ASTRO's 60th Annual Meeting

Translating Discovery to Cure

Advances in Breast and Lung Cancers

ASTRO News Briefing

Sunday, October 21, 2018

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Sunday, October 21, 1:00-2:00pm CT

Moderator: Catherine Park, MD, FASTRO, UCSF

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Beryl McCormick, MD, Memorial Sloan Kettering Cancer Center

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B. McCormick

Memorial Sloan Kettering Cancer Center, New York, NY

Disclosure for Dr. McCormick

- Author's Affiliations
  - Memorial Sloan Kettering Cancer Center (BMc), NRG Oncology Statistics and Data Management Center/ACR (KW, JM), M D Anderson Cancer Center (HK, NS, ES), Odette Cancer Centre-Sunnybrook Health Sciences Centre (ER DV), Massachusetts General Hospital (BS), L Hotel-Dieu De Quebec (IG), Dartmouth-Hitchcock Medical Center (AH), Greenville CCOP Cancer Centers of The Carolinas (MO), Henry Ford Hospital (EW), Southeast Cancer Control Consortium, Inc. CCOP ((JA), University of Michigan Medical Center (LP), Sutter Medical Center Sacramento(accruals Radiological Associates of Sacramento) (AP), University of Hawaii Cancer Research Center (KS), Ohio State University (JW)
- Grant/Sponsor Acknowledgements
  - Grant Info: U10CA180868 (NRG Operations), U10CA180822 (NRG SDMC), UG1CA189867 (NCORP) from the National Cancer Institute
  - NCT00003857

Background

- RTOG 9804 was designed to address whether radiation therapy after breast-conserving surgery would decrease local failure (invasive, in situ) and need for mastectomy among a cohort of DCIS patients at low risk of recurrence

- Unlike previous prospective RCTs comparing whole breast radiation therapy with no RT for DCIS, RTOG 9804 included only “good risk” patients
  - Detected by mammogram, size ≤ 2.5 cm, final margins ≥ 3 mm, and low or intermediate nuclear grade

Schema

STRATIFY

Age
1. < 50
2 ≥ 50

Final Path Margins
1. Negative (re-excision)
2. 3-9 mm
3. ≥ 10 mm

Mammographic/Pathologic Size of Primary
1. ≤ 1 cm
2. > 1 cm to ≤ 2.5 cm

Nuclei Grade
1. Low
2. Intermediate

Tamoxifen Use
1. No
2. Yes

RANDOMIZE

Arm 1
Observation ± tamoxifen 20 mg per day for 5 years

Arm 2
Radiation therapy to the whole breast, ± tamoxifen 20 mg per day for 5 years

Endpoints

- Local failure
- Contralateral breast failure
- Salvage mastectomy

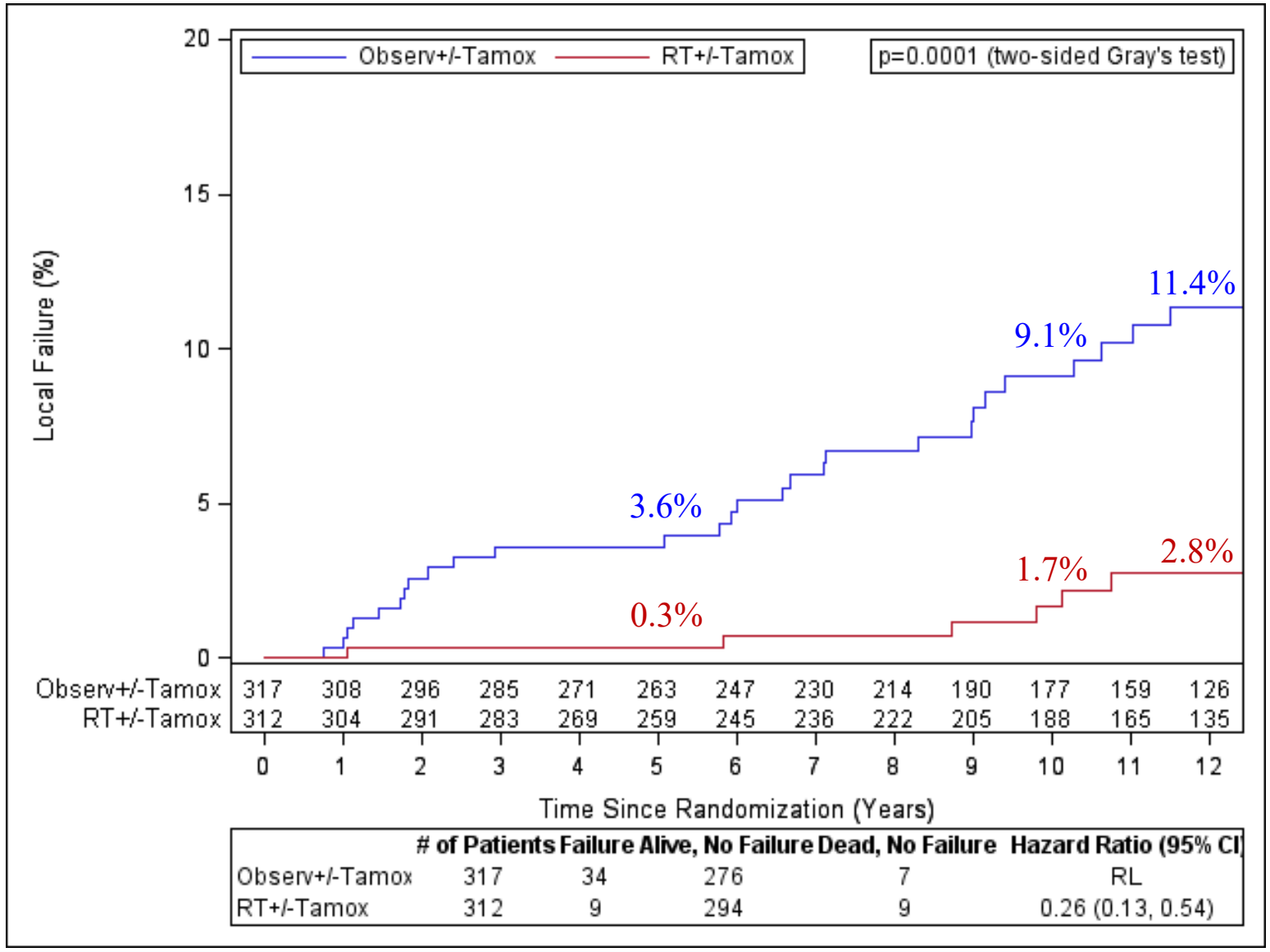
Median follow-up

- 12.4 years

Patient age and pathology

	Observation (n=317)	Radiation Therapy (n=312)
Age		
< 50	69 (21.8%)	60 (19.2%)
≥ 50	248 (78.2%)	252 (80.8%)
Final Microscopic Margins		
3mm - 9mm	111 (35.0%)	110 (35.3%)
≥ 10mm	50 (15.8%)	51 (16.3%)
Negative by negative re-excision	156 (49.2%)	151 (48.4%)
Mammographic Size of Primary Tumor		
≤ 1cm	229 (72.2%)	223 (71.5%)
> 1cm	88 (27.8%)	89 (28.5%)
Nuclei Grade		
NG1	141 (44.5%)	135 (43.3%)
NG2	176 (55.5%)	177 (56.7%)

