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Luminal metastatic breast cancer:

Therapy and prespectives through discussion of clinical cases

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CLINICAL CASE # 1

Karine, 63 years

- No relevant medical history
- Menopausal since the age of 50

- **Apr 2009:** lumpectomy + ALD:
  - pT1c (12 mm) N1a (1+LN/13)M0
  - Moderately differentiated – grade 2, Ki-67:10%
  - ER-8/8, PR-8/8, HER2 1+
  - Mindact: clinical high, genomic low →R to follow clinical risk

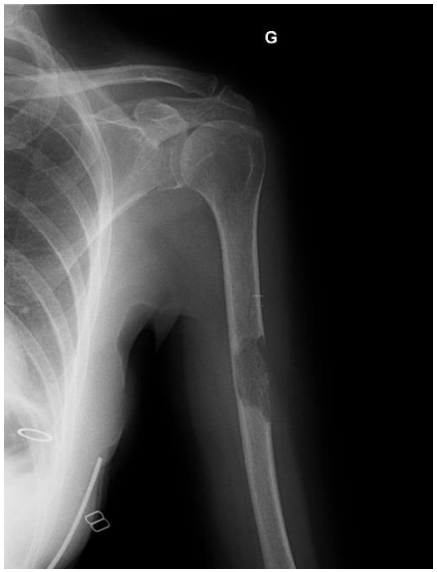
Adjuvant treatment

- 18/05/2009-20/07/2009: 4 x EC
- Radiotherapy
- 7 years of ET
  - Tamoxifen: 10/2009 – 10/2011
  - Letrozole: 10/2011-10/2016

September 2017
(11 month after the end of adjuvant NSAI)

- pain in the left humerus
- ECOG PS-1
- CA 15-3: 15 U/ml (N)
- x-ray of the humerus: large lytic lesion, risk of fracture

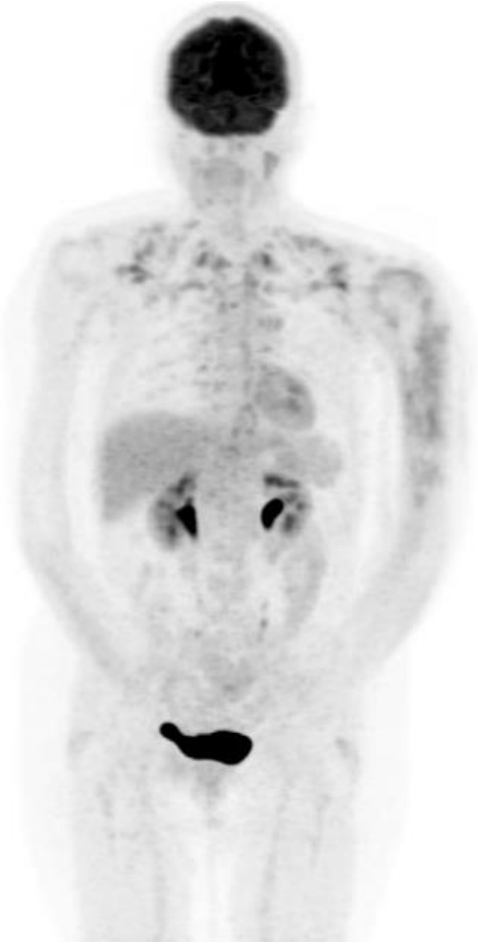
06/09/2017



Surgery → radiotherapy

Pathology:
-bone metastasis of breast cancer origin
-ER: 8/8, PR: 5/8, HER2 1+

FDG/PET-CT: 21/09/2017



FDG PET/CT
21/09/2017

No other lesion suggesting metastasis

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What would you choose for systemic therapy?

- Fulvestrant alone
- Fulvestrant + CDK 4/6 inhibitor
- NSAI + CDK 4/6 inhibitor
- Exemestane + everolimus
- Watchful waiting

- 10/2017 - 02/2018: **tamoxifen**
- 02/2018: new bone lesions L1,L2, left iliac
- Inclusion in Aurora “bone only” cohort: ctDNA not detected → NGS not performed
- 02/2018 – 12/2018: **fulvestrant + palbociclib**
- 12/2018: multiple bone metastases, one liver met (segment II), no symptoms, ECOG PS-1

PFS and OS with 1st and 2nd line CDK 4/6 inhibitors

	PALOMA-2	MONALEESA-2	MONARCH 3	MONALEESA-7	PALOMA-3	MONARCH 2	Monaleesa 3
Study design	Phase III Placebo-controlled **1st-line** (n=666) Postmenopausal	Phase III Placebo-controlled **1st-line** (n=668) Postmenopausal	Phase III Placebo-contr **1st-line** (n=493) Postmenopau				
Prior therapy	No prior systemic therapy **for ABC**	No prior systemic therapy **for ABC**	No prior syste therapy **for ABC**				
Endocrine therapy	Letrozole	Letrozole	NSAI	Tamoxifen NSAI/LHRHa	Fulvestrant	Fulvestrant	Fulvestrant
CDK4/6 inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Palbociclib	Abemaciclib	Ribociclib
HR PFS	**0.58**	**0.56**	**0.54**	**0.55**	**0.46**	**0.55**	**0.59**
Median PFS (mo)	24.8 vs 14.5	25.3 vs 16.0	28 vs 14.7	23.8 vs 13.0	11.2 vs 4.6	16.4 vs 9.3	20.5 vs 12.8
HR OS	NA	NA	NA	**0.71**	**0.81**	**0.75**	**0.72**
Median OS	NA	NA	NA	NR vs 40.9	34.9 vs 28	46.7 vs 37.3	NR vs 40

Trial	Paloma 3	Monarch 2	Monaleesa 3
Prior ET			
(Neo)adjuvant	22%	60%	60%
MBC setting	**77%**	38%	20%
Prior chemo	**34% 1 line for MBC**	none	none

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Cristofanilli et al, Lancet Oncol 2016; Finn et al, NEJM 2016, Hortobagyi et al NEJM 2016, Tripathy et al, Lancet 2018, Sledge et al, JCO 2017; Goetz et al, JCO 2017; Slamon et al, JCO 2018; Turner et al, NEJM 2018; Sledge et al, JAMA 2020, Im et al, NEJM 2019

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What would you choose for systemic therapy?

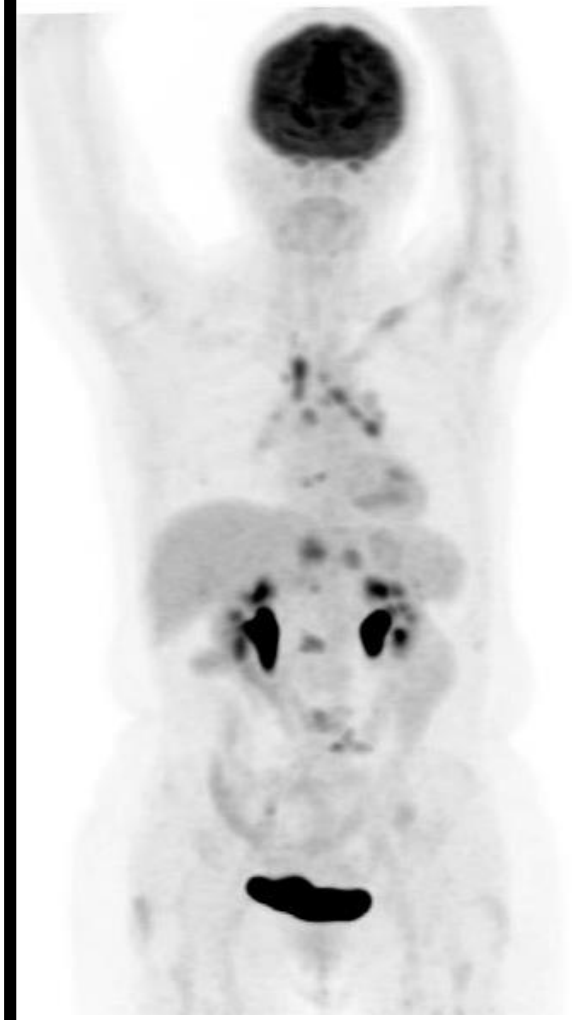
- Cytotoxic chemotherapy
- Exemestane – Everolimus
- Inclusion in a clinical trial with oral SERDs
- New biopsy (liver) and NGS before treatment decision

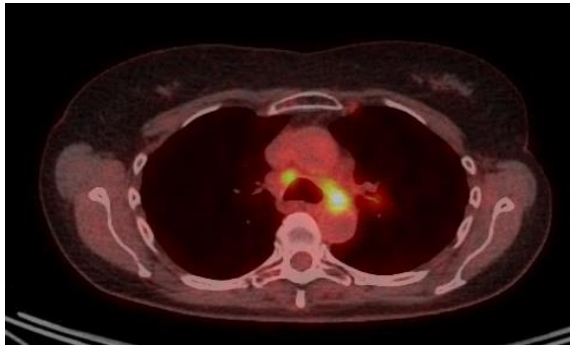
- **Liver biopsy:**
  - adenocarcinoma of breast cancer origin
  - ER: 8/8, PR: 0/8, HER2 2+, FISH: negative
  - TGS of 48 genes (1000x, Illumina MiSeq):
    no pathogenic mutation detected

- 12/2018-02/2019: **exemestane – everolimus**

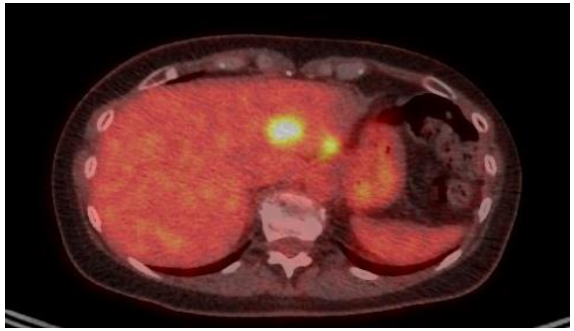
- 02/2019: new bone and lymph node metastases, progression of the liver lesion;
  no symptoms, ECOG PS-0

