bjclub
breast Journal Club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

04-05 Aprile 2024
Padova

PALAZZO BO - Aula Nievo - Via VIII Febbraio, 2

CENTRO ALTINATE - Auditorium - Via Altinate, 71

SNP of Aromatase Predict Long-term Survival and Aromatase Inhibitor Toxicity in Patients with Early Breast Cancer: Biomarker Analysis of the GIM4 and GIM5 Trials
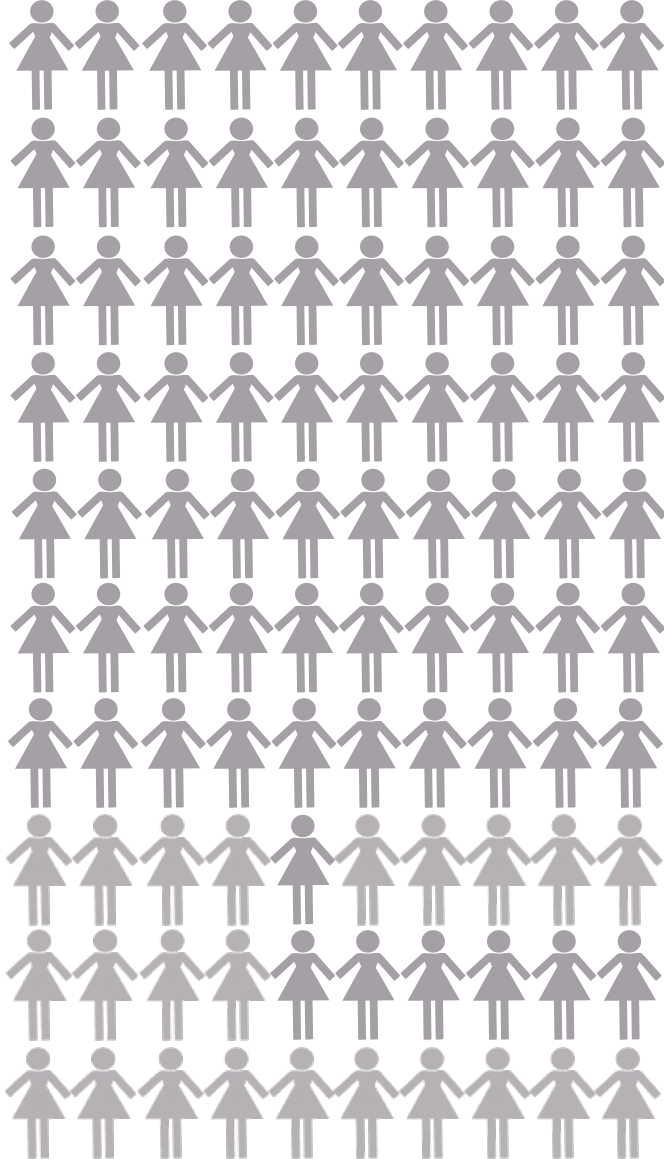
Benedetta Conte

1. Dipartimento di Medicina Traslazionale Università del Piemonte Orientale
2. SCDU Oncologia AOU Maggiore della Carità Novara
3. Translational Genomics and Targeted Therapies in Solid Tumors, Instituto de investigaciones Biomédicas August Pi i Sunyer (IDIBAPS)

DISCLOSURE

- **None**

BACKGROUND
Extended adjuvant AIs in postmenopausal women with HR+ BC: risk and benefit

Benefits if we treat 100 patients with extended AI

1. Del Mastro et al, Lancet Oncol 2021; 2. Tjan-Heijnen et al, Lancet Oncol 2017; 3. Goss et al, NEJM 2016

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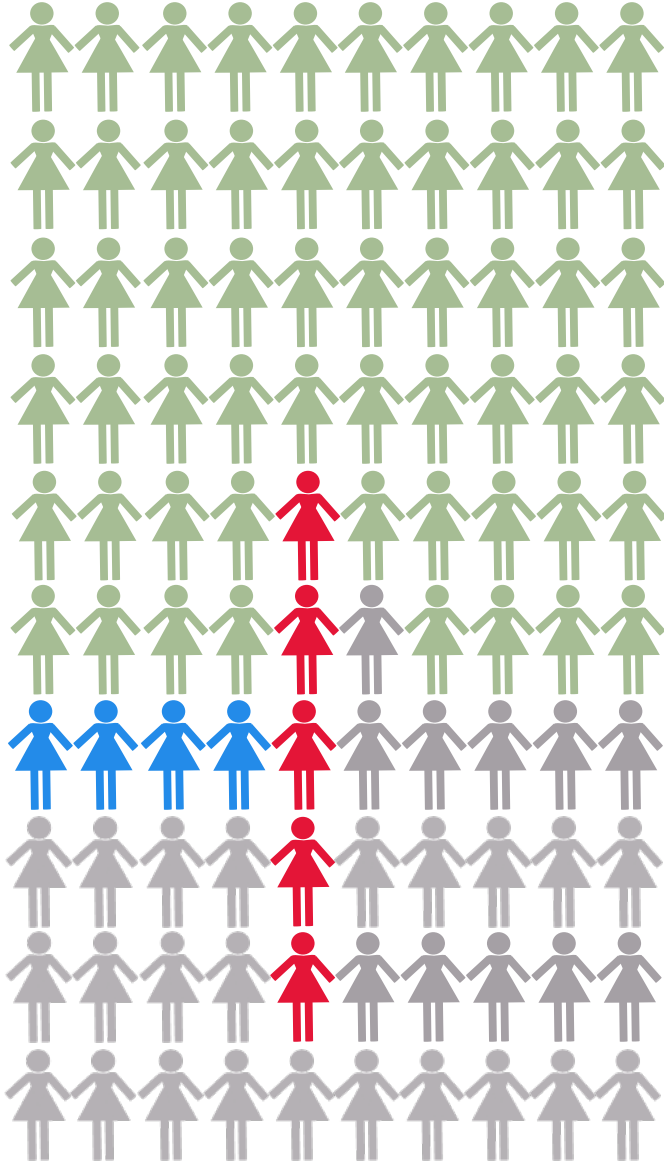## Extended adjuvant AIs in postmenopausal women with HR+ BC: risk and benefit

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However…

2-5 more will develop skeletal events[1-3]

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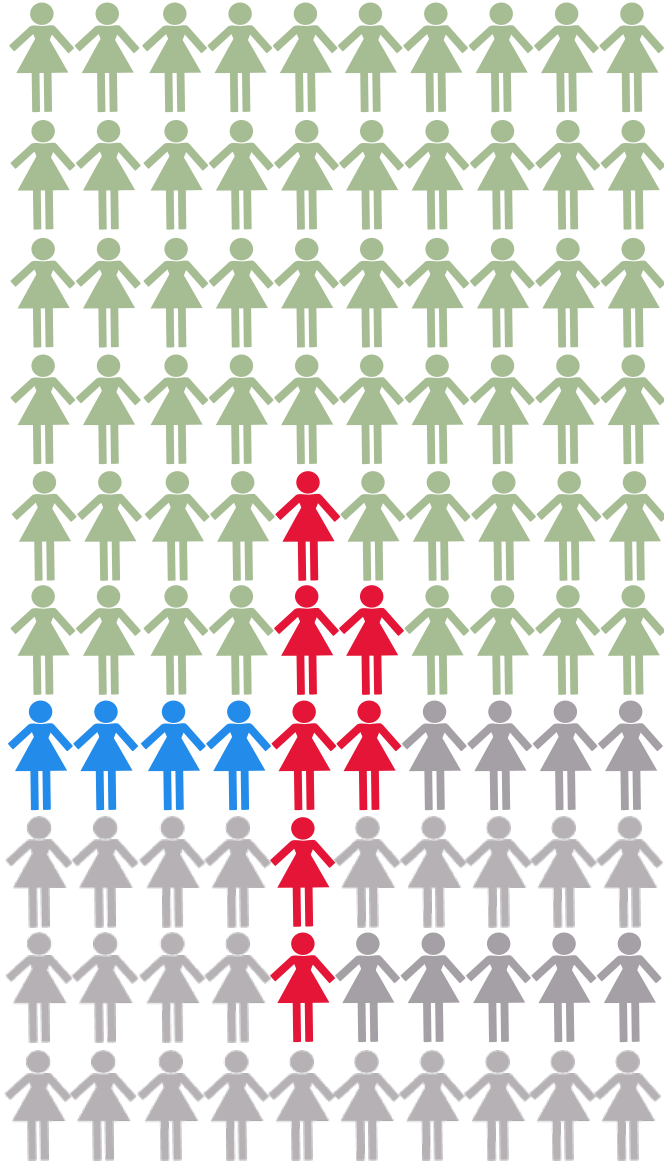
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1-2 more will develop CV events[1-3]

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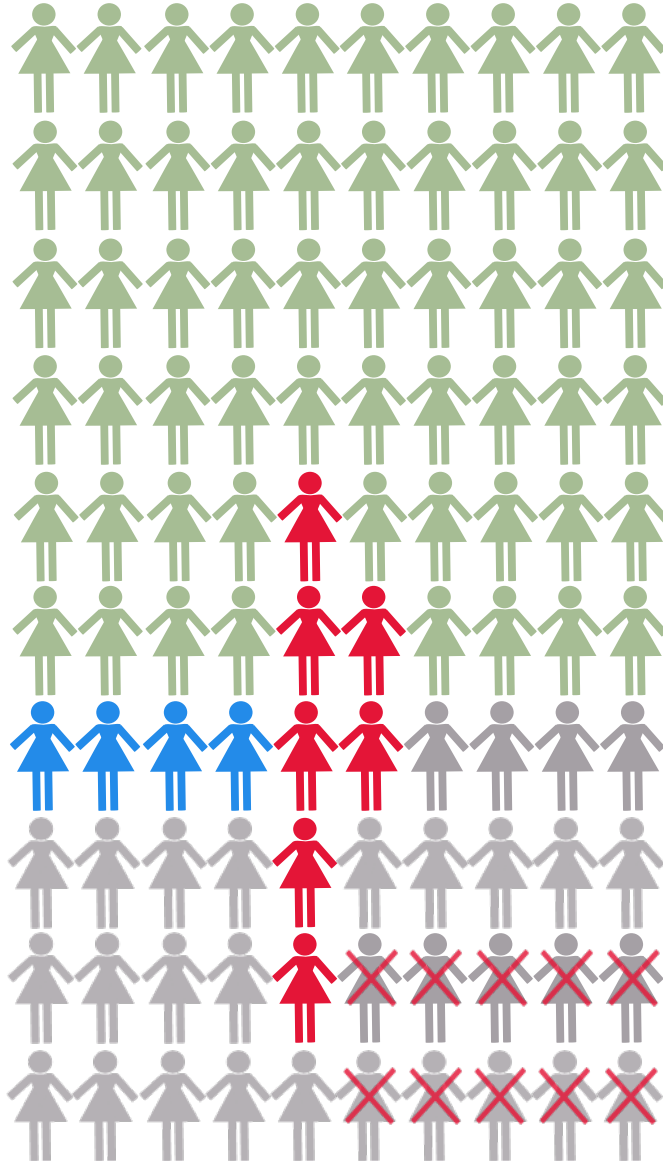
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Some will die for other causes

