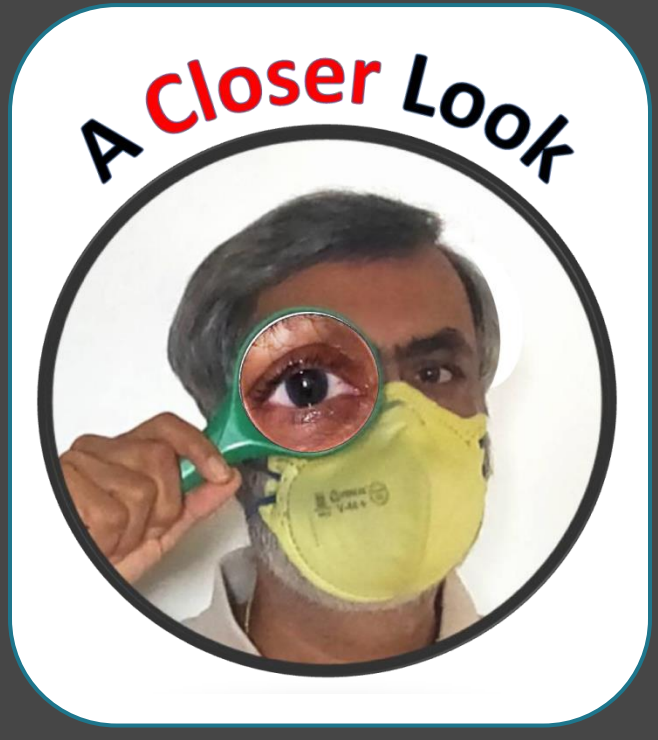
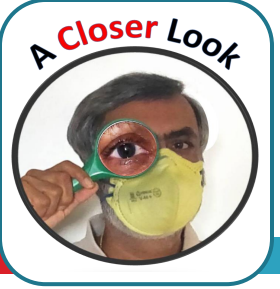


SEQUENCING STRATEGY FOR ER+ HER2- METASTATIC BREAST CANCER

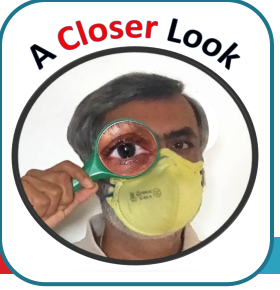
purvish1@gmail.com



Assumptions for this panel discussion

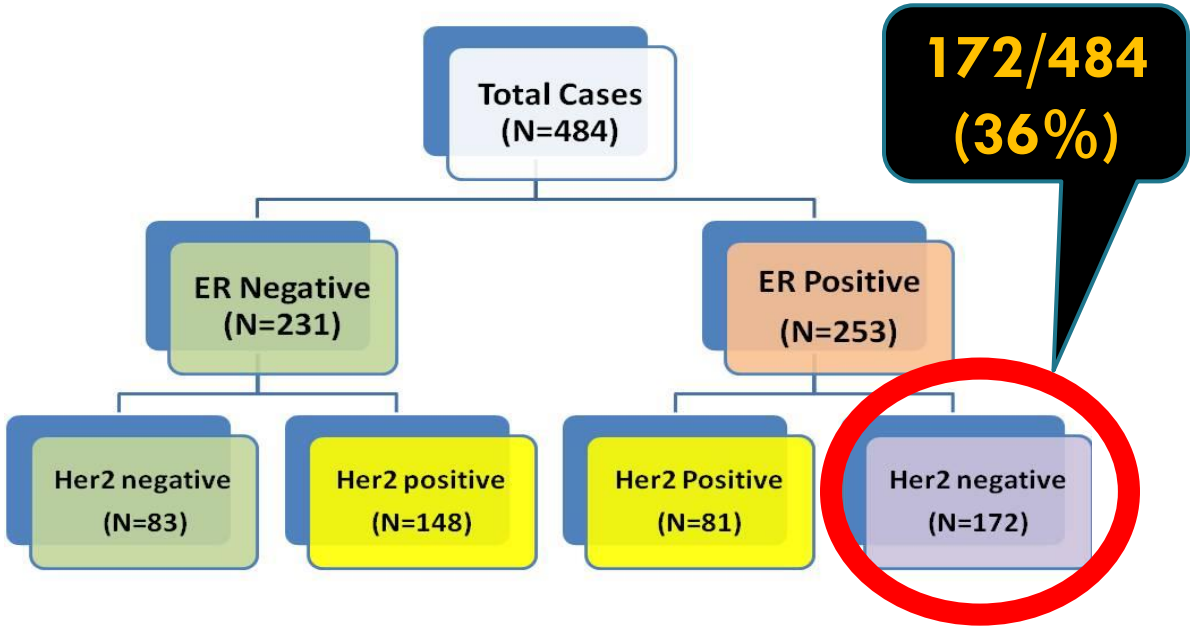
- Audience are oncologists or other doctors with adequate experience in treating breast cancer
- Audience is familiar with published data and standard of care

