bjclub breast Journal club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

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Intermediate clinical endpoints in early-stage breast cancer: an analysis of individual patient data from the Gruppo Italiano Mammella and Mammella Intergruppo trials

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Disclosure Information

Eva Blondeaux reports speakers fee from Eli Lilly and research support to the Institution from Gilead Science

Introduction

- In the early stage breast cancer setting, intermediate clinical endpoints, such as DFS or invasive-DFS, are frequently used as primary endpoint in randomized trials and OS is often included as secondary endpoint[1-5]

- Improving the OS should be considered the main goal of anticancer treatment[6]. OS is the preferred endpoint for regulatory purposes[7,8]

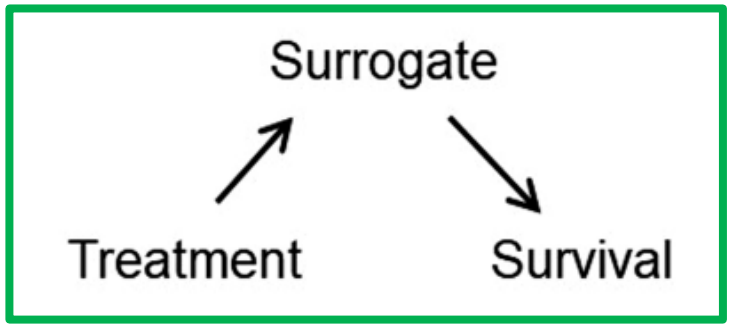
- Showing OS improvements in randomized trials require the inclusion of a substantial number of patients and long-term follow-up data

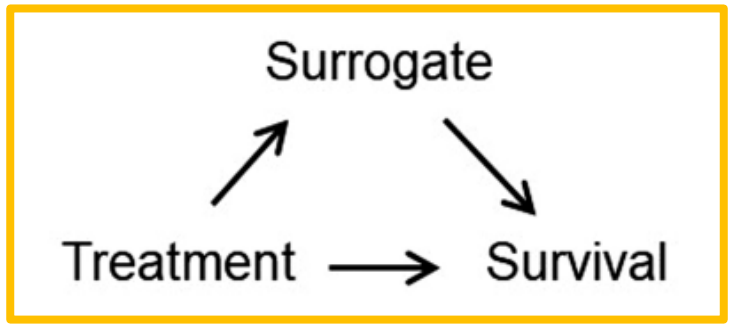
- By pooling individual patient data from the MIG and GIM adjuvant trials, we aimed to assess whether changes in intermediate clinical endpoints can be used to predict changes in OS in adjuvant breast cancer randomised trials

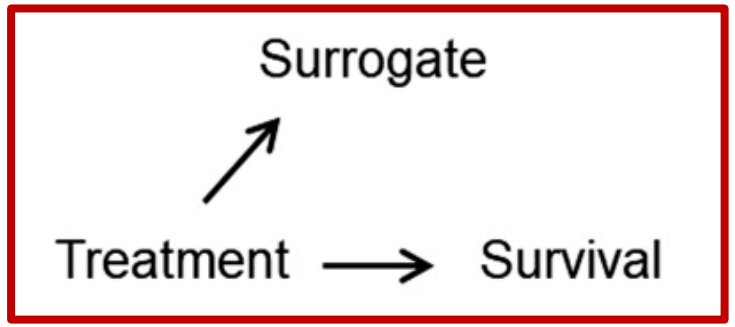
[1]Mamounas EP et al. *Lancet Oncol* 2019; 20: 88–99; [2]Pagani O et al. *J Clin Oncol* 2023; 41: 1376–82; [3]Perrone F et al. *Eur J Cancer* 2019; 118: 178–86; [4]Johnston SRD et al. *Lancet Oncol* 2023; 24: 77–90; [5]Loibl S et al. *J Clin Oncol* 2021; 39: 1518–30; [6]Gill S et al. *The Oncologist* 2006; 11: 624–9; [7]FDA. General Principles for Planning and Design of Multi-Regional Clinical Trials. 2020; [8]EMA. Evaluation of anticancer medicinal products in man - Scientific guideline. European Medicines Agency. 2018