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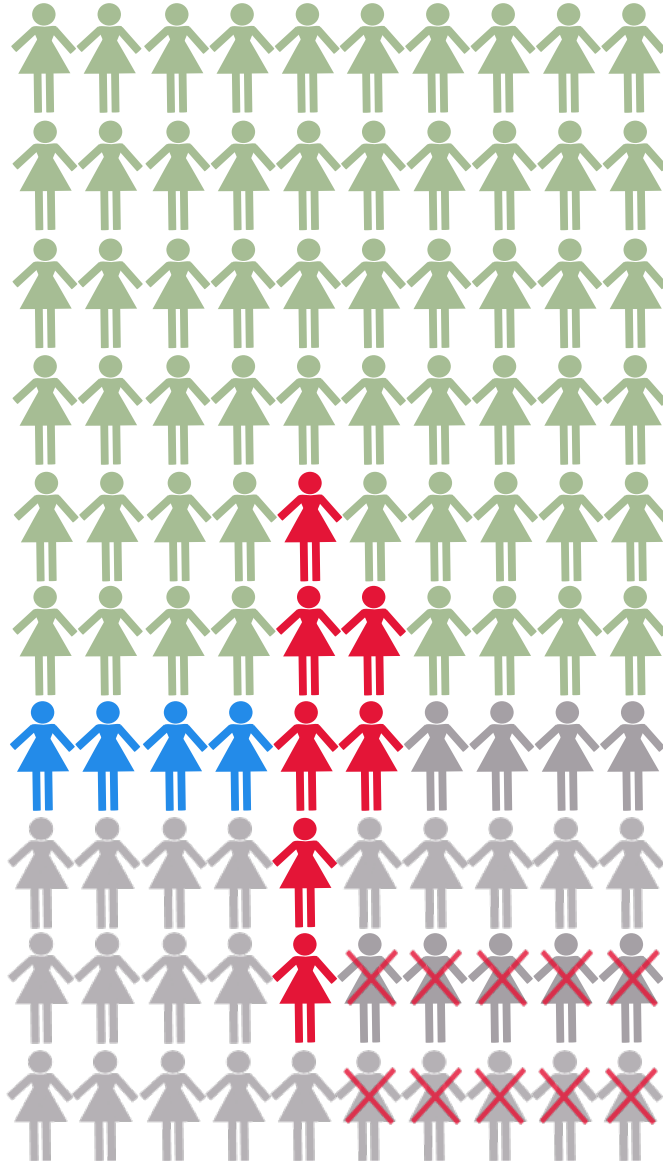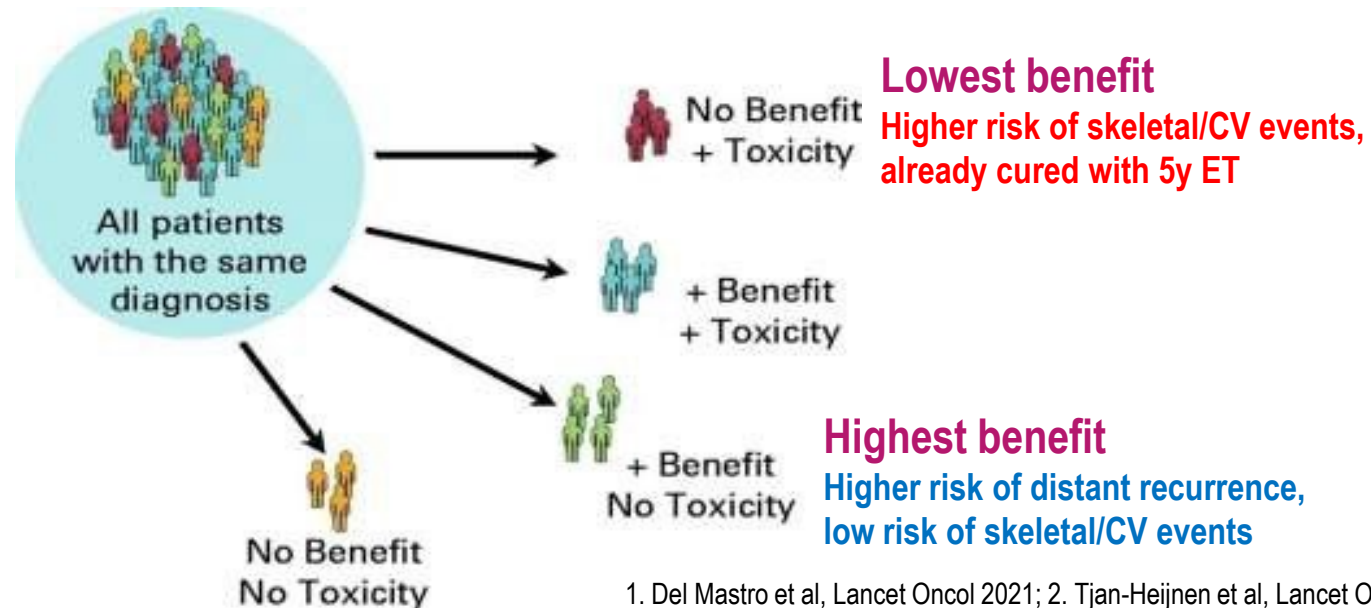
However…

2-5 more will develop skeletal events[1-3]

1-2 more will develop CV events[1-3]

Some will die for other causes

All patients with the same diagnosis

No Benefit + Toxicity

+ Benefit + Toxicity

No Benefit No Toxicity

+ Benefit No Toxicity

Lowest benefit
Higher risk of skeletal/CV events, already cured with 5y ET

Highest benefit
Higher risk of distant recurrence, low risk of skeletal/CV events

1. Del Mastro et al, Lancet Oncol 2021; 2. Tjan-Heijnen et al, Lancet Oncol 2017; 3. Goss et al, NEJM 2016

Background – Biological Rationale

CYP19A1 (aromatase) Gene

Different aromatase function/activity

15q21.2

Ancestral allele
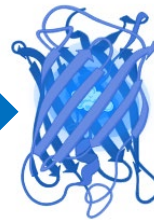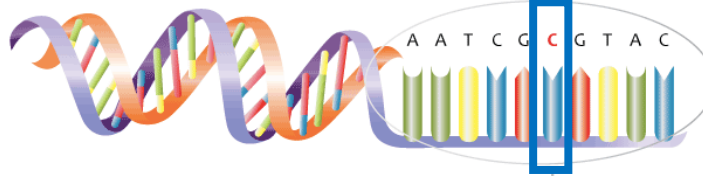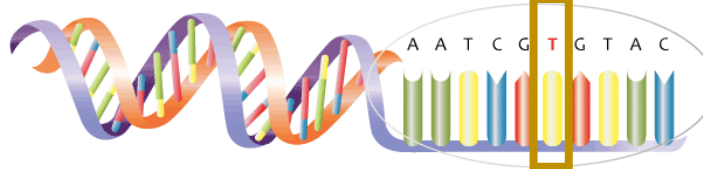
AATCGCGTAC

Variant allele

AATCGTGTAC

Smith et al, NEJM 2003

Background – Biological Rationale

Smith et al, NEJM 2003

Background – Biological Rationale

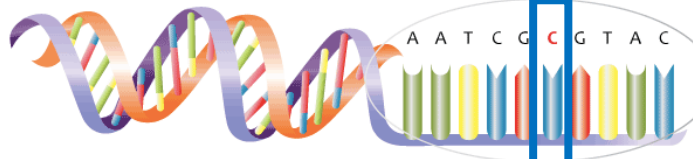| CYP19A1 (aromatase) Gene | Different aromatase function/activity | Different convertion rate from Androstenedione/Testosterone to Estradiol |

15q21.2

Ancestral allele

A A T C G C G T A C

Variant allele

A A T C G T G T A C
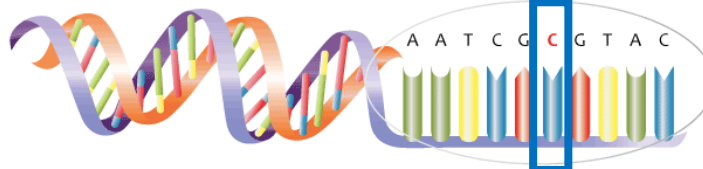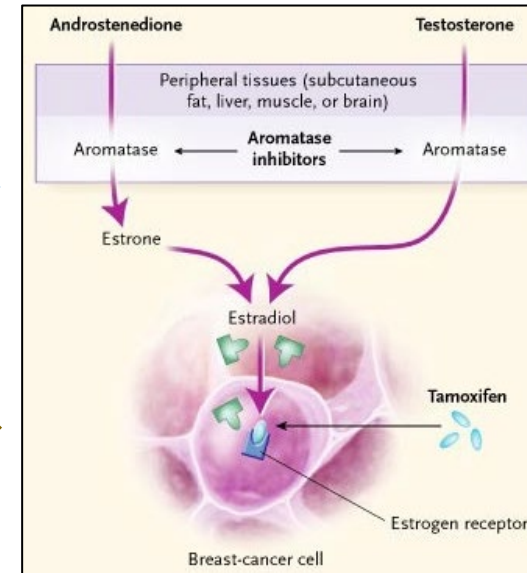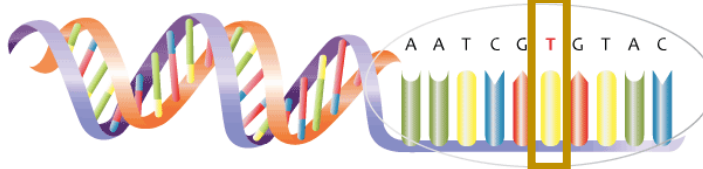
Do SNPs have any impact on:

- Prognosis
- AIs efficacy
- AIs toxicity

In ER+ BC?

