UNIVERSITY of WASHINGTON

Metastatic breast cancer

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Aug 18, 2020

Disclosures

I have nothing to disclose.

Learning objectives

- To review the appropriate diagnostic workup for metastatic breast cancer (MBC)
- To review current guidelines for the treatment and monitoring of metastatic breast cancer
- To understand recent key developments in drugs to treat MBC

Lecture structure

- Case based
- NCCN-guideline focused
- Emphasis on standard therapies

Locally recurrent disease: Case 1

60 yo patient with a history of stage IIIA ER/PR positive, HER2 negative L breast cancer treated 6 years prior with neoadjuvant anthracycline-based chemotherapy, lumpectomy with sentinel lymph node biopsy (SLNB), radiation and 5 years of an aromatase inhibitor, presents with an expanding mass near her lumpectomy scar. Biopsy demonstrates invasive ductal carcinoma with similar histology to her prior tumor. Your next step is:

A) Mastectomy with (SLNB)
B) Mastectomy with axillary lymph node dissection (ALND)
C) Chemotherapy
D) A and C
E) B and C

Locally recurrent disease: Case 1

- Answer: B Mastectomy with ALND
  (Of note, actual real first step: Probably restaging)
- Patients with prior mastectomy should undergo surgical resection (if possible) and radiation to the chest wall and supraclavicular area (if the chest wall was not previously irradiated). Benefit of repeat SLN biopsy after mastectomy is unknown, not encouraged.
- Patients with prior breast-conserving surgery and radiation therapy with prior SLNB: NCCN panel consensus recommendation is mastectomy and level I/II axillary dissection.

Locally recurrent disease: Chemotherapy?

- CALOR trial: Studied effect of chemotherapy after complete resection in patients with isolated locoregional recurrence
- Adjuvant chemotherapy improved DFS and OS. Five-year OS 88% vs. 76%, *P* .024 in chemo vs non-chemo group.
- Benefit of adjuvant chemotherapy greater in hormone-receptor negative disease: DFS = 67% versus 35% versus in ER-positive disease, DFS 70% versus 69% (HR, 0.94; 95% CI, 0.47–1.89).

Aebi S, Gelber S, Anderson SJ, et al. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. Lancet Oncol 2014;15:156-163

Diagnosis and workup: Case 2

A 52 yo woman presents with a self-detected R breast lump. Diagnostic mammogram demonstrates a 4 cm R breast mass at 3:00, N+8. MRI shows 5.1 cm unifocal mass, and 3 suspicious-appearing axillary lymph node. Biopsy reveals grade 2 invasive lobular carcinoma, ER+ (95%), PR+ (75%), HER2 1+. She inquires about next steps. You advise:

A.) Neoadjuvant chemotherapy with ddAC/T

B.) Surgical resection with SLNB

C.) PET scan

D.) Biopsy to evaluate extent of disease

E.) CT C/A/P and bone scan

Diagnosis and workup: Staging scans

- Answer: E.
  NCCN guidelines: “For patients presenting with disease confined to the breast (stage I to II) the NCCN Panel does not recommend routine systemic imaging in the absence of signs or symptoms suspicious for metastatic disease. According to the panel, additional tests may be considered in patients who present with locally advanced (T3 N1-3 M0) disease and in those with signs or symptoms suspicious for metastatic disease.”

Diagnosis and workup: PET vs. CT/bone scan

- Why not a PET?
- The non-diagnostic CT scans used for PET under-evaluate the lungs and the liver compared with contrast-enhanced diagnostic CT scans.
- FDG PET/CT is optional, may be most helpful when other imaging is equivocal

Diagnosis and workup: Case 2, con't

The patient undergoes CT C/A/P and bone scan, which reveal multiple lesions in liver, the largest measuring 2 cm, and diffuse metastases to the spine and axial skeleton. The patient endorses lower back pain x 2 months which you suspect corresponds to an L3 lesion. She inquires about next steps. You advise:

A) Initiate treatment with a CDK 4/6 inhibitor and endocrine therapy
B) MRI spine w/ referral to radiation oncology for RT to L3
C) Liver biopsy
D) L3 biopsy

Diagnosis and workup: Biopsy

- Answer: C, Liver biopsy
- Metastatic disease should be biopsied at first presentation or at first recurrence in order to confirm the diagnosis and determine tumor histology and molecular profile.
- Soft tissue tumor biopsy preferred over bone sites as demineralization procedures degrade proteins and DNA needed for IHC, FISH and molecular assays.
- Retest ER, PR and HER2 status: Primary and metastatic sites can be discordant.