Discussion will be focusing on real world experience and special circumstances



What is the incidence of such patients in your practice?

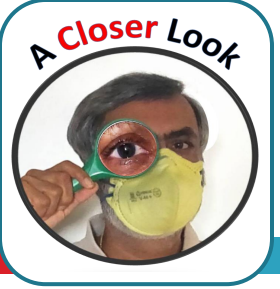
Figure 1: ER and Her2 status



MBC

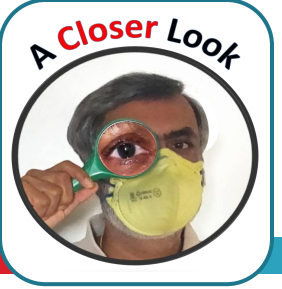
142/484
(29%)

Ajay Bapna et al 2020



Rx objective for ER+ Her2- MBC

- Are all patients to be treated with palliative intent ?
- Subset of oligometastatic disease – Rx with potentially curative approach ?
- What is the life expectancy horizon ?
  - What is the median duration of response to 1st line Rx
  - At what cutoff age will you plan for NO 2nd line Rx



Current Endocrine Rx options

Selective endocrine receptor modulators (SERM)

- Tamoxifen

Aromatase inhibitors (AIs)

- Anastrozole
- Letrozole
- Exemestane

Selective endocrine receptor downregulators (SERD)

- Fulvestrant

CDK4/6 inhibitors

- Palbociclib
- Ribociclib
- Abemaciclib

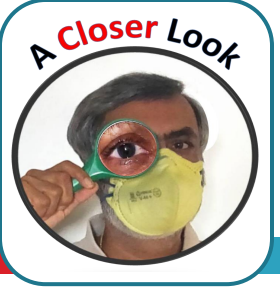
mTOR inhibitors

- Everolimus

Alternative agents

- Progestins (megestrol acetate)
- Estrogens (estradiol, diethylstilbestrol)

Have you used any agent not on this list?



Pre Menopausal status & Rx Decision

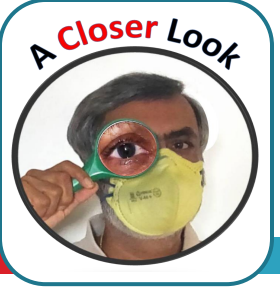
- In premenopausal patients, standard ET is
  - tamoxifen
  - ovarian function suppression
  - surgical castration

In your practice, which is the option of choice ?

- Meta-analysis of GnRH agonist + tamoxifen, significant increase in median PFS and OS

  (vs either agent alone)

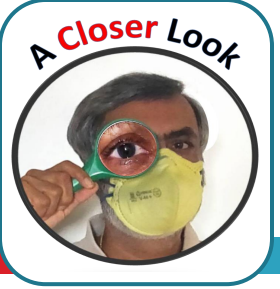
Klijn JG et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol 2001;19:343-53.



Tamoxifen

- more than 500,000 women are alive today as a result of tamoxifen therapy
- In metastatic setting, ORR is 34 %
- Is it
  - Out of fashion today in your practice
  - Suffering from old age

In your practice, do you see a median PFS of 13-16 months with 1st line endocrine therapy ?

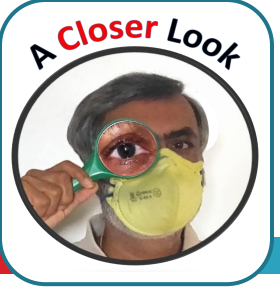


AI vs Tamoxifen

- AIs are superior to tamoxifen
- Pivotal meta-analysis of 8,504 patients with HR+ MBC
- HR 0.89; 95% CI: 0.80–0.99

Do you follow this in all patients in your practice?

