ESR1 Mutationstestung beim metastasierten ER+/HER2- Mammakarzinom

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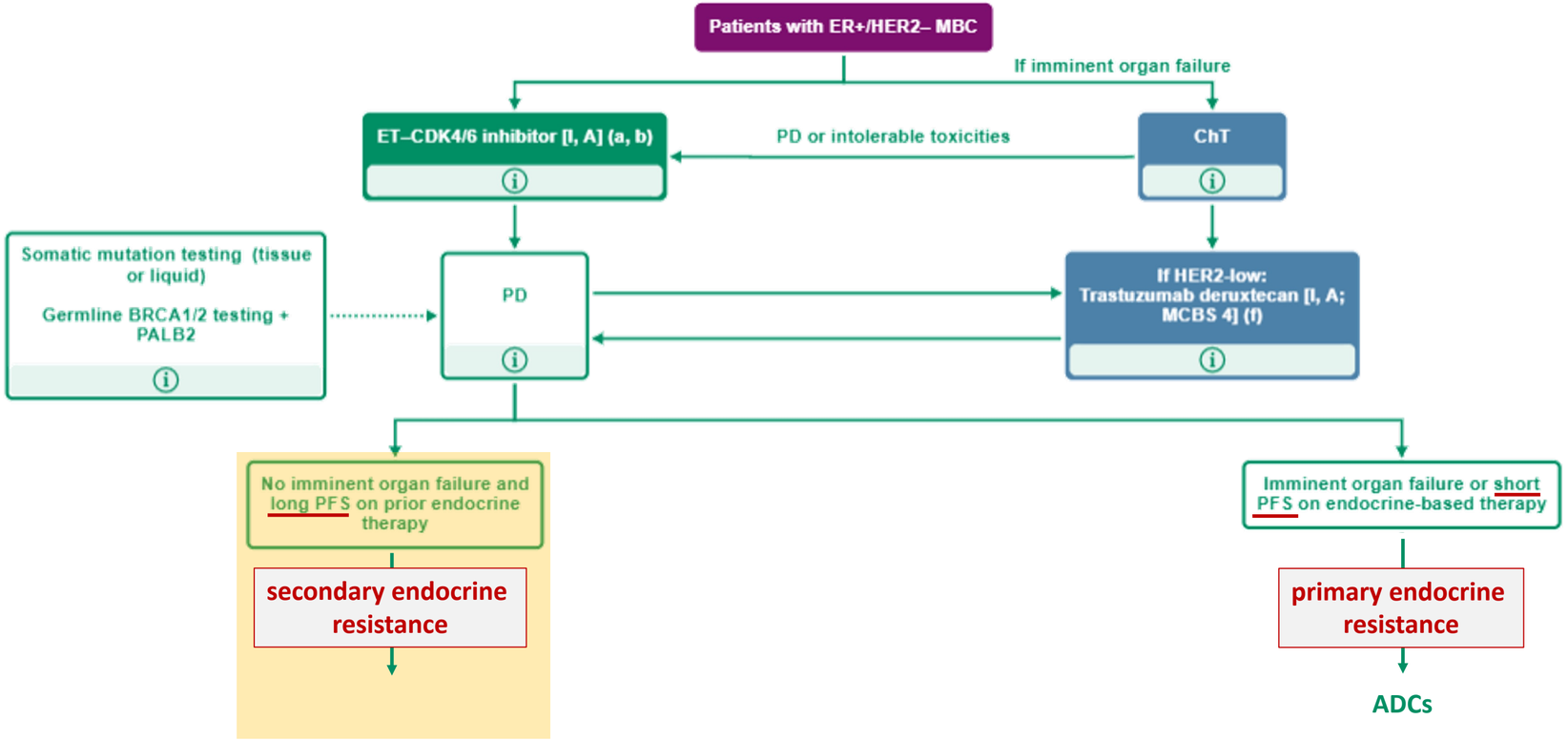
Brennpunkt Pathologie -Zürich, 19.01.2024

1st line treatment of metastatic breast cancer

Initial classification: **ER+, HER2-** vs. **HER2+** vs. **ER-,HR-, HER2-**



Adapted from Gennari et al., ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancerAnn Oncol. 2021 Dec;32(12):1475-1495 (ESMO Metastatic Breast Cancer Living Guideline, v1.1 May 2025)
Hartkopf et al., Endocrine-Resistant Breast Cancer: Mechanisms and Treatment, Breast Care. 2020 Aug; 15(4): 347–354.