Diagnosis and workup: Markers

- Molecular/IHC markers for MBC (i.e., not standard for early stage) w/ clinical significance: PIK3CA, MSI (rare), NTRK, TMB, PDL1, possibly ERBB2, others (FGFR2, AKT)
- Genetic testing: Germline BRCA1/2 mutations should be assessed in all patients with recurrent or metastatic breast cancer as positive results have implications for therapy

Treatment: Case 2, con't

This patient's biopsy of her largest liver mass returns with the same histology as index tumor (ER/PR+, HER2-). Molecular analysis reveals a PIK3CA mutation. You advise:

A) Tamoxifen

B) CDK 4/6 inhibition plus endocrine therapy

C) Alpelisib plus fulvestrant

D) Capecitabine

Treatment: First line therapy for HR+ disease

- Answer: B, CDK4/6 inhibition plus endocrine therapy.
- Aromatase inhibitor in combination with CDK4/6 inhibition is a preferred first-line treatment.
- Trials of all three medications in this class have demonstrated improved PFS over AI alone: MONALEESA-2 and -7 (ribociclib), PALOMA-2 (palbociclib), MONARCH-3 (abemaciclib).
- Ribociclib has also shown an OS benefit
- Only MONALEESA 7 looked at premenopausal patients, but all these agents are given to young patients along with ovarian suppression or BSO.

Treatment for HR+ MBC: Similarities and differences within the CDK4/6 class

- All CDK 4/6 inhibitors exhibit hematologic toxicities (neutropenia, leukopenia), GI toxicities, elevated LFTs, increased risk of pulmonary embolism, prolonged QTc
- Ribociclib: Higher rate of QTc prolongation, administration requires cardiac monitoring
- Abemaciclib: higher incidence of both all-grade and Grade 3/4 gastrointestinal toxicities, may (?) have some blood/brain barrier penetration, and can be given as monotherapy.

Sammons SL et al, Curr Cancer Drug Targets. 2017 Sep; 17(7): 637–649.

Treatment for HR+ MBC: Other first-line therapies

- Fulvestrant monotherapy. (Improved time to progression was seen with fulvestrant compared to anastrazole, FIRST study)
- Fulvestrant + AI (mixed trial results, FACT and SoFEA)
- Fulvestrant + CDK4/6 inhibitor
- Monotherapy with endocrine agents

Ellis MJ, Llombart-Cussac A, Feltl D, et al. J Clin Oncol 2015;33:3781-3787.
Bergh J, Jonsson PE, Lidbrink EK, et al. J Clin Oncol. 2012;30:1919-1925
Johnston SR, Kilburn LS, Ellis P, et al. Lancet Oncol 2013;14:989-998.

Treatment: Case 2, con't

Nine months later, scans reveal that the patient's tumor has progressed, demonstrating enlarging mediastinal nodes and new bone metastases. As a next line of therapy you choose:

> Fulvestrant monotherapy

> Exemestane + everolimus

> Targeted therapy

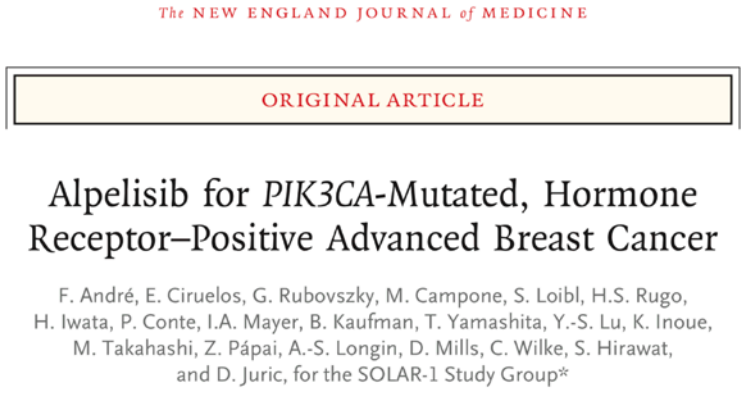
> Any of the above

Treatment: Case 2, con't

- Answer: D, any of the above. Acceptable second line regimens for HR+ MBC include:
  - Fulvestrant monotherapy
  - Fulvestrant + CDK 4/6 inhibitor
  - Exemestane + everolimus (only approved FDA second line)
  - Targeted therapy when appropriate. In this patient, many would choose a targeted therapy given her PIK3CA mutation.

