

Clinical Updates and Issues: Metastatic Breast Cancer

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Faculty Biography

Emily Olson, APRN, CNP, MSN, OCN is Nurse Practitioner, Division of Medical Oncology, at the Mayo Clinic in Rochester, Minnesota. She is also an Instructor of Oncology at the Mayo Clinic College of Medicine.

Ms. Olson received a Master of Science in Nursing from Winona State University in Winona, Minnesota. She completed the Family Nurse Practitioner Residency Program at Mayo Clinic School of Health-Related Sciences, Mayo Clinic College of Medicine in Rochester, Minnesota.

She currently focuses her clinical practice on caring for men and women with both early and late stage breast carcinomas and has a special interest in palliative medicine as well.

Ms. Olson is a member of several professional societies and services, including Sigma Theta Tau, Oncology Nursing Society, and the Association of Southeastern Minnesota Nurse Practitioners.



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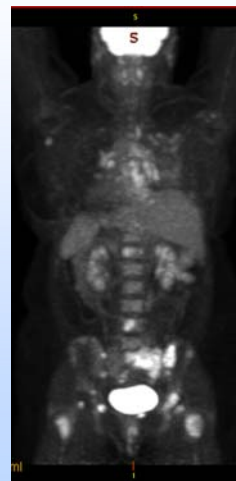
Overview

- Initial workup for metastatic breast cancer
- Updates in treatment of metastatic
 - Hormone Positive BC
 - Her2 Positive BC
 - Triple Negative BC
- Prevention of Skeletal Related Events (SRE)



My patient has an abnormal PET/ CT scan, now what?

- 51 y/o with history of T2, N0 ER/ PR+, HER2- BC 2005 (dx at age 41).
- Completed 5 years of adjuvant Tamoxifen in 2010.
- Premenopausal
- Reports new, progressive hip pain.

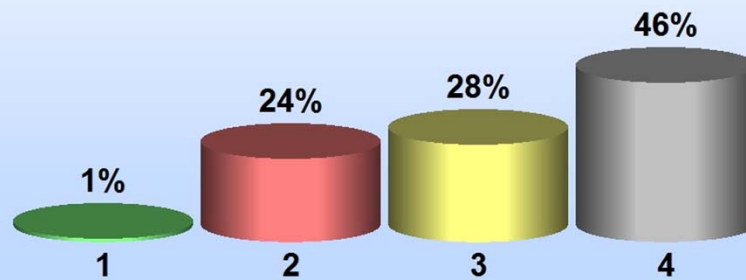


February 2015



My patient has an abnormal PET/ CT scan, now what?

1. Contact Hospice
2. Treat with carboplatin + paclitaxel, 3 weeks on, 1 week off. Plan to restage with PET/ CT in 3-4 cycles.
3. Start on aromatase inhibitor with concurrent goserelin injection with plan to restage with PET/ CT in 3 months.
4. Biopsy concerning lesion



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My patient has an abnormal PET/ CT scan, now what?

- Tissue is the issue
 - ER/ PR/ Her2/ Ki67
 - 15-30% of recurrences will have loss of ER
 - 10-15% will have change in HER2



Foukakis et al., 2012

Choosing Treatment

- Need to consider
 - Hormone receptor and HER2 status
 - Evidence of visceral crisis
 - Patient goals



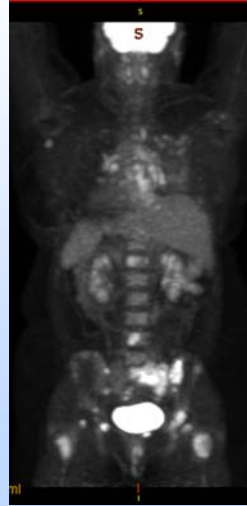
Estrogen Sensitive MBC



Estrogen Positive MBC

Our patient:

- Premenopausal
- Bone bx
 - ER positive >75%
 - PR positive >75%
 - Her2 negative 1+
 - Ki 67 12%