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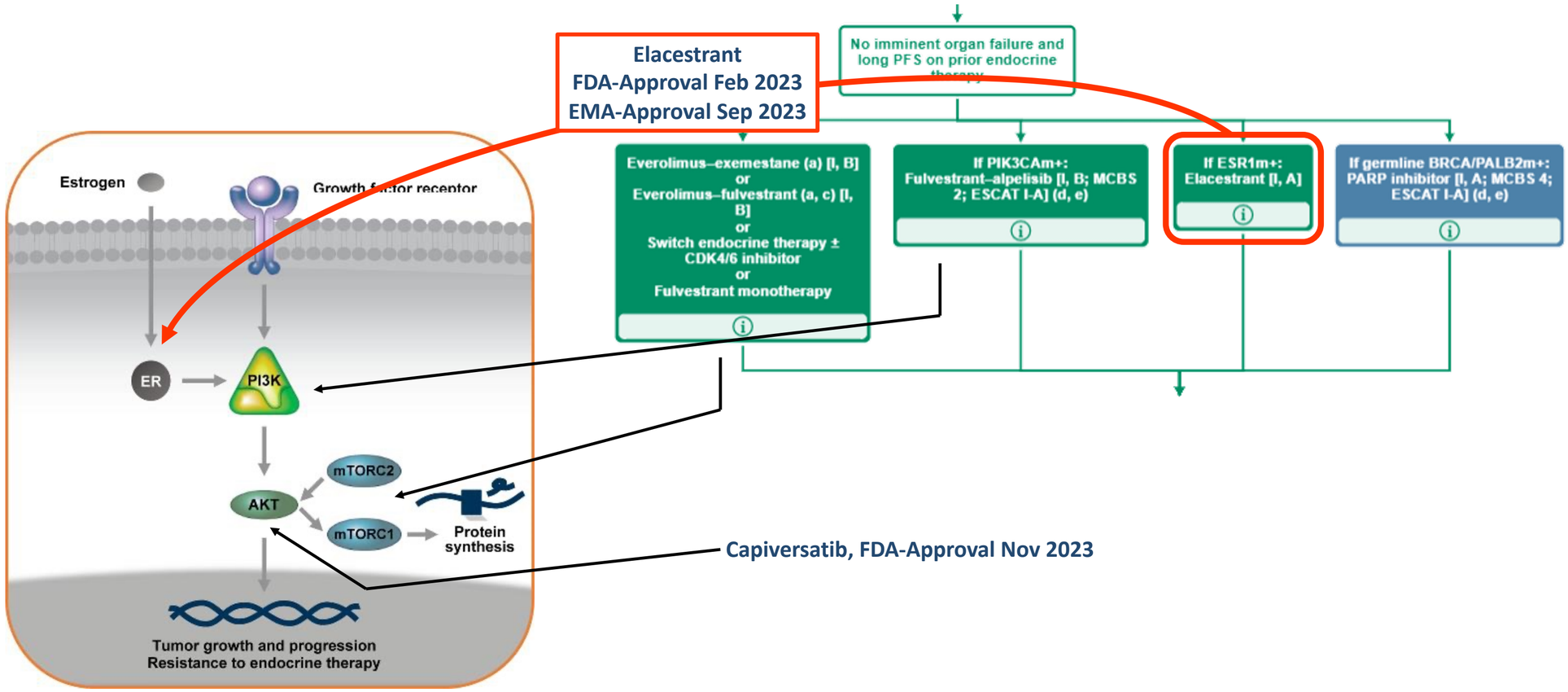
The PI3K/AKT/mTOR pathway in endocrine resistance



Adapted from Gennari et al., ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancerAnn Oncol. 2021 Dec;32(12):1475-1495 (ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023)
Nunnery et al., Targeting the PI3K/AKT/mTOR Pathway in Hormone Positive Breast Cancer, Drugs. 2020 Nov; 80(16): 1685–1697
https://www.pharmaceutical-technology.com/data-insights/camizestrant-astrazeneca-breast-cancer-likelihood-of-approval/
https://www.ema.europa.eu/en/medicines/human/EPAR/orserdu#ema-inpage-item-product-details
https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217639s000lbl.pdf
NOTE: Elacestrant is currently not approved by Swissmedic.

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European Commission Approves Menarini Group's ORSERDU® (Elacestrant) for the Treatment of Patients with ER+, HER2- Locally Advanced or Metastatic Breast Cancer with an Activating *ESR1* Mutation

- *Each year in Europe more than 550,000 patients are diagnosed with breast cancer, of whom 70% have estrogen receptor (ER)-positive disease[1]; more than 147,000 breast cancer patients in Europe die annually from the disease[2]*
- *ORSERDU is the first treatment specifically for patients with ER+, HER2- advanced or metastatic breast cancer tumors that harbor ESR1 mutations, representing the first innovation in endocrine therapy in nearly 20 years*
- *ESR1 mutations are present in up to 40% of ER+, HER2- advanced or metastatic breast cancers, and are a known driver of resistance to standard endocrine therapy, making these tumors more difficult to treat*

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
ORSERDU monotherapy is indicated for the treatment of postmenopausal women, and men, with estrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor.

4.2 Posology and method of administration Treatment with
ORSERDU should be initiated by a physician experienced in the use of anticancer therapies. Patients with ER-positive, HER2-negative advanced breast cancer should be selected for treatment with ORSERDU based on the presence of an activating ESR1 mutation in plasma specimens, using a CE marked in vitro diagnostic (IVD) with the corresponding intended purpose. If the CE-marked IVD is not available, the presence of an activating ESR1 mutation in plasma specimens should be assessed by an alternative validated test.

https://www.ema.europa.eu/en/medicines/human/EPAR/orserdu#ema-inpage-item-product-details
NOTE: Elacestrant is currently not approved by Swissmedic.

