Evidence and practice changing treatments in female tumors – breast cancer

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DECLARATION OF INTERESTS

None related to the presented work.

Hypofractionation

Partial Breast Irradiation

Omission of whole breast irradiation

Oligometastatic disease

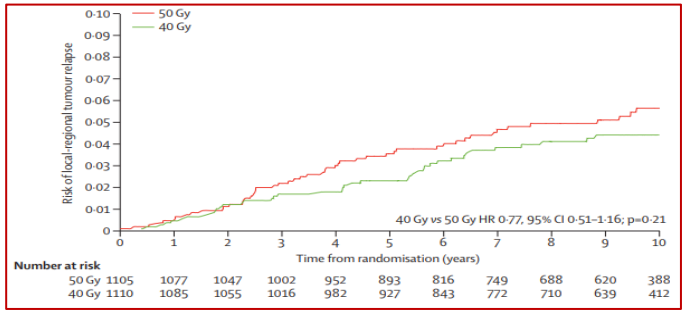
Integration with systemic therapies

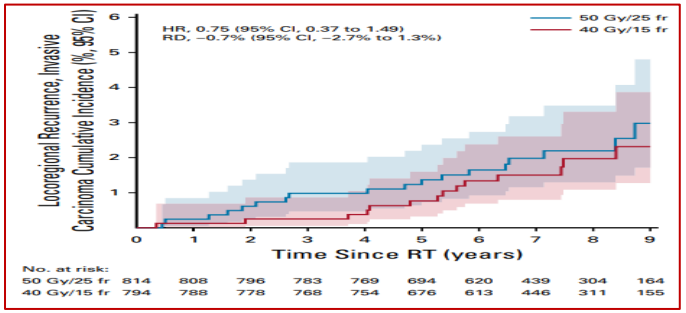
Moderate hypofractionation

Efficacy

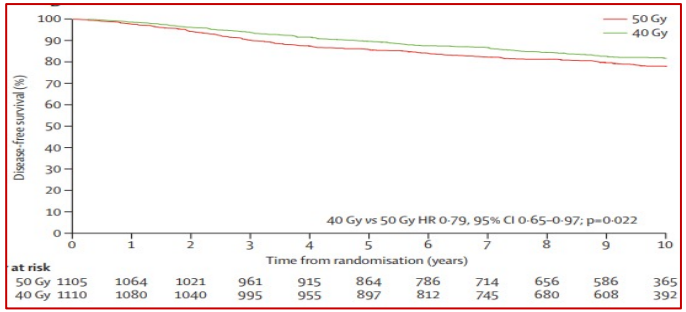
START B Haviland et al, 2013; **DBCG HYPO** – Offersen B et al, 2020

Cumulative risk of locoregional relapse

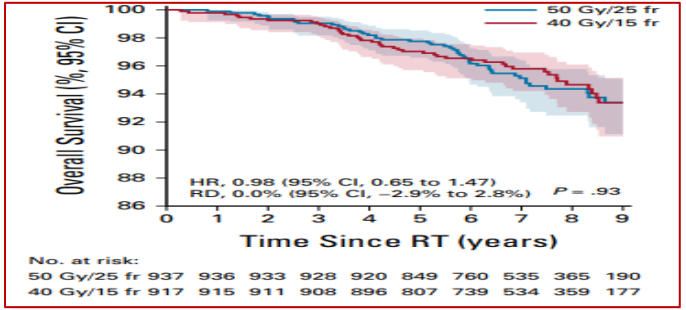




Disease free survival START B



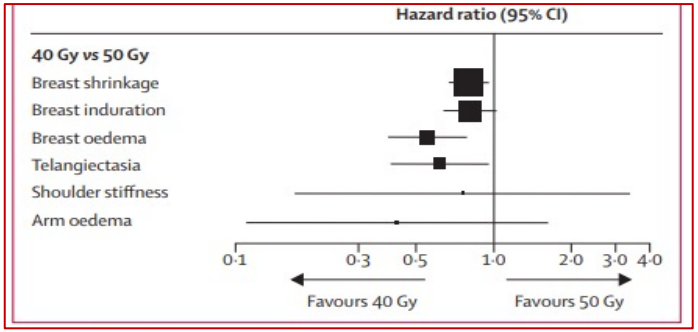
Overall Survival DBCG HYPO



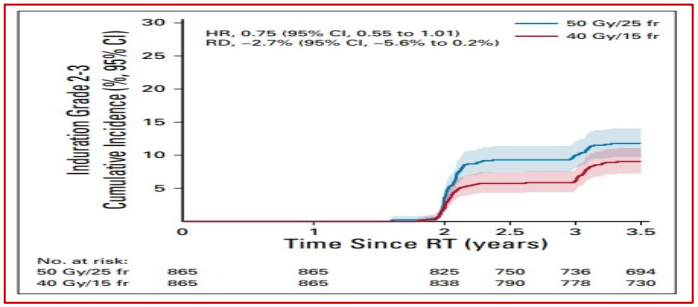
Moderate hypofractionation

Safety

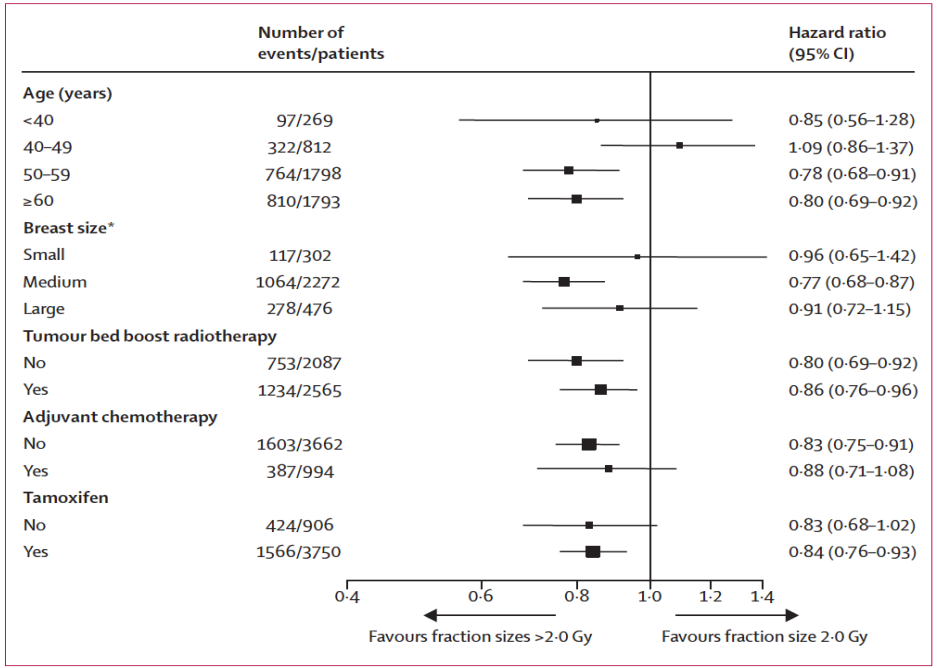
Moderate/marked late NTE from START A and B



Cumulative incidence of Grade 2-3 induration



Meta-analysis any moderate/marked physician-assessed NTE in breast comparing HF regimens *vs* 50 Gy/25



START B Haviland et al, 2013; **DBCG HYPO** – Offersen B et al, 2020

Hypofractionation for early breast cancer

Ultra Hypofractionation (5-fraction)

FAST-Forward trial (n=4096) showed that ultra-hypofractionation (**26Gy in 5 fractions**) leads to **non-inferior** **local control** rates and **similar adverse event profile** as compared to **40Gy in 15 fractions over 3 weeks**

Median follow up 6 years

→ 5-fraction regimen **non-inferior** in terms of **LR** as compared to 40 Gy in 15 fractions (HR 0.67, 95%CI 0.38 to 1.16)

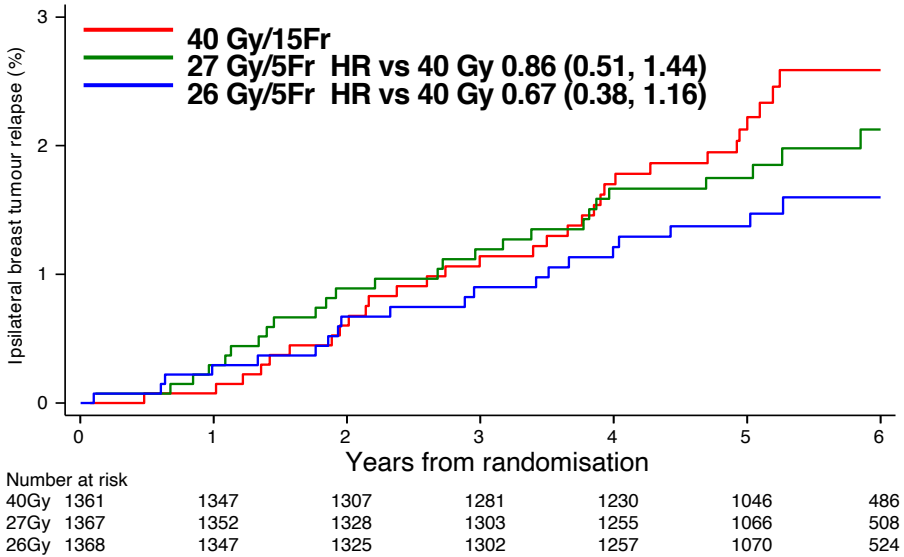
→ 5-year estimate 1.4% (26 Gy) *vs* 2.1% (40 Gy)

→ **Late NTE** as assessed by clinicians, patients, and photos **similar for 26 Gy** (HR 1.12, 95%CI 0.94 to 1.34; p=0.20)

Brunt AM, et al. Lancet 2020

Hypofractionation for early breast cancer

Ultra Hypofractionation (5-fraction)



	No. events	5yr estimate (95% CI)	Difference vs. 40 Gy (95% CI)
40 Gy	31	2.1% (1.4, 3.1)	-
27 Gy	27	1.7% (1.2, 2.6)	-0.3% (-1.0, 0.9)
26 Gy	21	1.4% (0.9, 2.2)	-0.7% (-1.3, 0.3)

