再発腫瘍の個別化医療

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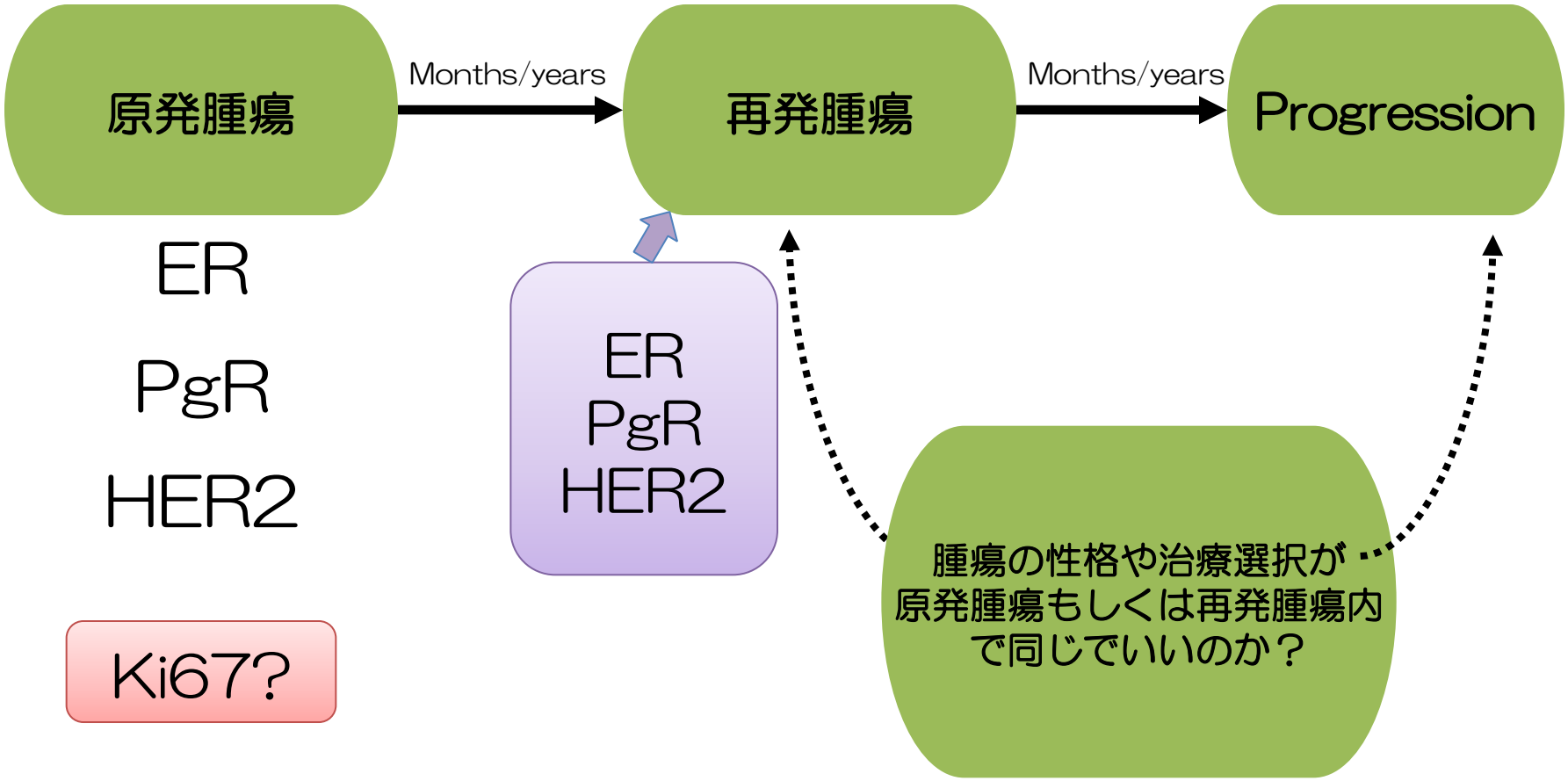
新倉　直樹

乳癌の治療におけるバイオマーカー



Abbreviations: ER, oestrogen receptor; HER2, human epidermal growth factor receptor-2; PgR, progesterone receptor.

Outline

1. 現在のガイドライン
2. Pathology Technique
3. Biomarker Discordanceのレヴュー
4. Biomarker Discordanceの臨床的意義
5. 進行再発乳癌への個別化治療の今後の展望

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SURVEILLANCE/FOLLOW-UP

- Interval history and physical exam every 4-6 mo for 5 y, then every 12 mo
- Annual mammography
- Women on tamoxifen: annual gynecologic assessment every 12 mo if uterus present
- Women on an aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter[ff]
- Assess and encourage adherence to adjuvant endocrine therapy.
- Evidence suggests that active lifestyle, achieving and maintaining an ideal body weight (20-25 BMI) may lead to optimal breast cancer outcomes.

RECURRENT WORKUP or INITIAL WORKUP FOR STAGE IV DISEASE

- History and physical exam
- CBC, platelets
- Liver function tests
- Chest diagnostic CT
- Abdominal ± pelvic diagnostic CT or MRI[gg]
- Brain MRI if suspicious CNS symptoms
- Bone scan or fluoride PET/CT[g] (category 2B)
- X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan
- First recurrence of disease should be biopsied
- Determination of tumor ER/PR and HER2 status if unknown, originally negative or not over-expressed[b,hh]
- Genetic counseling if patient is high risk for hereditary breast cancer[c]

→ Locoregional disease

→ Systemic disease

See Treatment of Recurrence/ Stage IV Disease (BINV-17)

[b] See Principles of HER2 Testing (BINV-A).

[c] See NCCN Genetics/Familial High-Risk Assessment: Breast and Ovarian Guidelines.

[g] If FDG PET/CT are performed and both clearly indicate bone metastases, bone scan or fluoride PET/CT may not be needed.

[ff] The use of estrogen, progesterone, or selective estrogen receptor modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. The use of a bisphosphonate is generally the preferred intervention to improve bone mineral density. Optimal duration of bisphosphonate therapy has not been established. Factors to consider for duration of anti-osteoporosis therapy include bone mineral density, response to therapy, and risk factors for continued bone loss or fracture. Women treated with a bisphosphonate should undergo a dental examination with preventive dentistry prior to the initiation of therapy, and should take supplemental calcium and vitamin D.

[gg] The use of PET or PET/CT scanning should generally be discouraged for the evaluation of metastatic disease except in those clinical situations where other staging studies are equivocal or suspicious. Even in these situations, biopsy of equivocal or suspicious sites is more likely to provide useful information.

[hh] False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).

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

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Pathology Technique

- 再発乳癌という診断は正しいですか？

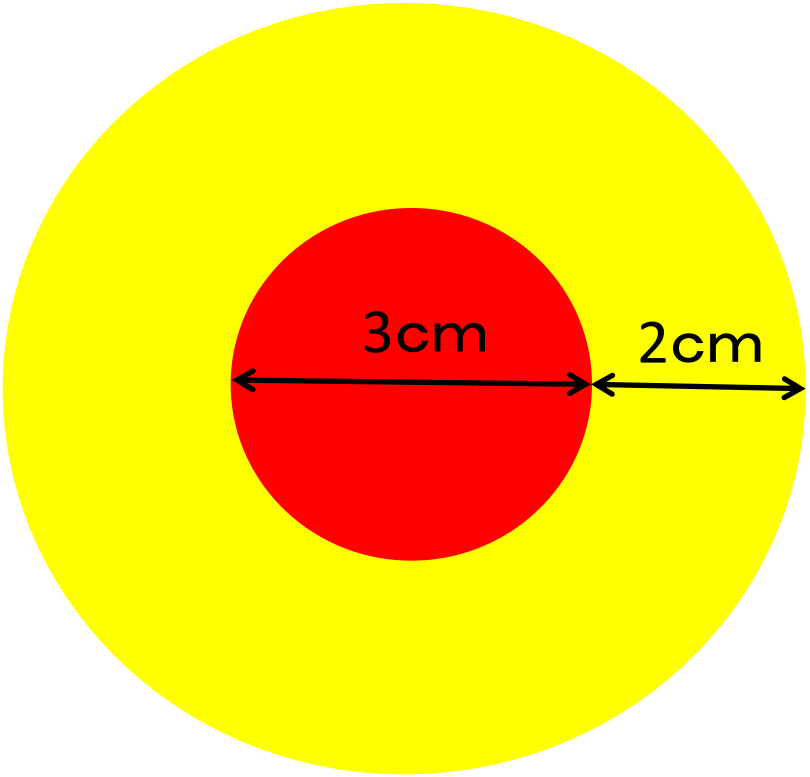
  1. 正確に組織が採取されているか？
  2. しっかりと組織がホルマリンで固定されているか？
  3. 乳癌以外からの転移の可能性はないか？