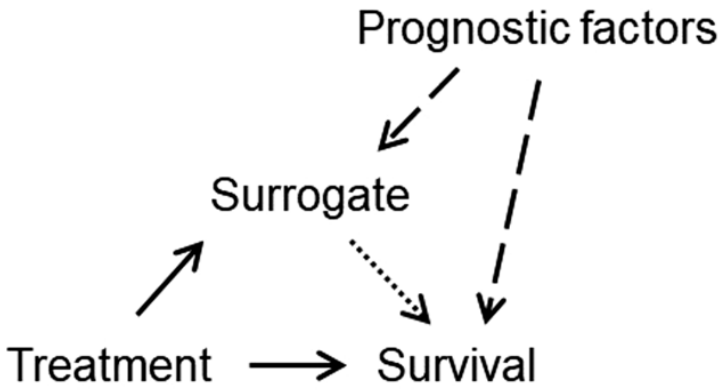
Introduction

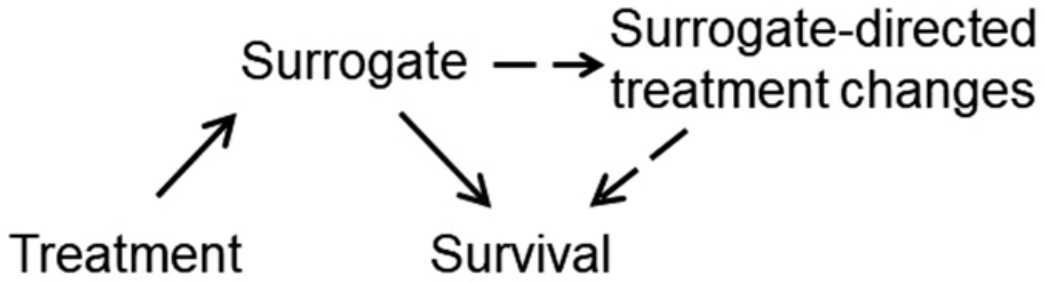
Endpoints, long lasting discussion











Buyse M et al, The Oncologist 2022;27, 266–271

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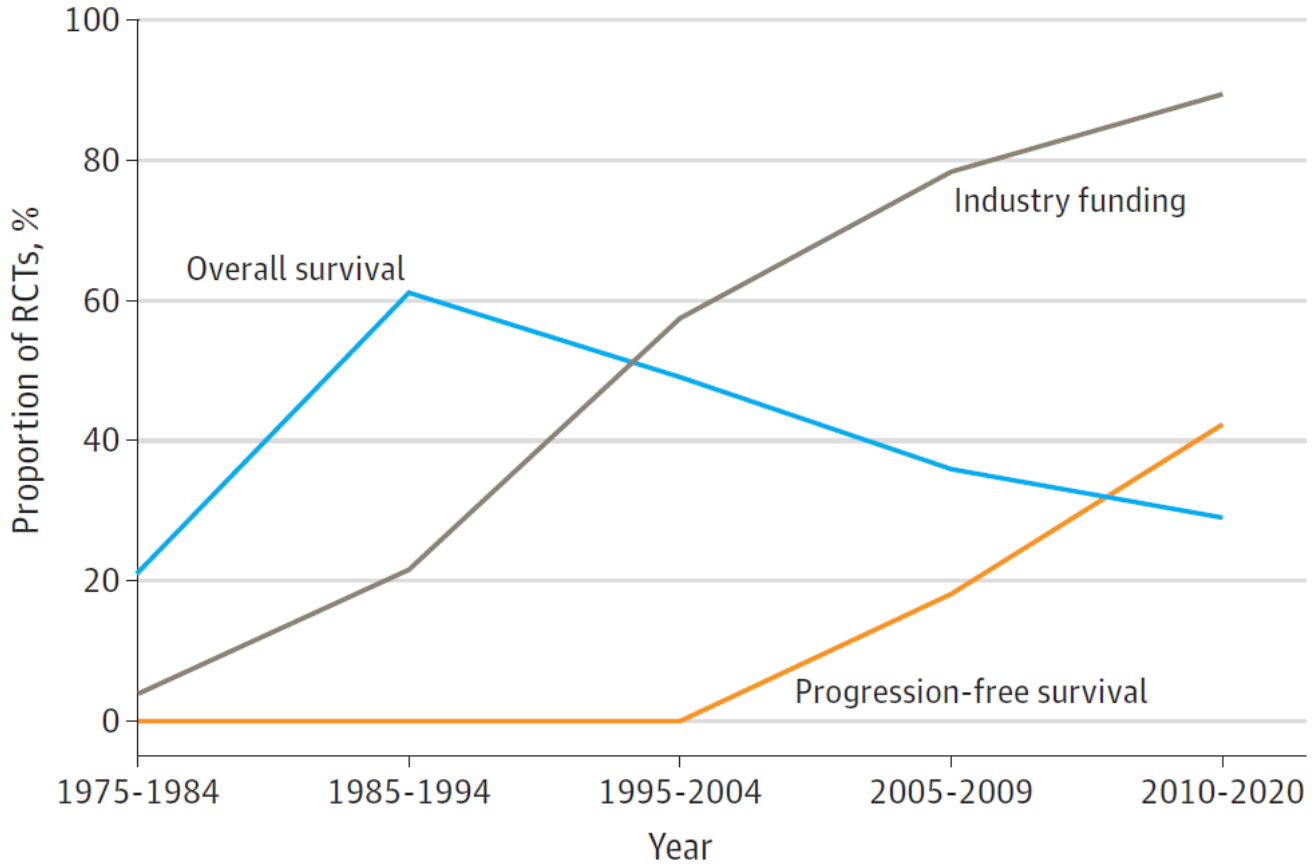