Estrogen Positive MBC



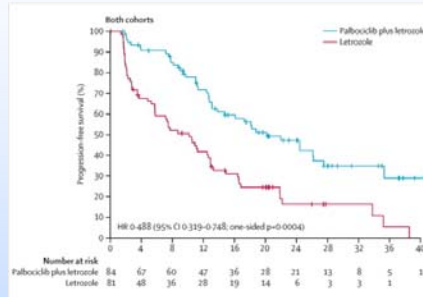
Treatment Plan:

1. Bilateral salpingo-oophorectomy
2. Started letrozole + palbociclib
3. zoledronic acid 4mg IV q 3 months for prevention of skeletal related events (SRE)



Estrogen Positive MBC

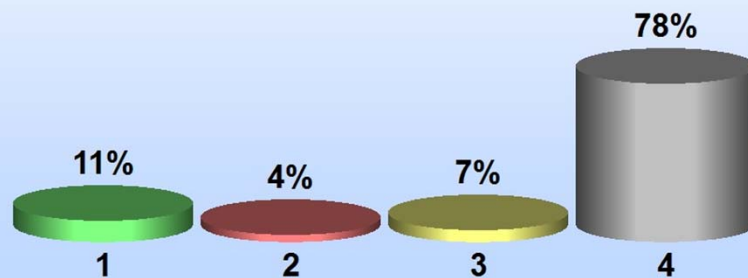
- 1st Line: palbociclib +letrozole
 - PALOMA- 1 trial
 - CDK 4/6 inhibitor
 - Postmenopausal
 - Non steroidal AI vs. non steroidal AI + palbociclib
 - 2.5mg letrozole QD
 - 125mg PO palbociclib 21 days on, 7 off
 - MPFS extended from 10.2 to 20.2 months
 - Study not powered for OS
 - Accelerated approval granted by FDA



Finn et al., 2015

Your patient is prescribed palbociclib and letrozole for first line therapy for metastatic estrogen positive breast cancer. You should counsel her on which of the following side effects when considering both medications.

1. Non febrile neutropenia
2. Fatigue
3. Vasomotor symptoms
4. All of the above



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Palbociclib Nursing Considerations

Most common all-cause adverse events that occurred in at least 10% of patients (safety population)

	Palbociclib plus letrozole (n=83)			Letrozole (n=77)		
	Grade 1 -2	Grade 3	Grade 4	Grade 1 -2	Grade 3	Grade 4
Any adverse event	19 (23%)	49 (59%)	14 (17%)	49 (64%)	16 (21%)	0
Neutropenia	17 (20%)	40 (48%)	5 (6%)	3 (4%)	1 (1%)	0
Leucopenia	20 (24%)	16 (19%)	0	2 (3%)	0	0
Fatigue	30 (36%)	2 (2%)	2 (2%)	17 (22%)	1 (1%)	0
Anaemia	24 (29%)	4 (5%)	1 (1%)	4 (5%)	1 (1%)	0
Nausea	19 (23%)	2 (2%)	0	9 (12%)	1 (1%)	0
Arthralgia	18 (22%)	1 (1%)	0	10 (13%)	2 (3%)	0
Alopecia	18 (22%)	NA	NA	2 (3%)	NA	NA

... to name a few...



Finn et al., 2015

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Palbociclib Nursing Considerations

- Non Febrile Neutropenia
 - CBC
 - Cycles 1 & 2 days 1 and 14.
 - Day 1 of each cycle.
 - Day 1 & 14 of any cycle with dose adjustment
- Fatigue
 - Cumulative
 - May require dose reduction
- Hair Thinning
 - Anticipatory Guidance
 - Due to arrest of cell cycle
- Drug-Drug Interactions
 - Metabolized through CYP3A pathway
 - Pharmacy consult recommended before initiation



Palbociclib Dose Adjustments- Non- Hematologic

Table 3. Dose Modification and Management – Non-Hematologic Toxicities

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade ≥ 3 non-hematologic toxicity (if persisting despite medical treatment)	Withhold until symptoms resolve to: <ul style="list-style-type: none"> • Grade ≤ 1; • Grade ≤ 2 (if not considered a safety risk for the patient) Resume at the next lower dose.

