2009年7月4日(土曜日)
日本乳癌学会ランチョンセミナー14

St.Gallen 2009
治療選択の考え方
- ホルモン療法編 -

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話の内容

- 若年性乳癌患者の治療は間違っていた？
- St.Gallen 2009　カテゴリーからスレッショルドへ
- 注目！　新しい標的薬剤　「PARP阻害剤」

CASE STUDY
31才 閉経前未婚女性

- 右乳癌　T2 N0 M0 stage IIA
- 乳房温存術＋センチネルリンパ節生検
- 浸潤性乳管癌, ly (-), v (-), SLN 陰性
  - t: 12×16　mm
  - grade 1
  - ER: 陽性　(染色陽性割合90%以上)
  - PgR: 陽性 (染色陽性割合90%以上)
  - HER2: 陰性

3

CASE STUDY
抗がん剤の選択は　?

1. 抗がん剤は使用しない
2. CMF 6サイクル
3. UFT　2年間内服
4. AC 4サイクル
5. AC → weekly paclitaxel (80mg/m^2)
6. TC (DTX + Cyclophosphamide)

4

CASE STUDY
ホルモン剤の選択は？

1. TAM　5年間
2. TAM　5年間　（生理が復活したらLH-RH agonist追加）
3. TAM　5年間＋LH-RH agonist 2年
4. TAM　5年間＋LH-RH agonist 5年
5. AI 5年間＋LH-RH agonist 5年

5

10th International Conference on Primary Therapy of Breast Cancer (2007)

低リスク
- ●腋窩リンパ節転移陰性で以下のすべてを充たす症例
  - 病理学的腫瘍径2cm以下
  - グレード　1
  - 腫瘍周囲の**広域な**脈管浸潤がない
  - HER2タンパク過剰発現/遺伝子増幅がない
  - **ER and/or PgR 発現あり**
  - **年令　35才以上**

中間リスク
- ●腋窩リンパ節転移陰性で以下の一つ以上を充たす症例
  - 病理学的腫瘍径2cmを超える
  - グレード　2,3
  - 腫瘍周囲の**広域な**脈管浸潤がある
  - HER2タンパク過剰発現/遺伝子増幅がある
  - **ER and PgR 発現なし**
  - **年令　35才未満**
- ●腋窩リンパ節転移1-3個陽性
  - **ER and/or PgR 発現あり かつ** HER2タンパク過剰発現/遺伝子増幅がない

高リスク
- ●腋窩リンパ節転移1-3個陽性
  - **ER and PgR 発現なし、または** HER2タンパク過剰発現/遺伝子増幅がある
- ●腋窩リンパ節転移４個以上

Age(>35 y)がリスクカテゴリーに追加されたのは1995年

Table 3. Definition of risk categories for patients with lymph node-negative breast cancer

Factor	Minimal risk–low risk (all of the listed factors)	Good risk	High risk (at least one of the listed factors)
Tumor size, cm*	<1	1-2	>2
Estrogen receptor status†	Positive	Positive	Negative
Grade†	Grade 1 (uncertain relevance for tumors <1 cm)	Grades 1-2	Grades 2-3
Age‡	>35 y		

*It was generally agreed that pathological tumor size (of invasive component) was the most important prognostic factor for defining additional risk of relapse.
†Estrogen receptor status and grade are expressions of the malignant transformation of the tumor cell, and it is difficult to precisely dichotomize these features to indicate a good versus bad prognosis.
‡Patients who develop breast cancer at a young age are considered to be at high risk of relapse, although an exact age threshold for this increased risk has not been defined. While acknowledging this fact, the panel did not accept age as a factor to influence the choice of the type of treatment (chemotherapy or endocrine therapy).

Journal of the National Cancer Institute, Vol. 87, No. 19, October 4, 1995　　COMMENTARY 1443

若年発症乳癌は再発リスクが高いと考えられているが、ハイリスク症例を、何歳で区分するかは明確ではない。また、年齢に基づいて治療方法（化学療法、内分泌療法）を選択ことはしない。

Adjuvant Therapy for Very Young Women With Breast Cancer: Need for Tailored Treatments

Aron Goldhirsch, Richard D. Gelber, Greg Yothers, Robert J. Gray, Stephanie Green, John Bryant, Shari Gelber, Monica Castiglione-Gertsch, Alan S. Coates