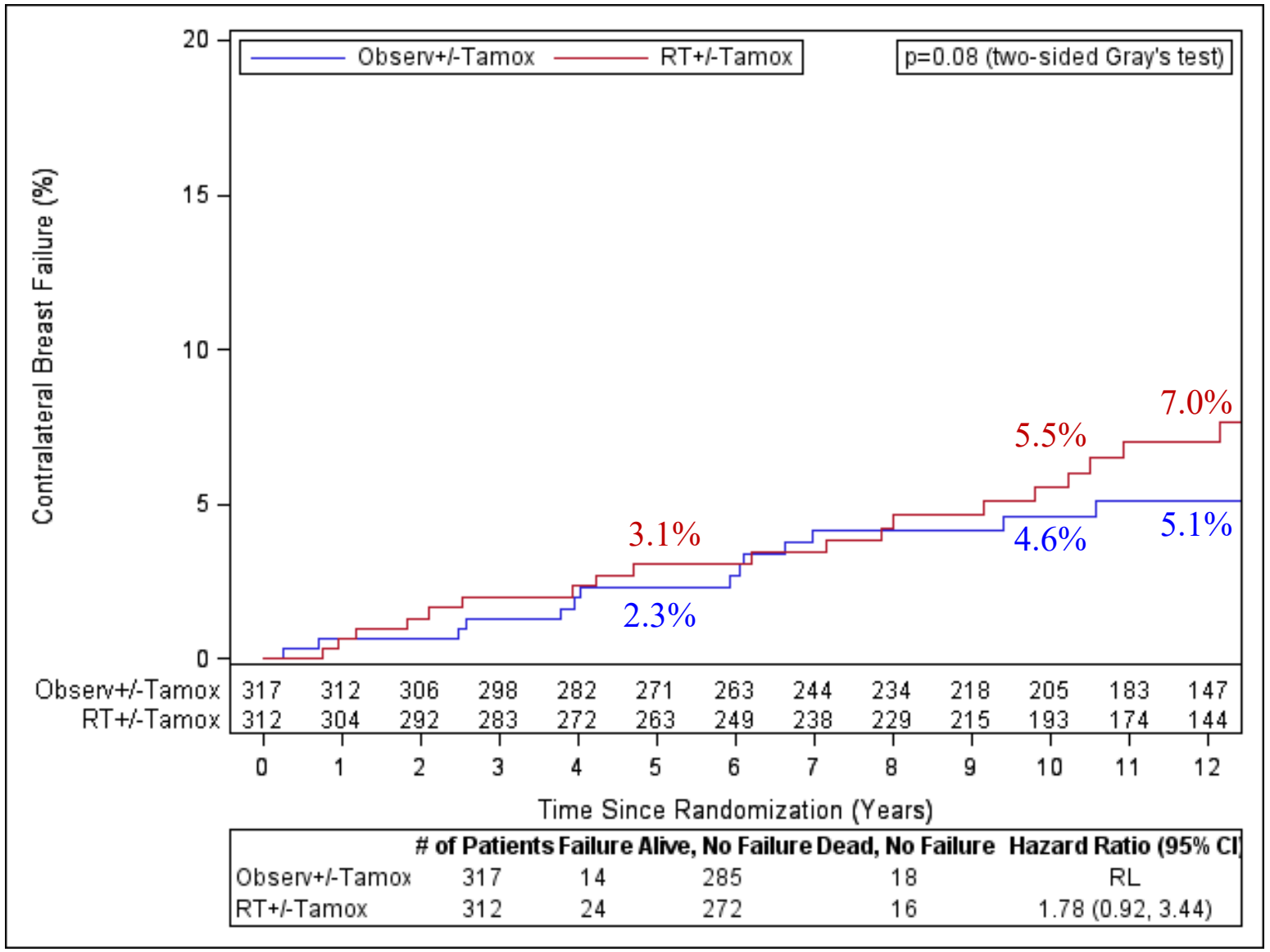
Local failure: Ipsilateral breast



Multivariable analysis: Local failure

Comparison	HR	p-value
Treatment: obs+tam vs RT+tam	0.25	0.0003
Age: <50 vs ≥50	0.93	0.84
Margins: neg vs 3-9mm	0.60	0.16
Margins: neg vs ≥10mm	0.37	0.098
Largest lesion: ≤0.5cm vs 0.6-1.0cm	1.14	0.72
Largest lesion: ≤0.5cm vs >1.0cm	1.81	0.16
Nuclei grade NG2 vs NG1	0.69	0.26
Tamoxifen received: no vs yes	0.50	0.024

Contra-lateral breast events



Mastectomy rates

Observation (n=317)	RT (n=312)
17 Mastectomies (5.4%)	**10 Mastectomies (3.2%)**
9 ipsilateral; 0 elective 8 bilateral; 2 elective	4 ipsilateral; 1 elective 6 bilateral; 1 elective

Adverse events/Toxicities

Acute Non-Hematological Toxicities

(Graded with CTC version 2.0)

Grade	Observation (n=317)	Radiation Therapy (n=312)
1	39 (12.3%)	107 (34.4%)
2	54 (17.0%)	124 (39.9%)
3	12 (3.8%)	11 (3.5%)
4	1 (0.3%)	2 (0.6%)
5	0 (0.0%)	0 (0.0%)

Late Radiation Therapy Toxicity

(Graded with RTOG/EORTC late toxicity criteria)

Grade	Radiation Therapy (n=307)
1	90 (29.3%)
2	15 (4.9%)
3	3 (1.0%)
4	1 (0.3%)
5	0 (0.0%)

Conclusions

- In this defined “good risk” DCIS population, the addition of whole breast radiation following breast conservation surgery significantly reduced the risk of any local recurrence and of invasive local recurrence.

- The larger-than-expected reduction has yielded meaningful results despite not meeting original targeted accrual.

- Findings should inform meaningful patient-doctor discussions about risks, benefits and the patient’s own degree of comfort, which varies greatly, with regards to local control with and without radiation therapy.

