Progetto CANOA

CARCINOMA MAMMARIO:

QUALI NOVITA' PER IL 2025?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

Coordinatori Scientifici:
Stefania Gori
Giovanni L. Pappagallo

Verona, 28 - 29 Marzo 2025
Hotel Crowne Plaza

AIGOM
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UPO
UNIVERSITÀ DEL PIEMONTE ORIENTALE

Ruolo della valutazione dei polimorfismi nella gestione della tossicità: dagli SNPs del gene dell'aromatasi agli SNPs del gene UGTA1

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Novara

Declaration of interests

Benedetta Conte, MD

Non profit research support: GILEAD

Can SNPs contribute to improving the management of treatment-related toxicities in breast cancer patients?

Should we test patients for SNPs before initiating antineoplastic therapy?

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Perhaps – but not yet

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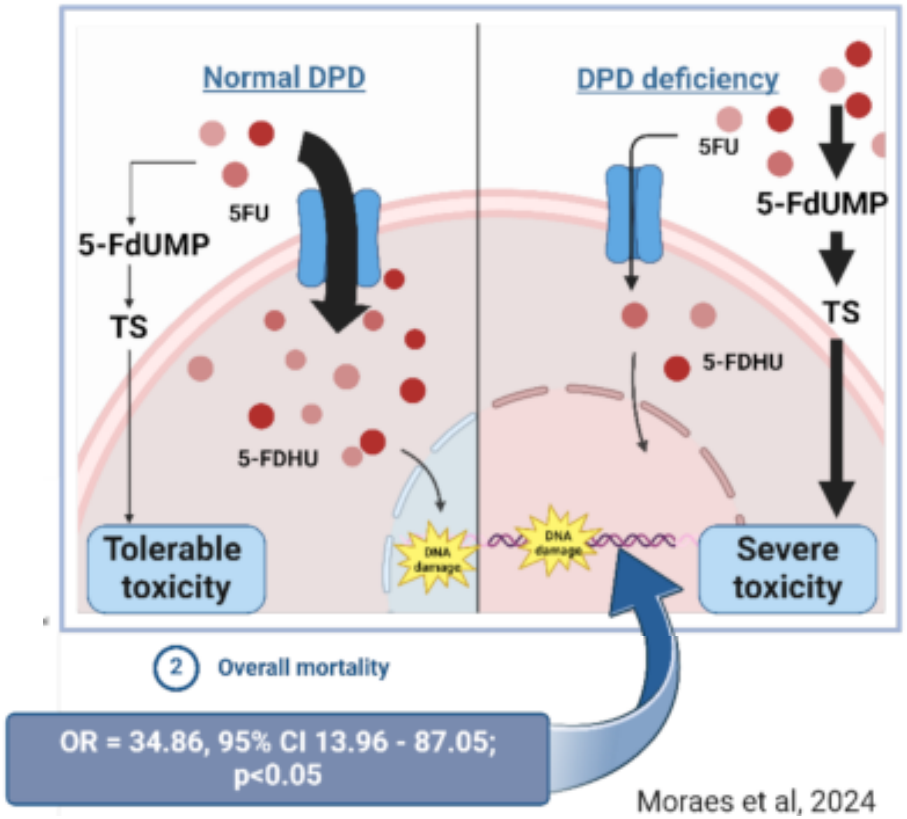
Perhaps – but not yet

Should we test patients for SNPs before initiating antineoplastic therapy?

NO

SNPs as a biomarker of treatment-related toxicity: limitations

The *DPYD* case:
One functional SNP = meaningful biological effect



Moraes et al, 2024

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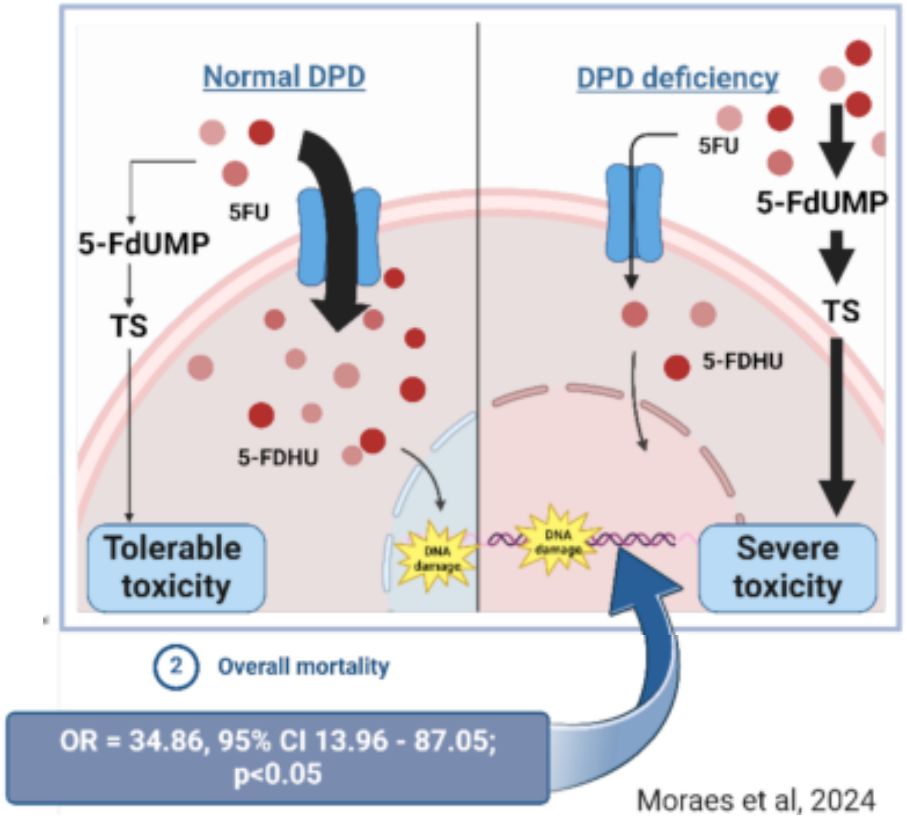
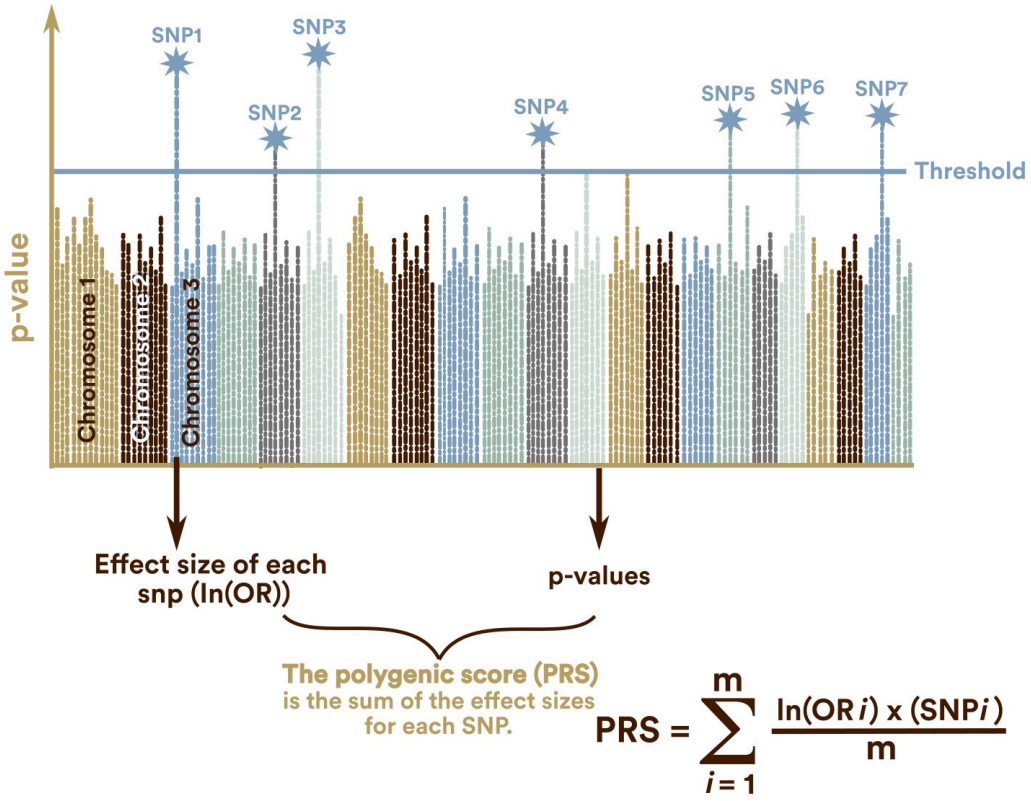
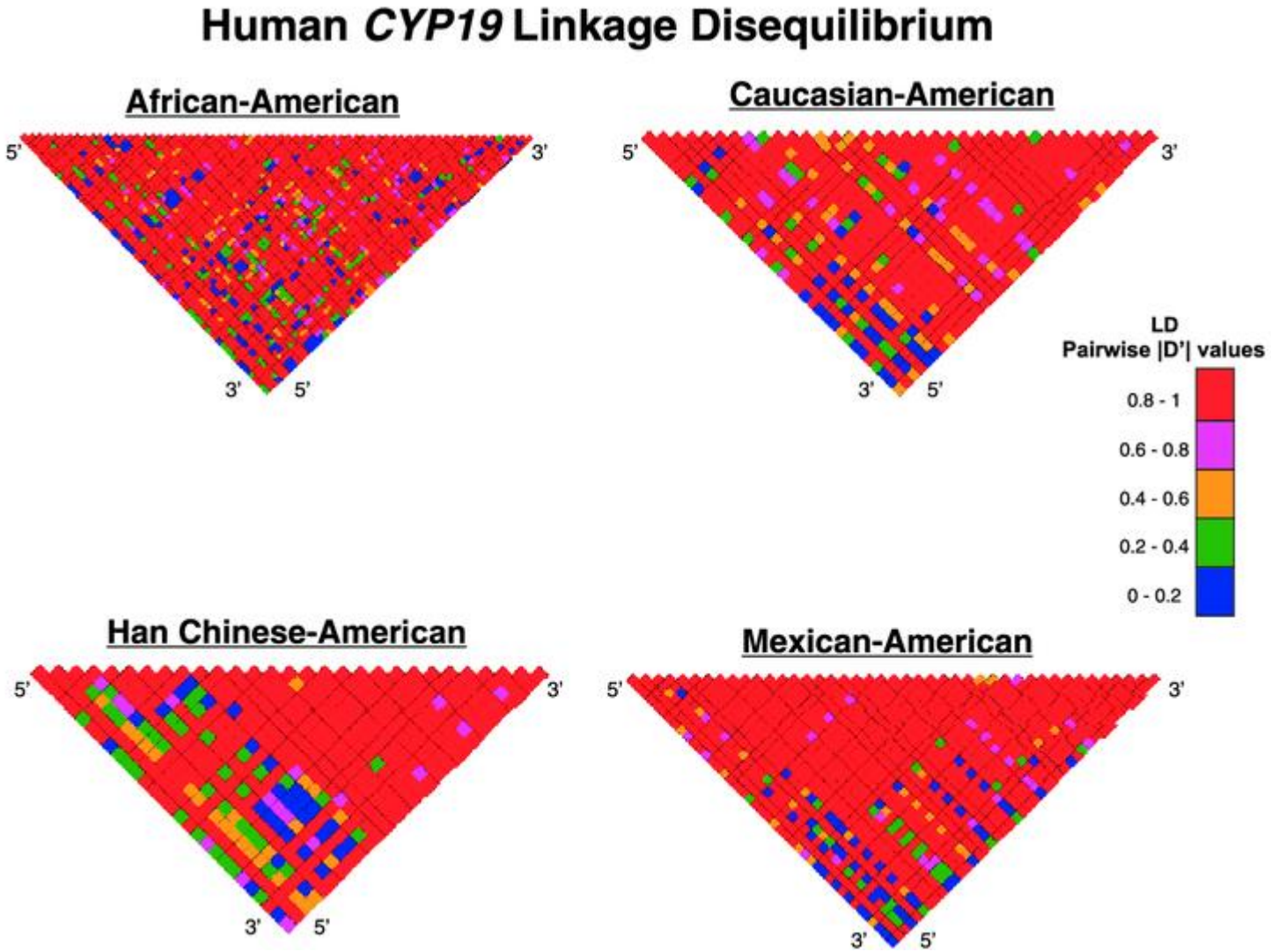


