Serum thymidine kinase activity in patients with HR-positive/HER2-negative advanced breast cancer treated with ribociclib plus letrozole: Results from the prospective BioltaLEE trial

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Luca Malorni

SOS Ricerca Traslazionale
SOC Oncologia
Ospedale di Prato
Azienda USL Toscana Centro

Disclosures

- Research support: Pfizer, Novartis
- Advisory role: Pfizer, Novartis, Lilly, Roche, Menarini Stemline
- Travel arrangements: Celgene, Menarini Stemline

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Original Research

Serum thymidine kinase activity in patients with HR-positive/HER2-negative advanced breast cancer treated with ribociclib plus letrozole: Results from the prospective BioItaLEE trial

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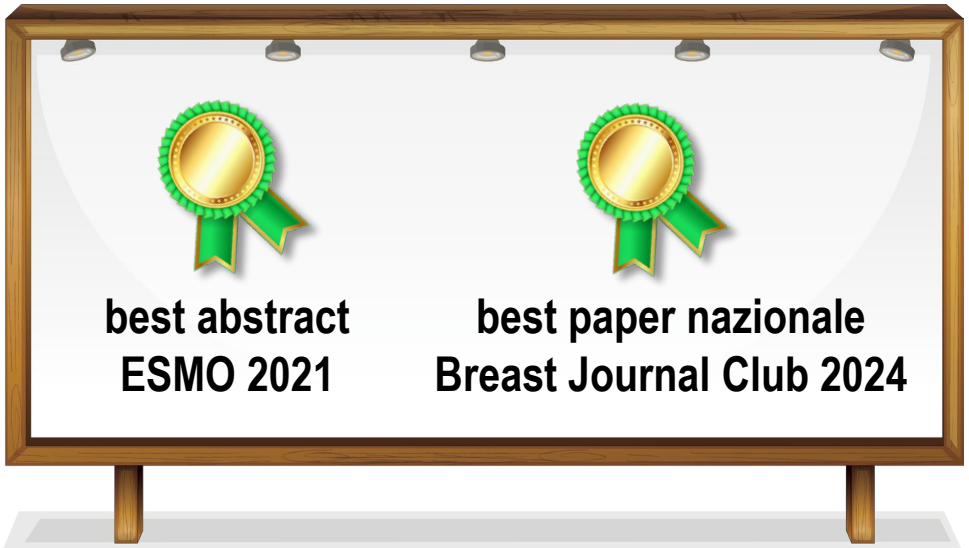
AWARDS:



MONALEESA
Mammary ONcology: Assessment of LEE011's Efficacy and SAfety

BioItaLEE
BIOLOGICAL ITALIAN STUDY WITH RIBOCICLIB IN 1L POSTMENOPAUSAL WOMEN WITH ABC

Monaleesa-2	January 2014- March 2015
Monaleesa-3	June 2015- June 2016
Monaleesa-7	December 2014- August 2016

BioItaLee- Study Design

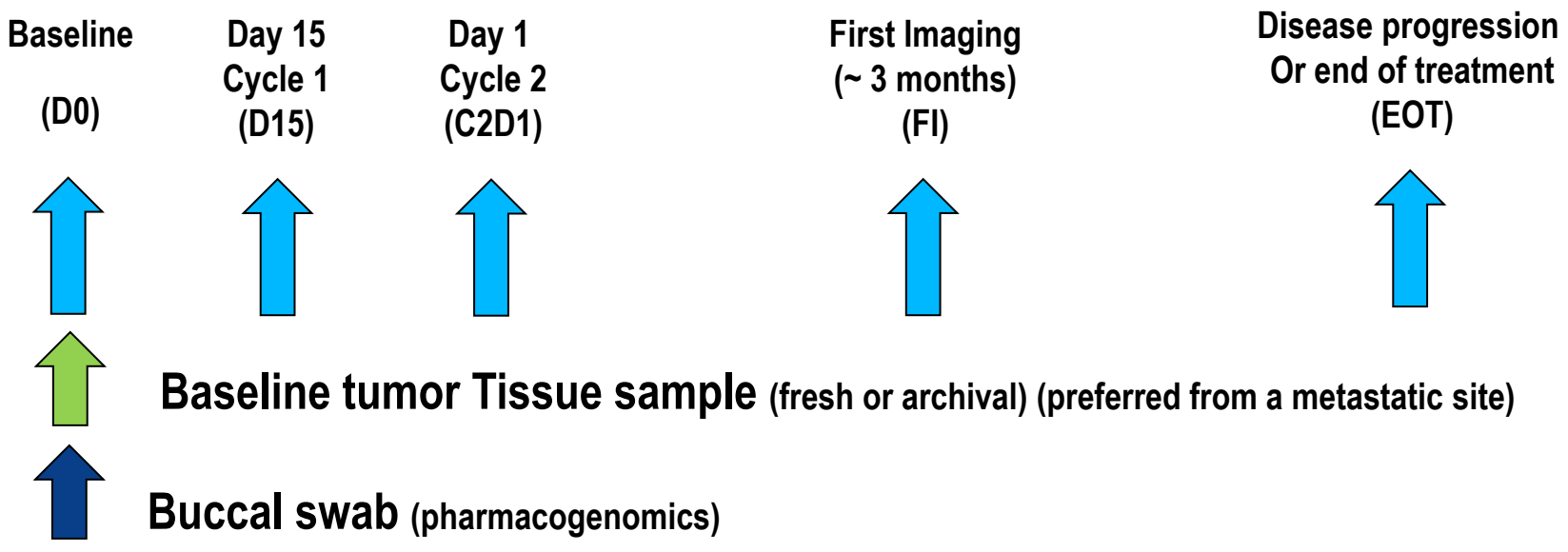
BioItaLEE
BIOLOGICAL ITALIAN STUDY WITH RIBOCICLIB IN 1L POSTMENOPAUSAL WOMEN WITH ABC

N=287

- Postmenopausal women with HR+, HER2– aBC (locoregionally recurrent not amenable to surgery or metastatic)
- No prior systemic hormonal therapy or chemotherapy for aBC
- TFI >12 months*
- Patients willing to undergo blood and tumor sample collection at baseline and at a scheduled timeframe

Enrollement from 02 February to 28 November 2018
Across 47 Italian centers

First-line ribociclib
(600 mg PO; 3 weeks on/1 week off)
+ letrozole (2.5 mg/d PO)



Liquid biopsy for:

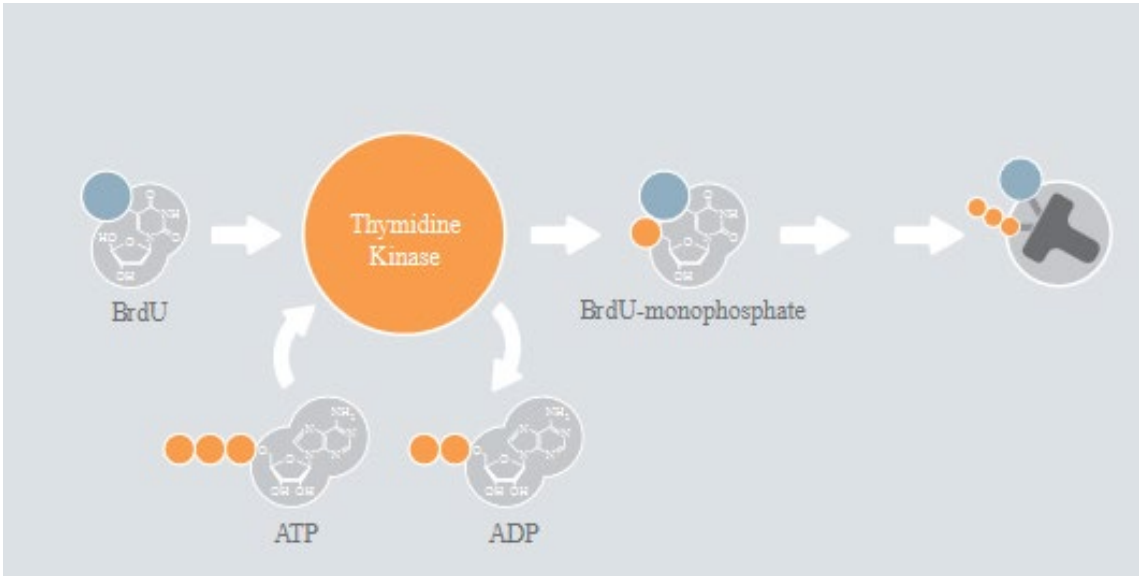
- ctDNA analysis
- Serum thymidine kinase activity

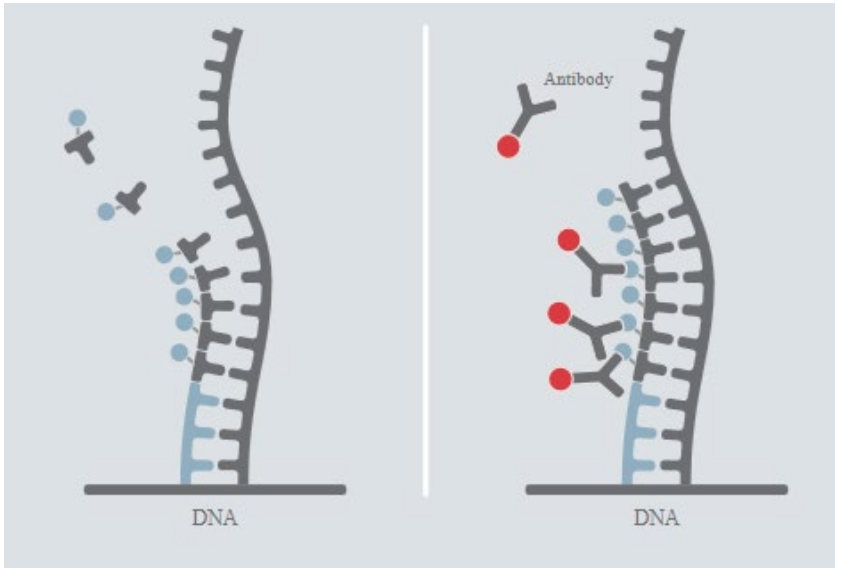
THYMIDINE KINASE ACTIVITY

- TK1 is a cell cycle dependent enzyme playing a critical role in cell proliferation
- TK1 activity rapidly increases after the G1-S transition and then declines
- Cancer cells can secrete pathological levels of TK1 detectable in blood

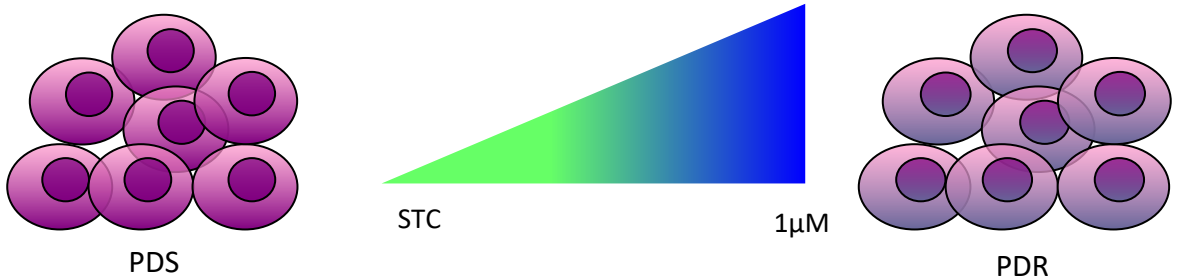
"Liquid Ki67"

The ELISA based DiviTum™ assay (Biovica International, Uppsala, Sweden) determines the enzymatic activity of TK1 in blood serum/plasma or cell cultures.



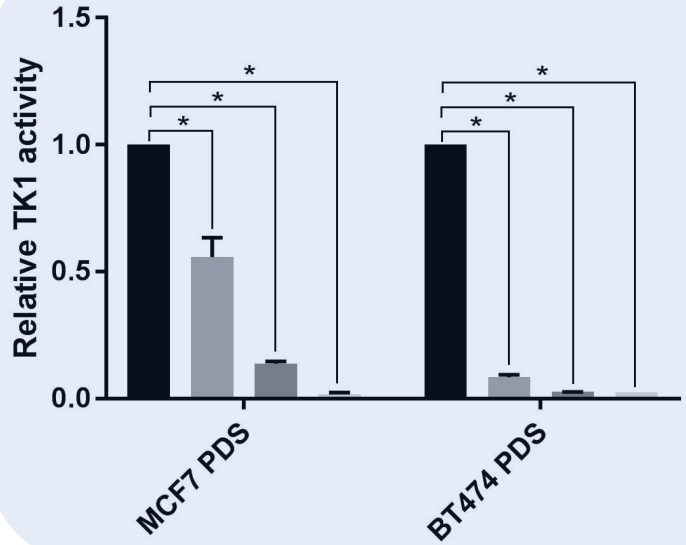


TK1 ACTIVITY AND CDK4/6 INHIBITION

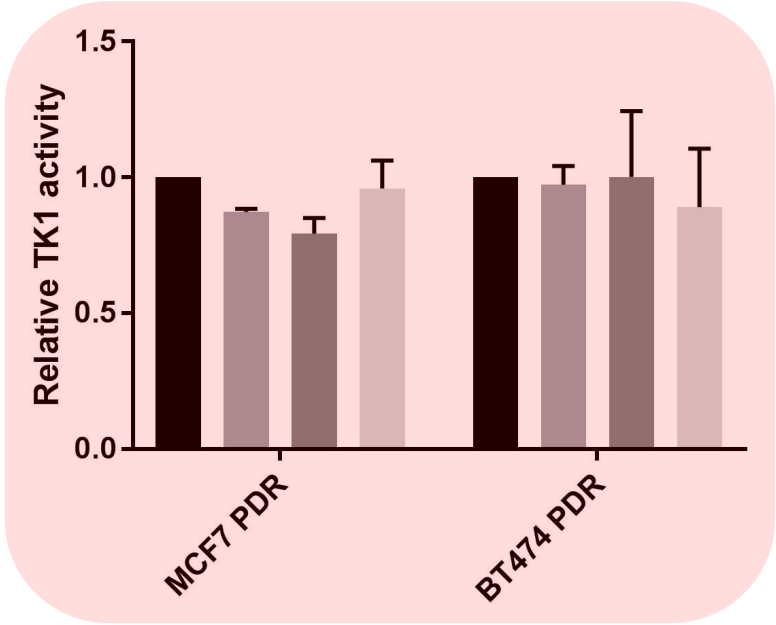


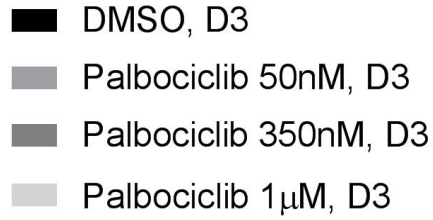
TK1 activity (assessed at day 3)

