Non surgical treatment in metastatic breast cancer

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Outline

- Introduction
- Radiotherapy in metastatic breast cancer
  - Primary site
  - Metastatic site
- Chemotherapy in metastatic breast cancer

Introduction

- Approximately 10% of patients with newly diagnosed breast cancer have metastatic disease at presentation.

- Management of metastatic breast cancer focuses in systemic therapy

  - The underlying assumption is that such therapy will control the primary tumor sufficiently well for the remainder of patients life

Introduction

This concept is being re-evaluated because the clinical course of metastatic breast cancer is changing

- Improved survival of metastatic breast cancer
- Tendency towards decreasing metastatic disease burden at diagnosis
- Accumulating data suggesting that local therapy for the primary site may be beneficial

Role Of Radiotherapy in The Management of Metastatic Breast Cancer

Radiotherapy in metastatic breast cancer

Primary site

Metastatic site

Local management of primary site

The primary role of local treatment → **Palliation**

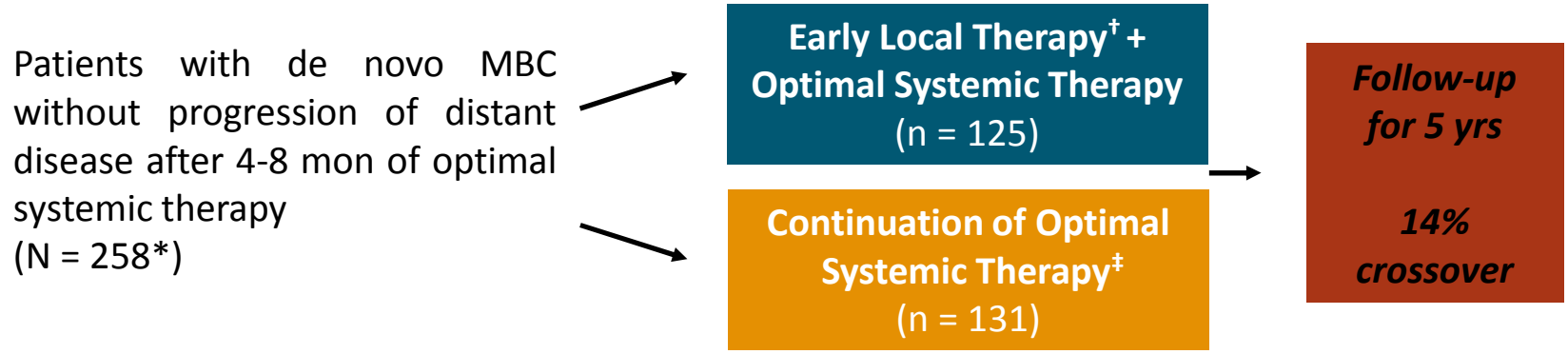
Control of local complication from the cancer:

Infection
Bleeding
Wound management

Role of radiotherapy to the primary site in asymptomatic patients

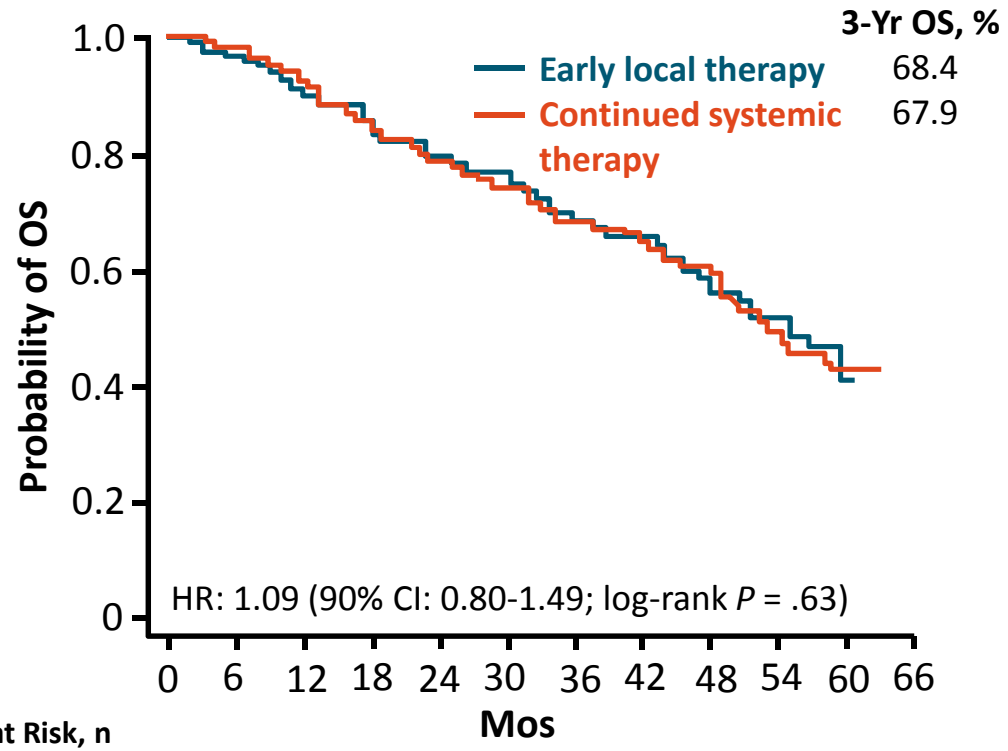
E2108: Study Design

- Randomized phase III trial (enrollment from 2011-2015)



- Primary endpoint: OS
- Secondary endpoint: Time to locoregional progression, HRQoL (by FACT-B TOI)

E2108: OS (Primary Endpoint)



Patients at Risk, n												
Early local therapy	124	111	103	97	91	85	75	70	54	36	8	2
Continued systemic therapy	129	125	115	105	93	87	77	71	58	40	12	3

- 121 deaths by December 2019 (80% of full information)
- Median f/u: 53 mos (range: 0-91)
- Median survival: 54 mos
- Also no statistical difference in Kaplan-Meier estimates of PFS (*P* = .40)

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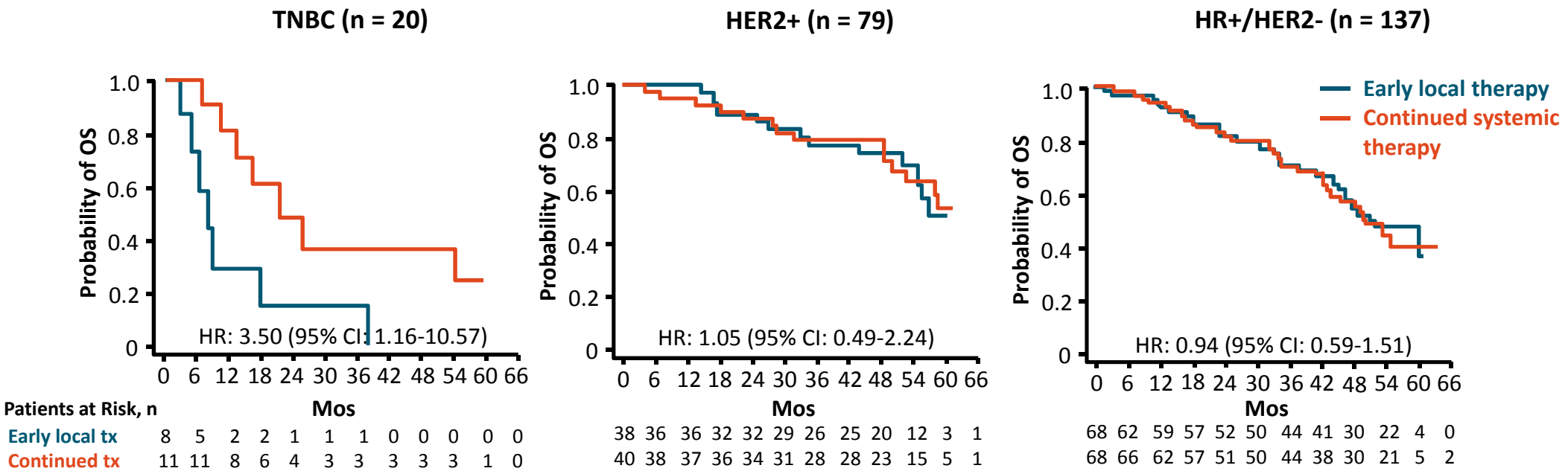
E2108: OS by Tumor Subtype



- Trend toward worse survival outcomes in patients with TNBC receiving early local therapy

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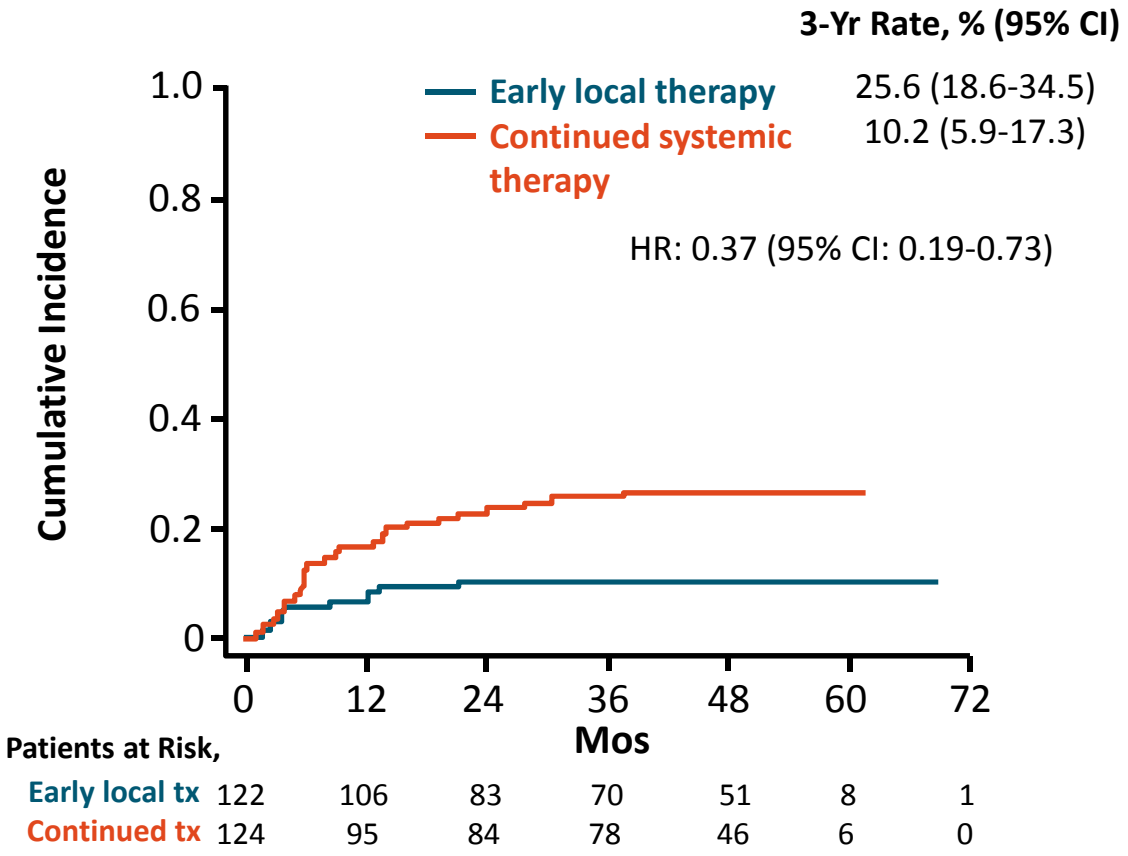
E2108: Locoregional Progression