The most common scenario:
Each SNP has a small biological effect
Multiple associated SNPs with similar effect → meaningful biomarker



SNPs as a biomarker of treatment-related toxicity: limitations



LD = **non-random association of alleles** in a population.

LD arises because of the **physical proximity of SNPs** on the chromosome, which makes them **more likely to be co-inherited during meiosis** (recombination is less likely to separate them).

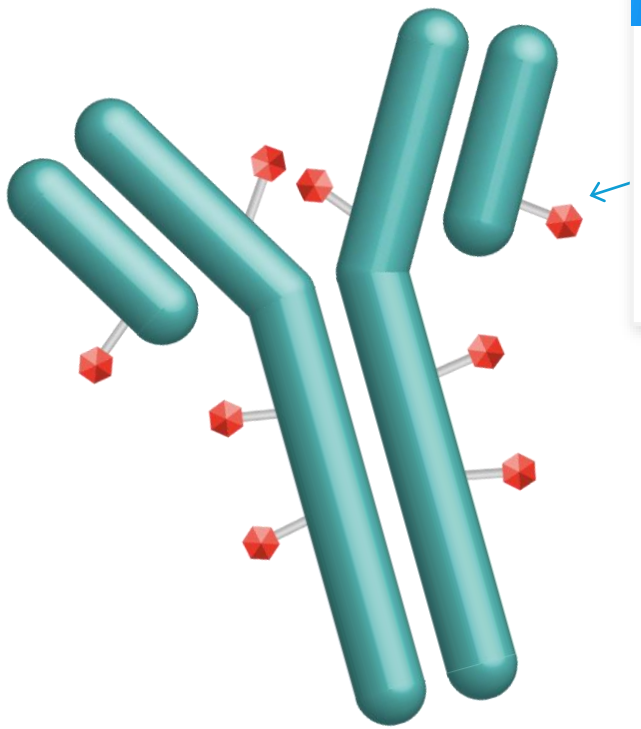
Genetic recombination rates vary across ancestries:
- **Higher** in **African ancestry**
- **Lower** in **European ancestry**

This makes **SNP-based polygenic risk scores non-transferable across populations**.

MA Cx et al, Cancer Res 2005

The lucky scenario: SNPs in the *UGTA1* gene

Sacituzumab Govitecan

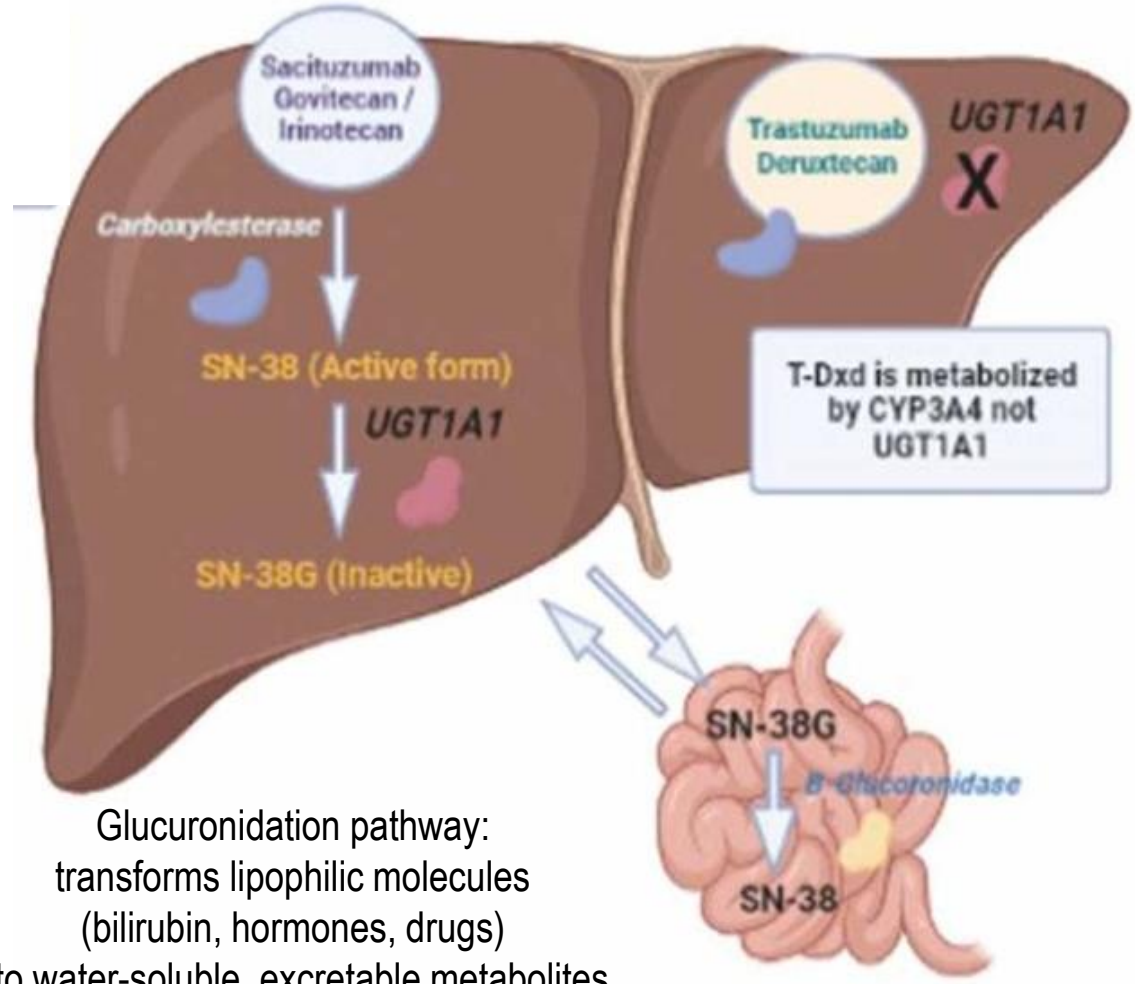


SN-38 payload

- Active metabolite of irinotecan
  Topoisomerase I inhibitor
- High drug-to-antibody ratio (~8:1)

Bardia A, et al. N Engl J Med. 2021
Ibrahim R et al, Crit Reviews in Oncol/Hematology 2024

UDP-glucuronosiltransferase 1A1



Glucuronidation pathway:
transforms lipophilic molecules
(bilirubin, hormones, drugs)
into water-soluble, excretable metabolites.