Second line therapy for HR+ MBC: Targeted agents

- *PIK3CA* mutations: ~40% of patients with hormone-receptor positive, HER2-negative breast cancer
- PFS=11.0 months in the alpelisib–fulvestrant group, vs 5.7 months in the placebo–fulvestrant group
- FDA approval: May 24, 2019, along with approval for companion diagnostic
- For ER/PR+ patients with advanced breast cancer following progression on or after endocrine-based treatment



Treatment: Case 3

45 year old woman with a history of stage IIIB ER/PR negative, HER2+ breast cancer presents with metastatic recurrence to liver and bone three years out from curative therapy. Liver biopsy reveals histology similar to her original tumor. Her performance status is ECOG 0-1. You recommend:

A) HER2 directed monotherapy
B) Taxane + trastuzumab
C) Taxane + trastuzumab and pertuzumab

Treatment: Case 3

- Answer: C, Taxane + trastuzumab and pertuzumab.
- CLEOPATRA: Compared efficacy and safety of docetaxel + trastuzumab and pertuzumab versus docetaxel versus docetaxel + trastuzumab as first-line treatment women with HER2-positive metastatic breast cancer. The addition of pertuzumab resulted in improvement in PFS (median, 18.5 versus 12.4 months. At 30 months: Statistically significant improvement in OS for pertuzumab-containing regimen.

Baselga J, Cortes J, Kim SB, et al. N Engl J Med 2012;366:109- 119.

Treatment for HER2+ MBC: Which taxane?

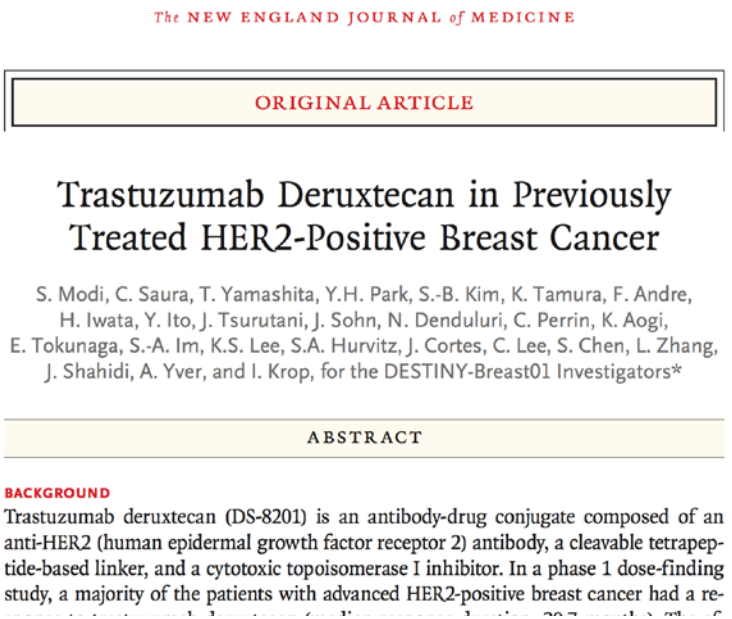
- PERUSE study: Patients with advanced HER2-positive breast cancer received docetaxel, paclitaxel or nab-paclitaxel with trastuzumab + pertuzumab: Median PFS comparable among agents. Paclitaxel demonstrated more neuropathy (31% vs. 16%) than docetaxel, but less febrile neutropenia (1% vs. 11%) and mucositis (14% vs. 25%).
- NCCN recommends a taxane plus pertuzumab and trastuzumab in first line: Docetaxel + HP is a category 1, paclitaxel + HP is a category 2A recommendation.