Del Paggio JC et al JAMA Oncol 2021

Description of Trials Included

Trial	No. of patients	Standard arm	Experimental arm	Main inclusion criteria	Stratification factors in randomization	Years of enrollment	Primary Endpoint
MIG1[1]	1214	FEC standard interval	FEC dose dense	N+ (65%N+) *or* N- and age ≤35 years or ER/PgR negative, T>2cm, G3, high Ki67	nodal status (N- vs N+) Centre	1992-1997	OS
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GIM3 FATA[4]	3697	Tam for 2 yrs→ Let for 3 yrs Tam for 2 yrs→ Exe for 3 yrs Tam for 2 yrs→ Ana for 3 yrs	Let for 5 yrs Exe for 5 yrs Ana for 5 yrs	Postmenopausal status ER+ any T / any N (35%N+)	ER and PgR status HER2 status previous CT nodal status (N0 vs N1 vs N2 vs N3)	2007-2012	DFS
GIM4 LEAD[5]	2056	Let for 2-3 yrs (5 yrs of ET)	Let for 5 yrs (7-8 yrs of ET)	Postmenopausal status ER+ any T / any N (45%N+)	Centre	2005-2010	DFS
GIM6 **PROMISE**[6]	281	CT alone	CT + GnRHa	Premenopausal candidate to CT any T / any N (55%N+)	Centre	2003-2008	CT-induced early menopause

Abbreviations: FEC, fluorouracil epirubicin, and cyclophosphamide; EC epirubicin, and cyclophosphamide; P, paclitaxel; N, nodal status; ER, estrogen receptor; PgR, progesterone receptor; OS, overall survival; DFS, disease free survival; ET, endocrine therapy; HER2, human epidermal growth factor; CT, chemotherapy; T, tumor size; Tam, tamoxifen; Let, letrozole; Exe, exemestane; Ana, anastrozole; GnRHa, Gonadotropin hormone-releasing hormone agonist.

[1]Blondeaux E et al. *Br J Cancer* 2020;122:1611–7; [2]Del Mastro L et al. *Breast Cancer Res Treat* 2016; 155: 117–26; [3]Del Mastro L et al. *Lancet Oncol* 2022; 23: 1571–82;
[4]De Placido S et al. *Lancet Oncol* 2018; 19: 474–85; [5]Del Mastro L et al. *Lancet Oncol* 2021; 22: 1458–67; [6]Lambertini M et al. *J Natl Cancer Inst* 2022; 114: 400–8.