The lucky scenario: SNPs in the *UGTA1* gene

TABLE 2. Clinical Recommendations for Patients Receiving Irinotecan on the basis of the Interpretation of the Results of the *UGT1A1* Genetic Test

UGT1A1 Genotype	Effect on UGT1A1 Activity or Expression	Clinical Implication	Clinical Intervention
**1/*1*	Normal	Average risk of irinotecan toxicity	Use standard starting dose[1,6,7] These patients may be able to tolerate irinotecan doses higher than the standard dose without compromising safety[5,45-48]
**1/*28*	Reduced expression	Higher risk of irinotecan toxicity	Use standard starting dose[1,6,7]
**1/*6*	Reduced activity		These patients may be able to tolerate irinotecan doses higher than the standard dose without compromising safety[5,45-48]
**28/*28*	Further reduction in expression	Highest risk of irinotecan toxicity	Reduce the starting dose to at least one level lower than the standard dose.[1] For specific dosing recommendations, see Table 3 After cycle 1 at a reduced dose, upward titration at subsequent cycles can be considered, on the basis of individual tolerance[1,6,7]
**6/*6*	Further reduction in activity		
**6/*28*	Further reduction in activity and expression		

UGTA1 *28/*28:

Severe neutropenia (G3-5): sensitivity of 11%, specificity of 94%

Severe diarrhea (G3-5): sensitivity of 13%, specificity of 92%

Karas S et al, JCO Oncology Practice 2021

The lucky scenario: SNPs in the *UGTA1* gene

N=67
TNBC N=52 (76.5%)
Median FU: 3.8 months (IQR 0.90-23.7)

Genotype	Discontinuation due to PD	PFS HR (95% CIs)	p value	Discontinuation due to toxicity	Toxicity HR (95% CIs)*	p value
Homozygous (25%)	07/17	0.80 (0.39-1.65)	0.54	04/17	5.52 (1.15-26.49)	0.03
Heterozygous (35.3%)	13/24	0.61 (0.33-1.12)	0.12	0/24	NA	NA
Wild-type (39.7%)	18/27	1 (ref)	-	02/27	1 (ref)	-

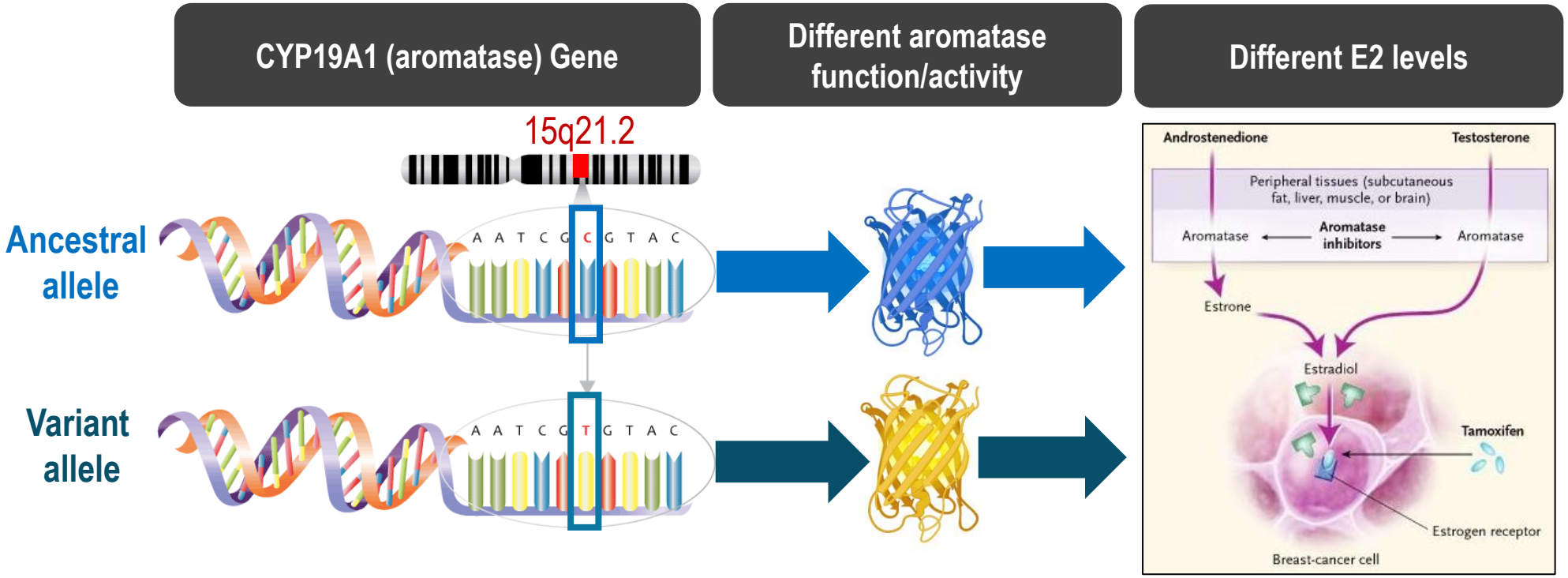
100% of African Americans were UGTA1 *28/*28 homozygous

***Competing risk analysis**

Wong M et al, ASCO 2023

The most common scenario: SNPs in the *CYP19A1* gene

- HR+ early breast cancer is characterized by a substantial risk of late metastasis. Extended therapy with AIs beyond 5 years reduces the risk of these late events by 20% to 30%[1-2]
- However, such benefit comes at the price of increased incidence of skeletal and cardiovascular (CV) events[3-6]
- SNP in the gene encoding for the aromatase enzyme (CYP19A1) may affect aromatase activity and circulating estradiol levels[7,8]



Do SNPs have any impact on:

- **Prognosis**
- **AIs efficacy**
- **AIs toxicity**

In ER+ BC?

1.Gray R, SABCS 2018; 2. Pala L, The Breast 2023; 3. Gnant M, NEJM 2021; 4. Goodwin PJ, NEJM 2021; 5. Mamounas EP, Lancet Oncol 2019; 6. Goldvaser H, JNCI 2018; 7. Dunning Am JNCI 2017; 8. Haiman CA, Cancer Res 2007; 9. Colomer R CCR 2008; 10. Johansson H, Pharmacogenomics J 2020; 11. Garcia-Casado, BMC Cancer 2010; 12. Johansson H, Breast Cancer Res 2016.

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

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

Germline SNPs
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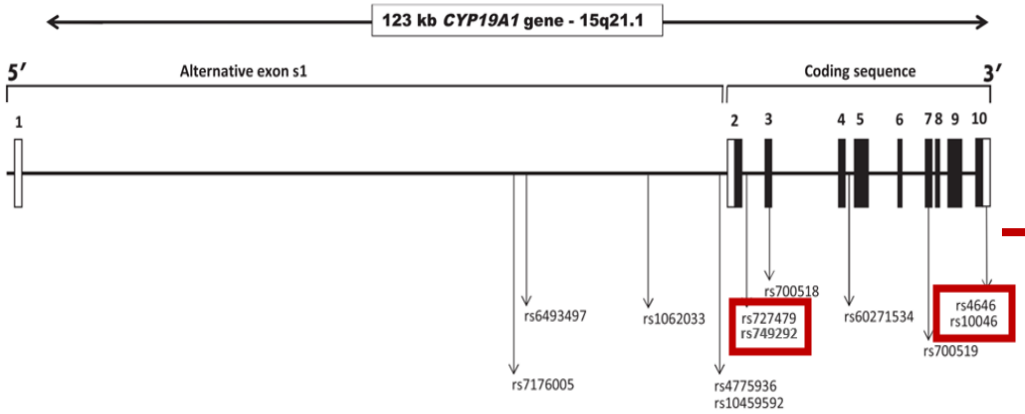
Per-protocol endpoints:

- DFS (primary)
- OS (secondary)
- Safety

Overall ET duration

Conte B et al, CCR 2023

SNPs analysis



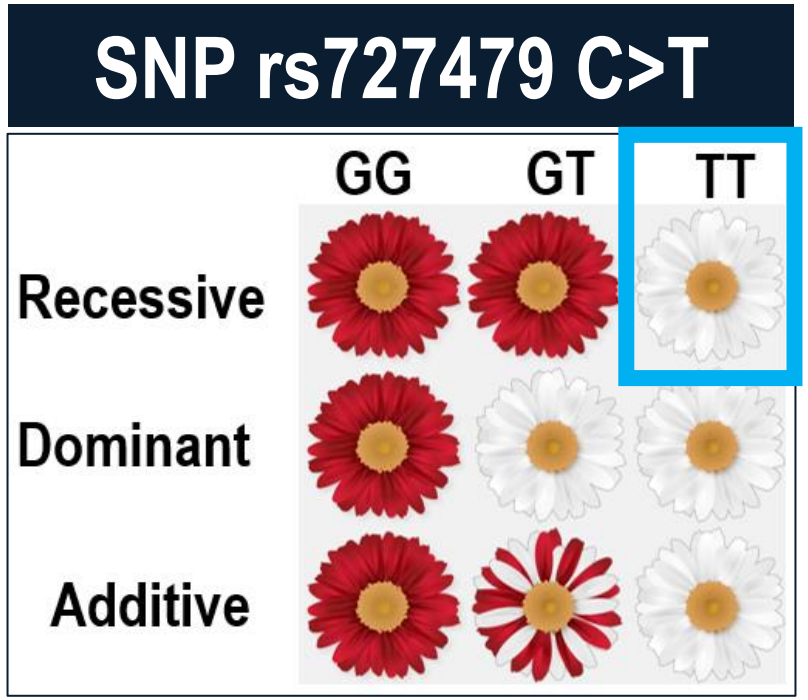
Previous evidence In patients with BC[1-3]

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

Association with endpoints assessed under Mendelian model

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



Conte B et al, CCR 2023

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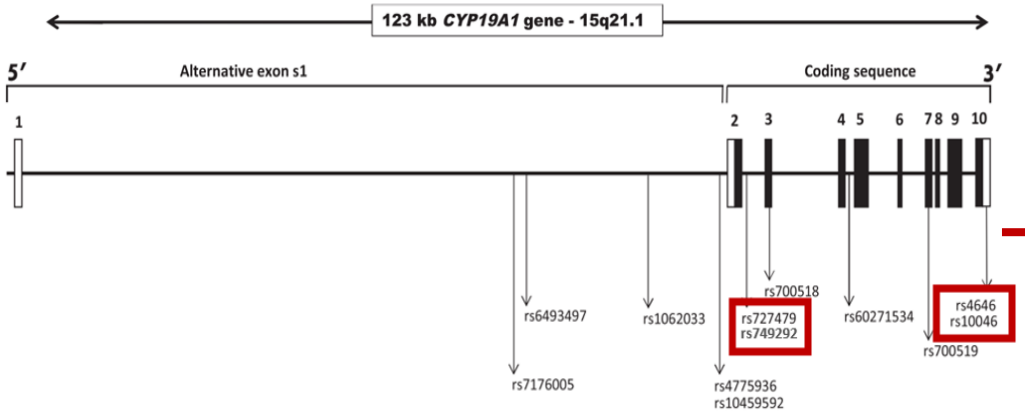

