

Un anno di ricerca italiana nel carcinoma della mammella

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Istituto Oncologico Veneto, IRCCS





Composite risk and benefit from adjuvant DD CT in HR+ BC

npj Breast Cancer

ARTICLE

OPEN

Composite risk and benefit from adjuvant dose-dense chemotherapy in hormone receptor-positive breast cancer

Fabio Puglisi notation Cappi^{1,2 ™}, Lorenzo Gerratana^{1,2}, Matteo Lambertini notation Cappi⁵, Luca Boni notation Montemurro notation Cappi⁵, Stefania Russo⁷, Claudia Bighin⁸, Michelino De Laurentiis⁹, Mario Giuliano notation Bisagni¹¹, Antonio Durando notation Turletti¹³, Ornella Garrone¹⁴, Andrea Ardizzoni notation Cappi notation Cappi notation Cappi notation Cappi notation Cappi notation Cappi notation National Cappi notation Nation Cappi notation Cappi notation Cappi notation Nation Cappi notation Cappi notation Cappi notation Nation Cappi notation Cappi notation

ARM A	ARM C		
EC x 4 \rightarrow T x 4 q. 3 w	EC x 4 → T x 4 q. 2 w + Pegfilgrastim		
ARM B	ARM D		
FEC x 4 \rightarrow T x 4 q. 3 w	FEC x 4 → T x 4 q. 2 w + Pegfilgrastim		

Ancillary analysis of the GIM2 phase III trial, which demonstrated that in patients with node-positive eBC, dose-dense adjuvant chemotherapy improved DFS as compared with standard interval chemotherapy.

Factorial study aimed at assessing two separate hypothesis:

- <u>Factor 1</u>: A+C vs B+D = the efficacy and safety of 5-FU in addition to EC→T
- <u>Factor 2</u>: A+B vs C+D = the efficacy and safety of a 50% increase in dose-density

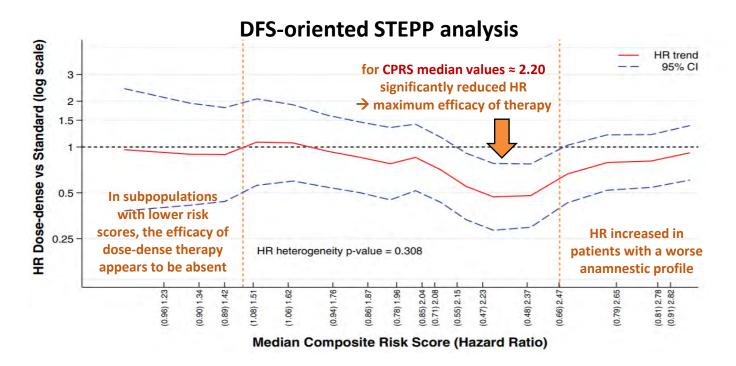


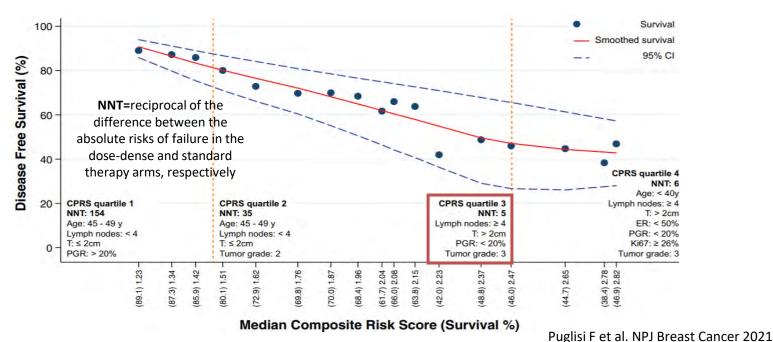
Evaluation of the absolute treatment effect through a composite measure of recurrence risk (CPRS) in patients with HR+/HER2- eBC.

Multivariate Cox regression model stratified by treatment for the variables used by the CPRS

	Log (HR)	HR	95% CI	P value
AGE		100	10100	
<35	0.425	1.53	0.72-3.24	0.268
35-39	0.859	2.36	1.39-3.99	0.001
40-44	0.113	1.12	0.68-1.84	0.665
45-49	0.000	1.00	Ref.	
≥50	0.322	1.38	0.94-2.03	0.100
NODES				
1-3	0.000	1.00	Ref.	
≥4	0.737	2.09	1.61-2.71	<0.001
T		152		
≤2	0.000	1.00	Ref.	
>2	0.577	1.78	1.36-2.34	< 0.001
ER%				
<50	0.262	1.30	0.92-1.82	0.135
≥50	0.000	1.00	Ref.	
PGR%	0.293	1.34	0.96-1.86	0.083
20-49	0.140	1.15	0.82-1.62	0.418
≥50	0.000	1.00	Ref.	0.410
HISTO G			6.16	
G1	0.000	1.00	Ref.	
G2	1.022	2.78	1.13-6.80	0.026
G3	1.092	2.98	1.20-7.40	0.018
KI67%				
<14	0.000	1.00	Ref.	
14–19	0.166	1.18	0.75-1.85	0.483
20-25	0.068	1.07	0.72-1.58	0.741
≥26	0.095	1.10	0.77-1.57	0.605

Number of positive nodes, tumor size and histological grade were the most important prognostic factors in terms of DFS → contributed the most to the CPRS.