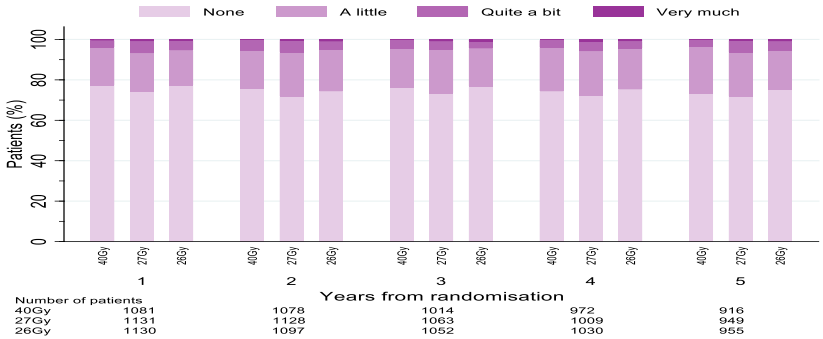
Brunt AM, et al. Lancet 2020

Ultra Hypofractionation (5-fraction)

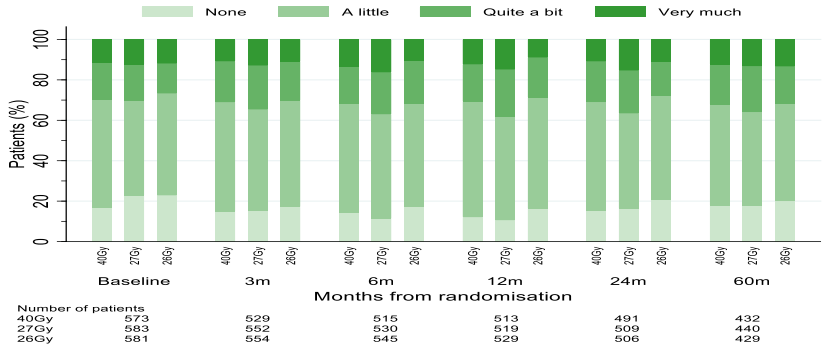
Clinician & patient assessments of adverse effects up to 5 years

Clinician assessments | **Patient assessments**

Breast distortion



Change in breast appearance



At 5 years → any clinician-assessed **moderate/marked** AE: **10% in 40Gy** *vs* 15% in 27Gy ***vs* 12% in 26Gy**

Courtesy of Charlotte Coles

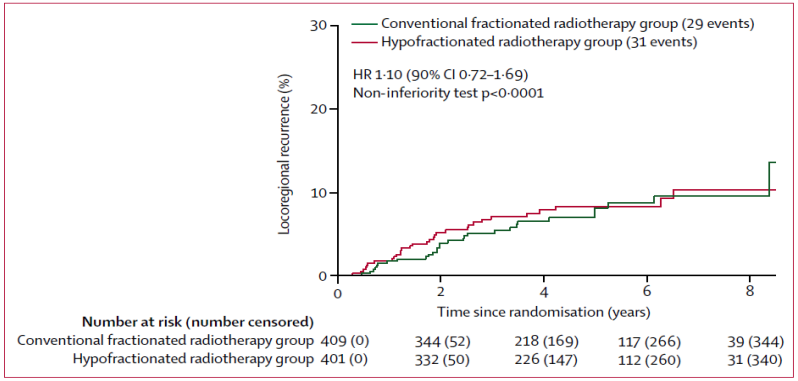
Postmastectomy setting
Efficacy of hypofractionation

Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial

Shu-Lian Wang, Hui Fang*, Yong-Wen Song, Wei-Hu Wang, Chen Hu, Yue-Ping Liu, Jing Jin, Xin-Fan Liu, Zi-Hao Yu, Hua Ren, Ning Li, Ning-Ning Lu, Yu Tang, Yuan Tang, Shu-Nan Qi, Guang-Yi Sun, Ran Peng, Shuai Li, Bo Chen, Yong Yang, Ye-Xiong Li*

820 high-risk BC patients (2008-2016)

Hypofractionated PMRT (43.5Gy in 15 fractions) is as efficacious and safe as 50Gy in 25 fractions



Results
Median follow-up of **58.5 months**

8.3% of 5-year cumulative incidence of LRR in the hypo-RT group ***vs* 8.1%** in the CF-group *(p<0.0001)*

Wang SL, et al. Lancet Oncol 2019

Postmastectomy setting
Safety of hypofractionation

No significant differences in acute and late toxicities

Grade 3 acute skin toxicity in **3% in the hypo-RT group *vs* 8% in the CF-group** *(p<0.0001)*

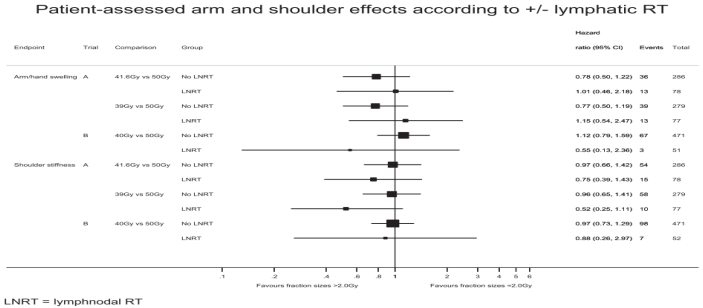
Hypofractionated PMRT was non-inferior to CF-RT with similar toxicities in high-risk breast cancer

	Conventional fractionated radiotherapy group (n=409)	Hypofractionated radiotherapy group (n=401)	p value
Acute toxicity			
Skin toxicity	..	..	<0·0001
Grade 1–2	357 (87%)	351 (89%)	..
Grade 3	32 (8%)	14 (3%)	..
Pneumonitis	..	..	0·278
Grade 1	62 (15%)	61 (15%)	..
Grade 2	7 (2%)	14 (3%)	..
Grade 3	..	..	..
Late toxicity			
Skin toxicity	..	..	0·669
Grade 1–2	90 (22%)	86 (21%)	..
Grade 3	0	1 (<1%)	..
Lymphoedema	..	..	0·961
Grade 1–2	81 (20%)	78 (19%)	..
Grade 3	3 (1%)	3 (1%)	..
Shoulder dysfunction	..	..	0·734
Grade 1–2	13 (3%)	7 (2%)	..
Grade 3	1 (<1%)	1 (<1%)	..
Lung fibrosis	..	..	0·081
Grade 1–2	42 (10%)	62 (15%)	..
Grade 3	0	0	..
Ischaemic heart disease	..	..	0·569
Grade 1–2	1 (<1%)	3 (1%)	..
Grade 3	3 (1%)	4 (1%)	..

Wang SL, et al. Lancet Oncol, 2019

RNI setting

Safety of hypofractionation



LNRT = lymphnodal RT

Fig. 1. Patient-assessed arm and shoulder effects according to ± lymphatic RT. RT, radiotherapy; LNRT, lymph nodal radiotherapy.

Table 3

Physician-assessed moderate/marked normal tissue effects in the arm or shoulder following lymphatic radiotherapy in START-pilot, START-A and START-B.

Schedule	Total moderate/ marked events (n/total, %)	Estimated cumulative incidence by 5 years, % (95%CI)	Estimated cumulative incidence by 10 years, % (95%CI)	Hazard ratio (95% CI)	P-value[1]	Prevalence of moderate/ marked events at 5 years, n/total (%)	P-value[2]	Prevalence of moderate/ marked events at 10 years, n/total (%)	P-value[2]
Arm oedema									
START-B									
50 Gy	7/73 (9.6)	6.0 (2.3-15.3)	13.5 (6.4-27.0)	1		0/51 (0)		0/27 (0)	
40 Gy	3/81 (3.7)	2.8 (0.7-10.7)	4.7 (1.5-14.0)	0.42 (0.11-1.63)	0.21	2/57 (3.5)	0.50	0/20 (0)	-
Shoulder stiffness									
START-B									
50 Gy	4/73 (5.5)	2.9 (0.7-11.0)	8.2 (2.9-21.8)	1		1/51 (2.0)	>0.99	1/27 (3.7)	>0.99
40 Gy	3/81 (3.7)	3.1 (0.8-11.9)	3.1 (0.8-11.9)	0.76 (0.17-3.39)	0.72	1/57 (1.8)	>0.99	1/20 (5.0)	>0.99

START A&B nodal patients only (n=864), Haviland 2018

ESTRO-ACROP 2022 consensus statements

European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer

Icro Meattini, Carlotta Becherini, Liesbeth Boersma, Orit Kaidar-Person, Gustavo Nader Marta, Angel Montero, Birgitte Vrou Offersen, Marianne C Aznar, Claus Belka, Adrian Murray Brunt, Samantha Dicuonzo, Pierfrancesco Franco, Mechthild Krause, Mairead MacKenzie, Tanja Marinko, Livia Marrazzo, Ivica Ratosa, Astrid Scholten, Elżbieta Senkus, Hilary Stobart, Philip Poortmans*, Charlotte E Coles*

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Whole breast irradiation

Moderate hypofractionated WBI should be offered regardless of:

- age at breast cancer diagnosis
- pathological tumour stage
- breast cancer biology
- surgical margins status
- tumour bed boost
- breast size
- invasive or pre-invasive DCIS disease
- oncoplastic breast conserving surgery
- use of systemic therapy

Ultra-hypofractionated WBI can be offered as:

- Standard of care
- Within a randomised controlled trial or prospective registration cohort

Nodal irradiation

- **Moderate** hypofractionation should be offered for **RNI**
- **Ultra-hypofractionation** should **not** be offered for RNI until ongoing trials results are reported