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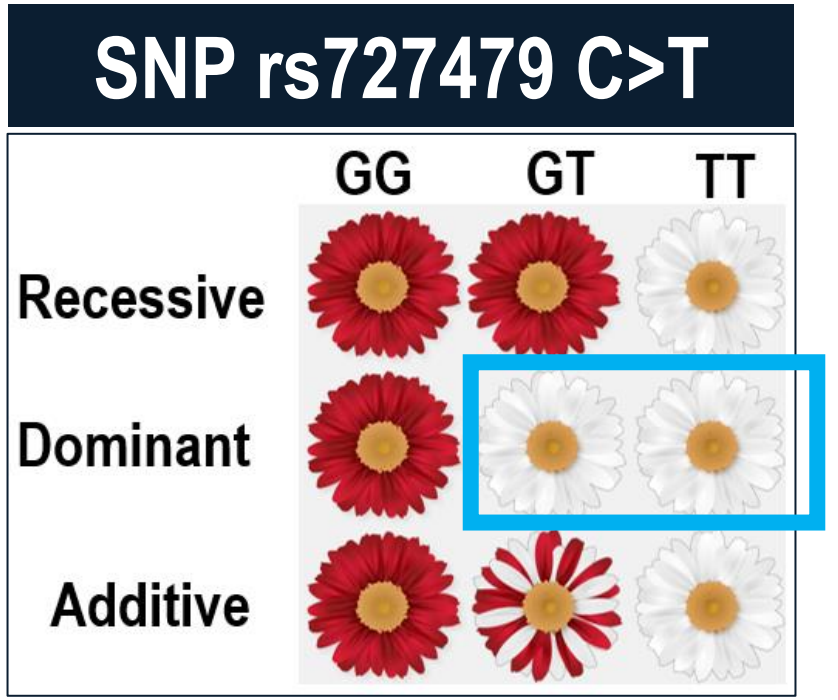
Association with endpoints assessed under Mendelian model

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



Conte B et al, CCR 2023

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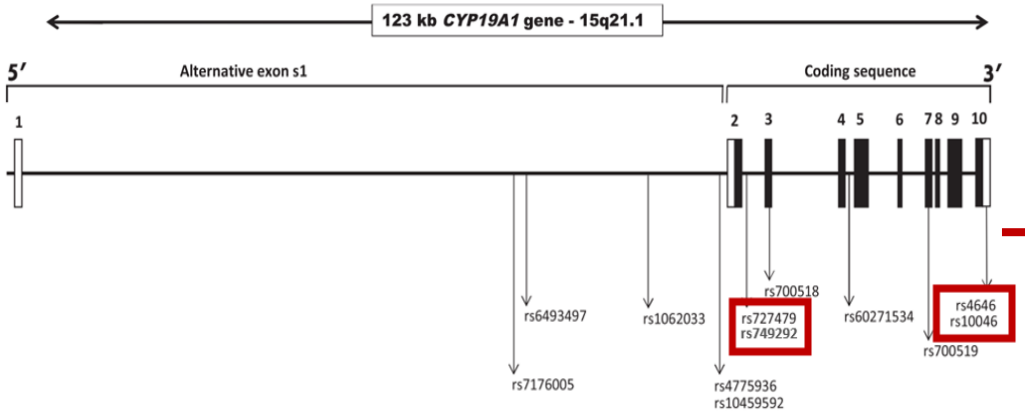

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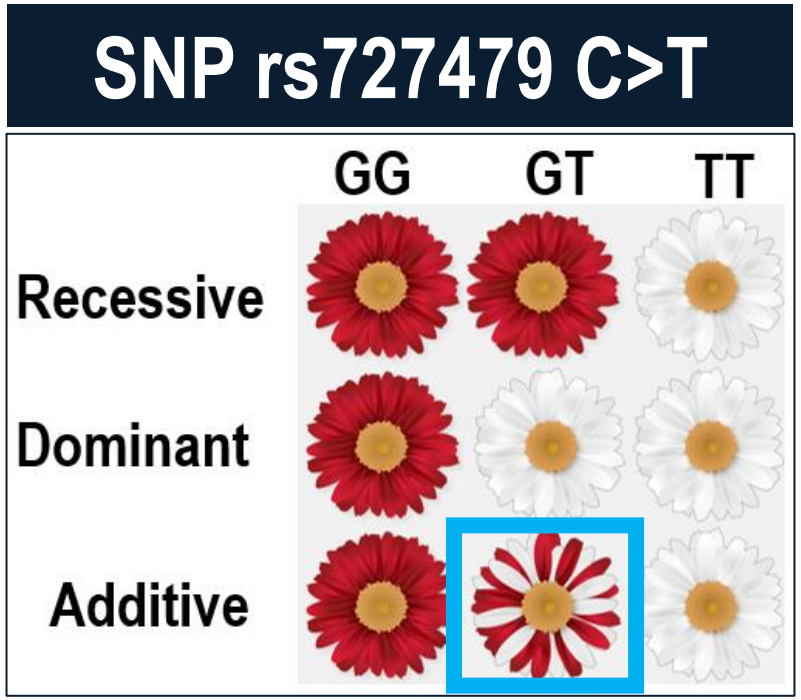
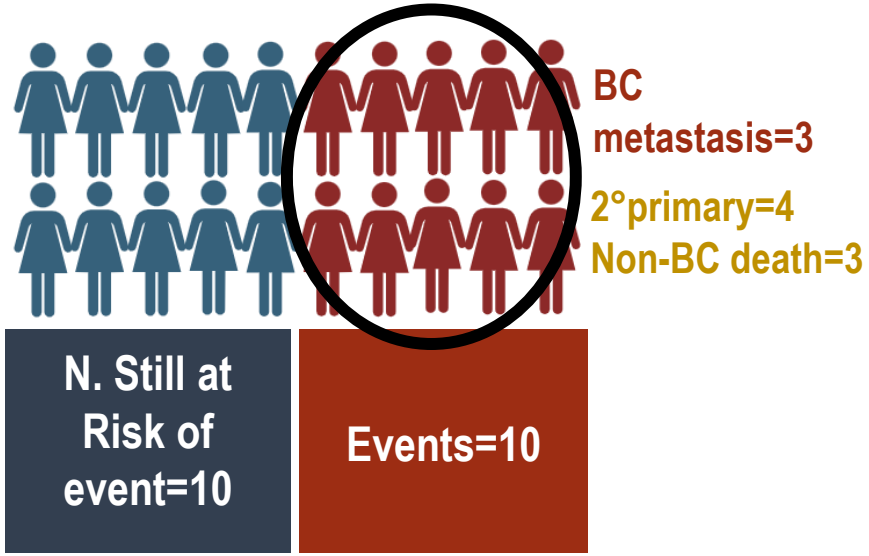


T in heterozygosis gives a **mixed** phenotype
(i.e. **intermediate** aromatase activity)

Conte B et al, CCR 2023

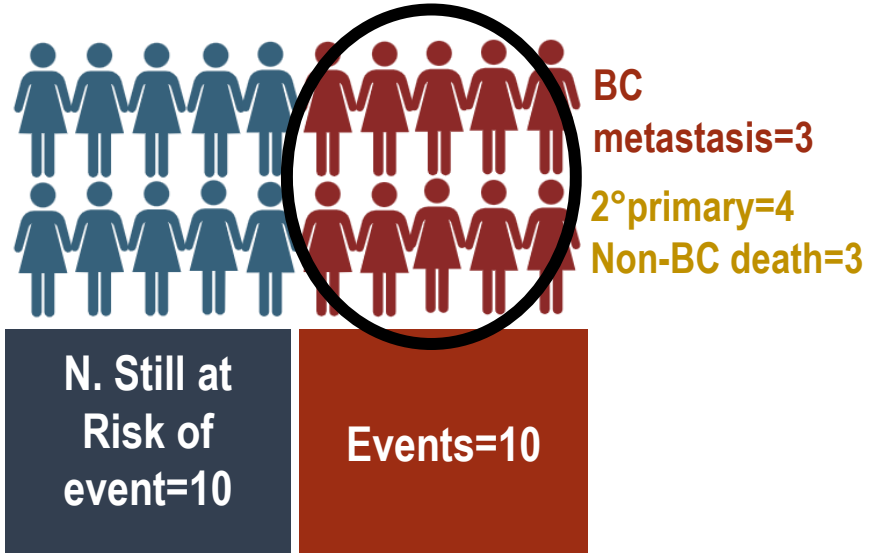
Standard Survival Model



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



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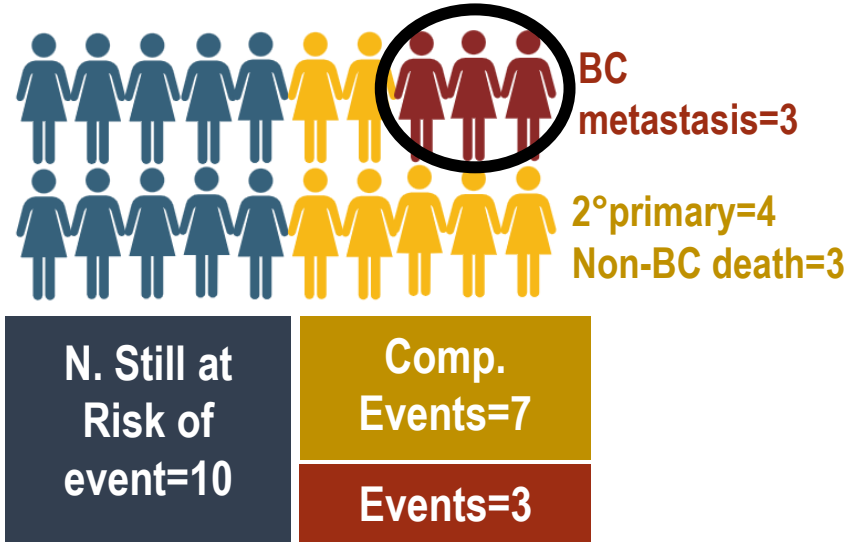