- ER, PgR, HER2の診断は正しいですか？

  1. しっかりと組織がホルマリンで固定されているか？
  2. 過固定になっていないか？
  3. 染色は正確に行われているか？

ホルマリンの組織への浸潤速度

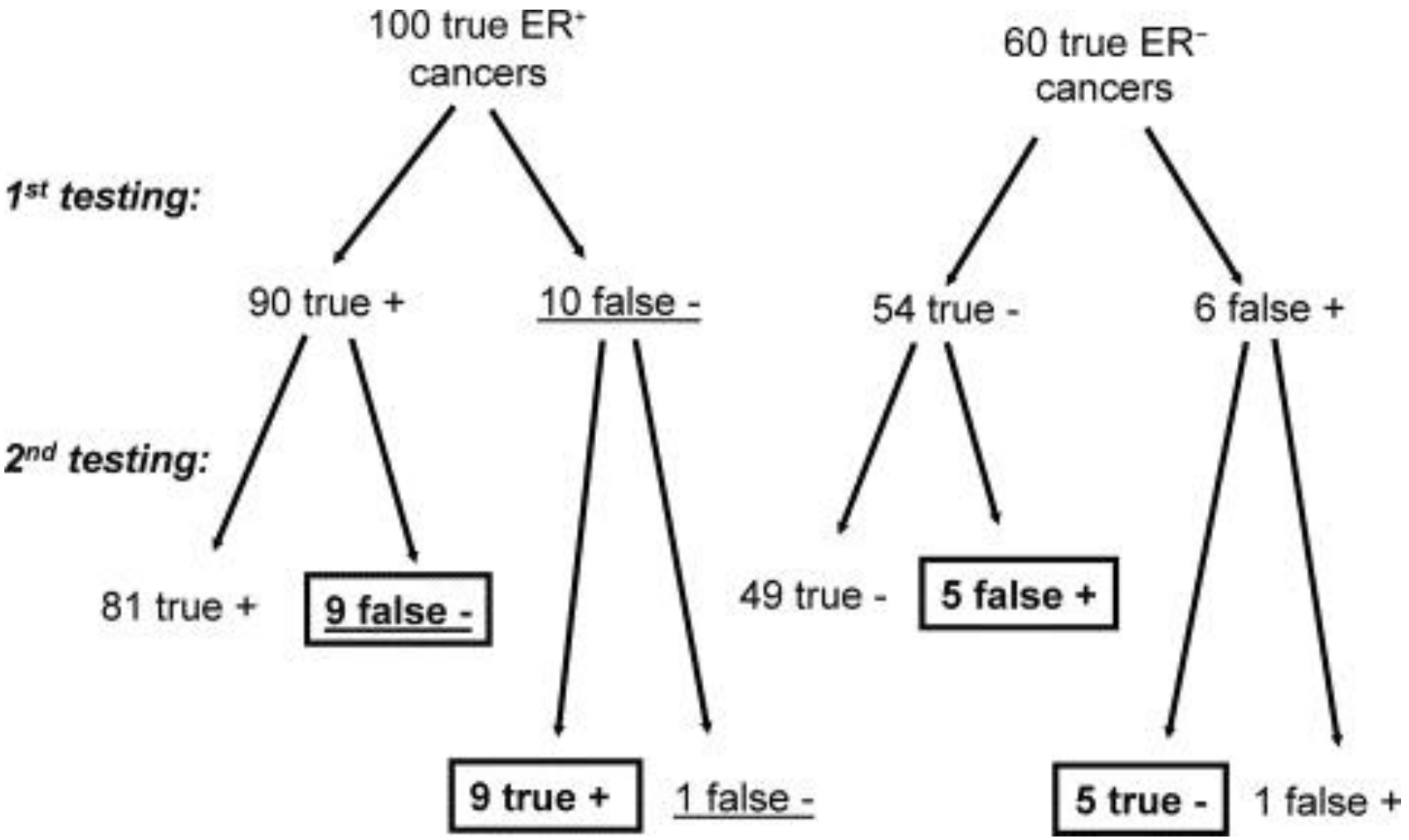
浸潤速度＝ 1mm/h



2cm+1.5cm=3.5cm

中心までホルマリンが到達するまでに35時間かかる

Receptor re-evaluation



Pusztai L, et al: Oncologist. 2010

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HER2 status in primary tumors and metastatic tumor

Primary tumor
HER2 positive
N=182

IHC 3+, FISH +	*60*
IHC 3+, FISH −	*14*
IHC 3+, FISH unknown	*58*
IHC −, FISH +	*16*
IHC unknown, FISH +	*34*

Metastatic lesion
HER2 positive
N=139

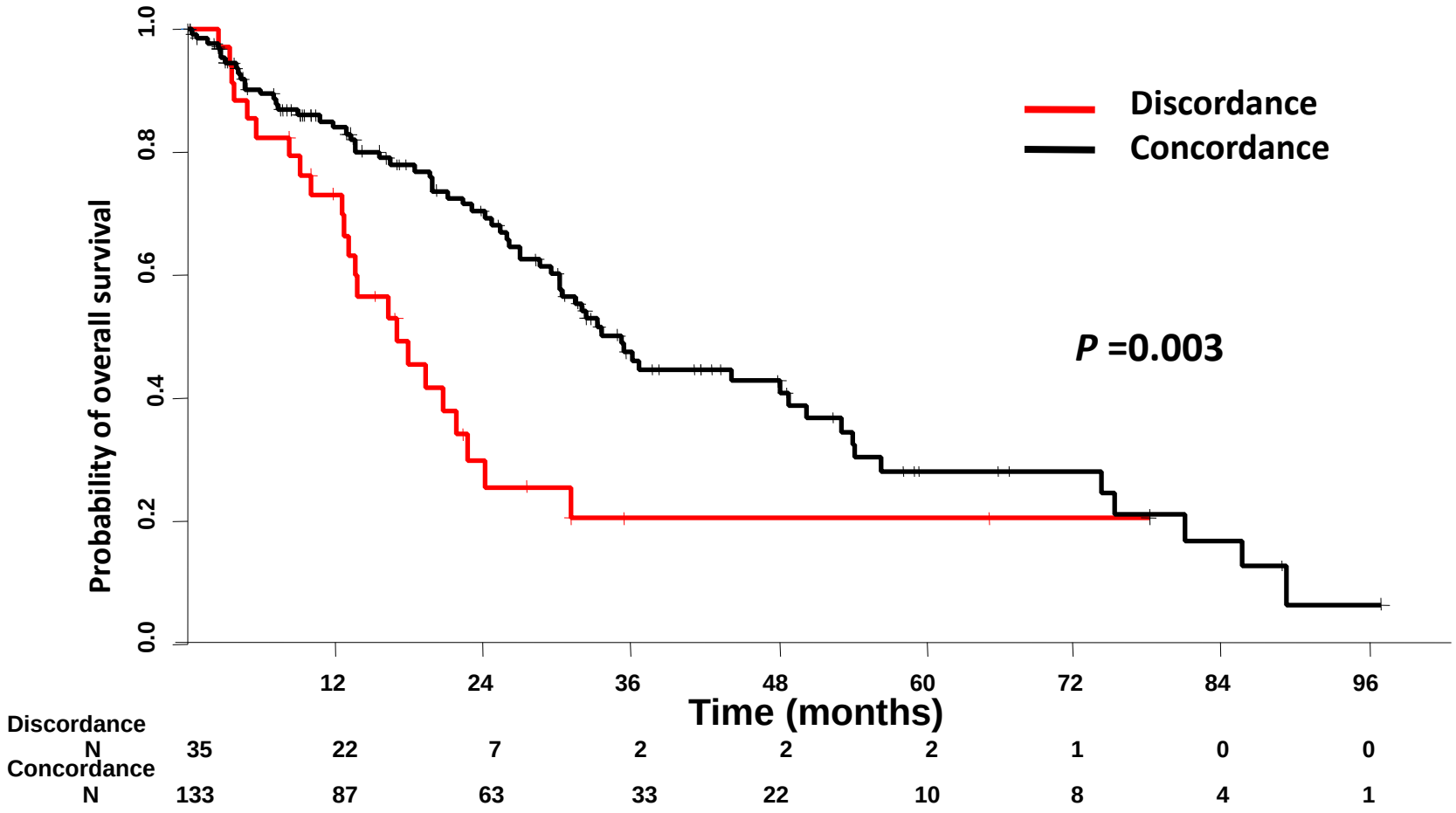
IHC 3+, FISH +	*16*
IHC 3+, FISH −	*0*
IHC 3+, FISH unknown	*25*
IHC −, FISH +	*7*
IHC unknown, FISH +	*91*

Metastatic lesion
HER2 negative
N=43

IHC −, FISH −	*6*
IHC −, FISH unknown	*3*
IHC unknown, FISH −	*34*

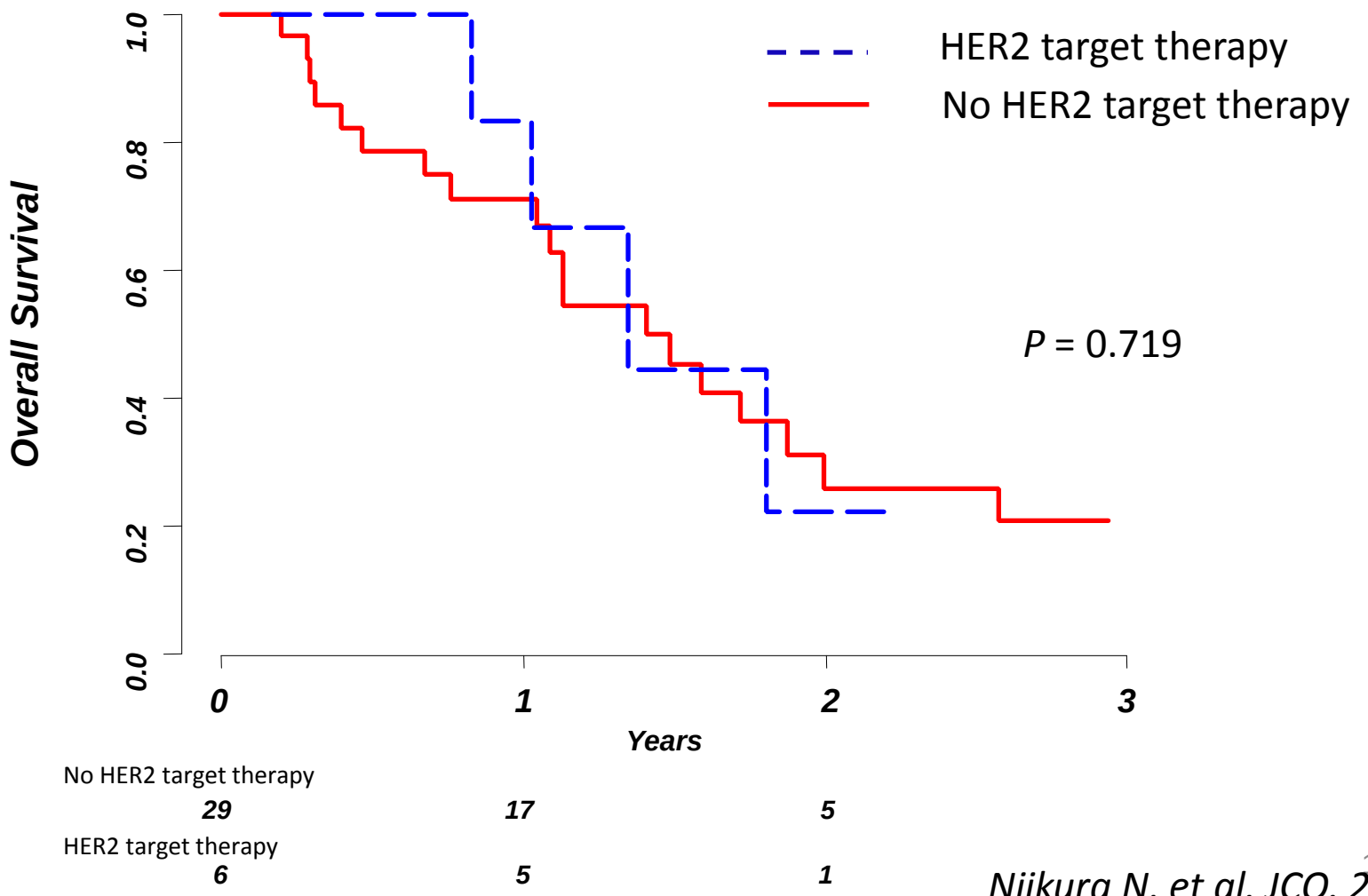
Niikura N, et al. JCO. 2012

Kaplan-Meier overall survival curves by HER2 status for patients with distant metastases