FDG/PET-CT: 11/02/2019

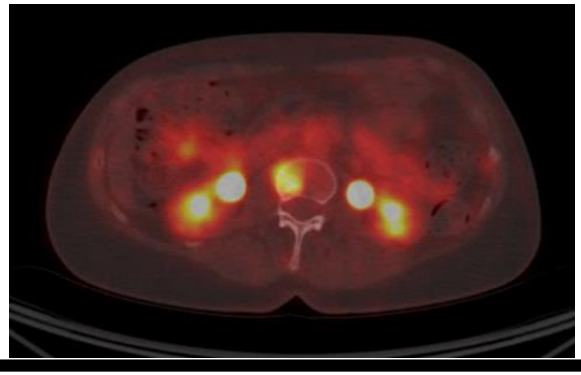




Adénopathies médiastinales



Atteinte hépatique

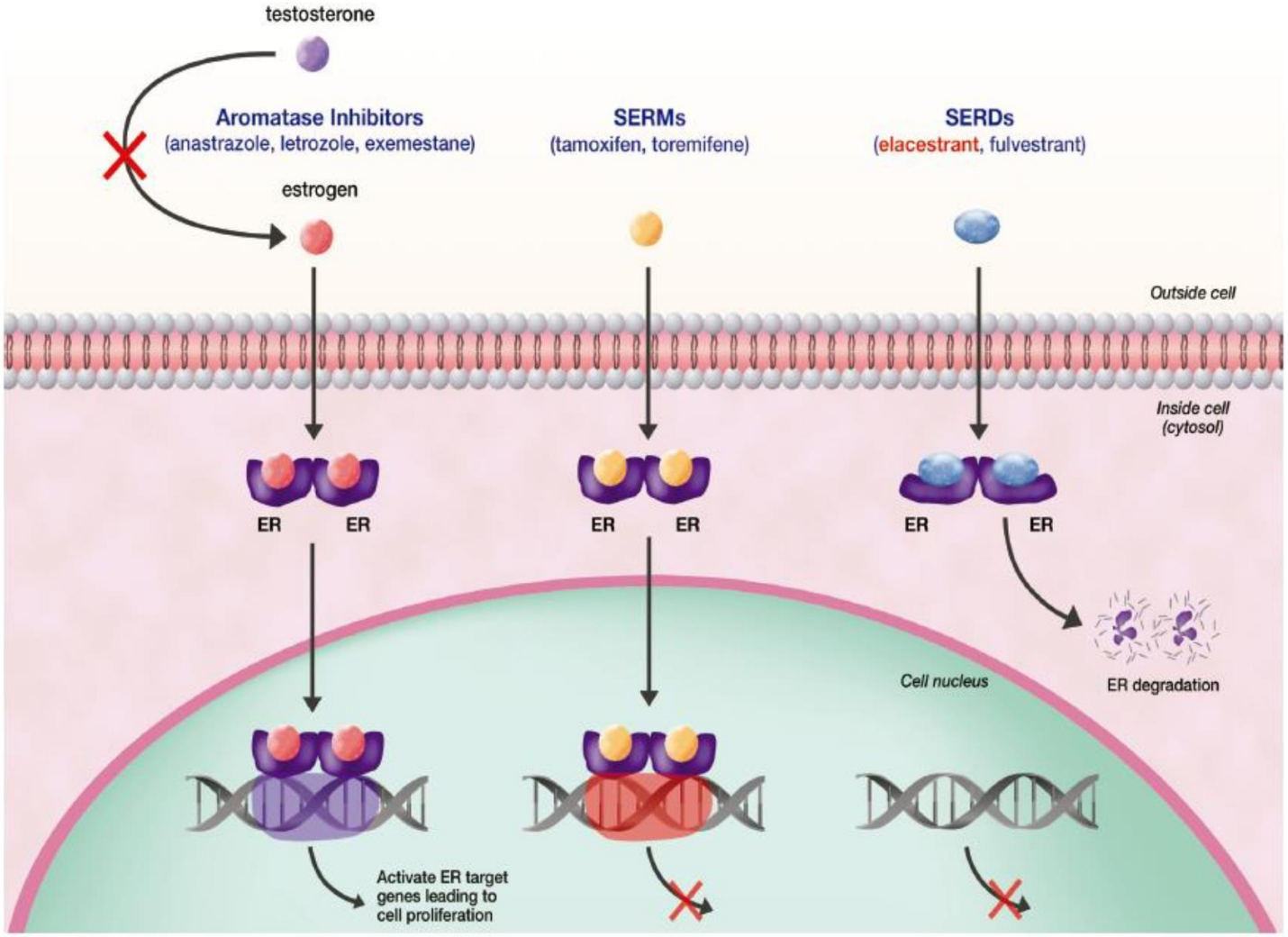


Atteinte osseuse

What would you choose for systemic therapy?

- Single agent chemotherapy using a taxane
- Single agent chemotherapy using capecitabine
- Combined chemotherapy (ex. capecitabine + taxane)
- Inclusion in a clinical trial with oral SERDs

New oral SERDs

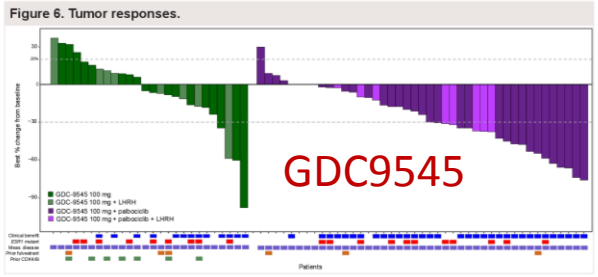


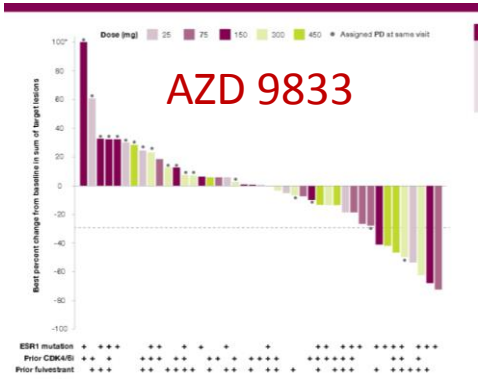
Bardia et al, Future Oncol 2019

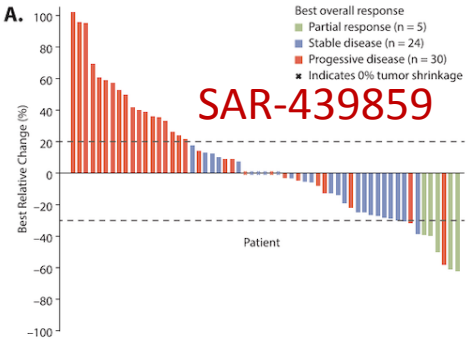
Oral SERDs clinical development

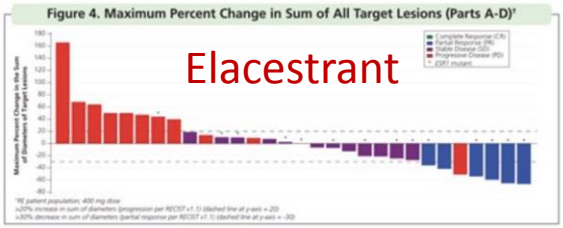
Drug	Company	Completed Trials	Ongoing Trials
GDC-9545	Genentech		Phase I dose escalation and expansion as a single agent and + palbociclib
RAD-1901/ Elacestrant	Radius	Phase 1 dose escalation and expansion Phase 1B FES-PET study	Phase III study of single agent vs TPC
AZD-9496	Astra Zeneca	Phase I dose escalation and expansion	Window pre-op study compared to fulvestrant x 1 dose accrual completed
AZD-9833	Astra Zeneca		Phase I dose escalation and expansion as a single agent and + palbociclib
SAR-439859	Sanofi	Part A presented at ASCO 2019	Phase I/II dose escalation and expansion as a single agent and + palbociclib
LSZ102	Novartis	Phase I single agent data presented at SABCS 2018	Phase I/Ib: Single agent, + ribociclib, + alpelisib
G1T48	G1 Therapeutics		Phase I: Single agent dose escalation and expansion
ZN-C5	Zeno		Phase I/II dose escalation and expansion as a single agent and + palbociclib
LY3484356	Lilly		

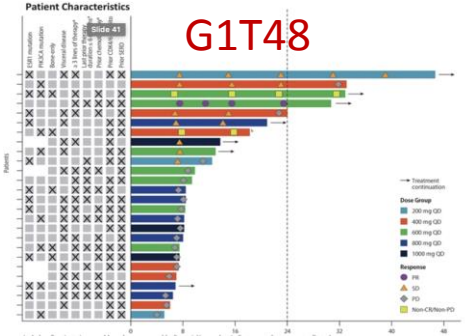
Favorable clinical properties (oral)
Good safety profile
RR: 13-20%, mPFS: 4.5-7.8 mo
Effective in ESR1m and ESR1 wt tumors
Effective after CDK 4/6 inh and after fulvestrant
Partners well with CDK 4/6 inh and PI3K inh











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Lim et al, ASCO 2020; Kaklamani et al, SABCS 2019; Dees et al, ESMO 2020, Hamilton, ASCO 2020; Linden, SABCS 2020

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28/02/2019- 23/05/2019: clinical trial using an **oral taxane**

			Baseline (02/26/2019 - CT SCAN STUDY THO+ABD)	Follow-up 1 (04/18/2019 - C T SCAN STUDY THO+ABD)	Follow-up 2 (05/16/2019 - C T SCAN STUDY THO+RET)
Target lesions					
	1	**T01 Liver Segment III** *Liver Segment III*	*LA: 22.6 mm*	*LA: 15.2 mm*	*LA: 12.3 mm*
Non-target lesions					
	1	**NT01 Bone vertebrae lumbar** *Bone vertebrae lumbar*	*LA: -- mm* **State**: *Present*	*LA: -- mm* **State**: *Present*	*LA: -- mm* **State**: *Present*
Findings					
	1	**F01 Other** *Other*	*LA: -- mm* **State**: *Defined*	**State**: *Undefined*	**State**: *Undefined*
	2	**F02 Pleura** *Pleura*	**State**: *Undefined*	**State**: *Undefined*	*LA: -- mm* **State**: *Defined*
	3	**F03 Peritoneum** *Peritoneum*	**State**: *Undefined*	**State**: *Undefined*	*LA: -- mm* **State**: *Defined* *ascite*
Evaluation	**Target sum**		**22.6 mm**	**15.2 mm** *-32.9% ΔB / -32.9% ΔN / -32.9% ΔP*	**12.3 mm** *-45.6% ΔB / -19.0% ΔN / -19.0% ΔP*
	Target response			**Partial Response**	**Partial Response**
	Non-target response			**Non-CR/Non-PD**	**Non-CR/Non-PD**
	New lesions present			**No**	**No**
	Timepoint response			**Partial Response**	**Partial Response**