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A. M. Brunt[1], J. Haviland[2], M. Sydenham[2], H. Algurafi[3], A. Alhasso[4], P. Bliss[5], D. Bloomfield[6], M. Emson[2], A. Goodman[7], A. Harnett[8], H. Passant[9], Y. M. Tsang[10], D. Wheatley[11], J. Bliss[2], and J. Yarnold[1]

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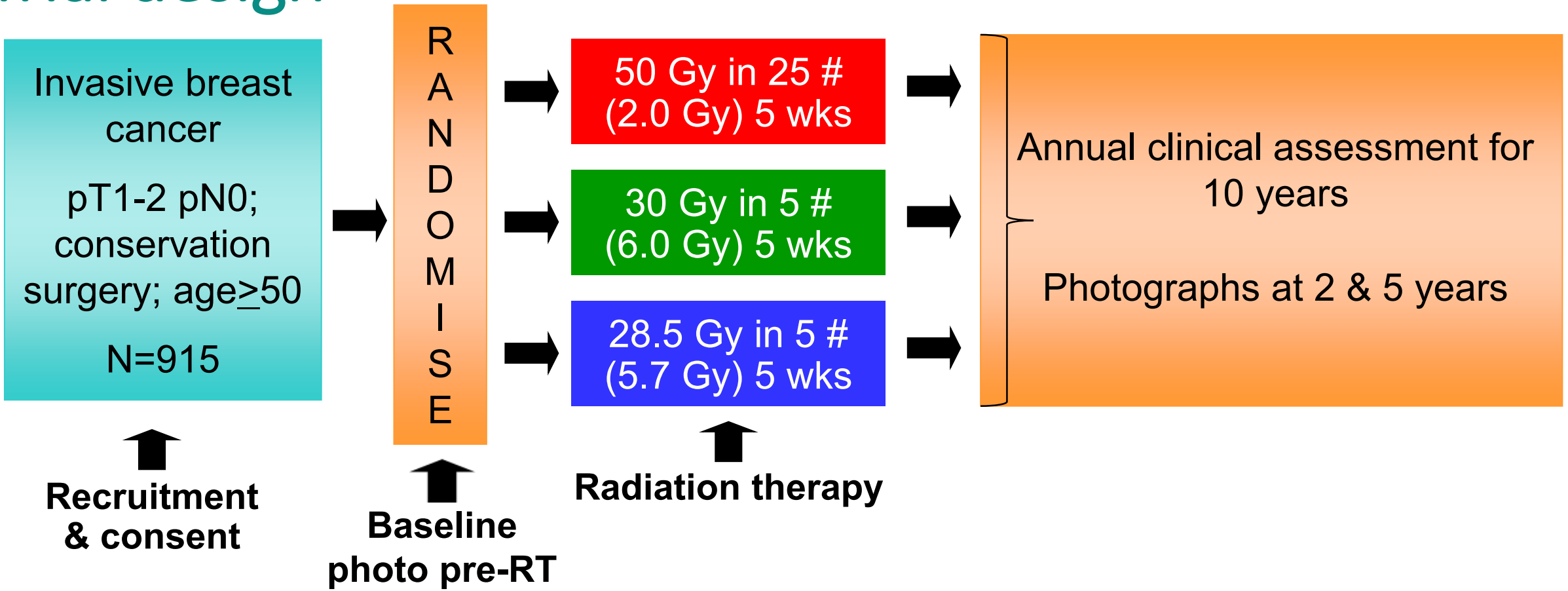
Disclosure for Dr. Brunt

- Dr. Brunt is employed as a Consultant Clinical Oncologist at University Hospitals of North Midlands, Stoke-on-Trent, UK

- Dr. Brunt has no conflicts of interest to disclose.

Trial design



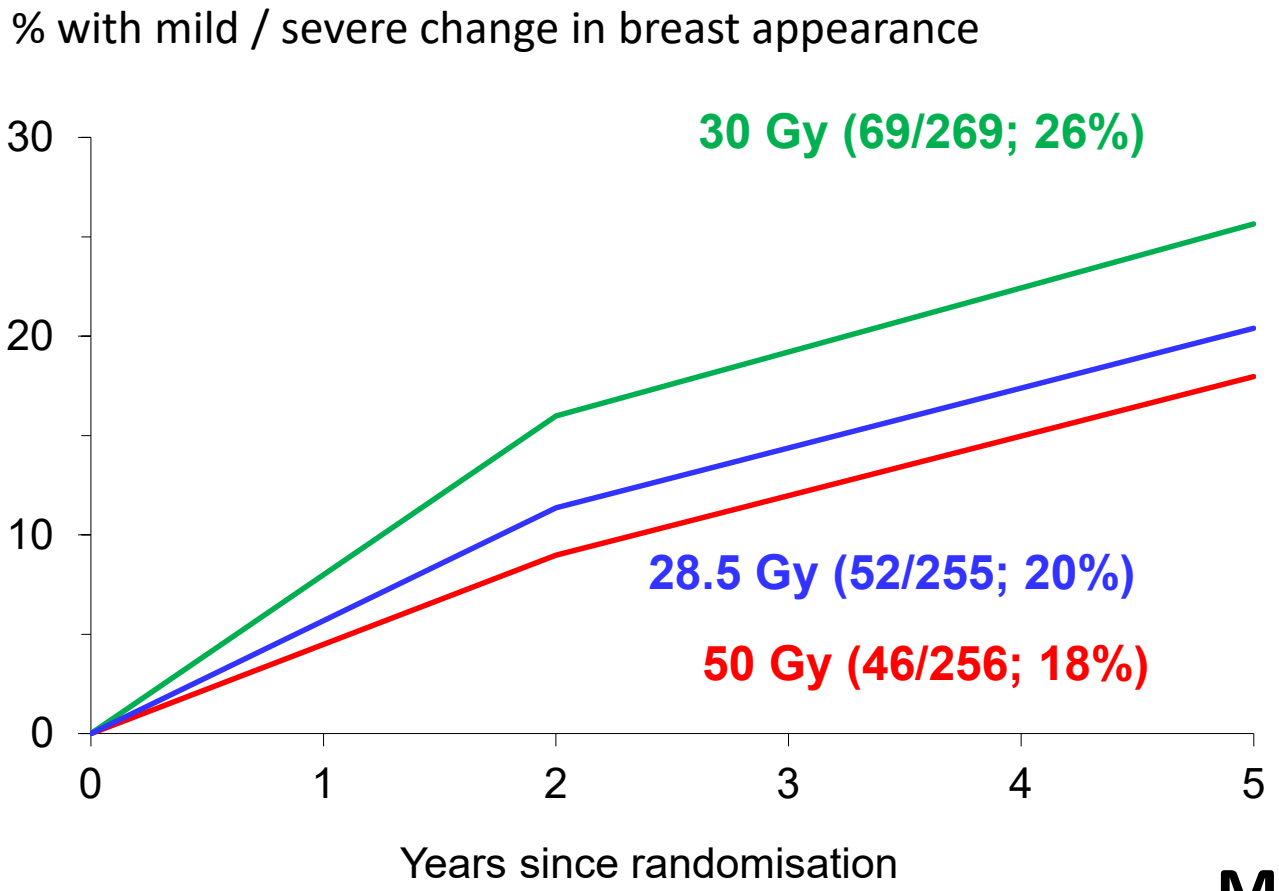
Primary endpoint:

