Early Results of the French Multicenter, Randomized SHARE Trial Comparing Whole Breast Irradiation vs. Accelerated Partial Breast Irradiation in Postmenopausal Women with Early-Stage Breast Cancer

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On behalf of the SHARE trialists

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DISCLOSURES

SHARE Trial

NCT01247233

No conflict of interest to declare in relation with this presentation

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BACKGROUND TRIALS OVERVIEW

Trials (ref)	N	Patients' eligibility criteria	Radiation schedules	Median FU	IBTR	Toxicity and cosmesis
FLORENCE	520	Age > 40y pT1-2 (<2.5cm), negative margins , pN0 DCIS: not allowed	APBI: 30Gy/5f (once daily) versus WBI: 50Gy/25f +/- boost	**10.7y**	2.5% 3.7%	**Reduced acute and late toxicities in APBI.** Better cosmetic results after APBI.
NSABP B39	4216	Age > 18y pT1-2 (<3cm), negative margins pN0-1 DCIS: allowed	APBI: 38.5Gy/10f (twice per day) or 34Gy/10fr BID (brachytherapy) versus WBI: 50Gy/25f +/- boost	**10.2y**	3.4% 4.6%	**No difference** in terms of toxicity. Grade 3: 10% in APBI and 7% in WBI
RAPID	2135	Age > 40y pT1-2 (≤2cm), negative margins , pN0-1 DCIS: allowed	APBI: 38.5Gy/10f (twice per day) versus WBI: 50Gy/25f +/- boost	**8.6y**	3% 2.8%	Less acute but **increase of moderate late** (grade ≥ 2) toxicities and adverse cosmesis with APBI.
IMPORT LOW	2018	Age > 50y pT1-2 (<3cm), margins ≥ 2mm pN0-1 DCIS: not allowed	APBI: 40Gy/15f (APBI group) Versus WBI (control group): 40Gy/15f Versus WBI (reduced group): 36Gy/WBI and 40Gy/APBI	**6y**	1.1% 0.2% 0.5%	**Equivalent or fewer late** normal-tissue adverse **effects** were seen in APBI patients.
IRMA	3309	Age > 49y pT1-2 (<3cm), margins ≥ 2mm, pN0-1 DCIS: not allowed	APBI: 38.5Gy/10f (twice per day) versus WBI: 40-45Gy/15-18f or 50Gy/25f +/-boost	**5.6**	-	**Increased 5y-rates of late moderate soft tissue toxicities**, with a slight decrease in patient-reported cosmetic outcomes

SHARE TRIAL DESIGN

Post-menopausal ≥50 years,
Unifocal, invasive carcinoma, pT1, margins > 2mm, all grades,
pN0 or pN0(i+), M0
Conservative surgery + **4-5 clips placement in the tumor bed**

Verification of inclusion and exclusion criteria
Signature of informed consent and randomization

Arm A

WBI: Whole Breast Irradiation Conventional Arm

50Gy in 25 fractions
(1 fraction per day)
+/- Boost: 16Gy in 8 fractions
during 6-7 weeks

Arm B

WBI: Whole Breast Irradiation Hypofractionated Arm

40Gy in 15 fractions
(1 fraction per day)
or 42.5Gy in 16 fractions
during 3 weeks

Arm C

APBI Arm: Accelerated Partial Breast Irradiation

34 to 40Gy in 10 fractions (2 fractions per day)

during 1week

Control arm

APBI arm (EBRT)

SHARE STUDY DESIGN

Non-inferiority, randomized phase III trial

Invasive carcinoma,
pN0 - pN0(i+), M0
Conservative surgery
with clips placement

R

APBI ARM
34-40 Gy in 10 fractions /
Over one week

Control ARMS
Whole Breast Irradiation
- **Conventional**

or
- **Moderate fractionation**

Initially randomized,
then investigator's choice

Stratification:
- Age: < 70y, ≥ 70
- Her2+, Her2-
- HR+, HR-
- Nodes: pN-, pN(i+)

Primary endpoint

Ipsilateral breast invasive recurrence

Secondary endpoints

- Acute and late toxicities (NCI-CTCAE v4 grade ≥ 2)
- Cosmetic results (physicians and patients)
- iDFS, OS
- Quality of life