- Definitions of locoregional progression:
  - Continued systemic therapy: presentation of symptoms that would prompt local therapy
  - Early local therapy: regional node progression or chest wall disease/invasive breast recurrence
- Report of later locoregional progression/recurrence not precluded by occurrence of distant progression

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E2108: Conclusions

- **Early local therapy to intact primary tumors in patients with MBC did not achieve a survival benefit compared to continued systemic therapy**
- **Although a 2.5-fold increase of local disease progression was observed in patients who continued systemic therapy vs those who received local therapy, this did not translate to a survival benefit or improved QoL in these patients**

Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial

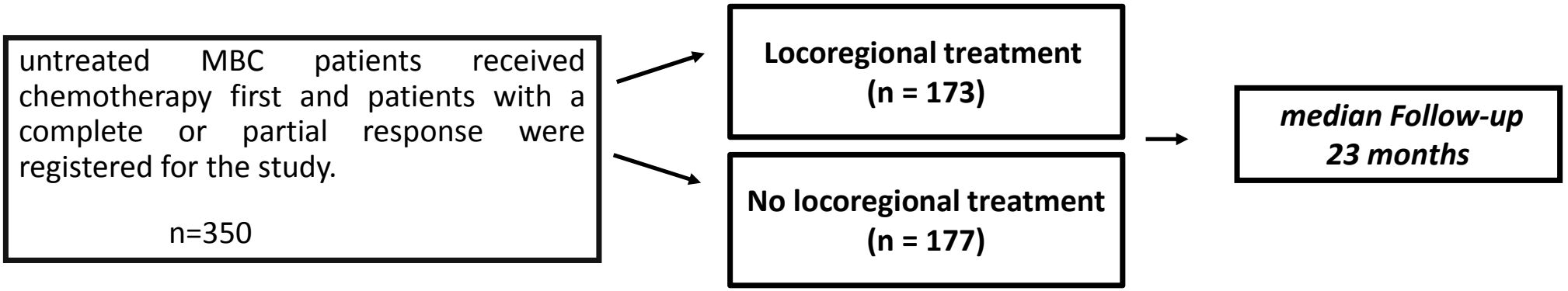
Rajendra Badwe, Rohini Hawaldar, Nita Nair, Rucha Kaushik, Vani Parmar, Shabina Siddique, Ashwini Budrukkar, Indraneel Mittra, Sudeep Gupta

Lancet Oncol 2015; 16: 1380–88
Published Online
September 10, 2015
http://dx.doi.org/10.1016/

Summary

Background The role of locoregional treatment in women with metastatic breast cancer at first presentation is unclear. Preclinical evidence suggests that such treatment might help the growth of metastatic disease, whereas many retrospective analyses in clinical cohorts have suggested a favourable effect of locoregional treatment in these patients. We aimed to compare the effect of locoregional treatment with no treatment on outcome in women with metastatic

- Randomized phase III trial



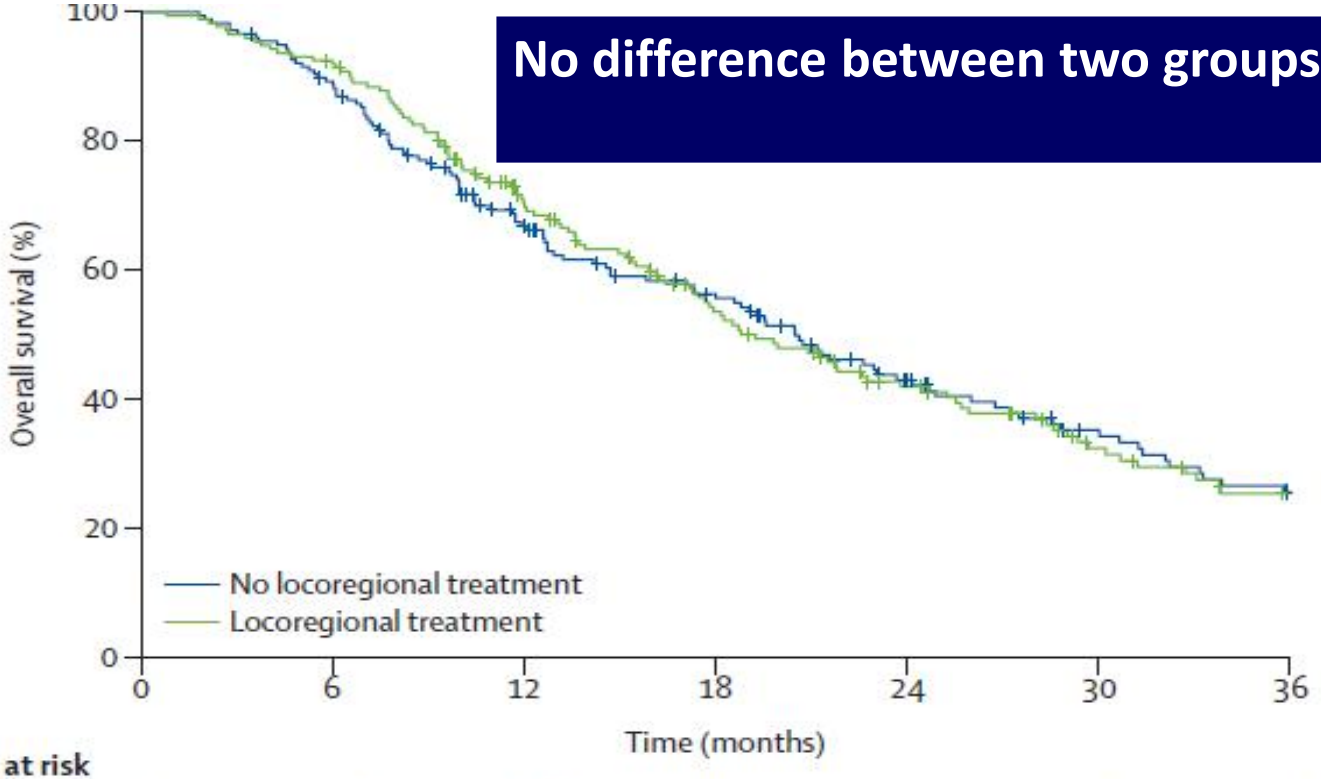
- Primary endpoint: OS

Surgery was followed by standard postoperative adjuvant radiation treatment to the chest wall or remaining breast as per standard institutional practice for non-metastatic patients.

- All patients who underwent breast-conserving surgery received postoperative radiation.

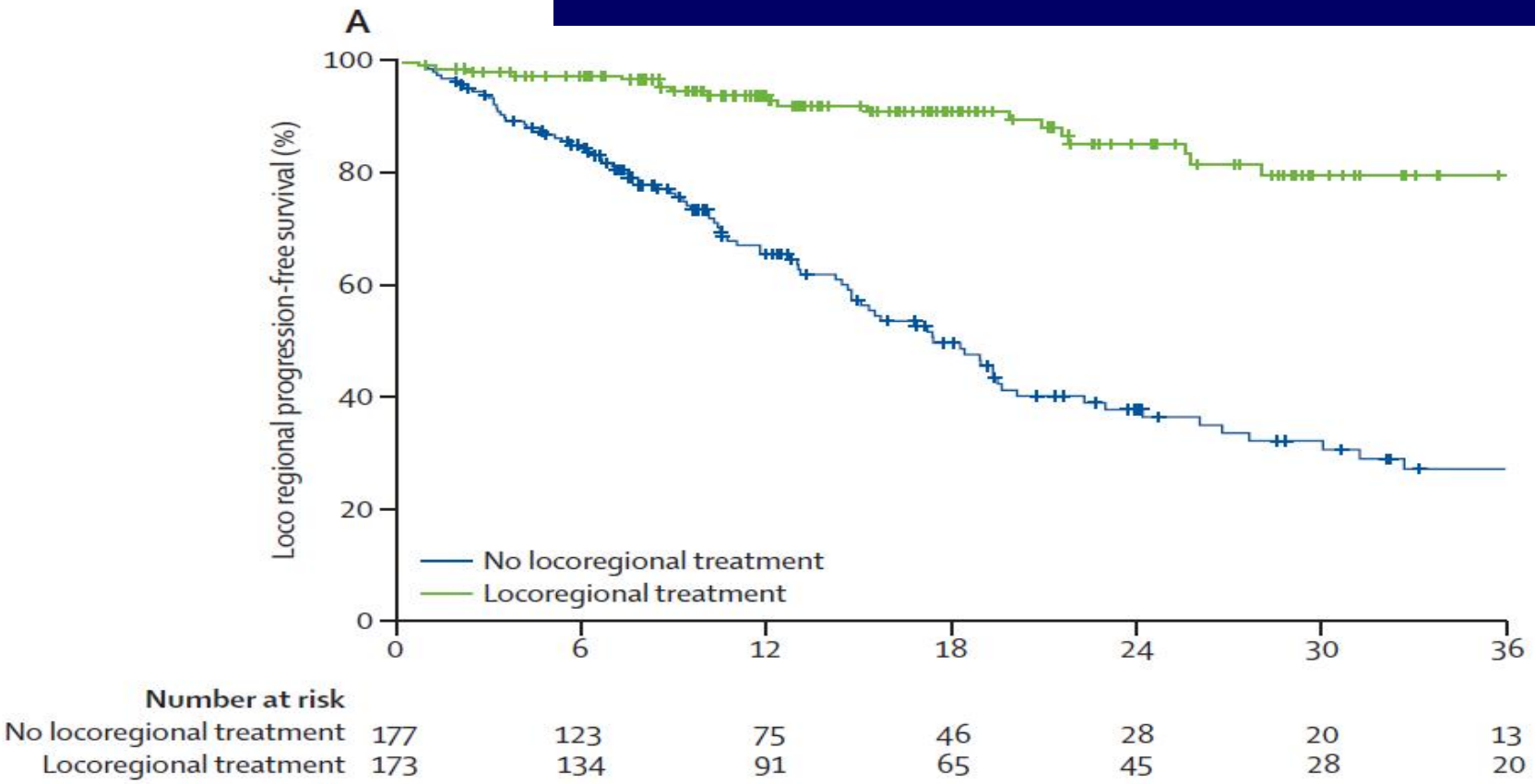
- In those patients who underwent mastectomy, those with a pre-chemotherapy tumor size of more than 5 cm or skin or chest wall involvement or axillary lymph node-positive disease received postoperative radiation.