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Methods

- Intermediate clinical endpoints were computed according to STEEP criteria v2.0

Endpoint	Invasive ipsilateral recurrence	Local-regional invasive recurrence	Distant recurrence	Death from breast cancer	Death from unknown or non-breast cancer cause	Invasive contralateral breast cancer	Ipsilateral or contralateral DCIS	Second primary malignancy (non-breast)
OS				X	X			
DFS	X	X	X	X	X	X	X	X
iDFS	X	X	X	X	X	X		X
DDFS			X	X	X			X
RFS	X	X	X	X	X			
DRFS			X	X	X			
IBCFS	X	X	X	X	X	X		
RFI	X	X	X	X				
DRFI			X	X				
BCFI	X	X	X	X		X	X	

Adapted from Tolaney SM et al. *J Clin Oncol* 2021.

Abbreviations: DFS, disease-free survival; DDFS, distant disease–free survival; DRFS, distant relapse–free survival; RFS, recurrence-free survival; RFI, recurrence-free interval; DRFI, distant recurrence-free interval; IBCFS, invasive breast cancer–free survival; BCFI, breast cancer-free interval.

Methods

- We evaluated the surrogacy of the different intermediate clinical endpoints and OS using a meta-analytic two-stage validation model [1,2]

- Two conditions must be satisfied to claim for OS surrogacy:
  - Outcome-level surrogacy (the intermediate clinical endpoint and OS are correlated irrespective of treatment)
    - Outcome-level surrogacy was tested at both the patient level and trial level
  - Trial-level surrogacy (the treatment effects on intermediate clinical endpoint and OS are correlated)

- We defined a priori a clinically relevant surrogacy of both R^2 value and Kendall's τ value ≥0.7, estimated by weighted linear regression and copula models respectively

[1]Buyse M et al. *Biostatistics* 2000; 1: 49–67;

[2]Ciani O et al. *Int J Technol Assess Health Care* 2014; 30: 312–24.

Results

12,397 patients included from 6 randomised trials

- Median age at enrolment was 57 years (IQR 49-65)
- 8,209 (66.2%) of the patients had node positive disease
- 7,718 (62.3%) had hormone-receptor positive/HER2-negative tumours

- Median follow-up was 10.3 years (IQR 6.4-14.5)

	OS events among all patients N=12397 (%)	OS events among patients with HR+/HER2- tumors N=7718 (%)
No OS event	10266 (82.8)	6703 (86.8)
OS event	2131 (17.2)	1015 (13.2)
Breast cancer related death	1390 (65.2)	616 (60.7)
Non-breast cancer related death	331 (15.5)	202 (19.9)
Death from unknown cause with prior recurrence	56 (2.6)	19 (1.9)
Death from unknown cause without prior recurrence	354 (16.6)	178 (17.5)

Results - Outcome-level Surrogacy

ICE	Outcome-level surrogacy (OS and ICE are correlated irrespective of treatment)			
	Correlation at the Patient Level		Regression of 8-Year OS Rate v 5-Year ICE Rate by Trial, Arm, and nodal status (No. of units = 22)	
	No. of events out of 10,394 patients included	Kendall's τ (95% CI)	No. of events out of 12,397 patients included	R^2 (95% CI)
DFS	2,773	0.75 (0.73 - 0.76)	3,526	0.95 (0.89 - 0.97)
DDFS	2,346	0.82 (0.81 - 0.82)	3,007	0.95 (0.88 - 0.97)
RFS	2,392	0.80 (0.79 - 0.81)	3,053	0.96 (0.92 - 0.98)
DRFS	2,163	0.84 (0.84 - 0.85)	2,779	0.96 (0.92 - 0.98)
IBCFS	2,595	0.77 (0.76 - 0.78)	3,306	0.97 (0.92 - 0.98)
RFI	1,853	0.73 (0.72 - 0.74)	2,437	0.96 (0.91 - 0.97)
DRFI	1,582	0.77 (0.76 - 0.79)	2,117	0.95 (0.89 - 0.97)
BCFI	2,073	0.69 (0.68 - 0.71)	2,709	0.96 (0.91 - 0.97)

Abbreviations: DFS, disease-free survival; DDFS, distant disease–free survival; DRFS, distant relapse–free survival; RFS, recurrence-free survival; RFI, recurrence-free interval; DRFI, distant recurrence-free interval; IBCFS, invasive breast cancer–free survival; BCFI, breast cancer-free interval.