Meattini I, et al. Lancet Oncol 2022

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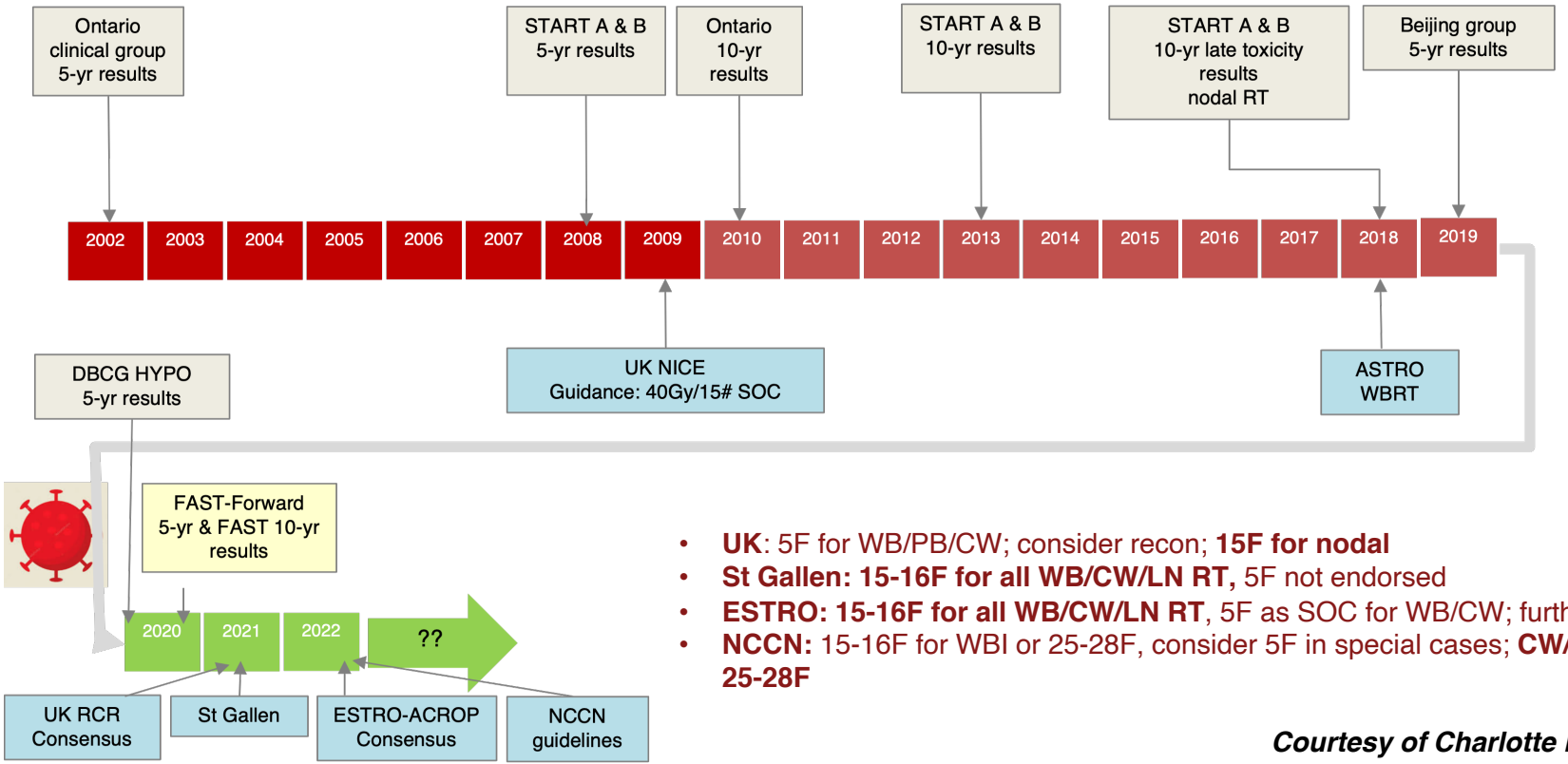
Moderate hypofractionation can be offered:
- for **chest wall irradiation without breast reconstruction**
- for **chest wall irradiation** regardless of **time and type** of **breast reconstruction**

Ultra-hypofractionation for **chest wall irradiation without breast reconstruction** can be offered as:
- Standard-of-care
- Within a randomised controlled trial or prospective registration cohort

Ultra-hypofractionation for **chest wall irradiation after breast reconstruction** can be offered within:
- A randomised controlled trial
- Prospective registration cohort

Meattini I, et al. Lancet Oncol 2022



- **UK**: 5F for WB/PB/CW; consider recon; **15F for nodal**
- **St Gallen: 15-16F for all WB/CW/LN RT,** 5F not endorsed
- **ESTRO: 15-16F for all WB/CW/LN RT**, 5F as SOC for WB/CW; further RCTs
- **NCCN:** 15-16F for WBI or 25-28F, consider 5F in special cases; **CW/LN RT - 25-28F**

Courtesy of Charlotte E. Coles

Hypofractionation

Partial Breast Irradiation

Omission of whole breast irradiation

Oligometastatic disease

Integration with systemic therapies

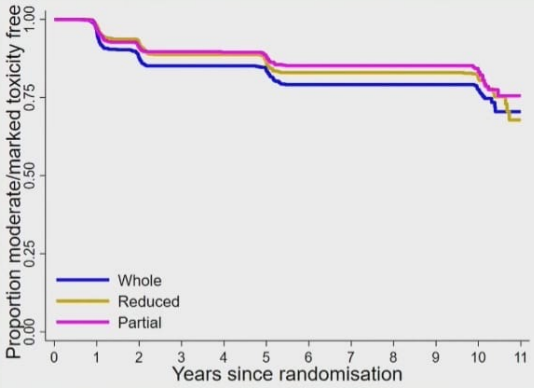
Primary endpoint: Ipsilateral breast tumour relapse

	Whole N=674	Reduced N=673	Partial N=669
Number of IBTR events	17	11	17
KM 10 year cumulative IBTR estimate (95% CI)	**2.8% (1.8, 4.5)**	**1.9% (1.1, 3.4)**	**2.8% (1.7, 4.5)**
Hazard ratio (95% CI)		0.63 (0.30, 1.35)	0.99 (0.51, 1.94
Absolute difference in IBTR rate compared with control group at 10 years (95% CI)		**-1.02% (-1.97, 0.97)**	**-0.02% (-1.38, 2.58**

ASTRO 65TH ANNUAL MEETING | October 1-4, 2023

Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial

Time to *any** moderate/marked clinician assessed breast NTE



10 year event-free estimates:
Whole: 70.5% (95%CI 64.1, 75.9)
Reduced: 75.3% (95%CI 69.6, 80.0)
Partial: 75.6% (95%CI 69.1, 80.9)

NB. Clinician assessments of NTEs were conducted at years 1, 2, 5 and then at 10 years

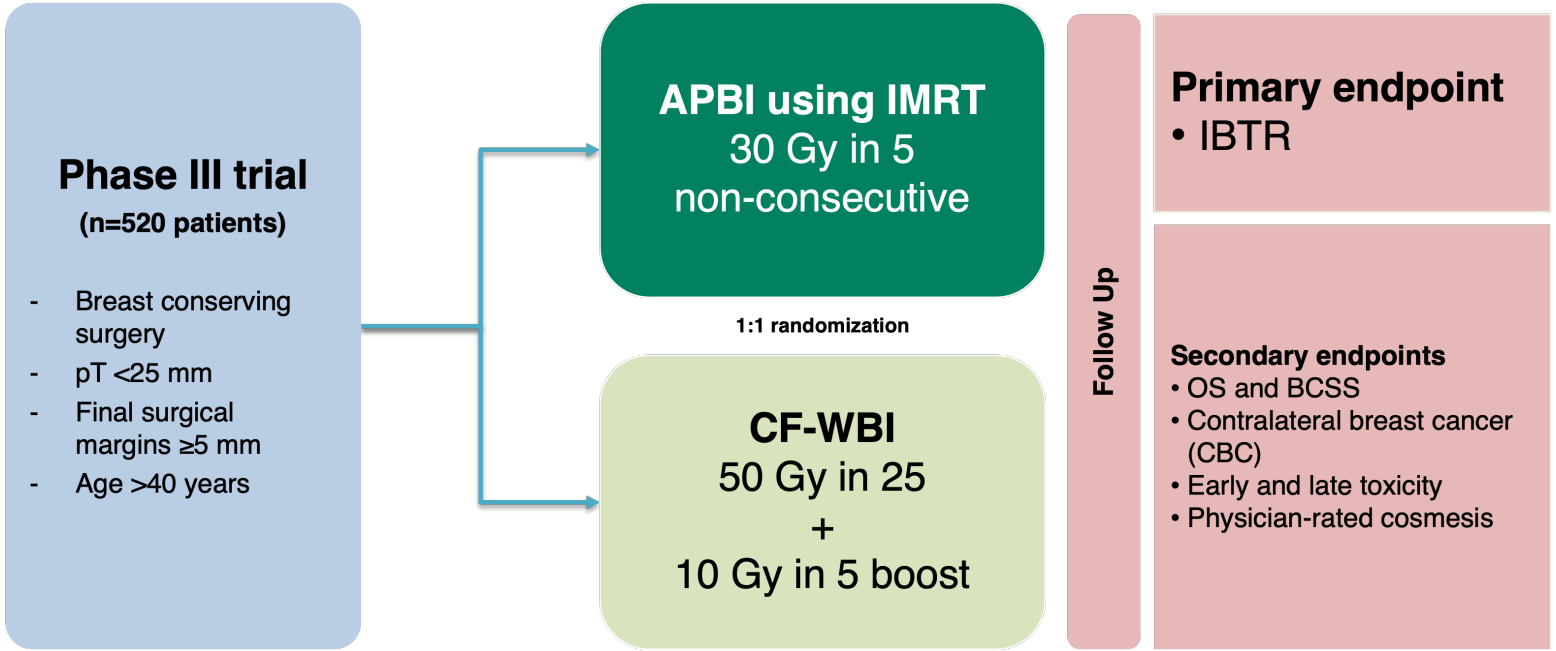
* *any*=breast shrinkage, breast induration (index), breast induration (outside index), telangiectasia, breast oedema, other RT related adverse event

ASTRO 65TH ANNUAL MEETING | October 1-4, 2023 #ASTRO23

Coles CE, et al. Lancet 2017; **Kirby A, et al.** ASTRO 2023

Partial breast irradiation

Trial design – APBI IMRT Florence (NCT 02104895)



