MODULE 1: Breast Cancer

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1. In what situations, if any, do you order a genomic assay other than the 21-gene Recurrence Score for your patients with ER-positive, HER2-negative localized breast cancer (BC)? What is your usual approach to adjuvant therapy for premenopausal and postmenopausal patients with low and intermediate Recurrence Scores? When, if at all, do you use genomic assays in the neoadjuvant setting?

- BCI for late risk of recurrence and extended endocrine therapy
- Postmenopausal pts 0-3+LN Oncotype≤25 no chemo
  - Results based on TAILORx and RxPONDER
- Premenopausal pts LN-
  - 0-18 no chemo
  - 18-25 RSClin
- Premenopausal pts 1-3+LN in general I recommend chemo

2. Which patients with ER-positive, HER2-negative localized BC should be offered treatment with adjuvant abemaciclib?

- Inclusion Criteria for monarchE:
  - ≥4+LN
  - 1-3+LN and
    - Grade 3 or
    - Tumor ≥5cm or
    - Ki67 ≥20%
- Data showing benefit of abemaciclib regardless of Ki67

3. Which patients with localized BC should undergo genetic testing, and what type (eg, germline versus somatic, panel versus one-off)? In which situations should patients be offered treatment with adjuvant olaparib?

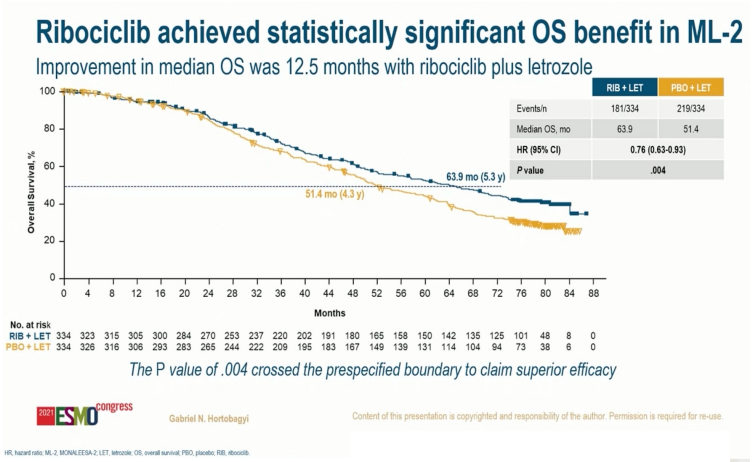
- Germline testing based on NCCN guidelines
- Germline testing based on OlympiA trial
  - TNBC non-pCR
  - ER+ CPS+EG score ≥ 3
  - TNBC: ≥ pT2 or ≥ pN1
  - HR+≥ 4 positive lymph nodes

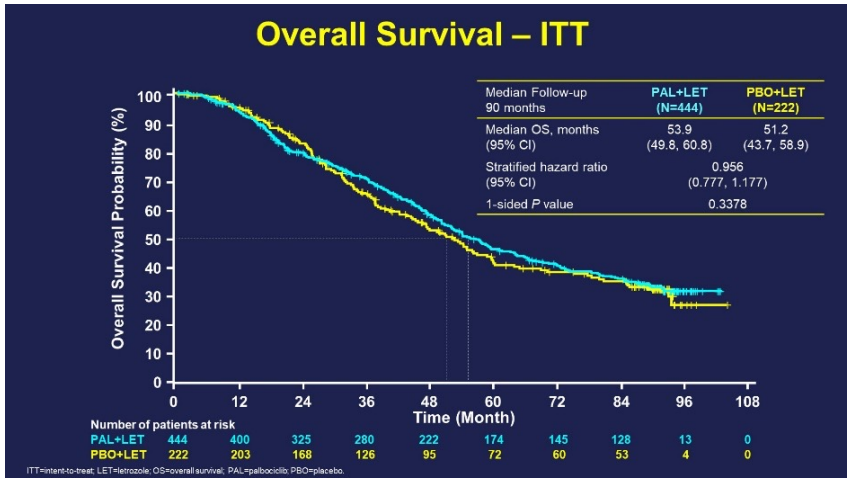
3. Cont'

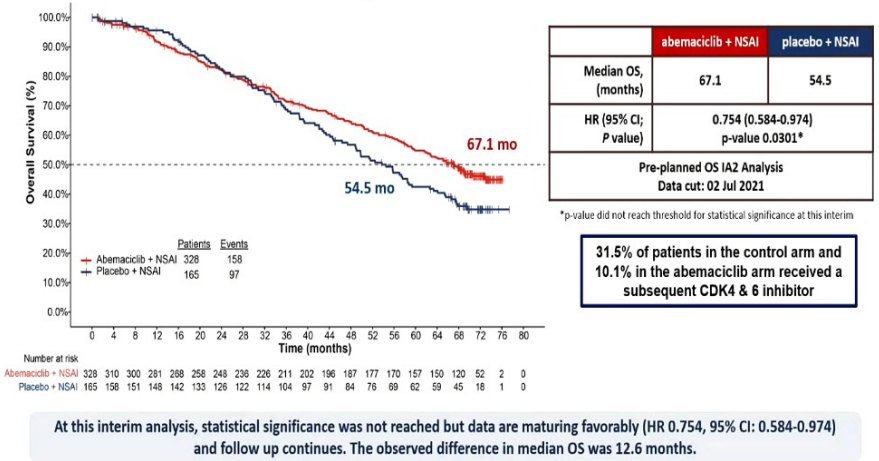
- Benefits of germline to somatic testing
  - No del/dup analysis therefore deletions aren't captured
  - Some deleterious mutations may be called VUS due to different data sets
  - It may be somatic mutation and not germline
  - Somatic reversion mutations (germline mutation gets "corrected" in cancer tissue)
  - Some companies do both at the same time
  - Types of somatic testing matter. Is there full sequencing analysis?
  - Intronic changes may also be missed (coverage level of NGS)-see above

4. Which CDK4/6 inhibitor do you generally add to first-line endocrine therapy for premenopausal and postmenopausal patients with ER-positive metastatic BC (mBC), and how, if at all, have recently reported overall survival findings with these agents affected your response?