恐るべし! Goldhirsch

Breast cancer rarely occurs in women below the age of 35 years. Data from various sources indicate that diagnosis at such an age is associated with a dire prognosis mainly because of a more aggressive presentation. Although the effect of chemotherapy for premenopausal patients is substantial, recent evidence on 2233 patients suggested that very young women with endocrine-responsive tumors had a statistically significantly higher risk of relapse than older premenopausal patients with such tumors. In contrast, results for younger and older premenopausal patients were similar if their tumors were classified as endocrine nonresponsive. Information from studies on 7631 patients who were treated with chemotherapy alone in trials of three major U.S. cooperative groups showed a similar interaction between the effect of age and steroid hormone receptor status of the primary tumor. Better treatments for very young patients are required and may involve ovarian function suppression in addition to other endocrine agents in patients with endocrine responsive tumors and a more precise investigation of chemotherapy and its timing, duration, and intensity in those with endocrine nonresponsive tumors. Very young women with this disease are faced with personal, family, professional, and quality-of-life issues, which further complicate the phase of treatment decision making. The development of more effective therapies for younger patients requires tailored treatment investigations and cannot rely on information predominantly contributed from older premenopausal women. [J Natl Cancer Inst Monogr 2001;30:44–51]

might explain this finding. Results from the same,
lished, study also indicated that patients under 35
had a higher grade and higher expression of K
percentage of vessel invasion, and less expressio
receptor (ER) and progesterone receptor but simila
sion of HER2/neu in the primary tumor.

Results from two population-based studies ind
risk of death is highest among the youngest and
horts when compared with the patients of interme
even when the analysis allows for differences in
stage *(5)*. A review of the National Cancer Data Base *(6)* reveals that patients younger than 35 years of age have more advanced disease at diagnosis and a poorer 5-year survival than older premenopausal patients. Similar findings have been reported from the National Cancer Institute SEER[3] database *(7)*, from the Finnish Cancer Registry *(8)*, from the Southwest Oncology Group (SWOG) database *(9)*, and from a recent Danish study on young patients who did not receive adjuvant therapy *(10)*, as well as from several series described from single centers *(11–13)*.

Why Focus on Breast Cancer in Women Less Than 35 Years Old?

In addition to considerations related to presentation of disease and prognosis, women under 35 years of age with breast cancer face some specific problems that are less relevant for older premenopausal patients. It is clear, however, that trials reporting results for premenopausal women largely reflect outcomes for patients in their 40s. Table 1 indicates some of the issues that are

若い乳癌患者の諸問題

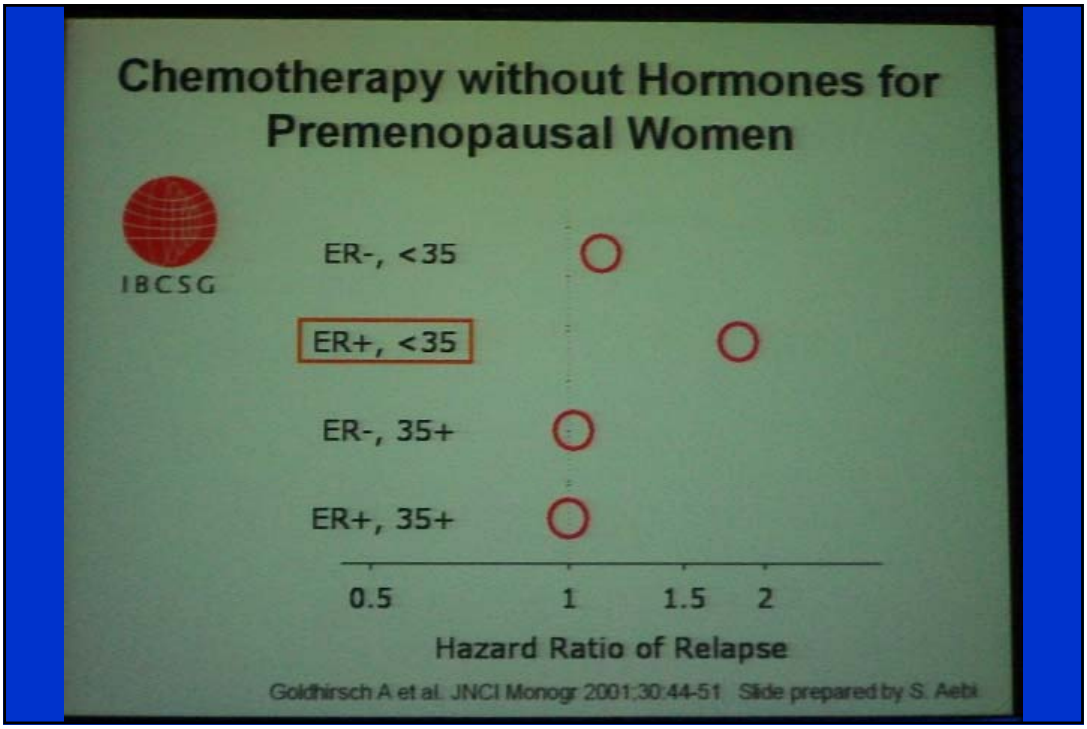
Table 1. Treatment and personal issues: evidence and current options of approach