Smith et al, NEJM 2003

GIM4 and GIM5 study design

GIM4

Female ER+ and/or PgR+ T1-3; N0-N+

→ 2-3 yrs TAM →

Postmenopausal Free of relapse

→ **Control 3-2 y Letrozole**

→ **Extended 5 y Letrozole**

GIM5

Female ER+ and/or PgR+ and one of the following: N+; G3; T3; T2 and G>1

→ 4-6 yrs TAM →

Postmenopausal Free of relapse

→ **Extended 5 y Letrozole**

GIM4 and GIM5 study design

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GIM4

Female ER+ and/or PgR+ T1-3; N0-N+ → 2-3 yrs TAM → Postmenopausal Free of relapse → Control 3-2 y Letrozole / Extended 5 y Letrozole

↓ Germline SNPs of aromatase

GIM5

Female ER+ and/or PgR+ and one of the following: N+; G3; T3; T2 and G>1 → 4-6 yrs TAM → Postmenopausal Free of relapse → Extended 5 y Letrozole

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Per-protocol endpoints:

- DFS (primary)
- OS (secondary)
- Safety
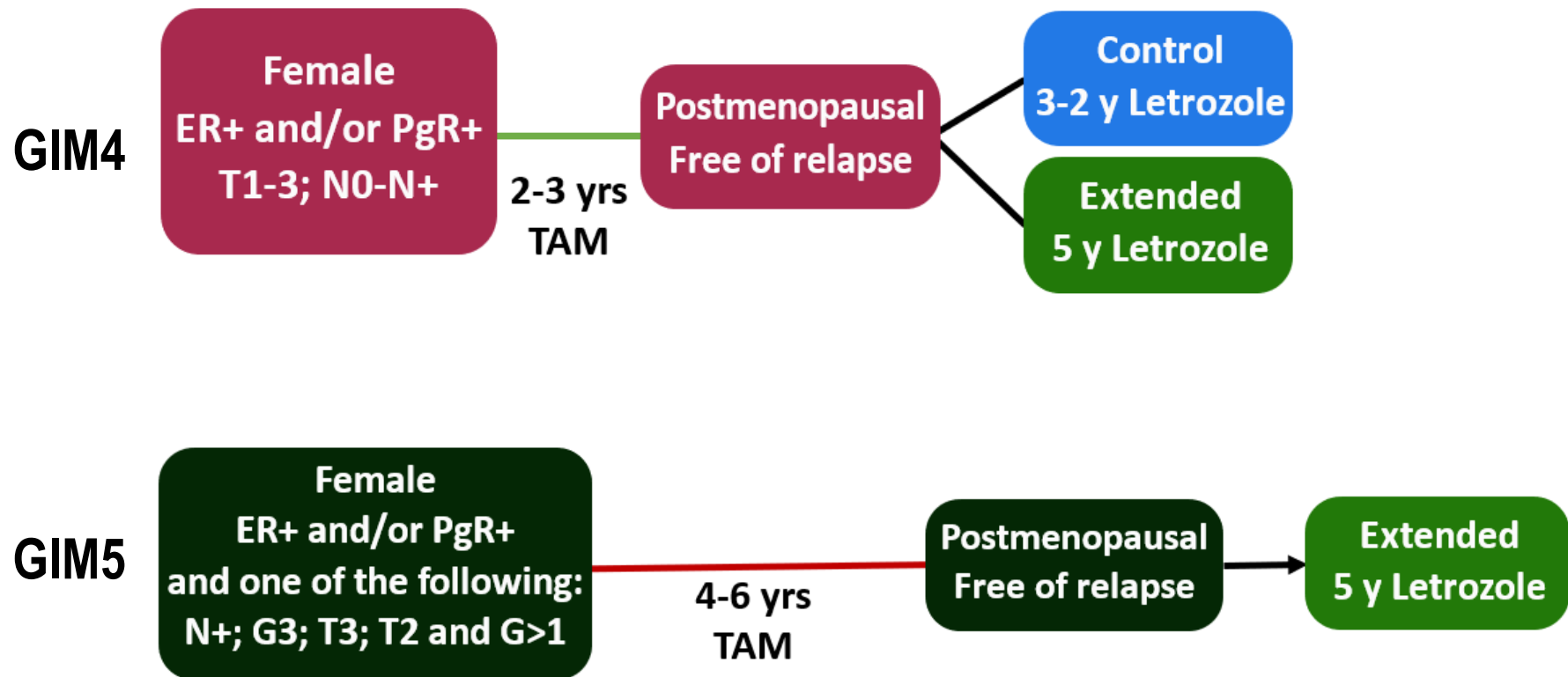
Overall ET duration

5 years — GIM4 short arm

7-8 years — GIM4 long arm

9-11 years — GIM5
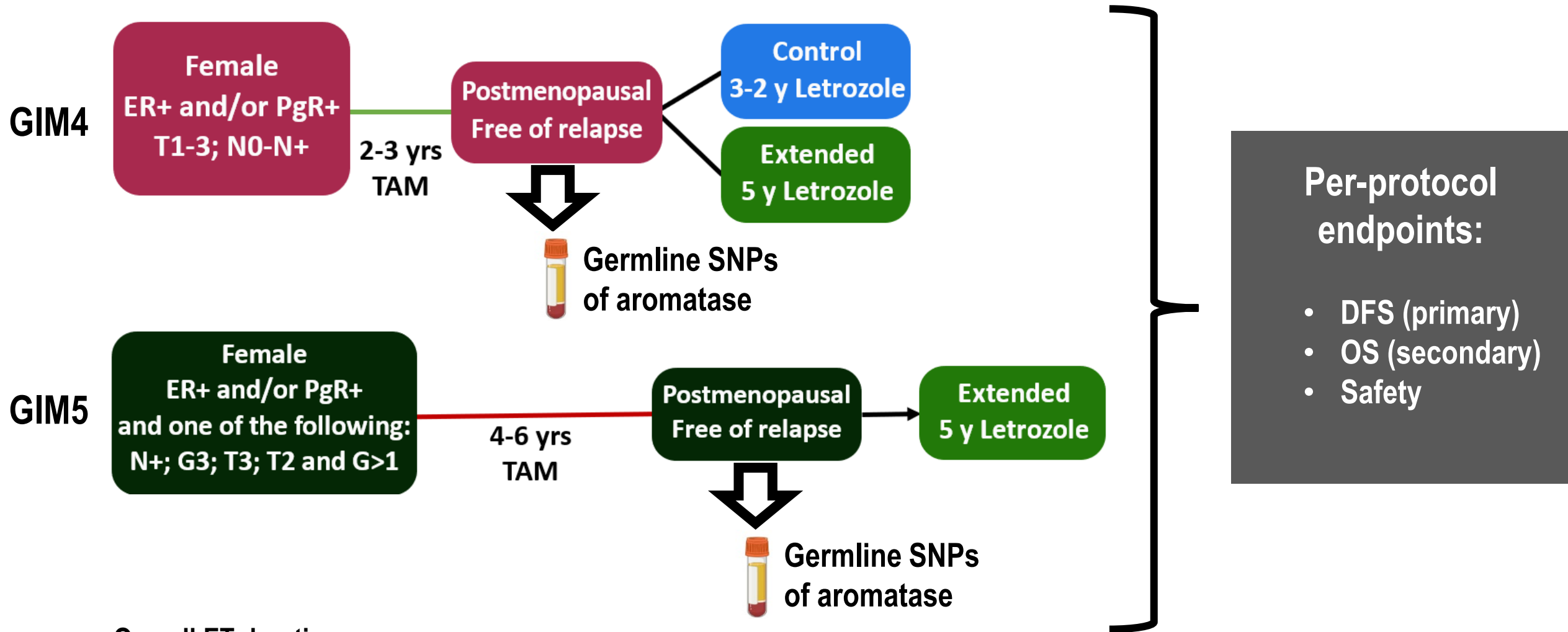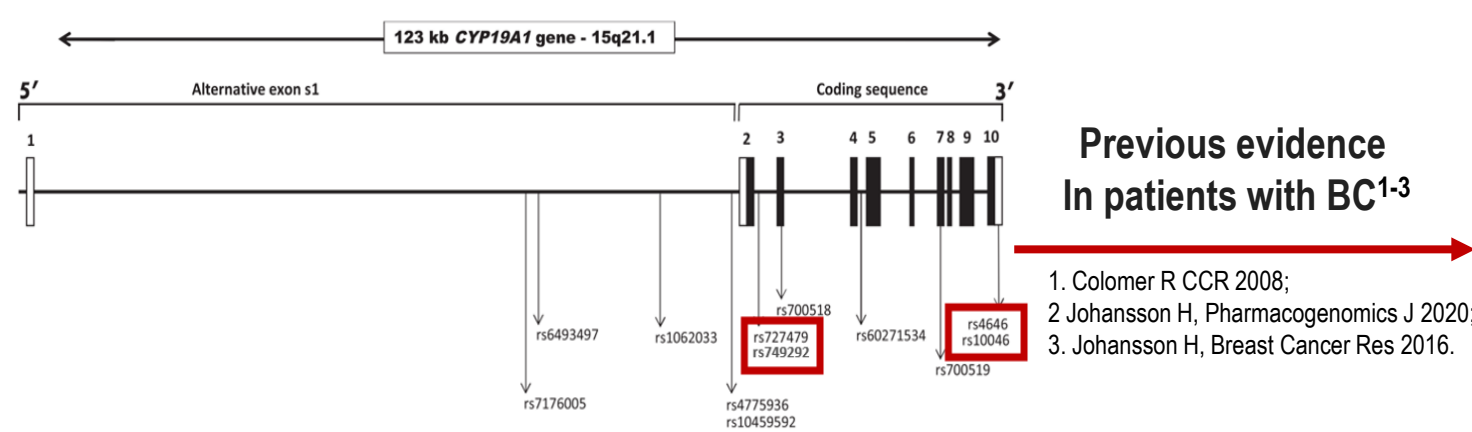
SNPs analysis

Previous evidence In patients with BC[1-3]

1. Colomer R CCR 2008;
2. Johansson H, Pharmacogenomics J 2020;
3. Johansson H, Breast Cancer Res 2016.

SNPs	Region functionality	Variant	Phenotype
rs4646	3' UTR variant	G>T	benign
rs10046	3' UTR variant	C>T	benign
rs727479	intronic	C>T	higher E2 levels
rs749292	exonic	T>G	unknown

SNPs analysis
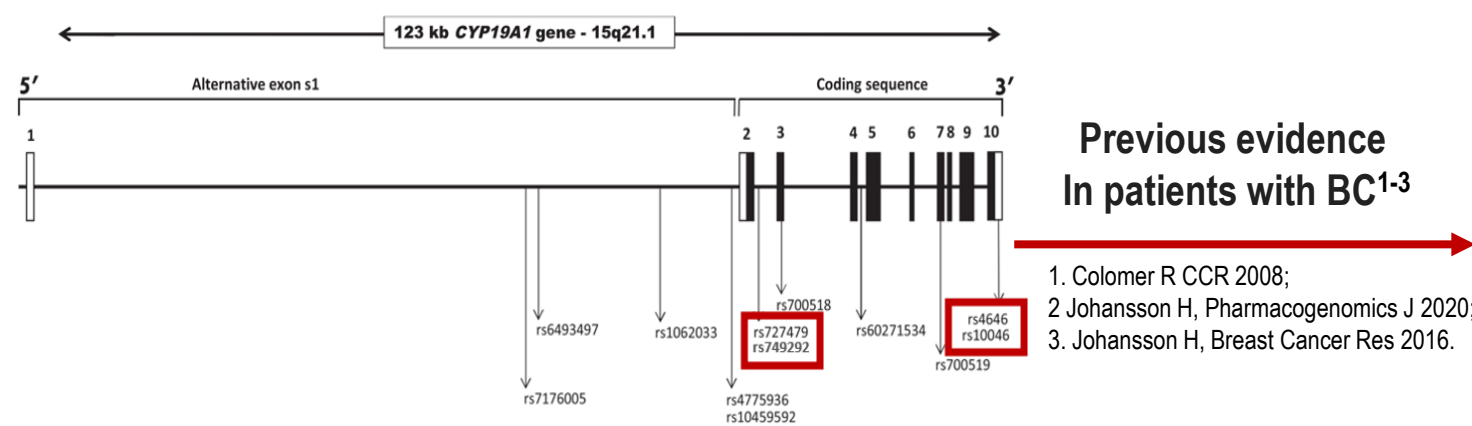
123 kb *CYP19A1* gene - 15q21.1