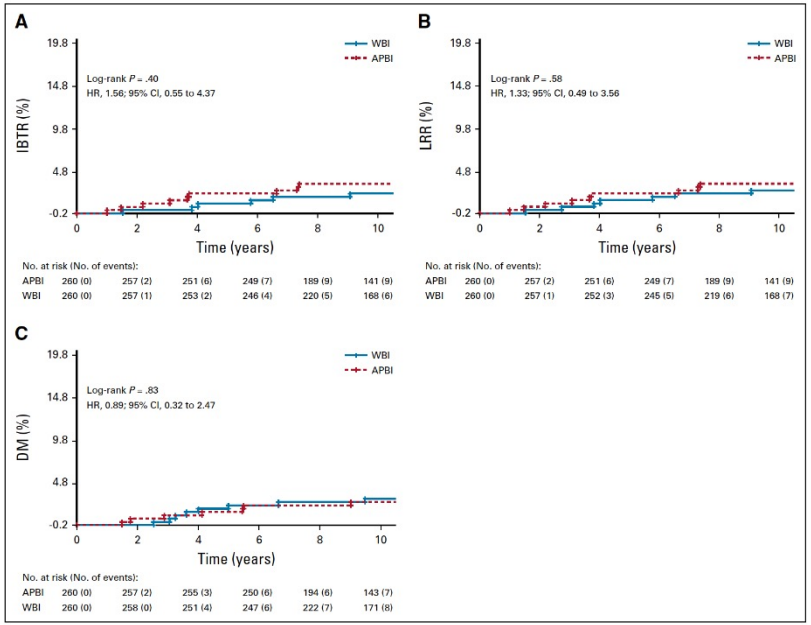
Partial breast irradiation

Long term follow-up – APBI IMRT Florence (NCT 02104895)

original reports

Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial

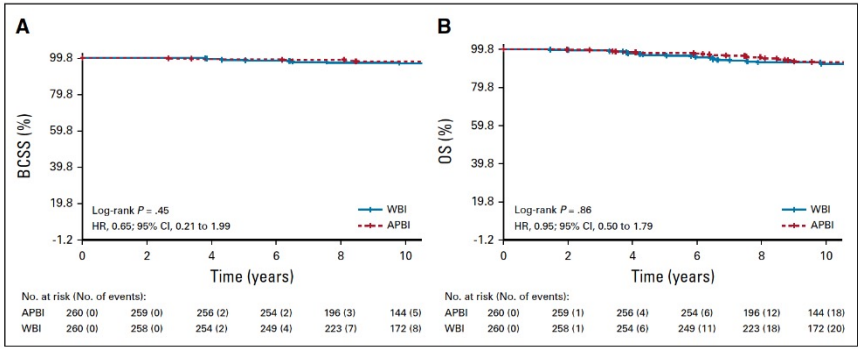
Icro Meattini, MD[1,2]; Livia Marrazzo, MS[3]; Calogero Saieva, MD[3]; Iacopo Desideri, MD[1,2]; Viori Scotti, MD[2]; Gabriele Simontacchi, MD[2]; Pierluigi Bonomo, MD[2]; Daniela Greto, MD[2]; Monica Mangoni, MD, PhD[1,2]; Silvia Scoccianti, MD[2]; Sara Lucidi, MD[1]; Lisa Paoletti, MD[4]; Massimiliano Fambrini, MD[1,2]; Marco Bernini, MD, PhD[2]; Luis Sanchez, MD[2]; Lorenzo Orzalesi, MD[1,2]; Jacopo Nori, MD[2]; Simonetta Bianchi, MD[1,2]; Stefania Paliotta, MS[1,2]; and Lorenzo Livi, MD[1,2]



Median **follow-up 10.7 years**

10-year **IBTR** **2.5% (WBI) *vs* 3.7% (APBI)** *(HR 1.56; P = 0.40)*

10-year **BCSS** **96.7% (WBI) *vs* 97.8% (APBI)** *(HR 0.65; P = 0.45)*



Meattini I, et al. JCO 2020

Partial breast irradiation

Long term follow-up – APBI IMRT Florence (NCT 02104895)

Assessment	APBI (n = 246)	WBI (n = 260)	P
Acute period adverse events[a]			
None	194 (78.9)	87 (33.5)	.0001
Yes, any grade	52 (21.1)	173 (66.5)	
Grade 1	47 (19.1)	75 (28.8)	.0001
Grade 2	5 (2.0)	81 (31.2)	
Grade 3	—	17 (6.5)	
Grade 4	—	—	
Grade 0-1	241 (98.0)	162 (62.3)	.0001
Grade ≥ 2	5 (2.0)	98 (37.7)	.0001
Late period adverse events[a]			
None	235 (95.5)	182 (70.0)	.0001
Yes, any grade	11 (4.5)	78 (30.0)	.0001
Grade 1	11 (4.5)	71 (27.3)	.0001
Grade 2	—	7 (2.7)	
Grade 3	—	—	
Grade 4	—	—	
Grade 0-1	246 (100)	253 (97.3)	.015
Grade ≥ 2	0	7 (2.7)	
Physician-rated cosmesis[b]			
Excellent	233 (94.7)	189 (72.7)	.0001
Good	13 (5.3)	66 (25.4)	
Fair	—	5 (1.9)	
Poor	—	—	
Patient-rated cosmesis[b]			
Excellent	44 (17.9)	13 (5.1)	.0001
Good	200 (81.3)	209 (80.3)	
Fair	2 (0.8)	38 (14.6)	
Poor	—	—	

original reports

Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial

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APBI significantly favoured:

- **acute and late adverse events**
- both **physician- and patient-rated cosmesis**

Meattini I, et al. JCO 2020

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Partial breast irradiation

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Low risk-features suitable for partial breast irradiation:

- luminal-like subtypes small tumour (≤3 cm)
- absence of lymph vascular space invasion
- non-lobular invasive carcinoma
- tumour grade 1-2
- low to intermediate grade DCIS (sized ≤2.5 cm with clear surgical margins ≥3 mm)
- age at diagnosis 50 years or more
- unicentric/unifocal lesion
- clear surgical margins (>2 mm)
- node negative (including isolated tumour cells)
- no use of primary systemic therapy/neoadjuvant chemotherapy

Meattini I, et al. Lancet Oncol 2022

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Partial breast irradiation–dose and fractionation:

- Moderate hypofractionation (**40Gy in 15 fractions**) and ultra hypofractionation (**26–30Gy in 5 fractions**) represent acceptable schedules for external beam partial breast irradiation

- **Twice a day** external beam partial breast irradiation dose and fractionations similar to those used in the RAPID trial (38.5 Gy in ten fractions delivered twice per day over 5-8 days) **should not be offered**

Meattini I, et al. Lancet Oncol 2022

Hypofractionation
Partial Breast Irradiation
Omission of whole breast irradiation
Oligometastatic disease
Integration with systemic therapies

Whole breast irradiation (WBI) omission
LUMINA trial

Prospective single-arm cohort study at 26 centres in Canada:
- Recruitment of **500 patients** from 2013-2017

Inclusion criteria
- Age ≥ 55 years
- Invasive breast carcinoma (NST, tubular, or mucinous)
- pT1a-c pN0 with a minimum of ASR 1 mm
- ER ≥ 1% PR ≥ 20% HER2 negative Ki67 ≤ 13.25%
- Planned ET for 5 years
- Omission of adjuvant RT

Statistical hypothesis
- LR rate in the operated breast after 5 years <5%

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	All Patients (N = 500)
Age	
Median (IQR) — yr	67.1 (62.9–71.6)
Distribution — no. (%)	
55 to <60 yr	61 (12)
60 to <65 yr	138 (28)
65 to <70 yr	136 (27)
70 to <75 yr	107 (21)
75 to <80 yr	42 (8)
≥80 yr	16 (3)
Tumor size	
Median (IQR) — cm	1.0 (0.7–1.4)
Distribution — no. (%)	
≤0.5 cm	39 (8)
0.5–1.0 cm	217 (43)
1.1–2.0 cm	244 (49)
Tumor grade — no. (%)	
1	330 (66)
2	170 (34)
Histologic cancer type — no. (%)	
Ductal	437 (87)
Tubular	25 (5)
Mucinous	26 (5)
Other	12 (2)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Omitting Radiotherapy after Breast-Conserving Surgery in Luminal A Breast Cancer

T.J. Whelan, S. Smith, S. Parpia, A.W. Fyles, A. Bane, F.-F. Liu, E. Rakovitch, L. Chang, C. Stevens, J. Bowen, S. Provencher, V. Théberge, A.M. Mulligan, Z. Kos, M.A. Akra, K.D. Voduc, T. Hijal, I.S. Dayes, G. Pond, J.R. Wright, T.O. Nielsen, and M.N. Levine, for the LUMINA Study Investigators*

Whelan TJ, et al. NEJM 2023

Whole breast irradiation (WBI) omission
LUMINA trial

- LR rate after 5 years was **2.3%** *(95%CI 1.2-4.1)*
- Only **marginally lower** than the rate of contralateral second carcinomas *(2.5% after 5 years)*
- DFS and OS at 5 years were 89.9% and 97.2%, respectively

Authors' conclusion: The prospective and controlled nature of this study supports our conclusion that such patients are candidates for omission of radiotherapy

Whelan TJ, et al. NEJM 2023

Whole breast irradiation (WBI) omission

Debunking

Key Details

- The **inclusion criteria for the study were quite broad**. The minimum age of 55 years was significantly lower than in most other studies of this kind; 40% <65 years old → particularly relevant due to **life expectancy** considerations

- The **Ki67 value** was determined centrally, and this was done for a good reason, as **inter-rater reliability can be problematic**. Indeed, **224 patients (30% of registered patients) were excluded in the screening after central testing** due to their high Ki67 levels

- The **Ki67 cut-off of 13.25% is arbitrary –** a large grey area between 5-30% was defined, where the use of gene expression analyses is recommended for luminal tumours

- **Compliance with ET** was significantly higher (**82.7%)** than expected outside of clinical studies

- The 5-year results of the LR rate **overlap with the CI** of comparable studies (i.e., PRIME II)

Whole breast irradiation (WBI) omission
The wrong answer at the right question!

65 years of age or older
HR+, N0, pT1 or pT2 (with tumors ≤3 cm in the largest dimension) treated with BCS with clear excision margins and adjuvant ET

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 16, 2023 VOL. 388 NO. 7

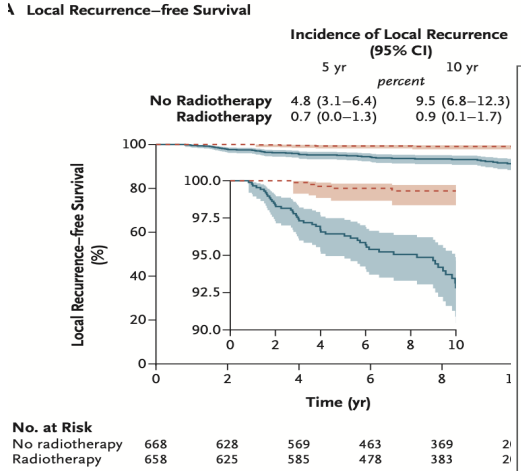
Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer

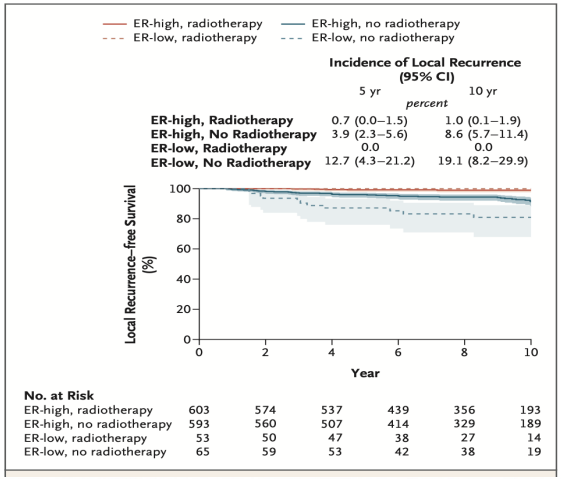
Ian H. Kunkler, M.B., B.Chir., Linda J. Williams, Ph.D., Wilma J.L. Jack, M.B., Ch.B., David A. Cameron, M.D., and J. Michael Dixon, M.D.