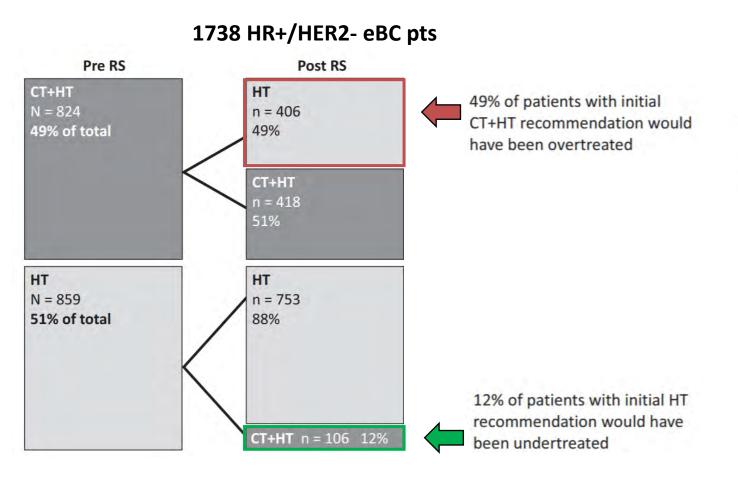


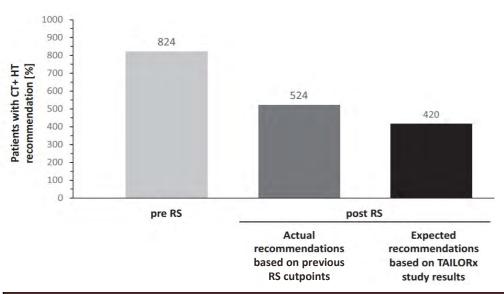


PONDx: real-life utilization of Oncotype-Dx

Multicenter, prospective, observational study to investigate the real-life use of RS® results in Italy (27 reference centers in Lombardia, Lazio, Emilia Romagna, Campania, Abruzzo, and Marche) and its impact on treatment decisions, by recording:

- 1) Pre-RS decision for HT +/- CT
- 2) RS results
- 3) Post-RS decision \rightarrow % changes in recommendations





Expected recom	Expected recommendations assuming decision-making according to TAILORx results			
Population	Change in CT + HT recommendations %			
Overall	-49%			
N0	-47%			

Real-life utilization of Oncotype-Dx across: Italian experiences

2017



First Prospective Multicenter Italian Study on the Impact of the 21-Gene Recurrence Score in Adjuvant Clinical Decisions for Patients with ER Positive/HER2 Negative Breast Cancer

MARIA VITTORIA DIECI, a,b VALENTINA GUARNERI, b TOMMASO GIARRATANO, MARTA MION, GIAMPAOLO TORTORA, COSTANZA DE ROSSI, S STEFANIA GORI, CRISTINA OLIANI, LAURA MERLINI, FELICE PASINI, GIORGIO BONCIARELLI, GAIA GRIGUOLO, ENRICO ORVIETO, SILVIA MICHIELETTO, TANIA SAIBENE, PAOLA DEL BIANCO, GIAN LUCA DE SALVO, PIERFRANCO CONTE^{a,b}

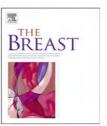
Impact of 21-Gene Breast Cancer Assay on Treatment Decision for Patients with T1–T3, N0–N1, Estrogen Receptor-Positive/Human Epidermal Growth Receptor 2-Negative Breast Cancer: Final Results of the Prospective Multicenter ROXANE Study



2019

MARIA VITTORIA DIECI, ^{a,b} VALENTINA GUARNERI, ^{a,b} FABLE ZUSTOVICH, ^d MARTA MION, ^e PAOLO MORANDI, ^f EMILIO BRIA, ^{g,b} LAURA MERLINI, ^h PIERLUIGI BULLIAN, ^l CRISTINA OLIANI, ^k STEFANIA GORI, ^m TOMMASO GIARRATANO, ^b ENRICO ORVIETO, ^l GAIA GRIGUOLO, ^a SILVIA MICHIELETTO, ^c TANIA SAIBENE, ^c PAOLA DEL BIANCO, ^b GIAN LUCA DE SALVO, ^b PIERFRANCO CONTE, ^{a,b} ON BEHALF OF THE VENETO ONCOLOGY NETWORK

2020



Prospective observational study on the impact of the 21-gene assay on treatment decisions and resources optimization in breast cancer patients in Lombardy: The BONDX study

Alberto Zambelli ^{a, *}, Edda Simoncini ^b, Monica Giordano ^c, Nicla La Verde ^d, Gabriella Farina ^e, Valter Torri ^f, Giorgio Colombo ^g, Giulia Piacentini ^a, Vittoria Fotia ^a, Lucia Vassalli ^b, Palma Pugliese ^c, Paola Poletti ^a, Elena Rota Caremoli ^a, Carlo Tondini ^a