Fine et al, J of American Stat Ass, 1999

Competing Risk Model

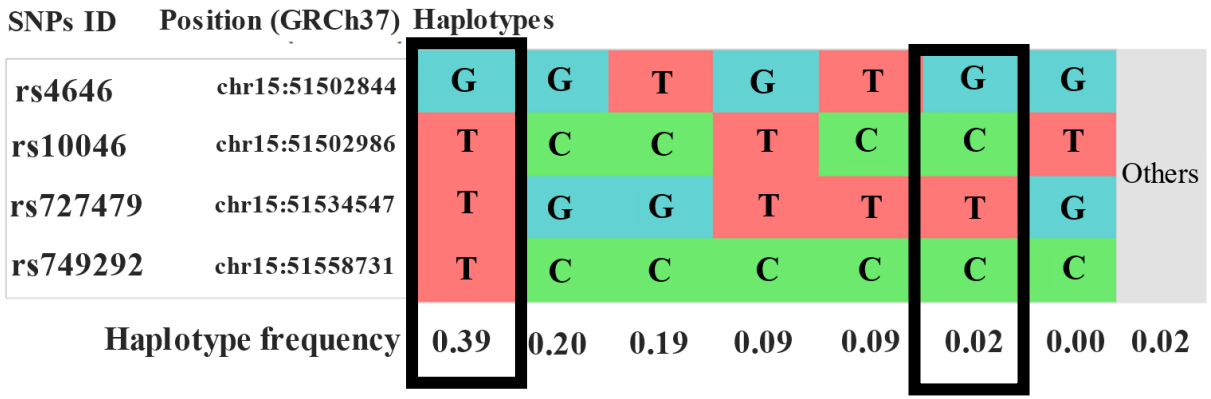
Events of interest
Distant recurrence
Death with BC

Competing events
Contralateral iBC
2nd primary malignancy
Death without BC

Fine-Gray model → 2 subdistribution HR (sHR), one for each event type

SNPs	sHR (95% CIs)	p value
rs10046-T/T	1.57 (0.96-2.57)	0.071
rs749292-T/T	1.83 (1.09-3.08)	0.023
rs727479-C/T+T/T	2.16 (1.00-4.97)	0.050

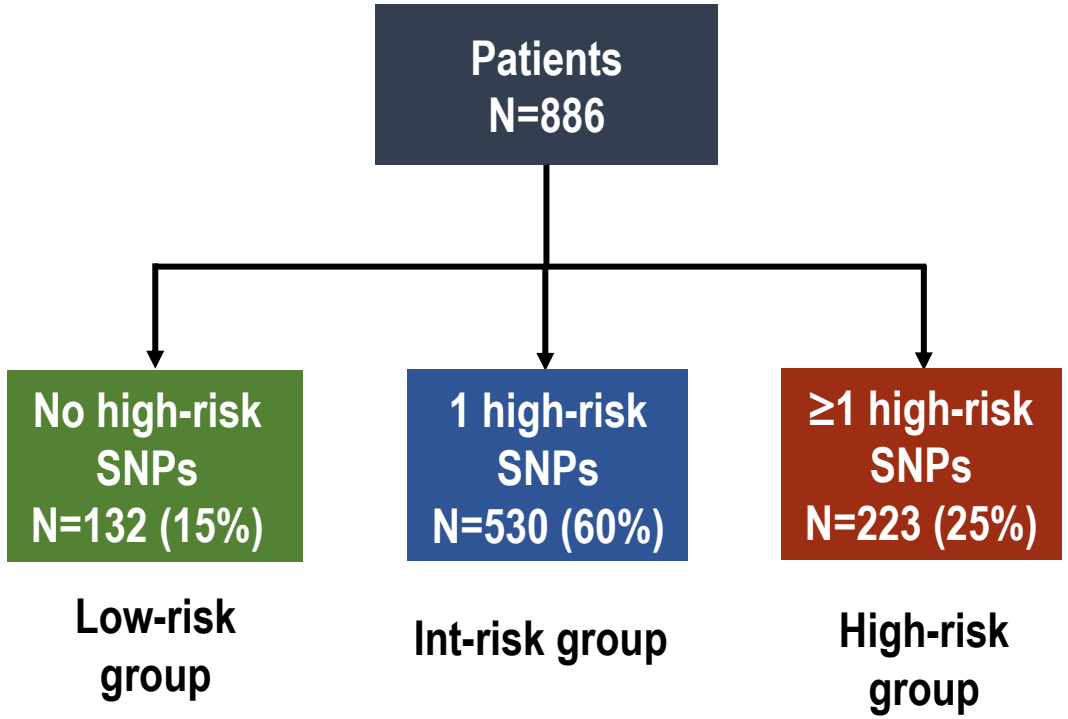
High-risk SNPs are in high positive Linkage disequilibrium with each other



Conte B et al, CCR 2023

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	Others
rs10046	chr15:51502986	T	C	C	T	C	C	T	
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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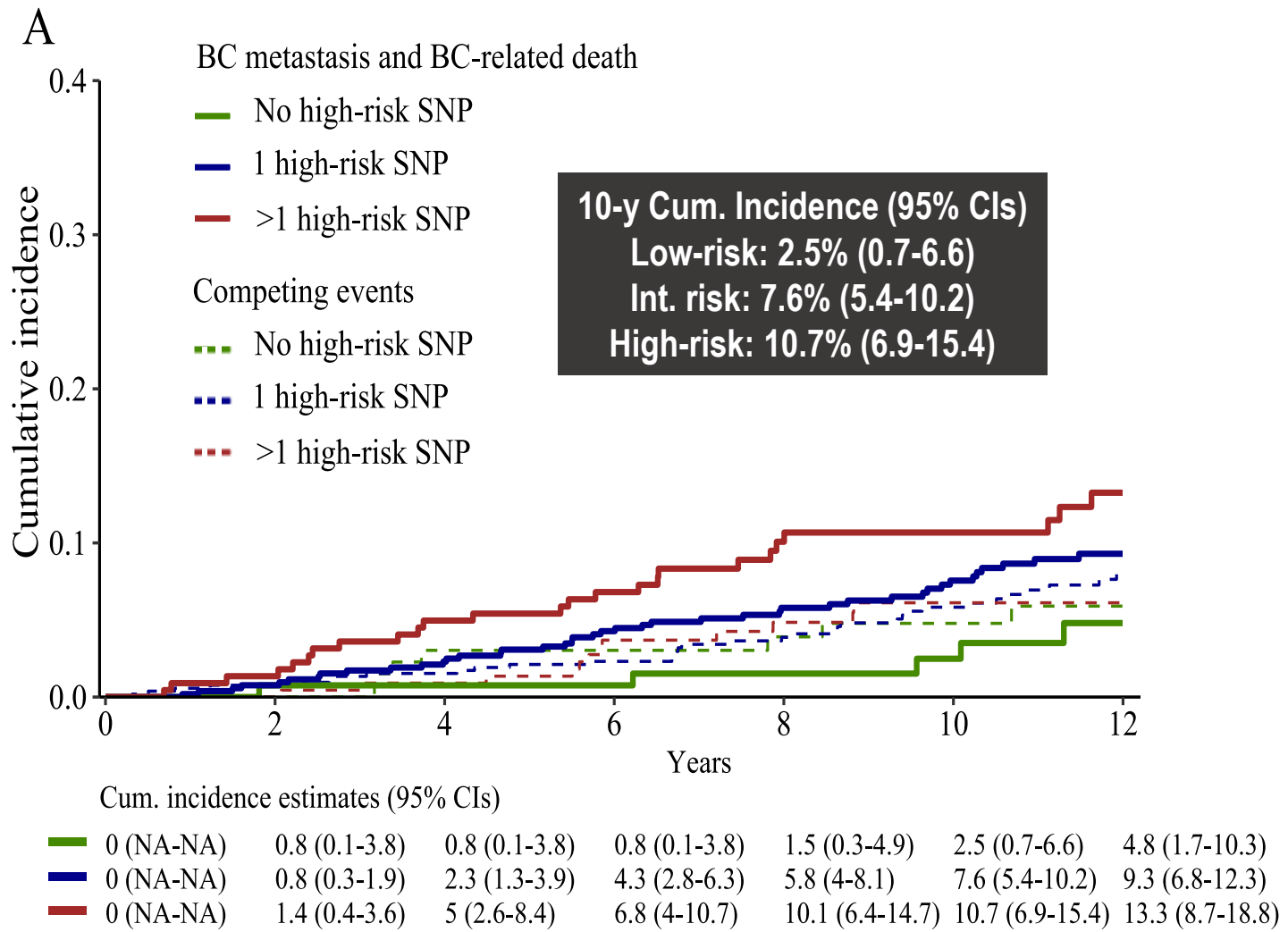