PRIME II study 10-year LR rates:

- **All** 9.5% (no RT) vs 0.9% (RT)
- **ER-low** 19.1% (no RT) vs 0.0% (RT)

No differences in DM and OS at 10-y





ER high was defined here as:
- ER ≥50% (!)
- Allred Score 7-8, or
- ER ≥20 fmol/mg (an obsolete method)

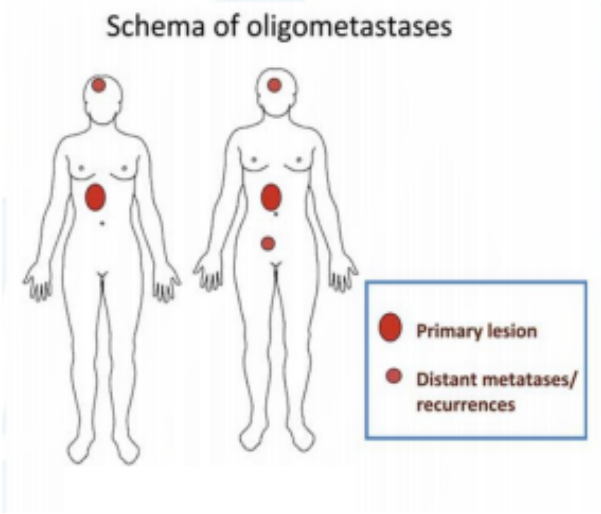
Kunkler IH, et al. NEJM 2023

Hypofractionation
Partial Breast Irradiation
Omission of whole breast irradiation
Oligometastatic disease
Integration with systemic therapies

Oligometastases

Definitions and Concepts

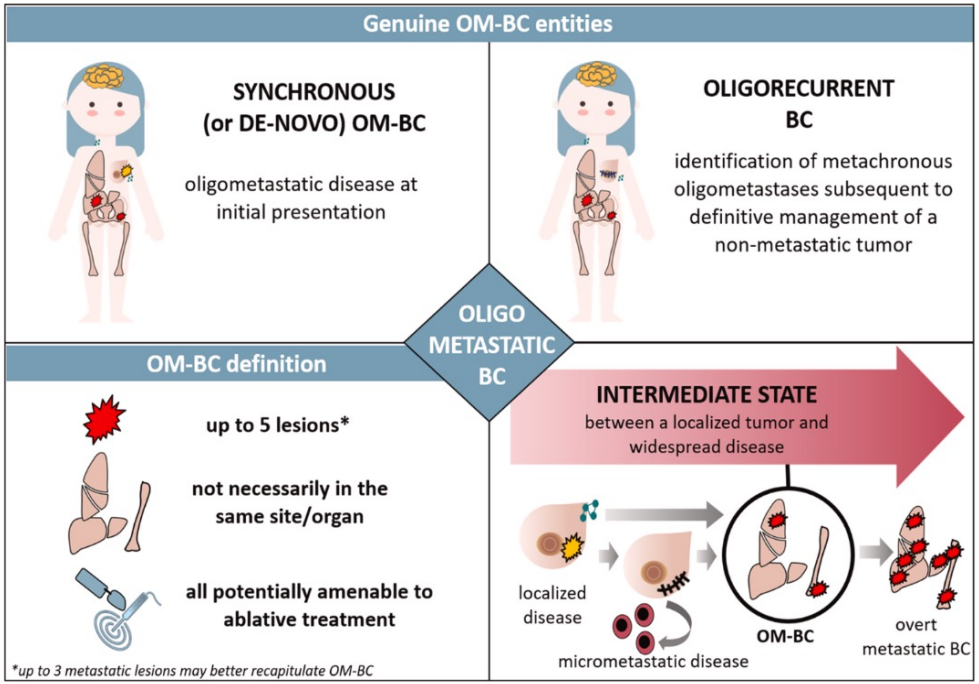
- Introduced for the first time in 1995
- Commonly used to describe an **intermediate state of cancer spread between localized disease and widespread metastases**
- Patients show only a limited number or regions involved
- (No more than five total lesions)

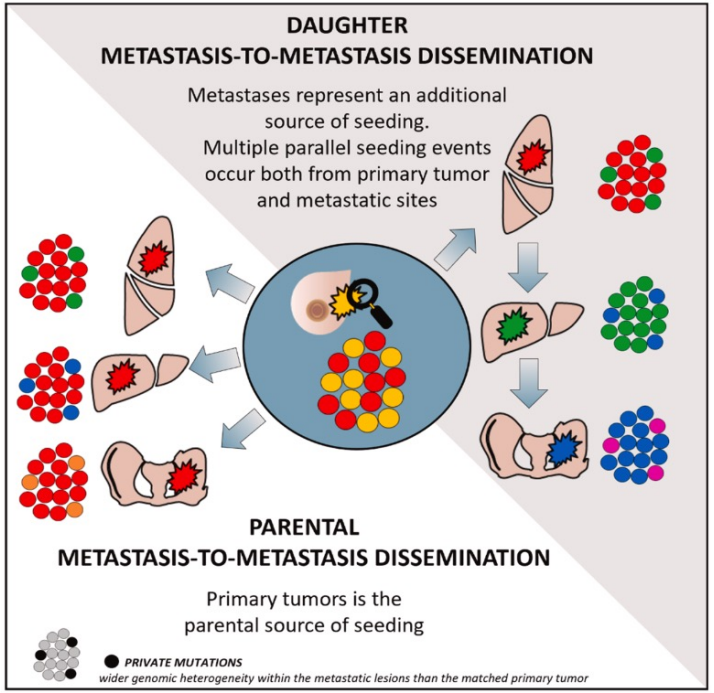


Hellman S, et al. J Clin Oncol 1995
Weichselbaum RR, et al. Nat Rev Clin Oncol 2011

Oligometastases

Definitions and Concepts



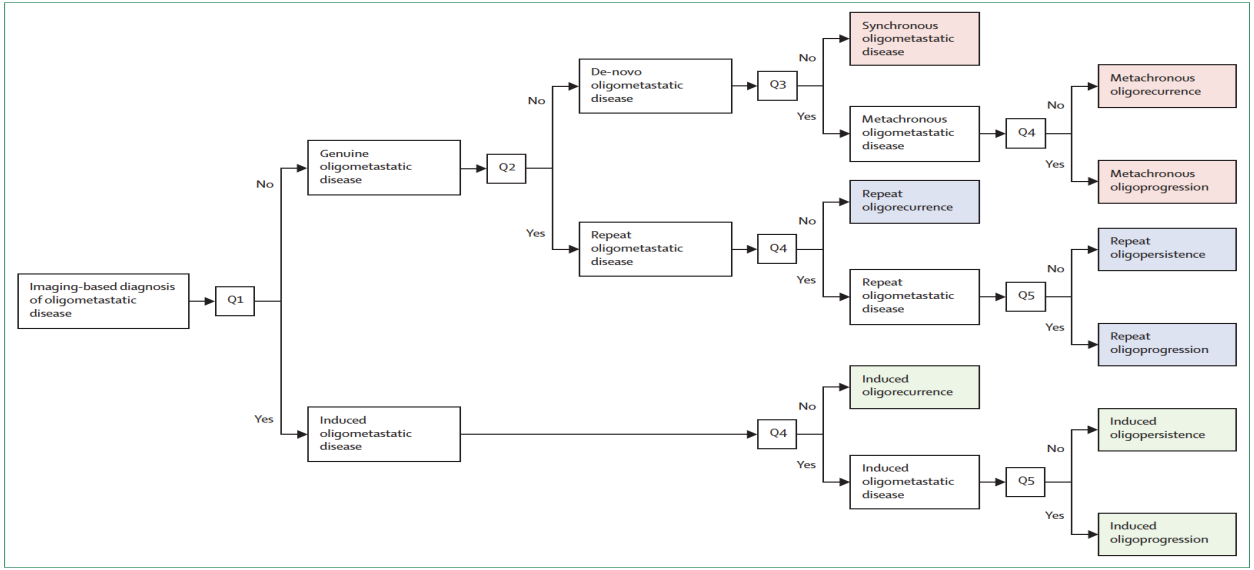


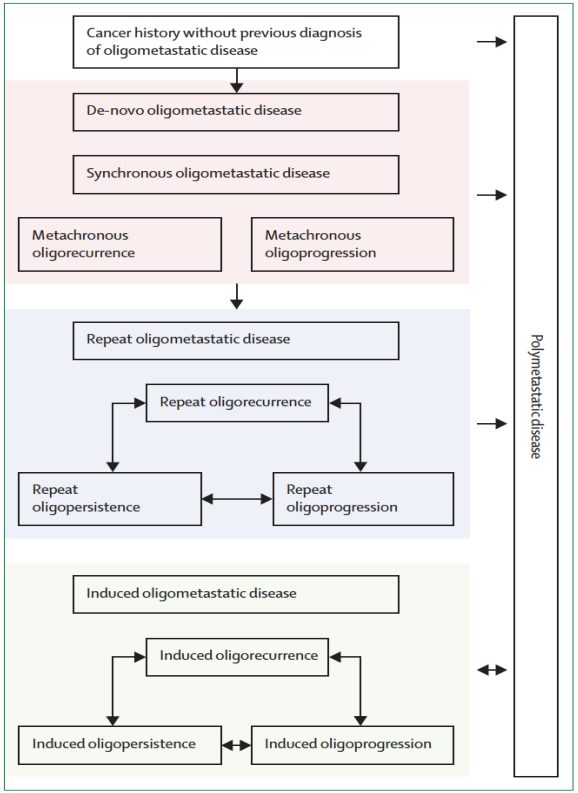
Miglietta F, et al. Cancer Treat Rev 2023

Oligometastases
Characterization and Classification

Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation

Matthias Guckenberger, Yolande Lievens, Angelique B Bouma, Laurence Collette, Andre Dekker, Nandita M deSouza, Anne-Marie C Dingemans, Beatrice Fournier, Coen Hurkmans, Frédéric E Lecouvet, Icro Meattini, Alejandra Méndez Romero, Umberto Ricardi, Nicola S Russell, Daniel H Schanne, Marta Scorsetti, Bertrand Tombal, Dirk Verellen, Christine Verfaillie, Piet Ost