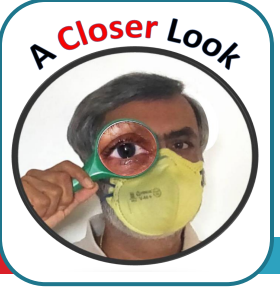
Mauri D, Pavlidis N, Polyzos NP, et al. Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. J Natl Cancer Inst 2006;98:1285-91



Post Menopausal status & Rx Decision

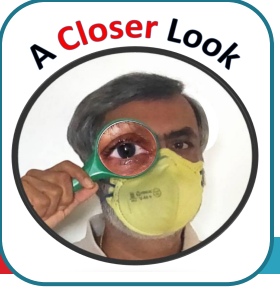
- In your practice, is AI monotherapy preferred therapeutic option in 1st line Rx for ER+ Her2- MBC?

- If not, what is your preference?



Combination Endocrine Rx?

- Combination of fulvestrant with anastrozole versus anastrozole monotherapy have reported conflicting results
- Any subset in which you use combination endocrine Rx?
  - Not previously exposed to tamoxifen
  - Both ER and PR positive
  - Dose of Fulvestrant ?? 250 mg vs 500 mg



1st Line Rx options also include

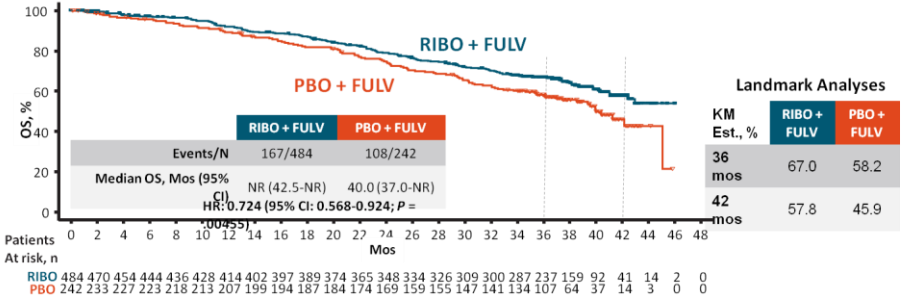
1. High-dose fulvestrant or everolimus (in combination with exemestane or letrozole or with other endocrine therapies),
2. PI3K inhibitors (e.g., buparlisib, alpelisib, pictilisib, taselisib), entinostat,
3. CDK 4/6 inhibitors (palbociclib, ribociclib, abemaciclib)

4. Novel selective estrogen receptor degradation agents targeting acquired ESR1 mutations

Do CDK4/6 inhibitors result in meaningful improvement in overall survival?

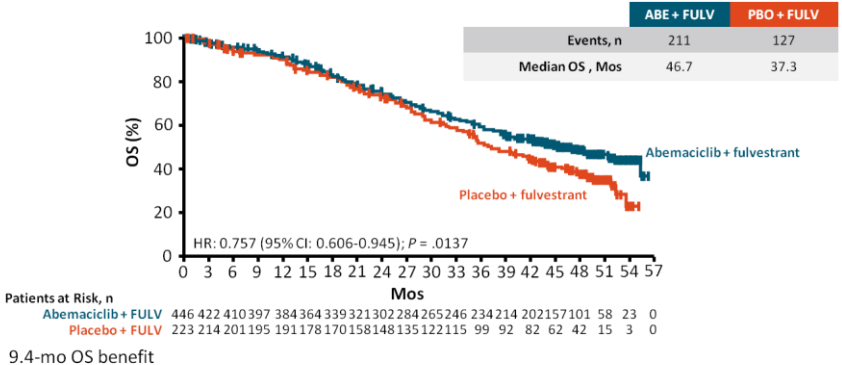
MONALEESA-3: Overall Survival

- Reduction in relative risk of death with ribociclib: 28%



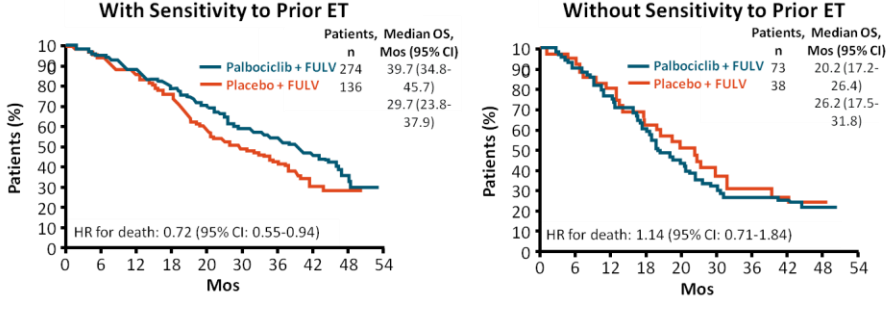
- $P = .00455$ crossed prespecified boundary for superior efficacy of $P < .01129$

