Allegheny General Hospital

SABCS (2024) Review

Loco-Regional therapy update

Selected lectures

Mark Trombetta M.D.

Department of Radiation Oncology

Academic Chair and Professor, Drexel University College of Medicine

Department of the Radiologic Sciences

Allegheny General Hospital

SABCS (2024) Review

Europa: Phase III trial in luminal-like early ER + breast cancer in women 70+ years (preplanned 2 yr nterim analysis)

*(19 Italian and 2 Slovenian centers)

Icro Meattini
University of Florence
Florence, Italy

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Europa

Inclusion criteria

1. pT1N0 (or cN0) invasive BC
2. ER/PR > 10%
3. Ki67 < 10%
4. 70 years or older

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Randomize 1:1

Exclusive XRT only

vs

Exclusive ET only

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Endpoints:

Primary

1. IBTR at 5 years
2. QOL at 2 years

Secondary

1. LRR
2. BCSS
3. Adverse events
4. HRQOL QLQ-C30/BR45 module domains

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XRT arm

WBT or PBI

WBT: 40 Gy / 15 fx or 26 Gy / 5 Fx

PBI: 32 Gy /8 XRT

30.3 Gy/ 7 (HDR brachytherapy)

50Gy 0.6-0.8 Gy/hr (PDR*)

*PDR-BT consists of using stronger radiation source than for LDR-BT producing a series of short exposures of 10 to 30 min/hr to the same biologic dose as LDR-BT.

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ET arm

AI or TMX for 5-10 years (at discretion of treating doc)

N= 926 (both cohorts)

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Results

IBTR, LRR, DM, BC related death (24 months)

RT (n=104) 0

ET (n= 103) 0

CBC (contralat BC)

RT 2

ET 1

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Adverse Events

RT 65 (67.0%)

ET 76 (85.4%)

Serious AE (Grade III +)

RT 1 (Depression)

ET 16 (arthralgia, depression, myalgia, bone pain, hot flashes, fatigue)

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Serious TR AE (Grade IV)

RT 0

ET 1 (arthralgia)

*ET: 22.5 % switched drugs

12.4% D/C all ET

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Limitations

Interim analysis

1. Limited long-term efficacy and safety data (median F/U 24 months)
2. Limited cohort (older women, luminal A: ER/PR pos, Her 2 neu normally expressed, Low Ki67)

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Summary

RT better QOL than ET at 24 months

Lower incidence of Significant AE’s in RT arm

No “Red Flags”

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Impact of TMX only after BCS for “Good Risk” DCIS

NRG Oncology/RTOG 9804 and ECOG-ACRIN E5194 Trials

Jean Wright MD
University of North Carolina

Allegheny General Hospital

NRG /RTOG 9804:ECOG-ACRIN E5194

Background

1. NRG/RTOG 9804 showed that XRT reduced IBRT by 50% at 15 years (15 -> 7%)
2. XRT omission reasonable in some pts
3. Impact of ET less well established: Historical data shows IBTR reduction in DCIS and IBC
4. Most modern studies leave ET to the discretion of the pt and physician. Use is highly variable across practices

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NRG /RTOG 9804:ECOG-ACRIN E5194

Both studies sub-classified DCIS

1. NRG/RTOG: “Good risk”; < 2.5 cm, Grade 1and 2, resection margins >3 mm
2. ECOG-ACRIN enrolled two prospective “observation” cohorts with same criteria

In both trials, the use of TMX was optional, but tracked

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NRG /RTOG 9804:ECOG-ACRIN E5194

Methods

Combined database used (n= 878); Well matched

TMX yes = 378 pts

TMX no = 500 pts

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NRG /RTOG 9804:ECOG-ACRIN E5194

Resection margins:

<3 mm 2-3%

3-9 mm 50% (TMX) vs 69%(no TMX)

>10 mm 21%(TMX) vs 18% (No TMX)

Tumor size

< 5 mm 57% (TMX) vs 41% (No TMX)

6- 10 mm 29% (TMX) vs 40% (No TMX)