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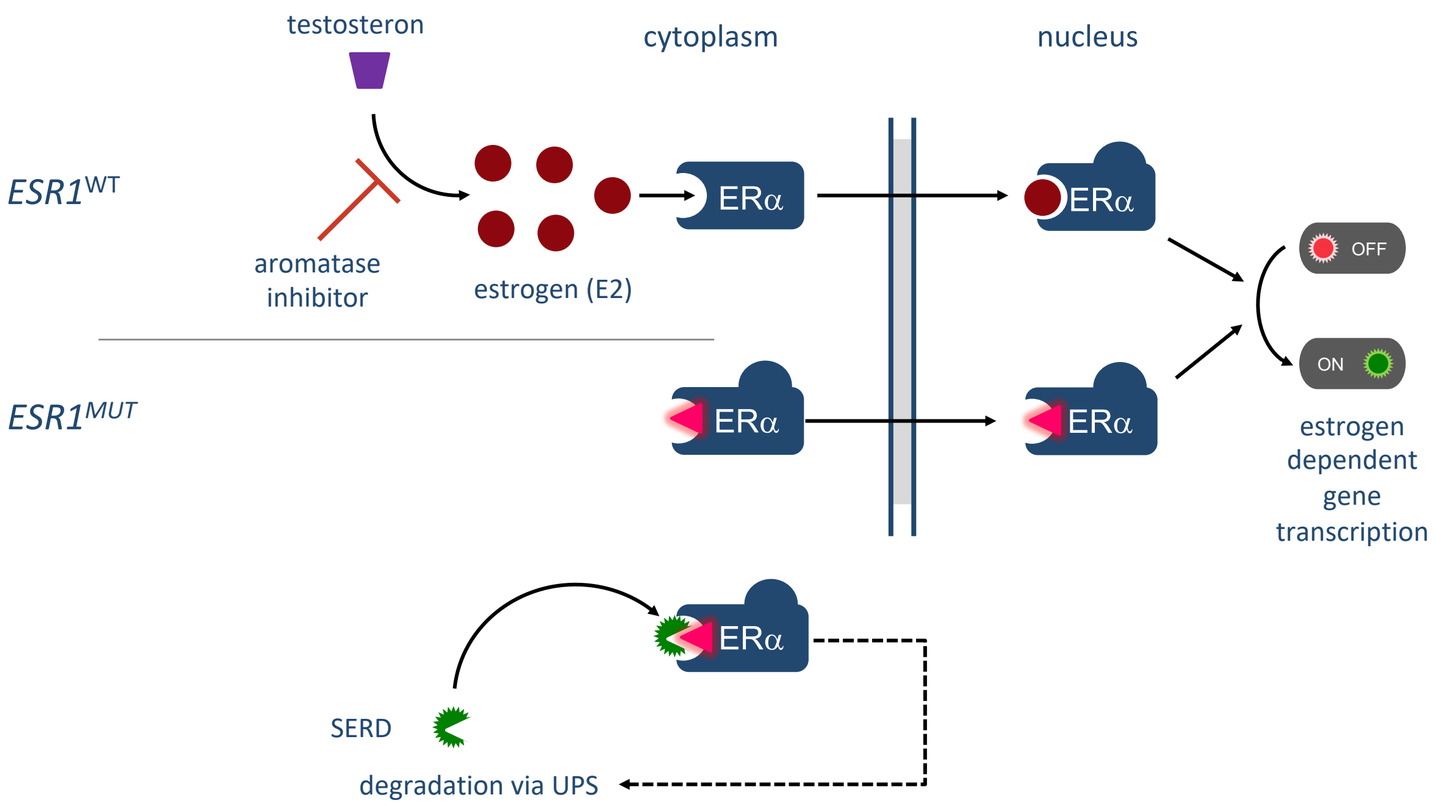
ESR1 mutations as a driver of endocrine resistance



Adapted from:
Bihani T, et al. Elacestrant (RAD1901), a Selective Estrogen Receptor Degrader (SERD), Has Antitumor Activity in Multiple ER+ Breast Cancer Patient-derived Xenograft Models Clin Cancer Res. 2017 Aug 15;23(16):4793-4804
Patel HK, et al. Selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs) in cancer treatment Pharmacol Ther. 2018 Jun;186:1-24
Piscuoglio S. et al. ESR1 and endocrine therapy resistance: more than just mutations Ann Oncol. 2018 Apr 1;29(4):787-789
Brett JO. Et al. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer Breast Cancer Res. 2021 Aug 15;23(1):85