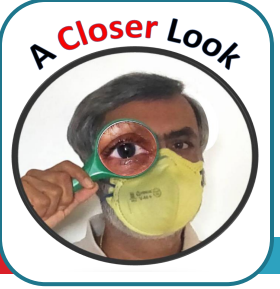
MONARCH 2: OS



- 9.4-mo OS benefit
- Median time to chemotherapy also significantly prolonged (50.2 vs 22.1 mos)

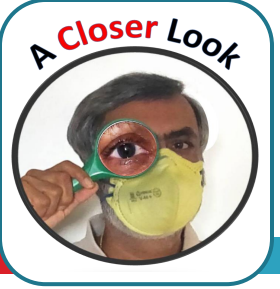
PALOMA-3: Impact of Fulvestrant ± Palbociclib on Survival





CDK4/6 inhibitors' impact on the treatment of HR+/HER2- MBC

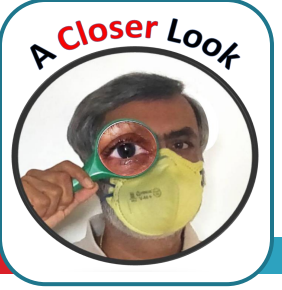
- Is OS of sufficient benefit to recommend them in 1st line Rx
- Do you use it only in combination with Fulvestrant
- Any preference in patient with brain metastasis
- In "aggressive disease", will they be better than std CT
- Should they be continued post-progression



What about first line for….

- ER positive
- Her2 negative
- MBC

- In **Male Patient** with no risk of visceral crisis



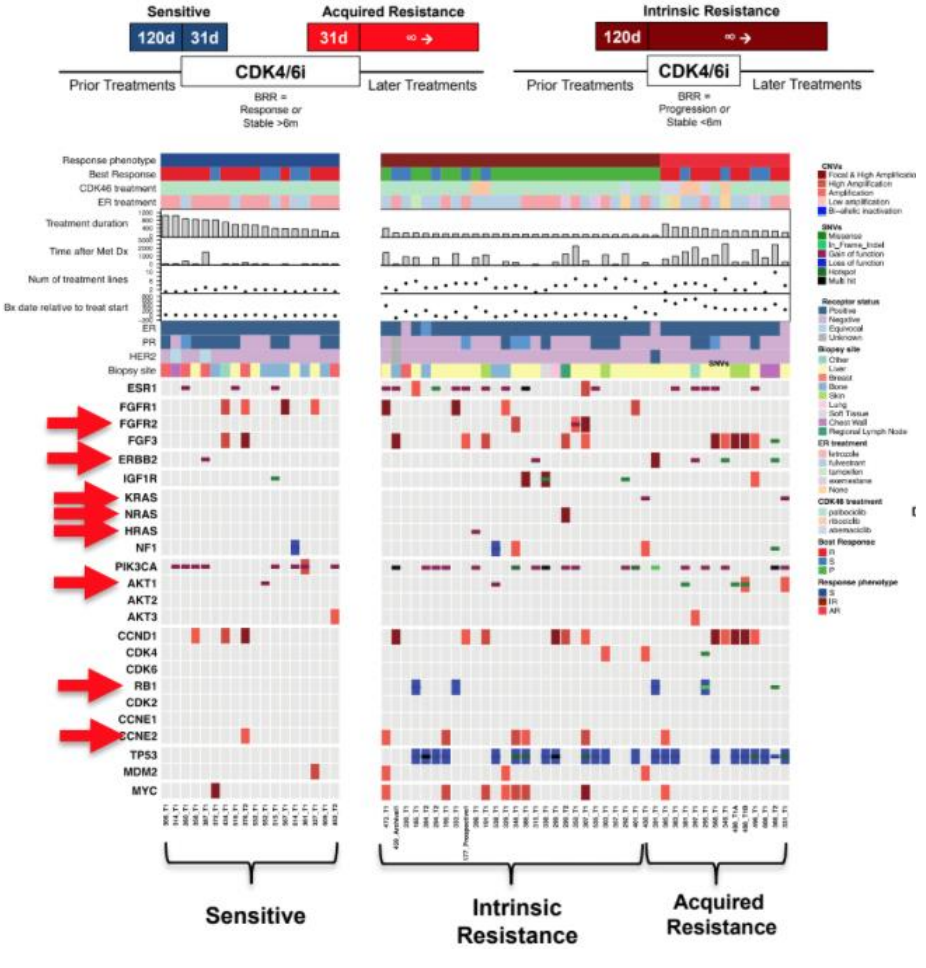
Endocrine resistance biomarkers?