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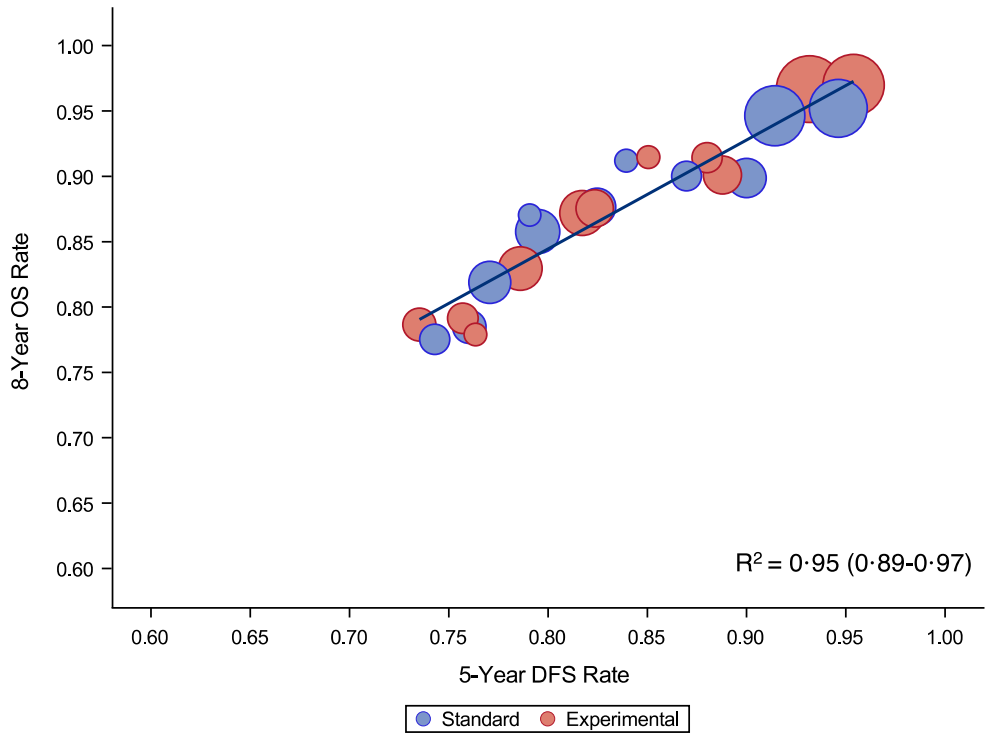
DFS endpoint



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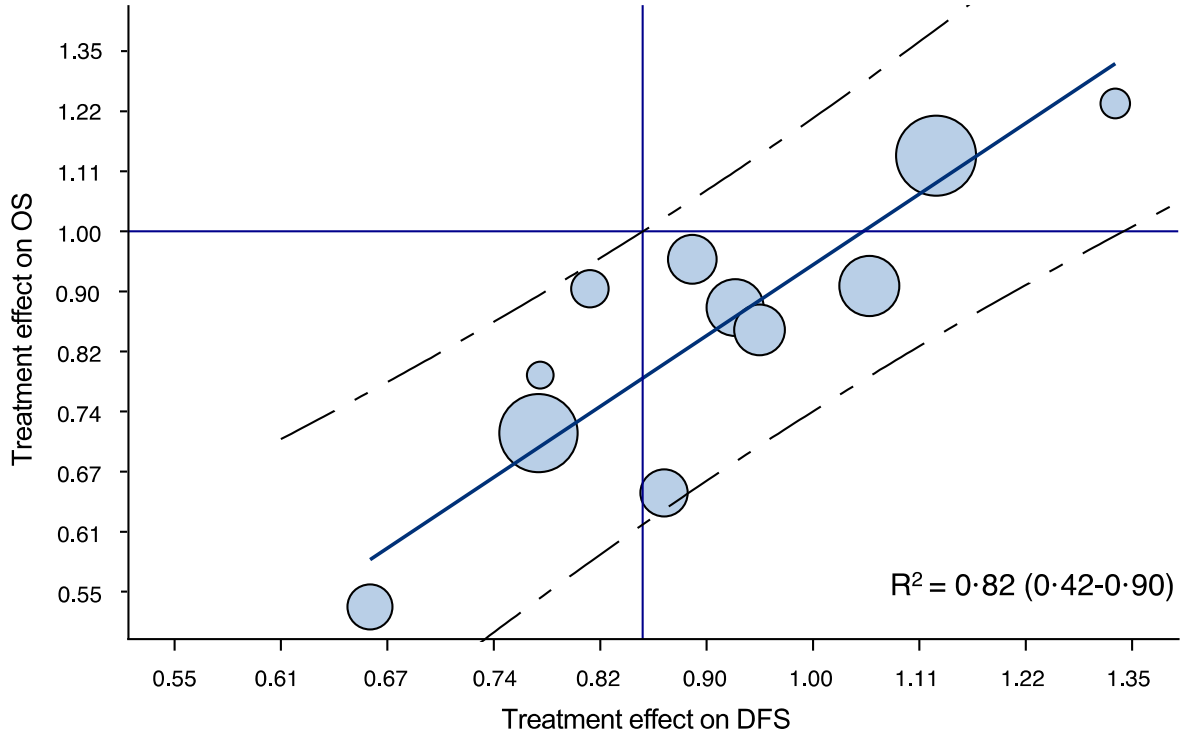
Results - Trial-level Surrogacy