2-year change in photographic breast appearance

Secondary endpoints:

5-year change in photographic breast appearance
clinical assessments of late adverse events
ipsilateral local tumour control

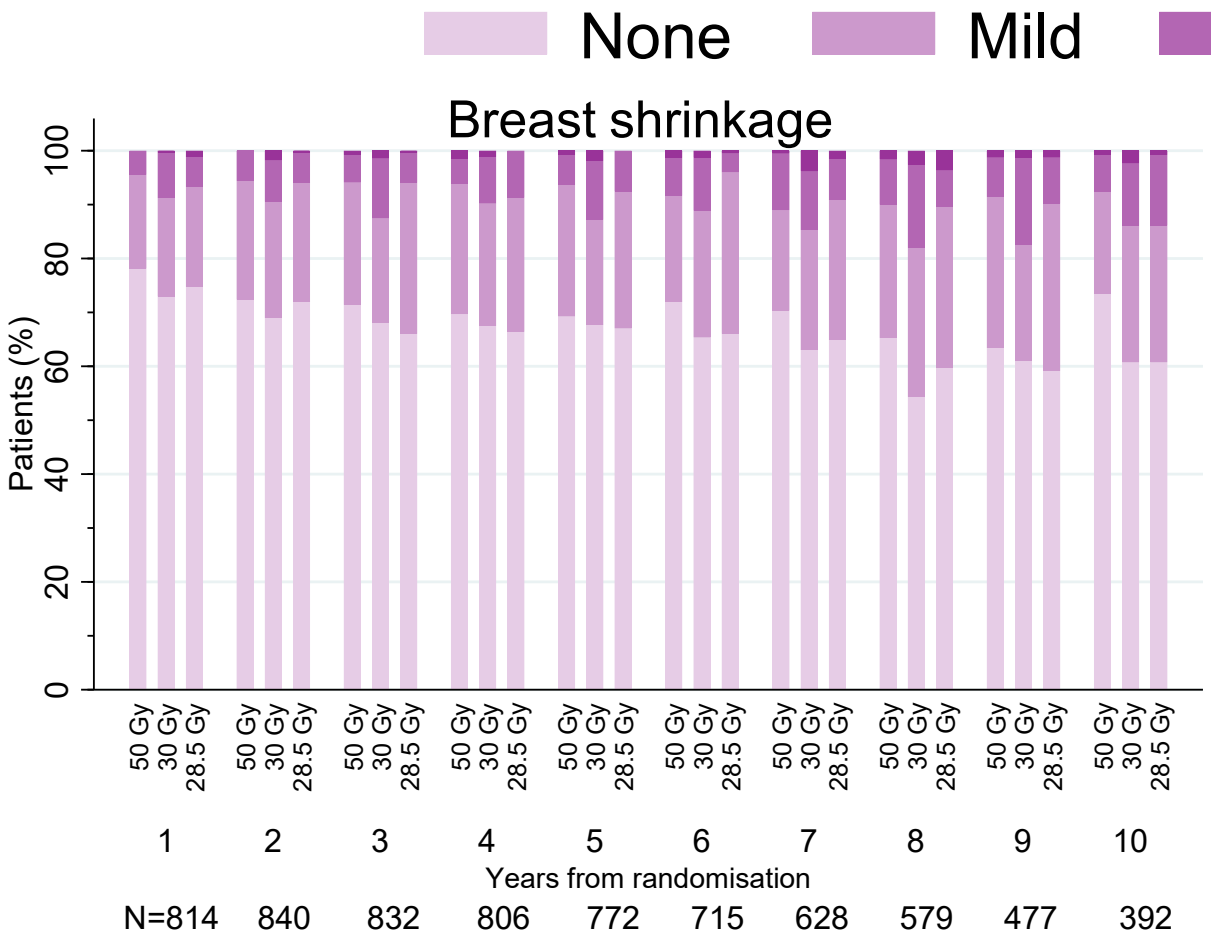
Photographic assessment of overall change in breast appearance by 5 years

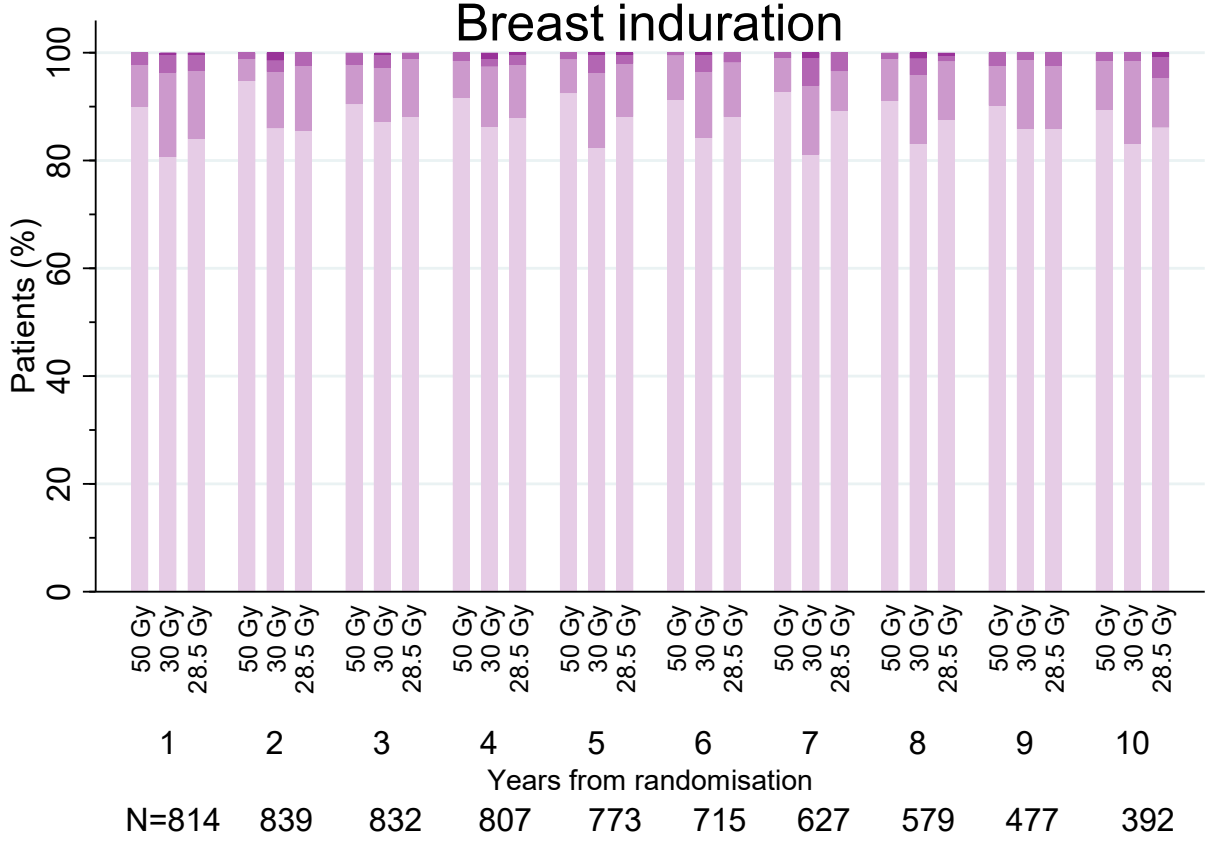


	Difference (95%CI)
30Gy vs **50Gy**	+7.4% (0.3, 16.7) p=0.03
28.5Gy vs **50Gy**	+2.4% (-3.8, 10.8) p=0.47