5' Alternative exon s1   Coding sequence 3'

1   2 3   4 5 6 7 8 9 10

rs6493497   rs1062033   rs700518   rs60271534   rs4646   rs10046

rs727479   rs749292   rs700519

rs7176005   rs4775936   rs10459592

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Association with endpoints assessed under Mendelian model

T in heterozygosis gives the same phenotype as **GG**
(i.e. same aromatase activity)
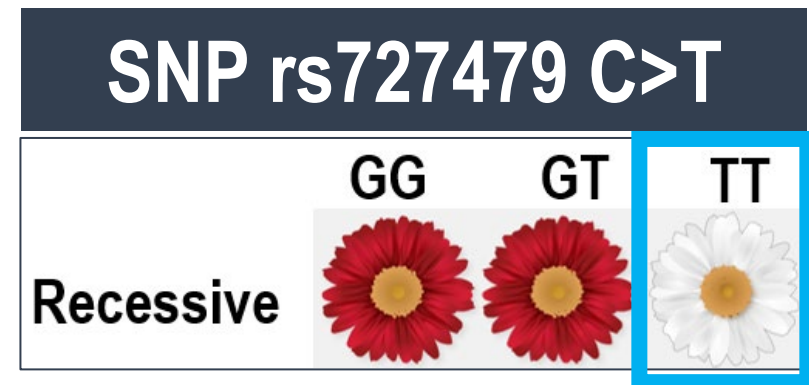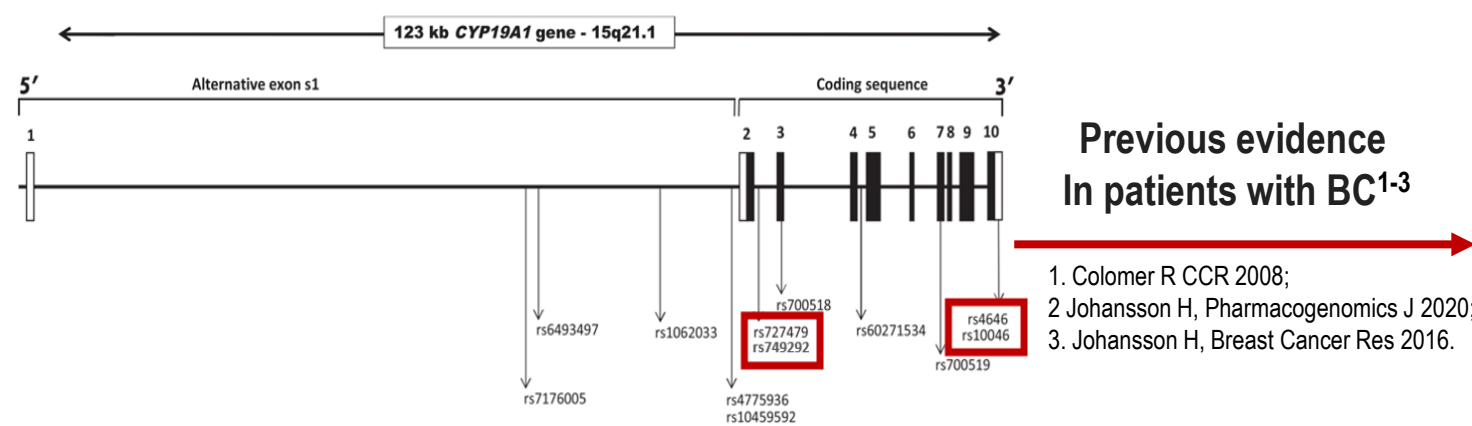
SNP rs727479 C>T

GG   GT   TT

Recessive

SNPs analysis

123 kb *CYP19A1* gene - 15q21.1

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rs749292	exonic	T>G	unknown

Association with endpoints assessed under Mendelian model

T in heterozygosis gives the same phenotype as **TT** (i.e. same aromatase activity)

SNP rs727479 C>T

	GG	GT	TT
Recessive	red	red	white
Dominant	red	white	white

SNPs analysis

123 kb *CYP19A1* gene - 15q21.1

5' Alternative exon s1 Coding sequence 3'

1   2 3   4 5   6   7 8 9 10

rs6493497   rs1062033   rs700518   rs60271534   rs4646 rs10046

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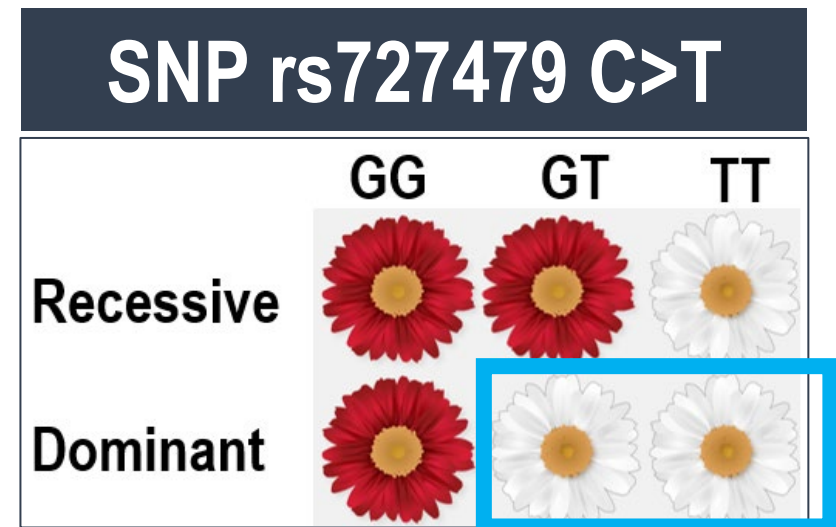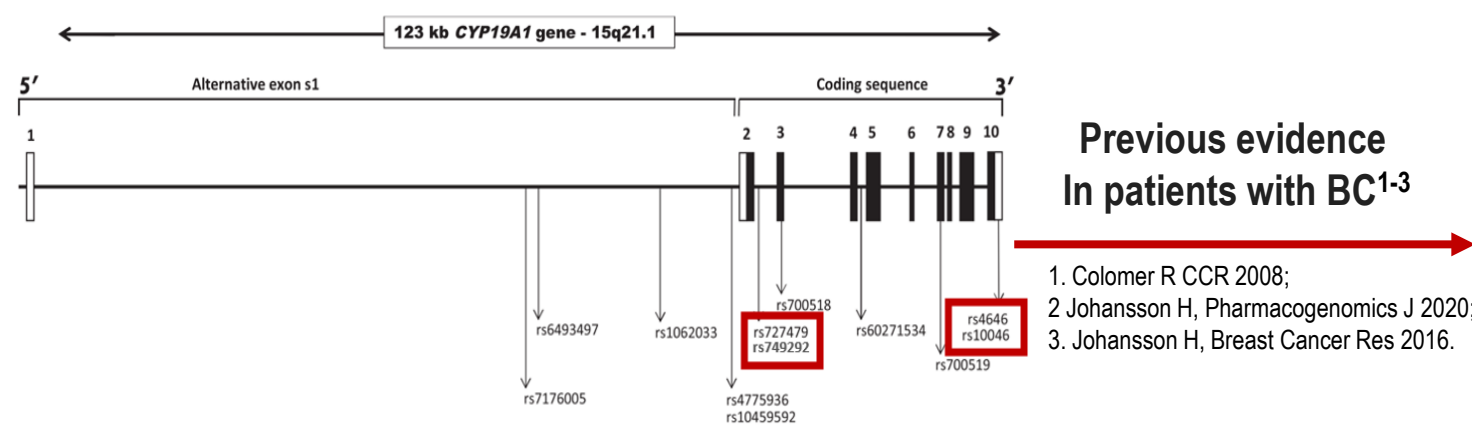| SNPs	Region functionality	Variant	Phenotype
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Association with endpoints assessed under Mendelian model

SNP rs727479 C>T

T in heterozygosis gives a **mixed** phenotype
(i.e. **intermediate** aromatase activity)
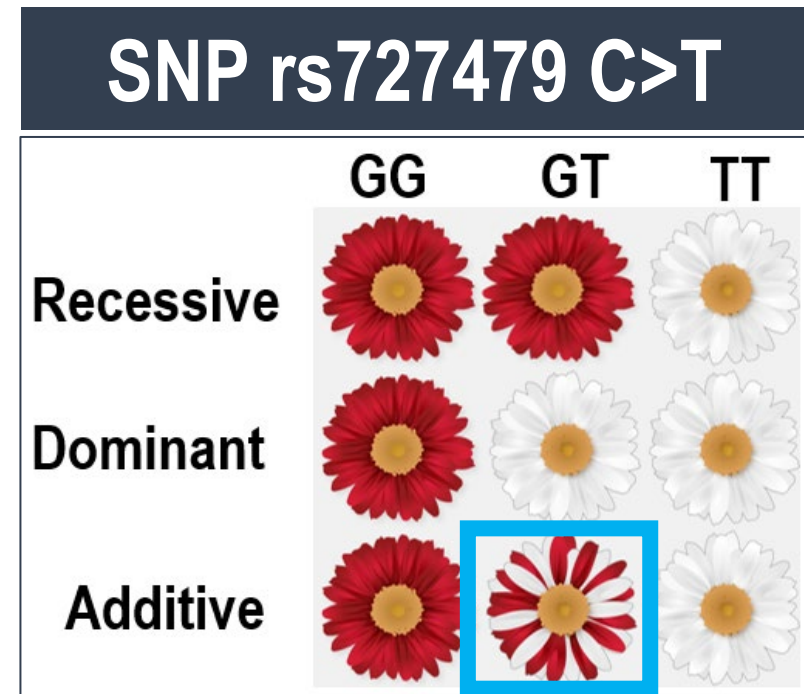
Survival outcomes

Patients with SNPs data N=886 (591 from GIM4, 295 from GIM5)
Median FU: 12 years from study enrollment (14-18 years from diagnosis)