34 centers

NCT01247233

SHARE STATISTICAL CONSIDERATIONS

Design to demonstrate that **APBI is not inferior to control arm in terms of ipsilateral breast invasive recurrence**

Sample size

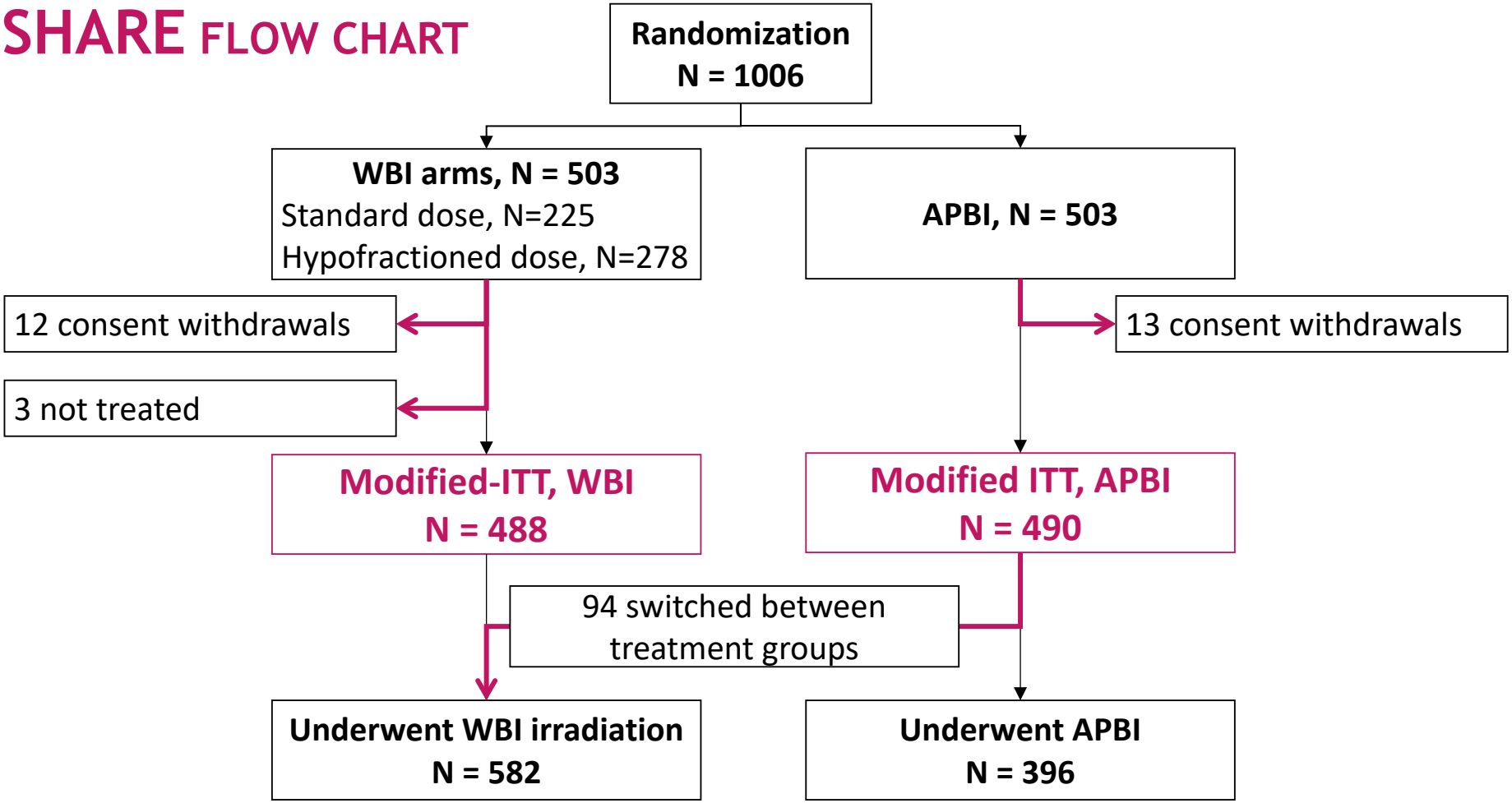
- Non-inferiority margin: Hazard Ratio for IBTR, HR=1.50
- One-sided Alpha = 5%, Power = 90% → **208 relapses, 3300 patients planned**