Marked changes: 2%, 4%, 2%

Clinical assessments of late AE in breast





	OR for moderate/marked shrinkage (95%CI)	OR for moderate/marked induration (95%CI)
30Gy vs **50Gy**	1.88 (1.32, 2.67), p<0.001	2.39 (1.31, 4.35), p=0.004
28.5Gy vs **50Gy**	1.11 (0.76, 1.64), p=0.59	1.67 (0.89, 3.16), p=0.11

Fractionation Sensitivity (α/β estimates)

Photographic change in breast appearance

α/β = 2.4Gy (95% CI 0.4–4.3)

Breast shrinkage (clinician assessment)

α/β = 2.4Gy (95% CI 1.3–3.5)

If α/β = 2.4Gy,

28.5Gy in 5# ≡ 52.5Gy in 2.0Gy fractions

30.0Gy in 5# ≡ 57.3Gy in 2.0Gy fractions

27.7Gy in 5# ≡ 50.0Gy in 2.0Gy fractions (calculated)

Relapse and survival at median 10 years' follow-up

	50Gy/25# N=302	30Gy/5# N=308	28.5Gy/5# N=305	Total N=915
Local relapse	3	4	4	11
Regional relapse	2	0	3	5
Distant relapse	17	15	15	47
Death (breast cancer)	30 (7)	33 (8)	33 (10)	96 (25)

Estimate of 10-year local relapse rate: 1.3% (95%CI 0.7, 2.3%)

Conclusions

- Severe changes to normal breast tissue were rare
- Late adverse events (AEs) after 28.5Gy/5# over 5 weeks similar to 50Gy/25#
- Little change in prevalence of AEs between 5 & 10 years
- Local tumour relapse rate extremely low in all schedules
- Once-weekly 5# schedule may be considered when daily visit for 3 or 5 weeks not acceptable
- UK FAST-Forward trial is testing 5# delivered in 1 week

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Daniel Gomez, MD, University of Texas MD Anderson Cancer Center

Local Consolidative Therapy (LCT) Improves Overall Survival (OS) Compared to Maintenance Therapy/Observation in Oligometastatic Non-Small Cell Lung Cancer (NSCLC): Final Results of a Multicenter, Randomized, Controlled Phase 2 Trial

D. R. Gomez[1], C. Tang[1], J. Zhang[1], G. R. Blumenschein[2], M. Hernandez[1], J. J. Lee[1], R. Ye[1], D. R. Camidge[3], F. Skoulidis[1], R. Doebele[4], L. E. Gaspar[3], D. L. Gibbons[1], J. Karam[1], B. D. Kavanagh[3,4], D. A. Palma[5], A. V. Louie[6], A. Tsao[1], B. Sepesi[1], S. G. Swisher[1], and J. Heymach[1]

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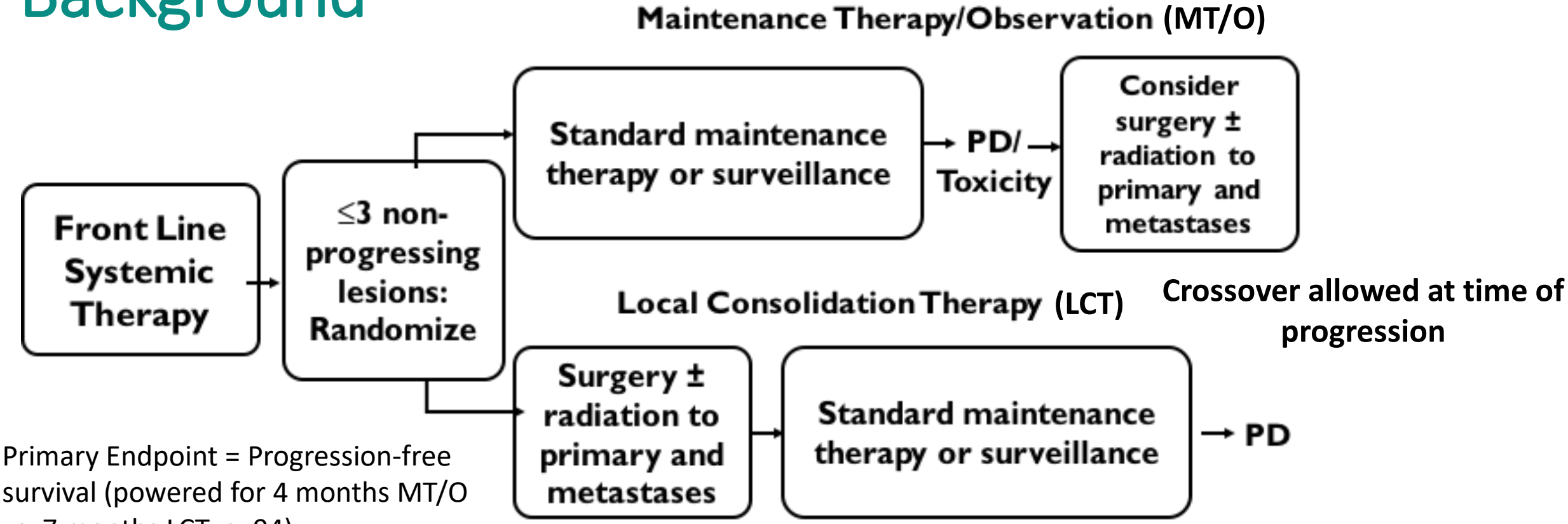
Disclosure for Dr. Gomez

- Honoraria/Travel Costs – Merck, Varian, Elekta, Driver Oncology, US Oncology, BMS, AstraZeneca, Reflexion
- Research Grants – Varian, Merck, AstraZeneca, BMS
- Advisory Boards – AstraZeneca

