\sqrt[3]{RR}}$$

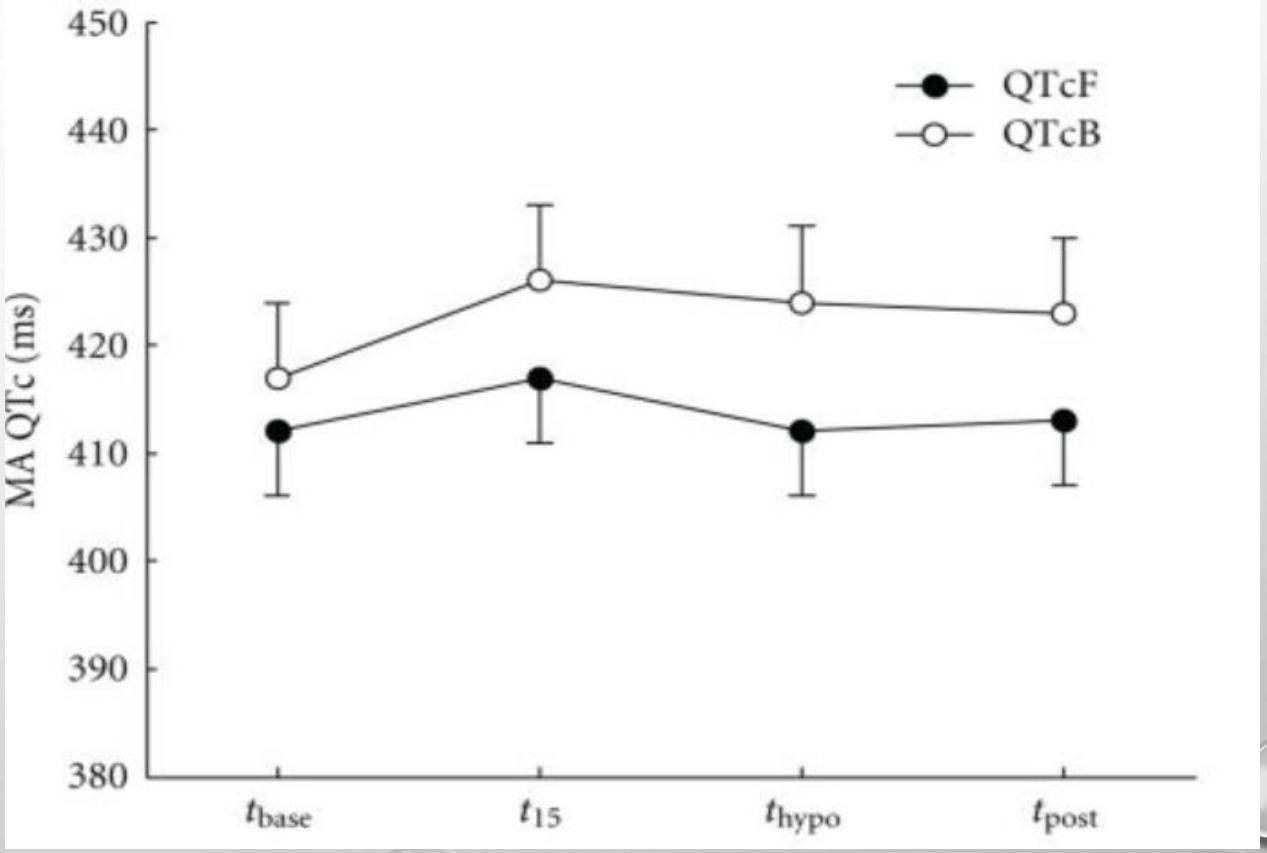
QTcF

QTc Hodges:[3]

$$QTc = QT + 0.00175 \times (HR - 60)$$

QTc Framingham:[4]

$$QTc = QT + 0.154 \times (1 - RR)$$



QTcF – MONITORING

ECG monitoring:

- Start of treatment
- Cycle 1 / day 14
- Cycle 2 / day 1
- If QTcF ↑ - repeat regularly

QTC–PROLONGATION: MANAGEMENT

Dose modifications and management for QTc prolongation	
ECGs with QTcF >480 msec	Interrupt ribociclib treatment If QTcF prolongation resolves to <481 ms, resume treatment at the same dose level If QTcF ⩾481 ms recurs, interrupt dose until QTcF resolves to <481 ms then resume ribociclib at next lower dose level
ECGs with QTcF >500 msec	Interrupt ribociclib treatment if QTcF greater than 500 ms on at least two separate ECGs (within the same visit) If QTcF prolongation resolves to <481 msec, resume treatment at the next lower dose level Permanently discontinue ribociclib if QTcF interval prolongation is either greater than 500 ms or greater than 60 ms change from baseline and associated with any of the following: *Torsades de Pointes*, polymorphic ventricular tachycardia, unexplained syncope, or signs/symptoms of serious arrhythmia

MANAGEMENT OF TOXICITIES

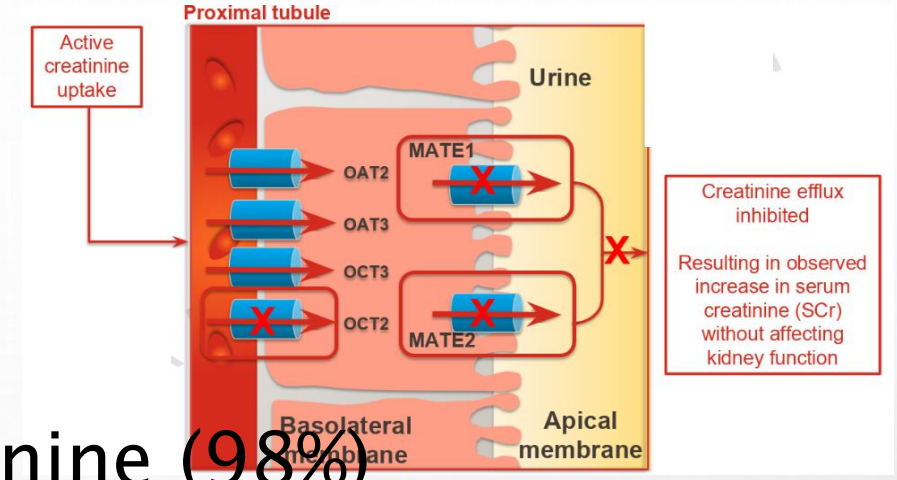
4) LAB PARAMETERS

ELEVATED TRANSAMINASES

- G3 <10 % (all CDK4/6 inhibitors)

	Grade 1 (– 3xULN)	Grade 2 (3–5 xULN)	Grade 3 (5–20 xULN)	Grade 4 (> 20 xULN)
Elevated transaminases if bilirubin < 2 x ULN	No change	1st time: Pause until normal, continue at same dose level 2nd time: Mal: Pause until normal, then reduce dose	1st time: Mal: Pause until normal, then reduce dose 2nd time: Stop	Stop
Elevated bili	Stop CDK 4/6 inhibitor			

ABEMACICLIB: ELEVATED CREATININE



- Reversible, slight elevation of creatinine (98%)
- Inhibition of creatinine transporter
- NO toxicity, no correlation with renal function (GFR)
- Assess renal function by urea level (or pause Abemaciclib before applying contrast agent)

THANK YOU!