No difference between two groups with regards to OS



Number at risk							
No locoregional treatment	177	148	101	75	50	36	24
Locoregional treatment	173	152	105	73	49	32	21

Improvement in locoregional progression free survival



Number at risk							
No locoregional treatment	177	123	75	46	28	20	13
Locoregional treatment	173	134	91	65	45	28	20

Ann Surg Oncol (2018) 25:3141–3149
https://doi.org/10.1245/s10434-018-6494-6

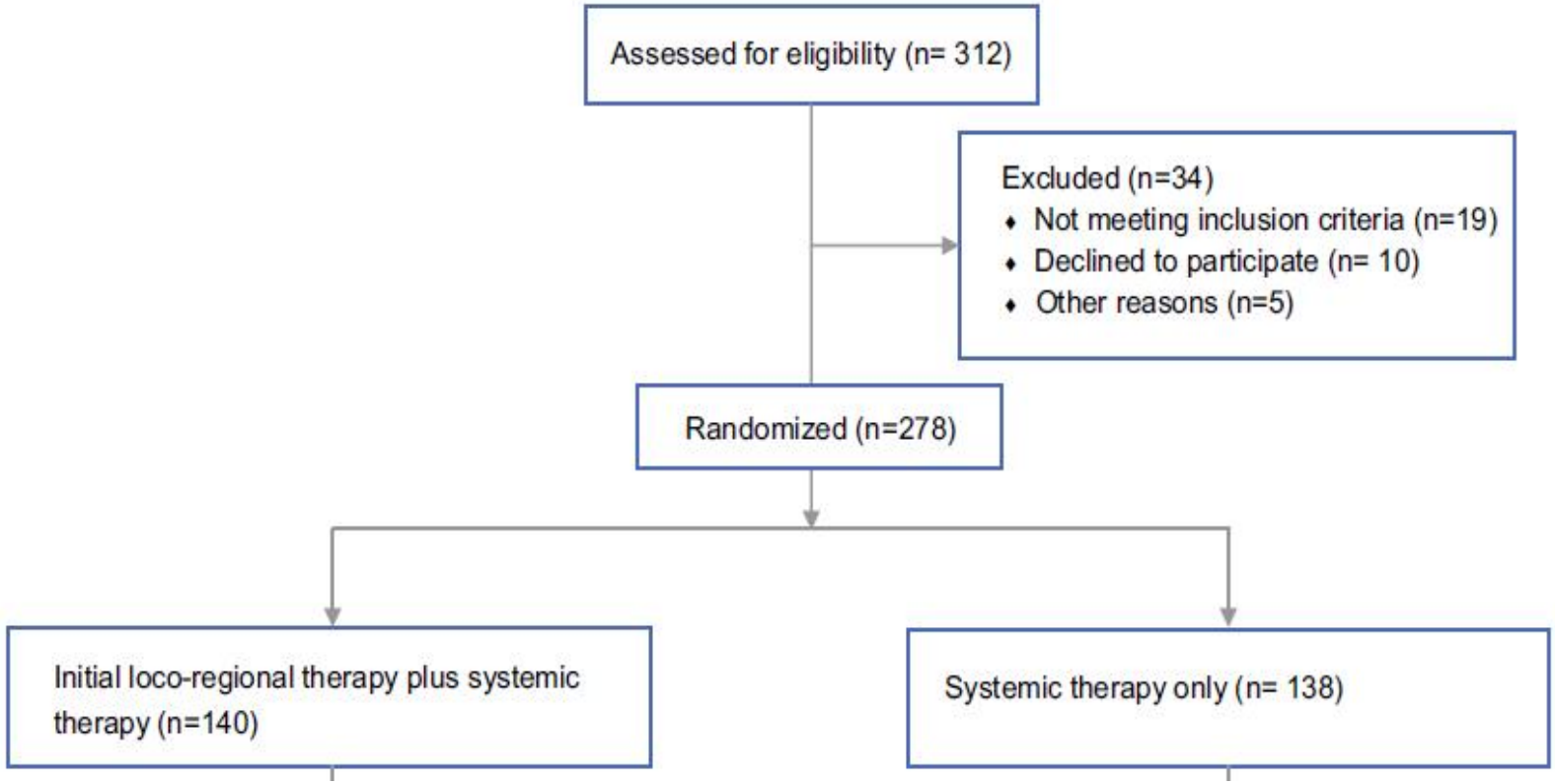
Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Randomized Trial Comparing Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at Presentation: Protocol MF07-01

Atilla Soran, MD, MPH, FNCBC, FACS[1], Vahit Ozmen, MD, FACS[2], Serdar Ozbas, MD[3], Hasan Karanlik, MD[4], Mahmut Muslumanoglu, MD[5], Abdullah Igci, MD[5], Zafer Canturk, MD[6], Zafer Utkan, MD[7], Cihangir Ozaslan, MD[8], Turkkan Evrensel, MD[9], Cihan Uras, MD[10], Erol Aksaz, MD[11], Aykut Soyder, MD[12], Umit Ugurlu, MD[13], Cavit Col, MD[14], Neslihan Cabioglu, MD[5], Betül Bozkurt, MD[15], Ali Uzunkoy, MD[16], Neset Koksal, MD[17], Bahadir M. Gulluoglu, MD, FACS[13], Bulent Unal, MD[18], Can Atalay, MD[10], Emin Yıldırım, MD[19], Ergun Erdem, MD[20], Semra Salimoglu, MD[21], Atakan Sezer, MD[22], Ayhan Koyuncu, MD[23], Gunay Gurleyik, MD[24], Haluk Alagol, MD[8], Nalan Ulufi, MD[25], Uğur Berberoglu, MD[8], Mustafa Dulger, MD[26], Omer Cengiz, MD[27], Efe Sezgin, PhD[28], and Ronald Johnson, MD, FACS[1]

[1]Division of Surgical Oncology, Department of Surgery, University of Pittsburgh Medical Center, Magee Womens Hospital


Assessed for eligibility (n= 312)
Excluded (n=34)
Not meeting inclusion criteria (n=19)
Declined to participate (n= 10)
Other reasons (n=5)
Randomized (n=278)
Initial loco-regional therapy plus systemic therapy (n=140)
Systemic therapy only (n= 138)

- All the patients who underwent BCS received radiotherapy (RT) to the whole breast as indicated in early-stage BC unless the patient died earlier.

- Breast RT was planned to be administered within 3–6 months after surgery.

- Patients treated by local management experienced an **improvement in five year survival** with locoregional treatment(46.4 versus 26.4 percent)

- In a post-hoc subgroup analysis, patients with:
  - Hormone positive & Her2 negative
  - younger than 55 years
  - solitary bone-only metastases

Have the greatest benefit from locoregional treatment.

National Comprehensive Cancer Network®

NCCN Guidelines Version 8.2021
Invasive Breast Cancer

NCCN Guidelines Index
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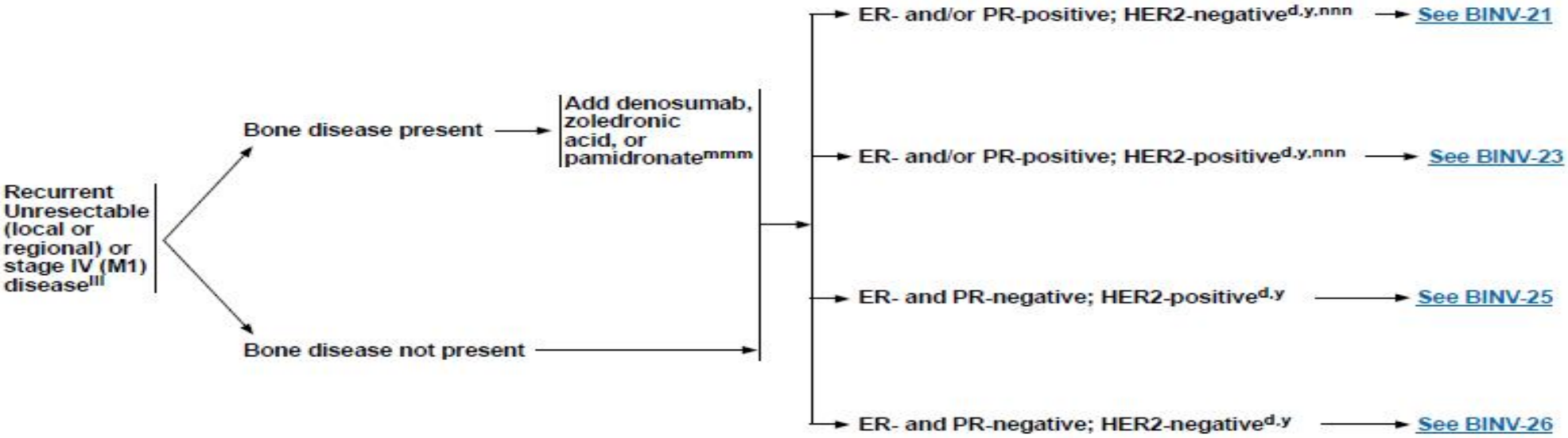
Discussion

SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE



[d] See Principles of Biomarker Testing (BINV-A).