Trial prematurely stopped after recruitment of **1006 pts** due to low accrual rate

Current analysis focused on acute and late toxicities and cosmetic results

- Cumulative incidence are estimated using Kalbfleish and Prentice method, considering relapse, secondary cancer and death as competing events
- The effect of treatment is estimated by cause-specific Hazard Ratios (cs-HR) using Cox models adjusted for stratification factors
- **Modified ITT analysis** (excluding consent withdrawals and no start of irradiation)
- **Secondary analysis as-treated population**

SHARE FLOW CHART



SHARE PATIENTS DISTRIBUTION

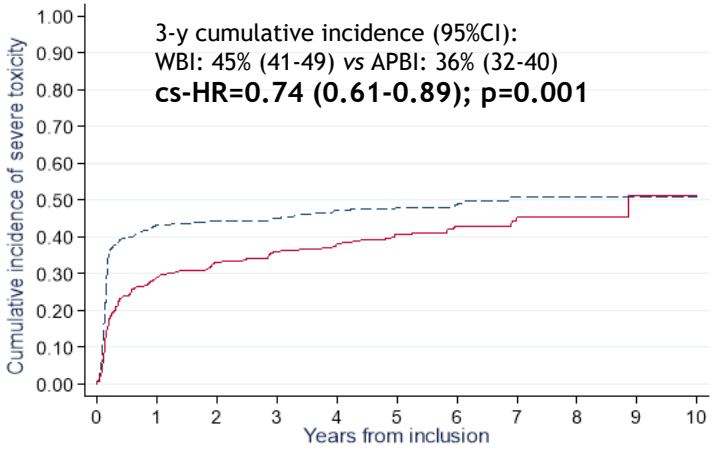
Characteristics	WBI N = 488		APBI N = 490		Total N= 978	
Age (y) median (Range)	65	(49-86)	65	(50-89)	65	(49-89)
Classification pT						
pT1	483	99%	480	98%	963	99%
pT2	2	<1%	8	2%	10	1%
pT3	0	0%	1	<1%	1	<1%
Micro-invasive + in Situ	2	<1%	1	<1%	3	<1%
Classification pN						
pN0	479	98%	485	99%	964	99%
pN0(i+)/ pN1	9	2%	5	1%	14	1%
Grade						
G1	230	47%	215	44%	445	46%
G2	241	50%	260	53%	501	51%
G3	12	2%	11	2%	23	2%
Type of surgery						
Lumpectomy	420	86%	417	85%	837	86%
Quadrantectomy	68	14%	72	15%	140	14%
Clip placement						
≤ 3	9	2%	12	3%	21	2%
4	282	58%	247	50%	529	54%
≥ 5	193	40%	229	47%	422	44%
Surgical margins						
Clear margins (>2mm)	485	99%	485	99%	970	99%
Close or positive margins	3	1%	5	1%	8	1%

SHARE ENDPOINTS

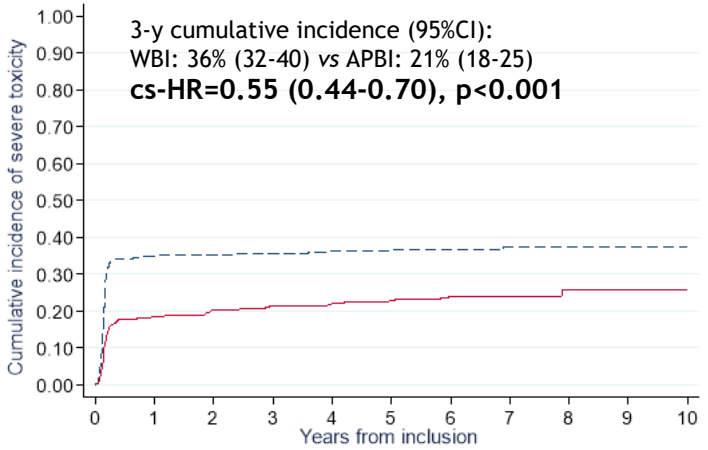
Median follow-up	5.8 years
Primary	
Number of LR	11
Secondary	
Number of deaths	27
3y-iDFS	96.2%
3y-OS	98.9%