Trial	CDKi + ET	ET	P value
MONALEESA-2	64 months	51 months	0.004
PALOMA-2	54 months	51 months	0.338
MONARCH 3	67 months	54 months	0.030







At this interim analysis, statistical significance was not reached but data are maturing favorably (HR 0.754, 95% CI: 0.584-0.974) and follow up continues. The observed difference in median OS was 12.6 months.

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Hortobagyi et al N Eng J Med 2022, Finn et al ASCO 2022, Goetz et al ESMO 2022

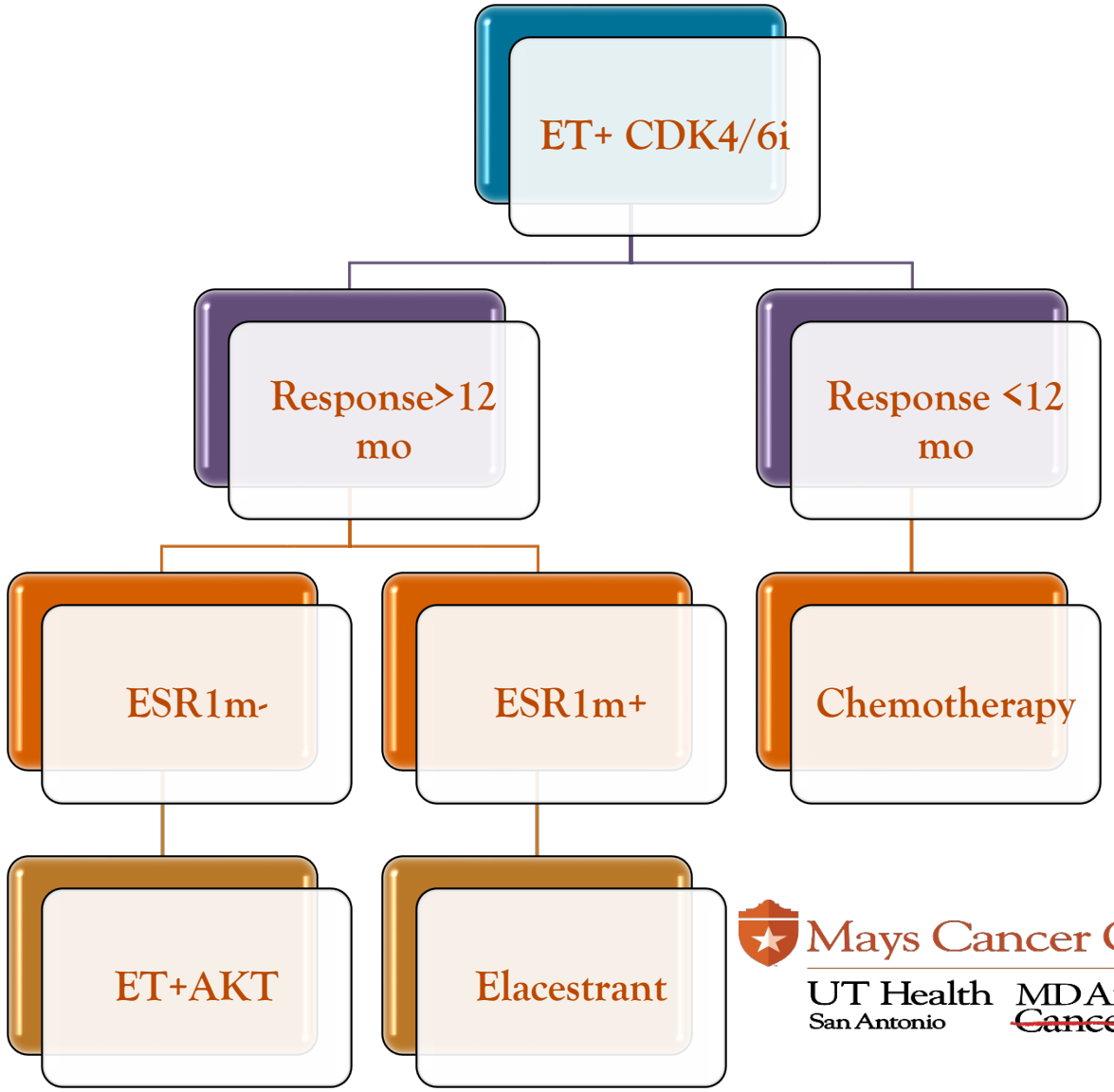
5. How do you approach the treatment of patients with ER-positive, HER2-negative mBC with disease progression on a CDK4/6 inhibitor/endocrine therapy, and where do alpelisib, sacituzumab govitecan and oral SERDs fit in? How would you sequence capivasertib if it was also available?

- If PIK3CA mutation consider alpelisib and ET
  - Results from SOLAR-1
- If ESR1m+ and at least 12mo on CDK4/6 give elacestrant
  - Results from EMERALD
- If no mutation consider giving everolimus and ET
- If endocrine resistant then switch to chemo and second line sacituzumab
  - TROPICS02 (approved in 3rd line setting)
- Results from CAPItello-291 encouraging
  - Toxicity (diarrhea, nausea, rash)

5. Cont'

Considerations:

- How to establish endocrine resistance
-Balancing toxicity and efficacy
-Genomic testing: when and how often



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