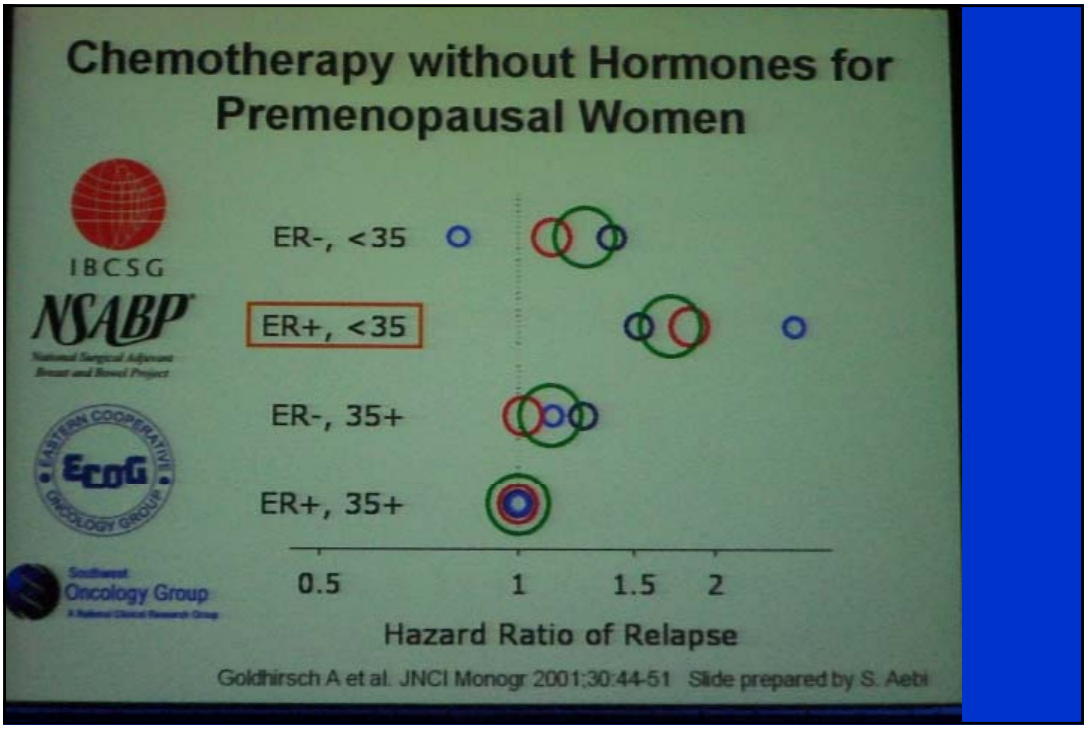
Considerations on differences between younger and older premenopausal patients	Status of evidence	Current options (sometimes despite evidence)
Local disease control and very late effects of radiation therapy	Young patients have a higher risk for locoregional relapse *(45,46)*. No data are available on late effects of anthracyclines and taxanes plus radiation therapy on the heart.	Breast conservation with radiation therapy is considered a standard *(47)*. Total or bilateral (prophylactic) mastectomy is increasingly discussed *(48)*.
Pregnancy after breast cancer	Pregnancy seems to be safe after breast cancer and after adjuvant systemic cytotoxic therapy *(49,50,51)* (except for BRCA1 and BRCA2 carriers) *(52)*. Uncertainty exists concerning pretreatment with tamoxifen and neonatal genital tract malformations *(53)*.	There is reluctance to consider pregnancy even for women with lymph node-negative disease *(54)*. Gonadotropin-releasing hormone analogue is available as an effective endocrine treatment, especially if given with tamoxifen *(55)*. (New endocrine therapies are being investigated, mainly in postmenopausal patients.)
Interpersonal and family relations; professional decisions	Younger women might be particularly vulnerable to the emotional distress of the disease *(56)* because they need to face disease and treatments before attaining many personal accomplishments.	Psychological support is an option that is being tested in trials.