Background

- Biologic state of “oligometastasis” still being defined
  - Defining patients in-between locally advanced state and true metastases that could be “cured”
- In 2012, we initiated phase II randomized study examining this question
  - Key eligibility criteria:
    - Diagnosis of stage IV NSCLC
    - ≤3 metastases after standard front-line systemic therapy
      - Four cycles of platinum-doublet chemotherapy or 3 months of EGFR/ALK targeted therapy for appropriate molecular alterations
    - ECOG performance status 0-2
    - Eligible for “local consolidative therapy” (surgery/radiation therapy=LCT) to all sites of disease
  - Treatment arms:
    - A) Standard = maintenance therapy/observation (MT/O)
    - B) Experimental = local consolidative therapy (LCT)

Background



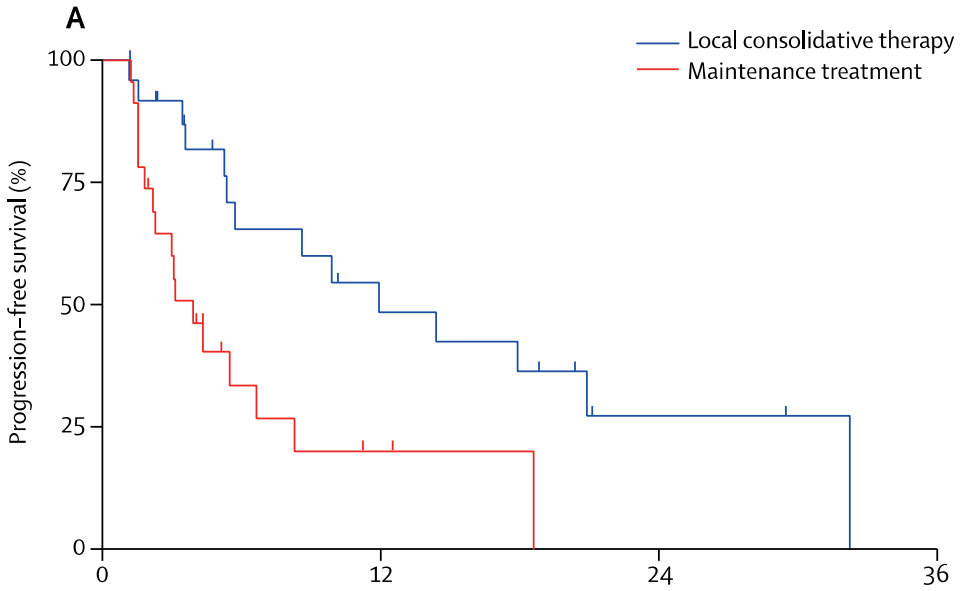
Primary Endpoint = Progression-free survival (powered for 4 months MT/O vs. 7 months LCT, n=94)

Secondary Endpoints: Overall survival, safety/toxicity, time to appearance of new lesions

Balanced randomization: 1) Number of metastases (0-1 vs. 2-3), 2) Response to first-line systemic therapy (stable disease vs. partial response), 3) N0-N1 vs. N2-N3, 4) CNS vs. no CNS metastases, 5) EGFR/ALK alteration vs. wild type

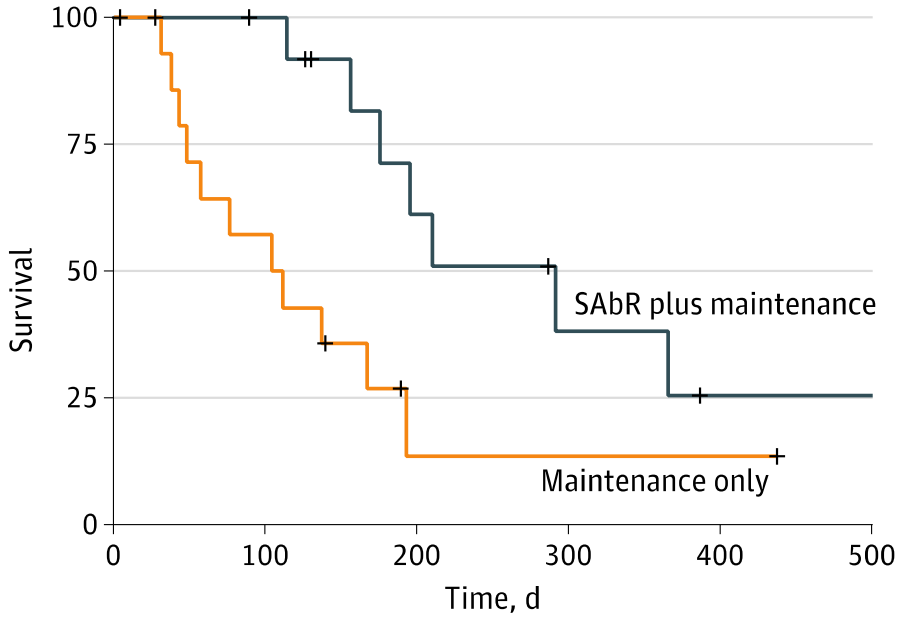
Gomez et al., *Lancet Oncol* 2016

Background



Number at risk (number censored)				
Local consolidative therapy	24 (0)	8 (6)	2 (3)	0 (1)
Maintenance treatment	24 (0)	2 (6)	0 (1)	0 (0)

Gomez et al., *Lancet Oncol* 2016



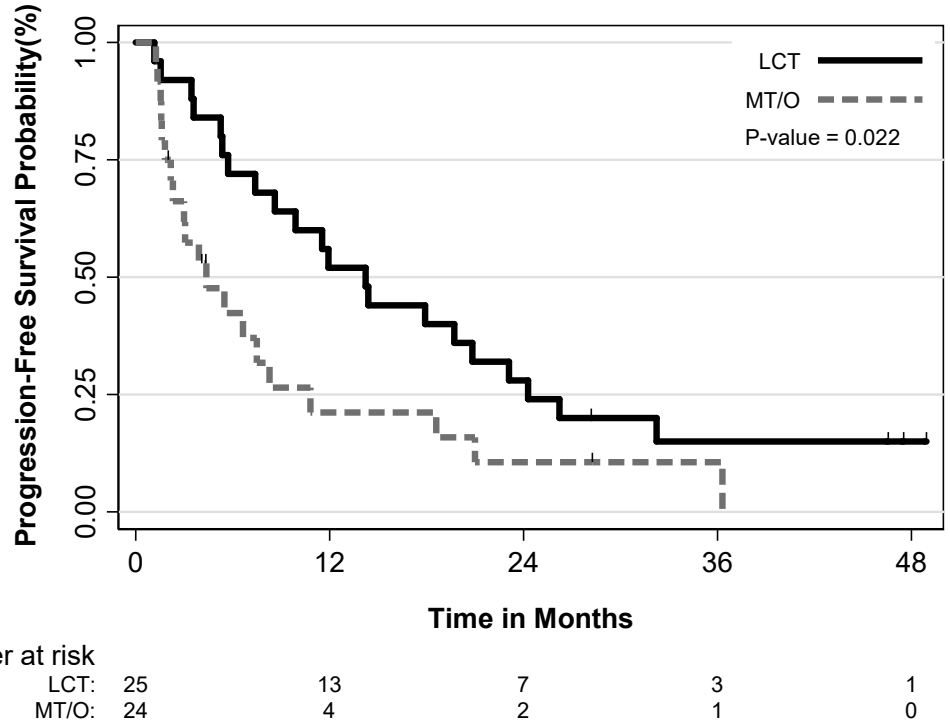
No. at risk					
SAbR plus maintenance	14	12	6	3	1
Maintenance only	15	8	1	1	1