DFS (primary endpoint)
Cox univariate model
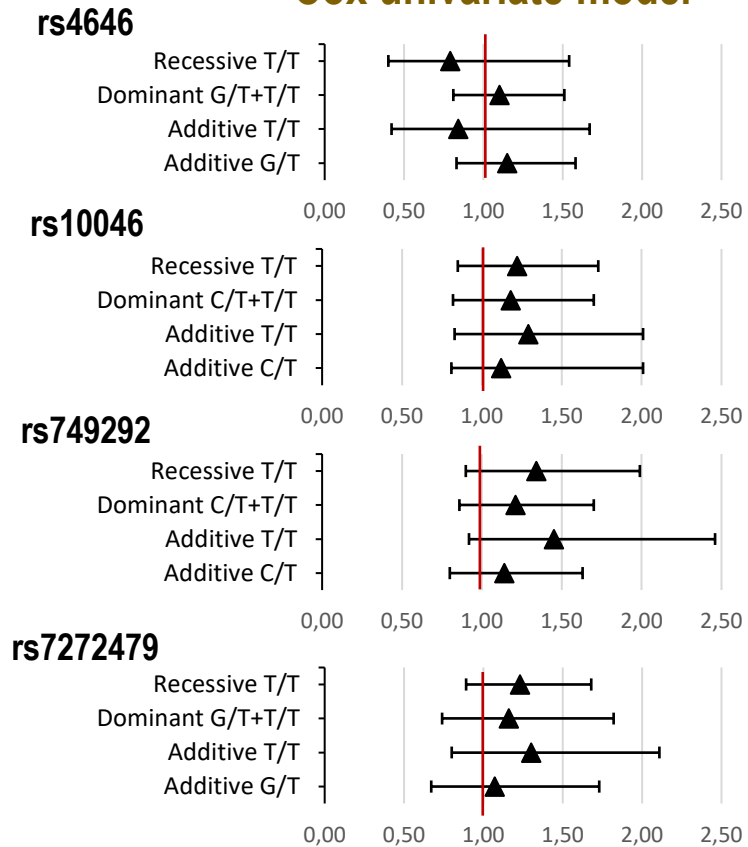
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Patients with SNPs data N=886 (591 from GIM4, 295 from GIM5)
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DFS (primary endpoint)
Cox univariate model

OS (secondary endpoint)
Cox univariate model
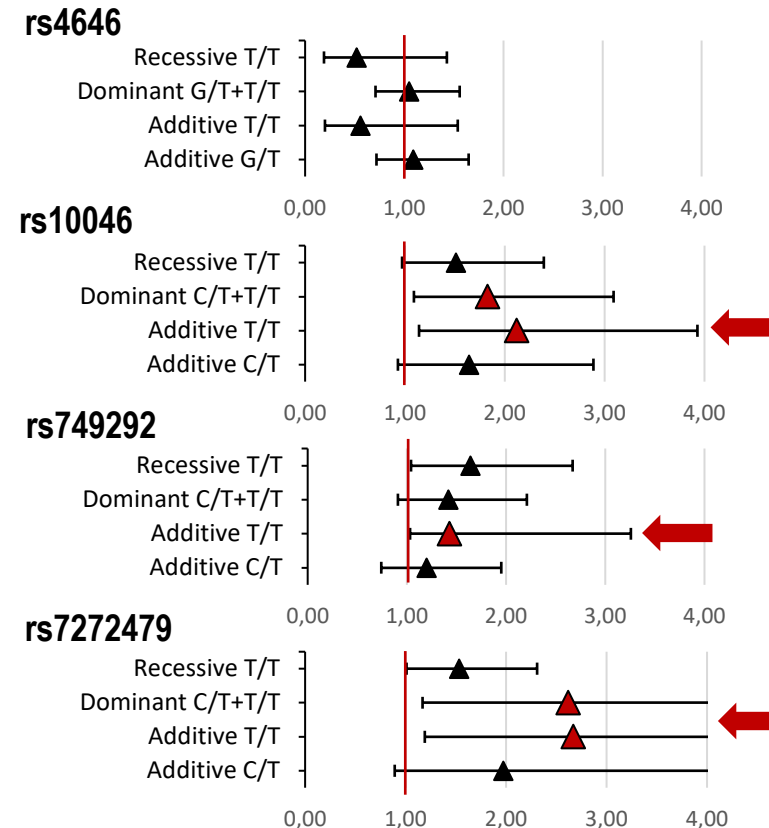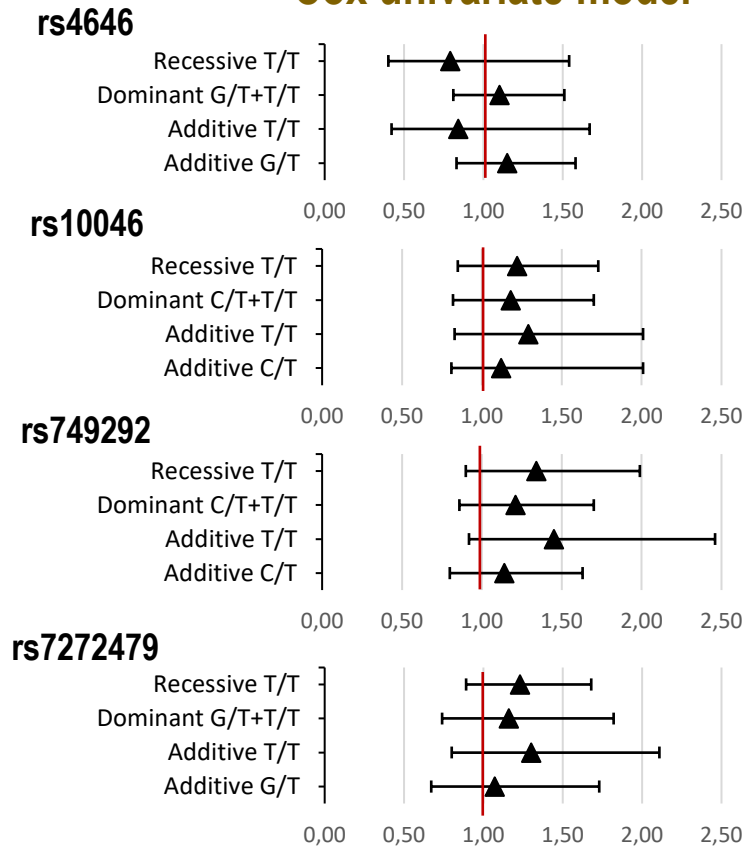
Is this due to chance? It's always the variant (T) allele to be associated with worse OS!

T allele in rs10046, rs749292 and rs727479 significantly associated with OS but not DFS

Analysis of DFS events show low prevalence of distant recurrence

Patients with SNPs data N=886 (591 from GIM4, 295 from GIM5)
Median FU: 12 years from study enrollment (14-18 years from diagnosis)

At 14-18 years from diagnosis,
<50% of DFS events
are distant breast cancer recurrences

| Type of recurrence	No (%)	
Distant	68	**43%**
Death with breast cancer	7	
Loco-regional	19	
Ipsilateral breast cancer	9	
Contralateral breast cancer	26	
Second primary	24	
Death without breast cancer	6	
Total	159	

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Type of recurrence	No (%)	
Distant	68	**43%**
Death with breast cancer	7	
Loco-regional	19	
Ipsilateral breast cancer	9	**22%**
Contralateral breast cancer	26	
Second primary	24	**19%**
Death without breast cancer	6	
Total	**159**	

Standard Survival Model

All types of DFS events are treated as equal		
One Hazard Ratio for all DFS events		
SNPs	HR (95% CIs)	p value
rs10046-T/T	1.29 (0.83-2.01)	0.259
rs749292-T/T	1.45 (0.92-2.46)	0.108
rs727479-C/T+T/T	1.16 (0.74-1.82)	0.513

BC metastasis=3
2°primary=4
Non-BC death=3

N. Still at Risk of event=10

Events=10

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Competing Risk Model

Events of interest Distant recurrence Death with BC	Competing events Contralateral iBC 2nd primary malignancy Death without BC
Fine-Gray model → 2 subdistribution HR (sHR), one for each event type	

Fine et al, J of American Stat Ass, 1999

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rs727479-C/T+T/T	2.16 (1.00-4.97)	0.050

BC metastasis=3
2°primary=4
Non-BC death=3
N. Still at Risk of event=10
Events=10

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Comp. Events=7
Events=3

Fine et al, J of American Stat Ass, 1999

High-risk SNPs are in high positive Linkage disequilibrium with each other

SNPs ID	Position (GRCh37)	Haplotypes							
rs4646	chr15:51502844	G	G	T	G	T	G	G	
rs10046	chr15:51502986	T	C	C	T	C	C	T	Others
rs727479	chr15:51534547	T	G	G	T	T	T	G	
rs749292	chr15:51558731	T	C	C	C	C	C	C	
Haplotype frequency		0.39	0.20	0.19	0.09	0.09	0.02	0.00	0.02
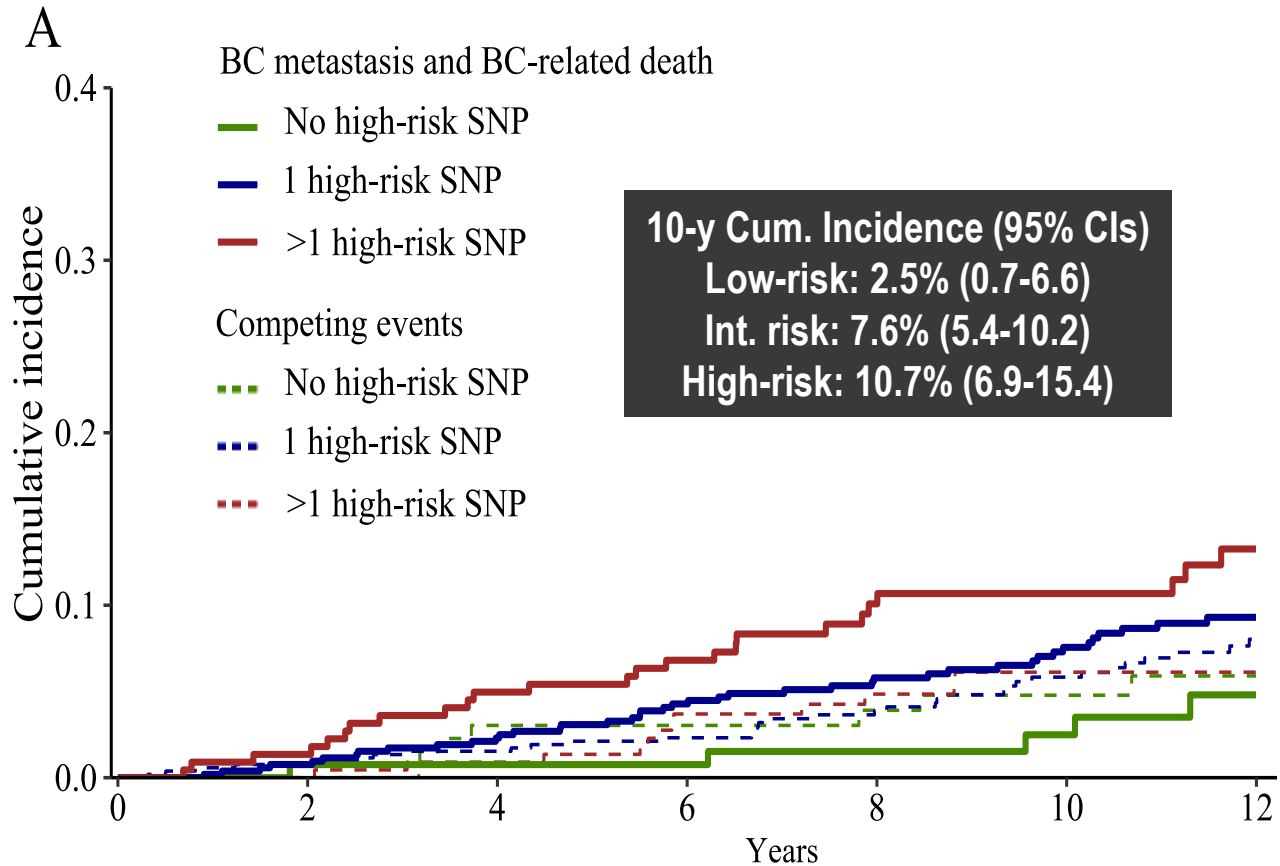
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Survival outcomes according to SNPs-based groups