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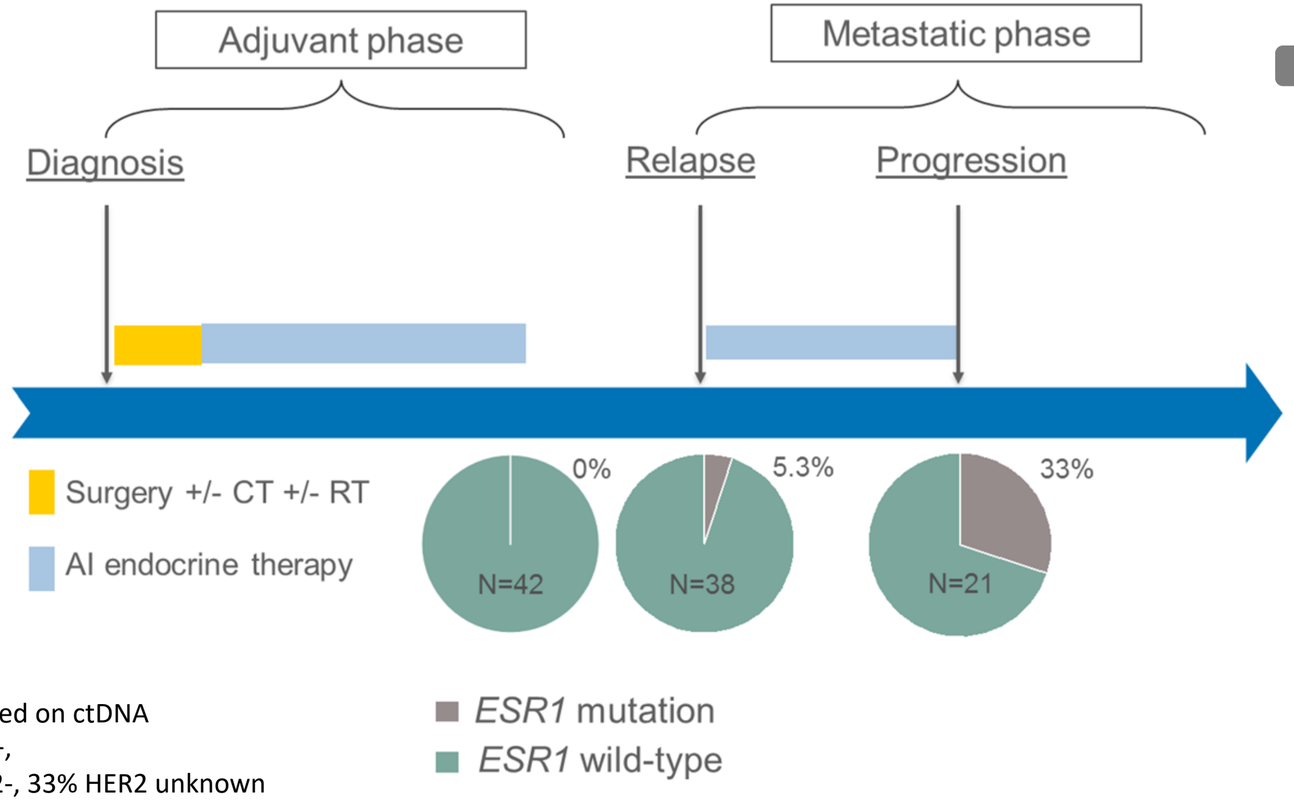
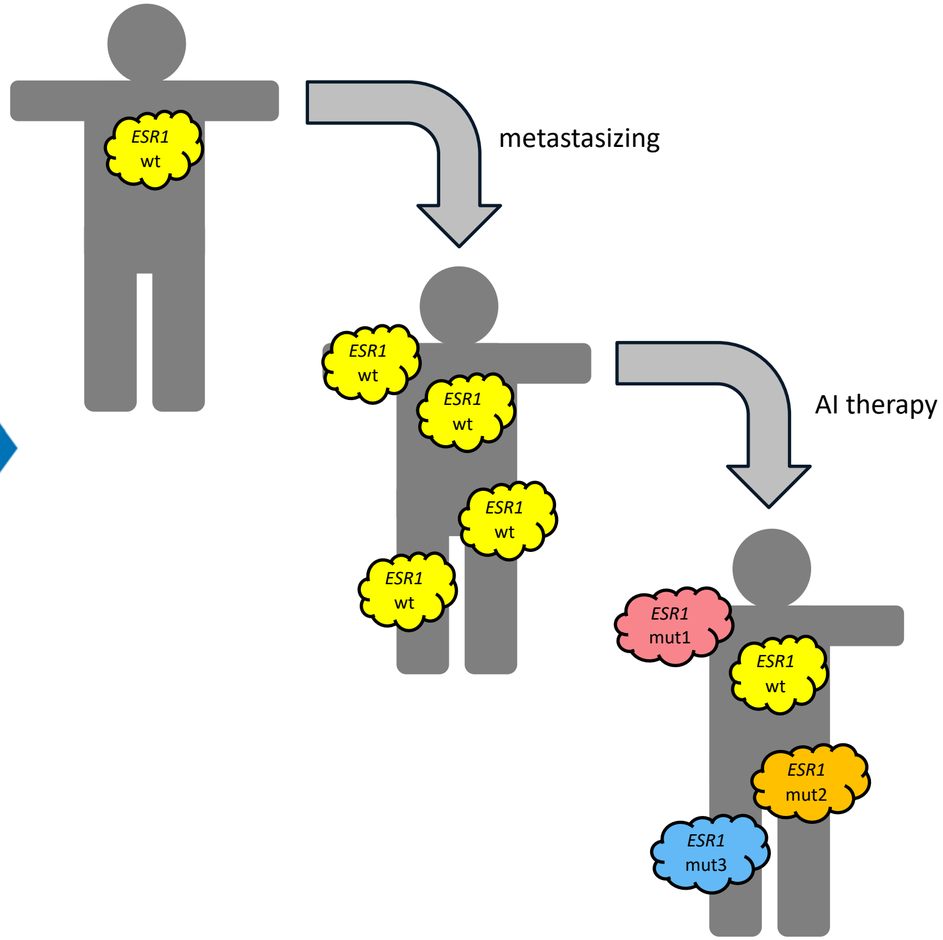
Clonal evolution of *ESR1* mutations



n=42, based on ctDNA
100% HR+,
60% HER2-, 33% HER2 unknown



Allouchery et al. Circulating ESR1 mutations at the end of aromatase inhibitor adjuvant treatment and after relapse in breast cancer patients Breast Cancer Res. 2018 May 16;20(1):40