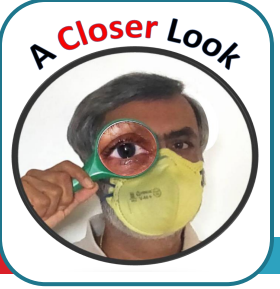
- mutations in the ligand-binding domain of the ESR1 gene
- overexpression or amplification of CDK6 and CCNE1,
- PI3K/mTOR-mediated CDK2 activation.

Primary vs Acquired Resistance to CDK4/6 Inhibitors

Primary Resistance:

- *RB1* loss, *IGFR1* amp, *RAS* mut
- *AKT1* mut or amp
- *FGFR2* mut or amp
- *AURKA* amp
- *CCNE2* amp

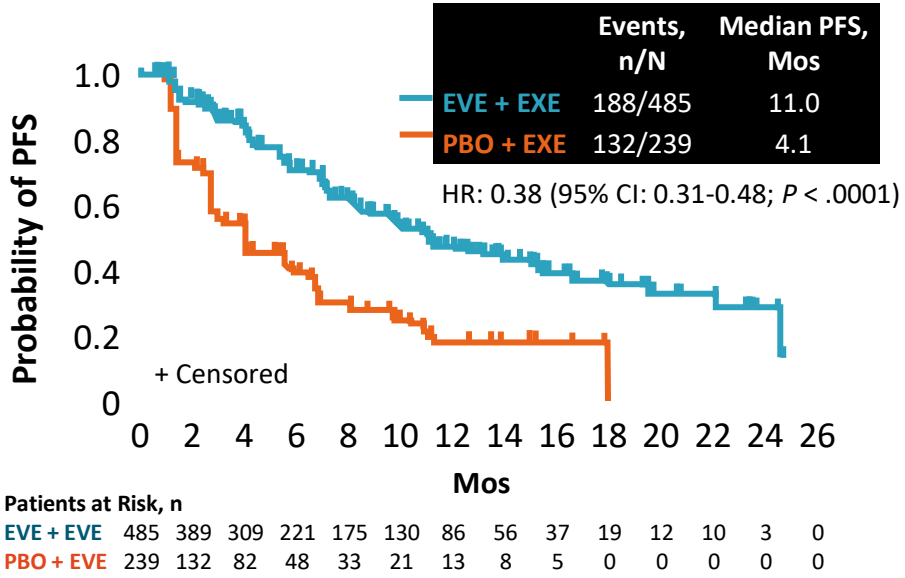




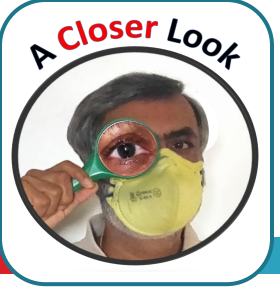
PIK3CA Mutation Is Associated With Poor Prognosis

- 28% of patients with HR+/HER2- MBC presented with a *PIK3CA* mutation
- less sensitivity to CT
- worse clinical outcome
- But still benefit from CDK 4/6 inhibition