Conte B et al, CCR 2023

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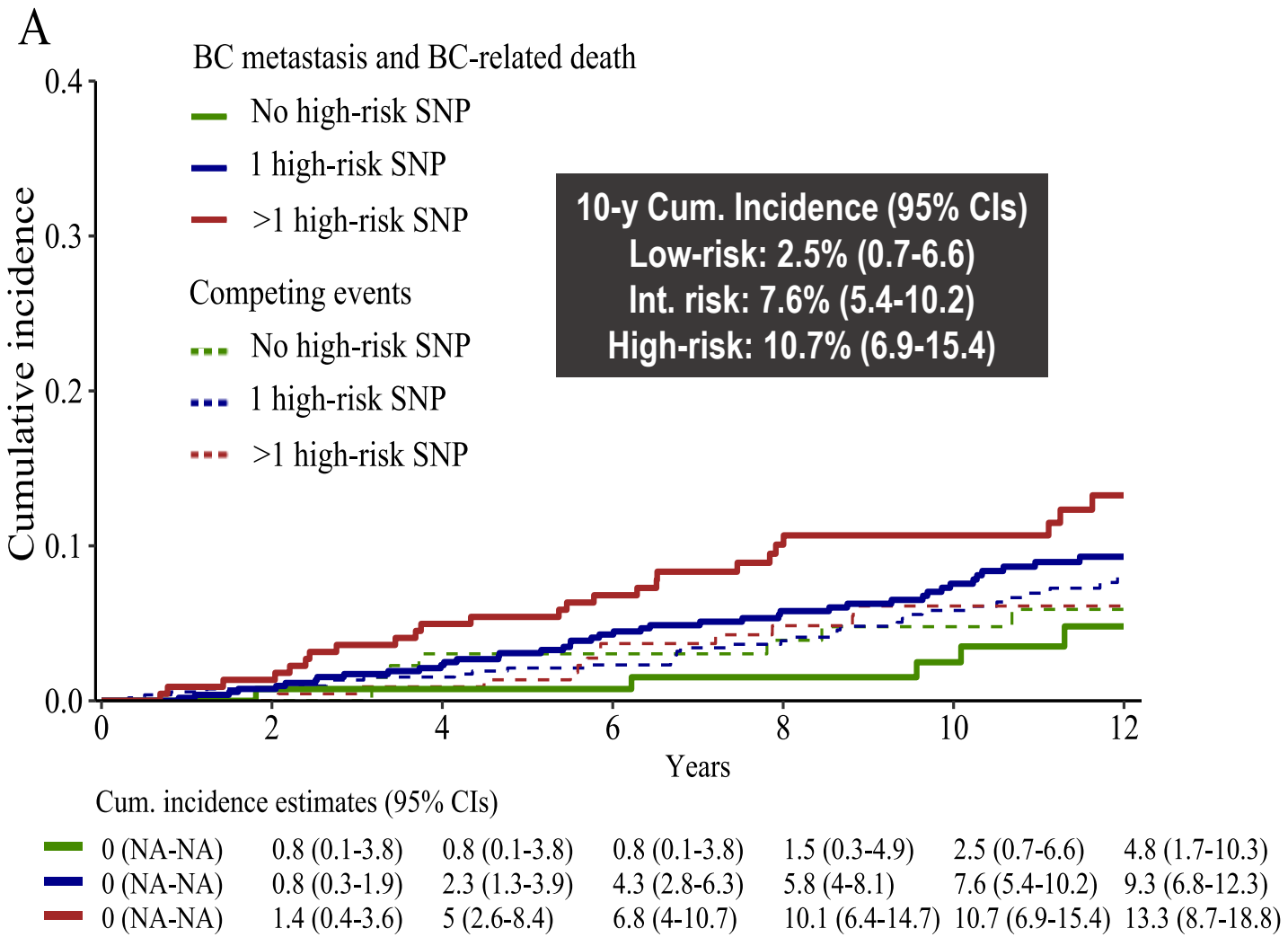
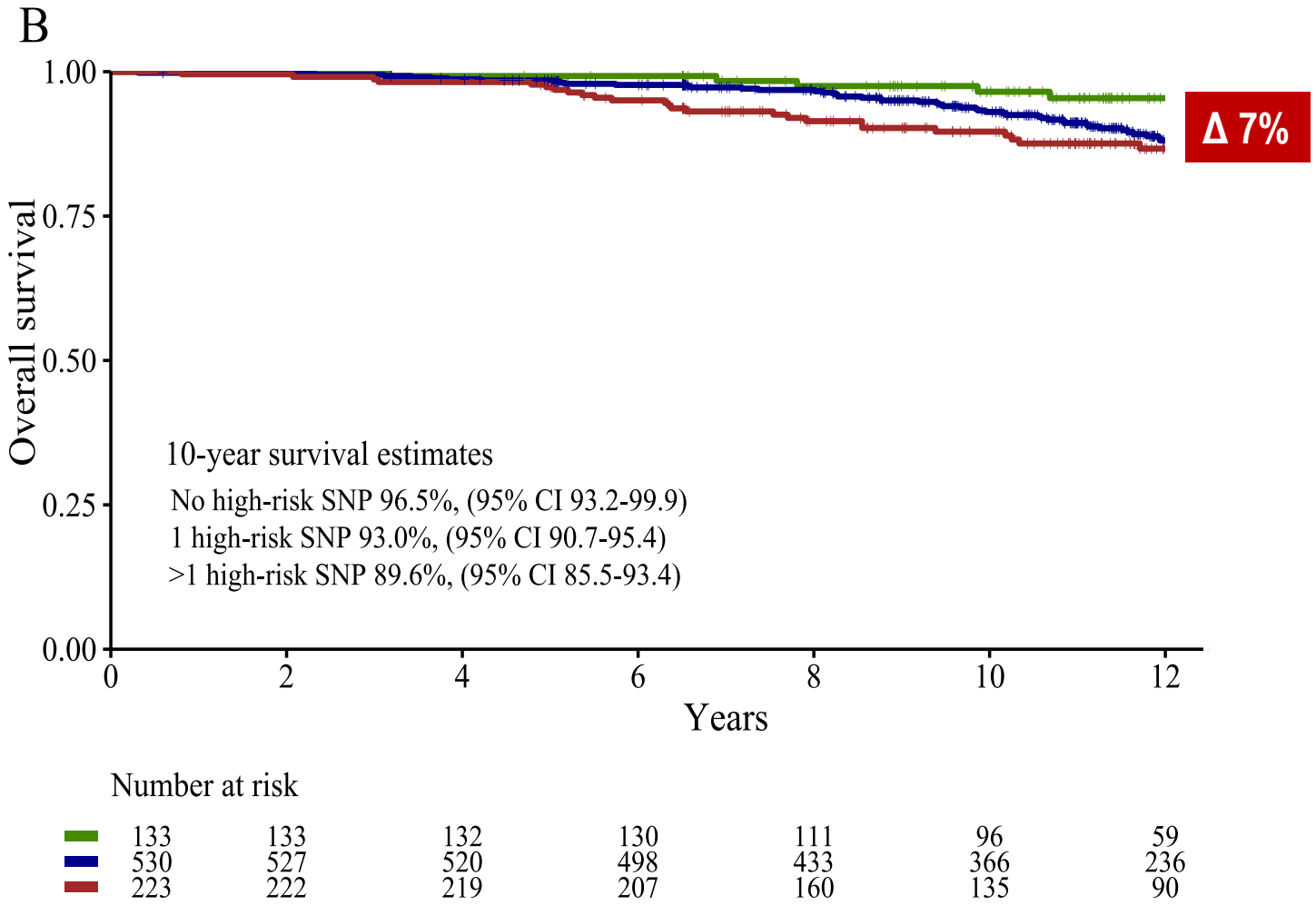


Fine-Gray multivariable model

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

Conte B et al, CCR 2023

Overall survival according to SNPs-based groups



Conte B et al, CCR 2023

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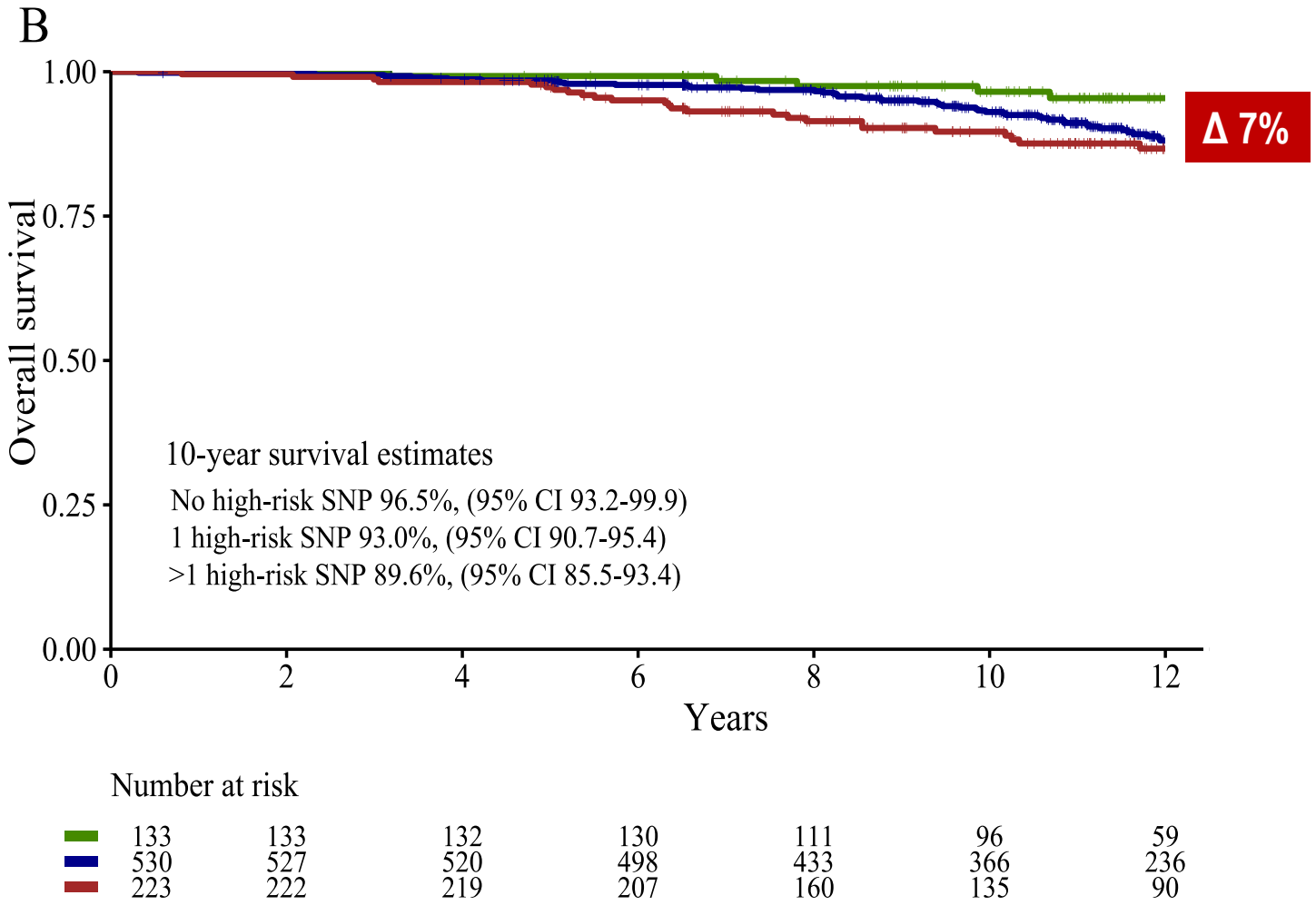