TOXICITY RESULTS

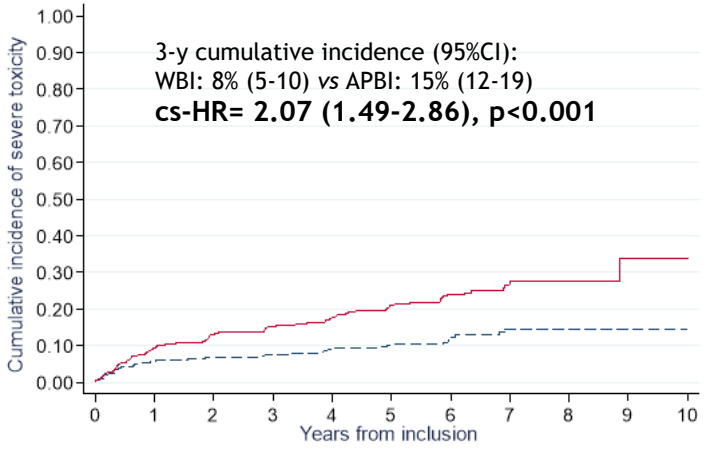
Any type of toxicities ≥ grade 2

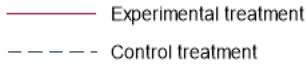


Breast skin toxicity ≥ grade 2

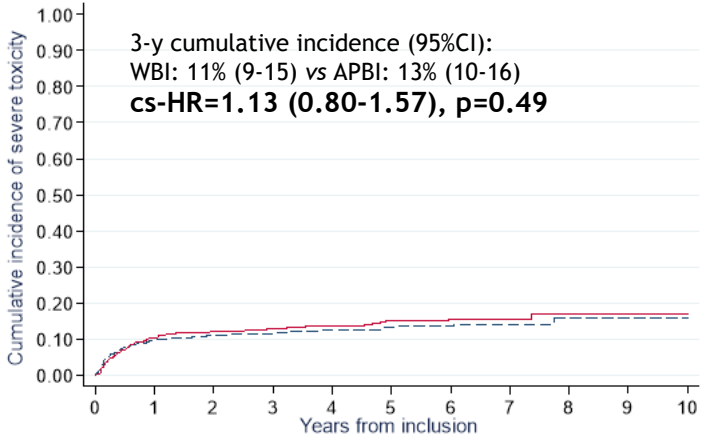


Breast other toxicities ≥ grade 2 (mainly breast fibrosis, fat necrosis…)