Grading according to CTCAE Version 4.0.



http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf

Palbociclib Dose Adjustments- Non- Hematologic

Table 1. Recommended Dose Modification for Adverse Reactions

Dose Level	Dose
Recommended starting dose	125 mg/day
First dose reduction	100 mg/day
Second dose reduction	75 mg/day*

*If further dose reduction below 75 mg/day is required, discontinue the treatment.



http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf

Palbociclib Dose Adjustments- Hematologic

Table 2. Dose Modification and Management^a – Hematologic Toxicities

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade 3 ^b	No dose adjustment is required. Consider repeating complete blood count monitoring one week later. Withhold initiation of next cycle until recovery to Grade ≤ 2 .
Grade 3 ANC (<1000 to $500/\text{mm}^3$) + Fever $\geq 38.5^\circ\text{C}$ and/or infection	Withhold palbociclib and initiation of next cycle until recovery to Grade ≤ 2 ($\geq 1000/\text{mm}^3$). Resume at next lower dose.
Grade 4 ^b	Withhold palbociclib and initiation of next cycle until recovery to Grade ≤ 2 . Resume at next lower dose.

^aGrading according to CTCAE Version 4.0.



Adapted from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf

Estrogen Positive MBC



“Complete metabolic response of all skeletal and nodal foci.”

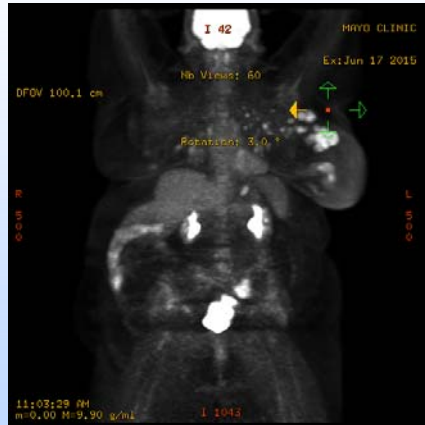
Patient continues on letrozole + palbociclib to date



June 2015

Estrogen Positive MBC

- 54 y/o, premenopausal
- Dx with MBC to lung 2014, ER/ PR +, Her2 –
- Premenopausal
- 2014 Tamoxifen
- 2015 progression of lung mets, new bone and adrenal mets

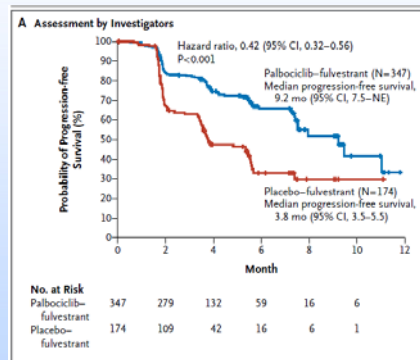


June 2015



Estrogen Positive MBC

- 2nd line: palbociclib
 - PALOMA- 3 trial
 - CDK 4/6 inhibitor
 - Postmenopausal
 - Fulvestrant (F) vs. F + palbociclib
 - 500mg F C1D1&14, C2D1, then q 28 days
 - 125mg PO palbociclib 21 days on, 7 off
 - MPFS extended from 3.8 to 9.2 months
 - OS data not mature



Turner et al., 2015.