Tumor grade

Well matched

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NRG /RTOG 9804:ECOG-ACRIN E5194

Results: DCIS and IBC (median 14.85 yrs)

IBTR: (No TMX) 19% vs 11.4% (TMX)

1. DCIS: (no TMX) 8.1 vs 5.5% NS
2. IBC: (no TMX) 11.5 vs 6.0%
3. CBE: 5.6% (no TMX) versus 8.8% (TMX) NS

Other Features of significance:

Grade III and tumors > 5 mm had higher LR rates

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NRG /RTOG 9804:ECOG-ACRIN E5194

Conclusions

NRG/RTOG 9804 and ECOG/ACRIN E5194 “good risk” pts

1. TMX reduced overall IBTR (19-11%) and Invasive IBR (11.5-6%) but not DCIS IBR or CBE
2. In the absence of survival benefit, the decision to use ET remains a shared decision between pt and doctor
3. Ongoing study of molecular profiling to inform RT decisions should also evaluate the impact of ET decisions, particularly in those not receiving RT

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Is Post Mastectomy Radiotherapy of benefit in "intermediate risk" breast cancer survival?

Ten year results of BIG 2.04 MRC-EORTC randomized trial on behalf of the SUPREMO trial investigators

Ian Kunkler MD
University of Edinburgh

BIG 2.04 MRC-EORTC randomized trial on behalf of the SUPREMO trial investigators*

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Background

Danish and Canadian trials have demonstrated a 9-10% survival benefit with post mastectomy XRT in addition to CTX (Lancet 1999)

LRR was higher than in contemporary US series

CMF CTX may have been suboptimal

Role of PMRT in 1-3 node + research priority of NIH (2000)

*BIG: Breast International Group

MRC: Medical Research Council

SUPREMO: **S**elective **U**se of **P**ostoperative **R**adiotherapy Aft**E**r **M**astect**O**my

EORTC: European Organization for Research and Treatment of Cancer

BIG 2.04 MRC-EORTC randomized trial on behalf of the SUPREMO trial investigators

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Main Eligibility criteria

1. pT1N1, pT2N1, or pT3N0 IBC
2. pT2N0 if grade 3 or LVSI
3. Mastectomy with minimum 0.1 cm margin
4. If ax nodes +, then ax diss (minimum 8 nodes) should be done
5. Ax node considered neg if Ax Diss, SNB or Ax sampling neg
6. Pt to be acceptable for systemic CTX (or ET if indicated)

BIG 2.04 MRC-EORTC randomized trial on behalf of the SUPREMO trial investigators

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Endpoints

1. <u>Primary:</u>
    a. OS 10 year

2. <u>Secondary:</u>
    a. LRR
    b. DFS: Met FS
    c. Acute and late morbidity
    d. QOL
    e. Cost effectiveness

BIG 2.04 MRC-EORTC randomized trial on behalf of the SUPREMO trial investigators

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Powering

1. 1600 pr (800 per arm) to detect a sig diff at the 5% level
2. Requires 609 events (deaths)

Randomization

Arm A : No chest wall XRT (834 pts; 799 fit for analysis)

Arm B: Chest Wall XRT (40 Gy in 15 fx or 50 Gy in 25 fx) (n= 845; 808 fit for analysis)

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Basic characteristics well matched

HR 1.04

NO XRT: 799 pts. 695 alive at 5 years and 205 alive at 10 years

PM RT: 808 pts. 689 alive at 5 years and 191 alive at 10 years.

Met FS HR 1.06

DFS HR 0.97

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Conclusions

In pts with 1-3 nodes+ or pN0 with other risk factors PMRT:

1. Does not improve 10-year survival
2. Results in clinically insignificant chest wall recurrence
3. Has no impact on Met F or DFS
4. Should be omitted in SUPREMO criteria Pts.