Iyengar et al., *JAMA Oncol* 2017

Conclusions/Remaining Questions

- Since 2016, benefit of consolidative therapy in PFS endpoint has been demonstrated in at least four prospective randomized trials
  - Two in lung cancer (Gomez et al., Iyengar et al), one in prostate cancer (Ost et al., *JCO* 2018), one in colorectal cancer (Ruers et al., *JNCI* 2017)
- However, does PFS benefit translate to OS improvement?
  - Particularly relevant in current trial because crossover allowed between arms
  - Will "late LCT" (e.g. at time of progression) lead to similar OS times as "early LCT," when measured from the time of randomization?

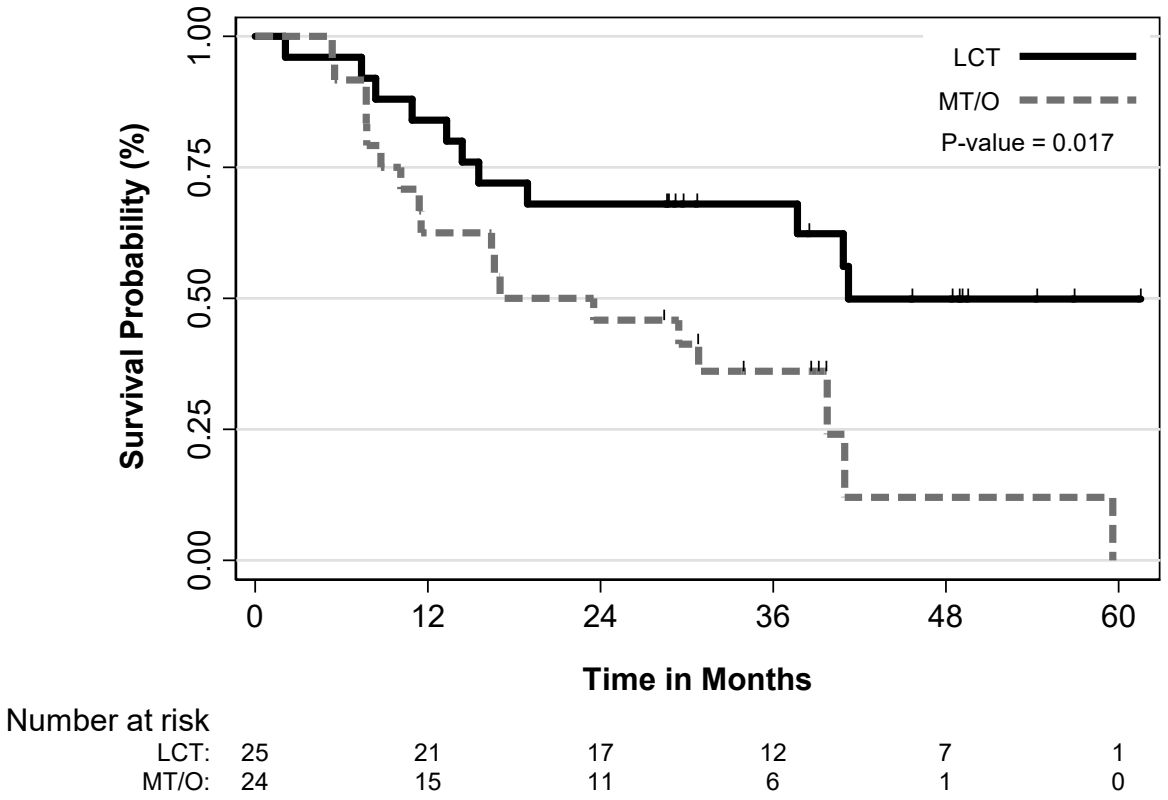
Progression Free Survival



Median 4.4 months in MT/O arm [95% CI 2.2-8.3] and 14.4 months in LCT arm [95% CI 7.4-23.1, p=0.022]

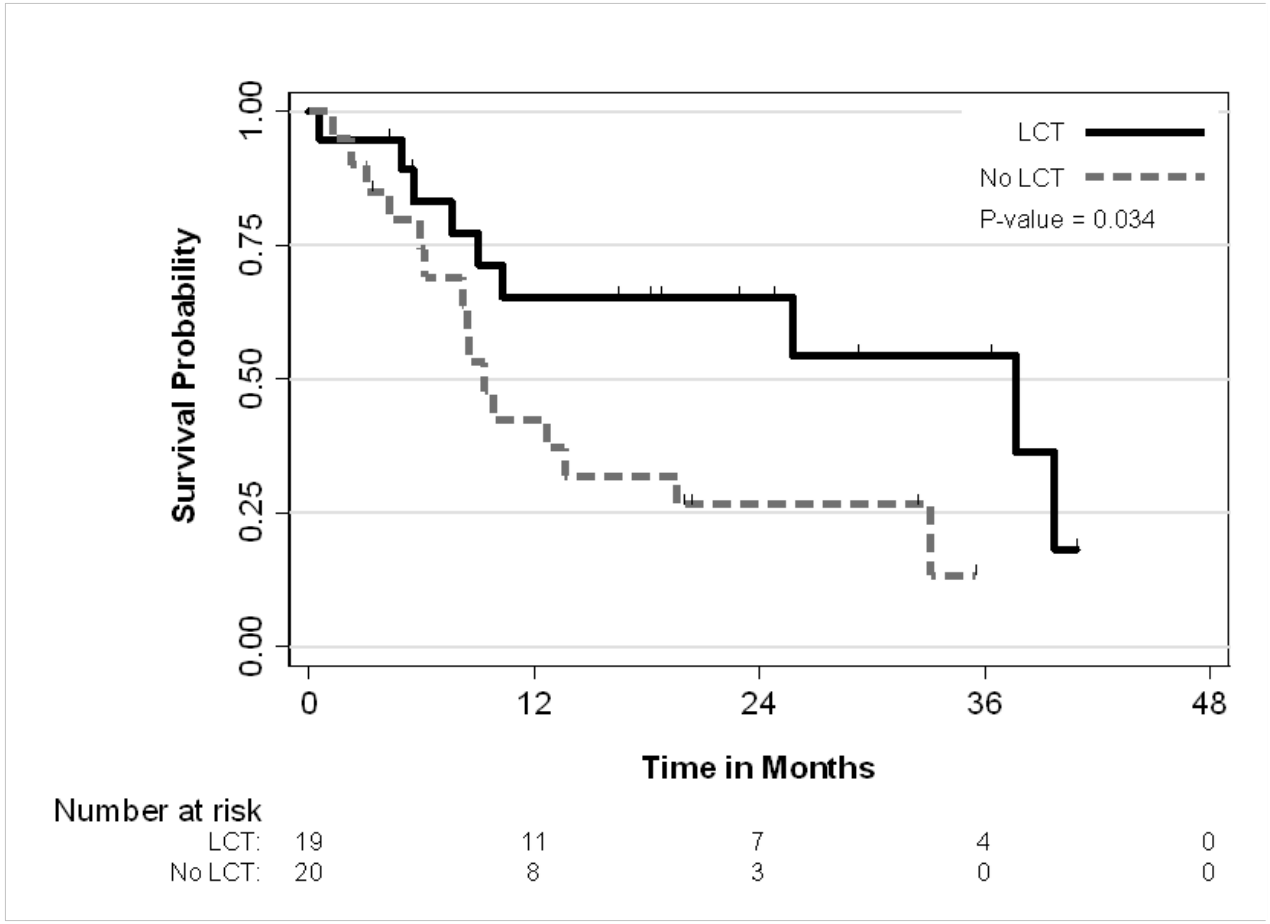
No additional Grade 3 or higher adverse events in either arm