[y] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus, individualized consideration of risks and benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).

[III] Routine surgical resection of the primary breast tumor is generally not indicated in the management of patients presenting with de novo stage IV (M1) disease. Although there is no survival benefit, it may be considered for local control of the primary tumor. Discussion regarding management of the primary tumor in this setting must be individualized.

[mmm] Denosumab, zoledronic acid, or pamidronate (all with calcium and vitamin D supplementation) should be given (category 1) in addition to chemotherapy or endocrine therapy if bone metastasis is present, expected survival is ≥3 months, and renal function is adequate. Patients should undergo a dental examination with preventive dentistry prior to initiation of this therapy. The optimal schedule for zoledronic acid is every 12 weeks.

[nnn] Baseline assessment of bone density recommended for patients receiving an aromatase inhibitor who are at risk of osteoporosis (eg, age >65, family history, chronic steroids).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

[d] See Principles of Biomarker Testing (BINV-A).

[y] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus, individualized consideration of risks and benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).

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Role of radiotherapy to the primary site in asymptomatic patients

Radiotherapy in metastatic breast cancer

Primary site

Metastatic site

Symptomatic metastases

- Pain
- Loss of function
- Oncologic emergency(cord compression)

Asymptomatic metastases

- Retrospective data suggest a survival benefit for aggressive local therapy in patients with oligometastatic disease prospective data are not available.

- RT is an option to potentially improve survival for patients with oligometastatic disease.

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Radical radiation therapy for oligometastatic breast cancer: Results of a prospective phase II trial

Marco Trovo [a,*], Carlo Furlan [a], Jerry Polesel [b], Francesco Fiorica [c], Stefano Arcangeli [d], Niccolò Giaj-Levra [e], Filippo Alongi [e], Alessandro Del Conte [f], Loredana Militello [f], Elena Muraro [g], Debora Martorelli [g], Simon Spazzapan [e,f], Massimiliano Berretta [f]

[a] *Department of Radiation Oncology, Udine General Hospital, Udine;* [b] *Department of Epidemiology and Biostatistics, Centro di Riferimento Oncologico of Aviano;* [c] *Department of Radiation Oncology, University Hospital Ferrara;* [d] *Department of Radiation Oncology, San Camillo and Forlanini Hospitals, Rome;* [e] *Department of Radiation Oncology, Sacro Cuore Cancer Care Center Hospital;* [f] *Department of Medical Oncology, Centro di Riferimento Oncologico of Aviano; and* [g] *Department of Translational Research, Centro di Riferimento Oncologico of Aviano, Italy*

ARTICLE INFO

Article history:

ABSTRACT

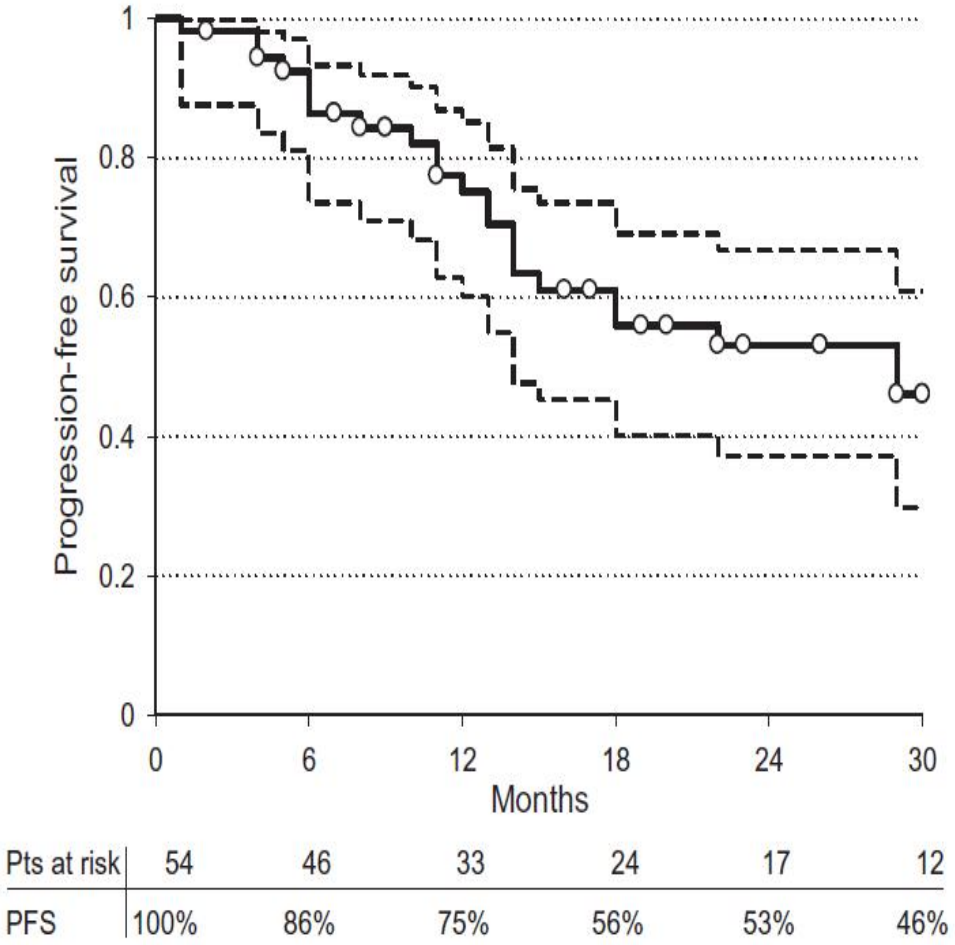
Background and purpose: We conducted a prospective phase II multicentric trial to determine if radical

- **Inclusion criteria were the following:**

- Olig-ometastatic breast cancer with <5 metastatic sites
- The extent of disease had to be assessed with FDG-PET/CT
- No brain metastases
- Primary tumor controlled
- ECOG performance status <2

❖ Radiotherapy could be delivered using stereotactic body radiotherapy (SBRT) technique or fractionated intensity modulated radiotherapy (IMRT).

❖ Primary endpoint: PFS



After a median follow-up of 30 months (range, 6–55 months), 1- and 2-year PFS was 75% and 53%, respectively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A Phase IIR/III Trial of Standard of Care Therapy with or without Stereotactic Body Radiotherapy (SBRT) and/or Surgical Ablation for Newly Oligometastatic Breast Cancer
Principal Investigator
Steven Chmura, MD PhD

summary

Systemic therapy is first line treatment for most patients in metastatic disease

- Local therapies such as surgeruy and/or radiation may be targeted to the breast/chest wall, regional lymph nodes or to distant metastases.

Goal may be symptom palliation or prolonging survival in situations such as oligometastases disease.

Bone metastases

- Hormone receptor positive tumors are more likely to spread to bone.
- The axial skeleton is the most common site of bone metastases.
- The most common symptom of bone metastases is slowly, progressive pain that is well localized.

- In Painful bone metastases:

Radiotherapy cause :	Partial pain relief	**60-90%**
	Complete pain relief	**30-50%**

Dose:

30 Gy/10 Fr

20 Gy/5 Fr

8 Gy/1 Fr :poor PS, Limited LE ,extensive non osseous metastases

Short course radiotherapy :

May cause a flare reaction → temporary increase in pain at the site of the metastases.

Provide similar pain relief to longer treatment regimens.

Retreatment rates are higher.

- The use of bisphosphonates with EBRT may further improve the outcome in terms of

Pain and bone healing

Systemic treatment in metastatic breast cancer

ER-PR positive , Her2 negative

ER-PR positive ,Her2 positive

ER-PR negative , Her2 positive

ER-PR negative , Her2 negative

Luminal breast cancer

Visceral crisis

No visceral crisis

Luminal breast cancer

Visceral crisis

No visceral crisis

Initial chemotherapy

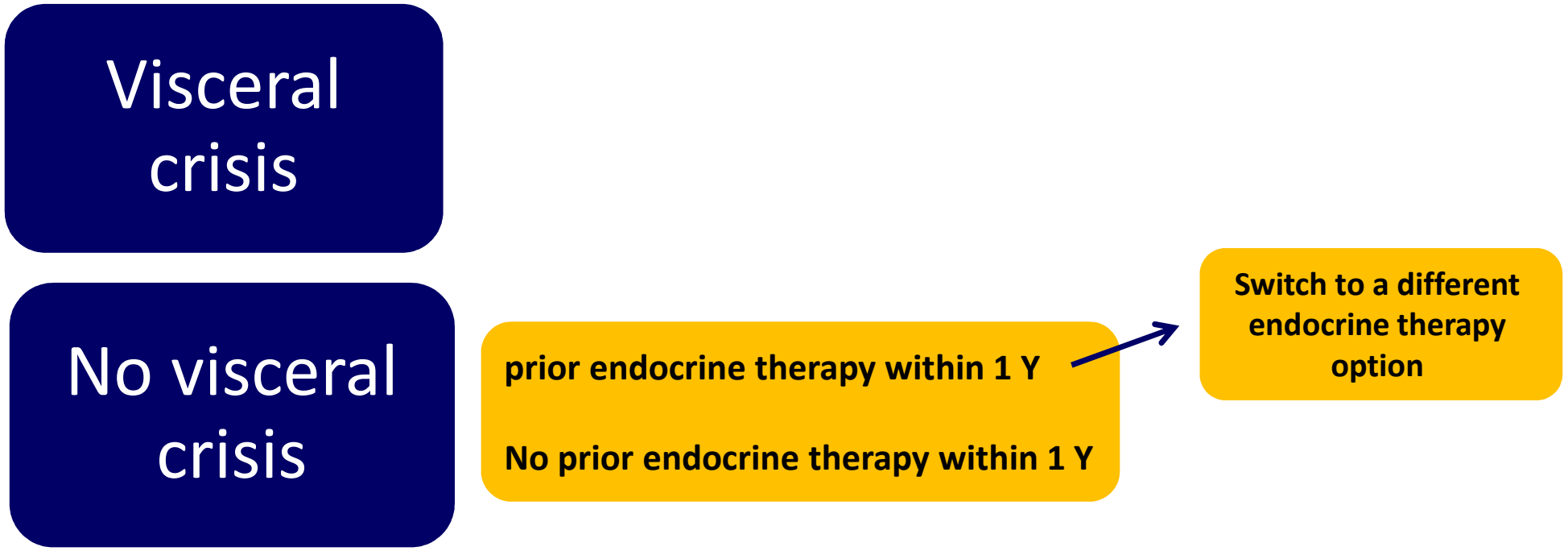
SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a,b,c]