ICE	Trial-level surrogacy (treatment effects on both end points are correlated)	
	Regression of Log(HR)-OS v Log(HR)-ICE by trial and nodal status (No. of units = 11)	
	R^2 (95% CI)	Regression Equation
DFS	0.82 (0.42 - 0.90)	$Log(HR)_{OS} = -0.056 + 1.179*Log(HR)_{DFS}$
DDFS	0.86 (0.51 - 0.92)	$Log(HR)_{OS} = -0.036 + 1.141*Log(HR)_{DDFS}$
RFS	0.88 (0.59 - 0.93)	$Log(HR)_{OS} = -0.023 + 1.124*Log(HR)_{RFS}$
DRFS	0.88 (0.59 - 0.93)	$Log(HR)_{OS} = -0.023 + 1.037*Log(HR)_{DRFS}$
IBCFS	0.84 (0.47 - 0.91)	$Log(HR)_{OS} = -0.046 + 1.117*Log(HR)_{IBCFS}$
RFI	0.76 (0.31 - 0.87)	$Log(HR)_{OS} = -0.018 + 0.942*Log(HR)_{RFI}$
DRFI	0.77 (0.31 - 0.87)	$Log(HR)_{OS} = -0.014 + 0.846*Log(HR)_{DRFI}$
BCFI	0.70 (0.20 - 0.83)	$Log(HR)_{OS} = -0.048 + 0.958*Log(HR)_{BCFI}$

DFS endpoint



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Conclusions

- We showed that all intermediate clinical endpoints tested, except for BCFI, are able to predict changes in OS
- Intermediate clinical endpoints that included death from any cause as event (i.e. DFS, DDFS, RFS, DRFS, IBCFS) presented the strongest correlation with OS
- Our study provides evidence supporting the use of all intermediate clinical endpoints, except for BCFI, defined by STEEP criteria v2.0, as primary endpoint in breast cancer adjuvant trials
- Future research should further investigate the application of intermediate clinical endpoints in different breast cancer subtypes and in the setting of new targeted treatment strategies

Abbreviations: OS, overall survival; BCFI, breast cancer-free interval; DFS, disease-free survival; DDFS, distant disease–free survival; DRFS, distant relapse–free survival; RFS, recurrence-free survival; IBCFS, invasive breast cancer–free survival..

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Thank you for the attention

Intermediate clinical endpoints in early-stage breast cancer: an analysis of individual patient data from the Gruppo Italiano Mammella and Mammella Intergruppo trials

Eva Blondeaux,[a,*] Wanling Xie,[b] Luca Carmisciano,[c] Silvia Mura,[d] Valeria Sanna,[d] Michelino De Laurentiis,[e] Roberta Caputo,[e] Anna Turletti,[f] Antonio Durando,[g] Sabino De Placido,[h] Carmine De Angelis,[h] Giancarlo Bisagni,[i] Elisa Gasparini,[i] Anita Rimanti,[j] Fabio Puglisi,[k,l] Mauro Mansutti,[m] Elisabetta Landucci,[n] Alessandra Fabi,[o] Luca Arecco,[p,q] Marta Perachino,[p,q] Marco Bruzzone,[a] Luca Boni,[a] Matteo Lambertini,[p,q] Lucia Del Mastro,[p,q,r] and Meredith M. Regan[b,r]

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