Treatment stopped for toxicity: grade III hand-foot syndrome, fatigue, fluid retention

Dec 2019: progressive disease

(bone, lymph node, liver), LFTs-normal, bone pain

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Oral taxanes in luminal breast cancer: tesetaxel+capecitabine

Key Eligibility Criteria

- HR positive, HER2 negative MBC
- 0-1 prior chemotherapy regimens for MBC
- Prior taxane in the neoadjuvant or adjuvant setting required
  - No restriction on disease-free interval (DFI)
- Any number of prior endocrine therapies
- Any number of prior approved targeted therapies (*e.g.*, CDK 4/6 inhibitors, everolimus)
- Measurable disease per RECIST 1.1 or bone-only disease with lytic component

Multinational, Multicenter, Randomized

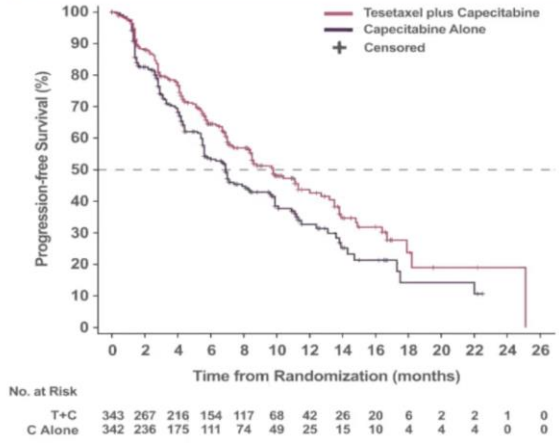
1:1 Randomization

Tesetaxel 27 mg/m² PO (Day 1 of a 21-day cycle) + **Capecitabine** 1,650 mg/m² PO (825 mg/m² BID) (Evening Day 1 to Morning Day 15 of a 21-day cycle)

Treat until progressive disease or unacceptable toxicity

Capecitabine 2,500 mg/m² PO (1,250 mg/m² BID) (Evening Day 1 to Morning Day 15 of a 21-day cycle)

PFS as Assessed by IRC



	Tesetaxel plus Capecitabine (N=343)	Capecitabine Alone (N=342)
Events	155	169
Median Months (95% CI)	9.8 (8.4 – 12.0)	6.9 (5.6 – 8.3)
	2.9-Month Improvement	
Hazard Ratio (95% CI)	0.716 (0.573 – 0.895)	
P-value	0.003	

CI=confidence interval

System Organ Class	TEAE	Tesetaxel plus Capecitabine (N=337) (%)		Capecitabine Alone (N=337) (%)	
		Grade 3	Grade 4	Grade 3	Grade 4
Hematologic	Neutropenia	32.6	38.3	7.4	0.9
	Febrile neutropenia	10.4	2.7	0.3	0.9
	Anemia	8.0	0.0	2.4	0.0
	Leukopenia	6.8	3.0	0.6	0.3
Gastrointestinal	Diarrhea	12.5	0.6	8.9	0.0
	Nausea	6.2	0.0	2.1	0.0
Other	Fatigue	8.6	0.0	4.5	0.0
	Hypokalemia	8.0	0.6	2.7	0.0
	Hand-foot syndrome	6.8	0.0	12.2	0.0
	Neuropathy[a]	5.3	0.6	0.9	0.0

No treatment-related hypersensitivity reactions

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O'Shaughnessy et al, SABCS, 2020

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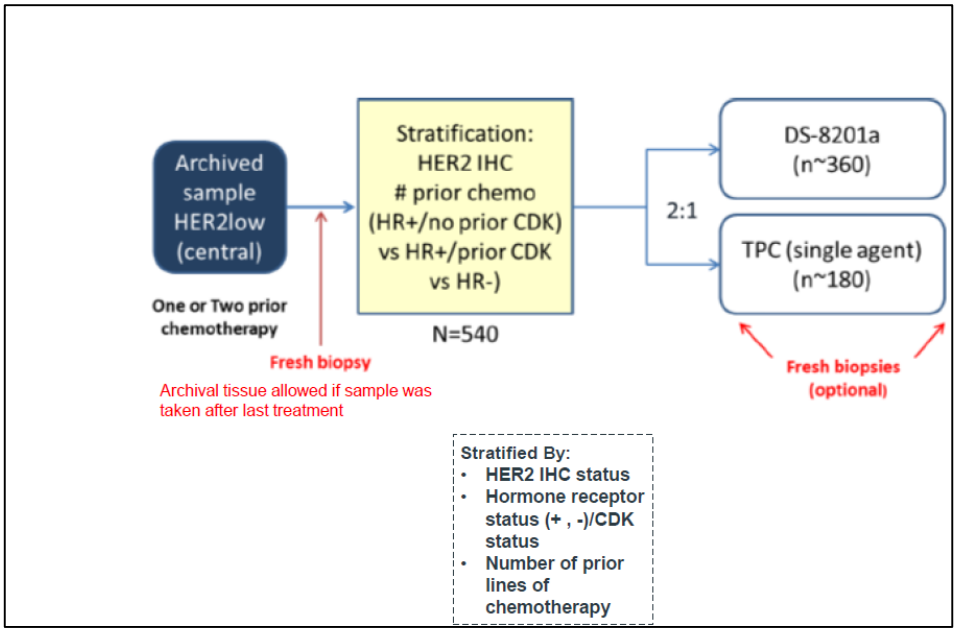
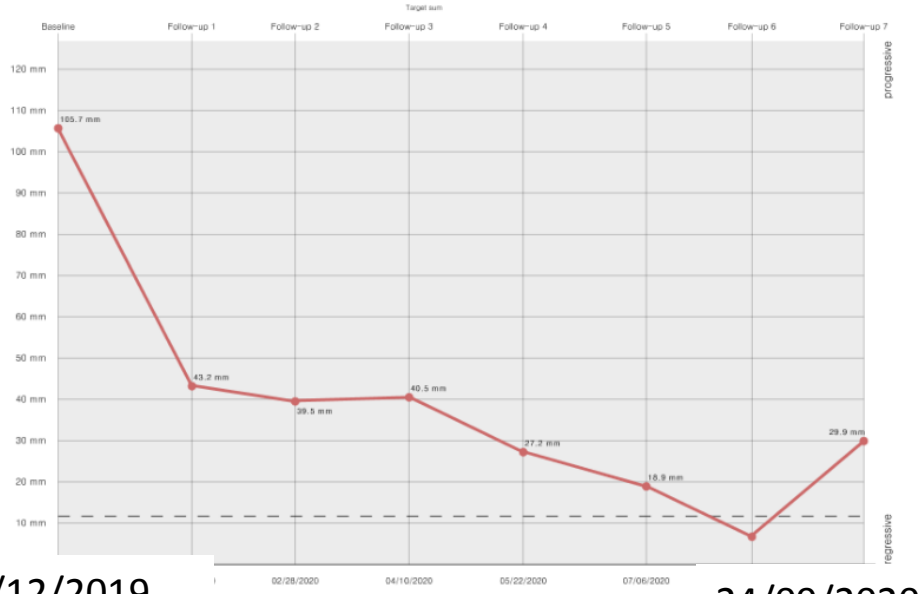
What would you choose for systemic therapy?

- Capecitabine
- Eribulin
- Combined chemotherapy (ex. platinum based)
- Inclusion in a clinical trial with HER2 or TROP 2 antibody-drug conjugate

09/12/2019-09/09/2020: **trastuzumab-deruxtecan**





03/12/2019

24/09/2020

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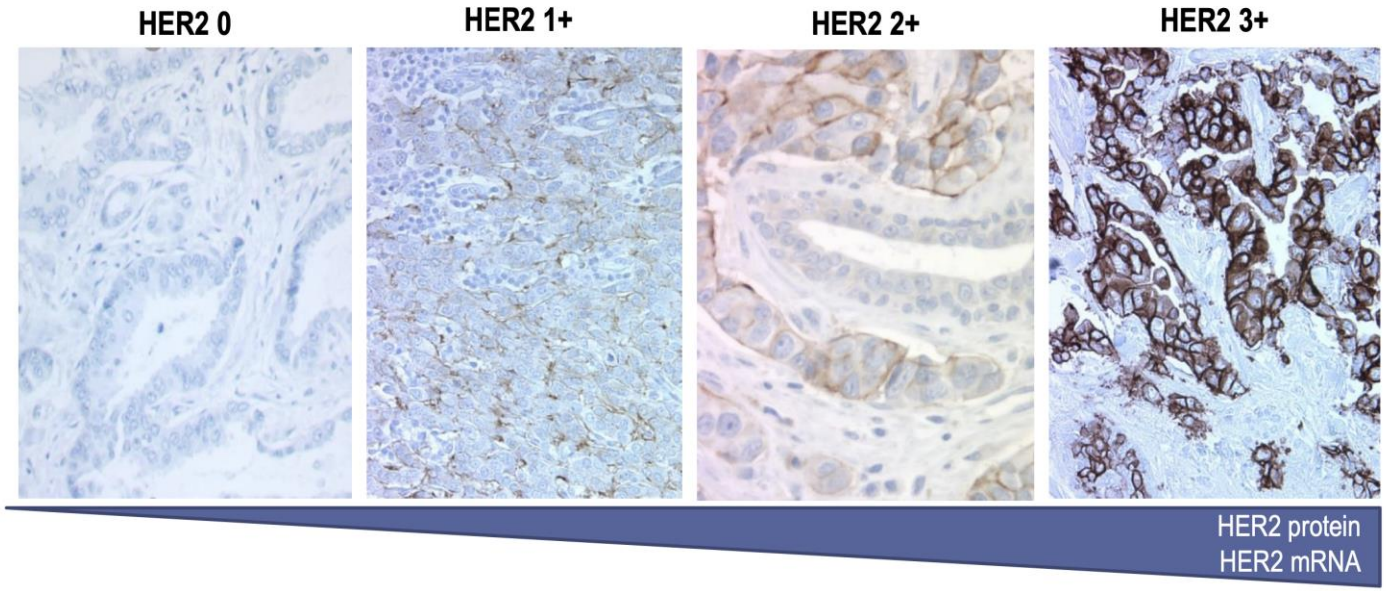
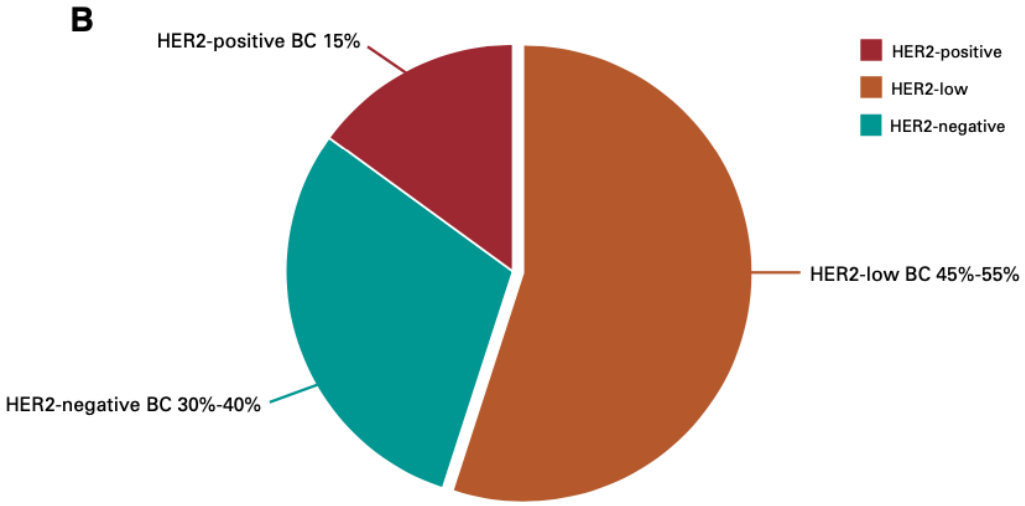
HER 2 low breast cancer