Palbociclib sensitive



Palbociclib resistant

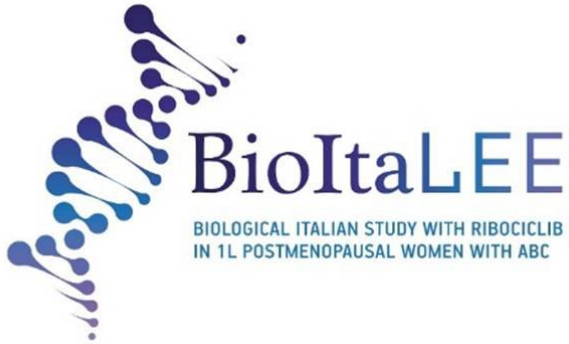




TK1 is strongly modulated by treatment in sensitive cells but not in resistant cells

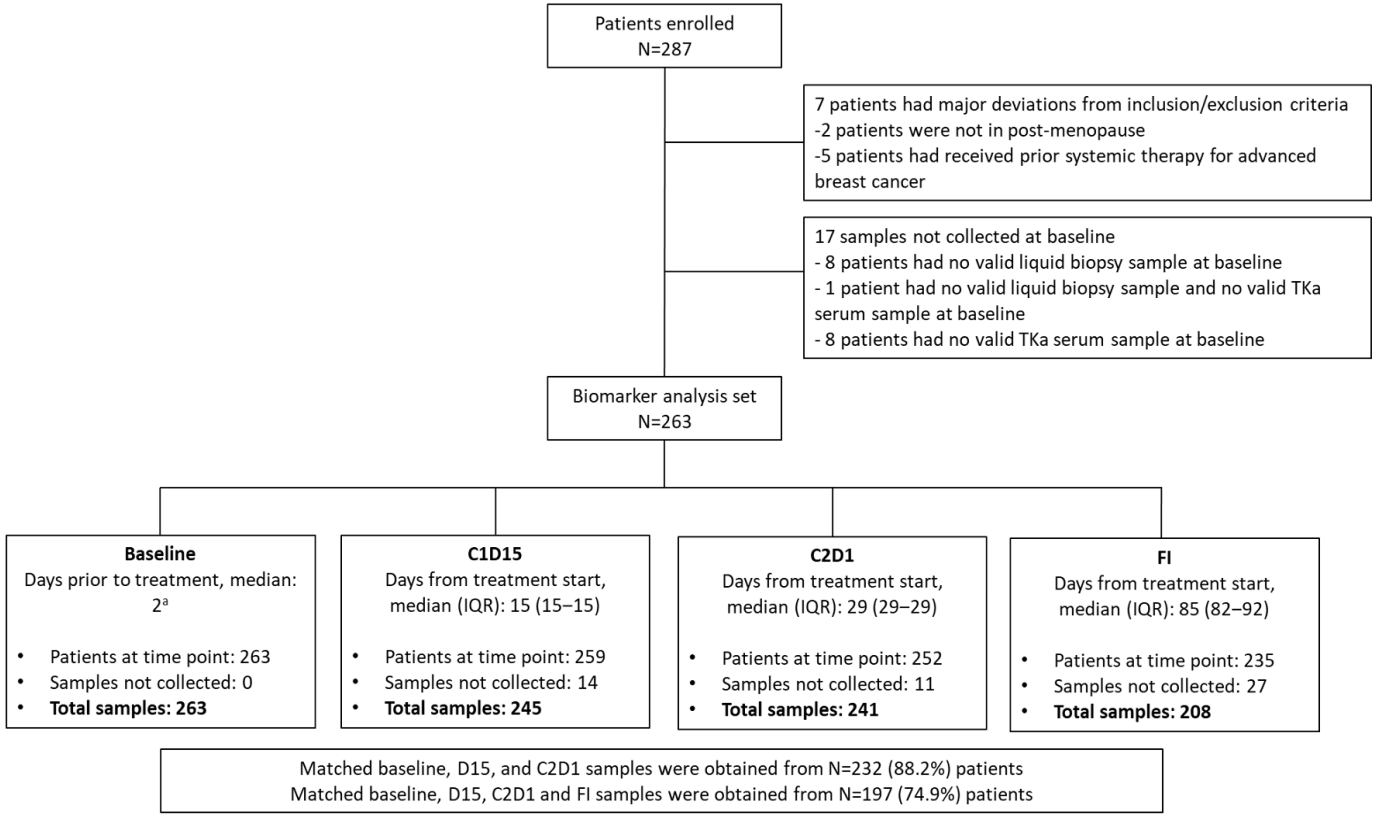
McCartney et al, CCR 2020

BioItaLee- Objectives and endpoints



- The primary objective of the BioItaLEE study was to identify ctDNA alterations, their changes during treatment and possible association with clinical outcomes;
- Evaluation of sTKa levels over time during treatment with ribociclib plus letrozole and their association with clinical outcomes was a key, pre-specified secondary objective of the study;
- time to progression and progression-free survival (PFS) were secondary end-points.

BioItaLee- CONSORT diagram



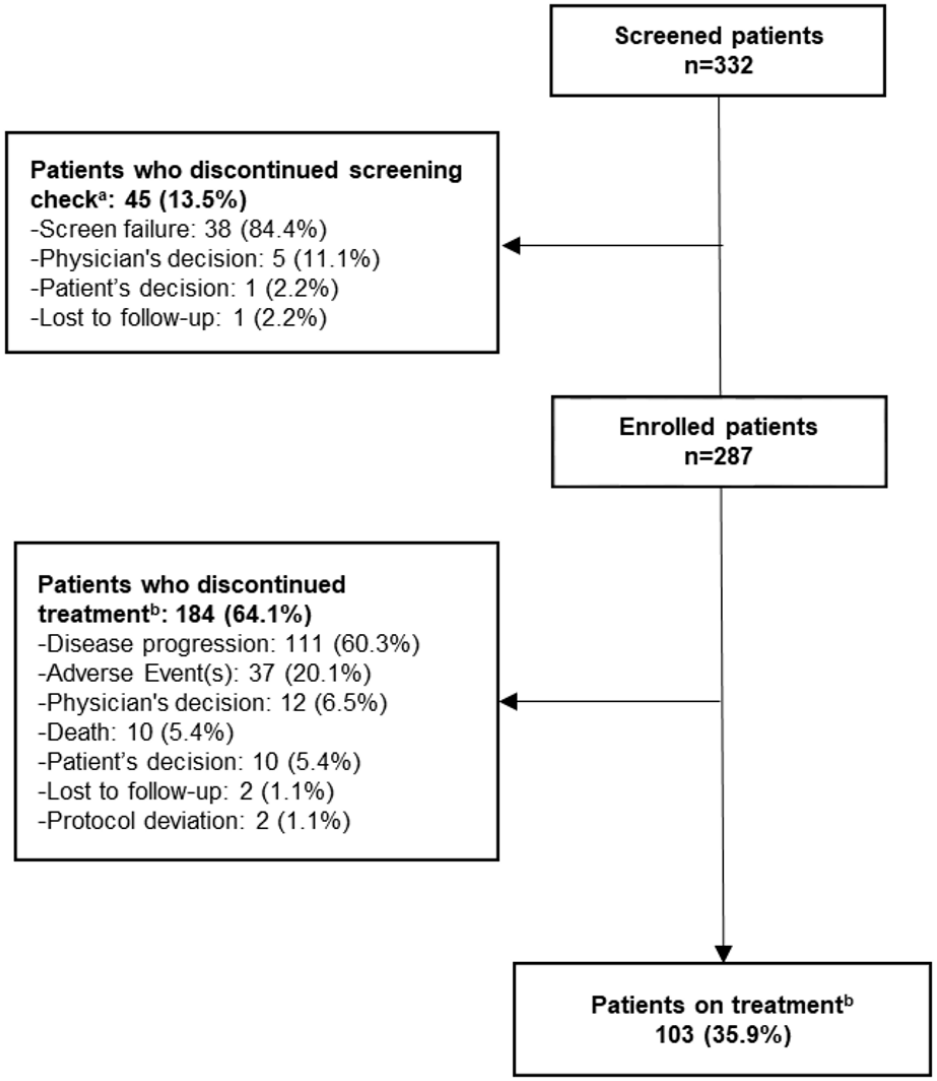
BioItaLEE
BIOLOGICAL ITALIAN STUDY WITH RIBOCICLIB IN 1L POSTMENOPAUSAL WOMEN WITH ABC

Out of 287 pts enrolled, 263 (92%) compose the Biomarker analysis set

matched Baseline, D15 and C2D1
232 (88%)

matched Baseline, D15, C2D1 and First Imaging
197 (75%)

BioItaLee- CONSORT diagram



BioItaLEE
BIOLOGICAL ITALIAN STUDY WITH RIBOCICLIB IN 1L POSTMENOPAUSAL WOMEN WITH ABC

at time of analysis
64.1% (n = 184) had discontinued treatment
35.9% (n = 103) were still on ribociclib plus letrozole

median follow-up was 26.9 months (range, 22.3–32.3)

BioItaLee- Patients' characteristics

Table 1
Patient demographics and disease characteristics.

Patient characteristic	Enrolled patients N = 287	Biomarker population N = 263
Age (years), median (IQR)	65.5 (59.0–71.0)	65.7 (60.0–72.0)
≥70 years, n (%)	98 (34.2)	93 (35.4)
ECOG PS, n (%)		
0	205 (71.4)	191 (72.6)
1	77 (26.8)	68 (25.9)
2	5 (1.7)	4 (1.5)
Disease characteristics, n (%)		
Tumour subtype		
Luminal A[a]	83 (28.9)	74 (28.1)
Luminal B	185 (64.5)	173 (65.8)
Unknown	19 (6.6)	16 (6.1)
Disease status		
De novo metastatic[b]	114 (39.7)	105 (39.9)
Recurrent	173 (60.3)	158 (60.1)
Disease-free interval period, n (%)[c]		
≤2 years	19 (11.0)	18 (11.4)
>2 years and ≤5 years	10 (5.8)	8 (5.1)
>5 years and ≤7 years	18 (10.4)	14 (8.9)
>7 years	118 (68.2)	111 (70.3)
Missing	8 (4.6)	7 (4.4)
Metastatic sites, n (%)[d]		
Bone	206 (71.8)	193 (73.4)
Bone only	64 (22.3)	62 (23.6)
Visceral	127 (44.3)	114 (43.3)
Liver	41 (14.3)	36 (13.7)
Lung	96 (33.5)	87 (33.1)
Other visceral	18 (6.3)	17 (6.5)
CNS	0	0
Lymph nodes	159 (55.4)	142 (54.0)
Skin	8 (2.8)	8 (3.0)
Breast	21 (7.3)	21 (8.0)
Other	28 (9.8)	26 (9.9)
Number of organs of interest involved, n (%)		
0	2 (0.7)	1 (0.4)
1	107 (37.3)	99 (37.6)
2	124 (43.2)	113 (43.0)
≥3	54 (18.8)	50 (19.0)

BioItaLEE
BIOLOGICAL ITALIAN STUDY WITH RIBOCICLIB IN 1L POSTMENOPAUSAL WOMEN WITH ABC

median age 65y (35%>70 y)
PS ECOG 0 72%

Luminal B 65%

de novo M+ 40%
long DFI (>7y) 70%

visceral M+ 43%
bone-only 23%

BioItaLee- efficacy

BioItaLEE
BIOLOGICAL ITALIAN STUDY WITH RIBOCICLIB IN 1L POSTMENOPAUSAL WOMEN WITH ABC

Of the 166 patients with measurable disease at baseline, 149 patients performed at least one post-baseline imaging evaluation up to the cut-off date.

Best overall response:

- PR 52.3%
- CR 0.7%
  (ORR 53%)
- SD 35.6%
- PD 10.7%
- unkn 0.7%

Median PFS was 23.4 months (95% CI, 20.8– NE)

BioItaLee- efficacy

BioItaLEE
BIOLOGICAL ITALIAN STUDY WITH RIBOCICLIB IN 1L POSTMENOPAUSAL WOMEN WITH ABC

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Monaleesa 2

Table 2. Best Overall Response, According to Local Assessment.