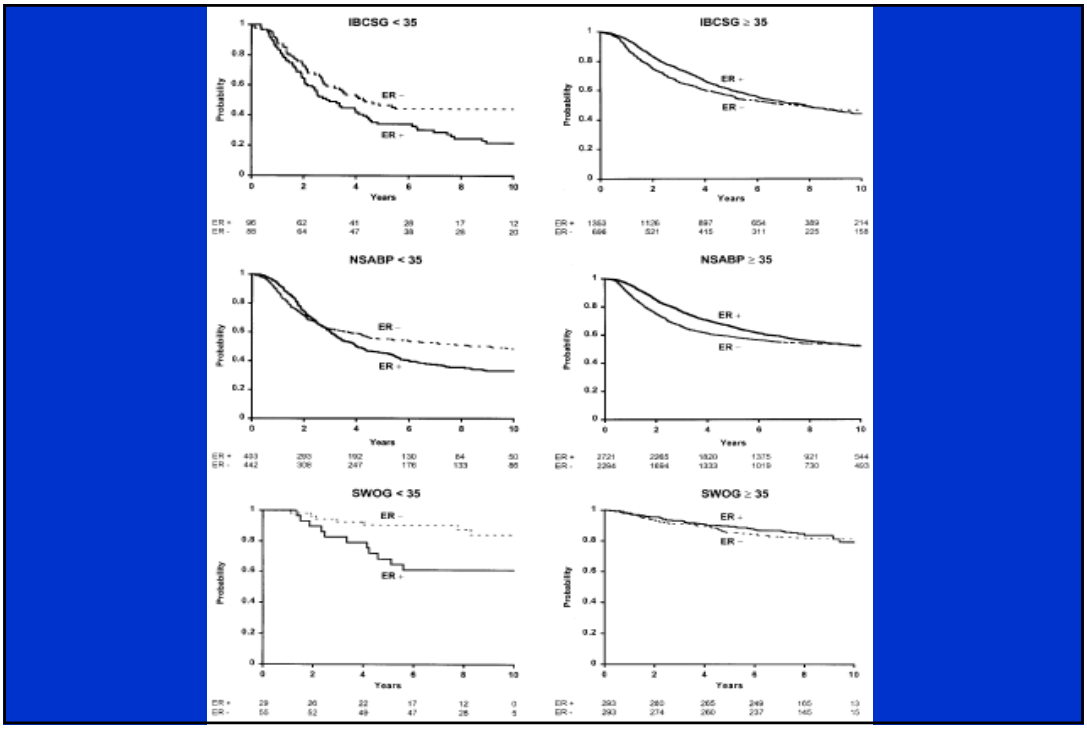
CMF後の無月経

Table 2. Endocrine effects of chemotherapy in premenopausal patients—percentage of patients with amenorrhea for at least 3 months in International Breast Cancer Study Group Trial VI according to age *(15)*

Age group, y	No. of patients (%)	No amenorrhea, %	Amenorrhea followed by resumption of menses, %	Permanent amenorrhea, %
<35	90 (8.5)	88	4	8
⩾35	964 (91.5)	34	7	59


Chemotherapy without Hormones for Premenopausal Women
IBCSG
ER-, <35
ER+, <35
ER-, 35+
ER+, 35+
0.5
1
1.5
2
Hazard Ratio of Relapse
Goldhirsch A et al. JNCI Monogr 2001;30:44-51 Slide prepared by S. Aebi


Chemotherapy without Hormones for Premenopausal Women
IBCSG
NSABP
ECOG
Southwest Oncology Group
ER-, <35
ER+, <35
ER-, 35+
ER+, 35+
0.5
1
1.5
2
Hazard Ratio of Relapse
Goldhirsch A et al. JNCI Monogr 2001;30:44-51 Slide prepared by S. Aebi



Primary Therapy of Early Breast Cancer

回	開催年	参加者数	文献
1	1978	79	
2	1984	225	JAMA 254: 3461, 1985
3	1988	540	JNCI 80: 471, 1988
4	1992	820	JNCI 84:1479, 1992
5	1995	1250	JNCI 87:1441, 1995
6	1998	1800	JNCI 90:1601, 1998
7	2001	2500	J Clin Oncol 2001;19:3817-3827
8	2003	3100	J Clin Oncol 2003;21:3357-3365
9	2005	4100	Annals of Oncology
10	2007	4700	Annals of Oncology
11	**2009**	**5000<**	**Annals of Oncology**