HER2-Negative			
Preferred Regimens		**Other Recommended Regimens[f]**	**Useful in Certain Circumstances[f]**

• Anthracyclines
  ▸ Doxorubicin
  ▸ Liposomal doxorubicin
• Taxanes
  ▸ Paclitaxel
• Anti-metabolites
  ▸ Capecitabine
  ▸ Gemcitabine
• Microtubule inhibitors
  ▸ Vinorelbine
  ▸ Eribulin
• Sacituzumab govitecan-hziy (for TNBC)[g]
	• For germline *BRCA1/2* mutations[d] see additional targeted therapy options (BINV-R)[e]
	• Platinum (for TNBC and germline *BRCA1/2* mutation)[d]
	  ▸ Carboplatin
	  ▸ Cisplatin
	• For PD-L1–positive TNBC see additional targeted therapy options (BINV-R)[e]
		• Cyclophosphamide
		• Docetaxel
		• Albumin-bound paclitaxel
		• Epirubicin
		• Ixabepilone
			• AC (doxorubicin/cyclophosphamide)
			• EC (epirubicin/cyclophosphamide)
			• CMF (cyclophosphamide/ methotrexate/fluorouracil)
			• Docetaxel/capecitabine
			• GT (gemcitabine/paclitaxel)
			• Gemcitabine/carboplatin
			• Paclitaxel/bevacizumab[h,i]
			• Carboplatin + paclitaxel or albumin-bound paclitaxel

- Sequential single agents are preferred but chemotherapy combinations may be used in select patients with **high tumor burden** **rapidly progressing disease** **visceral crisis**

Luminal breast cancer



- For patients who did not relapse on an AI, or within 12 months of stopping adjuvant AI:

CDK4/6 inhibitor + AI

no clear advantage of fulvestrant seen in a phase II study

- In patients who relapsed on adjuvant AI therapy, or within 12 months of stopping adjuvant AI:

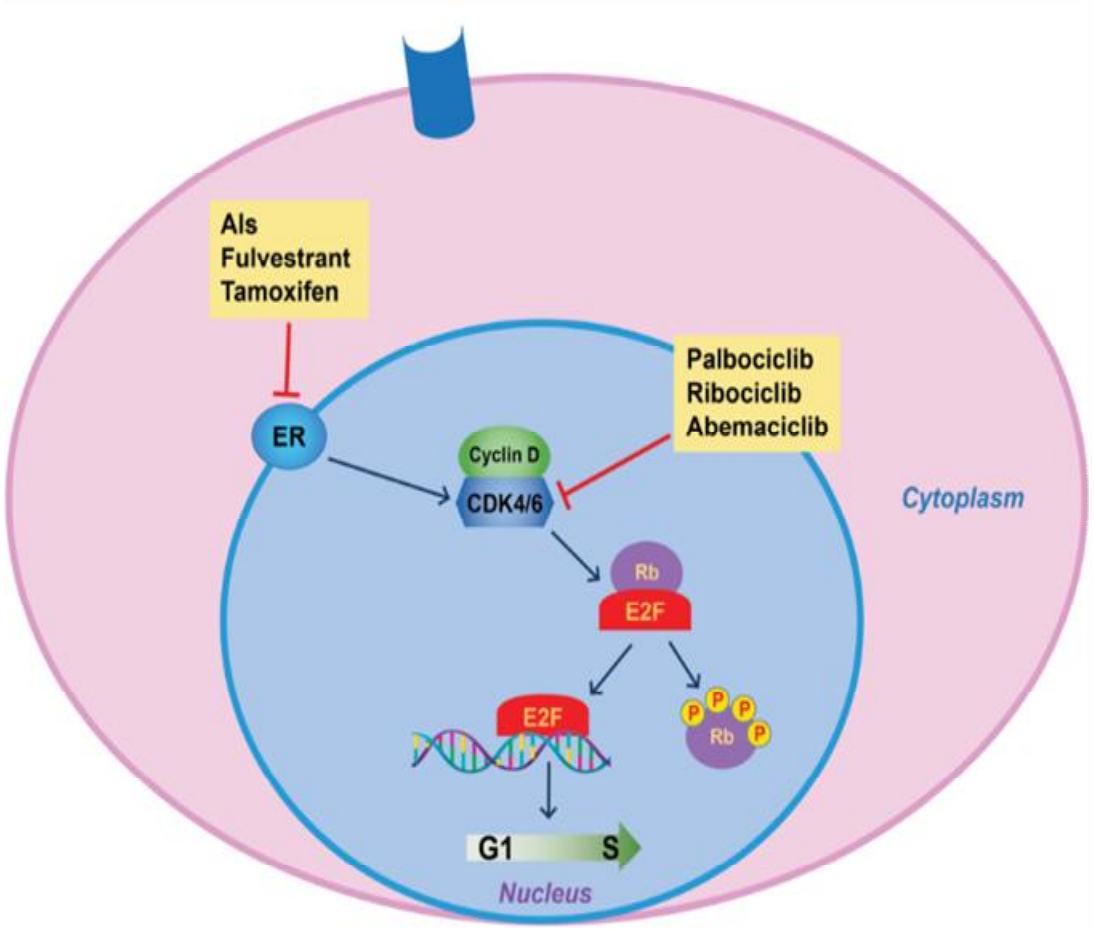
CDK4/6 inhibitor + Fulvestrant

CDK4/6 Inhibitors

Palbociclib

Abemaciclib

Ribociclib



- there have been no head-to-head comparisons of the three approved CDK4/6 inhibitors, the efficacy of the three drugs in the metastatic setting appears similar.

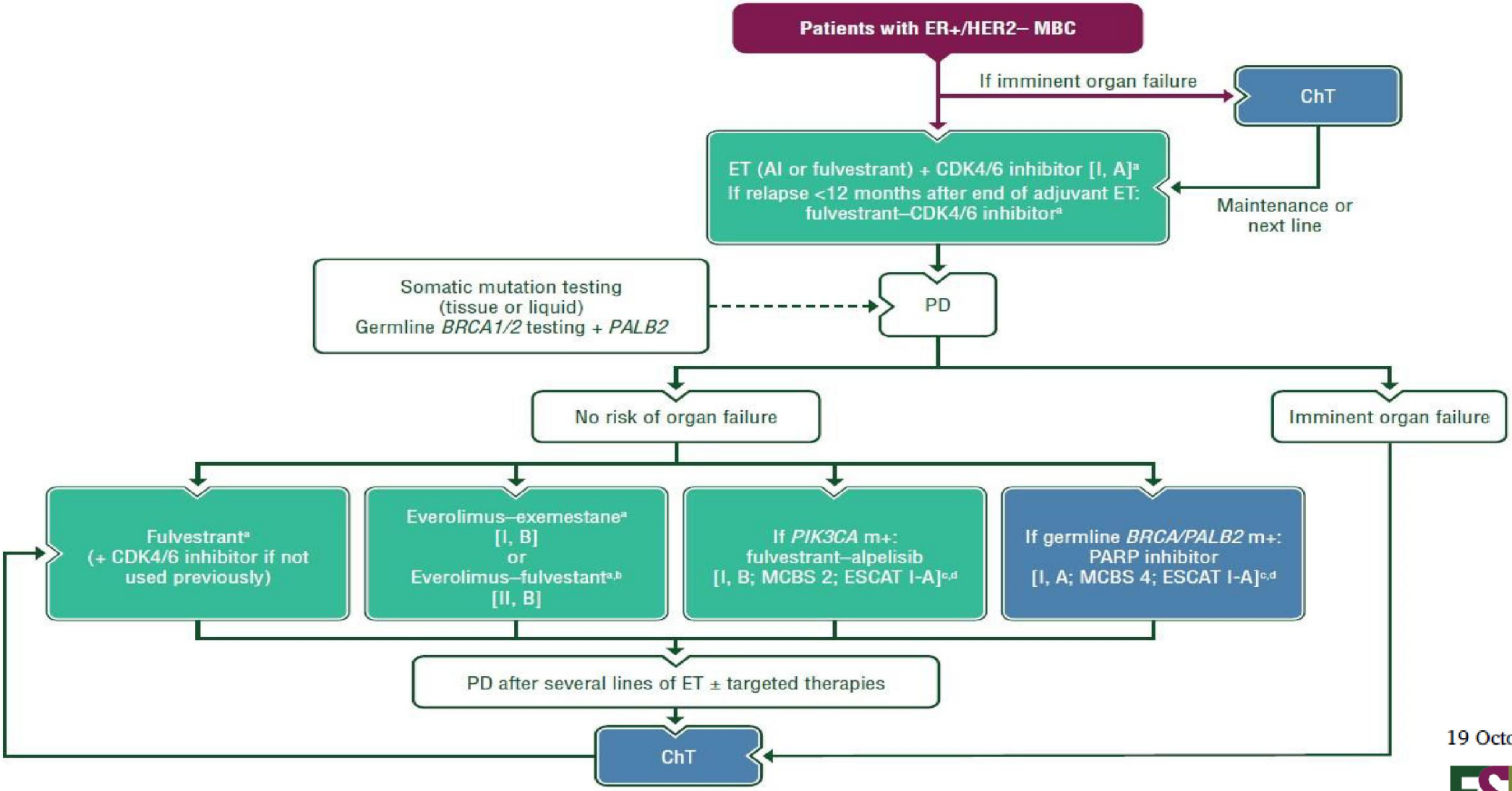
- Palbociclib and Ribociclib have not demonstrated single-agent efficacy and must be combined with ET.