Treatment for HER2+ MBC: Other regimens

- TDM-1, a drug antibody conjugate, trastuzumab to the microtubule-inhibitory agent DM1 (first line, MARIANNE study, has activity in second line as well, EMILIA)
- Trastuzumab + paclitaxel +/- carboplatin, docetaxel, vinorelbine, capecitabine
- Lapatinib + capecitabine or trastuzumab
- HER2 directed agents + anthracycline and cyclophosphamide CONTRAINDICATED (27% rate of cardiac dysfunction)

Treatment for HER2+ MBC: New agents

- Patients with HER2 positive disease previously treated with trastuzumab, untreated or symptomatic brain metastases excluded
- Primary endpoint was overall response rate: 60.9% (95% CI, 53.4 to 68.0), of which 6.0% had a complete response. Disease control rate was 97.3% (95% CI, 93.8 to 99.1),



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop, for the DESTINY-Breast01 Investigators*

ABSTRACT

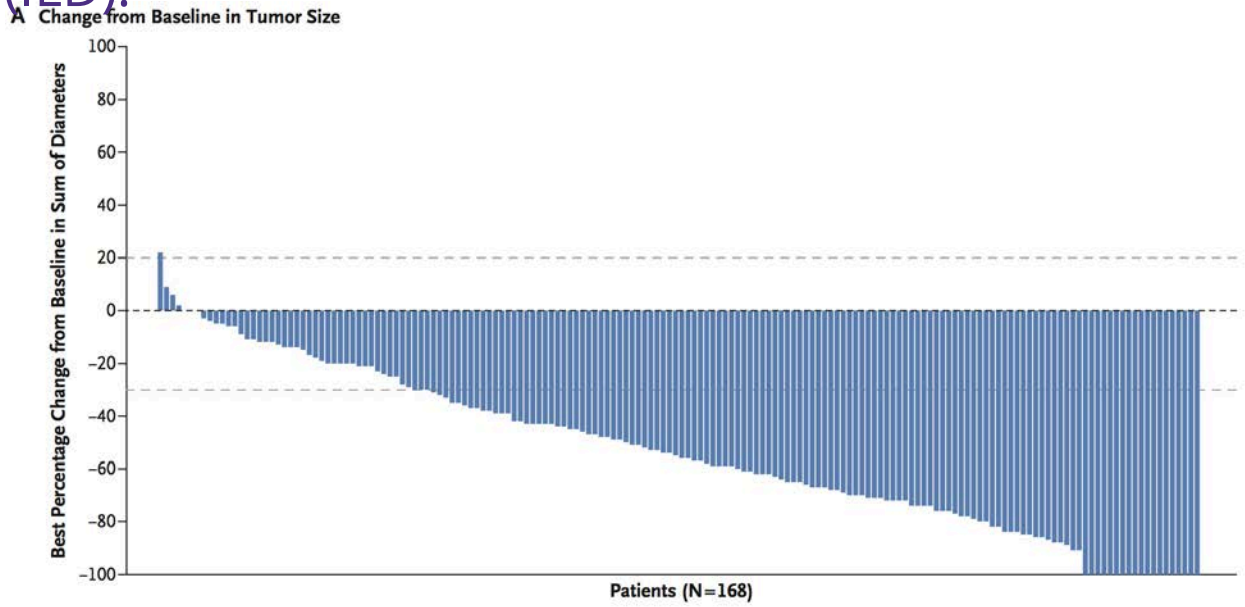
BACKGROUND

Trastuzumab deruxtecan (DS-8201) is an antibody-drug conjugate composed of an anti-HER2 (human epidermal growth factor receptor 2) antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor. In a phase 1 dose-finding study, a majority of the patients with advanced HER2-positive breast cancer had a re-

Modi S et al. N Engl J Med 2020;382:610-21.