ARTICLE OPEN

PONDx: real-life utilization and decision impact of the 21-gene assay on clinical practice in Italy

npj Breast Cancer

2021

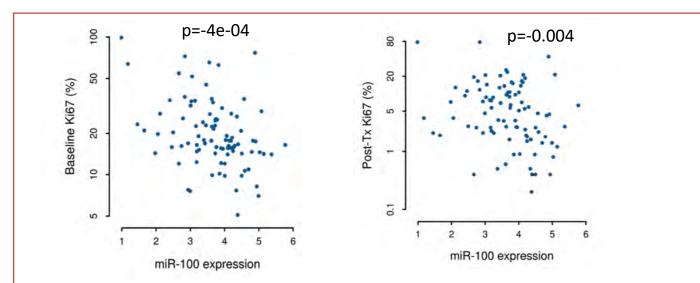
MiR-100 as a predictor of endocrine responsiveness and prognosis

MiR-100 is a predictor of endocrine responsiveness and prognosis in patients with operable luminal breast cancer

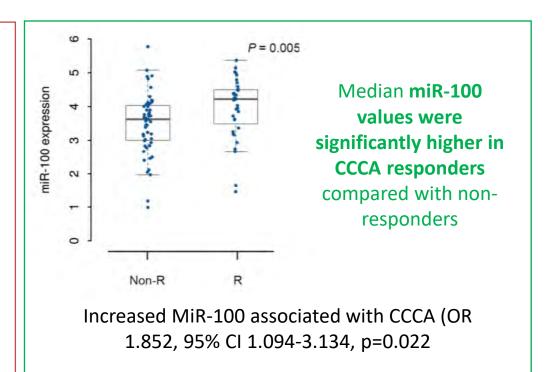
Annalisa Petrelli,¹ Sara Erika Bellomo,² Ivana Sarotto,³ Franziska Kubatzki,⁴ Paola Sgandurra,⁴ Furio Maggiorotto,⁴ Maria Rosaria Di Virgilio,⁵ Riccardo Ponzone,⁴ Elena Geuna,⁶ Danilo Galizia,⁶ Anna Maria Nuzzo,⁷ Enzo Medico,^{2,8} Umberto Miglio,³ Enrico Berrino,^{3,9} Tiziana Venesio,³ Salvatore Ribisi,¹ Paolo Provero,^{10,11} Anna Sapino,^{3,9} Silvia Giordano,^{1,2} Filippo Montemurro

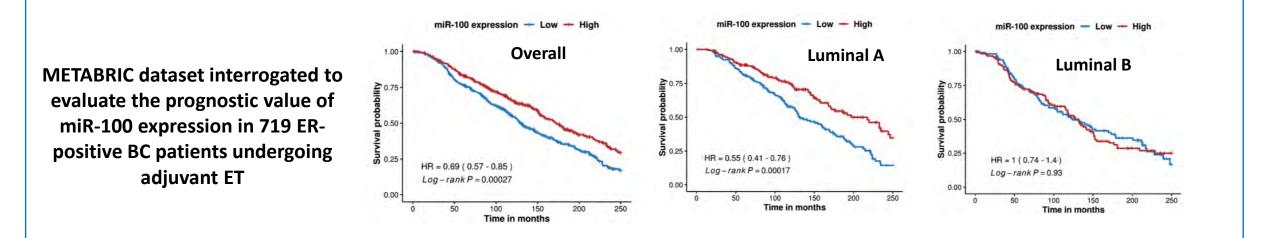
The predictive value of baseline tumor levels of miR-100 with respect to response to endocrine therapy (tamoxifene or letrozole) was explored in a prospective study of endocrine therapy given either preoperatively, or for the treatment of de-novo MBC→ 90 evaluable patients.

Response = Ki67 ≤2.7% after 21 +/- 3 days of treatment



MiR-100 levels showed a **significant negative correlation with** both baseline and post-treatment **Ki67 values**, both in the overall population and in post-menopausal pts receiving letrozole





High MiR-100 associated with improved OS in the overall population and in <u>Luminal A subgroup</u>. <u>NO effect on Luminal B subgroup</u>.

GIADA study: neoadjuvant CT + immunoT in Luminal B-like BC

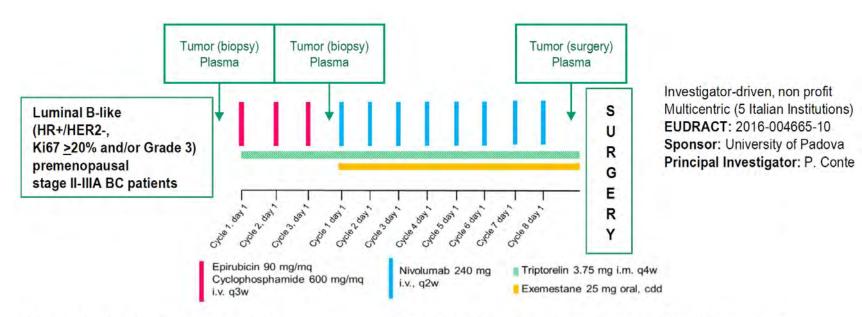


CLINICAL CANCER RESEARCH



Neoadjuvant chemotherapy and immunotherapy in Luminal B-like breast cancer: results of the phase II GIADA trial