Tarantino, JCO 2020, Penault-Llorca-ESMO

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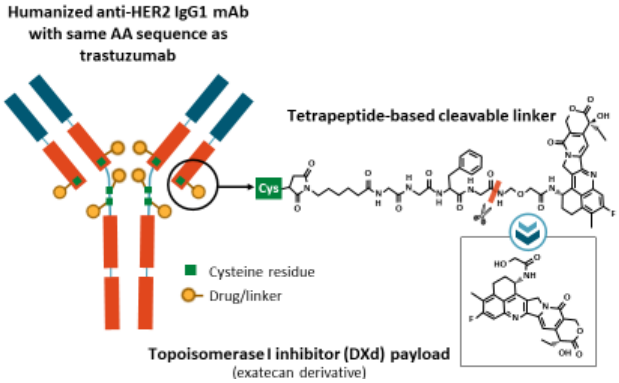
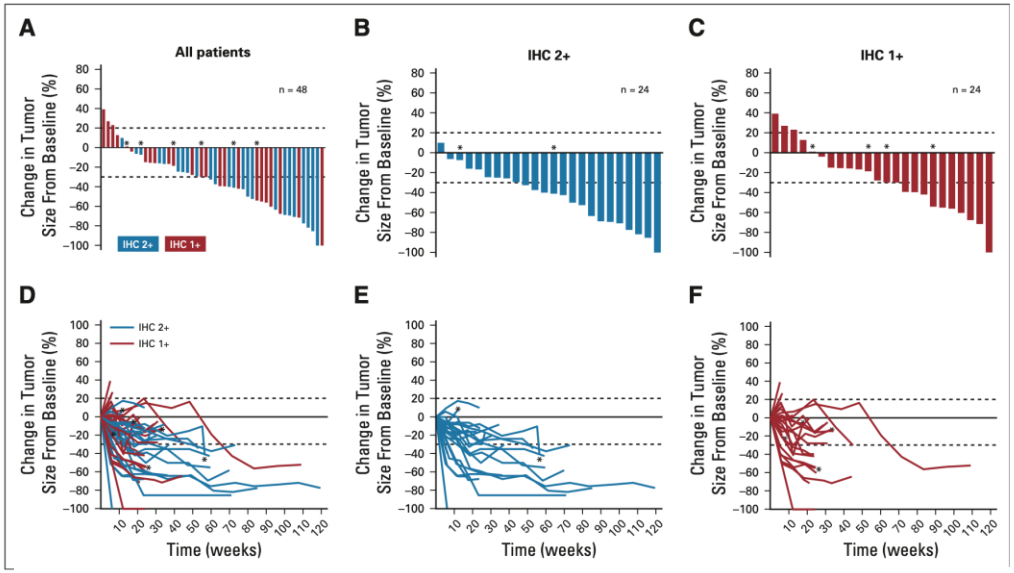
HER2 ADC: trastuzumab deruxtecan (T-DXd)

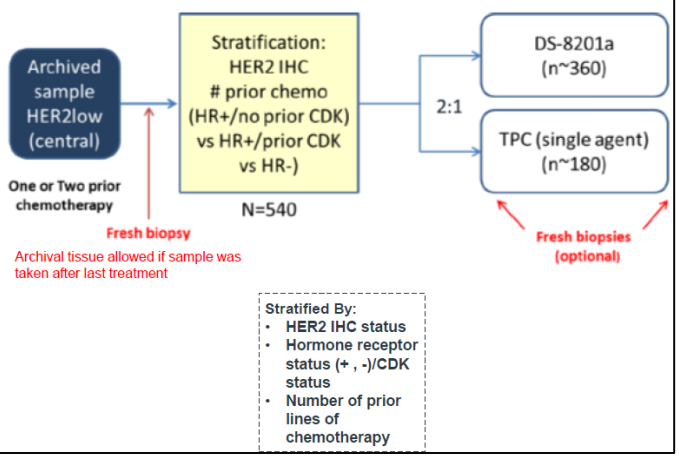


- High drug:antibody ratio: ~ 8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