Niikura N, et al. JCO. 2012

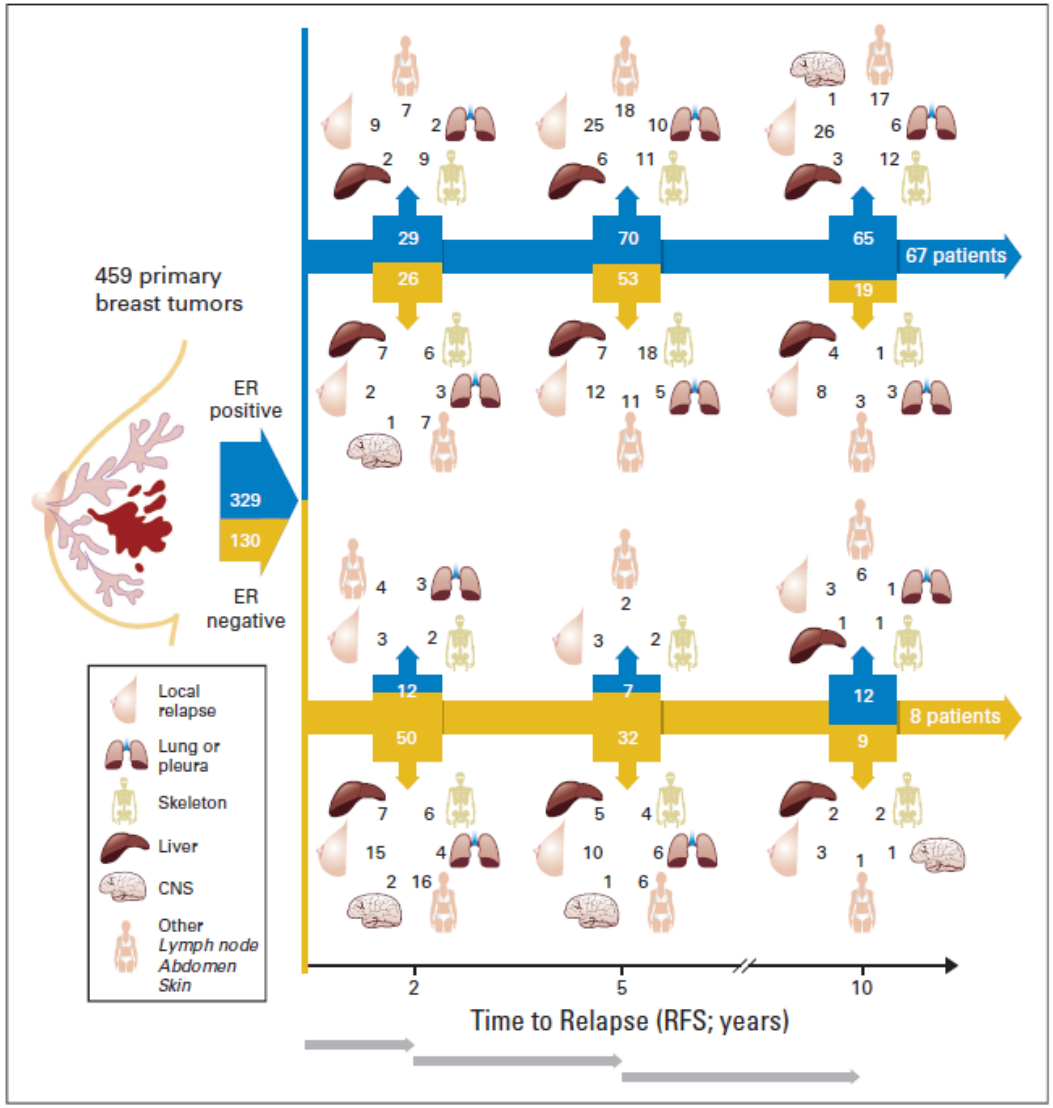
HER2 target therapy for patients with discordance



Niikura N, et al. JCO. 2012

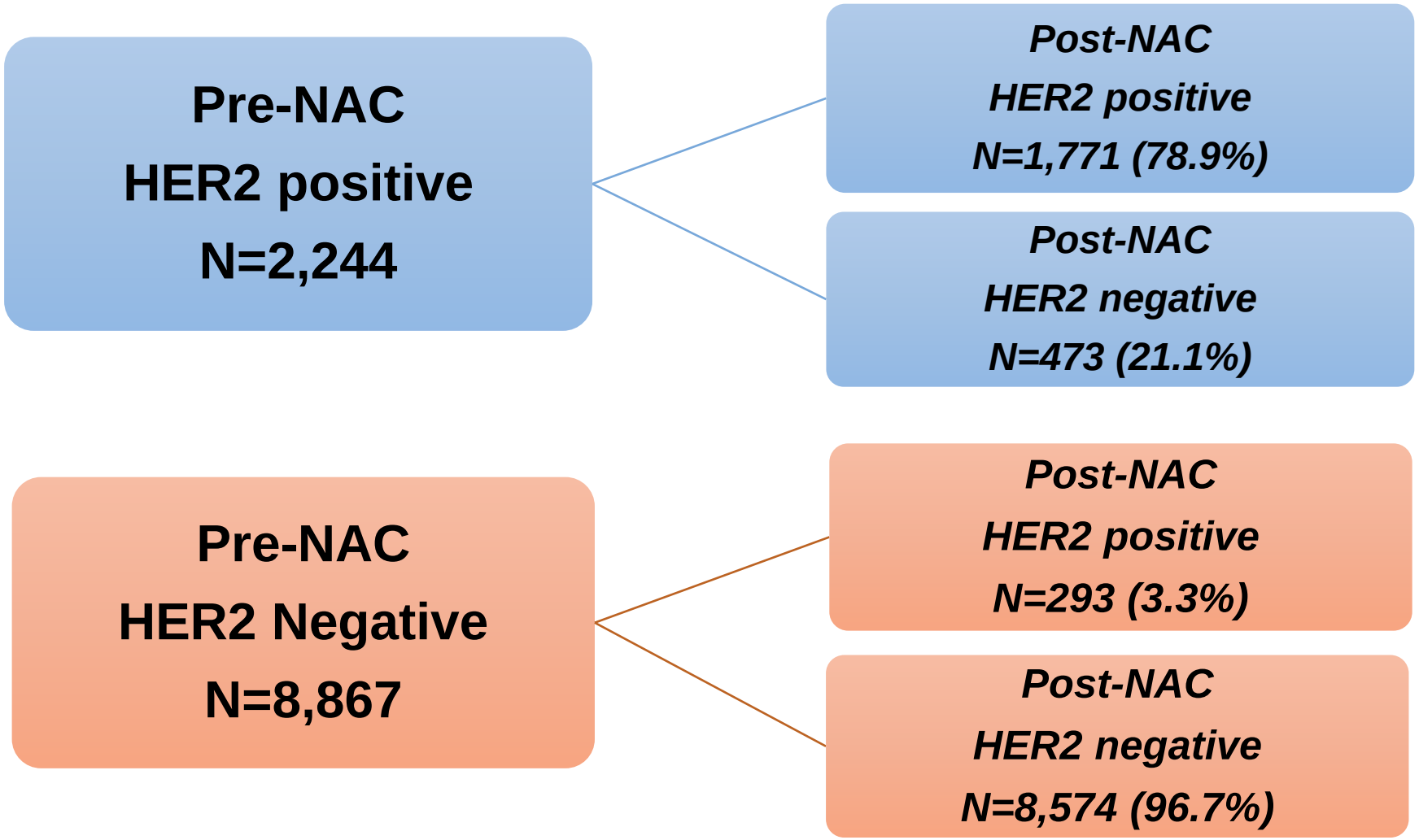
ER Discordance between Early and Late relapse

ER



Lindstrom LS, et al, JCO 2012

HER2 status in Primary tumor between Pre and Post Neoadjuvant therapy



(Unpablished Data)

今までの研究

- Receptor discordance between primary and recurrence:
  - Mostly retrospective
  - Used pathology reports—did not reanalyse samples
  - Rates of discordance for receptor determination:
    - Hormone receptors, 15% to 40%
    - HER2, 7% to 26%

Abbreviation: HER2, human epidermal growth factor receptor-2.

Amir E, Clemons M. *Lancet Oncol*. 2009;10(10):933-935; Amir E, et al. *J Clin Oncol*. 2012;30(6):587-592; Amir E, et al. *Cancer Treat Rev*. 2012;38(6):708-714; Wu JM, et al. *Clin Cancer Res*. 2008;14(7):1938-1946.