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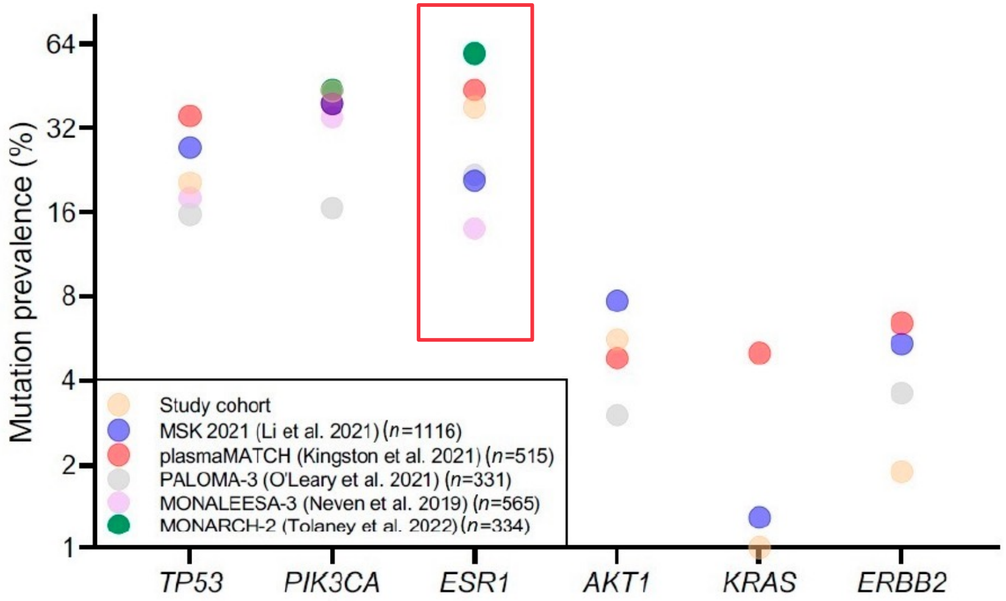
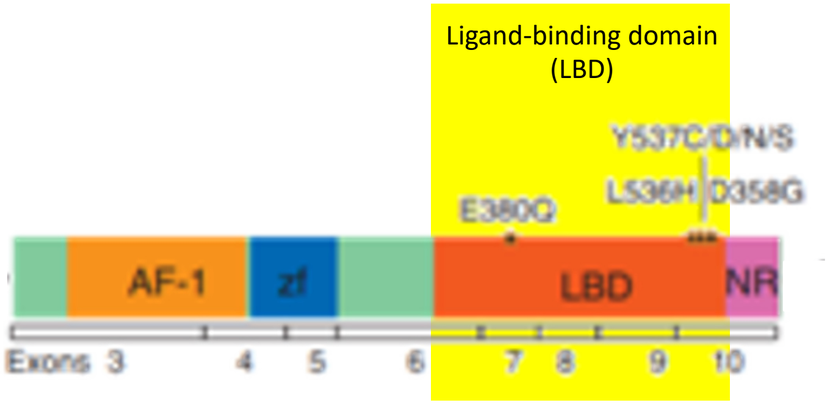
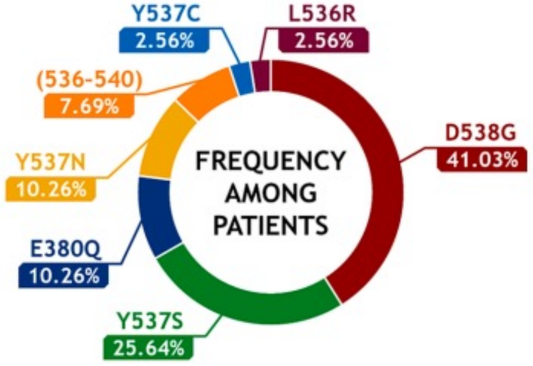
ESR1 mutations in endocrine resistance







Fuentes-Antrás et al. Real-World Use of Highly Sensitive Liquid Biopsy Monitoring in Metastatic Breast Cancer Patients Treated with Endocrine Agents after Exposure to Aromatase Inhibitors Int. J. Mol. Sci. 2023, 24(14), 11419
Callens C. et al. Real-Time Detection of ESR1 Mutation in Blood by Droplet Digital PCR in the PADA-1 Trial: Feasibility and Cross-Validation with NGS Anal. Chem. 2022, 94, 16, 6297–6303
Corné et al. Development of sensitive and robust multiplex digital PCR assays for the detection of ESR1 mutations in the plasma of metastatic breast cancer patients Clinica Chimica Acta Volume 545, 1 May 2023, 117366

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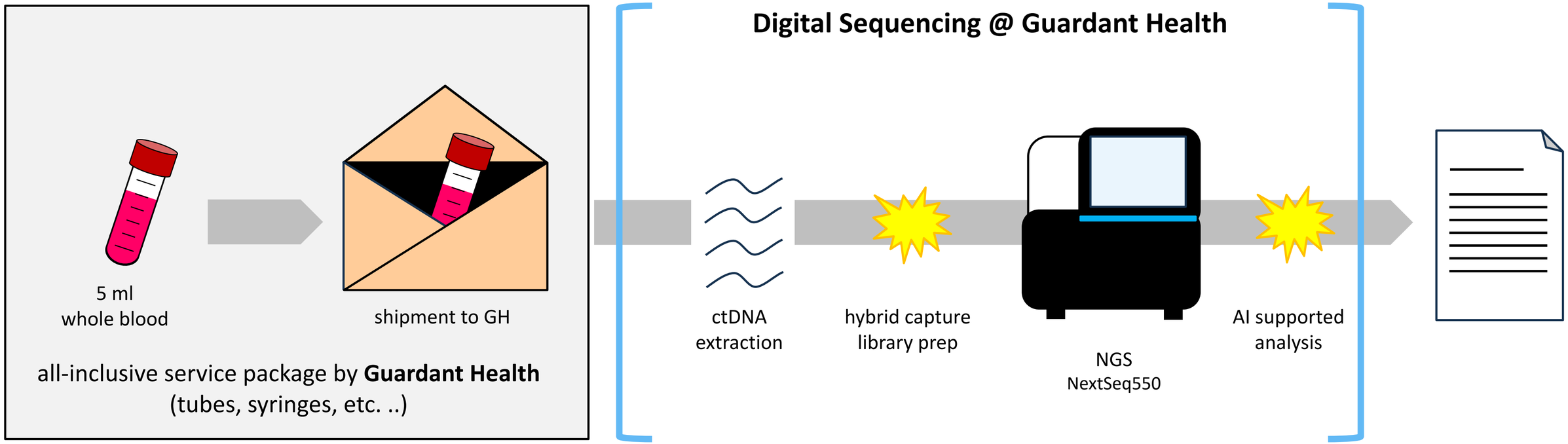
ESR1 testing in the pivotal EMERALD trial