Maria Vittoria Dieci, Valentina Guarneri, Anna Tosi, Giancarlo Bisagni, Antonino Musolino, Simon Spazzapan, Gabriella Moretti, Grazia Maria Vernaci, Gaia Griguolo, Tommaso Giarratano, Loredana Urso, Francesca Schiavi, Claudia Pinato, Giovanna Magni, Marcello Lo Mele, Gian Luca De Salvo, Antonio Rosato, and Pierfranco Conte



Primary endpoint: pCR (ypT0/is ypN0)
Secondary endpoints*: RCB, cOR in the breast by

ultrasound, safety, tumor tissue biomarkers

*in this presentation

Statistical design: 2-steps, H0=0.10, H1=0.25, α =0.05, β =0.20

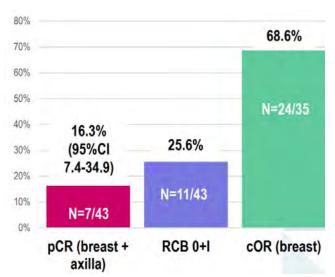
1st step: ≥3 pCR/18 pts (achieved in November 2018)

2nd step ≥8 pCR/43 pts

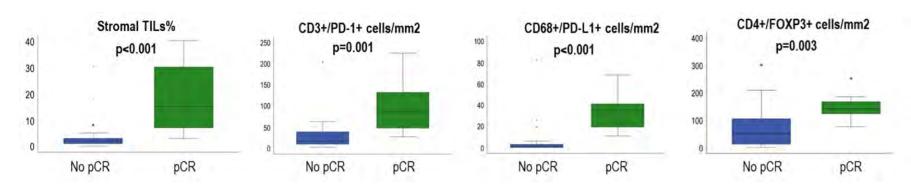
Neoadjuvant immunotherapy in pre-menopausal HR+/HER2- EBC

N=43 patients enrolled from October 2017 to October 2019

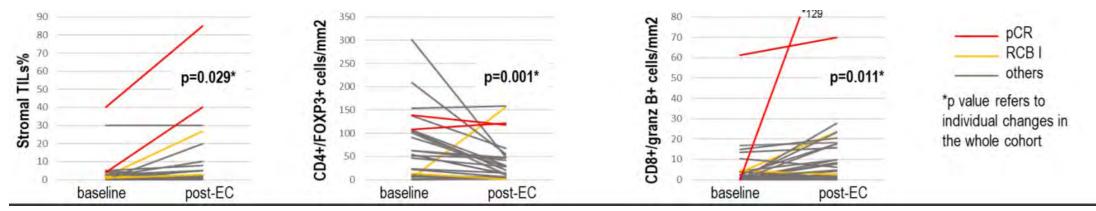
Efficacy results



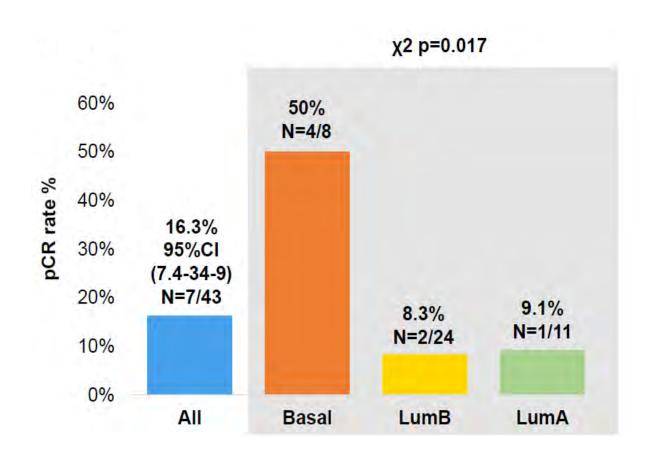
Baseline biopsy: pCR vs non-pCR (n=39 including n=7 pCR)



Changes from baseline to post-EC biopsy (n=30 paired samples suitable for analyses)



GIADA study: neoadjuvant CT + immunoT in Luminal B-like BC



GIM11-BERGI study: eribulin + bevacizumab in HER2- mBC



Eribulin in combination with bevacizumab as second-line treatment for HER2-negative metastatic breast cancer progressing after first-line therapy with paclitaxel and bevacizumab: a multicenter, phase II, single arm trial (GIM11-BERGI)

C. De Angelis¹, D. Bruzzese², A. Bernardo³, E. Baldini⁴, L. Leo⁵, A. Fabi⁶, T. Gamucci⁷, P. De Placido¹, F. Poggio⁸, S. Russo⁹, V. Forestieri¹, R. Lauria¹, I. De Santo¹, A. Michelotti¹⁰, L. Del Mastro^{8,11}, M. De Laurentiis¹², M. Giuliano^{1*}, S. De Placido¹ & G. Arpino¹

Multicenter, single-arm, Simon's two-stage, phase II study

HER2-negative MBC
Progression after first-line
paclitaxel + bevacizumab
(n=61)

ERIBULIN + BEVACIZUMAB

PD

Second-line

Primary endpoint: BORR (best ORR)