Prospective clinical trials evaluating the impact of metastatic biopsy

Table 1 | Prospective clinical trials evaluating the impact of metastatic biopsy

Trial	*n*	Patients without recurrent disease on biopsy (%)	Patients switching receptor status (%)			Patients in whom switch in receptor status led to treatment change (%)
			ER	PR	HER2	
Simmons *et al.* (2009)[10]	40	4 (10)	3/29 (10)	7/29 (24)	2/29 (7)	6/29 (20)
Thompson *et al.* (2010)[54]	205	18 (8.8)	14/137 (10)	34/137 (25)	4/137 (3)	24/137 (18)
Amir *et al.* (2012)[34]	121	4 (3)	15/94 (16)	38/94 (40)	8/83 (10)	17/94 (18)

Niikura, N. *et al. Nat. Rev. Clin. Oncol.* **10**, 711–719 (2013);

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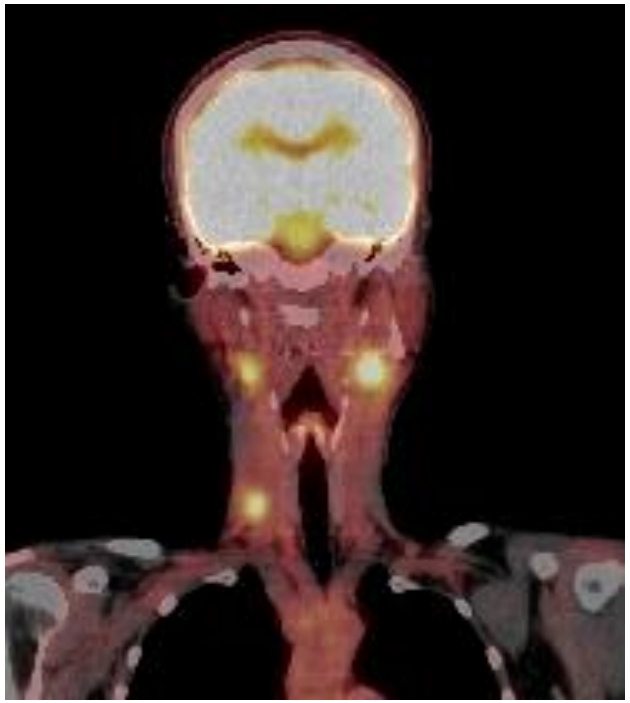
症例 （1）

63歳女性
5年前左乳癌　T2 N0 M0 StageII
ER: 0-10%, PgR 0%, HER2 3+, HG 3, NG 3
Adjuvant: EC- T Herceptin + AI

CC) 両側リンパ節主張

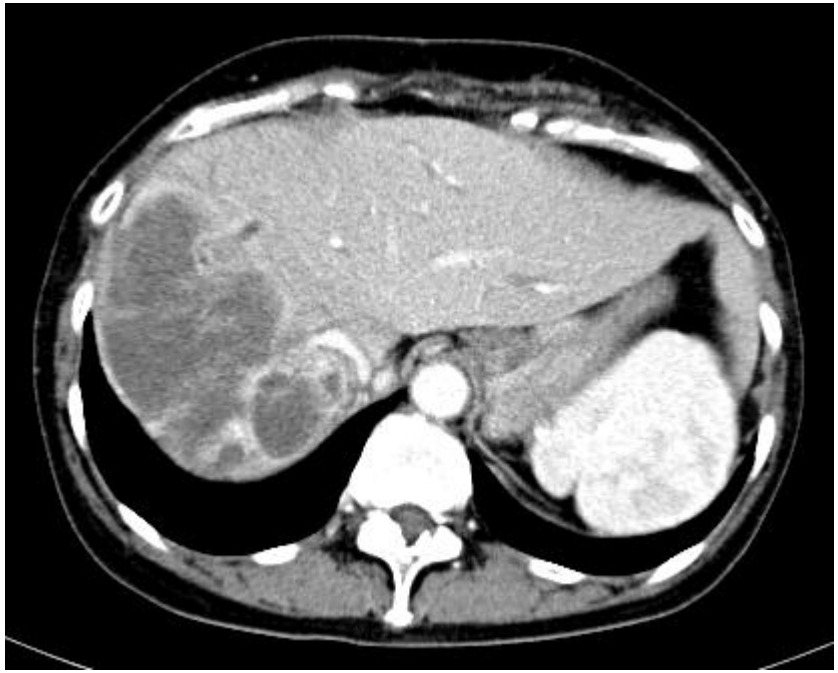


画像診断:
乳癌の頸部リンパ節転移

病理診断:
No Carcinoma cell seen

症例（2）

47歳女性
5年前左乳癌　T2 N2 M0 StageIII　右乳癌　T3 N0 M0　Stage II
ER: 陽性, PgR 陽性, HER2 1+, Ki67　60%
PH:褐色細胞腫　7年前　右副腎摘出術
Adjuvant:　LHRH + TAM
CC:　なし



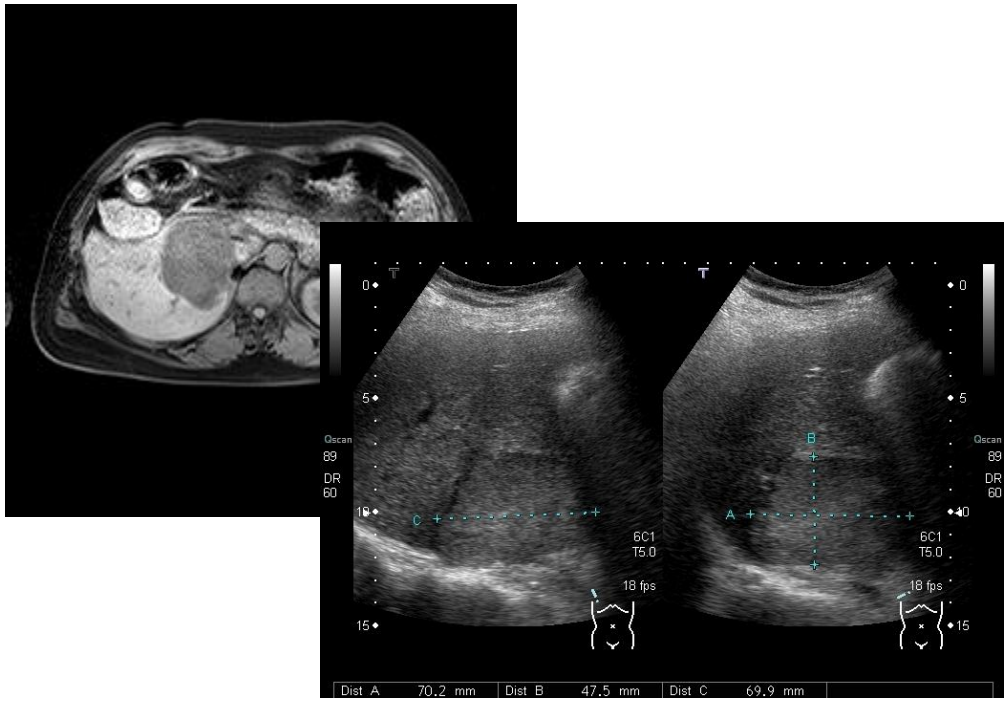
画像診断:
肝　S6　8cm Liver Meta疑い

病理診断:
Metastases from Phenochromocytoma

症例（3）

61歳女性
10年前左乳癌　T4d N3 M0 StageIIIc
ER: 陰性, PgR 陰性, HER2 3+, Ki67　20%
Adjuvant: AC- T＋ Herceptin

CC) 発熱、肝機能障害



画像診断:
乳癌肝転移、胆管細胞がん　疑い

病理診断:
Bile duct Adenocarcinoma

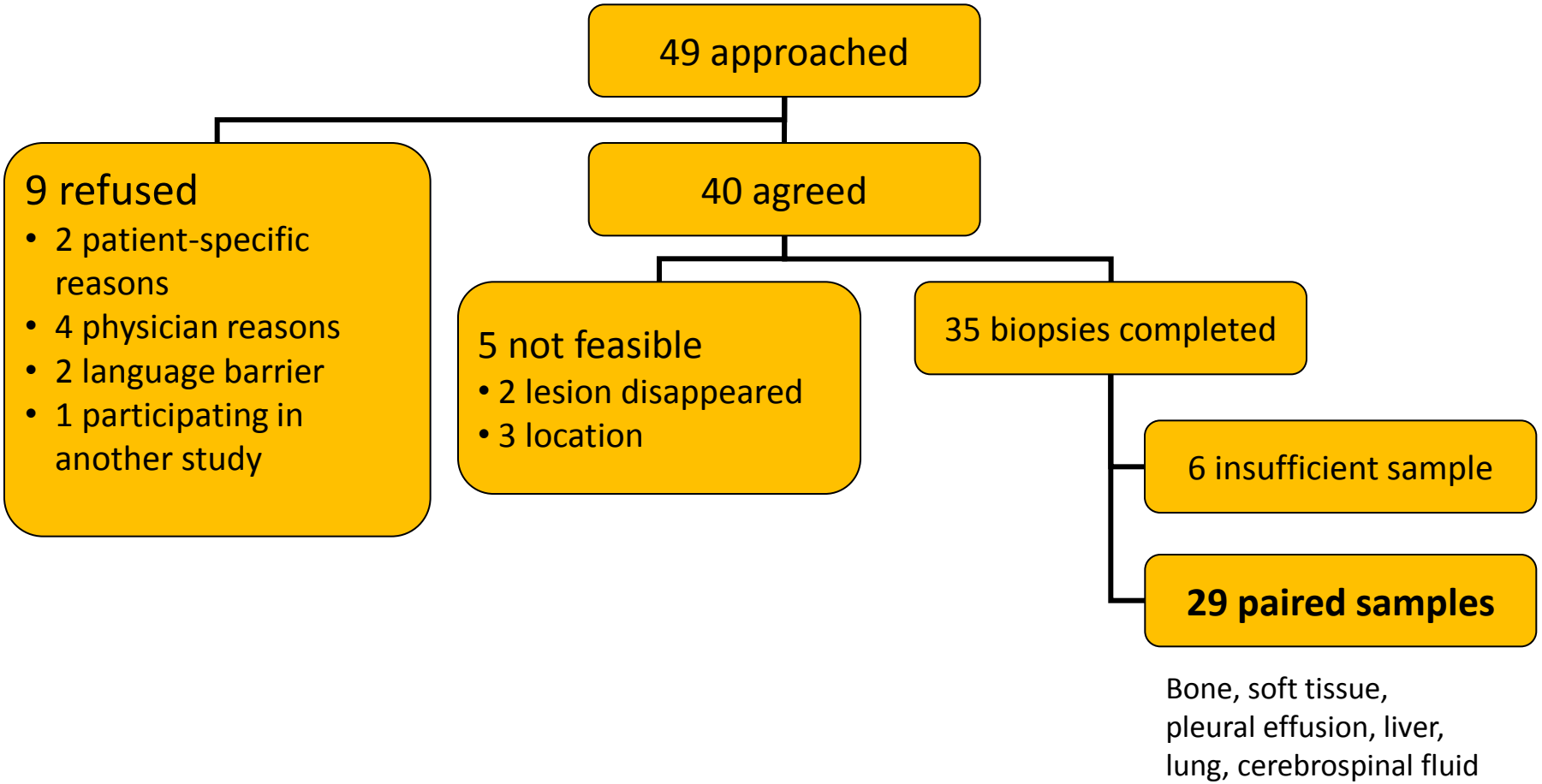
Does Performing a Confirmatory Biopsy at the Time of Metastatic Recurrence Alter Patient Management?