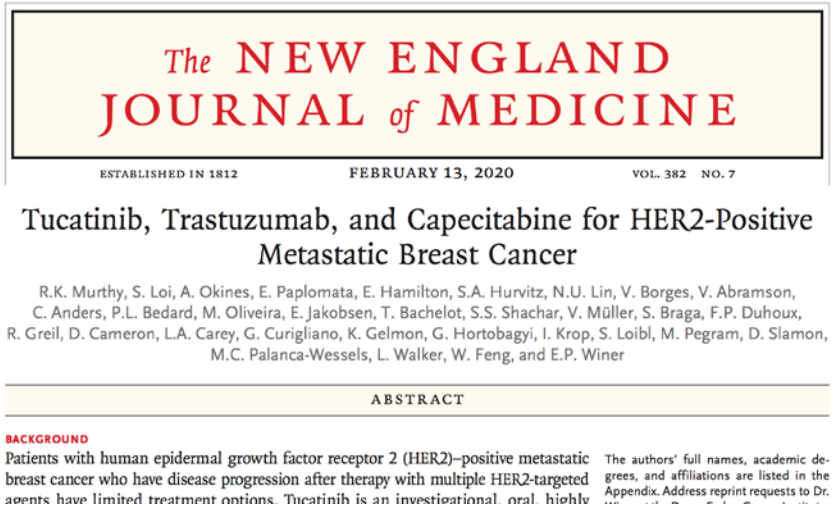
Treatment for HER2+ MBC: New agents

- FDA grants accelerated approval in Dec. 2019 for patients with HER2+ disease after two prior lines of therapy
- 13.6% of patients developed interstitial lung disease, leading to at least four deaths. Agent is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).



Treatment for HER2+ MBC: New agents

- HER2CLIMB: Tucatinib + trastuzumab + capecitabine
- Patients with HER2+ disease with progression on two prior lines of therapy
- PFS for Tucatinib combo vs. placebo combo 7.8 vs. 5.6 months ($p<0.001$)
- FDA approval in April 2020 for use after ONE prior line of therapy



The NEW ENGLAND JOURNAL of MEDICINE

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Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

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ABSTRACT

BACKGROUND

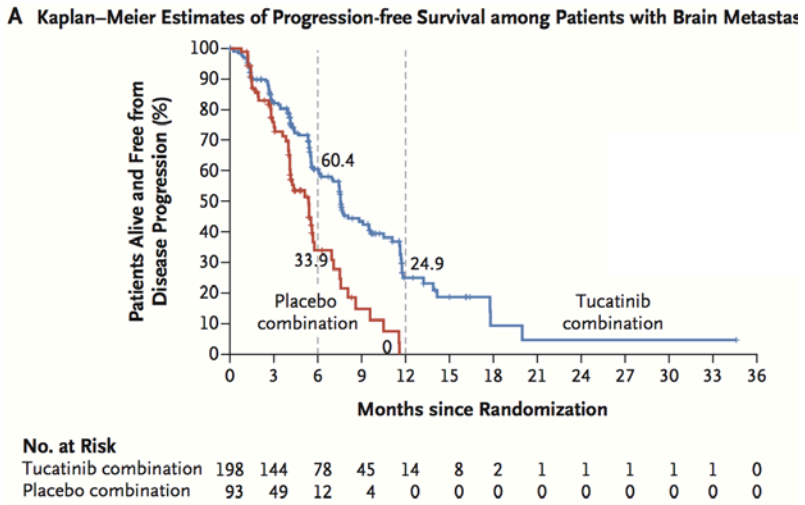
Patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer who have disease progression after therapy with multiple HER2-targeted agents have limited treatment options. Tucatinib is an investigational, oral, highly

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr.

Murthy et al. N Engl J Med 2020; 382:597-609

Treatment of HER2+ MBC: New agents

- Patients with brain metastases included unless in need of immediate treatment. Patients with untreated brain mets >2 cm enrolled with approval from the medical monitor. Patients with leptomeningeal disease were excluded.
- Risk of CNS progression reduced by 68% in patients with brain metastases, with a median CNS-PFS of 9.9 vs 4.2 months.



Murthy et al. N Engl J Med 2020; 382:597-609

Treatment for HER2+ MBC: What about HR+ disease?

- PERTAIN trial: Postmenopausal women assigned to first-line pertuzumab plus trastuzumab and an AI or trastuzumab plus an AI, with a ~3 month improvement in PFS for triplet combo
- If patient is treated initially with chemotherapy and trastuzumab plus pertuzumab, and the chemotherapy is stopped, endocrine therapy may be added.
- NCCN includes other trastuzumab combinations (e.g., fulvestrant or tamoxifen), but should be considered only after chemotherapy plus HER2-directed therapy or in some patients with indolent disease

Rimawi M et al. J Clin Oncol 2018;36:2826-2835.