Response	Ribociclib Group
Patients with measurable disease at baseline — no.	256
Confirmed best overall response — no. (%)	
Complete response	8 (3.1)
Partial response	127 (49.6)
Stable disease	95 (37.1)
Progressive disease	13 (5.1)
Unknown	13 (5.1)
Overall response†	
No. of patients	135
Percentage of patients (95% CI)	52.7 (46.6–58.9)

Median PFS was 25.3 months (95% CI 23.0–30.3)

Hortobagyi GN et al, NEJM 2016

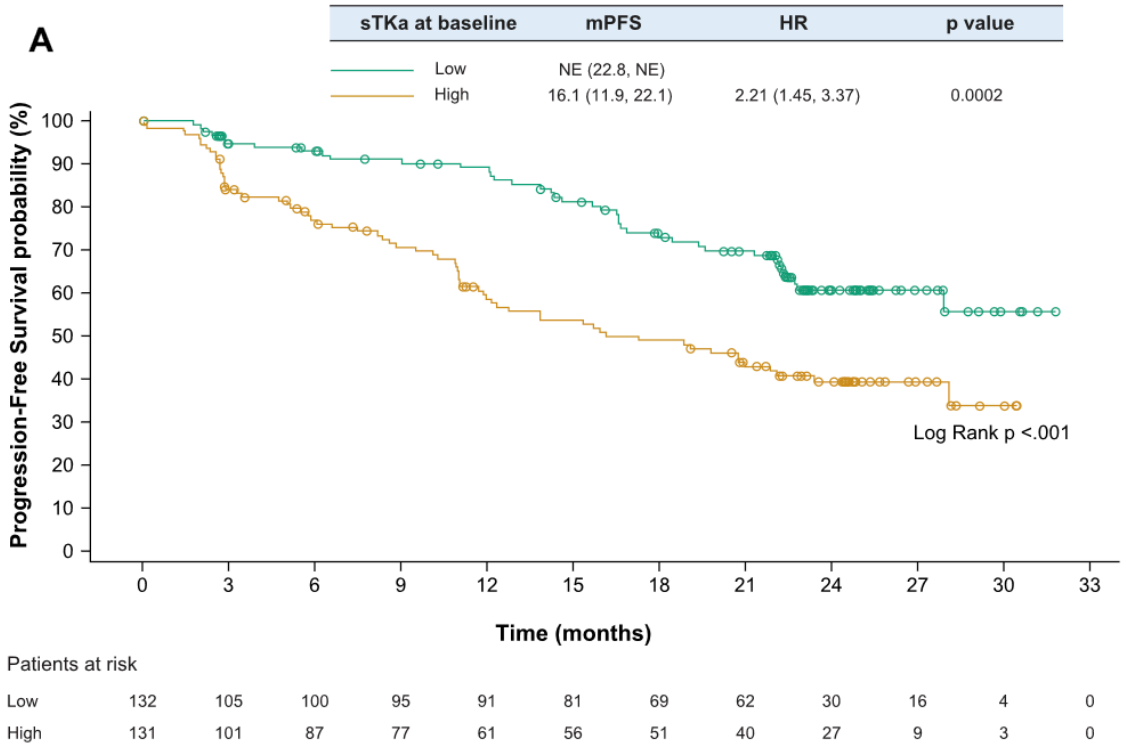
Serum Thymidine Kinase 1 (TKa) in the BIOITALee trial- key findings
BASELINE

From 263 available samples at baseline, median sTKa was 74.8 Du/L (19–9412)

11,8% of patients had sTKa levels below LOD (20Du/L)

Serum Thymidine Kinase 1 (TKa) in the BIOITALee trial- key findings BASELINE

Baseline (median cut-off)



From 263 available samples at baseline, median sTKa was 74.8 Du/L (19–9412)

11,8% of patients had sTKa levels below LOD (20Du/L)

patients with high sTKa had a worse PFS compared to those with low sTKa
HR 2.21; 95% CI, 1.45, 3.37; P = 0.0002

High sTKa at baseline was associated with worse prognosis

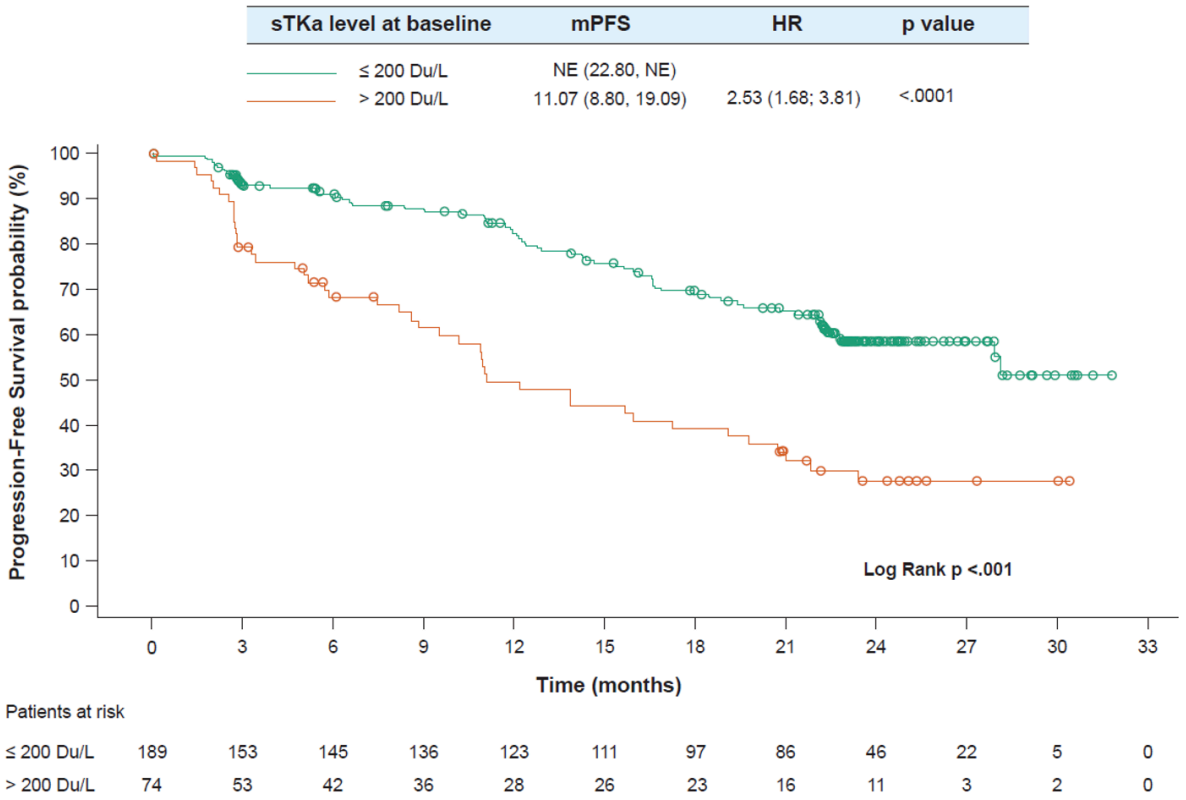
Serum Thymidine Kinase 1 (TKa) in the BIOITALee trial- key findings BASELINE

Characteristic	sTKa levels at baseline		p value
	Low N=132	High N=131	
Age (years), median (range)	67 (47–86)	64 (47–81)	0.0214[a]
ECOG PS at baseline, n (%)			
Grade 0	101 (76.5)	90 (68.7)	0.0725[b]
Grade 1	31 (23.5)	37 (28.2)	
Grade 2	0	4 (3.05)	
Time from first diagnosis to study treatment start (years), median (range)	7.43 (0.04–31.88)	2.97 (0.04–26.73)	0.0687[a]
Patient disease status, n (%)			
De novo	49 (37.1)	56 (42.75)	0.3515[b]
Recurrent	83 (62.9)	75 (57.25)	
Ki67 categories, n (%)			
<20%	62 (47.0)	45 (34.35)	0.0278[b]
20-35%	43 (32.6)	45 (34.35)	
>35%	16 (12.1)	33 (25.2)	
Missing	11 (8.3)	8 (6.1)	
Tumor type			
Luminal A	45 (34.1)	29 (22.1)	0.038[b]
Luminal B	77 (58.3)	96 (73.3)	
Unknown	10 (7.6)	6 (4.6)	

High sTKa at baseline was associated with younger age and LumB status

Serum Thymidine Kinase 1 (TKa) in the BIOITALee trial- key findings BASELINE

Baseline (200 Du/L cut-off)

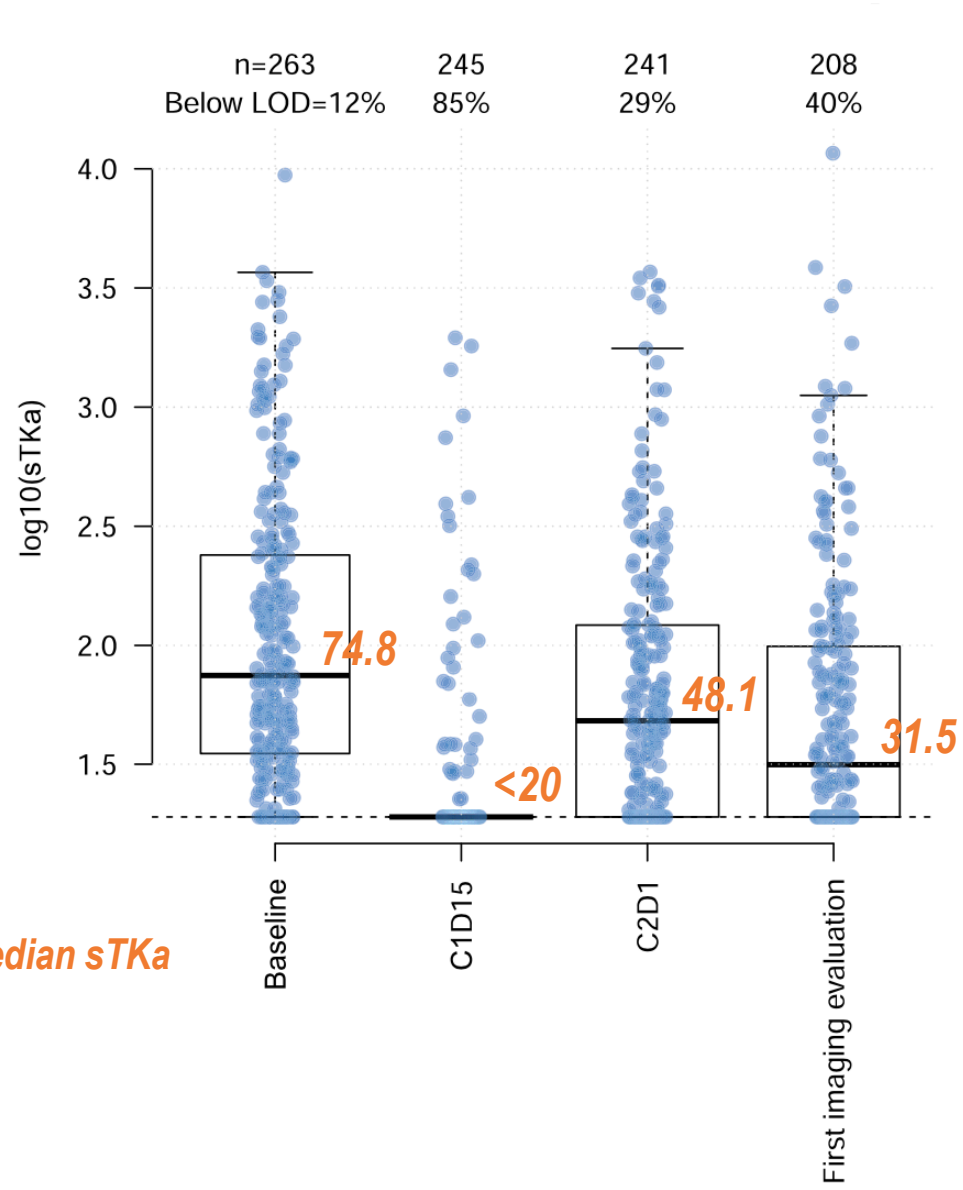


When using a cut-off of 200 Du/L, 74 (28.1%) patients had high and 189 (71.9%) had low sTKa levels at baseline.

patients with high sTKa had a worse PFS compared to those with low sTKa
HR, 2.53; 95% CI, 1.68, 3.81; P < 0.0001

Malorni L. et al, EJC 2023

Serum Thymidine Kinase 1 in the BIOITALee trial- key findings
Early changes during C1



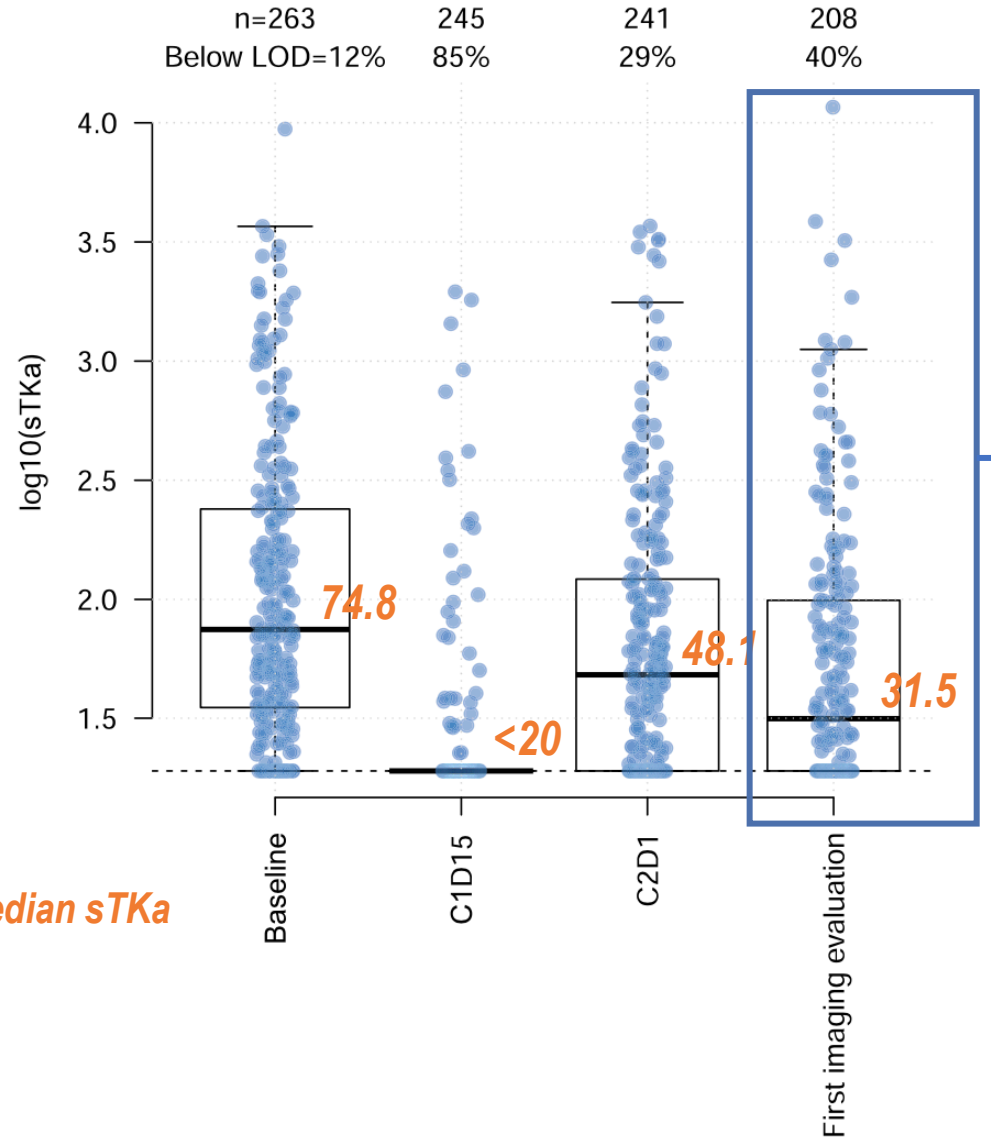
Early sTKa clearance (levels below LOD) was observed in:

- **85% of patients at D15 and**
- **29% of patients at C2D1**

A rebound at C2D1 was seen in 68.5% of patients

A significant reduction in sTKa was observed upon ribociclib + letrozole treatment at D15 and C2D1 but rebound is common

Serum Thymidine Kinase 1 in the BIOITALee trial- key findings
Early changes during C1



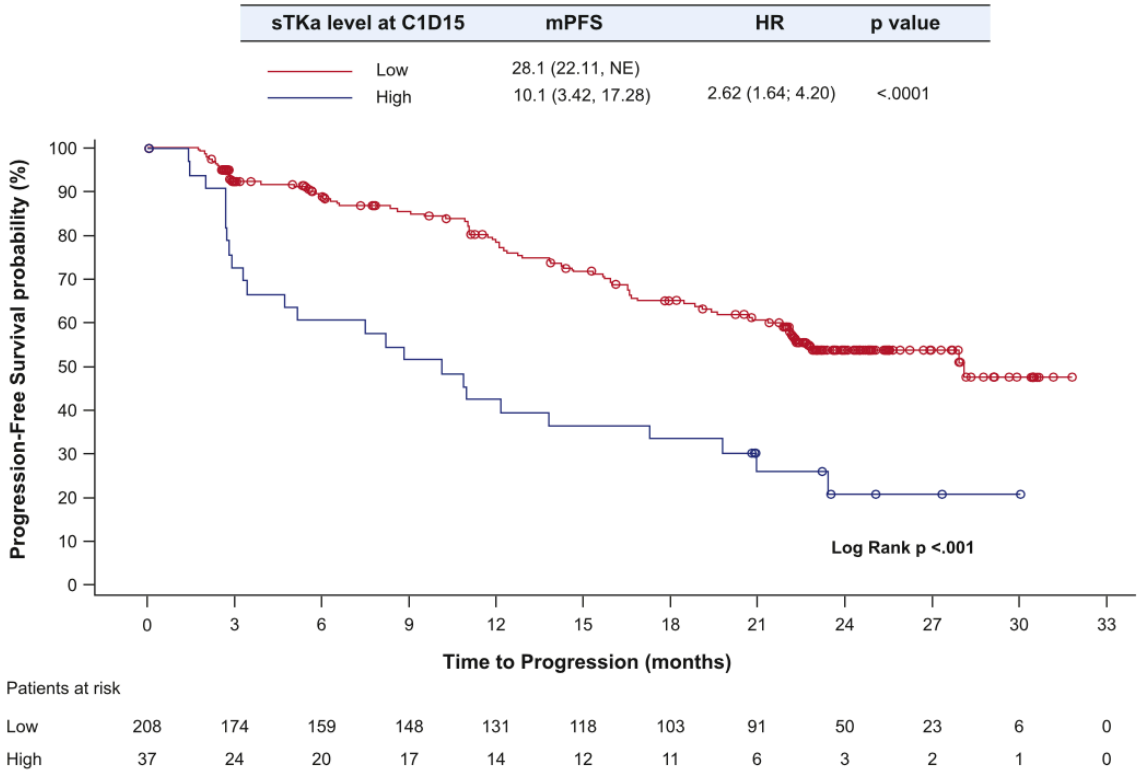
median sTKa at First Imaging was 31.5 Du/L (IQR, 19.0–99.2)

median sTKa at first imaging according to treatment interval from RIBO:

- **ongoing treatment** (n = 113; 54.3%),
  median sTKa **26.9** Du/L (IQR, 19.0–95.1)
- **off-treatment ≤7 days** (n=67; 32.2%)
  median sTKa **19.0** Du/L (IQR, 19.0–56.9)
- **off-treatment > 7 days** (n = 28; 13.5%)
  median sTKa **116.0** Du/L (IQR, 63.8–429.1)

Serum Thymidine Kinase 1 (TKa) in the BIOITALee trial- key findings D15

D15 (LOD cut-off)



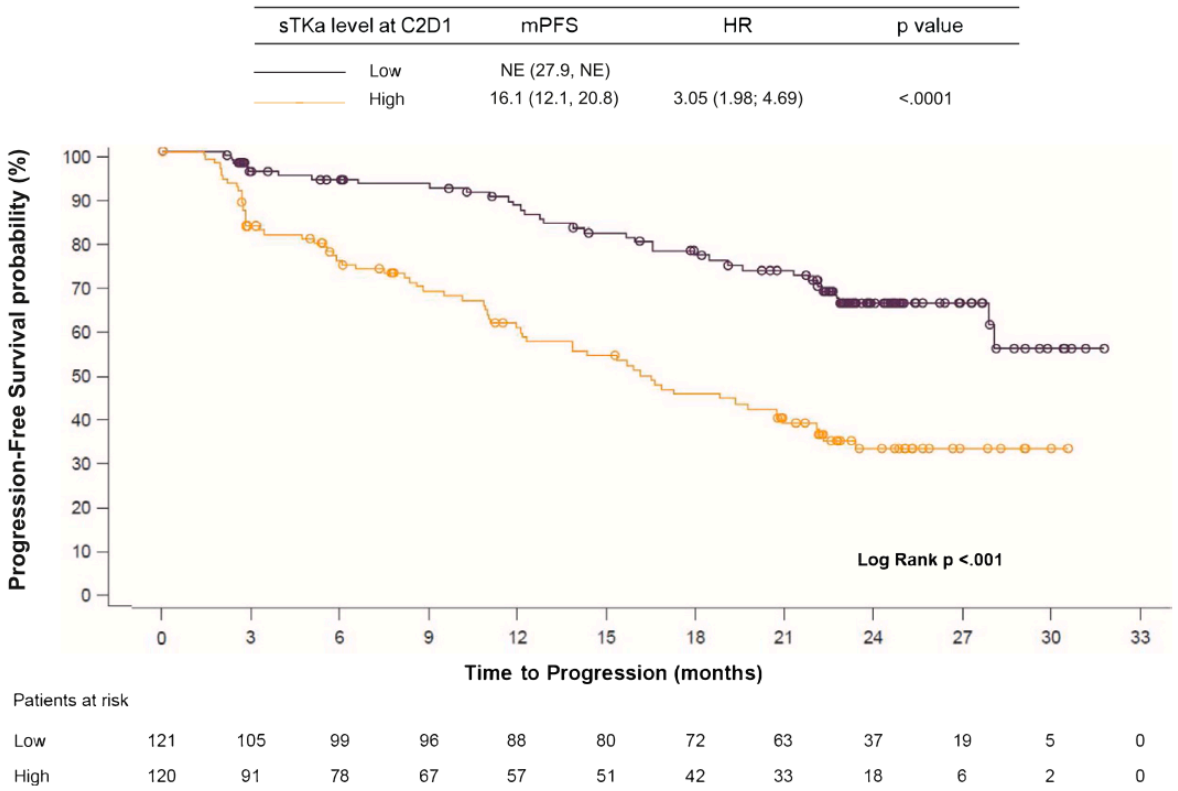
sTKa clearance at D15 was not observed in 37 pts (15%)

these pts had worse outcome compared to those with sTKa clearance HR, 2.62; 95% CI, 1.64, 4.20; P < 0.0001

Lack of sTKa clearance (<LOD) at D15 was associated with poor prognosis

Serum Thymidine Kinase 1 (TKa) in the BIOITALee trial- key findings C2D1

C2D1 (median cut-off)



median sTKa at C2D1 was

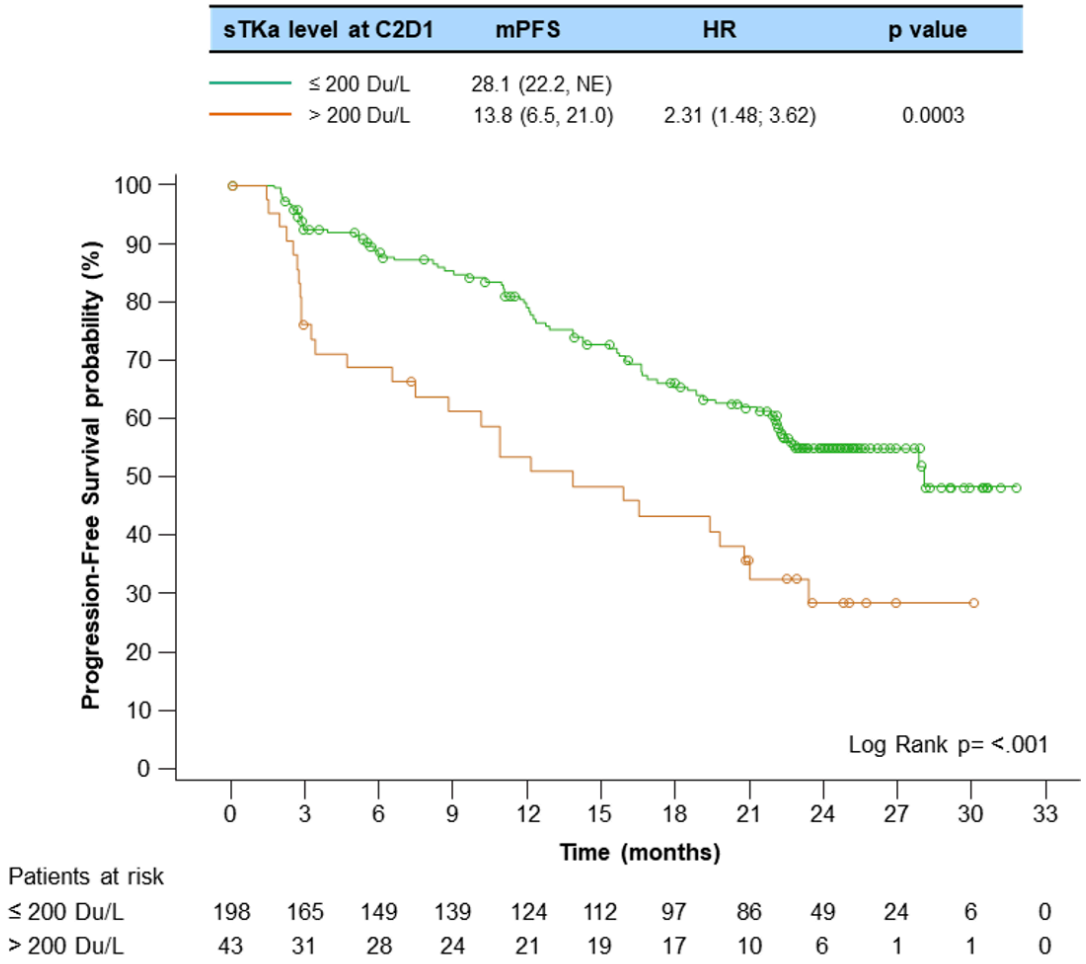
48.1 Du/L (IQR, 19.0–121.7)

pts with high sTKa at C2D1 had a worse PFS compared with pts with low sTKa
HR, 3.05; 95% CI, 1.98, 4.69; P < 0.0001

High sTKa (>median) at C2D1 was associated with poor prognosis

Serum Thymidine Kinase 1 (TKa) in the BIOITALee trial- key findings C2D1

C2D1 (200 Du/L cut-off)



When using a cut-off of 200 Du/L, 43 patients had high and 198 had low sTKa levels at C2D1

pts with high sTKa at C2D1 had a worse PFS compared with pts with low sTKa HR, 2.31; 95% CI, 1.48, 3.62; P 0.0003

High sTKa (>200 Du/L) at C2D1 was associated with poor prognosis

Multivariate analysis

Table 2
Multivariate analysis of PFS for sTKa levels at different time points in the study.

Characteristic	Baseline HR (95% CI)	*P* value	C1D15 HR (95% CI)	*P* value	C2D1 HR (95% CI)	*P* value
sTKa levels at time point (high versus low)	2.21 (1.45, 3.37)	0.0002	2.62 (1.64, 4.20)	<0.0001	3.05 (1.98, 4.69)	<0.0001
Recurrent versus *de novo* disease	0.98 (0.66, 1.45)	0.9147	0.98 (0.65, 1.46)	0.9037	1.06 (0.70, 1.59)	0.7877
Tumour type (luminal B versus luminal A)	1.38 (0.83, 2.27)	0.2097	1.69 (1.02, 2.80)	0.0431	1.63 (0.97, 2.74)	0.0631
No visceral metastases versus visceral metastases	0.65 (0.42, 1.02)	0.0612	0.75 (0.48, 1.17)	0.2096	0.66 (0.41, 1.05)	0.0783
≥3 organs involved by metastases versus <3 organs involved by metastases	0.9 (0.53, 1.51)	0.6860	0.94 (0.55, 1.59)	0.8085	1.05 (0.61, 1.81)	0.8713

C, cycle; CI, confidence interval; D, day; HR, hazard ratio; PFS, progression-free survival; sTKa, serum thymidine kinase activity.