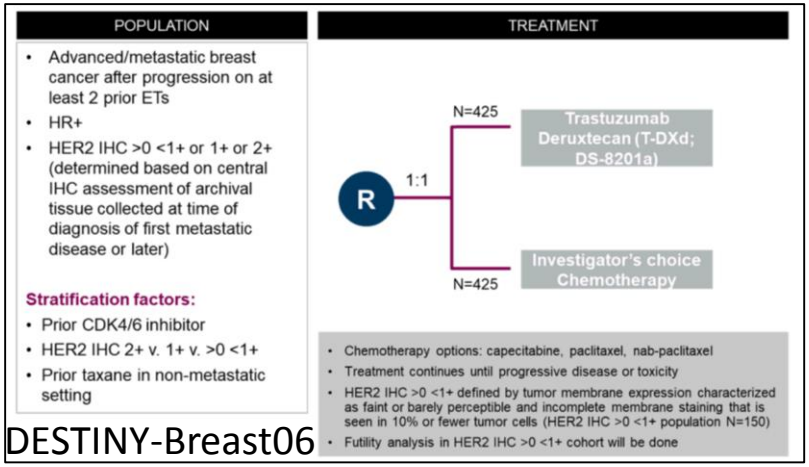


54 pts, median 7.5 lines of prior th, 87% ER+ MBC
ORR-37%; mPFS-11 mo, mOS-29 mo

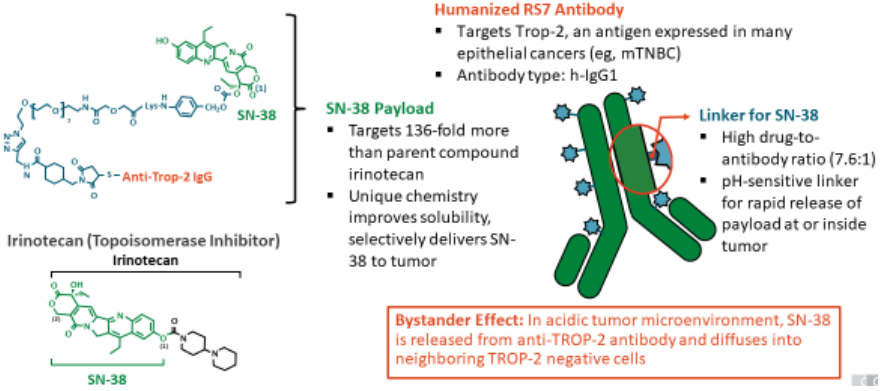
DESTINY-Breast04

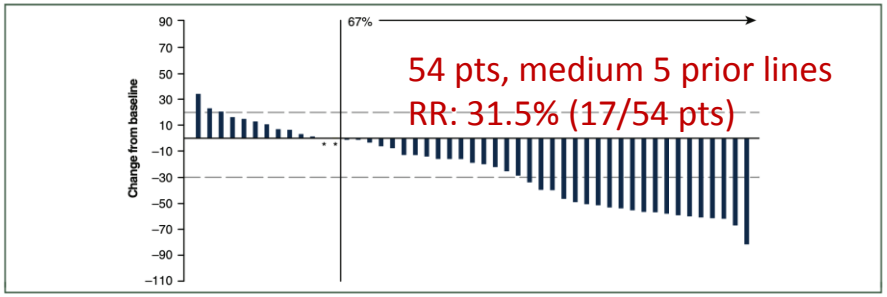


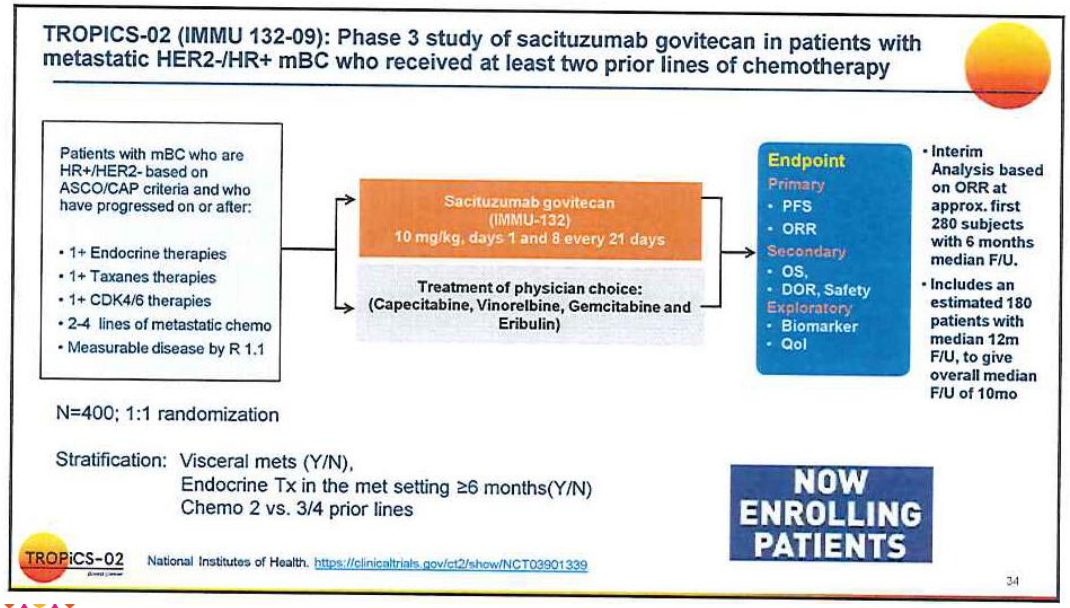
DESTINY-Breast06

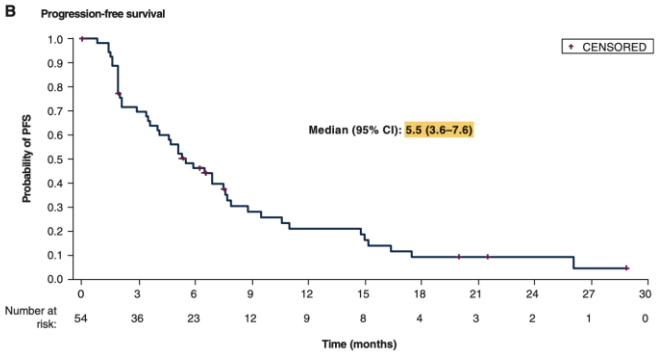


TROP2 ADC: Sacituzumab Govitecan









mPFS-5 month

Kalinsky et al, Ann Oncol, 2020

CLINICAL CASE # 2

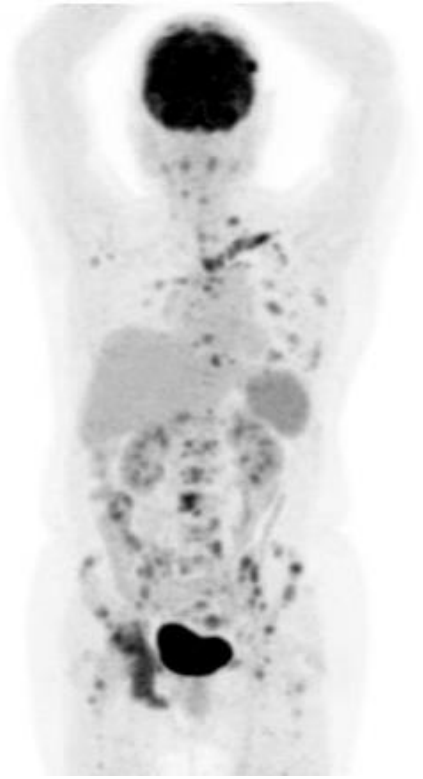
Maria, 60 years

- Medical history: hypothyroidism

- **04/2007**: lumpectomy + ALD:
  - adenocarcinoma grade III pT1cN1 (1+/9)M0
  - ER: 7/8, PR: 7/8, Ki67-25%
- **06-08/2007**: 3xFEC→3xDocetaxel
- Radiotherapy
- Tamoxifen 5 years (end: **09/2012**)

- **02/2016**: bone pain – cervical and lumbar spine

- **PET-Scan** (17/02/2016): multiple bone and lymph node metastasis



- **MRI** (29/02/2016):
- epidural involvement D5, C5

  CA 15-3: 51 U/l

→**radiotherapy** of threatening bone lesions

→**left iliac biopsy**: grade III adenocarcinoma of breast origin, ER: 8/8, PR: 5/8, HER2-neg

What would you choose for systemic therapy?

- NSAI alone
- NSAI + CDK 4/6 inhibitor
- Fulvestrant
- Fulvestrant + CDK 4/6 inhibitor
- Chemotherapy

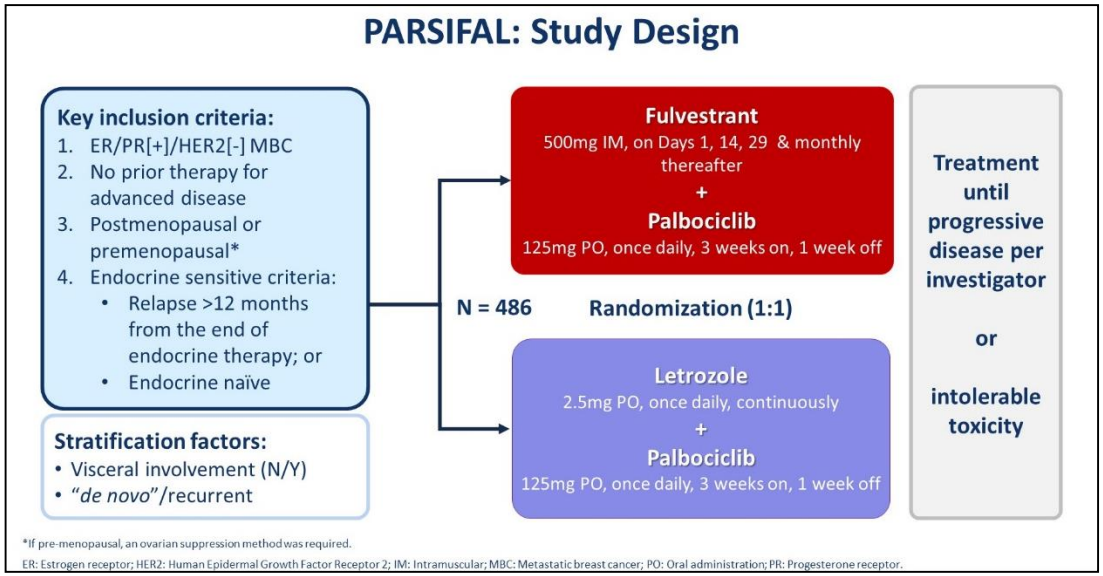
- 02/2016 – 05/2018: **letrozole**

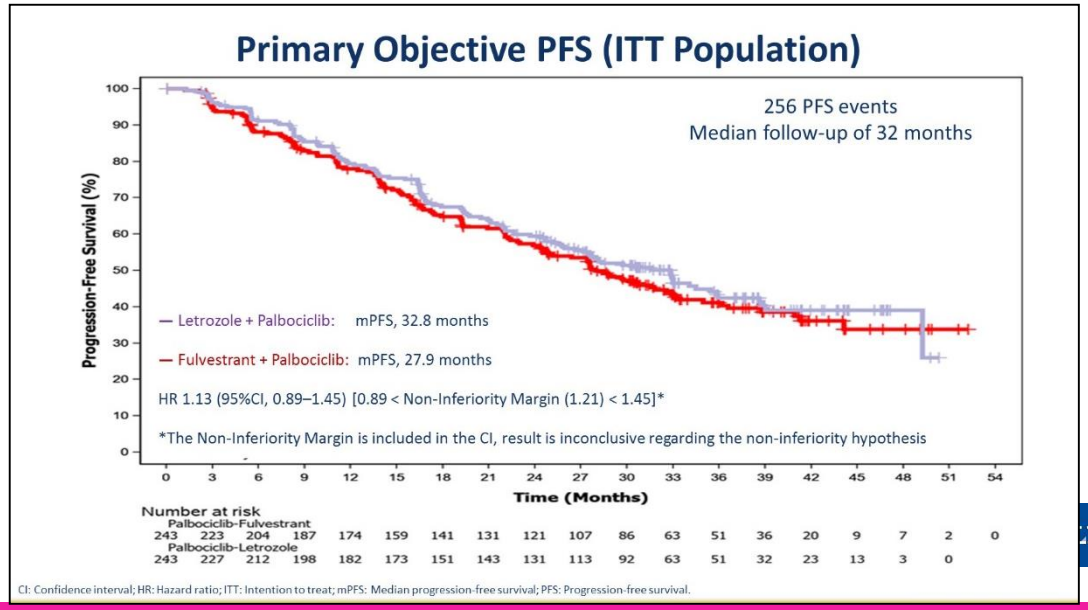
- 10/2016: metabolic complete response of bone lesions
- 05/2018: PET-reactivation of several bone lesions (D5, L4, ribs, S1)

- 05/2018 – 11/2020: **fulvestrant + palbociclib**

- 11/2020: progression of multiple bone lesions

Which endocrine backbone with CDK 4/6 inhibitors?





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Llombart-Cussac, ASCO 2020

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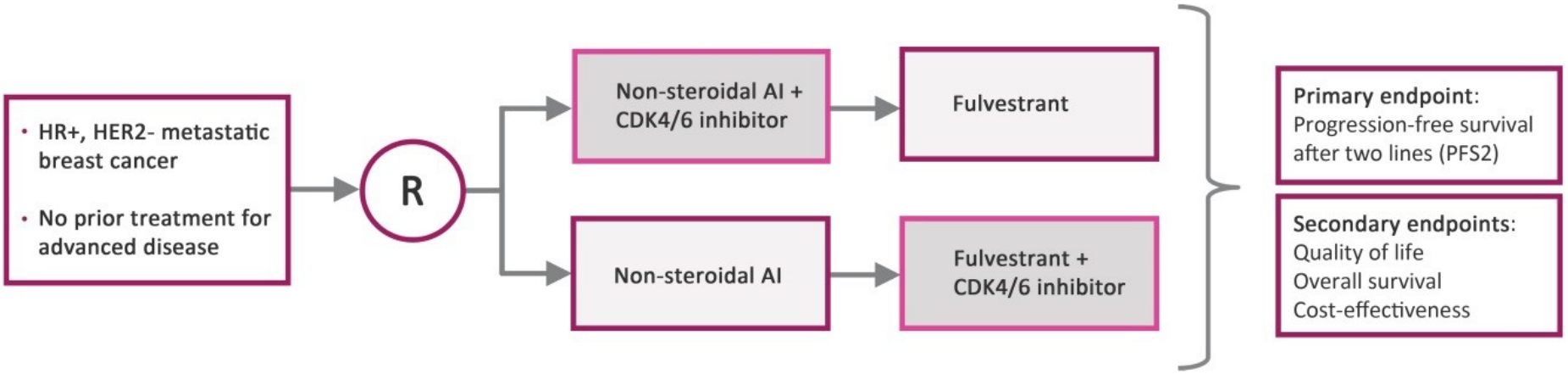
Defining optimal strategy: 1st or 2nd line