Overall Survival



Median 17.0 months MT/O [HR=0.40, 95% CI 10.1–39.8, *P*=0.017] vs. 41.2 months LCT [95% CI 18.9–not reached]

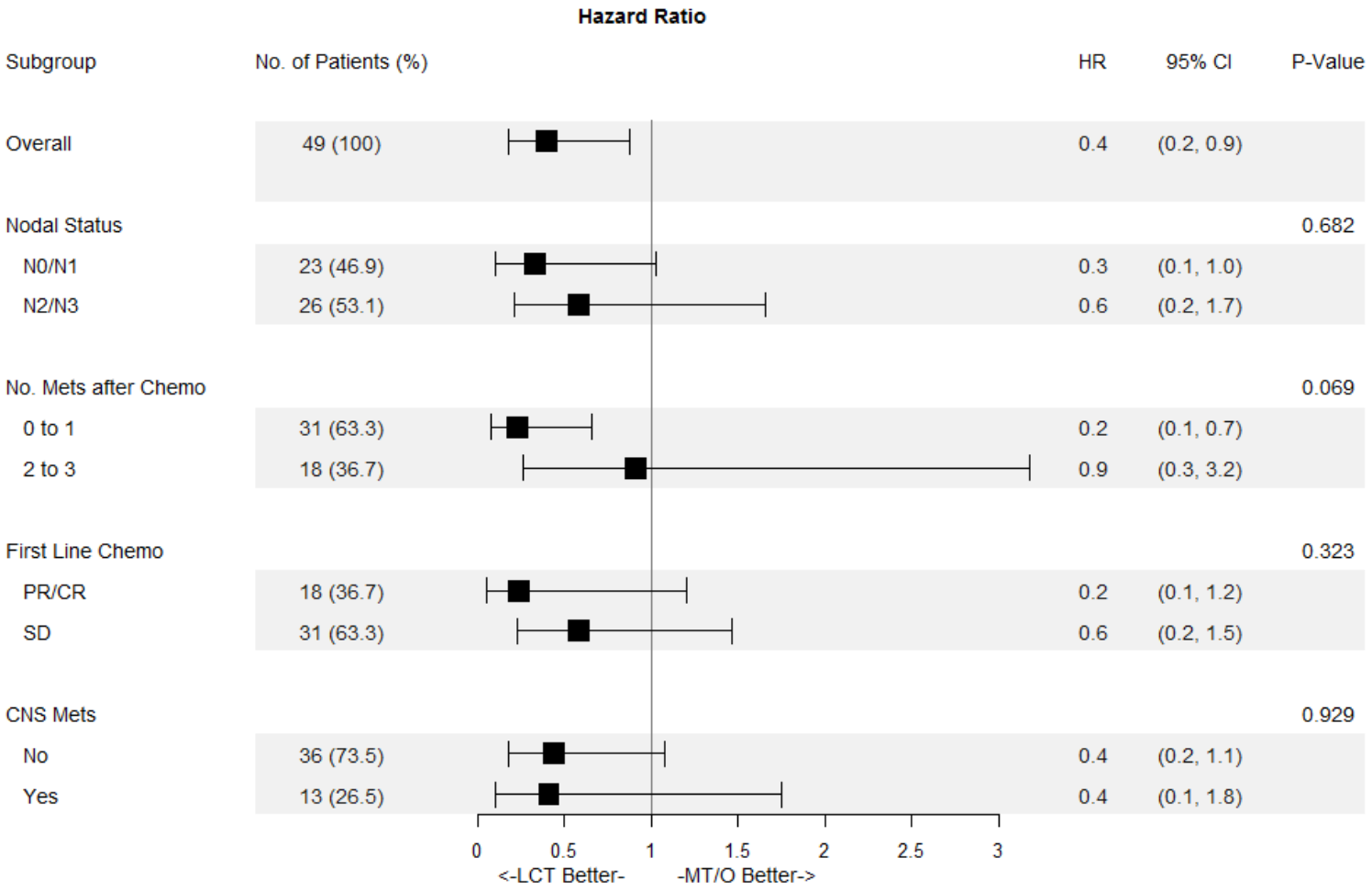
Survival After Progression



Median 37.6 months LCT [95% CI 9.0-not reached] vs. 9.4 months MT/O [95% CI 5.9–19.6, *P*=0.034]

Patients that received complete LCT at the time of progression (in either arm) did better than those that did not!

Subgroup Analysis of Prognostic Factors on OS



Limitations/Conclusions

Limitations included stopped early/small size, heterogeneity of maintenance arm treatments, no immunotherapy

1) With long-term follow-up, compared to MT/O, LCT in patients with oligometastatic disease who do not progress after front-line systemic therapy:
   - Improves PFS
   - Is associated with an improvement in OS
2) LCT with acceptable tolerance, long-term follow-up did not reveal further high-grade toxicity in either arm
3) Survival after progression improved in LCT arm
   - Complete LCT at the time of progression may improve OS compared to patients that do not receive this treatment
4) Identified patient subgroups that appeared to benefit from LCT

   Less nodal burden, less metastases, no CNS metastases

Expert Perspective

Dr. Catherine Park, MD, FASTRO
University of California, San Francisco

Q & A

Please use the “Question” tab in GoToWebinar to submit your questions.

Interview Requests and Other Questions

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Sunday-Tuesday, 7am-5pm CT; Wednesday, 7am-12pm CT

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