Palbociclib Nursing Considerations

Most common all-cause adverse events that occurred in at least 10% of patients (safety population)

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Finn et al., 2015

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Adapted from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf

Estrogen Positive MBC

Treatment Plan:

1. OFS with goserelin
2. fulvestrant + palbociclib
3. Continued zoledronic acid 4mg IV Q 3 months

Improvement in FDG of skeletal lesions, improvement in size of breast and adrenal lesion, mixed response in pulmonary nodules



September 2015



Her2 Positive MBC



HER2 Positive MBC

- 72 y/o
- Dx MBC ER-/PR-, HER2+ to liver, bone, lung, adrenals
- No history of previous BC treatment



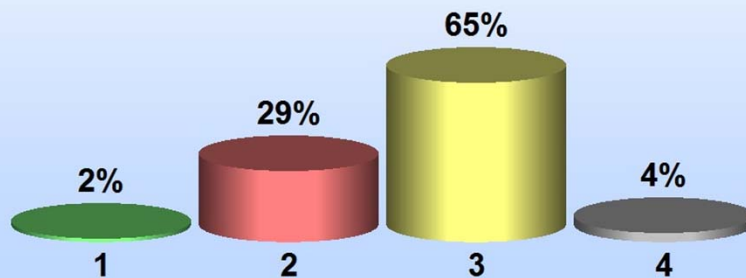
May 2014



HER2 Positive MBC

What would you choose to treat her with first?

1. Paclitaxel weekly 3 weeks on, 1 week off
2. Paclitaxel + trastuzumab (T) weekly for 12 weeks then trastuzumab q3 weeks ongoing
3. Docetaxel+trastuzumab (T)+pertuzumab (P) q 3 weeks for 6 cycles followed by P+T q 3 weeks ongoing
4. Capecitabine 2 weeks on, 1 week off + lapatinib daily



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HER2 Positive MBC

- 1st line: docetaxel (D) + T+ P q 3 weeks x 6, then T+P q3 weeks ongoing
 - Cleopatra: double blind placebo controlled
 - D+T vs D+T+P
 - PFS 12.4 mo vs. 18.5 mo ¹
 - PFS also improved when stratified by neoadjuvant/ adjuvant treatment
 - OS 40.8 mo vs. 56.5 mo ²

1. Baselga et al., 2012.

2. Swain et al., 2015.



Docetaxel + Pertuzumab+ Trastuzumab Nursing Considerations

- Docetaxel ¹
 - 75-100mg/m²
 - Neutropenia
 - Alopecia
 - Capillary Leak Syndrome
 - Neuropathy
 - Nausea
 - **Diarrhea**
- Dual Anti-Her2
 - Trastuzumab ³
 - 8mg/ kg C1, 6mg/kg ongoing
 - Acute cardiac failure
 - Fatigue
 - Pertuzumab ²
 - 840 mg C1, 420mg ongoing
 - **Diarrhea**
 - Fatigue



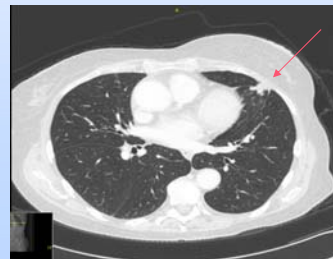
1. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020449s059lbl.pdf
2. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125409lbl.pdf
3. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf

HER2 Positive MBC

- Treatment complicated by colitis resulting in hospitalization
- Completed 4 cycles before omitting D
- Maintained on T+P for 18 months



July
2014

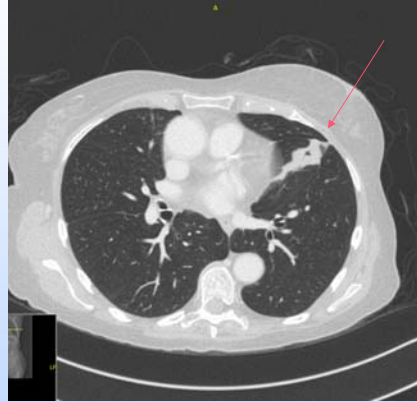


April
2015



HER2 Positive MBC

- Imaging December 2015
 - Progression in pulmonary metastasis
 - Patient maintaining ECOG 0

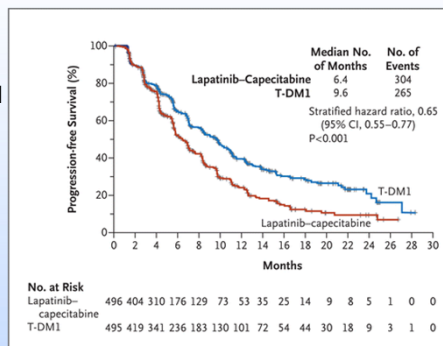


What do you do next?