Insert LBD

ESR1 (NM_001122742) – LLOD 0.3% MAF 30ng input, 1.1% MAF 5 ng input
SNV: K303R; **E380Q**; V392I; S436P; S463P; L469V; R503W; V534E; P535H; L536H**; L536P; L536R; L536Q;** L536G; L536K**; Y537S; Y537C; Y537D; Y537H; Y537N; D538G; D538E**; T594R

https://guardant360cdx.com/wp-content/uploads/guardant360-cdx-technical-information.pdf - accessed 20230210
https://axial.substack.com/p/axial-guardant-health - accessed 20230210

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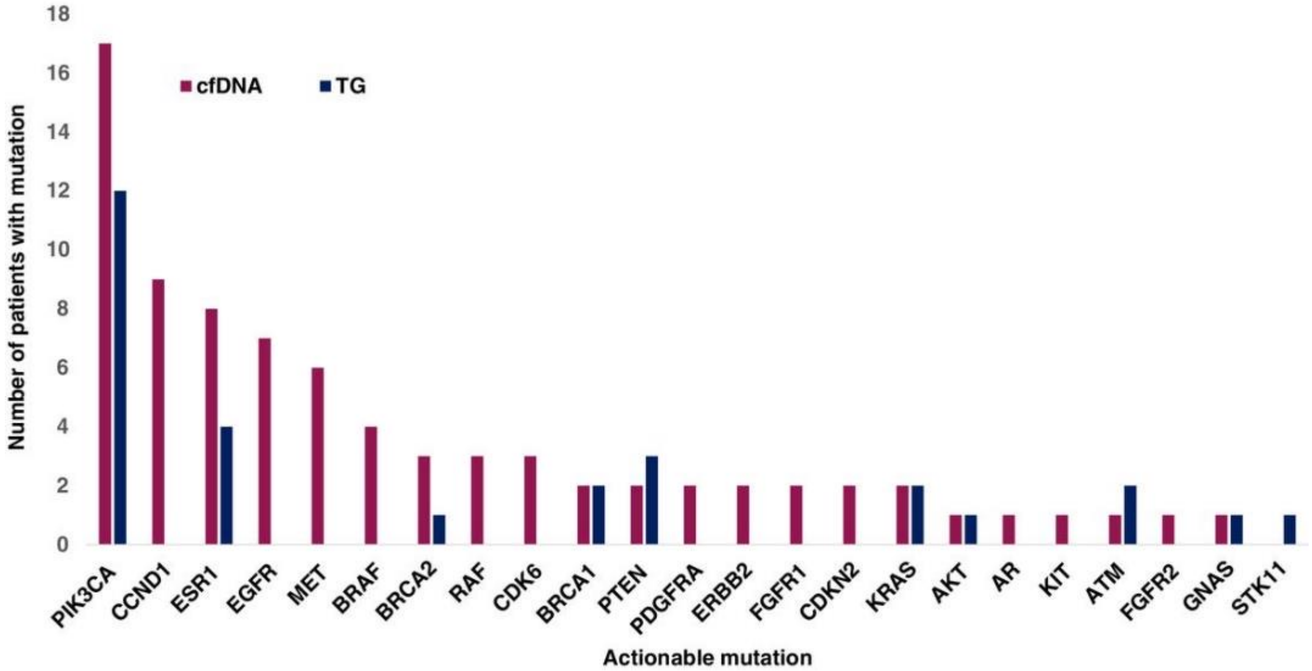
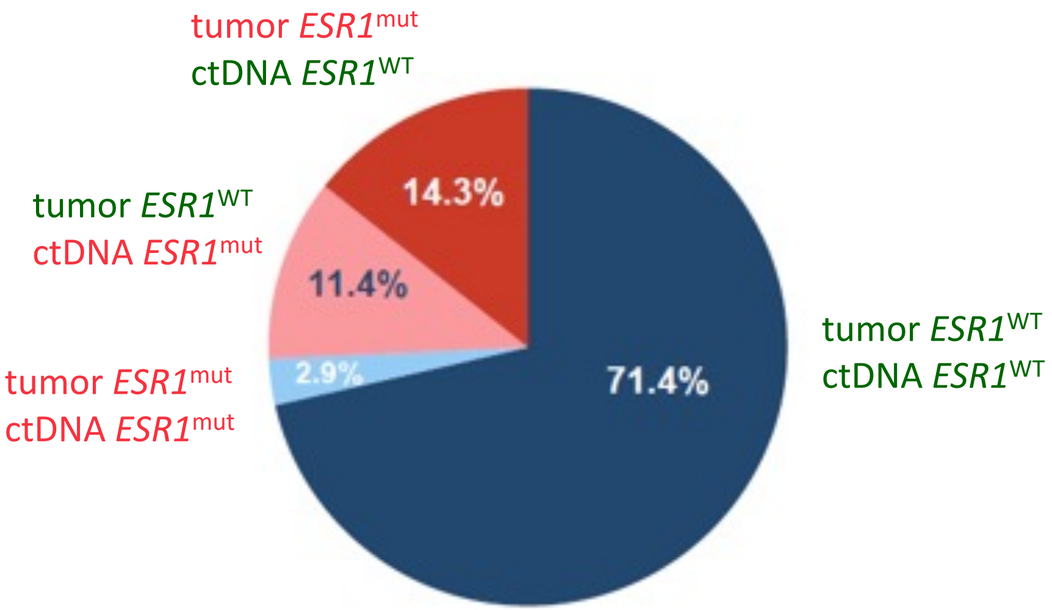
Concordance of *ESR1* mutations in tumor and plasma



cfDNA = cell-free DNA (80% actionable mutations)
TG = tumor genotyping (63% actionable mutations)
n=30 (97% HR+,HER2-), 83.1% simultaneous testing
tumor – custon 90 gene panel
ctdna – GH 73 gene panel



n=35 (90% ER+,91% HER2-), 52% simultaneous testing
ddPCR detecting 4 *ESR1* mutations: Y537S, Y537N, Y537C, and D538G