Cox multivariable model

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

Conte B et al, CCR 2023

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

High-risk SNPs

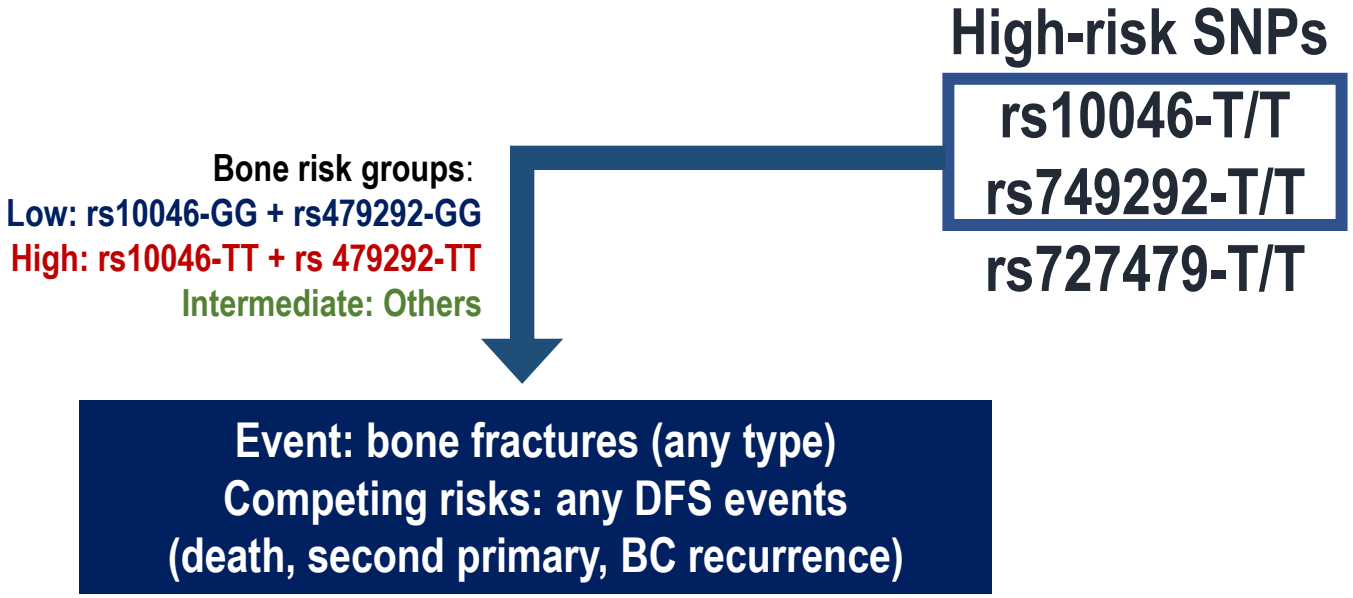
rs10046-T/T

rs749292-T/T

rs727479-T/T

Conte B et al, CCR 2023

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



Conte B et al, CCR 2023

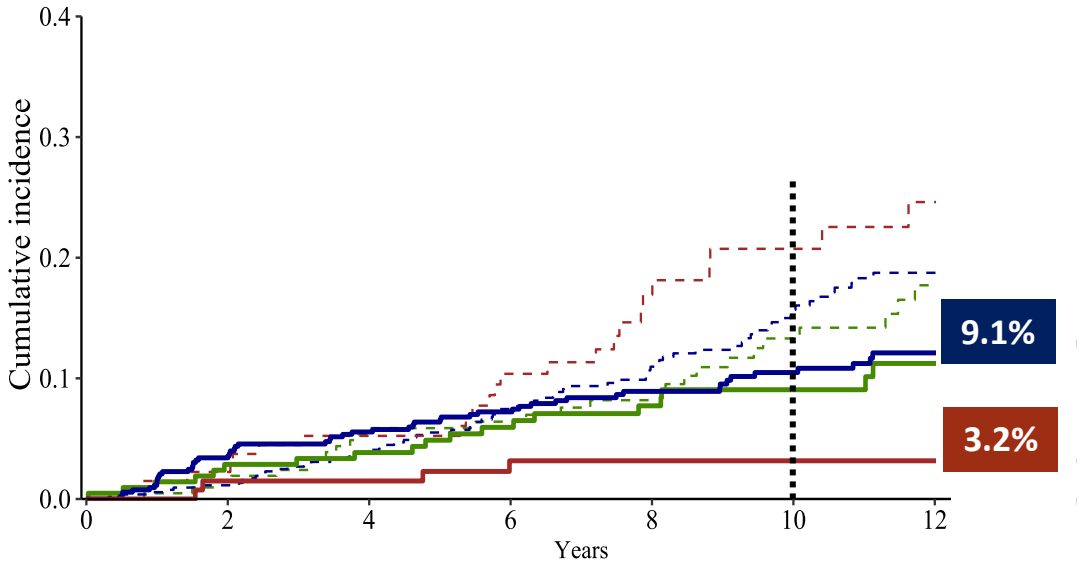
High-risk SNPs have a protective effect on Skeletal and CV events

High-risk SNPs

rs10046-T/T
rs749292-T/T
rs727479-T/T

Bone risk groups:
Low: rs10046-GG + rs479292-GG
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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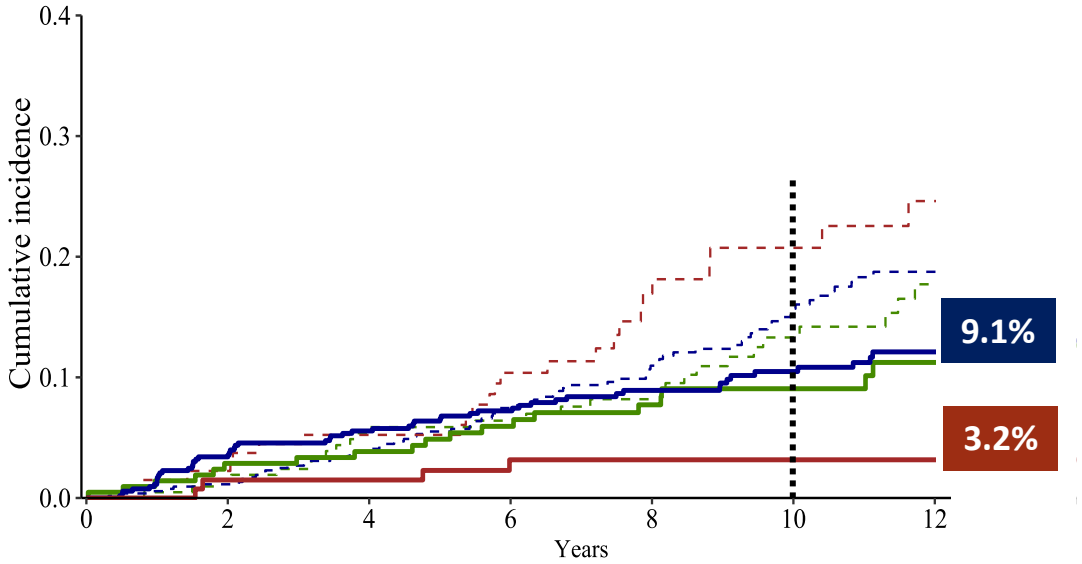
rs749292-T/T
rs727479-T/T

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



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High: rs10046-TT + rs 479292-TT
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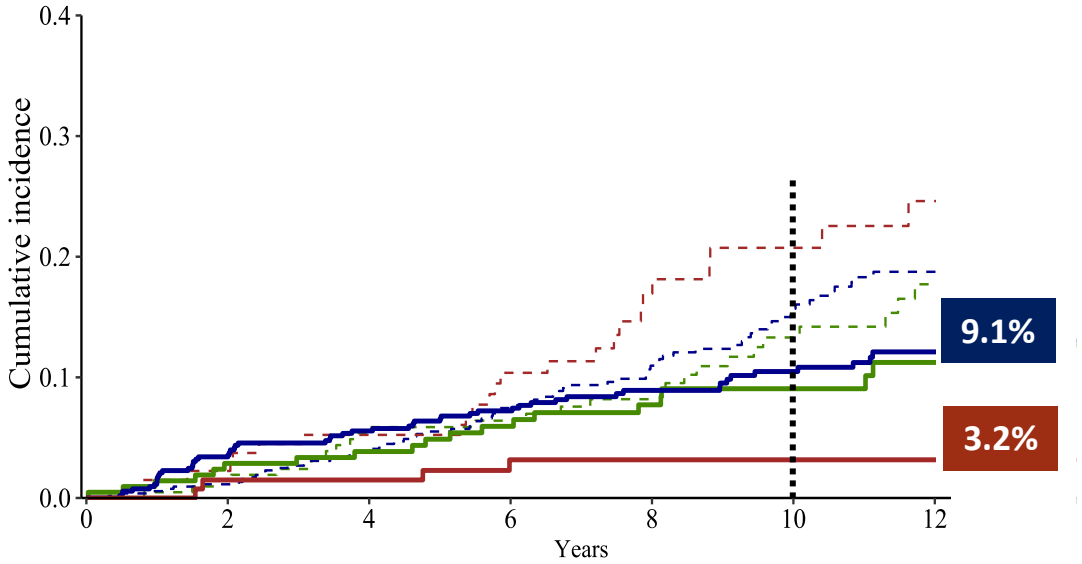
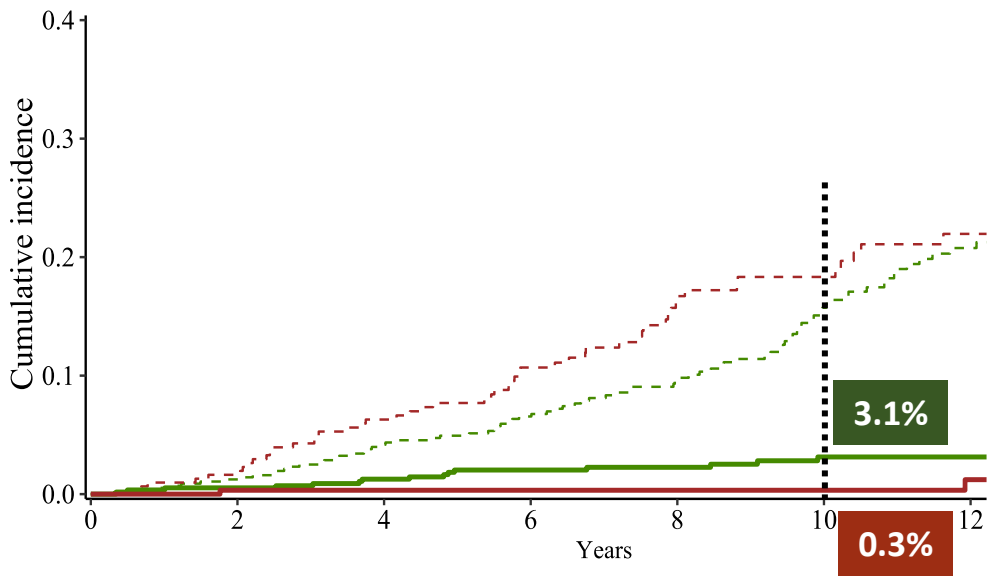