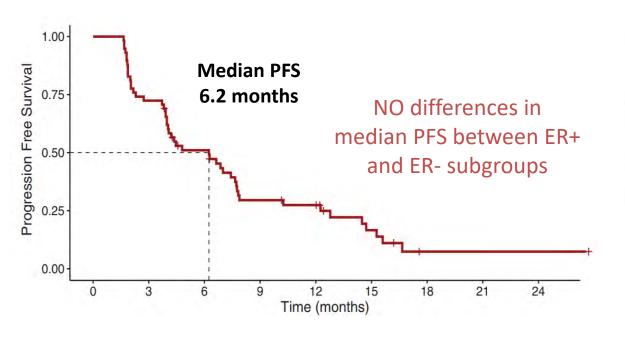
- Eribulin 1.23mg/m² on days 1, 8 every 3 weeks intravenously
- Bevacizumab 15 mg/kg every 3 weeks or 10 mg/kg every 2 weeks intravenously

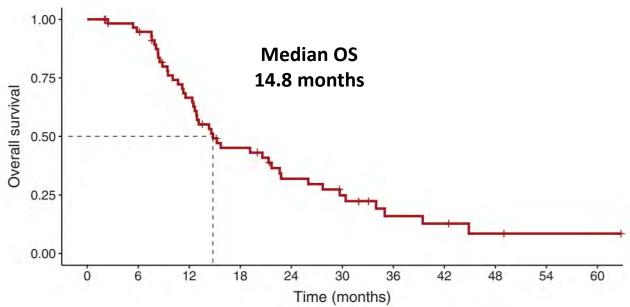
An overall clinical response rate of 25% as the target activity level and 12% as the lowest response rate of interest were considered \rightarrow in case of \geq 3 responses/19 patients monitored for a minimum of 18 weeks \rightarrow II stage \rightarrow 42 additional patients accrued (total 61 pts).

GIM11-BERGI study: eribulin + bevacizumab in HER2- mBC

Outcome	ITT population $(N = 61), n$ (%)	PP population * $(N = 58), n$ (%)	ER + (N = 44), n (%)	ER-(N=13), n(%)	ER+ versus ER- P value
Best overall response rate	15 (24.6)	15 (25.9)	11 (25.0)	4 (30.8)	0.727
Complete response	1 (1.6)	1 (1.7)	0 (0)	1 (7.7)	0.443
Partial response	14 (23.0)	14 (17.2)	11 (25)	3 (23.1)	
Stable disease	26 (42.6)	26 (44.8)	20 (45.5)	6 (46.2)	
Progressive disease	17 (27.9)	17 (29.3)	13 (29.5)	3 (23.1)	

^{*}Per-protocol analysis





Sars-CoV-2 silent carriers among actively treated cancer pts

Oncologist*

Symptom Management and Supportive Care

Enrollement: April, 1st 2020 – April, 30th 2020

Prevalence and Clinical Impact of SARS-CoV-2 Silent Carriers Among Actively Treated Patients with Cancer During the COVID-19 Pandemic

ALBERTO ZAMBELLI , ALDRENZO CHIUDINELLI, VITTORIA FOTIA, GIORGIA NEGRINI, TOMMASO BOSETTI, ANNAPAGIA CALLEGARO, ANDREA DI CROCE, ELENA ROTA CAREMOLI, CECILIA MORO, LAURA MILESI, PAGIA POLETTI, CRISTINA TASCA, MARIO MANDALA, BARBARA MERELLI, SEFANIA MOSCONI, ERMENEGILDO ARNOLDI, ANNA BETTINI, LUCIA BONOMI, CATERINA MESSINA, LAURA GHILARDI, ALESSANDRA CHIRCO, MICHELA MARACINO, CARLO TONDINI

Substantial prevalence of Sars-CoV-2 silent infection in actively treated cancer patients.

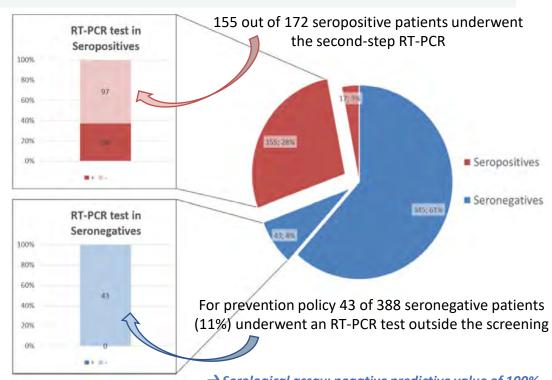
172 (31%) resulted positive for anti-SARS-CoV-2 IgM/IgG Ab

Among Ig-seropositive pts tested with RT-PCR nasopharyngeal swabs, 38% were SARS-CoV-2 silent carriers

2-step diagnostics: feasible and effective in detecting silent carriers

560 consecutive patients with cancer, asymptomatic for COVID-19 and on anticancer treatment at Papa Giovanni XXIII Hospital in Bergamo evaluated and tested for SARSCoV-2.

<u>Two-step diagnostics</u>: screening with rapid serological immunoassay for anti–SARS-CoV-2 immunoglobulin \rightarrow if $+ \rightarrow$ nasopharyngeal swab RT-PCR.