Her2 Positive MBC

- 2nd line: ado-trastuzumab emtansine (T-DM1)
 - EMILIA Trial, Phase III
 - T-DM1 in previously treated Her2+ MBC vs lapatinib + capecitabine
 - Antibody-drug conjugate
 - Trastuzumab bound to emtansine molecules
 - Binds to tubules and prevents microtubule formation
 - PFS 9.6 vs. 6.4 mo
 - OS 30.9 vs. 25.1



Verma et al., 2012



T-DM1 Nursing Considerations

- Infusion reaction: 2% incidence
- Thrombocytopenia ~30% incidence
 - 12% grade 3 or 4 on EMILIA
 - Dose reduce at 25,000 PLTs
- Elevated transaminases
 - Improves with dose reduction
 - Reduce to 3.0mg/kg for AST >3x ULN & Bili >2x ULN per EMILIA
- Cardiomyopathy
 - **Black Box Warning**
 - TTE or MUGA pre 1st dose & every three months thereafter



Verma, 2012

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125427lbl.pdf

Metastatic Breast Cancer Triple Negative



Triple Negative MBC

Who's at risk?

- History of TNBC
- Residual disease following neoadjuvant chemotherapy¹
- BRCA1 > BRCA2²
 - NCCN recommends women ≤ 60 with TNBC be screened



2. NCCN Guidelines for Genetic/ Familial High Risk Assessment: Breast and Ovarian, 2016

1. Liedtke et al., 2008

Triple Negative MBC

- Treatment considerations
 - Disease symptoms
 - Visceral crisis
 - Patient goals
- No clear guidelines, research emerging
 - PDL1 inhibitors
 - Platinums
 - eribulin



Triple Negative MBC pembrolizumab

- Anti PD-1
 - Inhibits cell death and allows cancer cell invasion
 - pembrolizumab blocks the PD-L1 and PD-L2 receptors
 - Approved in melanoma, metastatic NSCLCa
 - Not yet approved in TNMBC
 - Phase 1b trial: Keynote-012, N=27
 - TNBC expressing PD-L1
 - Pretreated patients
 - ORR 18.5%; 1 CR, 4 PR, 7 SD
 - Phase 2 currently enrolling
 - TNBC
 - Stratification between pretreated and de novo stage IV disease
- ...More to come...



Buisseret et al., 2015

Nursing Considerations pembrolizumab

Reference package insert for dose modifications and management of the following:

- Inflammatory response
 - Think “-itis” (nephritis, pneumonitis, colitis, hepatitis, etc)
- Fatigue
- Nausea
- Anorexia
- Infusion related reaction



http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf

Triple Negative MBC Platinums

- TNT, phase III
 - First line
 - TN or BRCA 1/2 + (any ER/ PR/ Her2 status)
 - Q3 week docetaxel vs. q 3 week carboplatin
 - Only benefit of platinums seen in the BRCA population
 - ORR 68.8% vs 33%
 - PFS 6.8 mo vs 4.8 mo
 - Carboplatin arm
 - BRCA status drove response
 - + PFS 6.8 mo vs. -3.1 mo
 - Mechanism of action suspected to be secondary to difficult DNA repair in BRCA mutated lesions after exposure to platinums



Tutt et al., 2015.

Triple Negative MBC eribulin

Study 301, phase III

- eribulin superior to capecitabine in TNBC
 - No superiority in non-TN patients
 - Improvement in OS 14.4% vs. 9.4%
 - Consider *for first line treatment* of TNMBC



Kaufman et al., 2015.

Skeletal Related Events (SRE)



Skeletal Related Events

- May occur in up to 64% of individuals with bone metastasis who are untreated
- Prevention
 - zoledronic acid - 4mg IV
 - denosumab- 120mg SQ

Costa et al., 2008.