- Abemaciclib has demonstrated limited single-agent efficacy

- ET alone in the first-line setting should be reserved for the small group of patients with comorbidities or a performance status (PS) that prevents the use of CDK4/6 inhibitor combinations.

- **Older age alone should not be used to select for endocrine monotherapy.**

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression	
Preferred Regimens **First-Line Therapy** • Aromatase inhibitor + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1) • Selective ER down-regulator (fulvestrant, category 1)[b] ± non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[b] • Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1) • Non-steroidal aromatase inhibitor (anastrozole, letrozole) • Selective estrogen receptors modulator (tamoxifen or toremifene) • Steroidal aromatase inactivator (exemestane)	**Preferred Regimens** **Second- and Subsequent-Line Therapy** • Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[c] • For *PIK3CA*-mutated tumors, see additional targeted therapy options (see BINV-R)[c,d] • Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[c,f] • Non-steroidal aromatase inhibitor (anastrozole, letrozole) • Steroidal aromatase inactivator (exemestane) • Selective ER down-regulator (fulvestrant) • Selective estrogen receptors modulator (tamoxifen or toremifene)
Useful in Certain Circumstances[d] • Megestrol acetate • Estradiol • Abemaciclib[c,e]	



19 October 2021

Her2 positive

- Trastuzumab/ pertuzumab/taxane is recommended in the first-line setting regardless of HR status.
  - **The CLEOPATRA trial** established the gold standard in the first-line setting: adding pertuzumab to docetaxel and trastuzumab increased median PFS by >6 months

- Taxane should be given for at least six cycles, if tolerated, followed by maintenance trastuzumab/pertuzumab until progression.

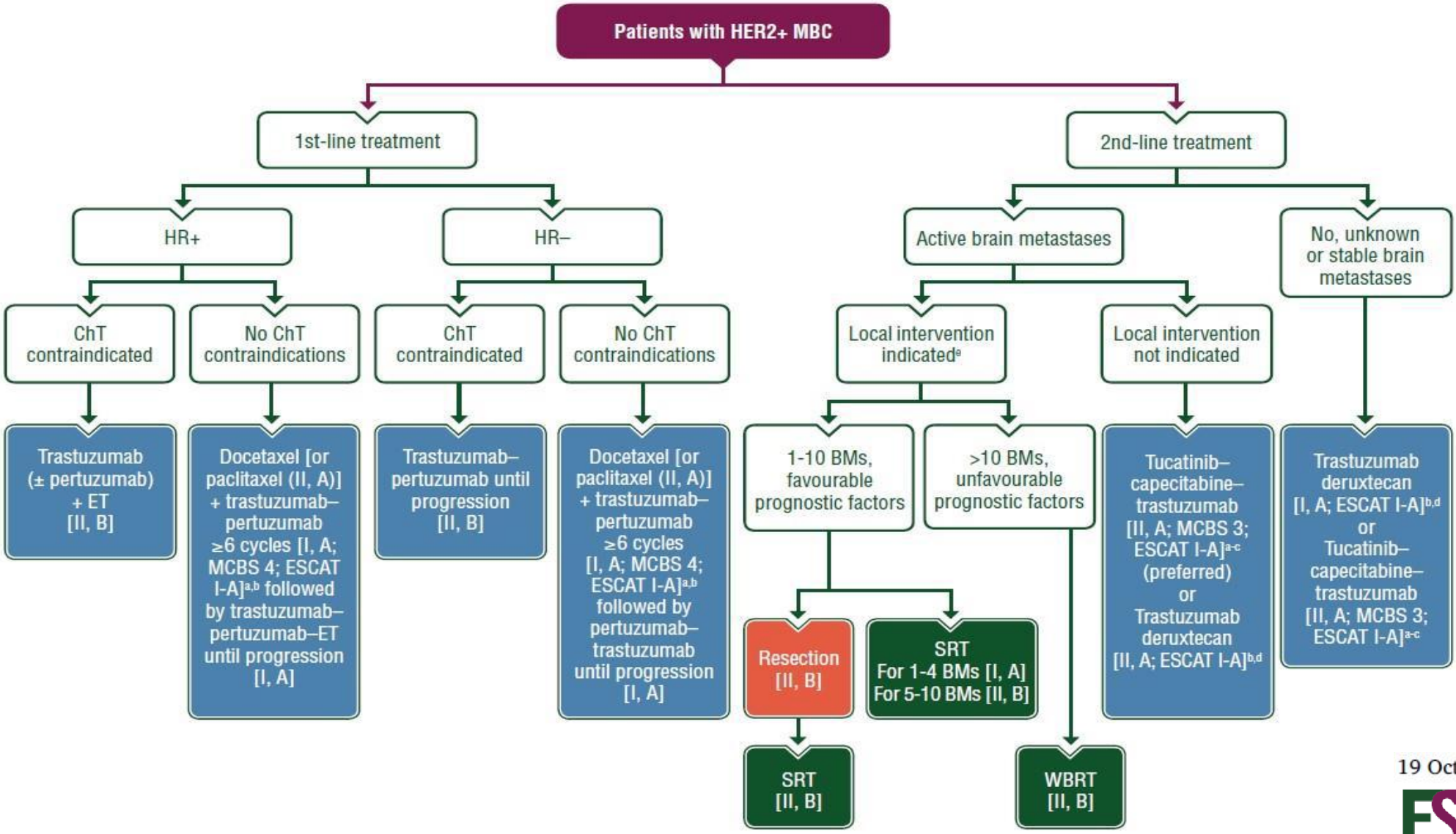
- In HR positive tumor after completion of chemotherapy: ET added to maintenance trastuzumab/pertuzumab.

- In case of patient comorbidities, personal preferences or PS preclude the use of ChT in patients with HER2-positive, HR-positive breast cancer**, ET in combination with a HER2-targeted therapy**.

HER2-Positive and Postmenopausal[g,h,i] or Premenopausal Receiving Ovarian Ablation or Suppression
• Aromatase inhibitor ± trastuzumab • Aromatase inhibitor ± lapatinib • Aromatase inhibitor ± lapatinib + trastuzumab • Fulvestrant ± trastuzumab • Tamoxifen ± trastuzumab

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[j]

HER2-Positive			
Setting	**Regimen**	**NCCN Category of Preference**	**NCCN Category of Evidence**
First line[k]	Pertuzumab + trastuzumab + docetaxel[l]	Preferred Regimen	1
	Pertuzumab + trastuzumab + paclitaxel[l]	Preferred Regimen	2A
Second line	Ado-trastuzumab emtansine (T-DM1)	Preferred Regimen	1
Third line and beyond	Tucatinib + trastuzumab + capecitabine[l,m,n]	Other Recommended Regimen	1
	Fam-trastuzumab deruxtecan-nxki[m,o,p]	Other Recommended Regimen	2A
	Trastuzumab + docetaxel or vinorelbine[l,q]	Other Recommended Regimen	2A
	Trastuzumab + paclitaxel ± carboplatin[l,q]	Other Recommended Regimen	2A
	Capecitabine + trastuzumab or lapatinib[l,q]	Other Recommended Regimen	2A
	Trastuzumab + lapatinib[l,q] (without cytotoxic therapy)	Other Recommended Regimen	2A
	Trastuzumab + other agents[l,q,r,s]	Other Recommended Regimen	2A
	Neratinib + capecitabine[q]	Other Recommended Regimen	2A
	Margetuximab-cmkb + chemotherapy[q] (capecitabine, eribulin, gemcitabine, or vinorelbine)	Other Recommended Regimen	2A
Additional targeted therapy options (See BINV-R)			



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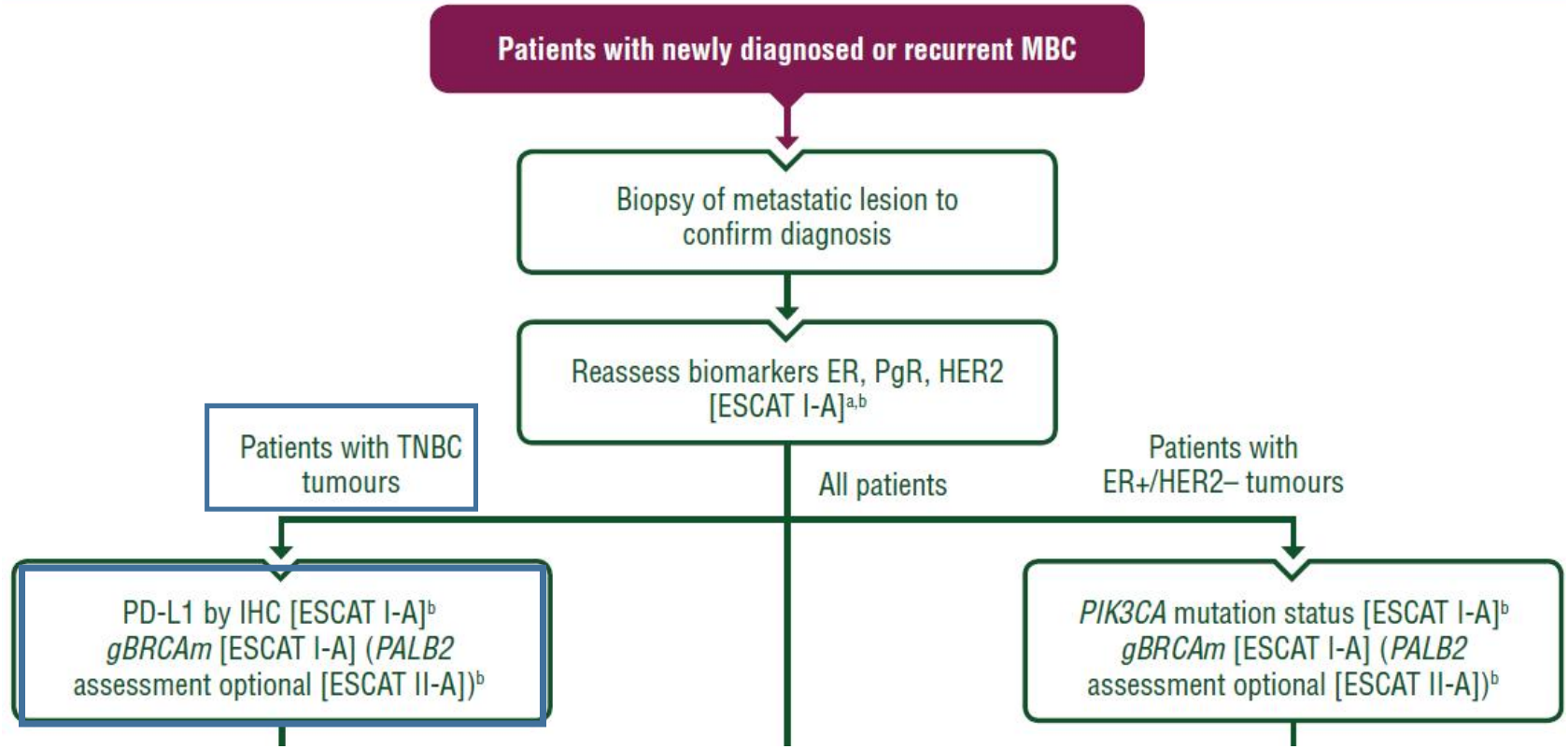
Triple negative