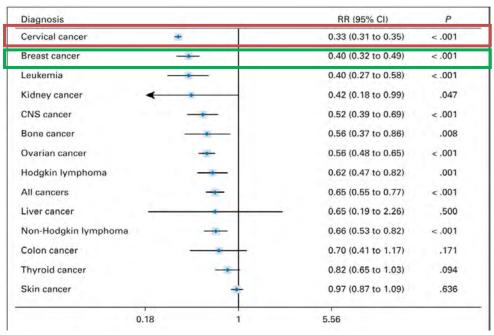
Pregnancy after BC



Pregnancy After Breast Cancer: A Systematic Review and Meta-Analysis

Matteo Lambertini, MD, PhD^{1,2}; Eva Blondeaux, MD^{1,3}; Marco Bruzzone, MSc⁴; Marta Perachino, MD^{1,2}; Richard A. Anderson, MD⁵; Evandro de Azambuja, MD, PhD⁶; Philip D. Poorvu, MD⁷; Hee Jeong Kim, MD⁸; Cynthia Villarreal-Garza, MD, PhD^{9,10}; Barbara Pistilli, MD¹¹; Ines Vaz-Luis, MD, PhD¹¹; Cristina Saura, MD, PhD¹²; Kathryn J. Ruddy, MD, MPH¹³; Maria Alice Franzoi, MD¹¹; Chiara Sertoli, MD¹; Marcello Ceppi, MSc⁴; Hatem A. Azim Jr, MD, PhD⁹; Frederic Amant, MD, PhD^{14,15}; Isabelle Demeestere, MD, PhD¹⁶; Lucia Del Mastro, MD^{1,3}; Ann H. Partridge, MD, MPH⁷; Olivia Pagani, MD¹⁷; and Fedro A. Peccatori, MD, PhD¹⁸

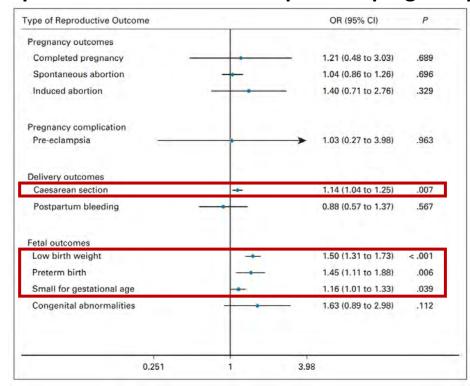
Likelihood of pregnancy after cancer diagnosis



Cervical cancer associated with the lowest likelihood of pregnancy
Among 46780 pts with BC, 2026
(4.2%) had a subsequent pregnancy

Patients with cancer had 35% reduced likelihood of having a subsequent pregnancy compared with the general population (RR 0.65: 95% CI 0.55-0.77).

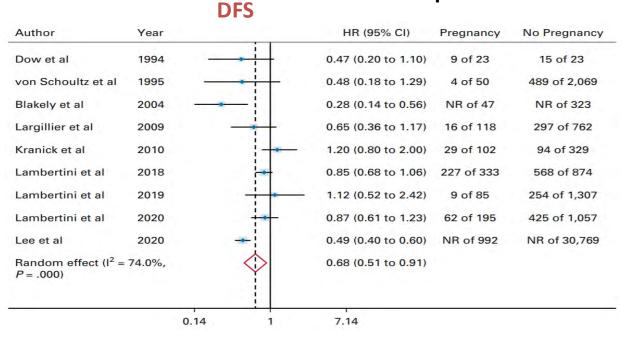
Reproductive outcome of BC pts with pregnancy

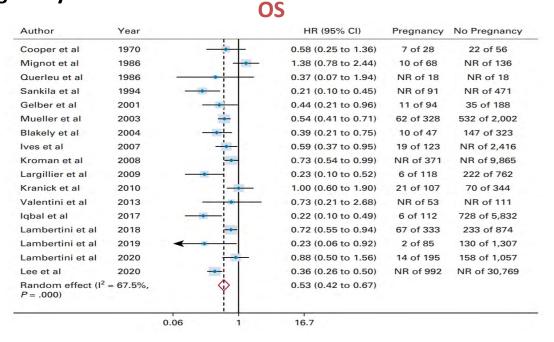


Increased risk among BC versus general population

Pregnancy after BC

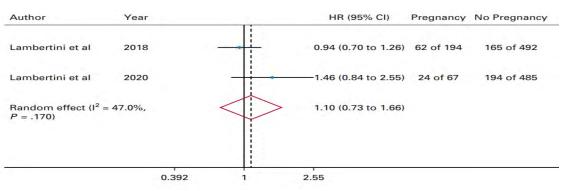
Survival in BC pts with vs without a pregnancy after BC



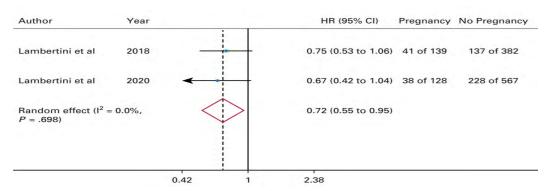


DFS in BC pts with vs without a pregnancy according to HR status

HR+











CHER-LOB, NSABP-B41, NeoALTTO and CALGB40601

CHER-LOB

HER2-positive operable breast cancer (N=121)

Stage II-IIIA



Phase II

randomized

R

Phase III

wT x 12 wks → FEC x 4 L x 26 wks

wT x 12 wks \rightarrow FEC x 4

H x 26 wks

wT x 12 wks \rightarrow FEC x 4 H + L x 26 wks



Hormone therapy (for HR+ BC patients) and RT were recommended postoperatively per local standards.