Guckenberger M, et al. Lancet Oncol 2020

Oligometastases

Use and evaluation of imaging methods in clinical trials

Review of the literature covering all aspects of oligometastatic breast cancer

35 experts from the **EORTC Imaging and Breast Cancer Groups**

Consensus recommendations:

- Oligometastatic breast cancer definition
- Optimal diagnostic pathways
- Clinical trials required to evaluate the effect of diagnostic imaging strategies and metastasis-directed therapies
- Strategies for the randomisation of imaging methods and therapeutic approaches in different subsets of patients

Pasquier D, et al. Lancet Oncol 2023

Designing clinical trials based on modern imaging and metastasis-directed treatments in patients with oligometastatic breast cancer: a consensus recommendation from the EORTC Imaging and Breast Cancer Groups

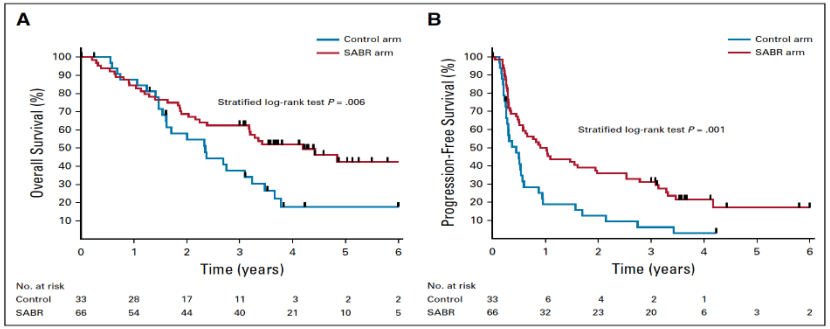
David Pasquier, Luc Bidaut, Daniela Elena Oprea-Lager, Nandita M deSouza, David Krug, Laurence Collette, Wolfgang Kunz, Yazid Belkacemi, Maria Grazia Bau, Caroline Caramella, Lioe-Fee De Geus-Oei, Alex De Caluwé, Christophe Deroose, Olivier Gheysens, Ken Herrmann, Isabelle Kindts, Michalis Kontos, Sherko Kümmel, Barbro Linderholm, Egesta Lopci, Icro Meattini, Ann Smeets, Orit Kaidar-Person, Philip Poortmans, Pelagia Tsoutsou, Nawale Hajjaji, Nicola Russell, Elżbieta Senkus, Jean-Noël Talbot, Lale Umutlu, Vincent Vandecaveye, Joost J C Verhoeff, Willemien Menke-van der Houven van Oordt, Helle D Zacho, Fatima Cardoso, Laure Fournier, Frederieke Van Duijnhoven, Frédéric E Lecouvet

Imaging methods in clinical trials	Consensus and round
Use of imaging in trials	
[^{18}F]FDG-PET-CT (or [^{18}F]FDG-PET-MRI) staging should be mandatory in trials enrolling oligometastatic disease breast cancer patients to ensure the true oligometastatic disease status	Consensus agreement=79% in round 1; absolute number=27; total number of responses=35; non-qualified=1
Whole-body MRI and diffusion-weighted imaging staging should be mandatory in trials enrolling patients with oligometastatic disease breast cancer to ensure the true oligometastatic disease status	Neither consensus nor (dis)agreement
Necessary evaluation of imaging in trials	
Prospective trials are needed to compare SIMs and MIMs for staging and response assessment in advanced breast cancer, including oligometastatic disease	Consensus agreement=86% in round 1; absolute number=30; total number of responses=35
Clinical trials aiming to compare SIMs and MIMs for staging and response assessment in advanced breast cancer should be designed in specific histological and breast cancer subtypes (eg, lobular cancer and triple negative)	Consensus agreement=87% in round 2 (74% in round 1); absolute number=28; total number of responses=33; non-qualified=1
The diagnostic performance of different MIMs (eg, PET-CT or PET-MRI, whole-body MRI, liver MRI, and [^{18}F]NaF plus [^{18}F]FDG-PET cocktail) deserves further comparisons in trials	Consensus agreement=89% in round 1; absolute number=31; total number of responses=35
The diagnostic performance of MIMs (eg, PET-CT or PET-MRI, whole-body-MRI, liver MRI, or brain MRI) should be compared in the different subtypes of breast cancer (eg, ductal, lobular, HR, and HER)	Consensus agreement=94% in round 1; absolute number=33; total number of responses=35
Diagnostic trials should further validate quantification with MIMs (ie, second order statistics) for tumour characterisation and prognostic purposes (in whole-body diffusion-weighted MRI and PET-CT [or PET-MRI])	Consensus agreement=91% in round 2 (74% in round 1); absolute number=29; total number of responses=33; non-qualified=1
Diagnostic trials should compare technical and diagnostic performance and robustness of MRI and diffusion-weighted imaging sequences from hybrid PET-MRI modalities and from stand-alone MRI, with the purpose of optimising and standardising technical and diagnostic performance across various instruments	Consensus agreement=90% in round 1; absolute number=28; total number of responses=35; non-qualified=4
HER2 PET-CT imaging is still experimental and is not recommended outside of clinical trials	Consensus agreement=78% in round 1; absolute number=25; total number of responses=35; non-qualified=3

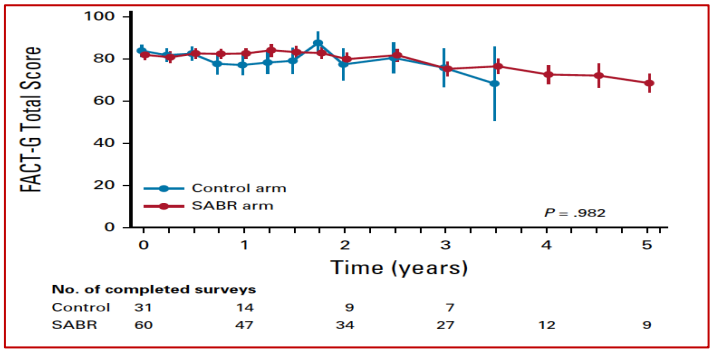
Oligometastases – Recent prospective studies

SABR-COMET 51-month follow-up Update

palliative standard of care treatments alone
(control group)
vs
standard of care plus SBRT to all metastatic lesions
(SBRT group)



Functional Assessment of Cancer Therapy: General



18 breast cancer patients enrolled *(13 in SBRT group)*

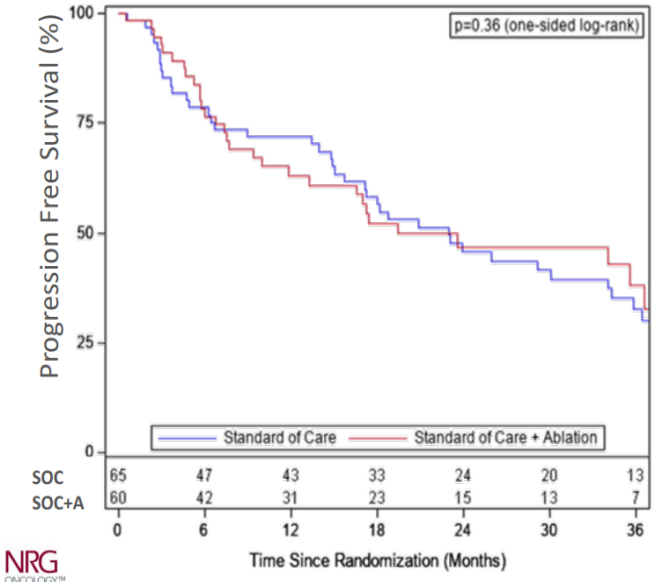
5-year OS rate 17.7% *(control)* *vs* 42.3% *(SABR)*

5-year PFS rate not reached 3.2% *(control)* *vs* 17.3% *(SABR)*

No new grade 2-5 adverse events and no differences in HRQoL between arms

Palma DA, et al. JCO 2020

NRG-BR002 trial - PFS



	PFS	
	24 mo	36 mo
SOC	46% (38.9%, 52.5%)	32.8% (26.0, 39.5)
SOC + Ablation	47% (39.2%,54.3%)	38.1% (29.7, 46.6)

- **HR: 0.92 (0.71, 1.17)**
- Median FU = 35 months (min-max: 0.03-62.74).
- **Median PFS**:
  SOC: 23.0 mo (18.0-29.2)
  SOC + ablation: 19.5 mo (17.0-35.6)

Meeting Abstract | 2022 ASCO Annual Meeting I
BREAST CANCER—METASTATIC

NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) for newly oligometastatic breast cancer (NCT02364557).

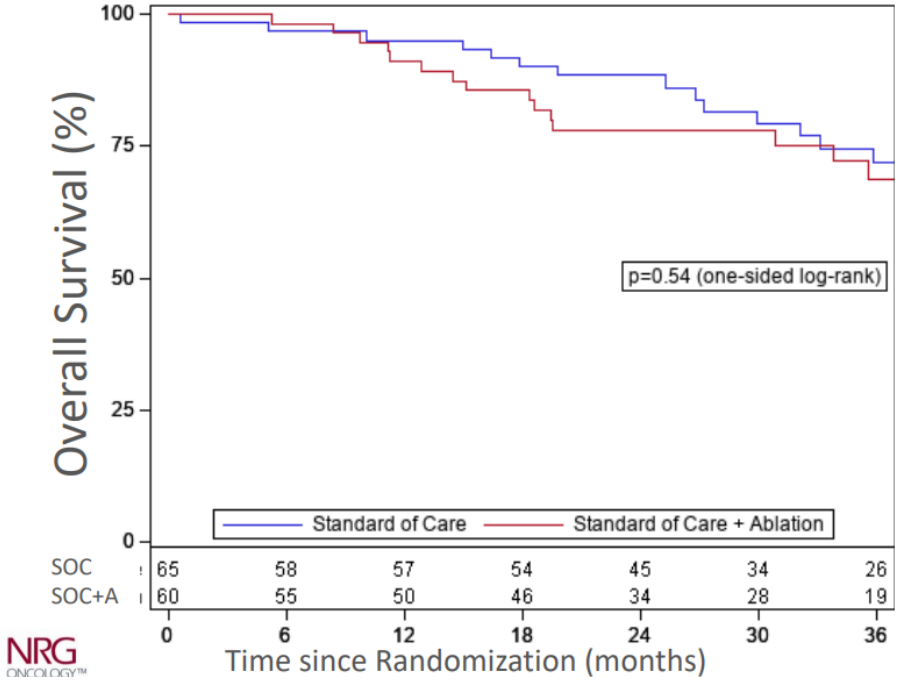
Steven J. Chmura, Kathryn A. Winter, Wendy A. Woodward, Virginia F. Borges, Joseph Kamel Salama, Hania A Al-Hallaq, ...