- defined by the absence of expression of ER and PgR receptors and of overexpression of HER2 or amplification of HER2neb

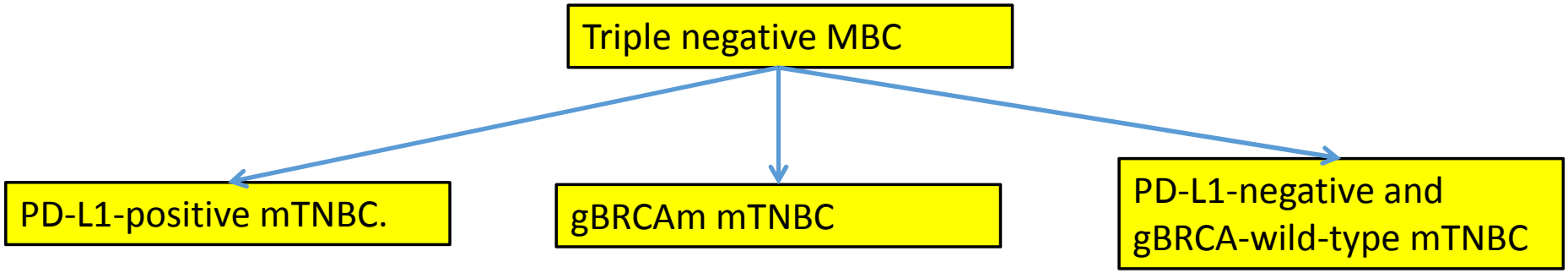
- 15%-20% of all BCs

Triple negative MBC



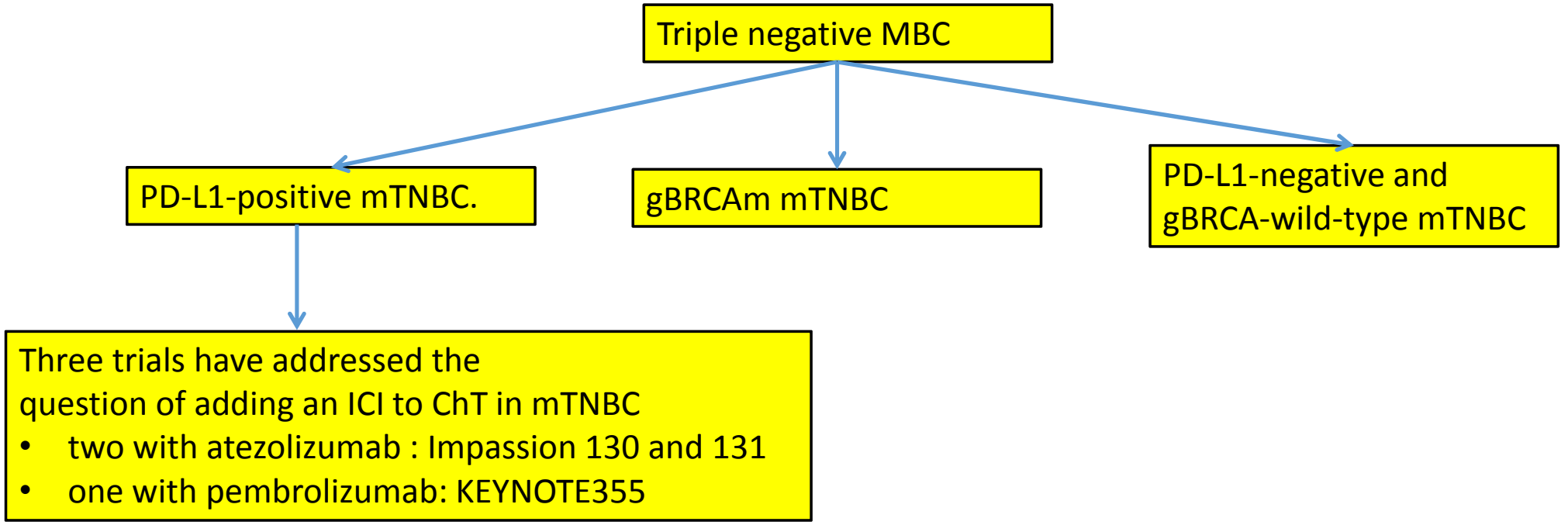
Triple negative MBC

- 1st treatment For most TNBCs, ChT remains the standard treatment.



Triple negative MBC

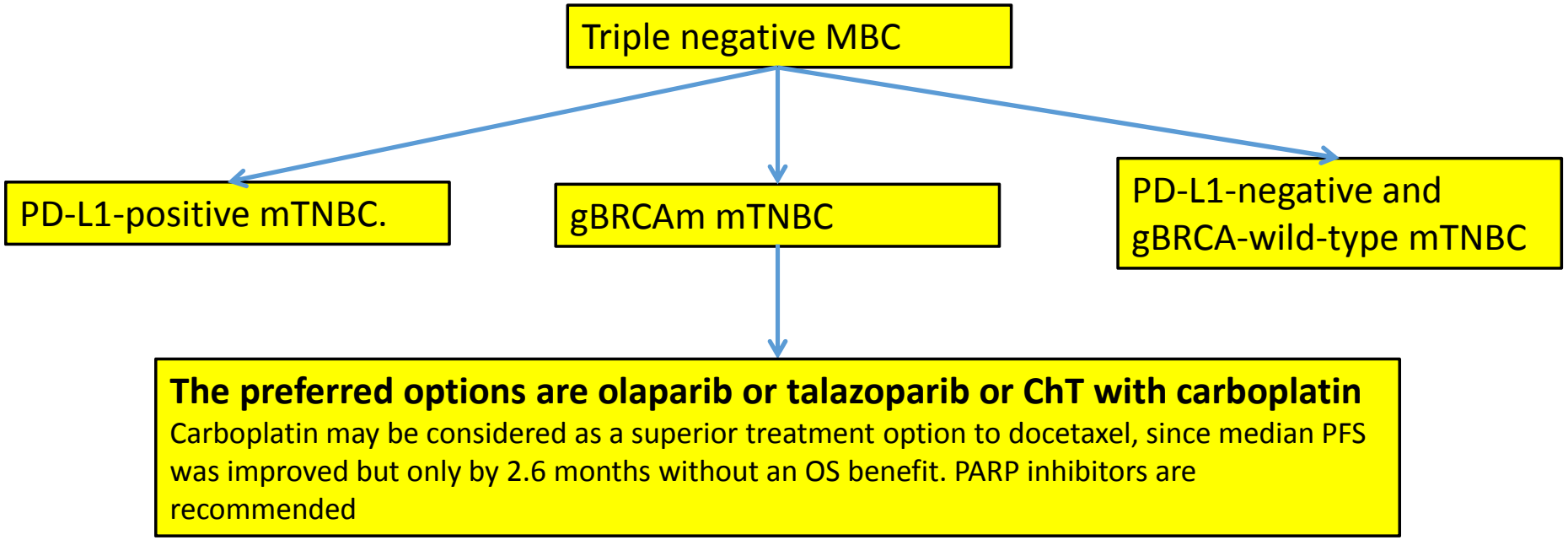
- 1st treatment For most TNBCs, ChT remains the standard treatment.



ICI: Immune Checkpoint Inhibitor

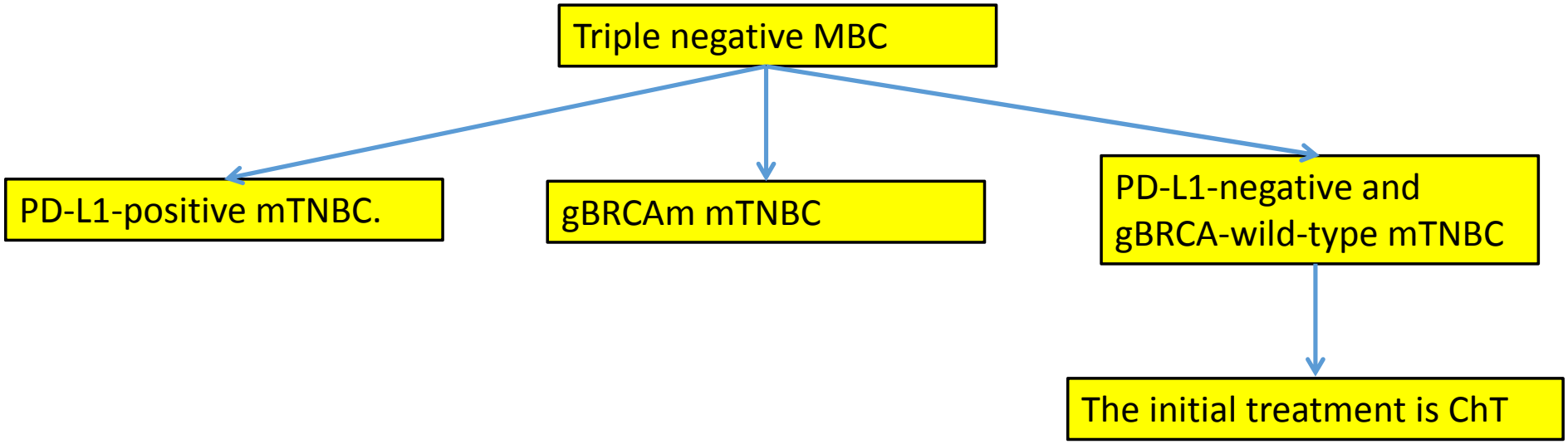
Triple negative MBC

- 1st treatment For most TNBCs, ChT remains the standard treatment.