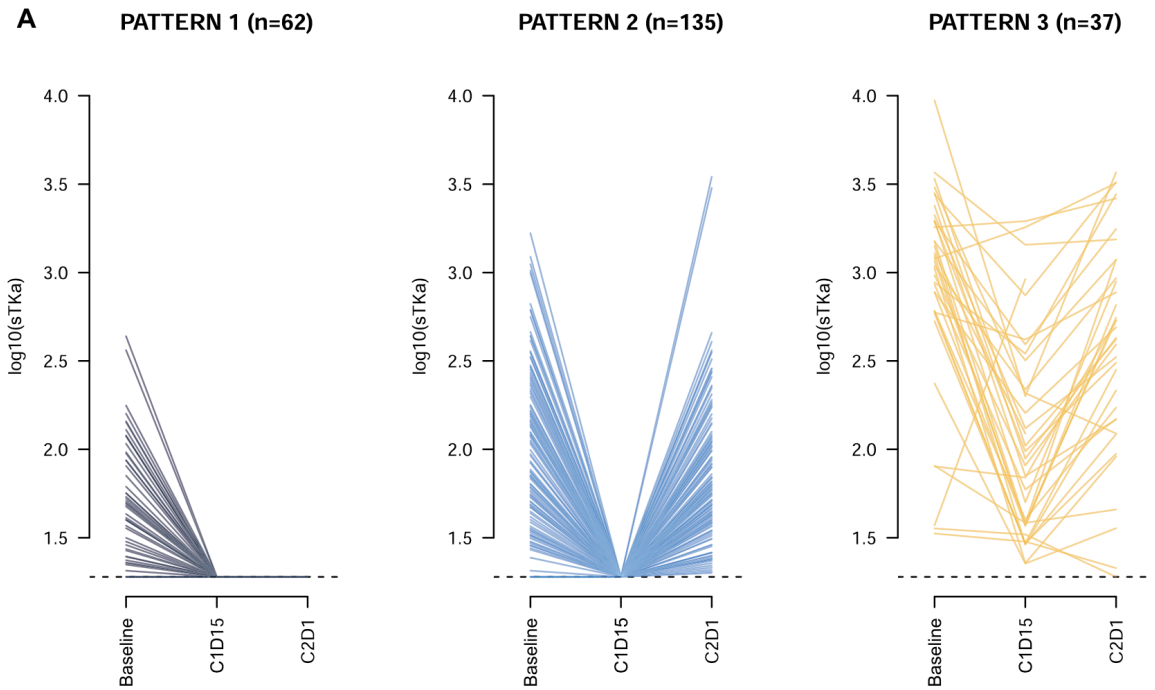
sTKa at all timepoints is independently prognostic

Serum Thymidine Kinase 1 (TKa) in the BIOITALee trial- key findings
Dynamic patterns

Pattern 1
TKa <LOD at D15 and C2D1

Pattern 2:
TKa <LOD at D15 and >LOD at C2D1

Pattern 3:
TKa >LOD at D15

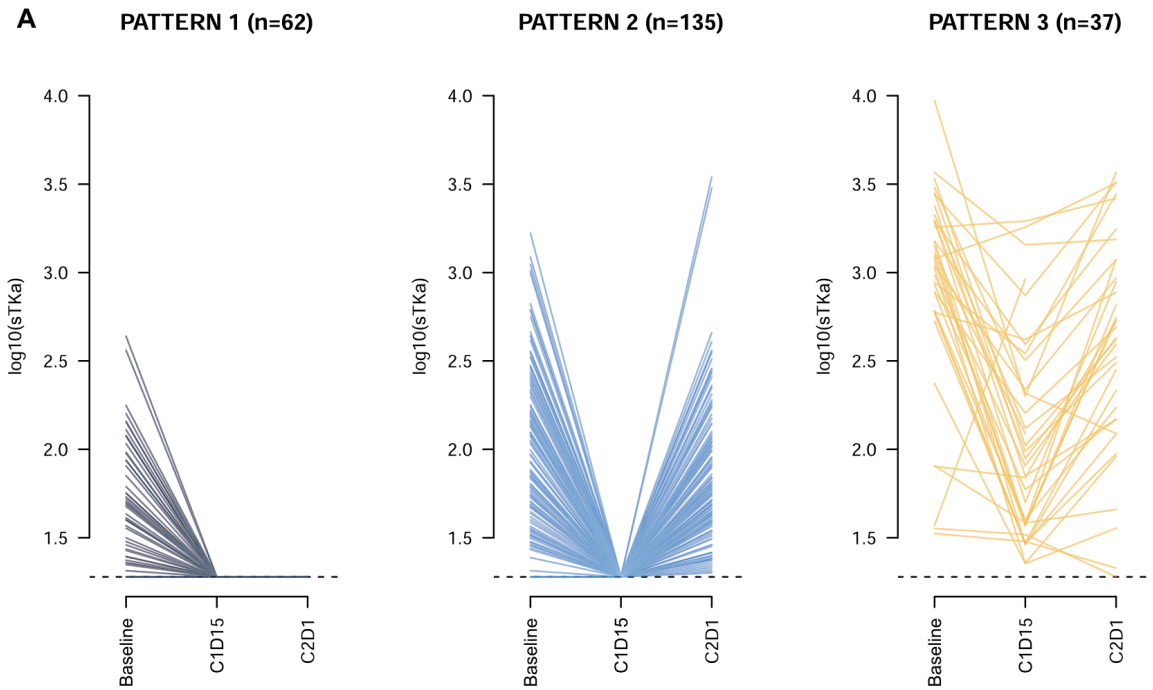


Serum Thymidine Kinase 1 (TKa) in the BIOITALee trial- key findings
Dynamic patterns

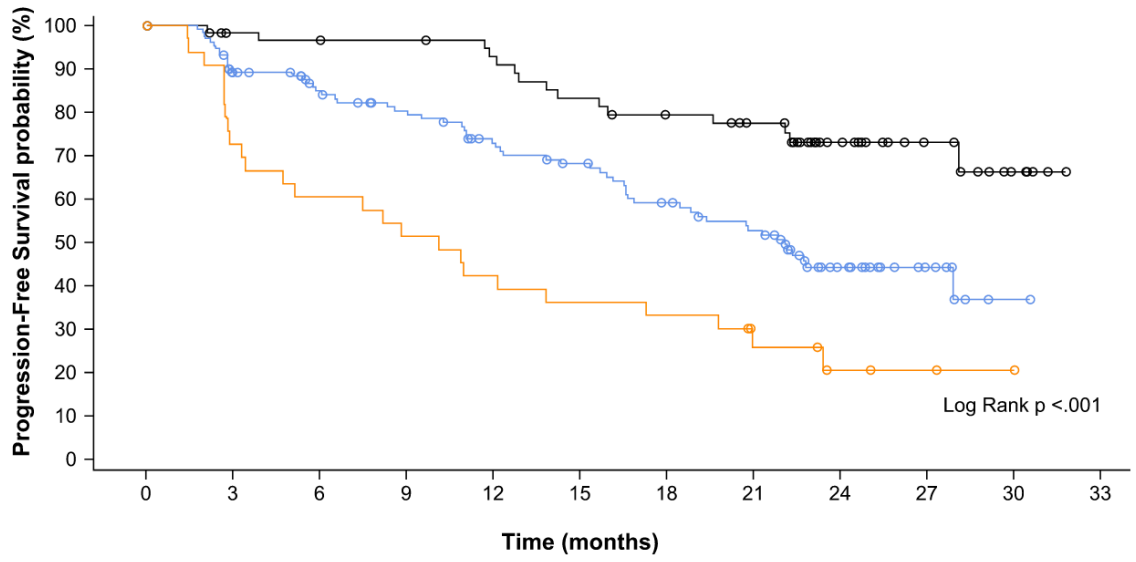
Pattern 1
TKa <LOD at D15 and C2D1

Pattern 2:
TKa <LOD at D15 and >LOD at C2D1

Pattern 3:
TKa >LOD at D15



sTKa pattern	mPFS	HR	p value
Pattern 1	NE (28.1, NE)		
Pattern 2	22.1 (16.8, NE)	2.89 (1.57, 5.31)	0.0006
Pattern 3	10.1 (3.1, 17.3)	5.65 (2.84, 11.23)	<0.0001



Patients at risk

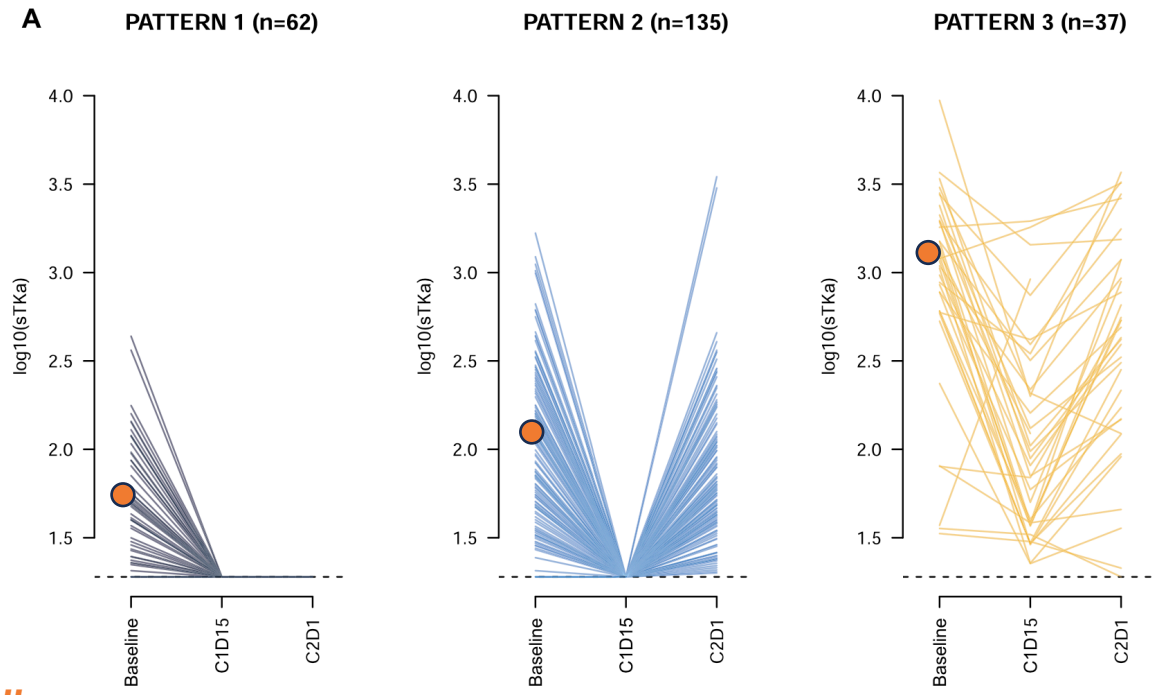
Pattern 1	62	54	53	52	49	44	40	36	22	12	5	0
Pattern 2	135	111	97	88	76	69	58	50	27	11	1	0
Pattern 3	37	24	20	17	14	12	11	6	3	2	1	0

Serum Thymidine Kinase 1 (TKa) in the BIOITALee trial- key findings
Dynamic patterns

Pattern 1
TKa <LOD at D15 and C2D1

Pattern 2:
TKa <LOD at D15 and >LOD at C2D1

Pattern 3:
TKa >LOD at D15



median sTKa

39.8 Du/L (19.0–80.6)

83.8Du/L (43.5–178.1)

1163.0Du/L (606.8–1950.8)

sTKa pattern	mPFS	HR	p value
Pattern 1	NE (28.1, NE)		
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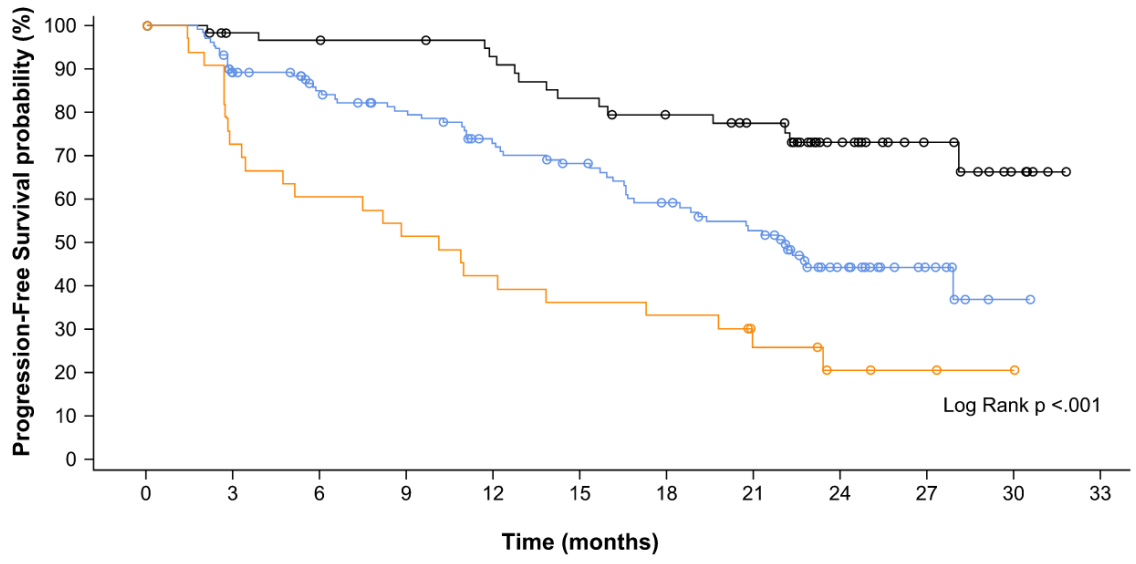