Methods: OMBC patients with ≤4 extracranial metastases with controlled primary disease eligible if on first line SOC ST for ≤12 months without progression

Median age 54 years
79% ER+ or PR+/HER2-, 13% HER2+, 8% triple negative
60% with 1 metastasis and 20% presented synchronously with primary disease
Median **follow-up 30 months**

Chmura SJ, et al. ASCO 2022

NRG-BR002 trial - OS



Conclusions

The addition of MDT to SOC ST did not show signal for improved PFS nor OS difference in patients with OMBC, so **the trial will not proceed to the Phase III component**

36 mo OS (95% CI)	
SOC	SOC+Ablation
71.8% (58.9, 84.7)	68.9% (55.1, 82.6)

- **HR: 1.23 (0.63, 2.39)**
  SOC + ablation arm v SOC arm;
- **Median OS = Not Reached**

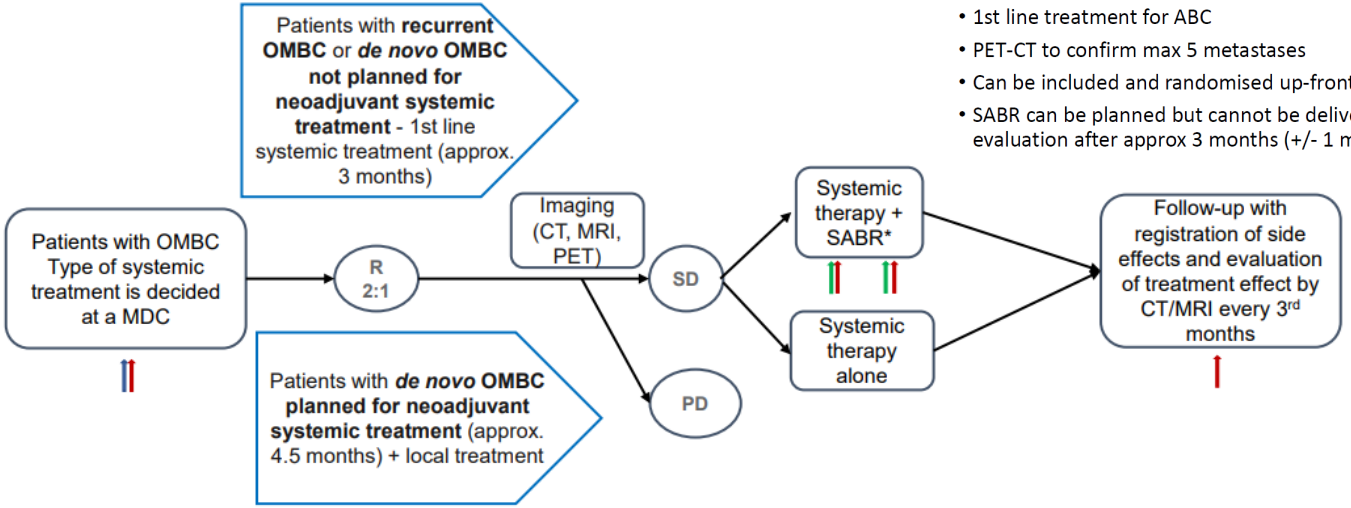
Ongoing trials - TAORMINA

*Tr**ea**tment of **O**ligometastatic breast cance**r** – a rando**mi**sed phase 3 trial comparing systemic treatment with or without stereotactic ablative radiotherapy*

TAORMINA

Recurrent OMBC

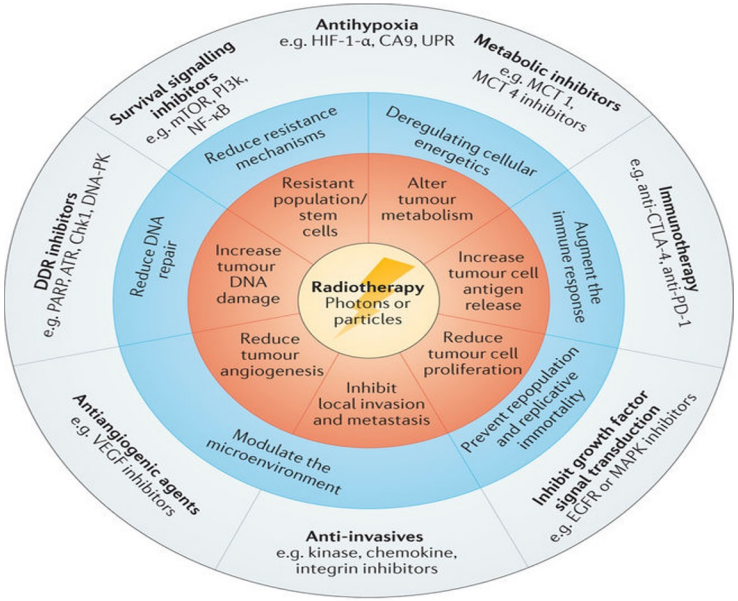
- 1st line treatment for ABC
- PET-CT to confirm max 5 metastases
- Can be included and randomised up-front
- SABR can be planned but cannot be delivered before the first evaluation after approx 3 months (+/- 1 months)



Hypofractionation
Partial Breast Irradiation
Omission of whole breast irradiation
Oligometastatic disease
Integration with systemic therapies

Integration of radiation therapy with targeted treatments for breast cancer

Treatment effectiveness
Treatment safety



Sharma RA, et al. Reviews Clinical Oncology 2016

Radiation and New Drugs

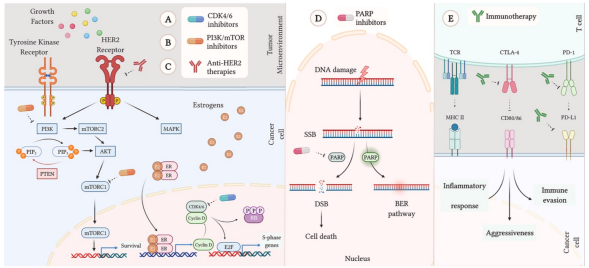
When is it concomitant?

RT is commonly considered given **concurrent** with systemic therapy when **administered in a range < than 5 half-lives of the drug**

Drug	Median Half-life	5 half-lives
Olaparib	15 hours	75 hours (≈ 3 days)
Lapatinib	24 hours	120 hours (≈ 5 days)
Abemaciclib	24.8 hours	124 hours (≈ 5 days)
Palbociclib	28.8 hours	144 hours (≈ 6 days)
Everolimus	30 hours	150 hours (≈ 6 days)
Ribociclib	29.7 – 54.7 hours	148.5 – 273.5 hours (≈ 6 - 11 days)
Talazoparib	90 hours	450 hours (≈ 19 days)
Trastuzumab-emtansine	96 hours	480 hours (≈ 20 days)
Trastuzumab-deruxtecan	168 hours	840 hours (≈ 35 days)
Trastuzumab	456 hours	2280 hours (≈ 95 days)
Bevacizumab	480 hours	2400 hours (≈ 100 days)
Nivolumab	578 hours	2890 hours (≈ 121 days)
Atezolizumab	648 hours	3240 hours (≈ 135 days)

Tallet AV, et al. Ann Oncol 2017

Preclinical and clinical findings



Family drug	Drug	Preclinical Effectiveness	Clinical Toxic effect	LoE°	Recommendation concomitant treatment	Drug 5-half-lives, days*
CDK4/6i	Palbociclib	**Increased**	**Increased**	4	Cautionary	5.8
	Ribociclib	**Increased**	**Increased**		Cautionary	6.7
	Abemaciclib	**Increased**	**Increased**		Cautionary	5
PI3Ki	Alpelisib	**Increased**	**Uncertain**	4	Unsuitable	1.9
mTORi	Everolimus	**Increased**	**Increased**		Unsuitable	6.2
Anti-HER	Trastuzumab	**Increased**	**Safe**	3	Suitable	175
	Pertuzumab	**Increased**	**Safe**		Suitable	90
	Lapatinib	**Increased**	**Safe**		Suitable	5
	T-DM1	**Uncertain**	**Uncertain/Safe**		Cautionary	20
PARPi	Olaparib	**Increased**	**Increased**	4	Unsuitable	3.1
	Talazoparib	**Increased**	**Increased**		Unsuitable	18.7
Immunotherapy	Atezolizumab	**Uncertain**	**Safe**	4	Suitable	135
	Pembrolizumab	**Uncertain**	**Safe**		Suitable	110

Abbreviations. CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitors; PI3Ki, phosphatidyl-inositol-3-kinase inhibitors; mTORi, mammalian target of rapamycin inhibitors; HER, human epidermal growth factor receptor; PARPi, poly(ADP-ribose) polymerases inhibitors; LoE, level of evidence.

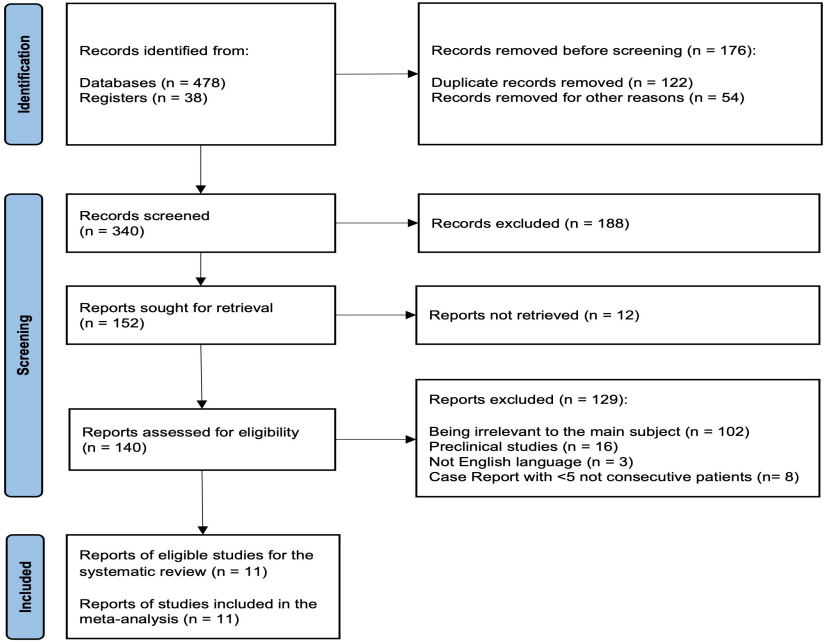
° Level of Evidence followed the OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf.