SONIA



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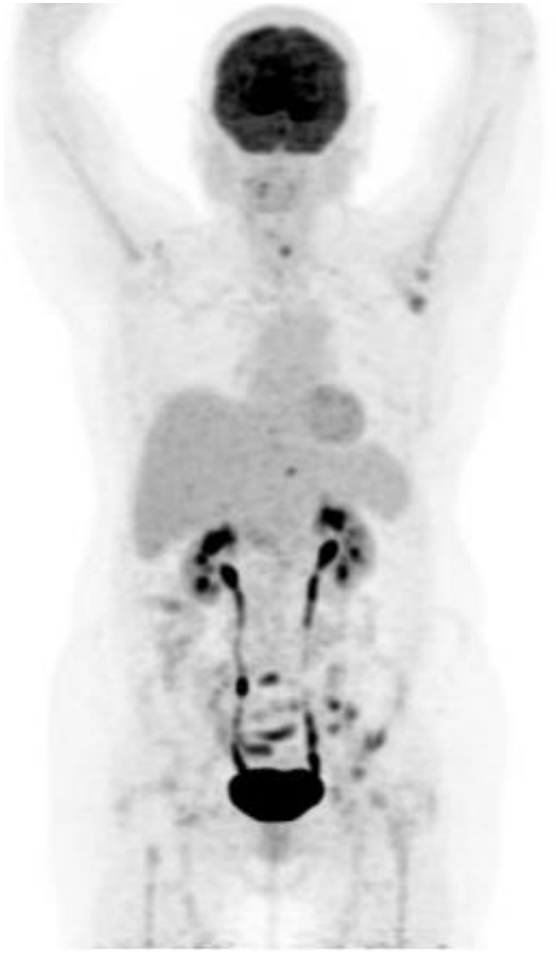
PET-Scan (30/11/2020)

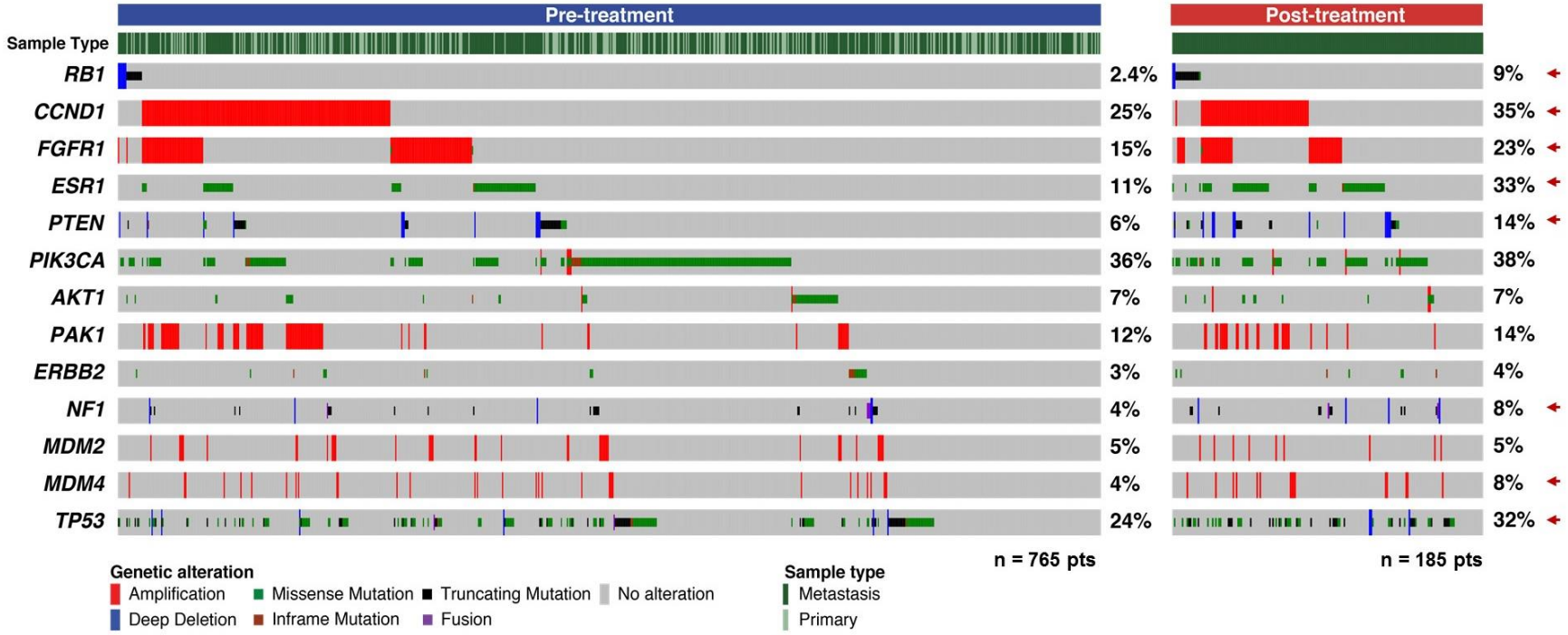


Progression of multiple bone metastases

Multidisciplinary discussion: propose NGS before treatment decision.
How do you proceed to do the NGS?

- TGS on the primary tumor
- TGS on a new plasma sample
- TGS on the bone biopsy (02/2016)

Molecular landscape after CDK 4/6 inhibitors



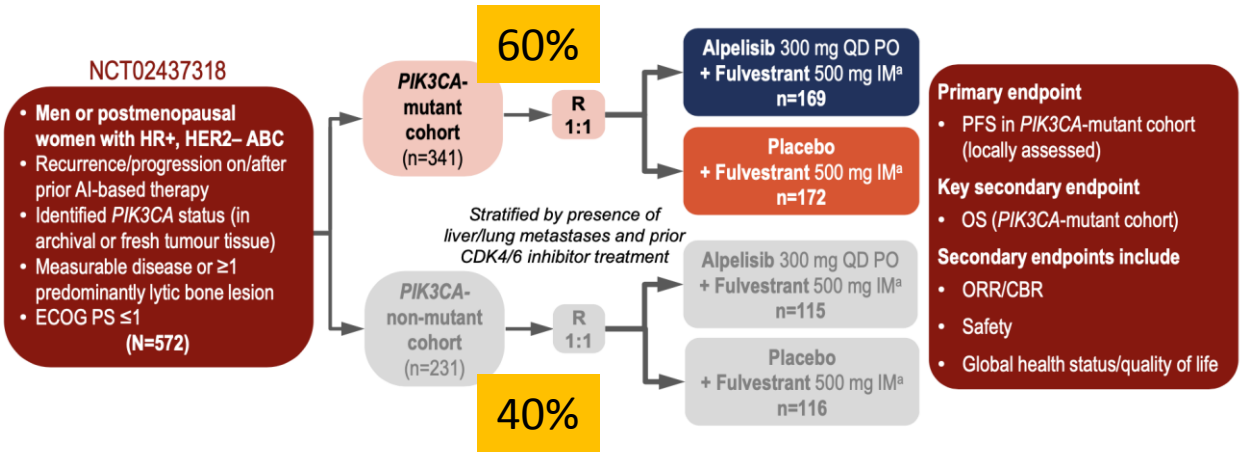
Razavi et al, ASCO 2019

TGS of 50 genes (1000x, Illumina MiSeq) on archival bone biopsy (02/2016):

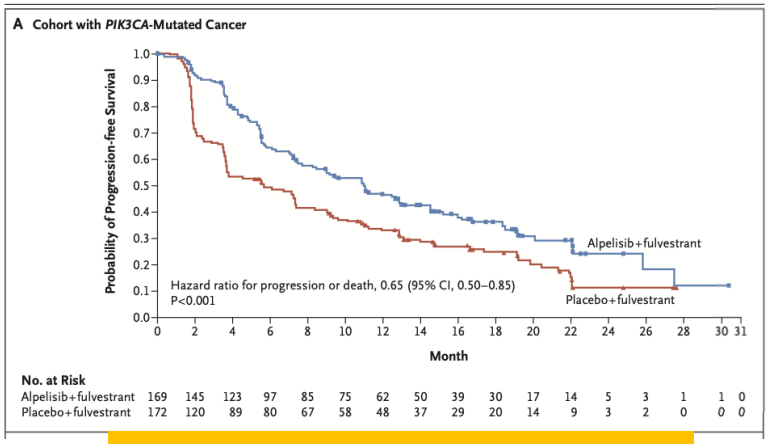
PIK3CA H1047R hotspot mutation (exone 20)

13/01/2021: start **Alpelisib-Fulvestrant**

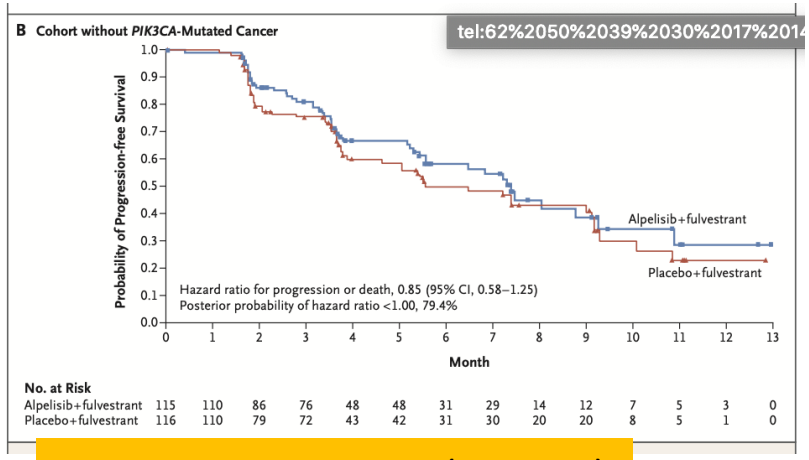
PIK3CA inhibition: alpelisib - **SOLAR 1**



PIK3CA mutation screening on **tumor tissue**:
***therascreen*®PIK3CA RGQ PCR Kit**
(11 specific mutations in exons 7, 9, 20)



PFS: 11 mo vs 5.7 mo (HR-0.65)



PFS: 7.4 mo vs 5.6 mo (HR-0.85)

No OS benefit: 39.3 mo vs 31.4 mo (Δ7.9 mo)

Only 6% had prior CDK 4/6 inhibitor

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André at al, NEJM 2019; André et al, ESMO 2020

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Alpelisib after CDK 4/6 inhibitors – **BYLieve**

Men or pre-/postmenopausal[a] women with HR+, HER2– ABC with a *PIK3CA* mutation

- Last line of prior therapy: CDKi + ET, systemic chemotherapy or ET
- ECOG PS ≤2
- Measurable disease (per RECIST v1.1) or ≥1 predominantly lytic bone lesion