A

BC metastasis and BC-related death

— No high-risk SNP
— 1 high-risk SNP
— >1 high-risk SNP

Competing events

--- No high-risk SNP
--- 1 high-risk SNP
--- >1 high-risk SNP

10-y Cum. Incidence (95% CIs)
Low-risk: 2.5% (0.7-6.6)
Int. risk: 7.6% (5.4-10.2)
High-risk: 10.7% (6.9-15.4)

Cumulative incidence

Years

Cum. incidence estimates (95% CIs)

0 (NA-NA)	0.8 (0.1-3.8)	0.8 (0.1-3.8)	0.8 (0.1-3.8)	1.5 (0.3-4.9)	2.5 (0.7-6.6)	4.8 (1.7-10.3)
0 (NA-NA)	0.8 (0.3-1.9)	2.3 (1.3-3.9)	4.3 (2.8-6.3)	5.8 (4-8.1)	7.6 (5.4-10.2)	9.3 (6.8-12.3)
0 (NA-NA)	1.4 (0.4-3.6)	5 (2.6-8.4)	6.8 (4-10.7)	10.1 (6.4-14.7)	10.7 (6.9-15.4)	13.3 (8.7-18.8)

Survival outcomes according to SNPs-based groups
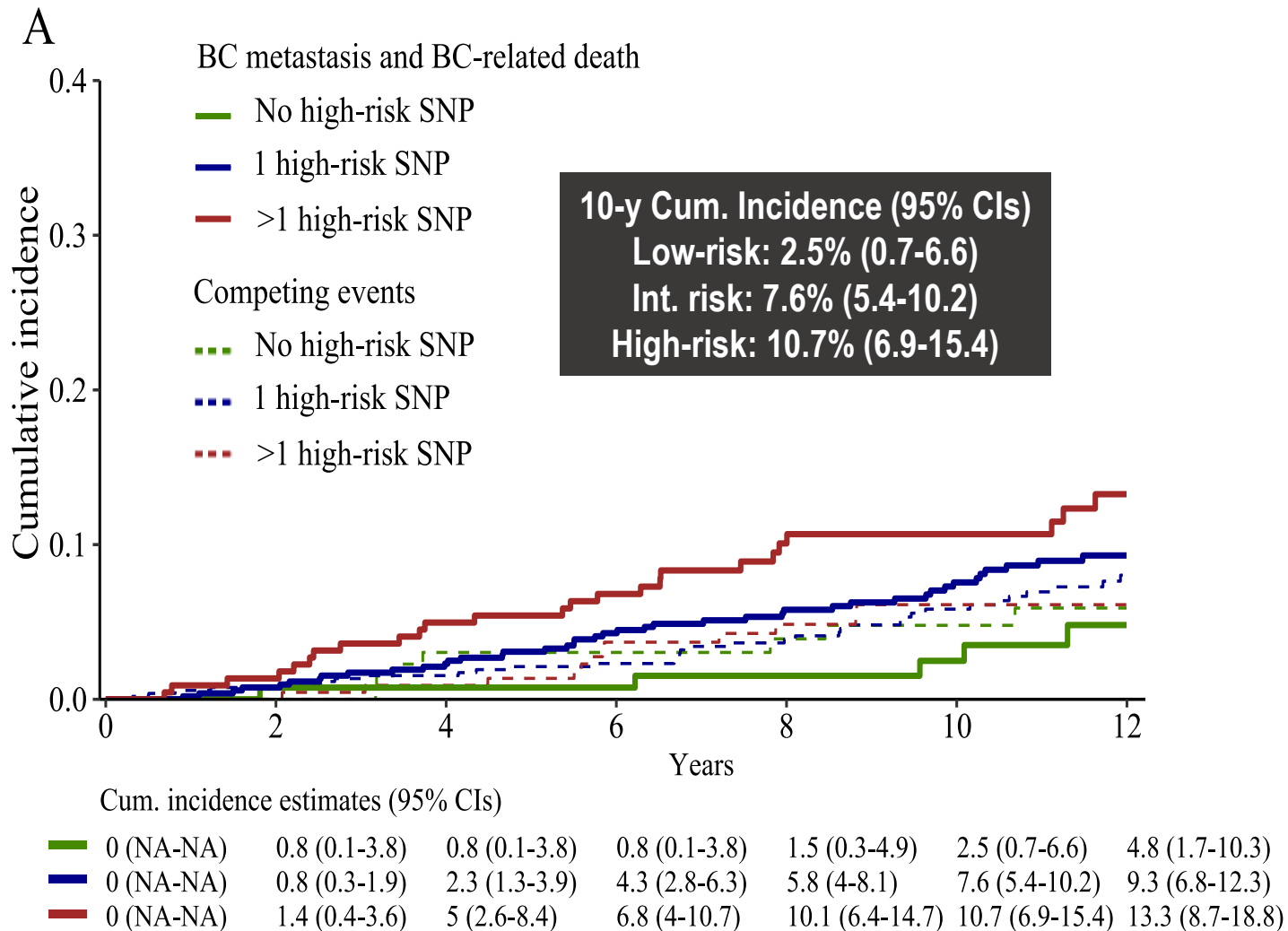
Fine-Gray multivariable model

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BC metastasis and BC-related death
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— >1 high-risk SNP

Competing events
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10-y Cum. Incidence (95% CIs)
Low-risk: 2.5% (0.7-6.6)
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High-risk: 10.7% (6.9-15.4)

Cum. incidence estimates (95% CIs)

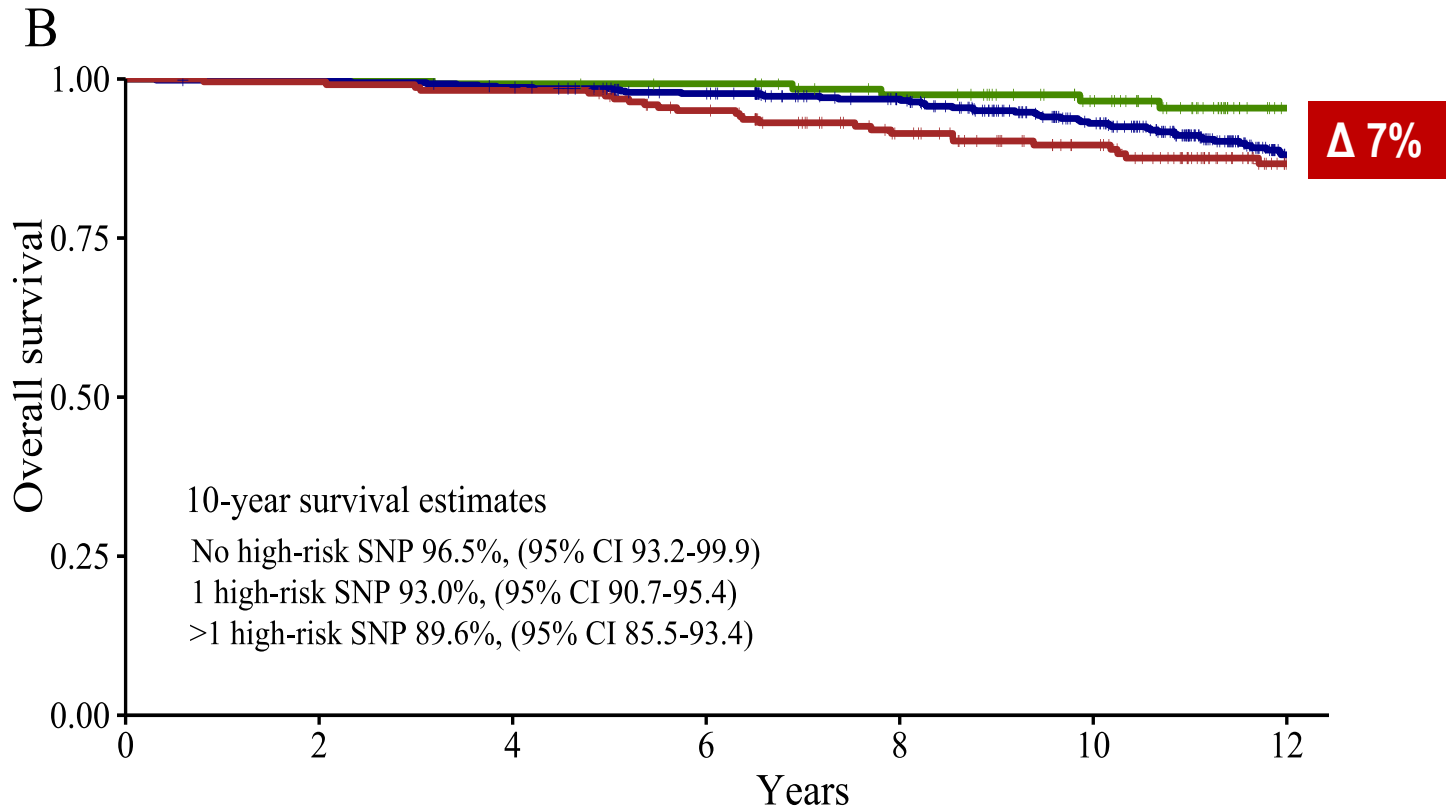|						
— 0 (NA-NA)	0.8 (0.1-3.8)	0.8 (0.1-3.8)	0.8 (0.1-3.8)	1.5 (0.3-4.9)	2.5 (0.7-6.6)	4.8 (1.7-10.3)
— 0 (NA-NA)	0.8 (0.3-1.9)	2.3 (1.3-3.9)	4.3 (2.8-6.3)	5.8 (4-8.1)	7.6 (5.4-10.2)	9.3 (6.8-12.3)
— 0 (NA-NA)	1.4 (0.4-3.6)	5 (2.6-8.4)	6.8 (4-10.7)	10.1 (6.4-14.7)	10.7 (6.9-15.4)	13.3 (8.7-18.8)

Variable	Subdistribution HR (95% CIs)	p value
SNPs-groups		
0 high-risk SNP	1	
1 high-risk SNP	**2.55 (1.00-6.45)**	**0.048**
>1 high-risk SNP	**3.48 (1.33-9.13)**	**0.011**
Tumor size		
pT1	1	
pT2	1.90 (1.13-3.20)	0.016
pT3-4	3.56 (1.79-7.10)	<0.001
Nodal status		
pN0	1	
pN+	3.15 (1.62-6.13)	<0.001
(Neo)adjuvant CT		
No	1	
Yes	1.22 (0.52-2.84)	0.652
Age at diagnosis	0.99 (0.97-1.03)	0.940
Study cohort		
GIM4	1	
GIM5	0.95 (0.58-1.56)	0.835