Triple negative MBC

- 1st treatment For most TNBCs, ChT remains the standard treatment.



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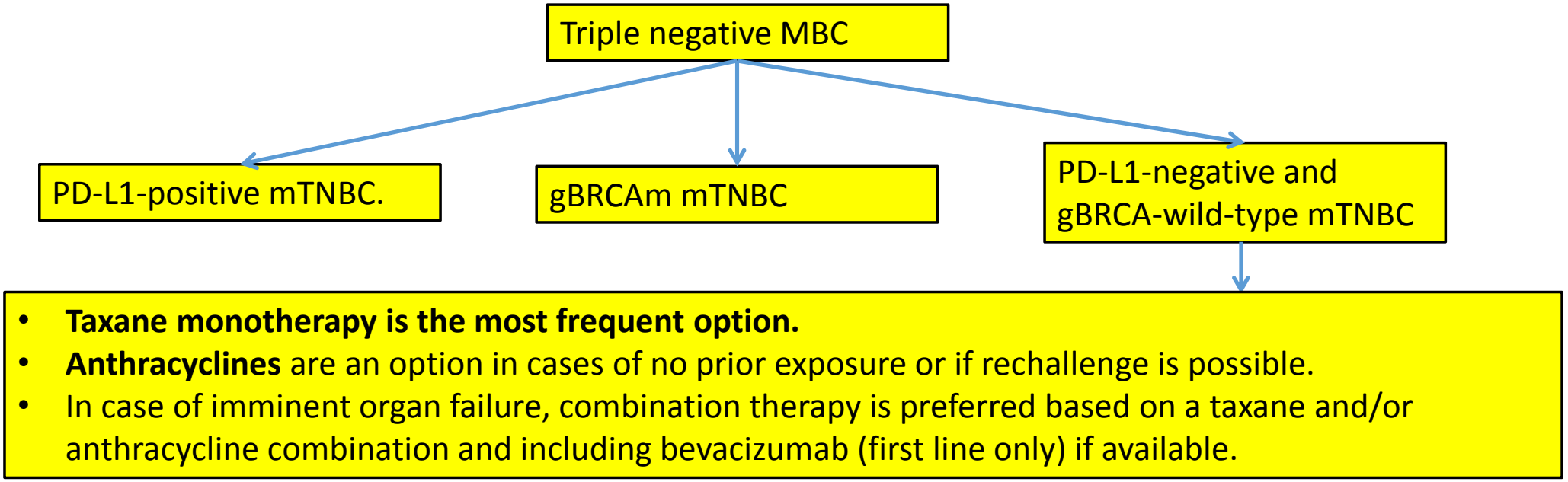


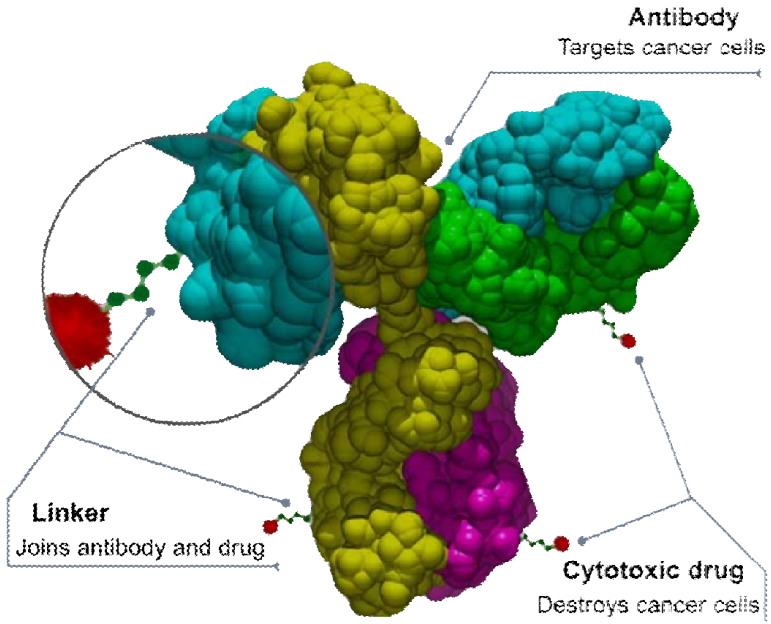
Triple negative MBC

- 1st treatment

- Progression after anthracyclines and taxanes
  - The ADC,sacituzumab govitecan-hziy (sacituzumab)
  - received accelerated FDA approval phase I/II dose escalation, dose expansion study (IMMU-132-01).
  - is not currently EMA approved

Antibody-drug conjugates

- Antibody-drug conjugates or ADCs
  - are a class of biopharmaceutical drugs designed as a targeted therapy for treating cancer.
- Unlike chemotherapy, ADCs are intended to target and kill tumor cells while sparing healthy cells



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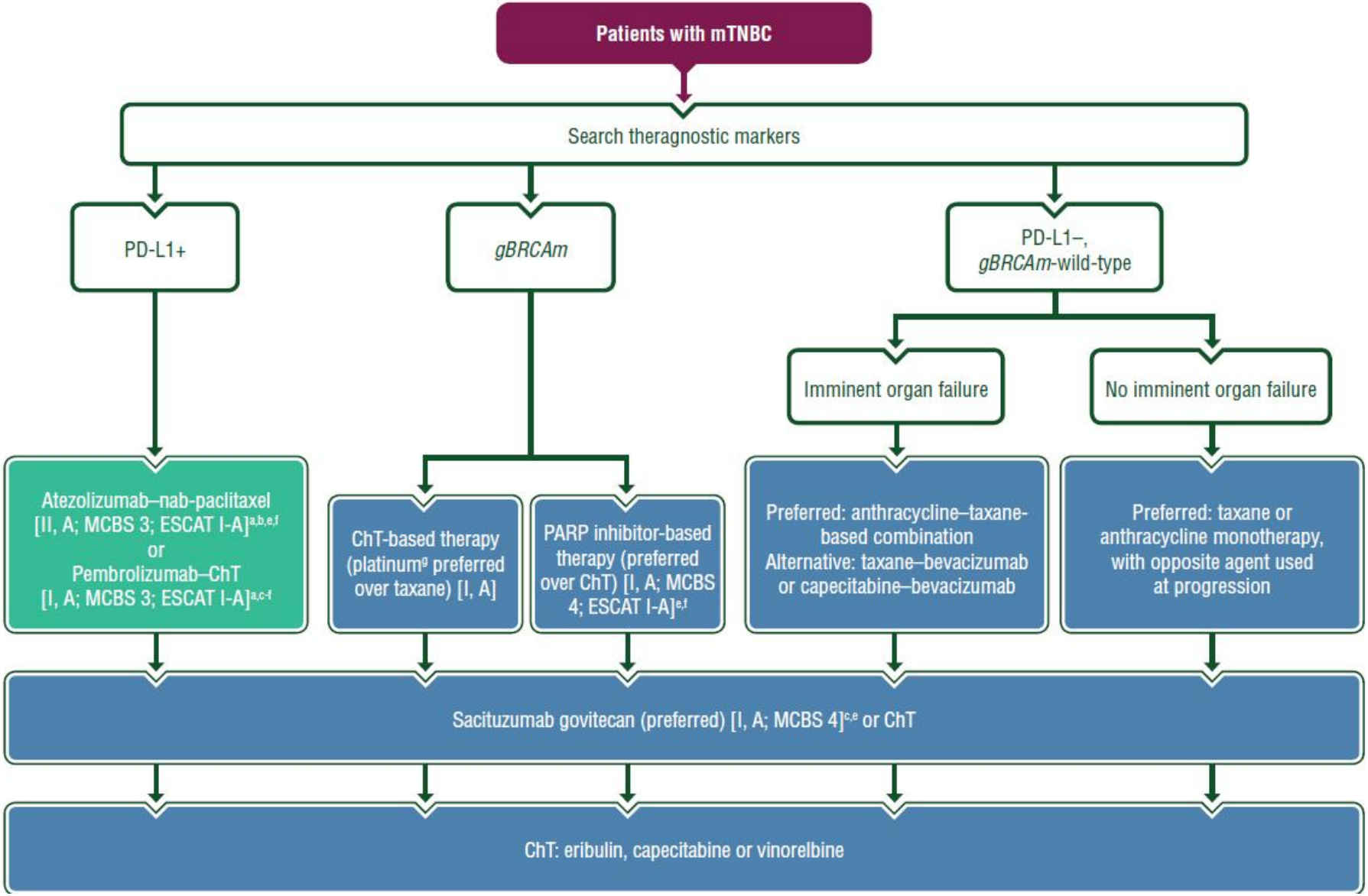
- After progression, all ChT recommendations for HER2- negative disease also apply for TNBC such as eribulin, capecitabine and vinorelbine.



19 October 2021

ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
Any[a]	*BRCA1* mutation *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1 Category 1	Preferred
HR-positive/ HER2-negative[b]	*PIK3CA* activating mutation	PCR (blood or tissue block if blood negative), molecular panel testing	Alpelisib + fulvestrant[c]	Category 1	Preferred second-line therapy
TNBC	PD-L1 expression Threshold for positivity combined positive score ≥10	IHC	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[d]	Category 1	Preferred first-line therapy[h]
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[e] Entrectinib[e]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, PCR (tissue block)	Pembrolizumab[d,f] Dostarlimab-gxly[g]	Category 2A	
Any	TMB-H (≥10 muts/mb)	NGS	Pembrolizumab[d,f]	Category 2A	

Summary

- Radiotherapy in metastatic breast cancer
  - Primary site
  - Metastatic site
- Chemotherapy in metastatic breast cancer

Thanks for your attention