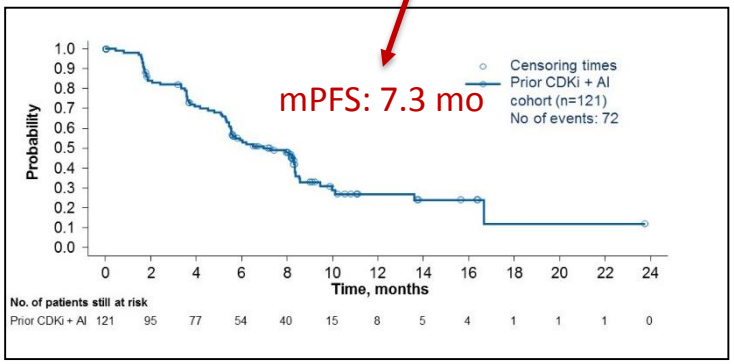
Patients who received CDKi + AI as immediate prior treatment (N=112)[b]
(Cohort A)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Patients who received CDKi + fulvestrant as immediate prior treatment (N=112)
(Cohort B)
Alpelisib 300 mg oral QD + letrozole 2.5 mg[d]

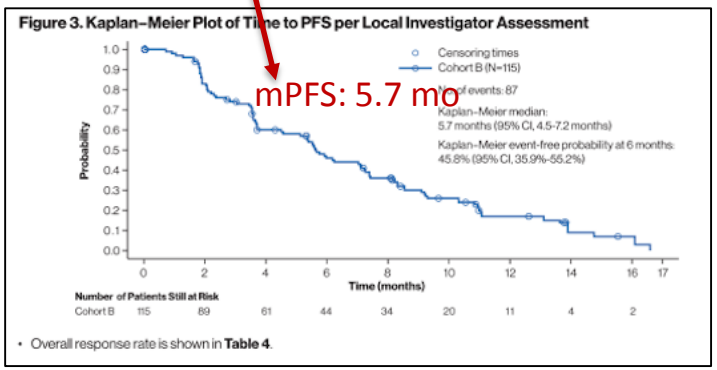
Patients who progressed on/after AI and received chemotherapy or ET as immediate prior treatment (N=112)
(Cohort C)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Primary endpoint
- Proportion of patients alive without PD at 6 months (RECIST v1.1) in each cohort
- **Secondary endpoints include**

(assessed in each cohort)
- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety



1st line: 11.8%
2nd line: 70%
3rd line: 16.5%



1st line: 1.6%
2nd line: 52.4%
3rd line: 44.4%

>80% progressed on NSAI before fulvestrant + CDK 4/6 inhibitor

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Rugo et al, ESMO 2020; Rugo et al, SABCS 2020

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How to test PIK3CA mutation?

NGS: FoundationOne® CDx 324-gene on tissue

60% PIK3CA +

40% PIK3CA -

→ 13% (n=31) not detected by PCR

NGS: FoundationOne® CDx 311-gene on plasma

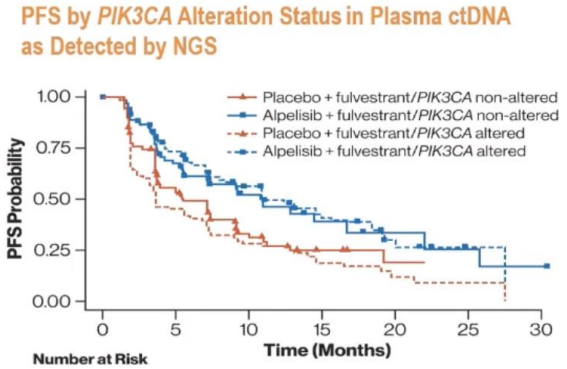
51% PIK3CA +

49% PIK3CA -

→ 39% (n=72) detected in tissue

Table. Clinical outcomes of patients with tumors harboring *PIK3CA* alterations—as detected by NGS—and/or PTEN loss in SOLAR-1

	Alpelisib + Fulvestrant		Placebo + Fulvestrant		HR (95% CI)
	Events/N (%)	mPFS, mo (95% CI)	Events/N(%)	mPFS, mo (95% CI)	
PIK3CA: altered vs non-altered (by NGS)					
Altered	68/121 (56.2)	11.01 (8.05 - 15.21)	85/118 (72.0)	5.52 (3.55 - 7.36)	0.59 (0.43 - 0.82)
Non-altered	36/82 (43.9)	7.29 (5.22 - 9.17)	39/83 (47.0)	7.16 (5.03 - 11.01)	0.99 (0.62 - 1.57)
PIK3CA: single vs multiple alterations (by NGS)					
Single	60/100 (60.0)	11.01 (7.49 - 14.55)	66/94 (70.2)	4.63 (3.38 - 7.39)	0.59 (0.41 - 0.84)
Multiple	8/20 (40.0)	9.36 (6.31 - NA)	19/24 (79.2)	7.29 (2.07 - 12.85)	0.56 (0.23 - 1.33)



PIK3CA altered: mPFS 11.0 vs 3.7, HR 0.47 (0.33-0.87)
PIK3CA not altered: mPFS 10.9 vs 5.5, HR 0.60 (0.40-0.91)

Some patients with no PIK3CA mutation in plasma (NGS) still benefit (driven by cases with tissue alteration?) –> reflex tissue testing if plasma negative!!

Juric et al, SABCS 2019; Ciurelos et al, SABCS 2020

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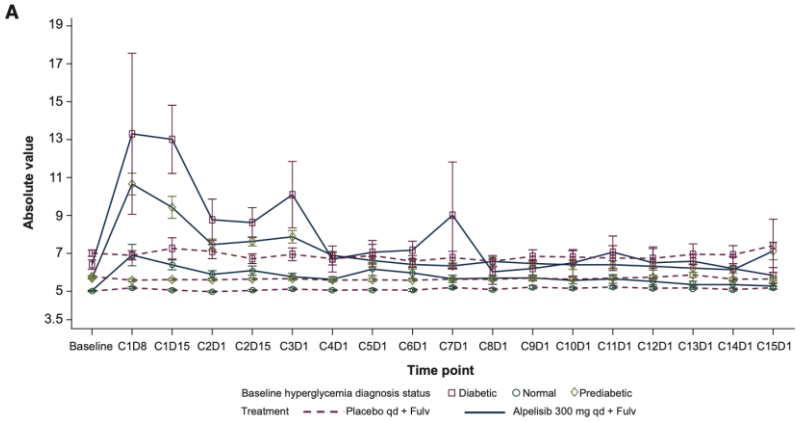
Alpelisib - toxicity

Table 2. Most frequently reported adverse events (≥20% incidence of any grade event in either treatment group) in the safety population[a]

AE, *n* (%)	Alpelisib plus fulvestrant (*n* = 284)					Placebo plus fulvestrant (*n* = 287)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any AE	282 (99.3)	12 (4.2)	54 (19.0)	183 (64.4)	33 (11.6)	264 (92.0)	69 (24.0)	92 (32.1)	87 (30.3)	15 (5.2)
Hyperglycemia[b]	181 (63.7)	32 (11.3)	45 (15.8)	93 (32.7)	11 (3.9)	28 (9.8)	19 (6.6)	7 (2.4)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	93 (32.7)	52 (18.3)	19 (6.7)	0	45 (15.7)	30 (10.5)	14 (4.9)	1 (0.3)	0
Nausea	127 (44.7)	90 (31.7)	30 (10.6)	7 (2.5)	0	64 (22.3)	49 (17.1)	14 (4.9)	1 (0.3)	0
Decreased appetite	101 (35.6)	75 (26.4)	24 (8.5)	2 (0.7)	0	30 (10.5)	21 (7.3)	8 (2.8)	1 (0.3)	0
Rash[c]	101 (35.6)	48 (16.9)	25 (8.8)	28 (9.9)	0	17 (5.9)	14 (4.9)	2 (0.7)	1 (0.3)	0
Vomiting	77 (27.1)	64 (22.5)	11 (3.9)	2 (0.7)	0	28 (9.8)	18 (6.3)	9 (3.1)	1 (0.3)	0
Decreased weight	76 (26.8)	34 (12.0)	31 (10.9)	11 (3.9)	0	6 (2.1)	1 (0.3)	5 (1.7)	0	0
Stomatitis	70 (24.6)	39 (13.7)	24 (8.5)	7 (2.5)	0	18 (6.3)	15 (5.2)	3 (1.0)	0	0
Fatigue	69 (24.3)	36 (12.7)	23 (8.1)	10 (3.5)	0	49 (17.1)	36 (12.5)	10 (3.5)	3 (1.0)	0
Asthenia	58 (20.4)	25 (8.8)	28 (9.9)	5 (1.8)	0	37 (12.9)	29 (10.1)	8 (2.8)	0	0



Hyperglycemia			
1	FPG > ULN to 160 mg/dl or FPG > ULN to 8.9 mmol/l	• No alpelisib dose adjustment required	• If FPG is <140 mg/dl, consider metformin • If FPG is 140–160 mg/dl, start or intensify metformin
2	FPG >160 to 250 mg/dl or FPG >8.9 to 13.9 mmol/l	• No alpelisib dose adjustment required • If FPG does not resolve to grade ≤1 within 21 days after antidiabetic treatment, reduce alpelisib by one dose level[a]	• Start oral antidiabetic treatment (e.g. metformin) • If FPG keeps rising beyond MTD of metformin, add an insulin sensitizer (e.g. pioglitazone)
3	FPG >250 to 500 mg/dl or FPG >13.9 to 27.8 mmol/l	• Discontinue alpelisib • If FPG resolves to grade ≤1 within 3 to 5 days while off alpelisib and on metformin, restart alpelisib and reduce by one dose level[a] • If FPG does not resolve to grade ≤1 within 21 days after antidiabetic treatment, permanently discontinue alpelisib	• Consider consultation with endocrinologist • Start metformin and add pioglitazone • Insulin may be used as rescue medication for 1 to 2 days
4	FPG >500 mg/dl or FPG ≥27.8 mmol/l	• Discontinue alpelisib for 24 H, then: – If grade ≤3, follow specific grade recommendations – If grade 4 persists (with no confounding factors), permanently discontinue alpelisib	• Consult with endocrinologist • See grade 3 recommendations; recheck in 24 H