- DESCRY study:
  - Single-centre study, Toronto, Ontario, Canada
  - ER/PgR by IHC using ASCO guidelines
  - HER2 by FISH
  - Reanalysis of primary
  - Planned sample size = 35

Canadian Breast Cancer Foundation
Ontario Chapter

Abbreviations: ER, oestrogen receptor; FISH, fluorescence in situ hybridisation; HER2, human epidermal growth factor receptor-2; IHC, immunohistochemistry; PgR, progesterone receptor.
Simmons C … Clemons MJ. *Ann Oncol*. 2009;20(9):1499-1504.

DESCRY Results: Feasibility



Adapted from Simmons C … Clemons MJ. *Ann Oncol*. 2009;20(9):1499-1504.

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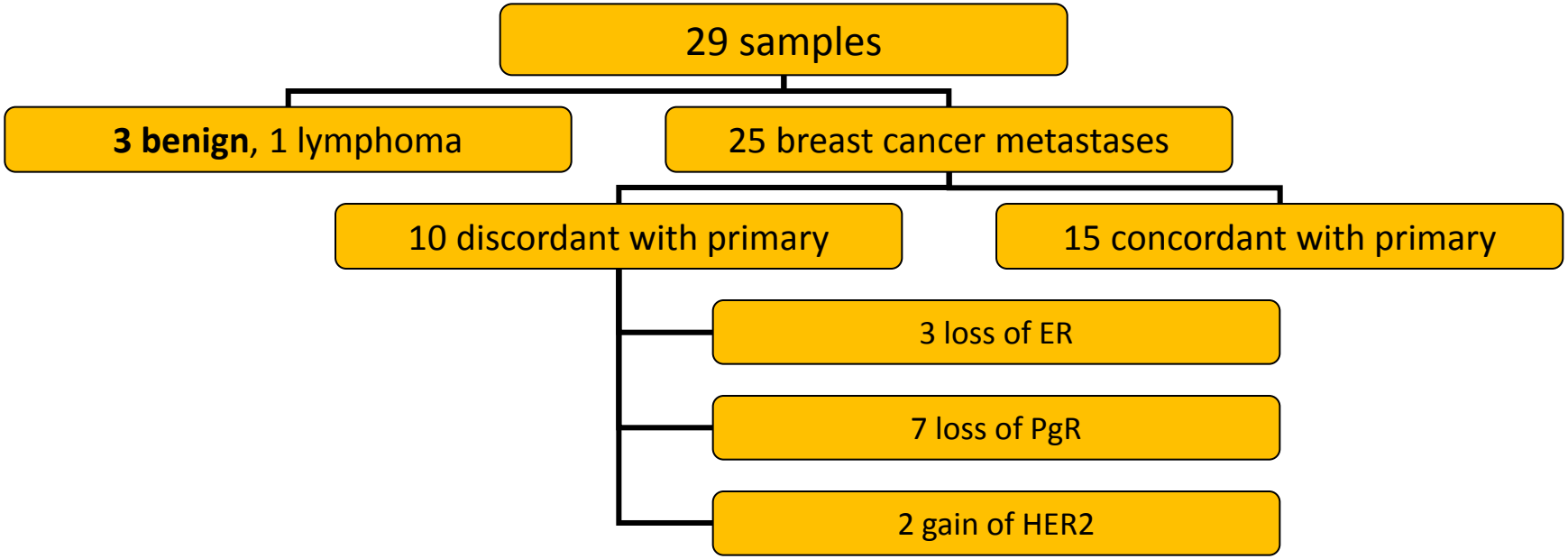
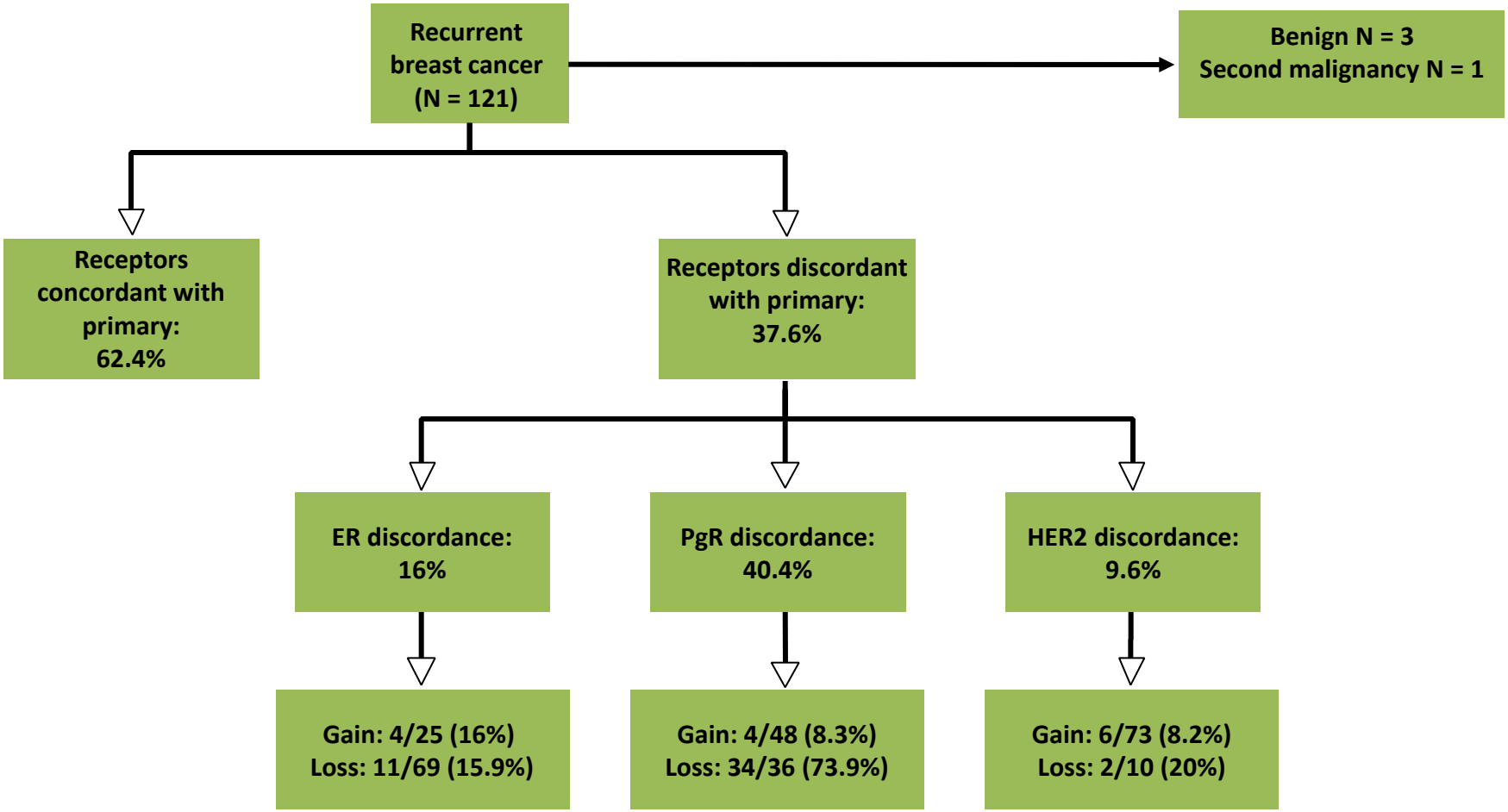
DESCRY Results: Discordance



- 4 patients had completely different diagnosis
- 40% discordance overall ($P < .001$)
  - 12% loss of ER, 28% loss of PgR
  - 8% gain of HER2
- 20% change in management

Reprinted from Simmons C … Clemons MJ. *Ann Oncol*. 2009;20(9):1499-1504.

DESTINY: Receptor Concordance



Abbreviations: ER, oestrogen receptor; HER2, human epidermal growth factor receptor-2; PgR, progesterone receptor.
Adapted from Amir E … Clemons MJ. *J Clin Oncol*. 2012;30(6):587-592.

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Conclusion: Change in Therapy

- Among 121 patients:
  - 17 (14%) had a change in therapy (95% CI, 8.4%-21.5%) based on recurrence biopsy results
    - Trastuzumab added for gain of HER2 over expression (n = 6)
    - Chemotherapy replaced endocrine therapy for loss of ER (n = 5)
    - Endocrine therapy replaced chemotherapy for gain of ER (n = 2)
    - No change in previous treatment for benign disease or second primary (n = 4)

Abbreviations: CI, confidence interval; ER, oestrogen receptor; HER2, human epidermal growth factor receptor-2.

Amir E … Clemons MJ. *J Clin Oncol*. 2012;30(6):587-592.