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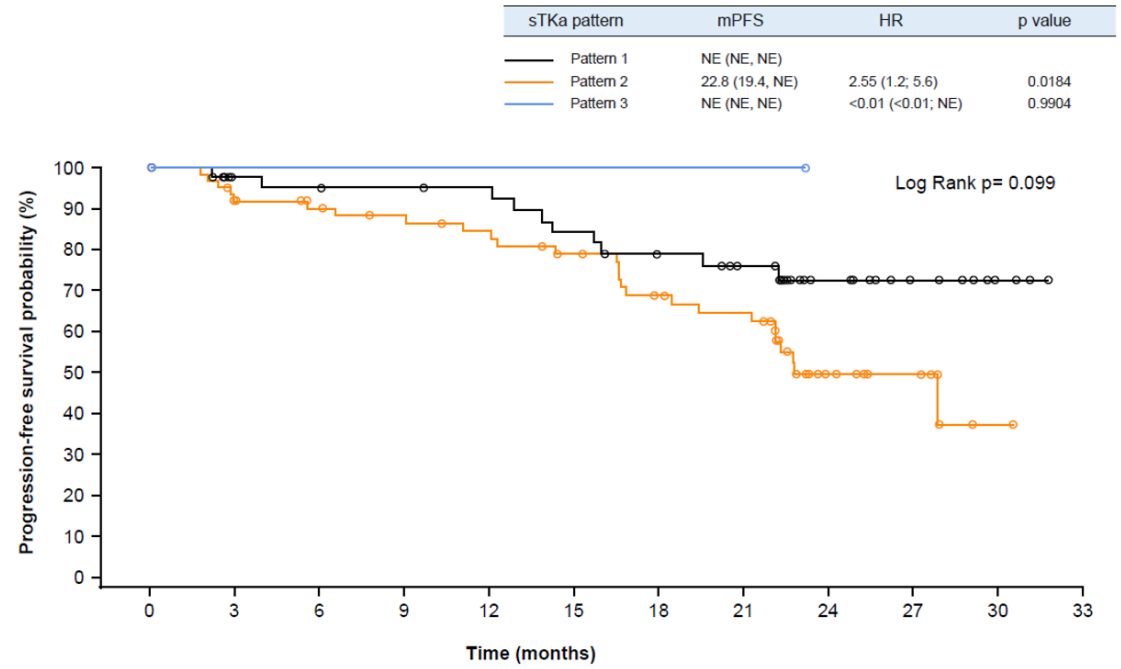
Serum Thymidine Kinase 1 (TKa) in the BIOITALee trial- key findings
Dynamic patterns

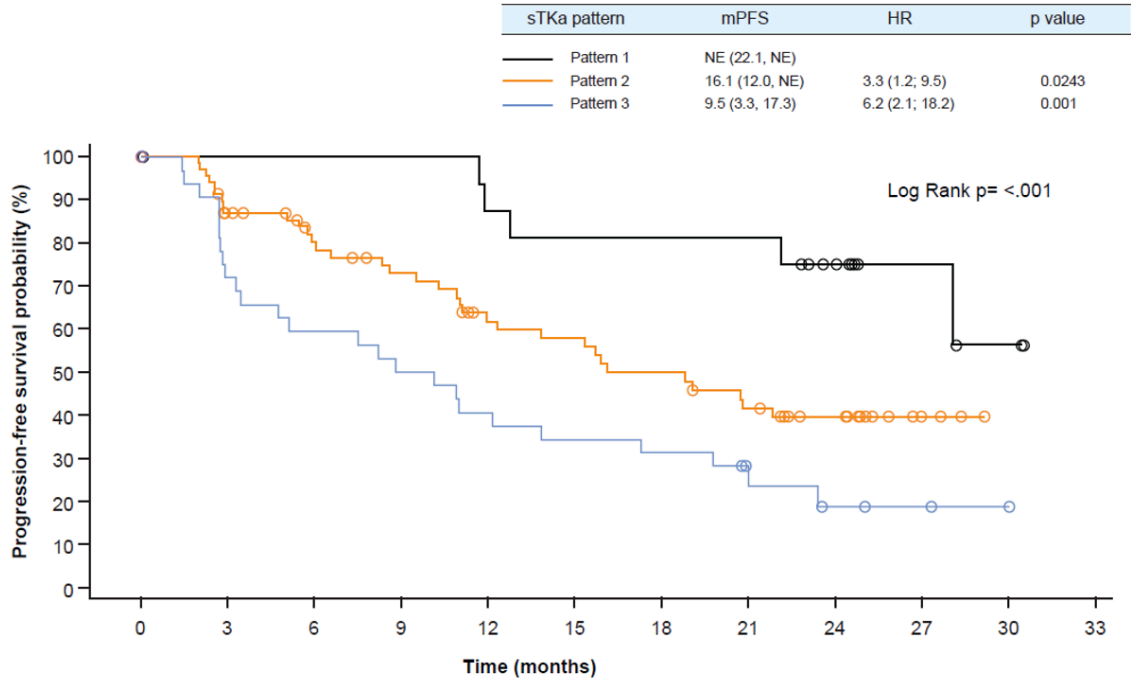
Low baseline sTKa (<median)



Patients at risk

Pattern 1	46	38	37	36	35	31	27	23	14	8	3	0
Pattern 2	65	55	51	48	45	40	33	30	12	8	1	0
Pattern 3	3	1	1	1	1	1	1	1	0			

High baseline sTKa (>median)



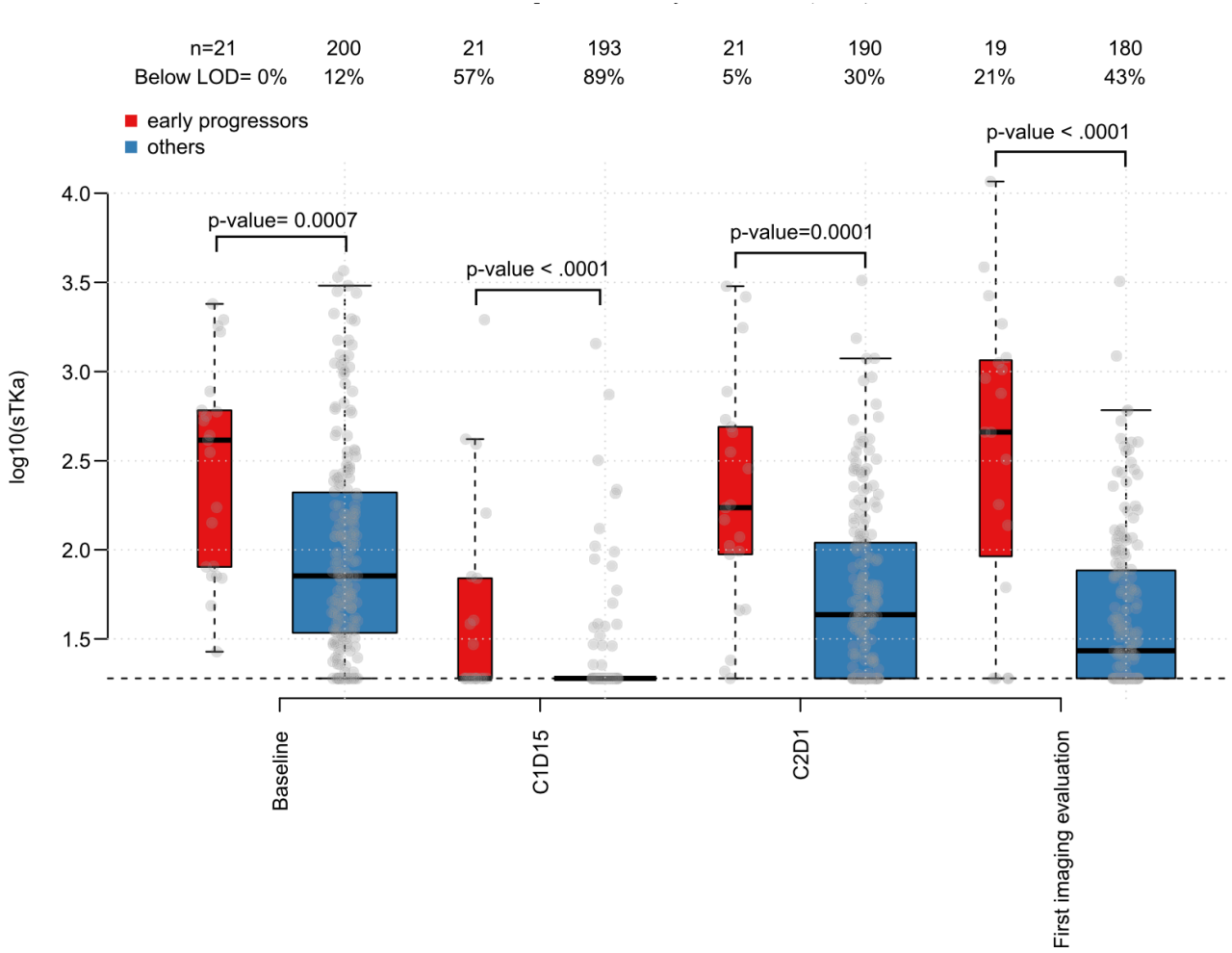
Patients at risk

Pattern 1	16	16	16	16	14	13	13	13	8	4	2	0
Pattern 2	70	56	46	40	31	29	25	20	15	3	0	
Pattern 3	34	23	19	16	13	11	10	5	3	2	1	0

Pts with High baseline sTKa with optimal sTKa response (pattern 1) have excellent prognosis

Serum Thymidine Kinase 1 (TKa) in the BIOITALee trial- key findings
First Imaging

Out of 208 patients with evaluable disease at FI and a valid sTKa value, 20 (9.6%) had progressive disease as assessed by imaging and clinical evaluation at this time point (early progressors)



- **Early progressors** had higher sTKa levels at all time-points
- Only 4 out of 101 (4.0%) patients with sTKa < median at FI had disease progression at this timepoint

Can we omit radiological evaluation at first imaging (3 months) if if sTKa is low?

TKa DATA IN PATIENTS TREATED WITH ET+CDK4/6i: changes during treatment

- First/second line tx with PALBO+FUL
- endocrine resistant MBC

- <LLOD D15 83%
- rebound at D28 54%

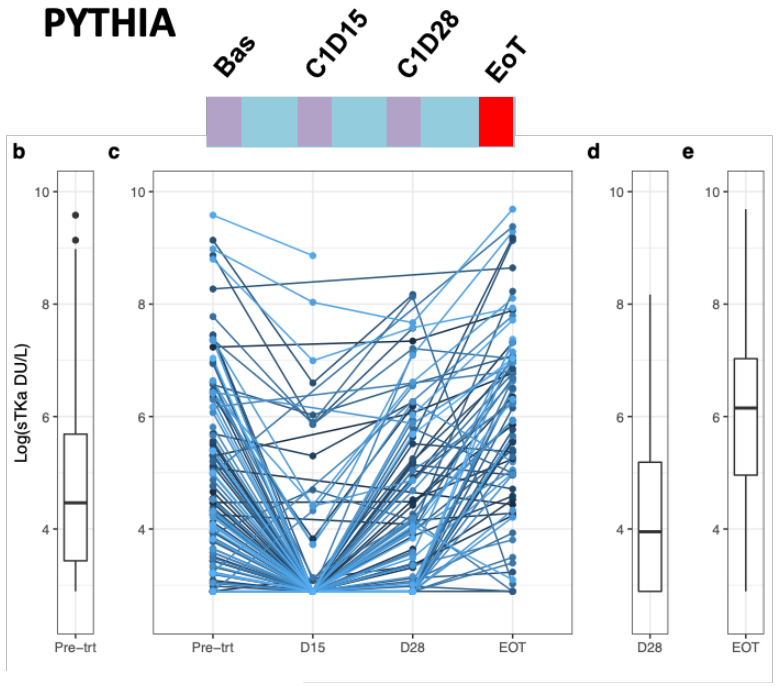
- First line tx with RIBO+LET
- endocrine sensitive MBC

- <LLOD D15 85%
- rebound at D28 68%

- First/second line tx with PALBO+HT
- endocrine sensitive/resistant MBC

- <LLOD D15 78%
- rebound D28 36%

PYTHIA



Malorni L. et al, EJC 2022

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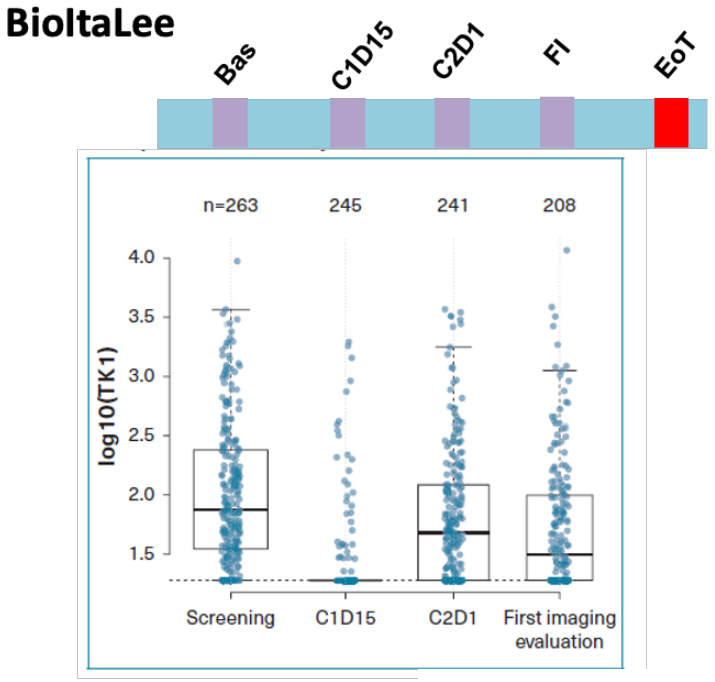
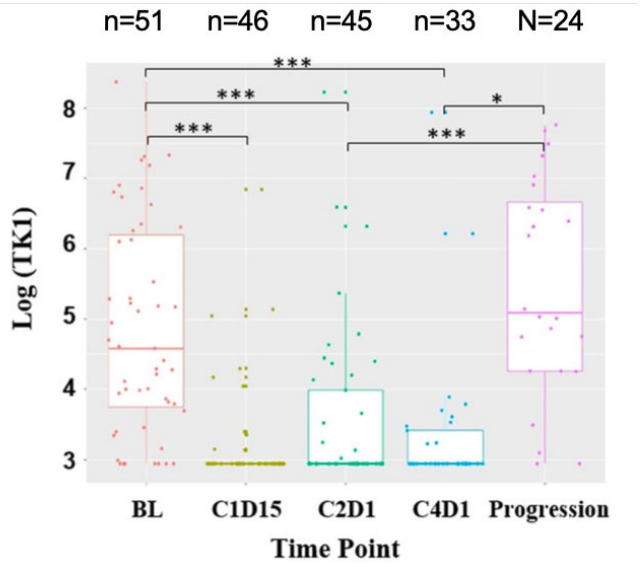