<u>Incremental improvements in multidisciplinary care probably explain the results</u>

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Primary Outcomes following Active Monitoring or surgery (=/- XRT) for low risk DCIS: COMET Study (AFT-25)

Shelley Hwang MD
Duke University

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Primary Outcomes: COMET* Study (AFT-25)

Background

1. DCIS is preinvasive cancer
2. 50,000 new case annually in US
3. Lumpectomy =/- XRT to prevent progression
4. Since DCIS does not always progress to IBC, is there an opportunity to monitor?
5. Prospective randomized non-inferiority trial

*COMET: **C**omparing an **O**peration to **M**onitoring, with or without **E**ndocrine **T**herapy,

AFT: Alliance Foundation Trials

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Primary Outcomes: COMET Study (AFT-25)

Primary outcome:

Two-year cumulative rate of ipsilateral IBC at any time following randomization

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Primary Outcomes: COMET Study (AFT-25)

Eligibility

1. >40 yrs
2. DCIS
3. Grade 1 or 2
4. ER+
5. Biopsy X 2 if tumor > 4 cm

Randomization stratified by

a. Age: < 55, 55-65, >65
b. Max diameter of calcs: < 2.0 cm, 2-5 cm, > 5 cm
c. DCIS nuclear grade

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Primary Outcomes: COMET Study (AFT-25)

N= 957 (XRT n= 473)

1. Usual care; surgery at diagnosis
2. BCS or mastectomy
3. Adjuvant XRT per Rad Onc
4. Adjuvant ET permitted

Primary Outcome:

Any IBC detected including recurrence

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Primary Outcomes: COMET Study (AFT-25)

Active monitoring (AM) (n= 484)

Ipsilateral MMG q 6 months

Biopsy for imaging changes

GCC upon diagnosis of IBC

Adjuvant ET permitted

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Primary Outcomes: COMET Study (AFT-25)

Statistical Analysis Plan

1. Primary Outcome: 2 yr IBC
2. Sample size based on 30% non-adherence arm allocation
3. Assumption: Based on 3-year cumulative rate of IBC for 10% of Guideline Concordant Care (including upstaging and recurrence)
4. One sided non-inferiority: 5% higher rate in AM compared to GCC

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Primary Outcomes: COMET Study (AFT-25)

Clinical Outcomes

Primary Endpoint:

1. 2 yr ipsilateral IBC rate

Secondary endpoints:

1. 2 yr mastectomy rate, Breast conservation rate
2. 2 yr CBC rate
3. 2 yr OS and DSS rate

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Primary Outcomes: COMET Study (AFT-25)

Clinical Outcomes

Other endpoints:

1. 2 year breast MRI rate
2. 2 year breast biopsy rate
3. 2 yr radiation rate
4. 2 yr CTX rate

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Primary Outcomes: COMET Study (AFT-25)

PRO QOL/ psychosocial outcomes (Baseline,1, 2 yrs)

<u>Secondary endpoint</u>:

1. Health related QOL
2. Anxiety and Depression

<u>Other Endpoints:</u>

1. Symptoms, pain, body image, sexual function
2. Decision making
3. Knowledge and risk perceptions
4. Financial burden/ employment

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Primary Outcomes: COMET Study (AFT-25)

Randomization and Study Flow

957 Eligible pts (pts well aligned): 484 Active monitoring

1. 427 initiated AM within 6 months
2. 57 underwent GCC per protocol within 6 months
3. 13 did not enter study
4. 484 included in 2 yr ITT analysis
5. 427 included in 2 yr protocol analysis

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Primary Outcomes: COMET Study (AFT-25)

Randomization and Study Flow

496 GCC

246 underwent GCC per protocol within 6 months

227 initiate AM within 6 months

25 did not start study

473 included in 2 yr ITT analysis

246 included in 2 yr protocol analysis

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Primary Outcomes: COMET Study (AFT-25)

Results

2 yr cumulative rate IBC (all)

GCC 5.9%

AM 4.2%

AM NOT INFERIOR TO GCC

Primary Outcomes: COMET Study (AFT-25)