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BRITS: Receptor Discordance and Subsequent Change in Treatment Plan

- 205 consented
- Paired samples from 137 women, change in
  - ER in 10%
  - PgR in 24.8%
  - HER2 in 2.9%
- Change in treatment plan: 17.5%

Abbreviations: ER, oestrogen receptor; HER2, human epidermal growth factor recptor-2; PgR, progesterone receptor.
Thompson AM, et al. *Breast Cancer Res.* 2010;12(6):R92.

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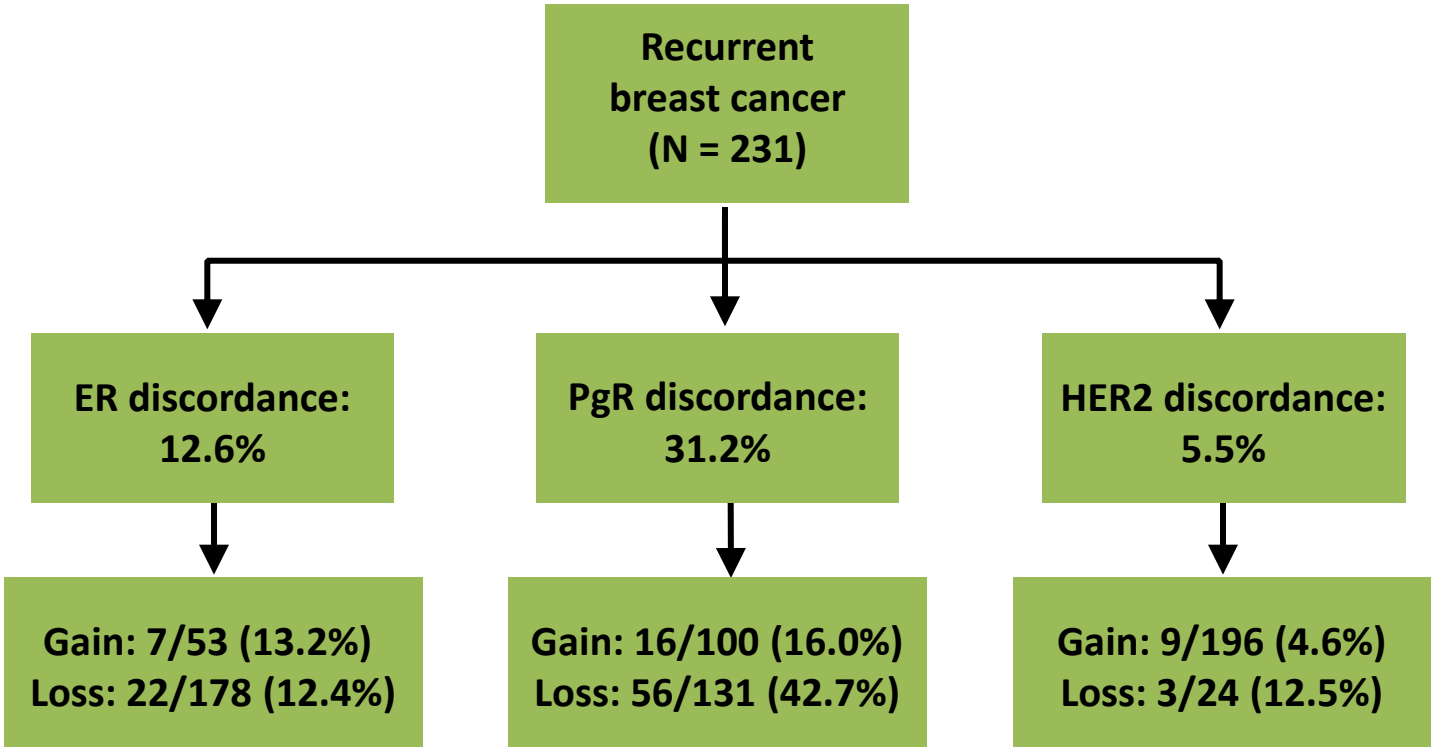
Receptor Concordance From Pooled Analysis of 2 Prospective Studies

(BRITS and DESTINY)

- Change in treatment: 14%



Abbreviations: ER, oestrogen receptor; HER2, human epidermal growth factor recptor-2; PgR, progesterone receptor.
Data from Amir E, Clemons M, et al. *Cancer Treat Rev*. 2012;38(6):708-714.

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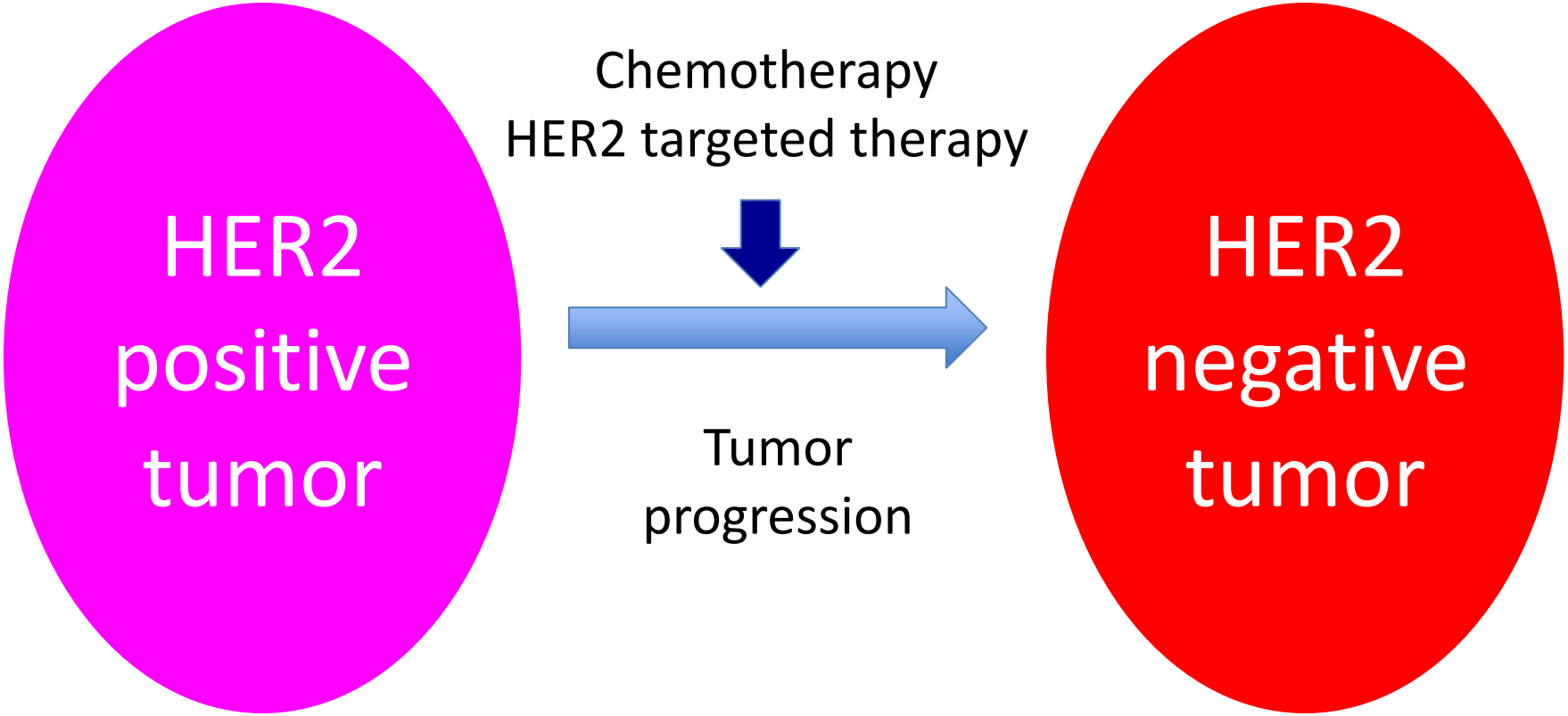
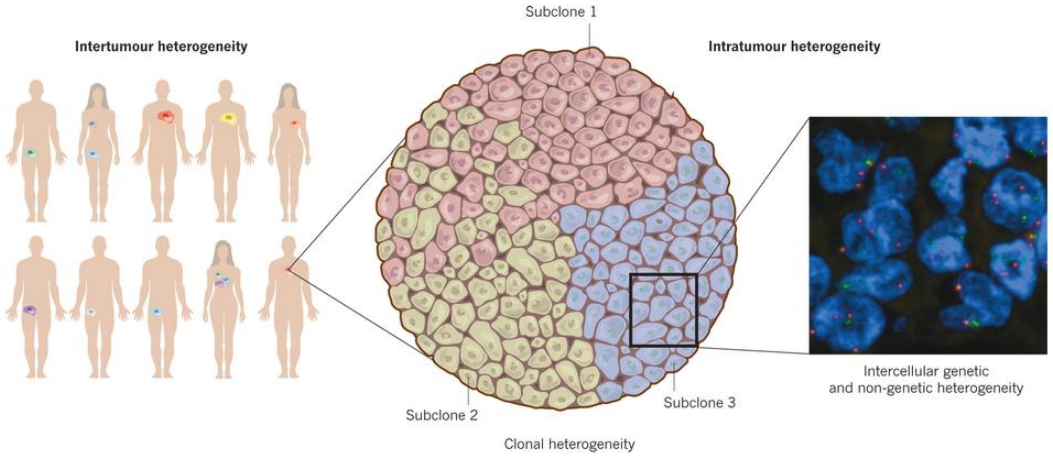
Hypothesis (Testing Problem)

- Fixation
- Fine needle aspiration vs. Core needle biopsy
- Immunostaning
- Sampling error

Hypothesis (Clonal Change)



Hypothesis (Intratumor heterogenity)