Malorni L. et al, EJC 2023

WashU palbo dosing trial

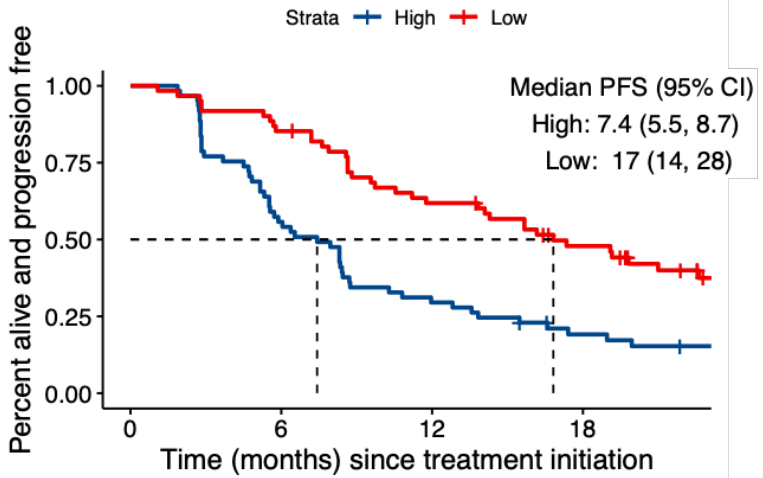


Krishnamurthy, J. npjBC 2022

TKa DATA IN PATIENTS TREATED WITH ET+CDK4/6i: BASELINE

PYTHIA

Baseline; median cut-off; 87 Du/L (<20- 14510)



Number at risk

High	61	34	18	10
Low	61	52	37	26

Multivariable
HR 1.38; 95% CI: 1.22-1.57
p<0.001

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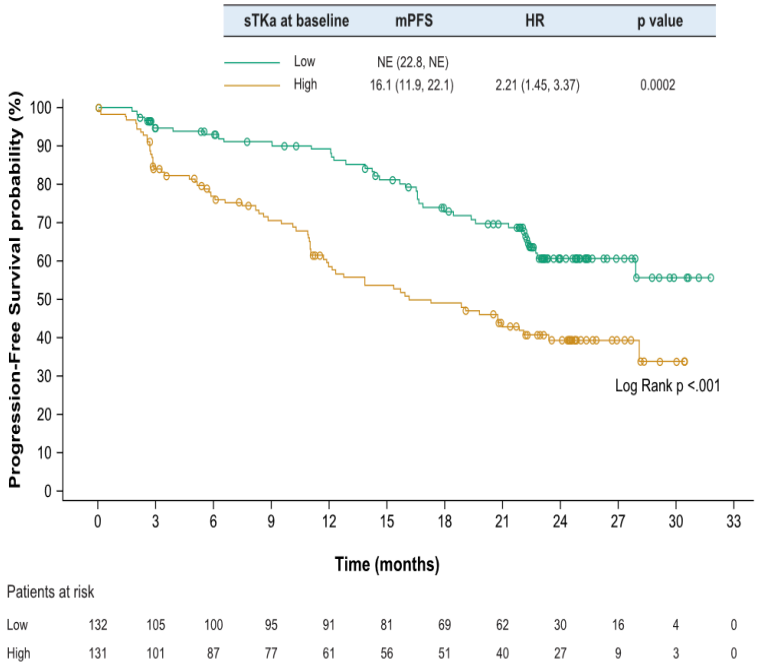
Baseline; median cut-off, 74.8 Du/L (19–9412)



Patients at risk

Low	132	105	100	95	91	81	69	62	30	16	4	0
High	131	101	87	77	61	56	51	40	27	9	3	0

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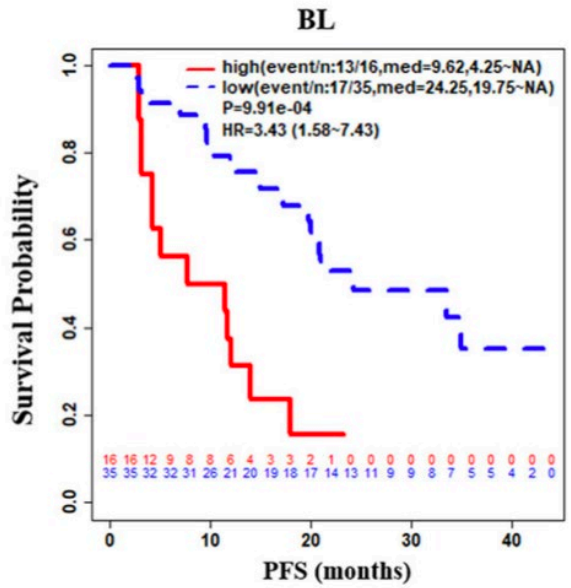
WashU palbo dosing trial

Baseline; median cut-off, 97.9 Du/L (42.4–490.3)

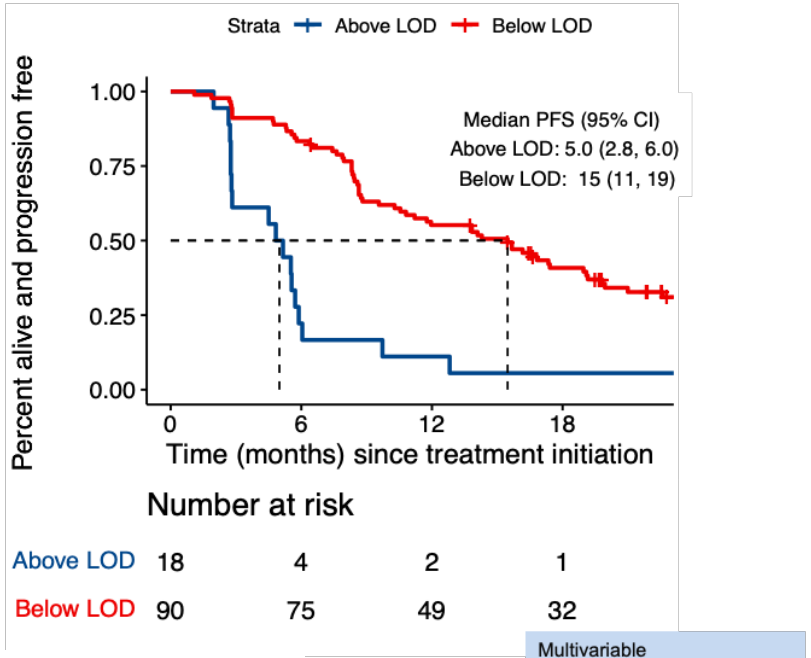


Krishnamurthy, J. npjBC 2022

TKa DATA IN PATIENTS TREATED WITH ET+CDK4/6i: CYCLE 1 DAY 15

PYTHIA

C1D15; LoD cut-off, median <20 Du/L (<20- 7060)



Multivariable
HR 1.46; 95% CI: 1.21-1.76
p<0.001

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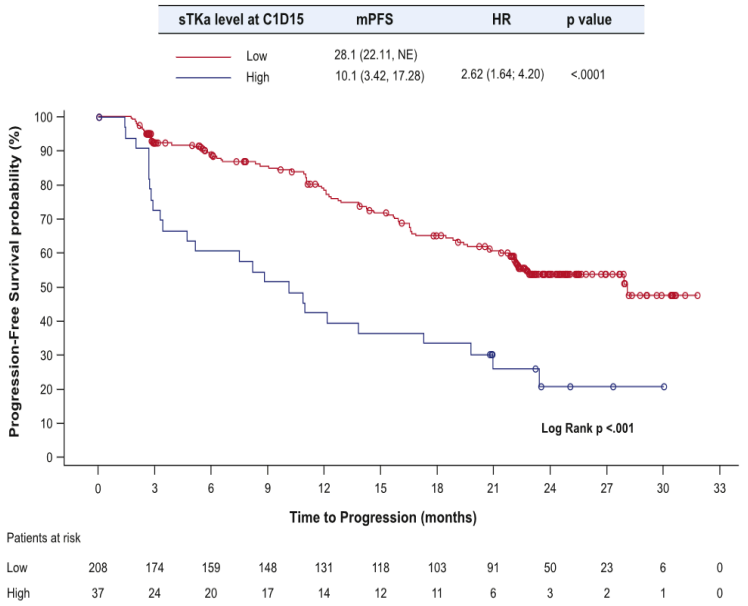
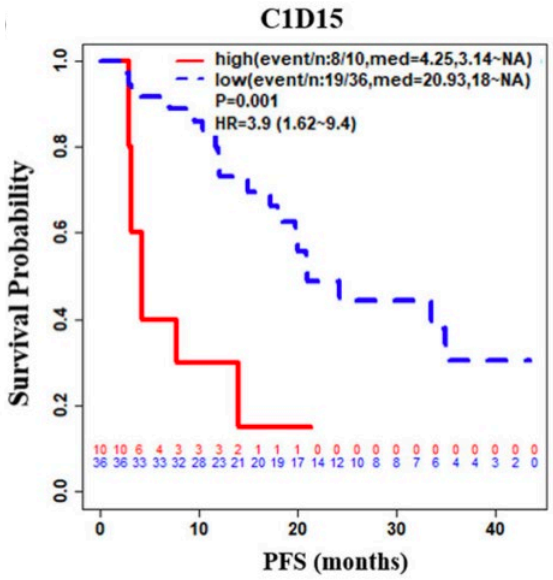
C1D15; LoD cut-off, median 19 Du/L (19–1953)



Malorni L. et al, EJC 2023

WashU palbo dosing trial

C1D15; LoD cut-off, median <20 Du/L (<20-<20)

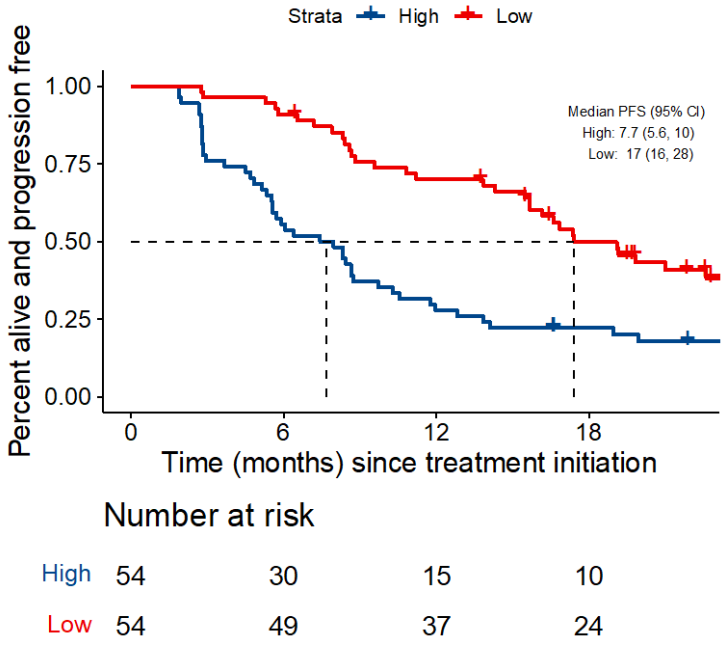


Krishnamurthy, J. npjBC 2022

TKa DATA IN PATIENTS TREATED WITH ET+CDK4/6i: CYCLE 2 DAY 1

PYTHIA

C2D1; median cut-off, 52 Du/L (<20, 3533)



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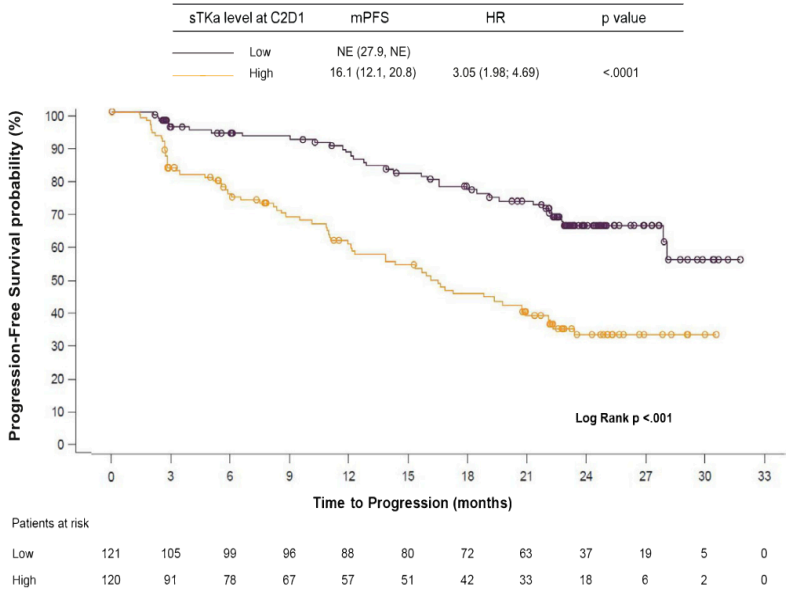
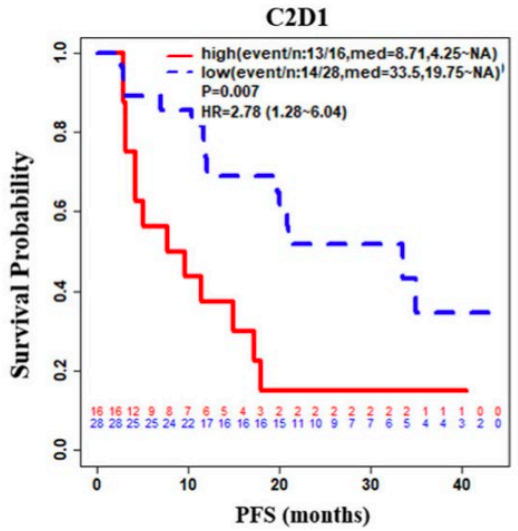
C2D1; median cut-off, 48.1 Du/L (19–3689)