Vidula N. et al. Tumor Tissue- versus Plasma-based Genotyping for Selection of Matched Therapy and Impact on Clinical Outcomes in Patients with Metastatic Breast Cancer Clin Cancer Res (2021) 27 (12): 3404–3413
Takeshita T. et al. Comparison of ESR1 Mutations in Tumor Tissue and Matched Plasma Samples from Metastatic Breast Cancer Patients Transl Oncol. 2017 Oct; 10(5): 766–771

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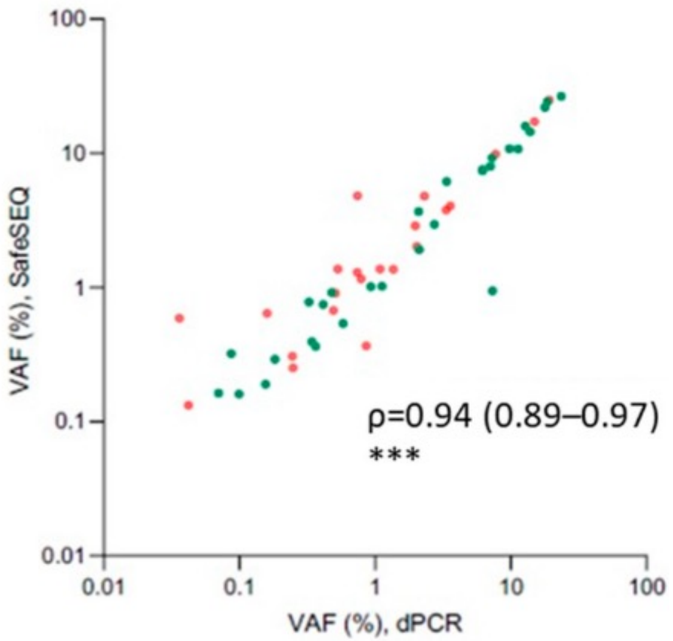
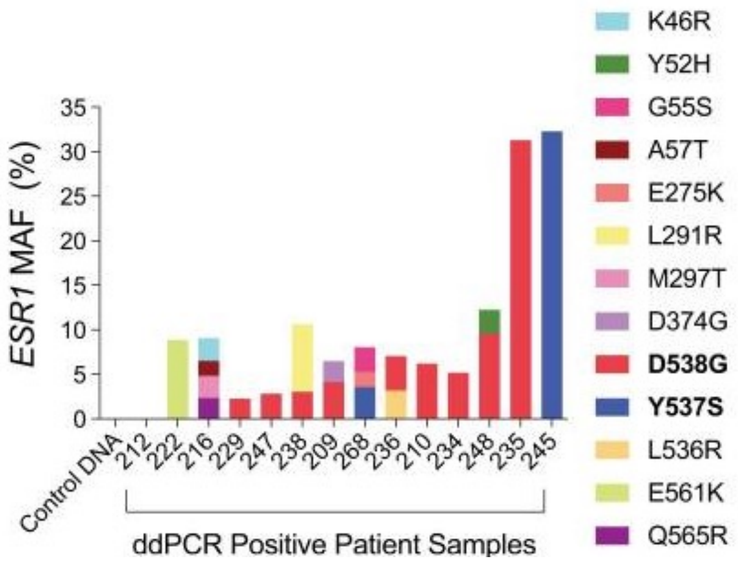
Variables for *ESR1* liquid biopsy: **methodology**