Burrell, Nature 2013

HER2 positive tumor

Chemotherapy
HER2 targeted therapy

Tumor progression

HER2 negative tumor

HER2 negative tumor

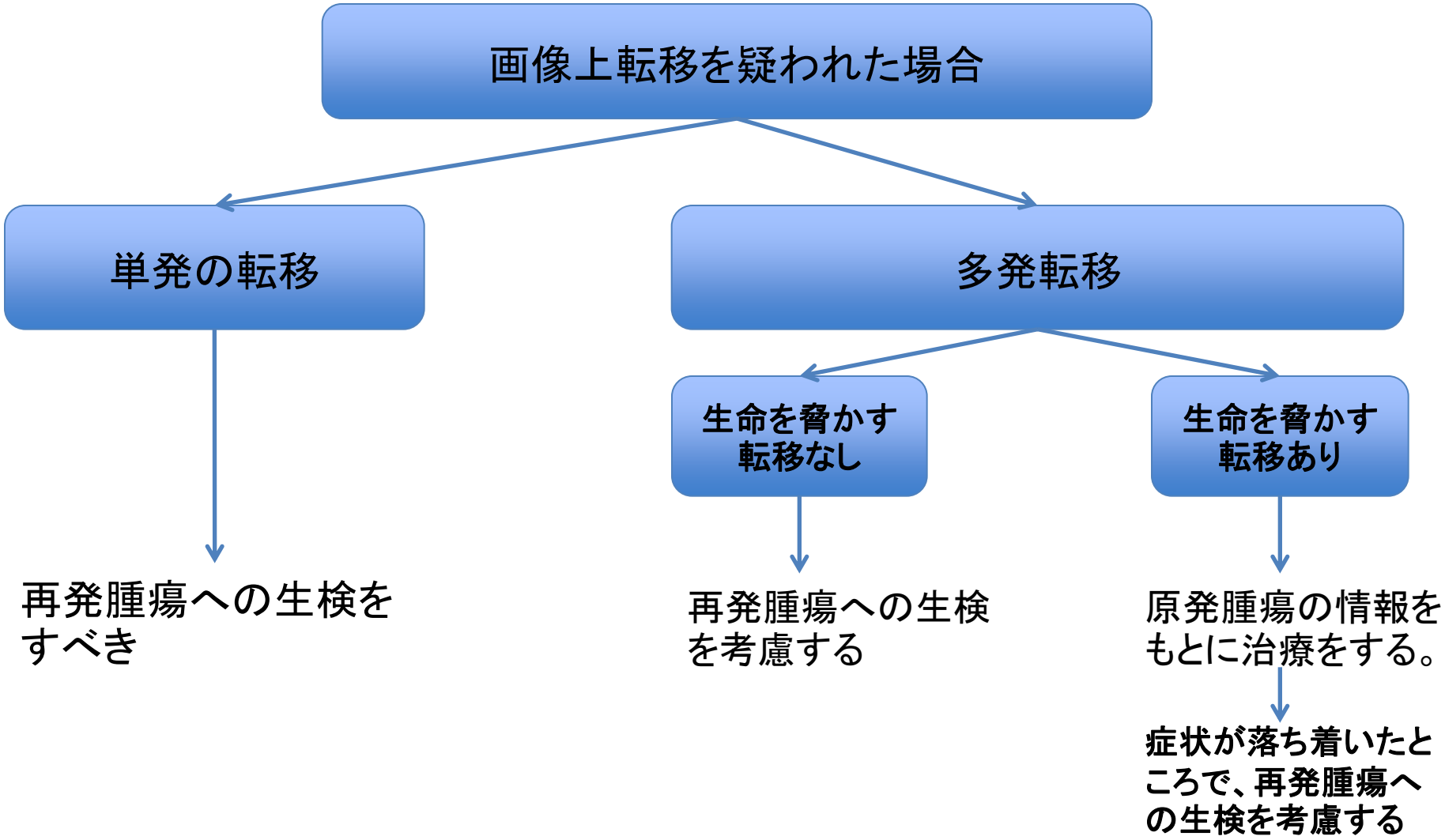
HER2 positive tumor

再発腫瘍のER, PgR, HER2 の再測定の推奨される症例

- 原発腫瘍が古い症例
- ER, PgR, HER2 が自施設以外で染色、判定されている症例。
- 標的治療に反応しない症例
- 容易に、かつ安全に再発腫瘍の生検が行える症例

Niikura N, et al Nature reviews Clin Oncol 2013(改)

An algorithm for metastatic biopsy



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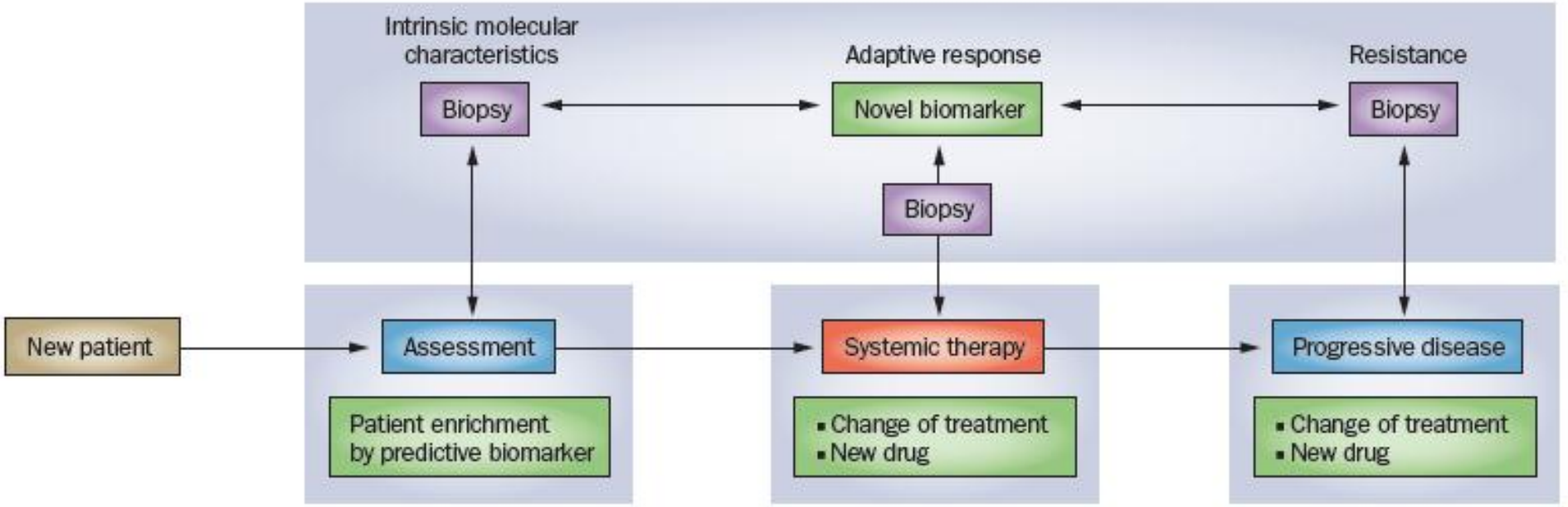
再発乳癌の個別化治療を進めるためのツール

- Metastatic Biopsy
- Liquid Biopsy
  → CTC, Circulating tumor DNA
- Functional and Molecular Imaging
  → FDG-PET/CT,
  FES-PET, ^{89}Zr-Trastuzumab PET/CT

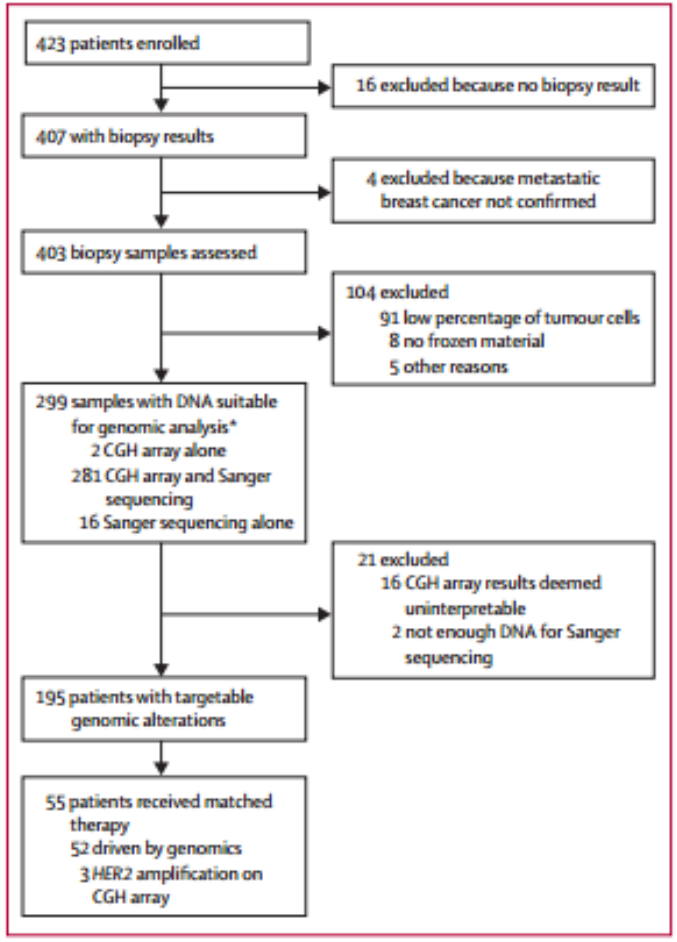
Redefining the treatment paradigm for metastatic breast cancer



Niikura, N. *et al. Nat. Rev. Clin. Oncol.* **10**, 711–719 (2013);

Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER)

Fabrice André, Thomas Bachelot, Frederic Commo, Mario Campone, Monica Arnedos, Véronique Dieras, Magali Lacroix-Triki, Ludovic Lacroix, Pascale Cohen, David Gentien, Jose Adélaide, Florence Dalenc, Anthony Goncalves, Christelle Levy, Jean-Marc Ferrero, Jacques Bonneterre, Claudia Lefeuvre, Marta Jimenez, Thomas Filleron, Hervé Bonnefoi