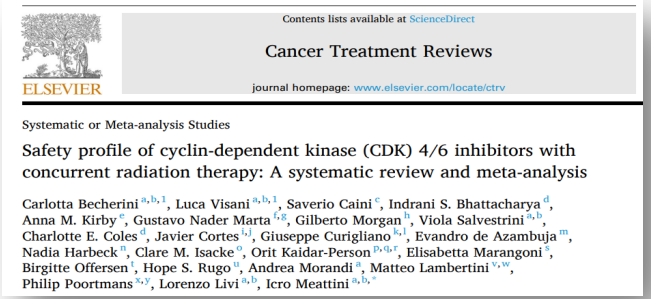
* Radiation therapy is defined concomitant if a drug is administered within its 5-half-lives.

Meattini I, et al. Cancer Treat Rev 2022

CDK4/6 inhibitors and RT

Systematic Review and Meta-analyses





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Systematic or Meta-analysis Studies

Safety profile of cyclin-dependent kinase (CDK) 4/6 inhibitors with concurrent radiation therapy: A systematic review and meta-analysis

Carlotta Becherini [a,b,1], Luca Visani [a,b,1], Saverio Caini [c], Indrani S. Bhattacharya [d], Anna M. Kirby [e], Gustavo Nader Marta [f,g], Gilberto Morgan [h], Viola Salvestrini [a,b], Charlotte E. Coles [d], Javier Cortes [i,j], Giuseppe Curigliano [k,l], Evandro de Azambuja [m], Nadia Harbeck [n], Clare M. Isacke [o], Orit Kaidar-Person [p,q,r], Elisabetta Marangoni [s], Birgitte Offersen [t], Hope S. Rugo [u], Andrea Morandi [a], Matteo Lambertini [v,w], Philip Poortmans [x,y], Lorenzo Livi [a,b], Icro Meattini [a,b,*]

Becherini C, et al. Cancer Treat Rev 2023

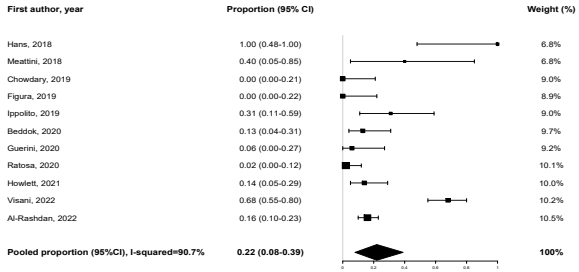
CDK4/6 inhibitors and RT

Systematic Review and Meta-analyses

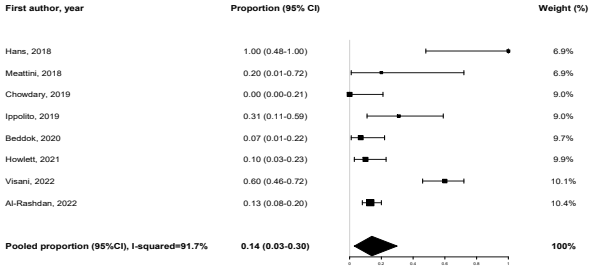
The most frequently reported toxicity was **hematologic**, with **neutropenia** being the predominant adverse event, accounting for 58.8% of grade 3+ hematologic toxicity events. However, the **overall pooled incidence of grade 3+ hematologic toxicity was moderate**, with a rate of 14%

Importantly, this level of **hematologic toxicity did not significantly impact** the continuation of CDK4/6 inhibitor treatment

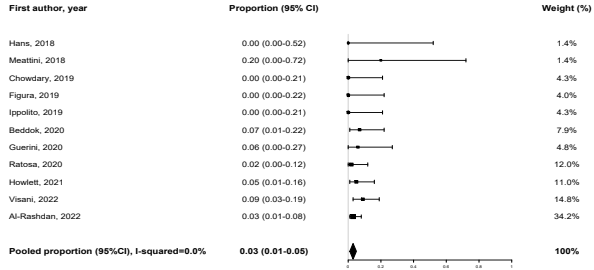
Any toxicity G3+



Haematological toxicity G3+



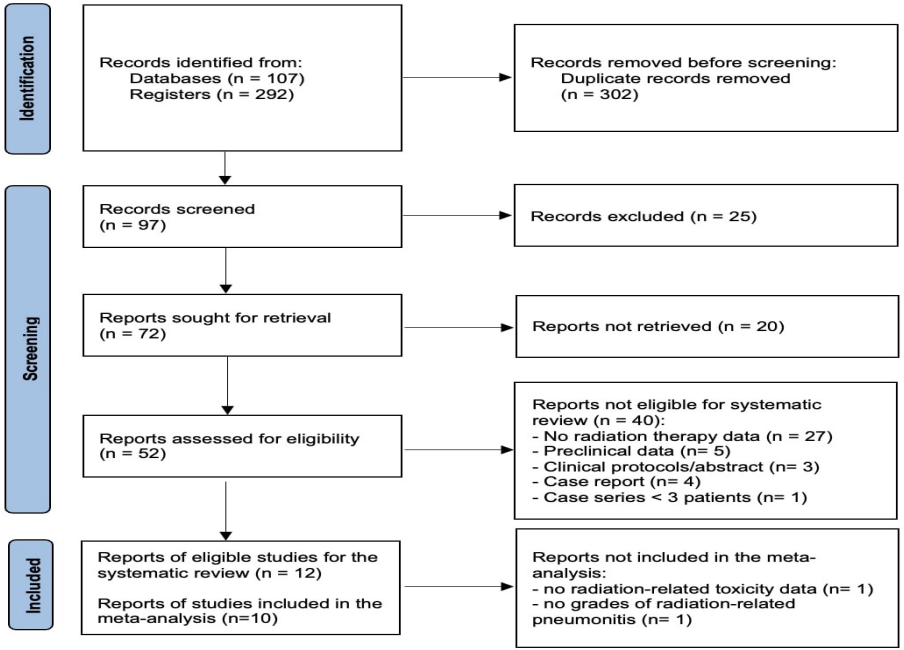
Non-haematological toxicity G3+

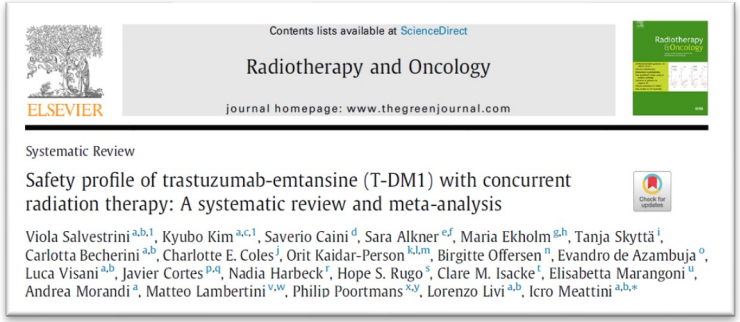


Becherini C, et al. Cancer Treat Rev 2023

T-DM1 and RT

Systematic Review and Meta-analyses





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journal homepage: www.thegreenjournal.com

Systematic Review

Safety profile of trastuzumab-emtansine (T-DM1) with concurrent radiation therapy: A systematic review and meta-analysis

Viola Salvestrini[a,b,1], Kyubo Kim[a,c,1], Saverio Caini[d], Sara Alkner[e,f], Maria Ekholm[g,h], Tanja Skyttä[i], Carlotta Becherini[a,b], Charlotte E. Coles[j], Orit Kaidar-Person[k,l,m], Birgitte Offersen[n], Evandro de Azambuja[o], Luca Visani[a,b], Javier Cortes[p,q], Nadia Harbeck[r], Hope S. Rugo[s], Clare M. Isacke[t], Elisabetta Marangoni[u], Andrea Morandi[a], Matteo Lambertini[v,w], Philip Poortmans[x,y], Lorenzo Livi[a,b], Icro Meattini[a,b,*]

Salvestrini V, et al. Radioter Oncol 2023

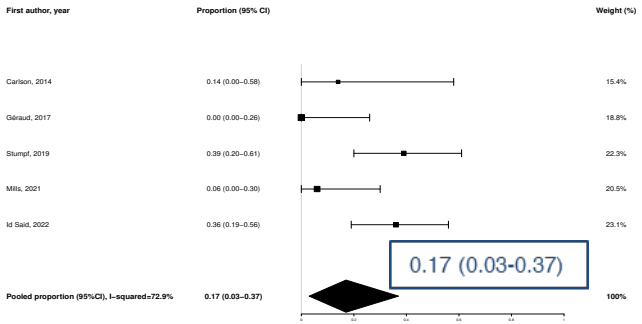
T-DM1 and RT

Systematic Review and Meta-analyses

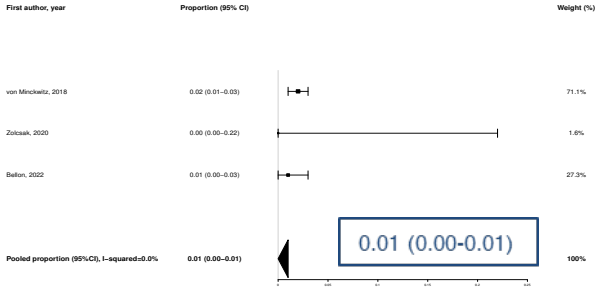
T-DM1 has been shown to **cross the blood-brain barrier** and exhibit clinical efficacy against **brain metastases**. However, combining T-DM1 with SRT significantly **increases the risk of later symptomatic radio-necrosis** compared to SRT alone

There is **insufficient data** to evaluate the safety of WBRT or extracranial palliative RT/SRT when combined with T-DM1

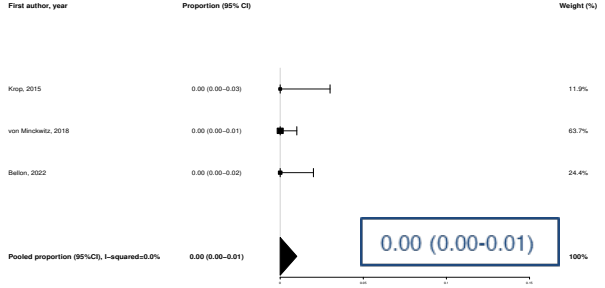
Intracranial Radionecrosis G3+



Skin reaction G3+



Pneumonitis G3+



Salvestrini V, et al. Radioter Oncol 2023

Recommendations on integration of radiation therapy with targeted treatments for breast cancer consensus
Florence, Italy – June 16-17
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THE LANCET Oncology

Meattini I, et al. Lancet Oncol 2023 (accepted)

THANKS FOR YOUR ATTENTION !

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