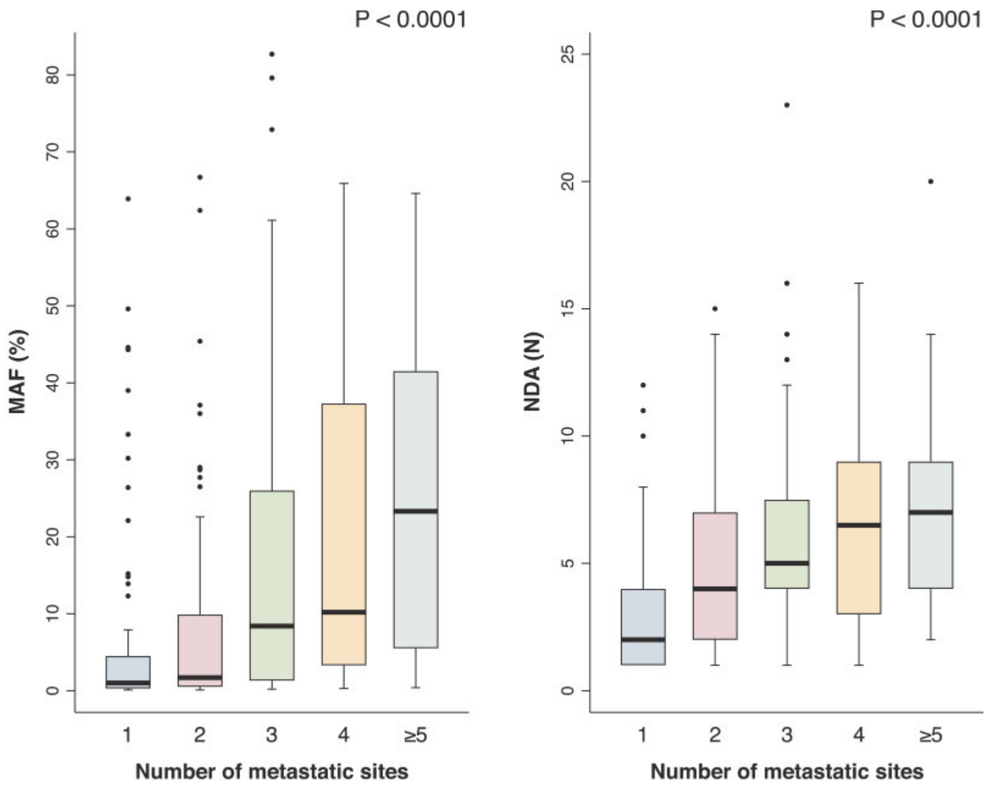
VAF = variant allele frequency
SafeSeq = UMI-based NGS approch to detect rate variants
dPCR = PIK3CA (E545K, E542K, and H1047R) and ESR1 (Y537S and D538G)
121 samples from 54 patients, prevalance: *PIK3CA* 44%, *ESR1* 39%

MAF = mutant allele frequency
dPCR = 5-plex assay
ER + mBC, stage IV, and a history of progression on a prior line of endocrine therapy

Fuentes-Antrás et al. Real-World Use of Highly Sensitive Liquid Biopsy Monitoring in Metastatic Breast Cancer Patients Treated with Endocrine Agents after Exposure to Aromatase Inhibitors Int. J. Mol. Sci. 2023, 24(14), 11419
Kumar et al. Tracking plasma DNA mutation dynamics in estrogen receptor positive metastatic breast cancer with dPCR-SEQ npj Breast Cancer 4, 39 (2018)

Variables for *ESR1* liquid biopsy: **ctDNA content**

blood ctDNA level
Increase with the number of metastatic sites



ctDNA heterogeneity
Increase with the number of metastatic sites

MAF = mutant allele frequency
NDA = number of detectable alteration
1.6 weeks median timeframe between blood and imaging analysis
left: ctDNA MAF of the highest variant
Right: NDA as surrogate for tumor heterogeneity
n=344 patients, stage IV mBC

Davis et al. Landscape of circulating tumour DNA in metastatic breast cancer EBioMedicine. 2020 Aug;58:102914

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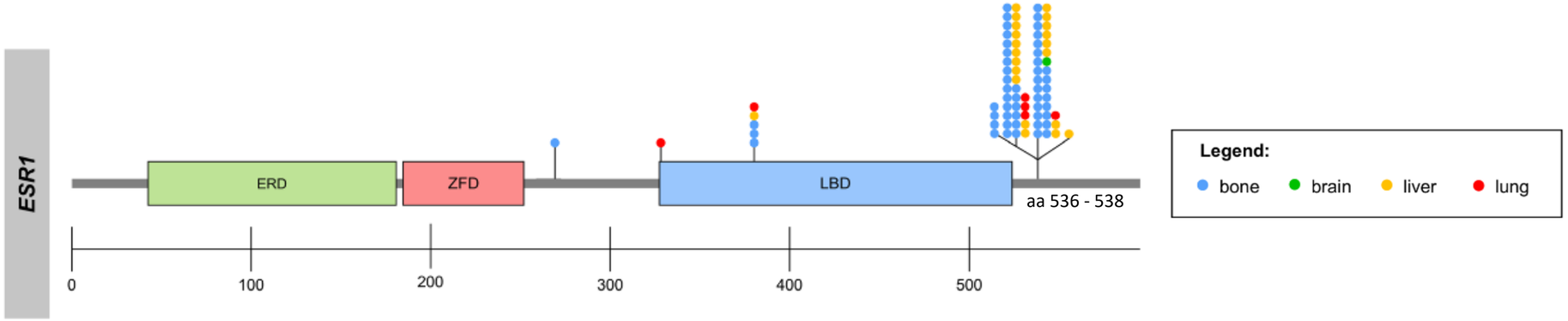
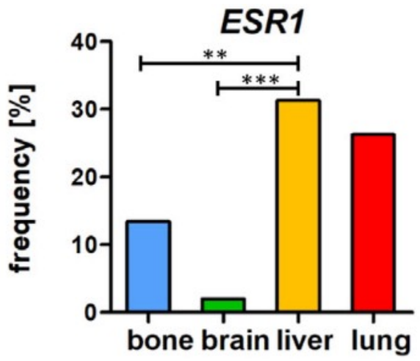
Variables for *ESR1* liquid biopsy: **metastatic site**





521 mBCs cases (389 bone lesions, 49 brain, 64 liver and 19 lung)
Samples were take at time point of metastatic diagnosis
ER/PR+, HER2- 63%, HER2+ 7%, TNBC 11%, unclassified 18%
NGS analysis with custom panel
*ESR1*m rate 15%

Grote et al., Frequency of genetic alterations differs in advanced breastcancer between metastatic sites, Genes Chromosomes Cancer.2023;1–10

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Things to be discussed..

- HR+/HER2- mBC is a considerable big patient collective
- negative test results
- VUS (variant of unknown significance) interpretation