Malorni L. et al, EJC 2023

WashU palbo dosing trial

C2D1; median cut-off, <20 (<20~54.1)



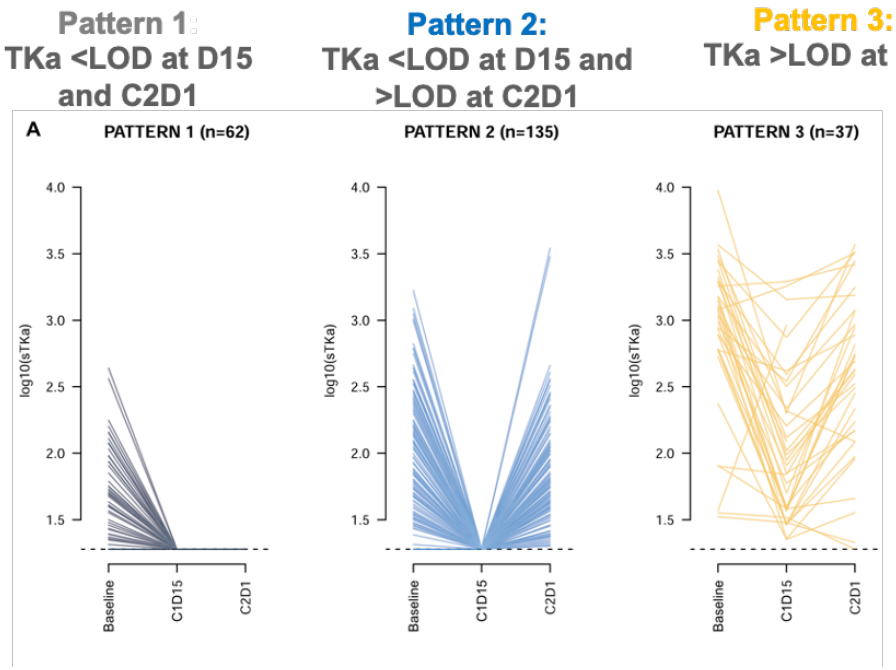
Krishnamurthy, J. npjBC 2022

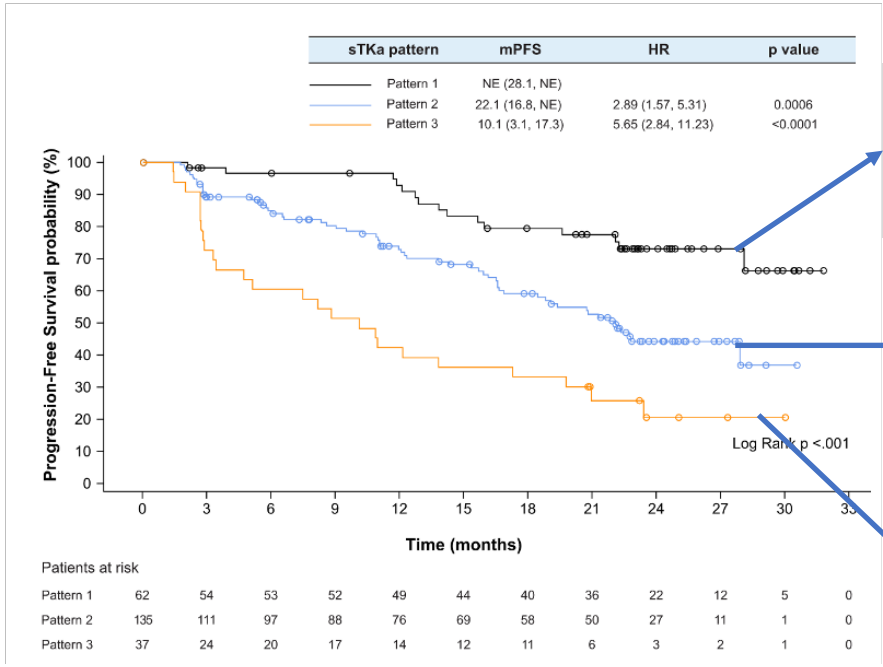
Take home messages:

- sTKa appears to be a new promising prognostic and pharmacodynamic biomarker in patients with HR+/HER2– ABC treated with ribociclib plus letrozole as first-line therapy

- Baseline and on-treatment sTKa may give important prognostic and predictive information

- At first imaging, low sTKa is associated with very low risk of clinial/radiological disease progression. Whether sTKa low status can be used to skip radiological examination is currently under investigation (TK IMPACT: NCT04968964)





26%
may forego CDK4/6i in first line?

58%
may need a better HT and/or a continuous CDK4/6i dosing?

16%
may need a better HT+ targeted agent or CHEMO/ADC?

Take home messages:

Les roses Safrano (Nature morte devant la fentre ouverte Nice, Place Charles-Flix) (1925)

Non c'è niente di più difficile per un pittore veramente creativo del dipingere una rosa, perchè prima di tutto deve dimenticare tutte le altre rose che sono state dipinte.

Henry Matisse

GRAZIE!

All the patients and their families;
All the participating centers.

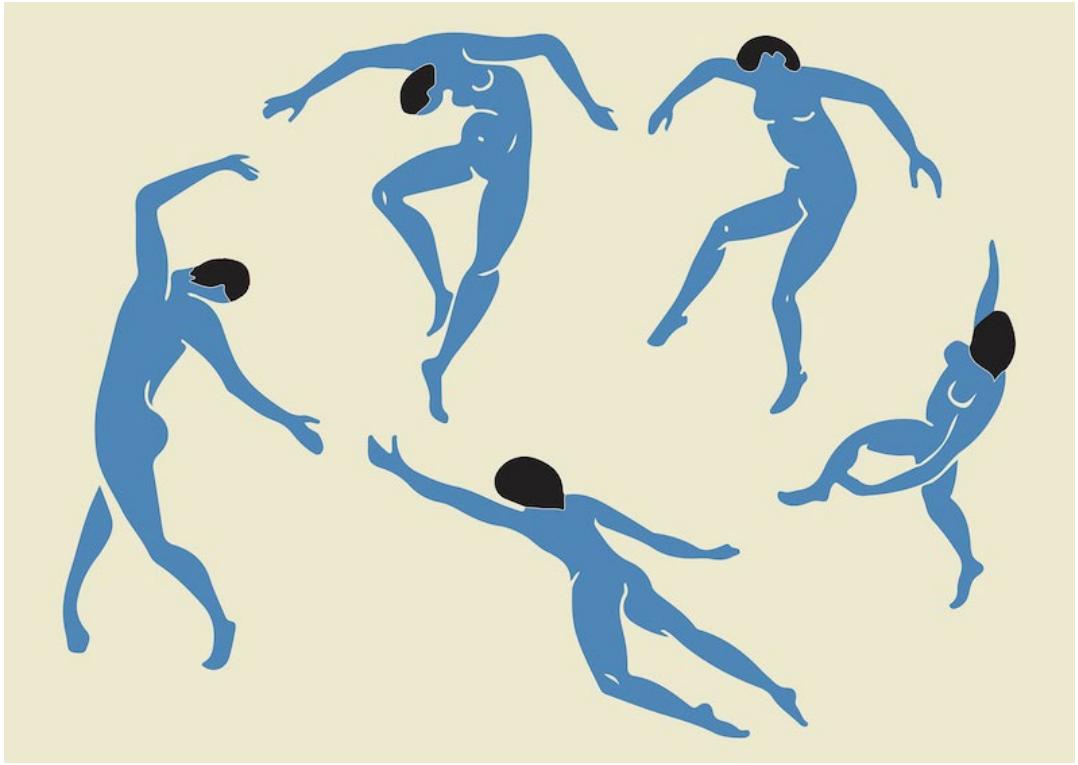
The BIOItaLee TEAM:

Michelino De Laurentiis
Giampaolo Bianchini
Grazia Arpino

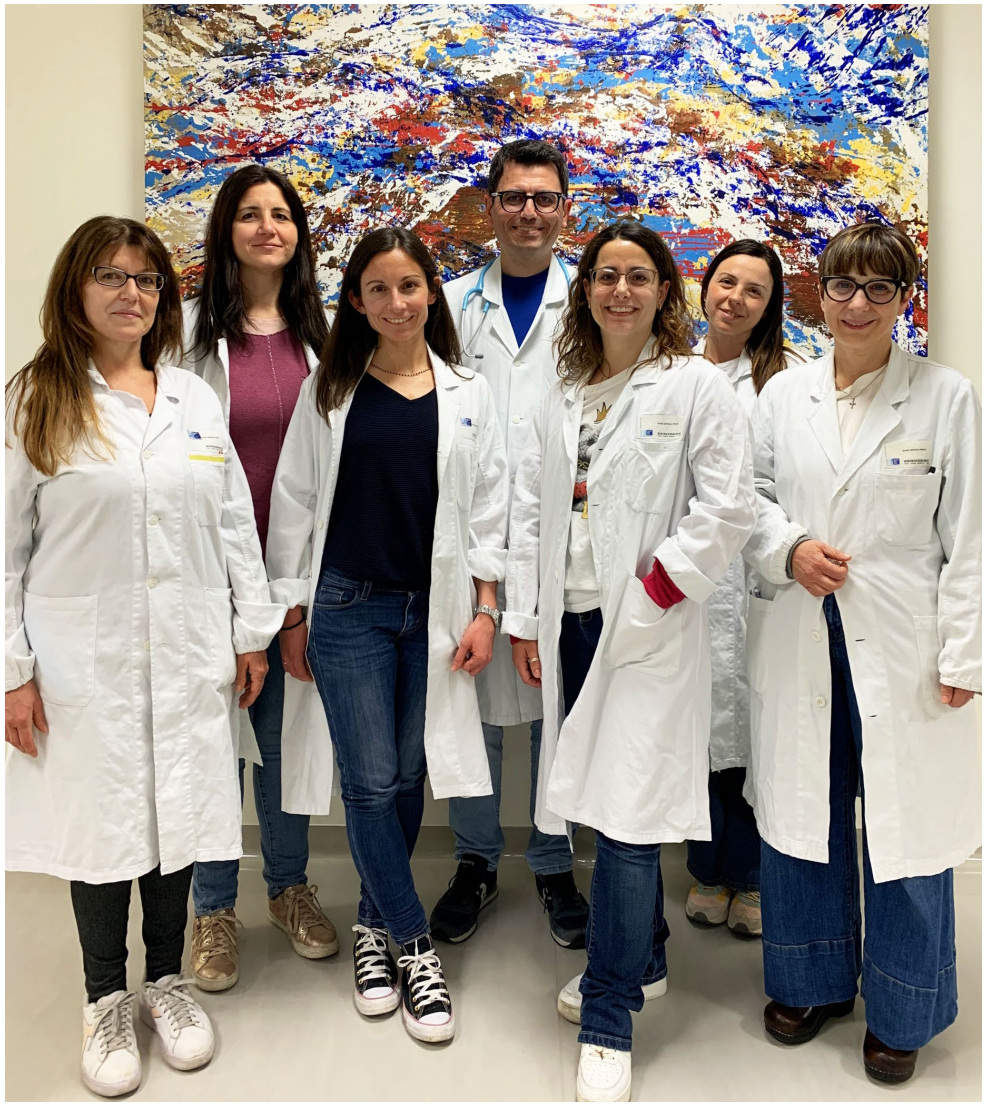
Matteo Benelli
Maurizio Callari

Matteo Suter

Donatella Grasso
Nicola Fenderico
Daniela Castelletti



THANK YOU!



AIRC

Azienda USL Toscana centro
Servizio Sanitario della Toscana

BIG
Breast International Group

IBCSG

Fondazione Sandro Pitigliani
per la lotta contro i tumori - ONLUS

Serum Thymidine Kinase 1 (TKa) in the BIOITALee trial- key findings
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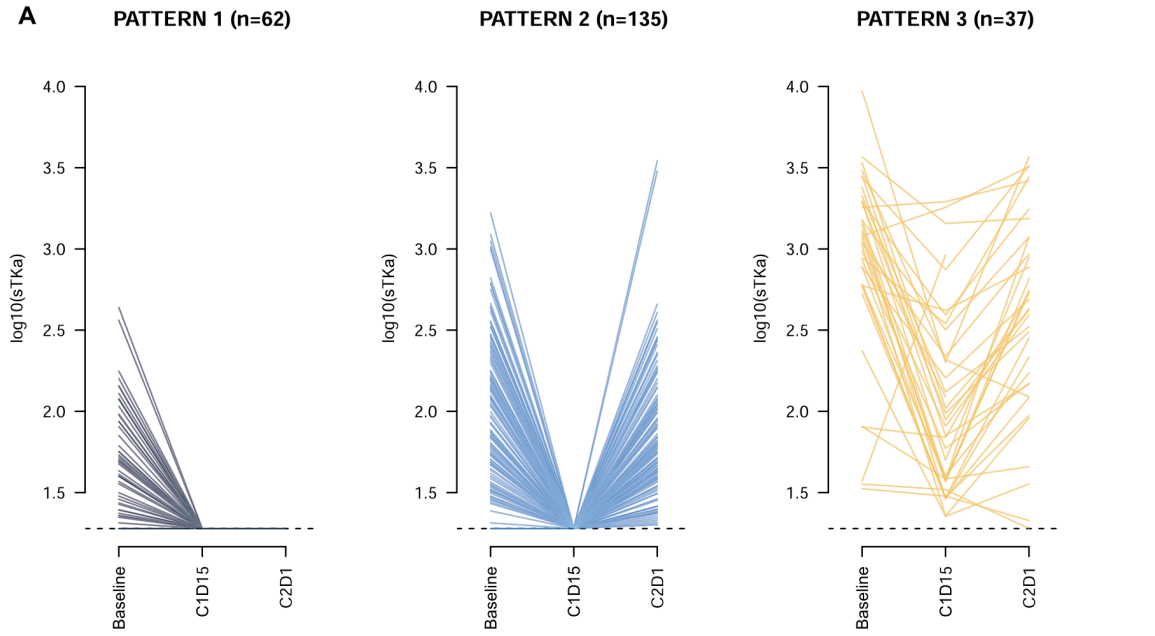

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