NSABP-B41

HER2-positive operable breast cancer (N=529)

T>2cm



AC x 4 → wT x 12 wks + L x 12 wks

 $AC \times 4 \rightarrow wT \times 12 \text{ wks}$

+ H x 12 wks

AC x 4 → wT x 12 wks + H + L x 12 wks



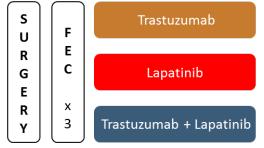
Hormone therapy (for HR+ BC patients) and RT were recommended postoperatively per local standards.

NeoALTTO

HER2-positive operable breast cancer (N=450)

T≥2cm





Hormone therapy (for HR+ BC patients) and **RT** were recommended postoperatively per local standards.

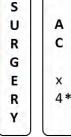
CALGB40601

HER2-positive operable breast cancer (N=305)

> Stage II-III T≥1cm



wT + H + L x 16 wks

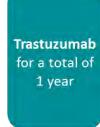


S

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Υ

*RECOMMENDED (protocol-defined therapy ended at surgery).



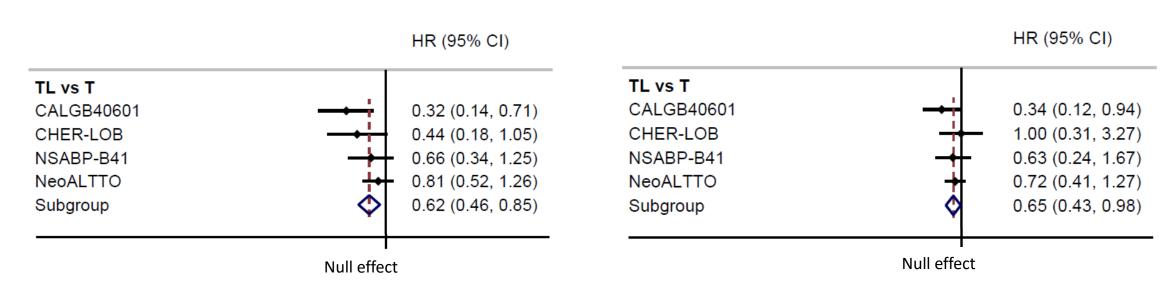
Hormone therapy (for HR+ BC patients) and RT were recommended postoperatively per local standards.



RESULTS: RELAPSE-FREE AND OVERALL SURVIVAL ACCORDING TO LAPATINIB USE (T+L vs T)

RELAPSE FREE SURVIVAL

OVERALL SURVIVAL





GIM4 study: extended therapy with letrozole



Extended therapy with letrozole as adjuvant treatment of postmenopausal patients with early-stage breast cancer: a randomised, phase 3 trial of the Gruppo Italiano Mammella.

Del Mastro L, Mansutti B, Bisagni g, Ponzone R, Durando A, Amaducci L, Cognetti F, Frassoldati A, Michelotti M, Mura S, Urracci Y, Sanna G, Gori S, De Placido S, Garrone O, Barone C, Bighin C, Poggio F, Lambertini M, Bruzzi P on behalf of GIM investigators

Median follow-up: 11-7 years (IQR 9-5-13-1)









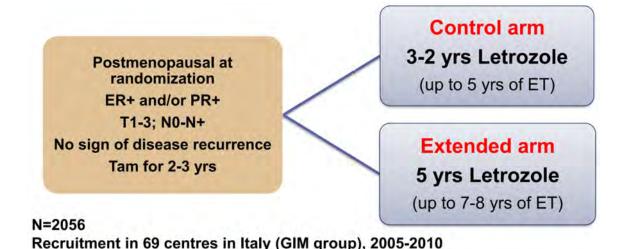
Extended therapy with letrozole as adjuvant treatment of postmenopausal patients with early-stage breast cancer: a multicentre, open-label, randomised, phase 3 trial



Lancet Oncol 2021

Published Online September 17, 2021 https://doi.org/10.1016/ 51470-2045(21)00352-1

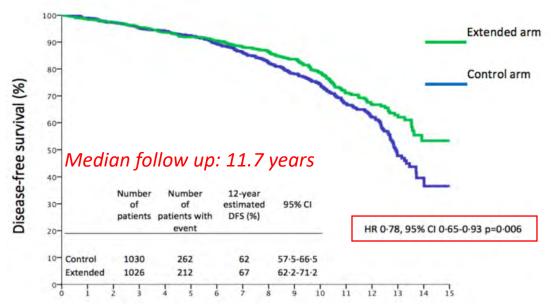
Lucia Del Mastro, Mauro Mansutti, Giancarlo Bisagni, Riccardo Ponzone, Antonio Durando, Laura Amaducci, Enrico Campadelli, Francesco Cognetti, Antonio Frassoldati, Andrea Michelotti, Silvia Mura, Ylenia Urracci, Giovanni Sanna, Stefania Gori, Sabino De Placido, Ornella Garrone, Alessandra Fabi, Carla Barone, Stefano Tamberi, Claudia Bighin, Fabio Puglisi, Gabriella Moretti, Grazia Arpino, Alberto Ballestrero, Francesca Poggio, Matteo Lambertini, Filippo Montemurro, Paolo Bruzzi, on behalf of the Gruppo Italiano Mammella investigators*