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Rugo et al, Ann Oncol 2020

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CLINICAL CASE # 3

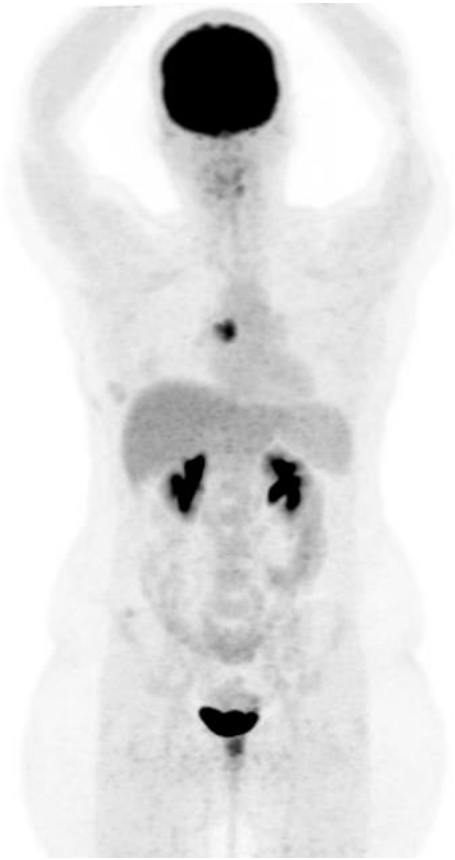
Stephanie (42 years)

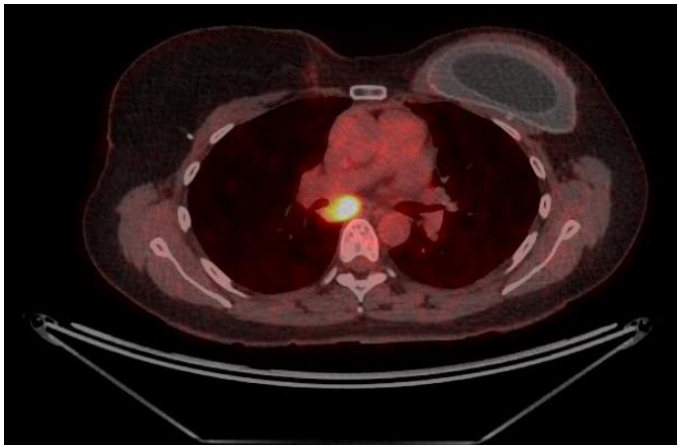
- Family history: 2 aunts breast cancer at 38 and 42 years;
  2 children

- **04/2012 (**during lactation) : adenocarcinoma of the right breast cT2 (37mm)N1M0, RO-8/8, RP-4/8, Ki67-60%
- Neoadjuvant chemotherapy: **12 paclitaxel-4 EC (DD)**
- **09/2012:** right mastectomy – ypT2 (22 mm)N2 (8+LN)-RCB III
- Adjuvant radiotherapy
- **10/2012-03/2017: tamoxifen + goserelin**

- **BRCA 2 +:** bilateral oophorectomy and left mastectomy in 08/2016

03/2016: mediastinal lymph node relapse





Biopsy: adenocarcinoma of breast cancer origin, ER+/PR+, HER2 ++ (ISH negative)

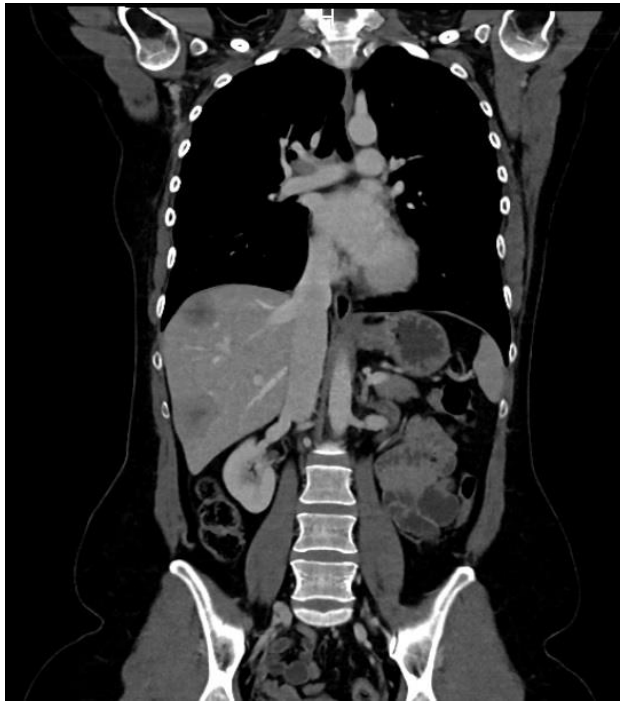
- 11/04/2017-03/01/2020: **letrozole-ribociclib**

- January 2020-two new liver metastases:
  - Segment VIII: 29 x 26 mm
  - Segment VI: 43 x 32 mm
- LFTs within normal ranges
- ECOG PS=0, no symptoms
- TGS on a liver biopsy (OncoDEEP 409 gene pannel – AURORA): no mutation found besides the known BRCA2

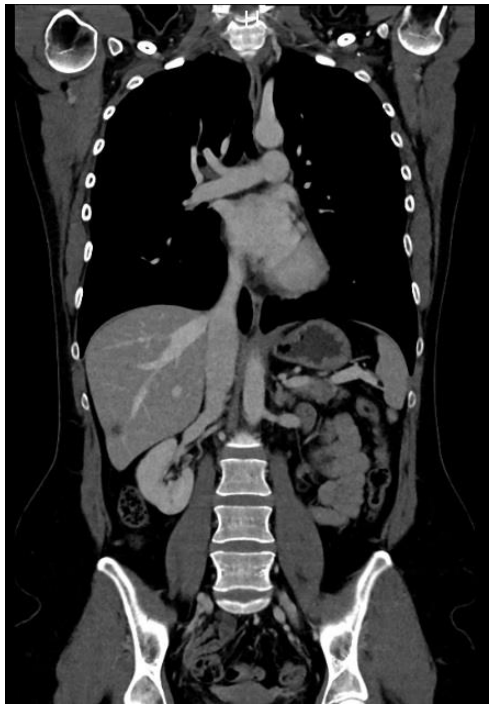
What would you choose for second line therapy?

- Single agent chemotherapy using capecitabine
- Platinum-based chemotherapy+PARP inhibitor
- Single agent platinum-based chemotherapy
- PARP inhibitor

Olaparib since Jan 2020



26/12/2019



26/01/2021

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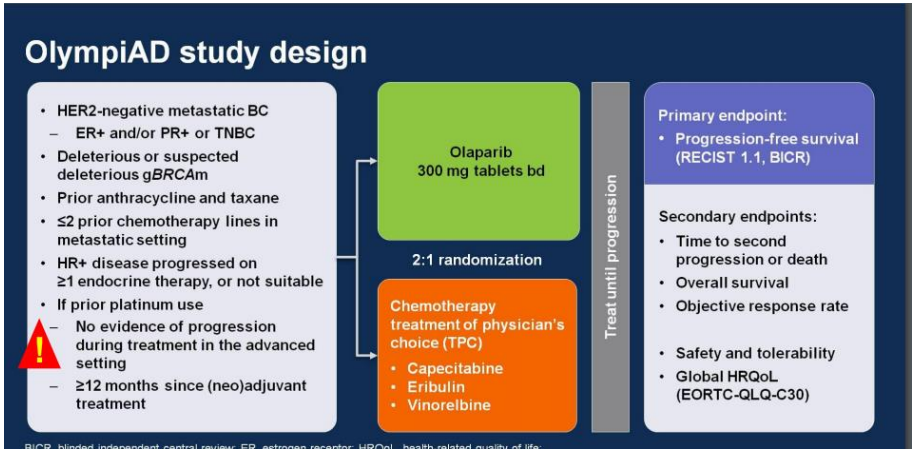
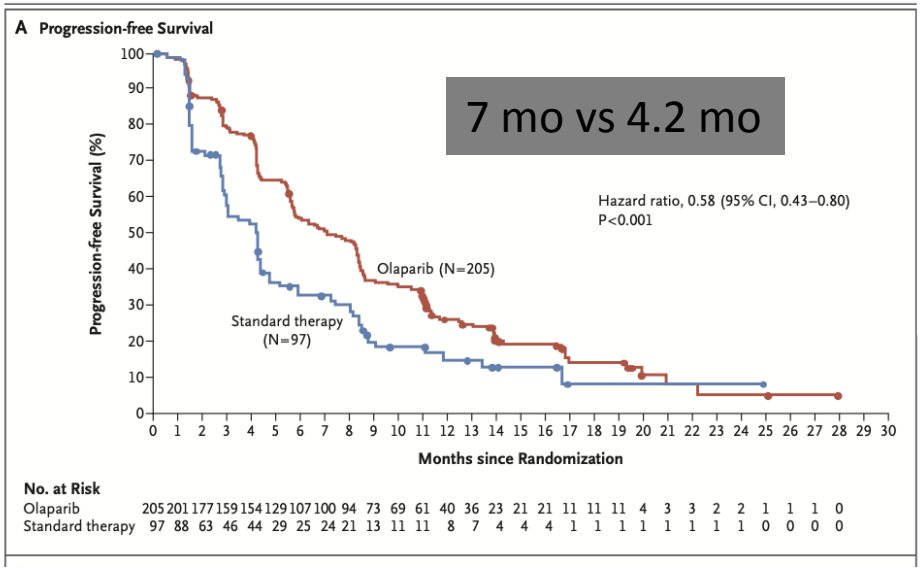
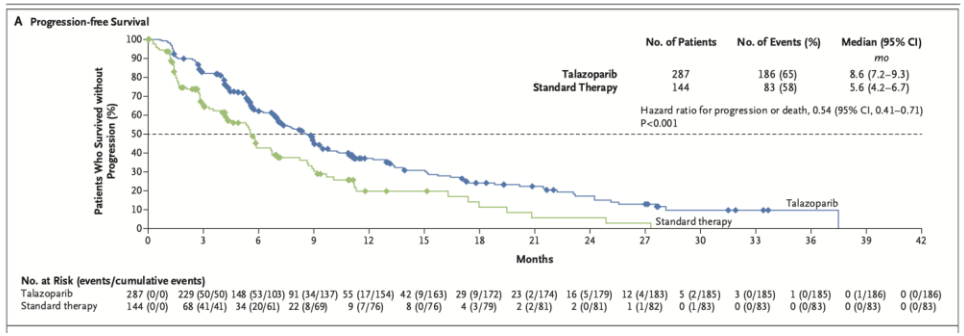


50.2% HR+

54.7% HR+





8.6 mo vs 5.6 mo