Overall survival according to SNPs-based groups

B

10-year survival estimates

No high-risk SNP 96.5%, (95% CI 93.2-99.9)
1 high-risk SNP 93.0%, (95% CI 90.7-95.4)
>1 high-risk SNP 89.6%, (95% CI 85.5-93.4)

Δ 7%

Number at risk

133	133	132	130	111	96	59
530	527	520	498	433	366	236
223	222	219	207	160	135	90

Overall survival according to SNPs-based groups
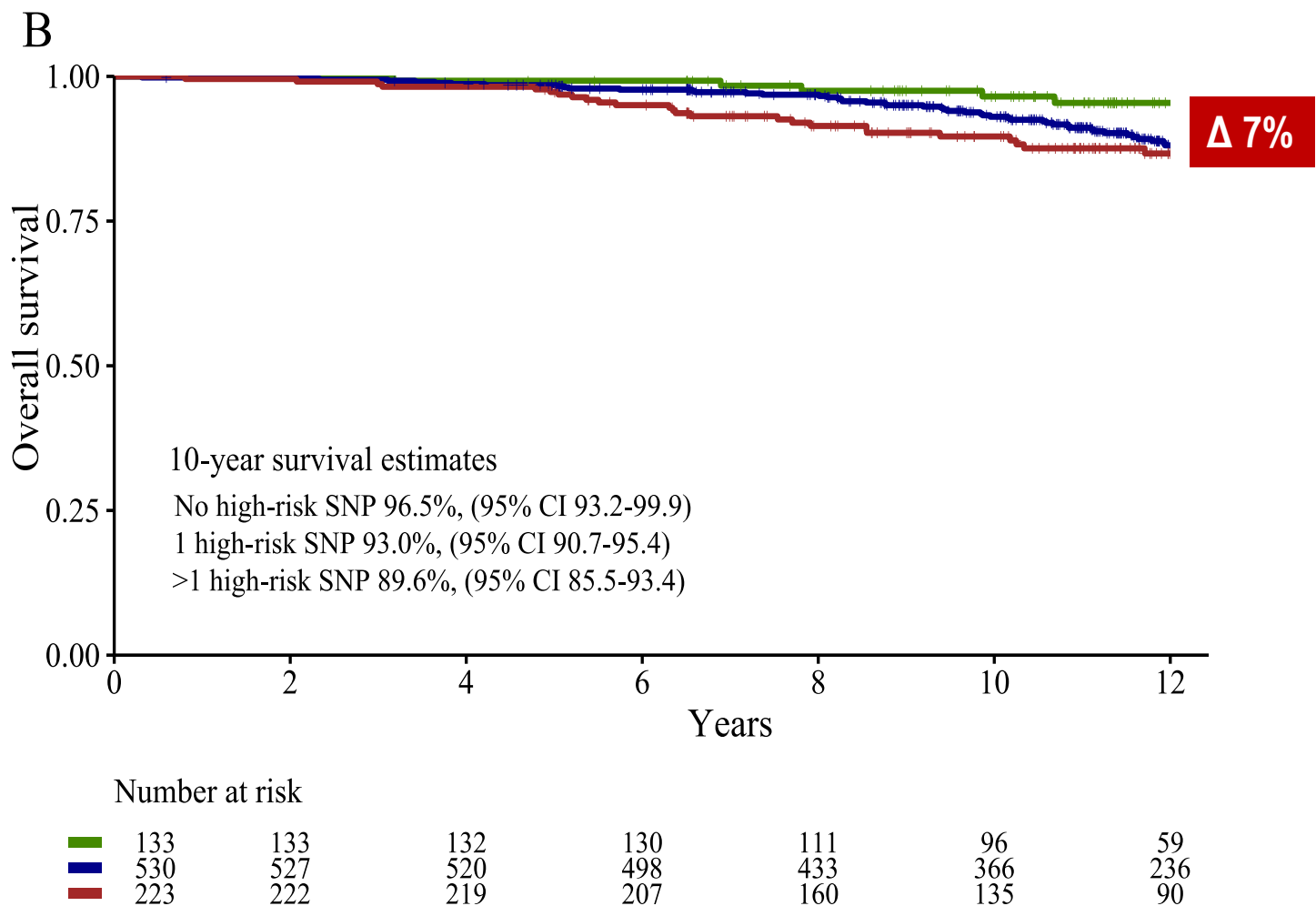
Cox multivariable model

Variable	HR (95% CIs)	p value
SNPs-based groups		
0 high-risk SNP	1	
1 high-risk SNP	**2.42 (1.04-5.70)**	**0.040**
>1 high-risk SNP	**3.00 (1.24-7.32)**	**0.015**
Tumor size		
pT1	1	
pT2	1.59 (0.99-2.59)	0.057
pT3-4	2.92 (1.55-5.51)	<0.001
Nodal status		
pN0	1	
pN+	2.16 (1.24-3.76)	0.007
(Neo)adjuvant CT		
No	1	
Yes	0.87 (0.45-1.66)	0.667
Age at diagnosis	1.06 (1.03-1.09)	<0.001
Study cohort		
GIM4	1	
GIM5	0.78 (0.46-1.28)	0.325

B

Overall survival

Δ 7%

10-year survival estimates

No high-risk SNP 96.5%, (95% CI 93.2-99.9)
1 high-risk SNP 93.0%, (95% CI 90.7-95.4)
>1 high-risk SNP 89.6%, (95% CI 85.5-93.4)

Years

Number at risk

133	133	132	130	111	96	59
530	527	520	498	433	366	236
223	222	219	207	160	135	90

High-risk SNPs have a protective effect on Skeletal and CV events

High-risk SNPs
rs10046-T/T
rs749292-T/T
rs727479-T/T

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Bone risk groups:
Low: rs10046-GG + rs479292-GG
High: rs10046-TT + rs 479292-TT
Intermediate: Others

Event: bone fractures (any type)
Competing risks: any DFS events
(death, second primary, BC recurrence)

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High-risk SNPs
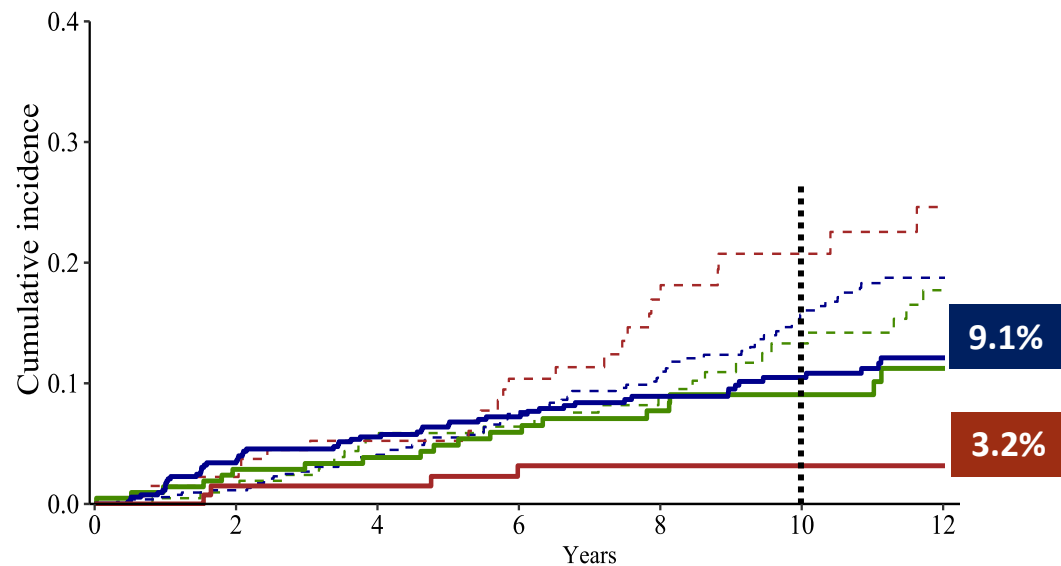
rs10046-T/T

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rs727479-T/T

Bone risk groups:

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9.1%

3.2%

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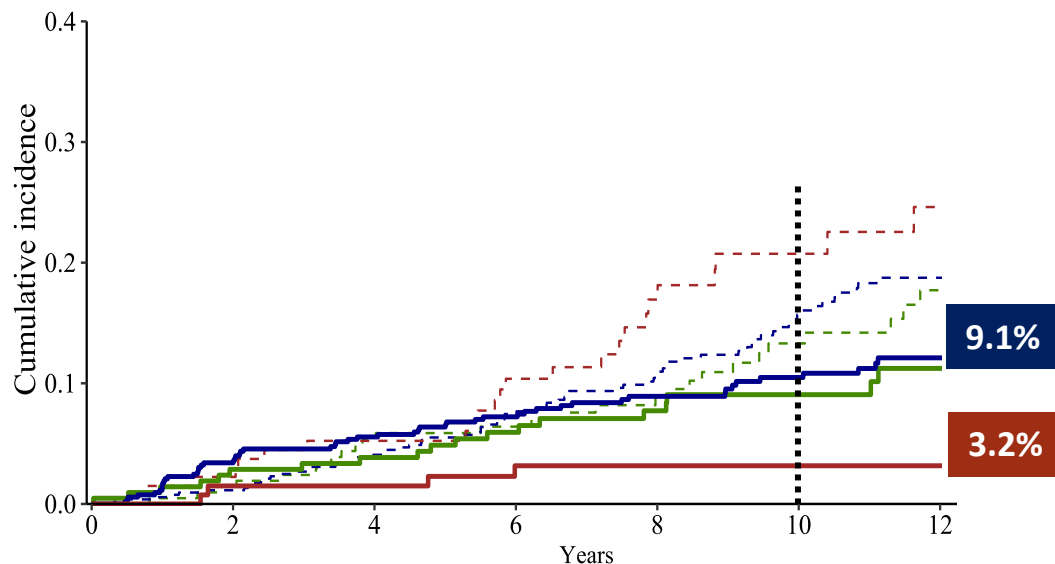
| rs10046-T/T |
| rs749292-T/T |

rs727479-T/T

Bone risk groups:
Low: rs10046-GG + rs479292-GG
High: rs10046-TT + rs 479292-TT
Intermediate: Others

CV risk groups:
Low: rs727479 – G/G
High: rs727479-T/T

Event: bone fractures (any type)
Competing risks: any DFS events
(death, second primary, BC recurrence)

Event: thrombosis, embolism, stroke, angina, myocardial infarction
Competing risks: any DFS events