Treatment: Case 4

A 58 year old woman with a large, clinically node positive breast tumor; biopsy demonstrates a high-grade invasive ductal carcinoma, ER/PR/HER2 negative. Aside from moderate axillary pain, she is asymptomatic. What will be the most important factor in choosing her first therapy?

A) Mutations on molecular testing
B) Additional immumohistochemistry testing
C) Presence of visceral disease
D) Brain MRI results

Treatment for mTNBC: Immunotherapy

- Answer: B, Additional immumohistochemistry testing (i.e., PDL1)
- IMpassion 130: Patients with treatment-naïve TNBC randomized to atezolizumab plus nab-paclitaxel vs. placebo plus nab-paclitaxel.
- At a median follow-up of 12.9 months, PFS was 7.2 vs. 5.5 months for treatment arm vs. placebo, also a trend towards better OS (not significant).

Schmid P et al. N Engl J Med 2018; 379:2108-2121

Treatment for mTNBC: Immunotherapy

- In patients with PD-L1-expressing tumors, PFS was 7.5 vs. 5 months and and OS (25 vs. 15.5 months; HR 0.62, 95% CI 0.45-0.86).
- In March 2019 FDA grants accelerated approval for atezolizumab + nab-paclitaxel in the first line for patients with PD-L1 expressing tumors; also approves the VENTANA PD-L1 Assay as the companion diagnostic for identifying PD-L1 expression.

Schmid P et al. N Engl J Med 2018; 379:2108-2121

Treatment for mTNBC: Chemotherapeutic agents

- Taxanes (paclitaxel), anthracyclines (doxorubicin and liposomal doxorubicin), anti-metabolites (capecitabine and gemcitabine), microtubule inhibitors (eribulin and vinorelbine), platinum agents
- Single agent chemotherapy → Lower response rates and time to progression, but multi-agent chemo → more toxicity and no overall survival benefit.

Treatment for mTNBC: Case 5

A 46 yo woman with a BRCA1 mutation transfers care to you. She has breast cancer metastatic to her lungs, pleura, liver, and mediastinum, ER/PR/HER2 neg. Her disease has progressed on paclitaxel. PDL1 is negative. She feels well, has few symptoms, is still working. What do you recommend next?

A) Capecitabine

B) Olaparib

C) Ixabepilone

D) Atezolizumab + nab paclitaxel

Treatment for mTNBC: BRCA mutations

- OlympiAD trial (NEJM 2017): Among patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation, olaparib monotherapy provided a significant benefit over standard therapy; median progression-free survival was 2.8 months longer and the risk of disease progression or death was 42% lower with olaparib monotherapy than with standard therapy.
- FDA has approved olaparib in advanced breast, ovarian, fallopian tube, peritoneal, and pancreatic cancer for patients with germline BRCA mutations.
- Other PARPi w/ FDA approval: rucaparib, talazoparib, niraparib (not yet approved for brea

Robson M et al. N Engl J Med 2017; 377:523-533

Treatment: Bone metastases

- In metastatic bone disease, bisphosphonate treatment is associated with fewer skeletal-related events (SREs), fewer pathologic fractures, and lower need for radiation and surgery to treat pain.
- No impact on OS
- Dosing can be Q4 vs Q12 weeks w/ no significant difference in SREs in multiple trials. Reminder: Q6 months is nonmetastatic dosing for osteoporosis.

Treatment: Role for surgery and radiation

- Multiple studies demonstrating no survival advantage for resection of breast tumor in setting of metastatic disease (exception: Turkish Federation MF07-01 trial, but groups were arguably not well balanced)
- Palliative role for surgery in case of painful breast tumors, impending fractures.
- Palliative role for radiation in pain control, stabilization of bone tumors, treatment of CNS disease

Surveillance: Principles of monitoring MBC

- Monitoring includes periodic assessment of symptoms, physical exam, lab tests, imaging, and blood biomarkers
- Same imaging modality should be used consistently to allow “apples to apples” monitoring
- Optimal frequency of testing is uncertain
- Frequency of monitoring can be reduced in patients who have long-term stable disease.

Thanks!