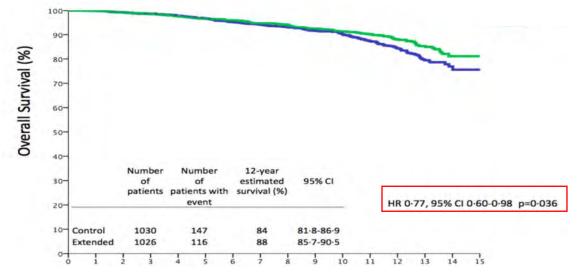
Primary endpoint: iDFS (from randomization to iDFS event or last follow up). **Secondary endpoints: OS, Aes.**

GIM4 study: extended therapy with letrozole

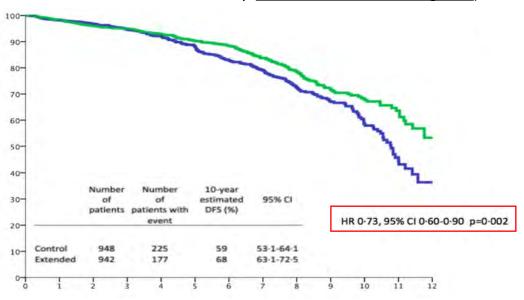
Primary endpoint analysis



Overall Survival

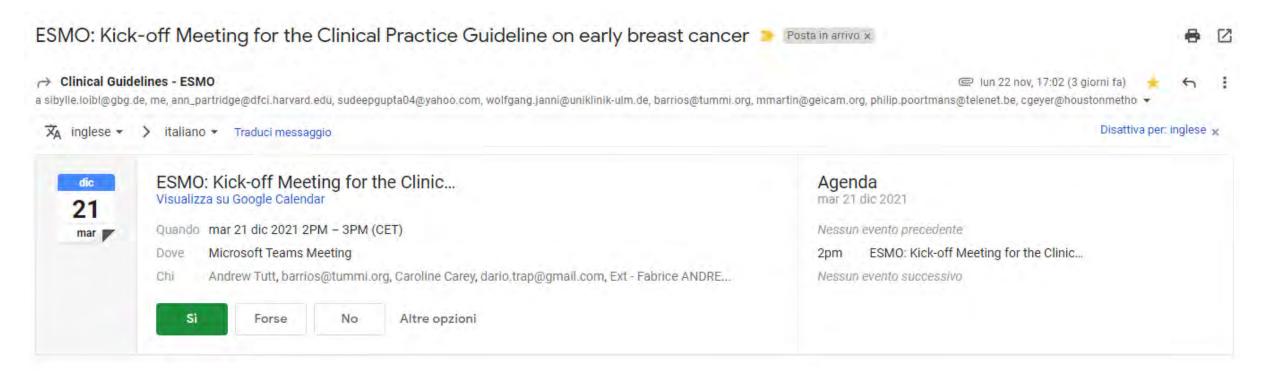


Landmark analysis (excluding patients with a disease-free survival event or those lost to follow- up <u>before treatment divergence</u>)



Safety

	Control arm 2-3-year letrozole (n=983)		5-year letrozole (n=977)	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Arthralgia	263 (27%)	22 (2%)	311 (32%)	29 (3%)
Myalgia	65 (7%)	7 (1%)	95 (10%)	9 (1%)
Hot flashes	119 (12%)		127 (13%)	
Alopecia	31 (3%)		35 (4%)	
Osteoporosis	47 (5%)		81 (8%)	
Hypertension	7 (1%)		19 (2%)	
Bone fractures ^a	5 (<1%)		9 (1%)	
Hypercholesterolemia ^b	32 (3%)		22 (2%)	
Cardiovascular event ^c	1 (<1%)		6 (1%)	







SPECIAL ARTICLE

ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer

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A. Gennari<sup>1</sup>, F. André<sup>2</sup>, C. H. Barrios<sup>3</sup>, J. Cortés<sup>4,5,6,7</sup>, E. de Azambuja<sup>8</sup>, A. DeMichele<sup>9</sup>, R. Dent<sup>10</sup>, D. Fenlon<sup>11</sup>, J. Gligorov<sup>12</sup>, S. A. Hurvitz<sup>13,14</sup>, S.-A. Im<sup>15</sup>, D. Krug<sup>16</sup>, W. G. Kunz<sup>17</sup>, S. Loi<sup>18</sup>, F. Penault-Llorca<sup>19</sup>, J. Ricke<sup>2,17</sup>, M. Robson<sup>20</sup>, H. S. Rugo<sup>21</sup>, C. Saura<sup>22</sup>, P. Schmid<sup>23</sup>, C. F. Singer<sup>24</sup>, T. Spanic<sup>25</sup>, S. M. Tolaney<sup>26</sup>, N. C. Turner<sup>27</sup>, G. Curigliano<sup>28</sup>, S. Loibl<sup>29</sup>, S. Paluch-Shimon<sup>30</sup> & N. Harbeck<sup>31</sup>, on behalf of the ESMO Guidelines Committee
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