ITT Analysis

	GCC (n= 473)	AM (n=484)
ET	310 (65.5%)	345 (71.3%)
XRT	126 (26.6%)	36 (7.4%)
CTX	5 (1.1%)	6 (1.2%)
Surgery		
Lumpectomy	228 (48.2%)	64 (13.2%)
Mastectomy	28 (5.5%)	18 (3.7%)
Re-excision	10 (2.1 %)	0 (0%)

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Primary Outcomes: COMET Study (AFT-25)

2 yr cumulative rate Ipsilat breast cancer

GCC 8.7%

AM 3.1%

As-Treated analysis (n=957)

Secondary endpoint: IBC (n= 46)

GCC/GCC	21
AM/GCC	7
AM/AM	12
GCC/AM	6

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Primary Outcomes: COMET Study (AFT-25)

Summary

1. In this prespecified primary analysis of the COMET study, the 2 yr cumulative rate of IBC was 5.9% (GCC) and 4.2% (AM)
2. No statistical differences for: Median IBC size, Nodal status or highest grade
3. Thirty-one percent did not adhere to their arm allocation with more pts favoring AM
4. All groups well matched, but participation bias cannot be excluded

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Primary Outcomes: COMET Study (AFT-25)

Conclusions

1. At 2 yrs, women with low-risk DCIS randomized to AM had a non-inferior rate of IBC in the ipsilateral breast compared to GCC
2. Additional follow up needed

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Patient reported outcomes (PRO) following Active Monitoring or Surgery (+/- XRT) for low-risk DCIS in the COMET Study (AFT-25)

Ann Partridge M.D.
Harvard/Dana- Farber

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PRO following Active Monitoring or Surgery for low-risk DCIS in the COMET Study

Background

1. Women with DCIS have a favorable overall QOL

   Risks: Reduced vitality and mental health

   a. Heightened Anxiety

   b. Fear of Recurrence

   c. Arm symptoms

   d. Persistent pain

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PRO following Active Monitoring or Surgery for low-risk DCIS in the COMET Study

Background

2. Interest in avoiding surgery for low-risk DCIS led to COMET study (AM non-inferior to GCC at 2 years)

3. No prior analyses have prospectively compared PRO's among women managed with GCC versus AM

Remember: Adjuvant ET was permitted in both groups

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PRO following Active Monitoring or Surgery for low-risk DCIS in the COMET Study

Survey: Three Domains

1. Health related QOL

a. **SF-36** (Short Form; 0-100 score). Eight domains: General health, physical functioning, role physical, role emotional, social functioning, bodily pain, vitality, mental health. Also mental and physical component scored (MCS and PCS).

2. Psychological/Emotional:

a. **STAI** (State Trait Anxiety Inventory)
b. **CES-D-10** (Center for Epidemiologic Studies Depression Scale-10)
c. **QLACS** (Quality of Life on Adult Cancer Survivors): Four items adopted to worries about DCIS

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PRO following Active Monitoring or Surgery for low-risk DCIS in the COMET Study

Survey: Three Domains

3. <u>DCIS Treatment Related Symptoms</u>

a. **BCPT** (Breast Cancer Prevention Trial) Symptom Checklist (modified). Eight symptom clusters: hot flashes, nausea, bladder control, vaginal problems, musculoskeletal pain, cognitive problems, weight problems, arm problems.
b. **BCPQ** (Breast Cancer Pain Questionnaire)
c. **BPI** (Breast Pain Inventory)

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PRO following Active Monitoring or Surgery for low risk DCIS in the COMET Study

Randomization and Study Flow

1. 953/957 (99.5%) completed at least one survey
2. Response rates (each time point) were 83%
3. Seven percent completed only the baseline questionnaire
4. Response to the 2-year survey did not vary by group

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PRO following Active Monitoring or Surgery for low risk DCIS in the COMET Study

Summary and Conclusion

1. COMET study PRO's demonstrated overall QOL, anxiety, depression, breast cancer worries, and symptom trajectories comparable between randomized groups at 2 years.
2. For select women considering AM or GCC for low-risk DCIS, both strategies have only limited impact, on average, on the lived experience of these patients in short-term follow up.

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Thank you