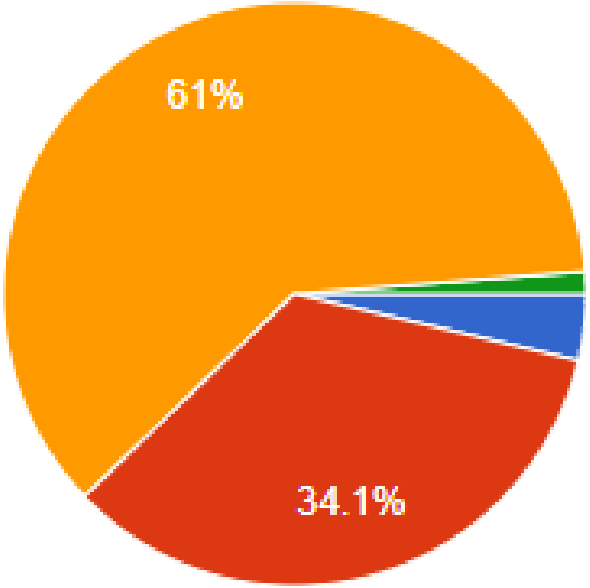
BOLERO-2 PFS with mTOR inhibition



regardless of *PIK3CA* mutation;
similar results with tamoxifen + fulvestrant

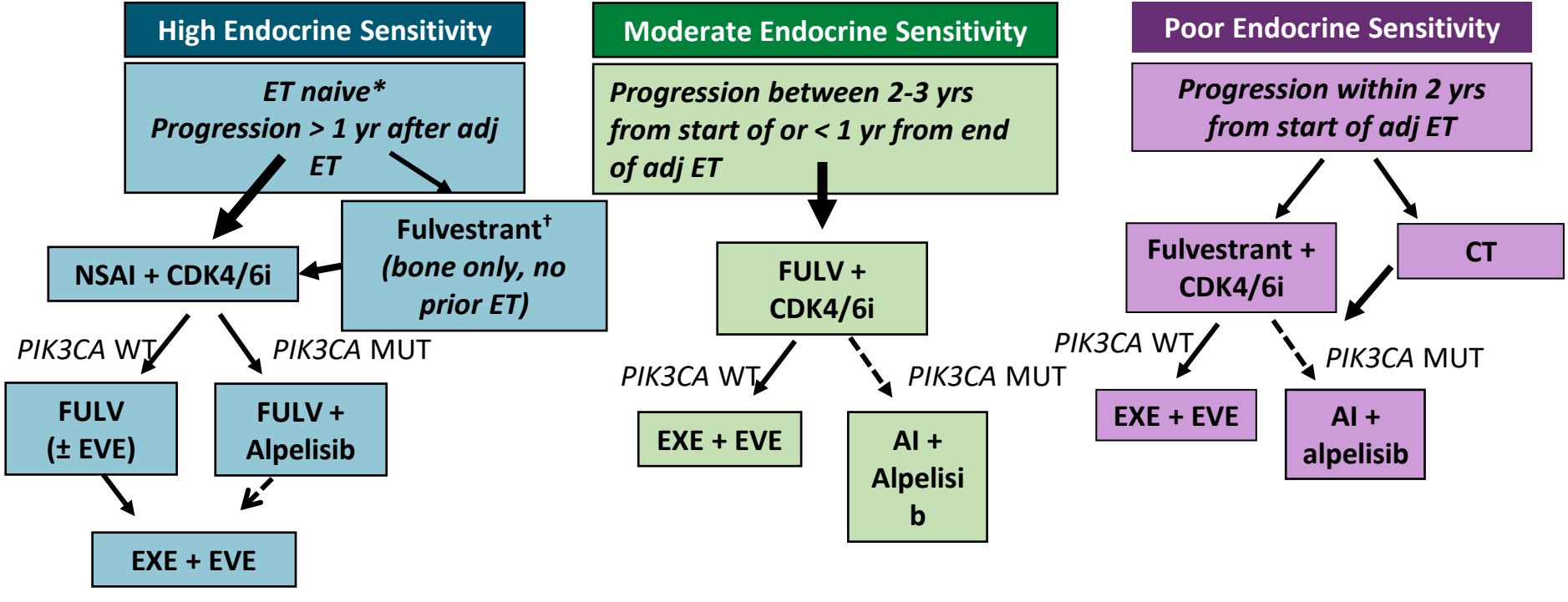


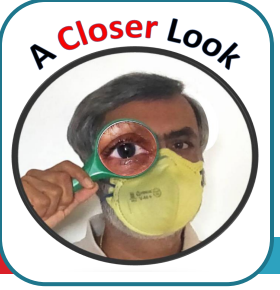
What is the first line CT for ER+ Her2- MBC
(survey amongst Indian oncologists)



- single agent taxane
- taxane plus cyclophosphamide
- AC followed by taxane single agent
- other

In you practice, do you decide Rx after classifying patients on basis of endocrine sensivitity?





Thank you