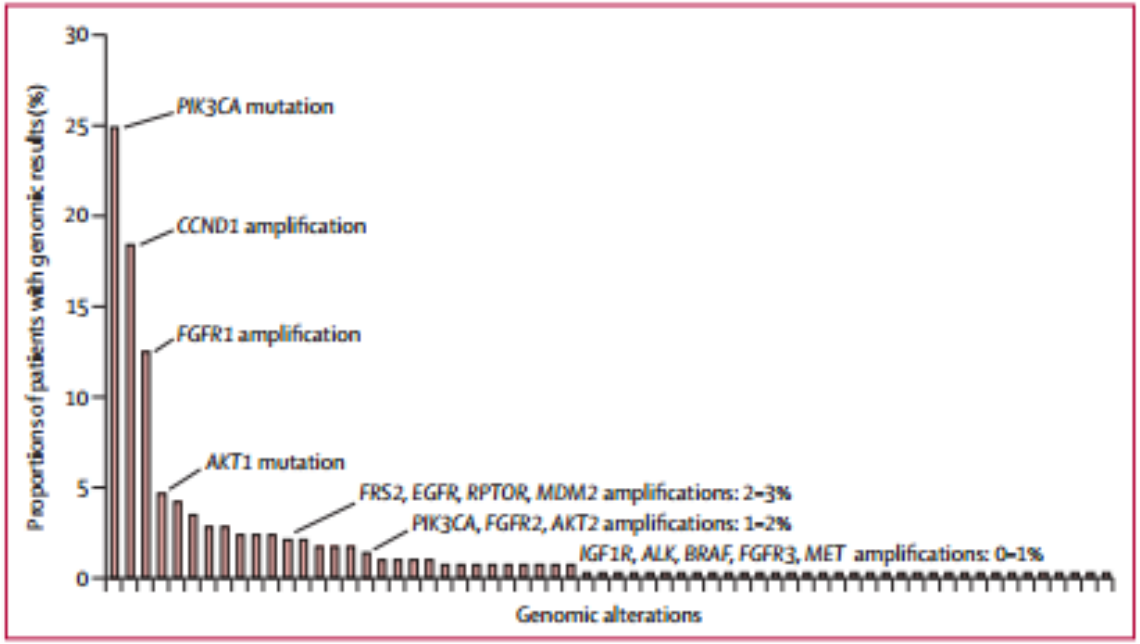


Figure 2: Distribution of targetable genomic alterations among screened patients

Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER)

Fabrice André, Thomas Bachelot, Frederic Commo, Mario Campone, Monica Arnedos, Véronique Dieras, Magali Lacroix-Triki, Ludovic Lacroix, Pascale Cohen, David Gentien, Jose Adélaide, Florence Dalenc, Anthony Goncalves, Christelle Levy, Jean-Marc Ferrero, Jacques Bonneterre, Claudia Lefeuvre, Marta Jimenez, Thomas Filleron, Hervé Bonnefoi

	Number of patients (assessable for efficacy)	Number of patients treated in phase 1 or 2 trials	Number of patients with antitumour activity (%)*
All patients	48 (43)	28	13 (30%)
FGF4 amplification, treated with FGFR inhibitor E-3810	2 (2)	2	1 (50%)
EGFR amplification, treated with EGFR inhibitors erlotinib and cetuximab-temsirolimus	2 (2)	1	1 (50%)
EGFR amplification or *AKT1* or *PIK3CA* mutation, treated with AKT or mTOR inhibitors (everolimus and GDC-0980)	2 (1)	1	1 (100%)
FGFR1 amplification, treated with FGFR inhibitors E-3810 (n=3) or BGJ398 (n=6)	9 (8)	9	2 (25%)
FGFR1 amplification or *PIK3CA* mutation, treated with FGFR inhibitor BGJ398	2 (1)	2	0
FGFR1 amplification or *PIK3CA* mutation, treated with mTOR inhibitor everolimus	1 (1)	0	0
FGFR2 amplification or *PIK3CA* mutation, treated with FGFR inhibitor BGJ398	1 (1)	1	0
IFG1R amplification or *PIK3CA* mutation, treated with mTOR inhibitor CCI-223	1 (1)	1	1 (100%)
MET gain, treated with MET inhibitor onartuzumab	1 (1)	1	0
FRS2 amplification, treated with Raf inhibitor sorafenib	1 (1)	0	0
AKT1 mutation or *AKT2* amplification, treated with AKT1 and/or mTOR inhibitor everolimus (n=4) or ridaforolimus plus MK2206 or 0752 (n=2) or plus CC223 (n=1)	7 (6)	3	3 (50%)
PIK3CA mutation or amplification†, treated with PI3K, AKT, or mTOR inhibitors (everolimus n=9, GDC-0980 n=2,[17] GDC-0068 n=1,[18] or cetuximab-temsirolimus n=1; associated with chemotherapy in one patient)	13 (12)	4	4 (33%)
RPTOR amplification, treated with mTOR inhibitor everolimus or axitinib-everolimus	2 (2)	1	0
CCND1 amplification, treated with CDK4 inhibitor BAY 1000394	1 (1)	1	0
AR amplification, treated with AR inhibitor bicalutamide	1 (1)	0	0
MDM2 amplification, treated with MDM2 inhibitor RO5503781	1 (1)	1	0
MGMT amplification, treated with alkylating agent temozolomide	1 (1)	0	0

*Objective response or stable disease for >16 weeks, seen overall in n=28. †*PIK3CA* amplification seen in only one patient.

Table 3: Genomic targets and matched drugs

個別化治療を目指した
コンパニオン診断薬としてのPETの可能性

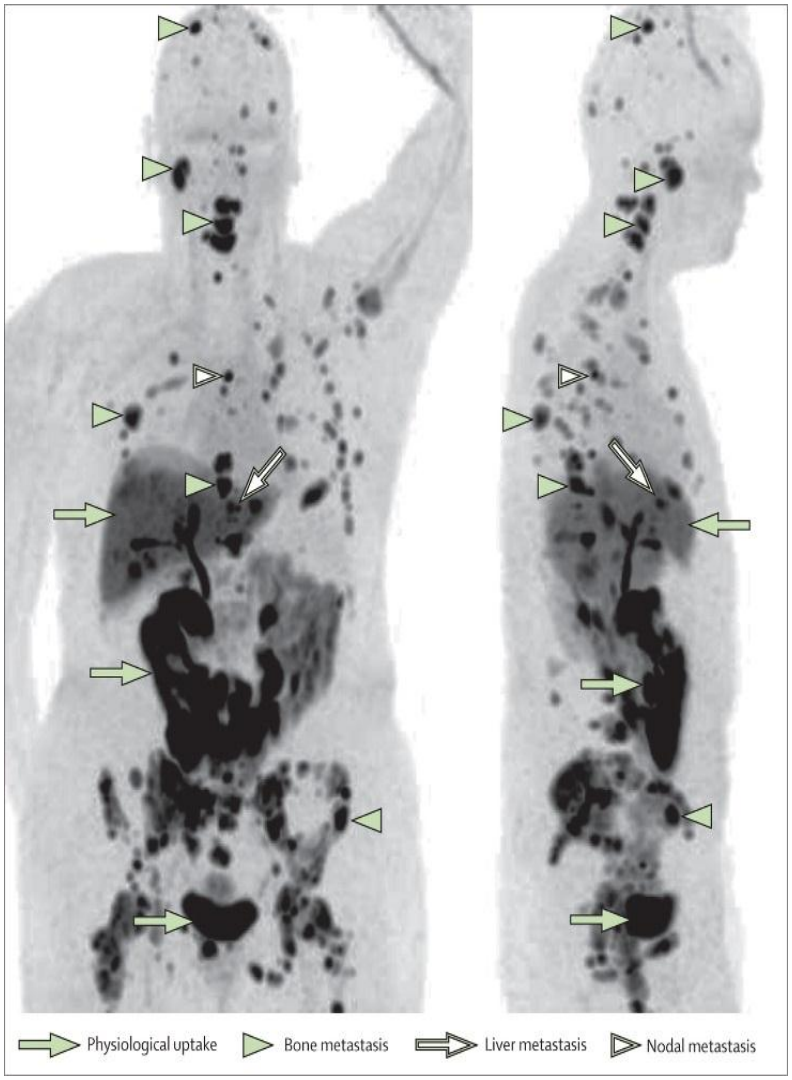
長所

- PETは高感度のイメージングツールである。
- 標的分子高選択的トレーサー（低分子、Biollogics)が合成可能
- いわば“IHC In Vivo”の方法

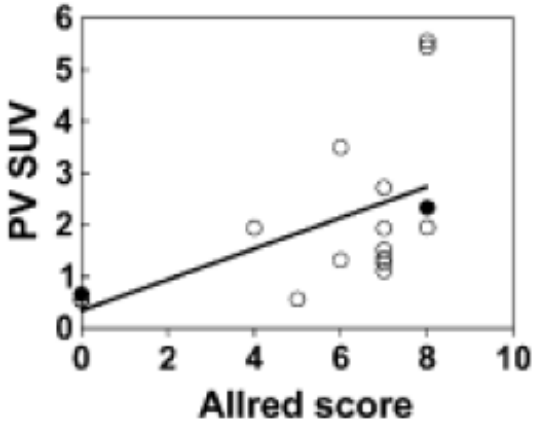
差別化のポイント

- Biopsyが不要
- 生検が難しい場所でもバイオマーカーの判定可能
- 多発転移巣も評価が可能
- 経時変化をリアルタイムで追跡できる。

16α-^{18}F-fluoro**Estradiol**-17β（FES)/PET



- **In vivo IHC**



- ER陽性乳癌とFES/PETの感度84%、特異度98%
- ER陽性乳癌患者の45%にFES陰性の転移巣がある
- 閉経状況とホルモン剤の使用状況でFESの取り込みに変化がある

Gray J, et al. Clin Cancer Res 2005
Michel van Kruchten, et al, The Lancet Oncology Volume 14, Issue 11 2013

Take home message

- 画像検査の進歩により転移部位への生検の侵襲が減り、安全に行えるようになってきた。
- がん治療医は検体の取り扱いには十分配慮し、病理学的、検査の限界を考慮し、レポートを読む必要がある。
- 転移臓器が一つの場合は、他のがん、もしくは良性の可能性があり、生検は必須である。
- 多発転移であっても臨床的な経過と、原発腫瘍の性格で乖離がある場合、生検による診断が必要である。
- 転移巣への生検を行うことで治療方針が14－20%変化する。
- 今後の治験、臨床研究ではより正確な検体の管理、再発腫瘍の生検が重要になってくる。