9.1%

3.2%

High-risk SNPs have a protective effect on Skeletal and CV events

High-risk SNPs
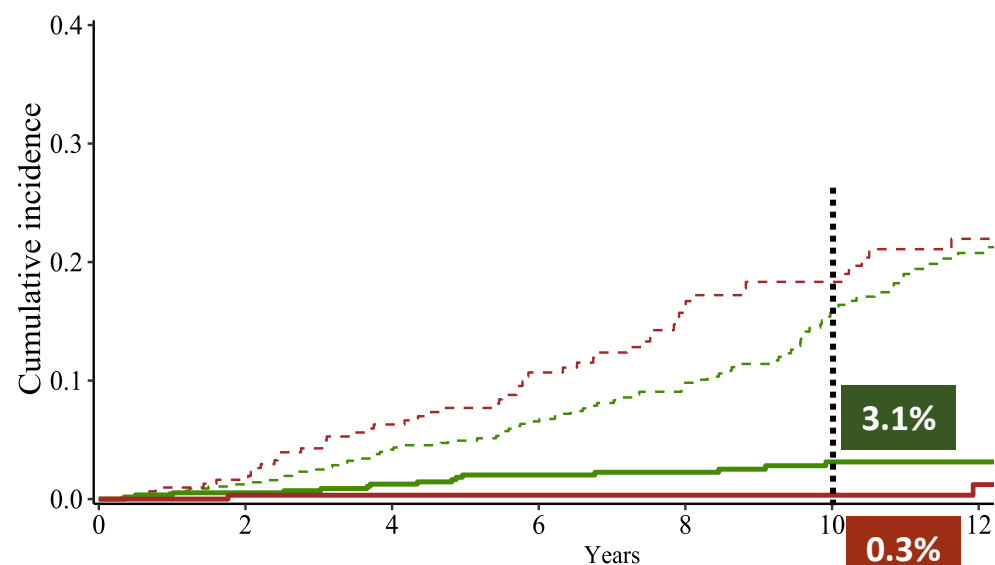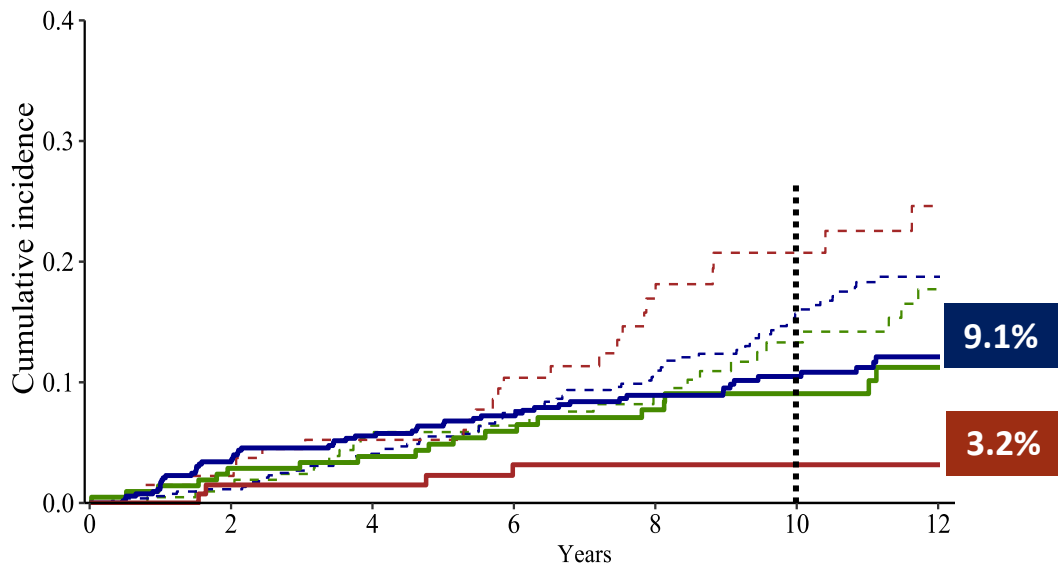
rs10046-T/T
rs749292-T/T

rs727479-T/T

Bone risk groups:
Low: rs10046-GG + rs479292-GG
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Intermediate: Others

CV risk groups:
Low: rs727479 – G/G
High: rs727479-T/T

Event: bone fractures (any type)
Competing risks: any DFS events
(death, second primary, BC recurrence)

Event: thrombosis, embolism, stroke, angina,
myocardial infarction
Competing risks: any DFS events

9.1%

3.2%

3.1%

0.3%

High-risk SNPs mantain the protective effect on Skeletal and CV events regardless of other risk factors

Variables	Skeletal events	
	Subdistribution HR (95% CIs)	p value
rs10046 and rs749292 genotypes rs10046 C/C + rs749292 C/C	-	-
intermediate genotypes	1.00 (0.60-1.68)	0.988
rs10046 T/T + rs749292 T/T	**0.30 (0.10-0.88)**	**0.028**
Ever smoker No	1	
Yes	1.27 (0.73-2.23)	0.395
Age at diagnosis <65	1	
>65	2.34 (1.48-3.69)	<0.001
BMI ≥24 <24	1 1.03 (0.98-1.08)	0.218
Previous bisphosphonates No Yes	1 2.02 (0.81-5.08)	0.134

Variables	Cardiovascular events	
	Subdistribution HR (95% CIs)	p value
rs727479 genotypes other genotypes	-	-
rs727492-G/G	**0.23 (0.05-1.02)**	**0.053**
Ever smoker No Yes	1 2.17 (0.81-5.78)	0.123
Age at diagnosis <65 >65	1 3.55 (1.40-9.00)	0.008
BMI ≥24 <24	1 3.47 (0.58-9.74)	0.217
Previous bisphosphonates No Yes	1 0.80 (0.20-3.45)	0.731

Conclusions

- SNPs of the aromatase are independent predictors of survival and AI-related adverse events.

- SNPs were strongly associated with incidence of late distant recurrence and OS but not with DFS, suggesting that DFS might not be the most appropriate surrogate survival endpoint to evaluate long-term outcomes. From this standpoint, our data confirm previous results from MA 17.R and NSABP B-42 trial.

- SNPs associated with risk of breast cancer metastasis had a protective effect on the incidence of skeletal and CV events, indicating that women at higher risk of distant recurrence were also less likely to experience major AI-related toxicities over time.

- SNPs of aromatase could be a cheap, ready-to use biomarker to personalize duration of adjuvant treatment and survivorship interventions based on the individual risk of late recurrence and AI-related toxicities.

Mamounas et al Lancet Oncol 2019; Goss et al, NEJM 2016

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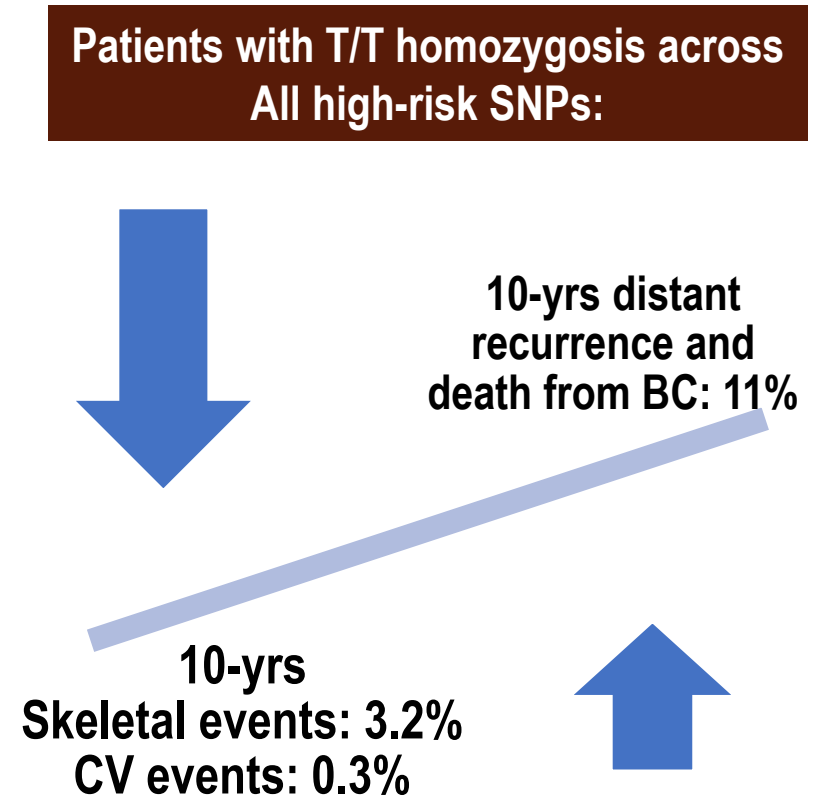*Mamounas et al Lancet Oncol 2019; Goss et al, NEJM 2016*

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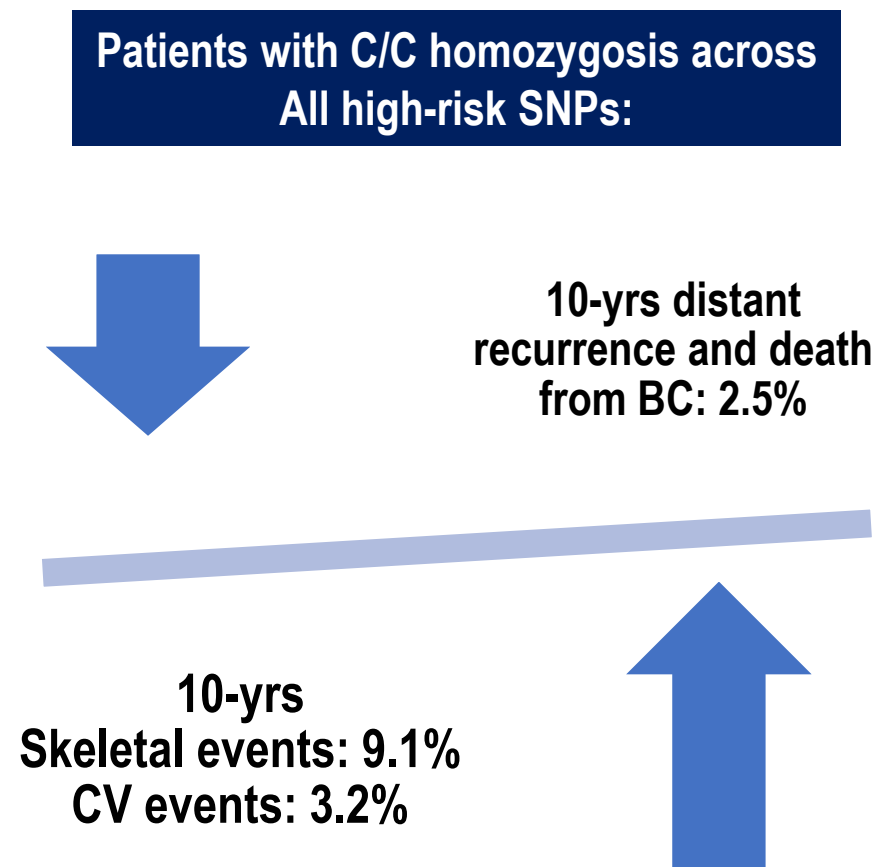*Mamounas et al Lancet Oncol 2019; Goss et al, NEJM 2016*

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Patients with T/T homozygosis across All high-risk SNPs:

10-yrs distant recurrence and death from BC: 11%

10-yrs Skeletal events: 3.2% CV events: 0.3%

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Patients with C/C homozygosis across All high-risk SNPs:

10-yrs distant recurrence and death from BC: 2.5%

10-yrs Skeletal events: 9.1% CV events: 3.2%

Acknowledgements

Prof. Alessandra Gennari

Prof. Lucia Del Mastro

Contacts

benedetta.conte@uniupo.it

@BenedettaConte5