Skeletal Related Events zoledronic acid (ZA)

- OPTIMIZE-2
 - Randomized ZA
 - Monthly vs. quarterly following 12 monthly treatments
 - Powered for non-inferiority
 - Results: quarterly non-inferior to monthly
 - 22% vs. 23.3% SRE rate
 - Fewer AEs and no cases of ONJ
 - Similar rates of bone turnover

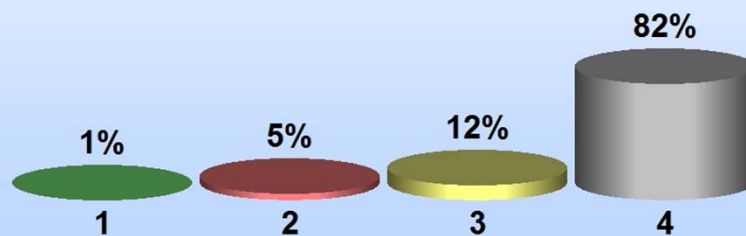


Hortobagyi et al., 2014

Skeletal Related Events

58 y/o female with metastatic breast cancer recently stubbed her R toe and developed acute, intractable R hip pain. She has been on zoledronate for 18 months along with an aromatase inhibitor. What disease related diagnosis should be in your differential based on her current treatment?

1. Fracture secondary to disease progression
2. Atypical femur fracture
3. Fracture secondary to aromatase inhibitor induced osteoporosis
4. All of the above



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Skeletal Related Events ZA Nursing Considerations

- Osteonecrosis of the Jaw (ONJ)
 - Fewer incidents with q3mo vs. q4 week¹
 - Those at risk
 - Poor dentition
 - Recent or upcoming extractions/ implants
 - Avoid invasive dental procedures
 - Pretreatment dental exam
- Atypical femur fractures
 - Uncommon, but real risk- approx 1.2%²
 - May present with prodromal thigh pain



1. Hortobagyi et al., 2014
2. Puhaindran et al., 2011
3. Jain TP, Thorn M. (2012). Atypical femoral fractures related to bisphosphonate therapy. Indian J Radiol Imaging 22, 178-181.

Skeletal Related Events ZA Nursing Considerations

- Renal impairment
 - Renally excreted
 - Pretreatment creatinine
 - Adjust dose for CC <60
 - Do not administer with CC <30
 - Hydration day of and day following treatment
- Arthralgia
 - Most common after first treatment
 - Premedicate with OTC analgesics and prn
- Encourage Ca & Vit D Supplementation



Skeletal Related Events denosumab

- RANK ligand inhibitor given every 4 weeks
 - Intercepts tumor secretion of RANKL
 - Reduces osteoclast formation
- Randomized controlled placebo trial
 - Measured uNTx/Cr to evaluate bone turnover
 - Goal to reduce uNTx/Cr by 90%
 - 120mg suggested to suppress 95% of individuals 90%



Lipton et al., 2007

Skeletal Related Events zoledronic acid vs. denosumab

- Randomized, double-blind, double-dummy active controlled study
- 4mg IV zoledronate vs. 120mg SQ denosumab
- Denosumab delayed for SRE by 23% over zoledronic acid
- Greater degree of uNTx/Cr suppression with denosumab (80% vs. 63%)
- OS, disease progression and AE rates were similar



Stopeck et al., 2010

Skeletal Related Events denosumab Nursing Considerations

- Hypocalcemia
 - Ca and Vit D supplementation suggested
 - Evaluate calcium before each injection
 - May result in treatment delays
- Osteonecrosis of the Jaw
 - ~2.0% incidence
 - Risk factors
 - Pretreatment dental exam
 - Avoid invasive dental procedures
- \$\$\$
 - Ongoing studies
 - Dynamic findings



Stopeck et al., 2010

Take Home Points

- Data is constantly emerging.
- Nurses are vital in the success of our patients.
- **Anticipatory Guidance. Anticipatory Guidance. Anticipatory Guidance.**



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