Event: thrombosis, embolism, stroke, angina, myocardial infarction
Competing risks: any DFS events



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

	Skeletal events	
Variables	**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	1	
<24	1.03 (0.98-1.08)	0.218
Previous bisphosphonates		
No	1	
Yes	2.02 (0.81-5.08)	0.134

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

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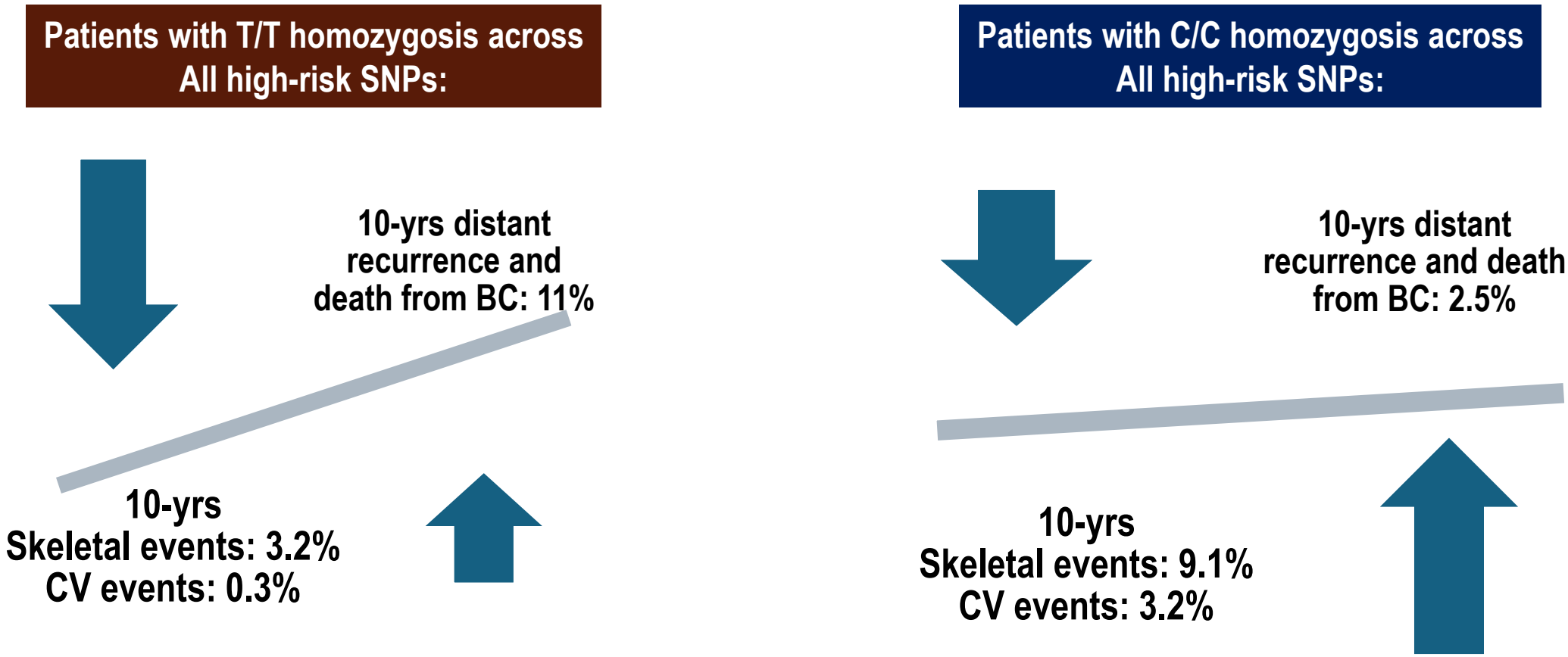
SNPs of aromatase as a biomarkers of prognosis and toxicity



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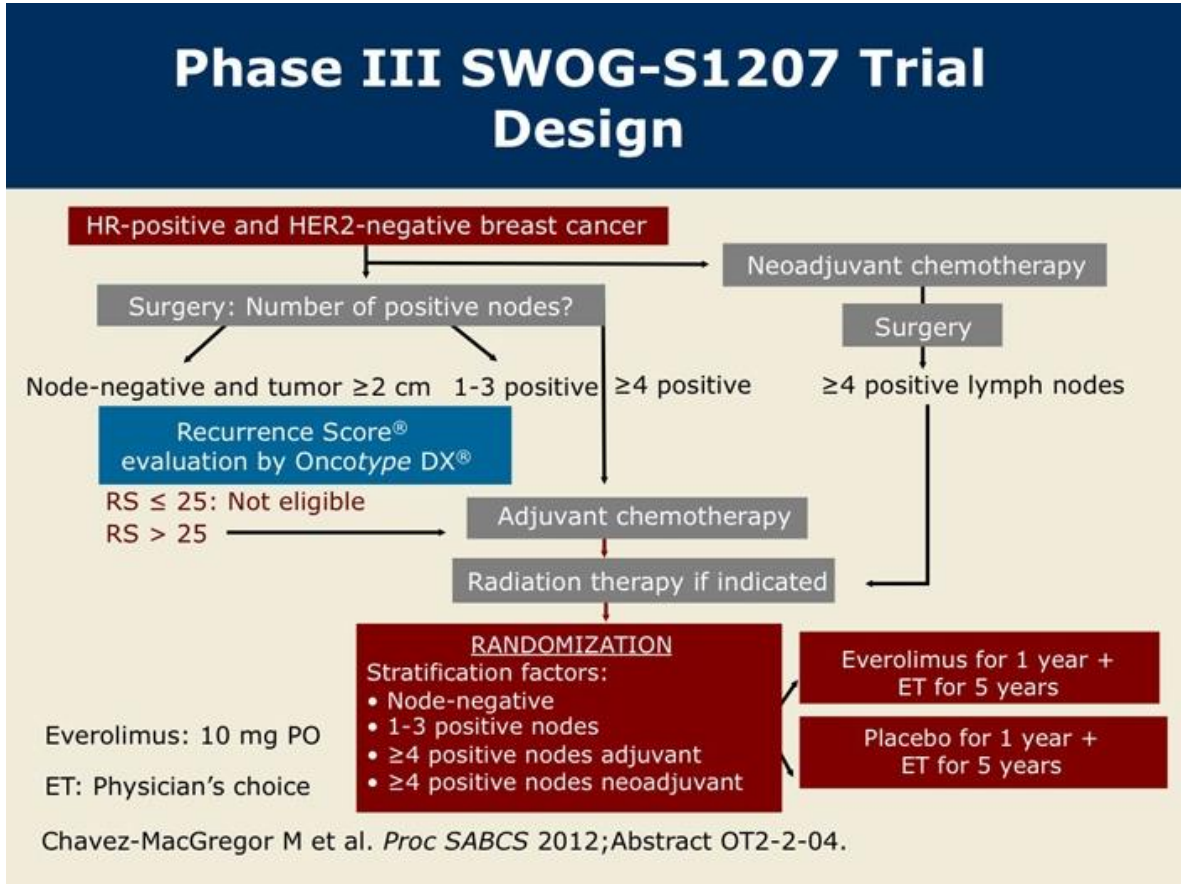
Conclusions

- Single functional SNPs (e.g., *DPYD*, *UGT1A1*) can significantly impact toxicity and support clinical decision-making (rare exceptions).
- Most SNPs have small individual effects, and meaningful biomarkers often arise only when multiple variants are analyzed together.
- SNPs in *CYP19A1* (aromatase) genes may predict prognosis and toxicity in ER+ breast cancer, (evidence from large clinical datasets).
- Germline genomic data hold promise for personalizing endocrine and cytotoxic therapy, but further validation is essential.
- **SNPs-based precision medicine is a powerful tool in the making – but not yet ready for broad clinical application**



HOBOE TRIAL

RANDOM
n=1065

- Tamoxifen + Triptorelin (T)
- Letrozole + Triptorelin (L)
- Zoledronic acid + Letrozole + Triptorelin (ZL)

T arm	**Tamoxifen** 20 mg/day for 2 years followed by an AI at standard dose for 3 years
L arm	**Letrozole** 2.5 mg/day for 5 years
ZL arm	**Zoledronic acid*** 4 mg i.v. every 6 months + **Letrozole** as above for 5 years
All arms	**Triptorelin** 3.75 mg, i.m. every 4 weeks for 5 years (or up to the age of 55)

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Grazie per l'attenzione

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