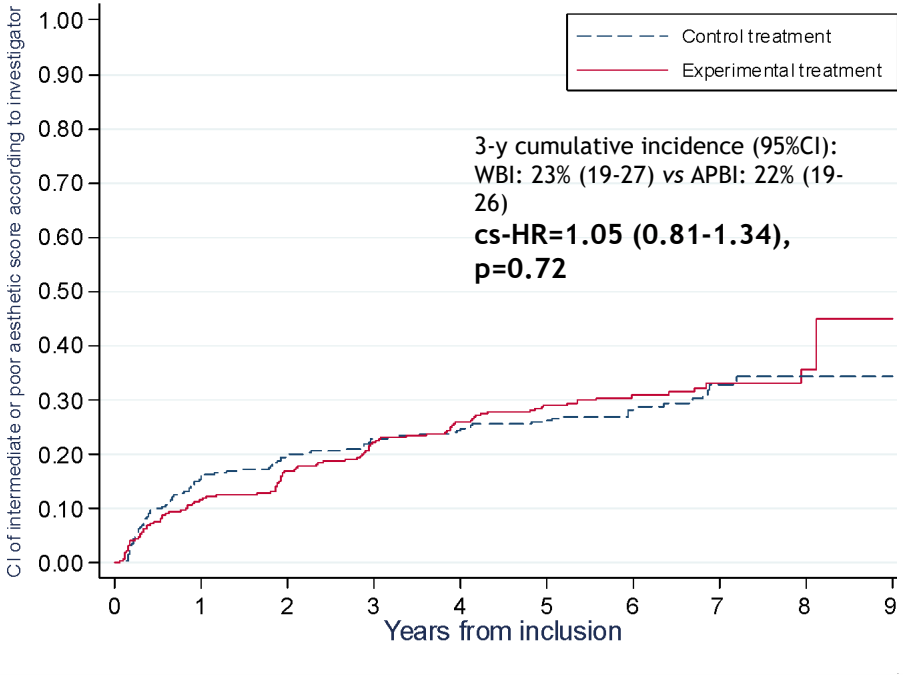


Other Adverse events ≥ grade 2

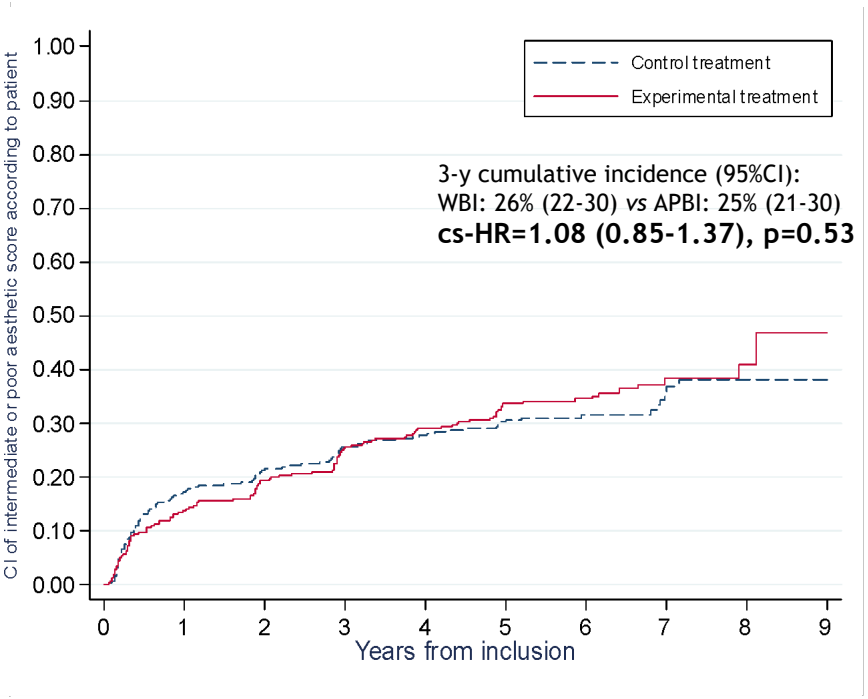


COSMETICS RESULTS
Incidence of poor cosmetic score

- **According to the investigator**



- **According to the patient**



SUMMARY

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SHARE	1006	Age > 50y pT1-2 (≤2cm), margins ≥ 2mm, pN0-N(i+) DCIS: not allowed	APBI: 34-40Gy/10f (twice per day) versus WBI: 40G/15f or 42.5Gy/16for 50Gy/25f +/- boost or	5.8	1.12%	**Global toxicities and specific skin toxicities in favor to APBI**. Breast other tox. increased in APBI similar cosmetic results
IRMA	3309	Age > 49y pT1-2 (<3cm), margins ≥ 2mm, pN0-1 DCIS: not allowed	APBI: 38.5Gy/10f (twice per day) versus WBI: 40-45Gy/15-18f or 50Gy/25f +/-boost	5.6	-	**Increased 5y-rates of late moderate soft T toxicities**, with slight decrease in patient-reported cosmesis

CONCLUSION

- After median FU of 5.8 years (modified-ITT analysis):
- Considering any type of toxicity (grade ≥ 2): significant reduction rate in APBI vs WBI (45% in WBI vs 36% in APBI arm)
- Considering breast skin toxicity only: difference in favor to APBI (36% in WBI vs 21% in APBI arm)
- Conversely, for breast other toxicities **(mainly breast fibrosis, fat necrosis…)**, WBI was found less toxic than APBI (CI of 8% vs 15%, respectively).
- Considering cosmetic results: no significant difference between the 2 arms in both evaluations by physicians and patients.

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❖ **SHARE investigators:**

Isabelle Gabelle-Flandin, Adeline Petit, Philippe Guilbert, Julien Geffrelot, Christian Carrie, Eleonor Rivin Del Campo, Chantal Hanzen, Claire Charra-Brunaud, Isabelle Lecouillard, Nicolas Magné, Agnès Richard-Tallet, Nicolas Leduc, Blaha Belgadi, Philippe Fourneret, Alexandre Coutte, Esther Capelo, Franck Darloy, Muriel Garcia-Ramirez, Philippe Dudouet, Pierre Clavere, Jean-Philippe Suchaud, Celine Bourgier, Eric Lartigau

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