Primary Therapy of Early Breast Cancer

回	開催年	おもな改訂ポイント
1	1978	ヨーロッパ各国の術後治療に関する意見統一をはかる
2	1984	n(+)症例では術後治療必要
3	1988	n(-)症例でも術後治療が必要な場合がある
4	1992	n(-)症例を「low risk」「high risk」に分類（リスクカテゴリー）
5	1995	n(-)症例を「minimal risk」「low risk」「high risk」に分類
6	1998	n(-)症例を「low risk」「intermediate risk」「high risk」に分類
7	2001	n(-) とn(+)がひとつの表に統合
8	2003	予後因子と予測因子を区別する考え方を導入
9	2005	脈管浸潤を予後因子として追加
10	2007	リスクよりもターゲット(ホルモン受容体、HER2)重視
11	2009	リスクカテゴリーからリスクスレッショルドの考え方へ

Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2009

Annals of Oncology
June 17, 2009

http://www.ganjoho.org
からダウンロードできます。

日本語訳も合わせて
ご利用ください。

「Category に分類する」

という考え方から

「Threshold を設定する」

という考え方へ

Treatment Threshold

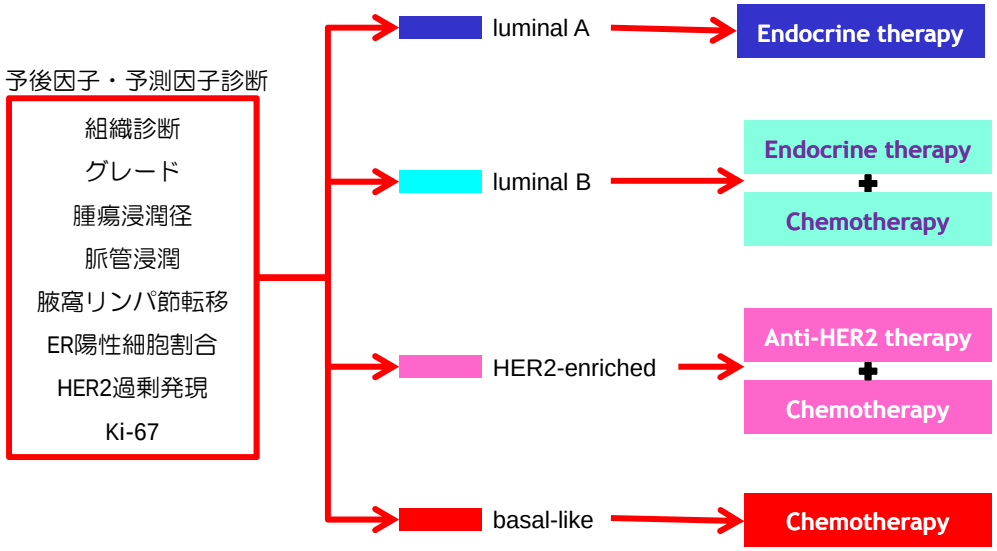
治療種別	適応	コメント
内分泌療法	ER 陽性細胞が１％以上	ER陰性，PgR陽性というのはおそらくアーチファクトである
抗HER2療法	ASCO/CAP ガイドラインに準じ ・IHC：強く全周性の染色陽性細胞が 30% 以上 ・FISH 2.2x 以上	臨床試験で使用された陽性の定義を使用してもよい
化学療法		
A. HER2陽性疾患 (+抗HER2療法)	臨床試験エビデンスはトラスツズマブ使用は化学療法併用に限定	ER強陽性、HER2陽性で化学療法非併用は理屈はわかるが根拠なし
B. Triple Negative Disease	ほとんどの患者	他に選択肢はない。 リスクに応じた十分な治療
C. ER陽性、HER2陰性疾患 (+内分泌療法)	リスクに応じて決定	☞ リスク分布を考慮

ER陽性症例における化学療法追加の閾（しきい）

	化学療法追加		内分泌療法単独
グレード	3	2	1
増殖指標（Ki67, MI)	高い	中程度	低い
ER、PgR陽性割合	低い		高い
腋窩リンパ節転移	4 個以上	1-3 個	陰性
腫瘍周囲の脈管浸潤	広汎		なし
病理学的浸潤径	> 5cm	2.1 - 5.0 cm	≤ 2cm
患者の意向	利用可能な治療希望		化療の副作用は避けたい
遺伝子発現解析	高スコア		低スコア

敷居（しきい）　　閾（しきい）

術後薬物療法の選択手順



CASE STUDY
31才 閉経前未婚女性

- 右乳癌　T2 N0 M0 stage IIA
- 乳房温存術＋センチネルリンパ節生検
- 浸潤性乳管癌, ly (-), v (-), SLN 陰性
  - t: 12×16　mm
  - grade 1
  - ER: 強陽性　(Allred Score 8)
  - PgR: 強陽性 (Allred Score 8)
  - HER2: 陰性

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

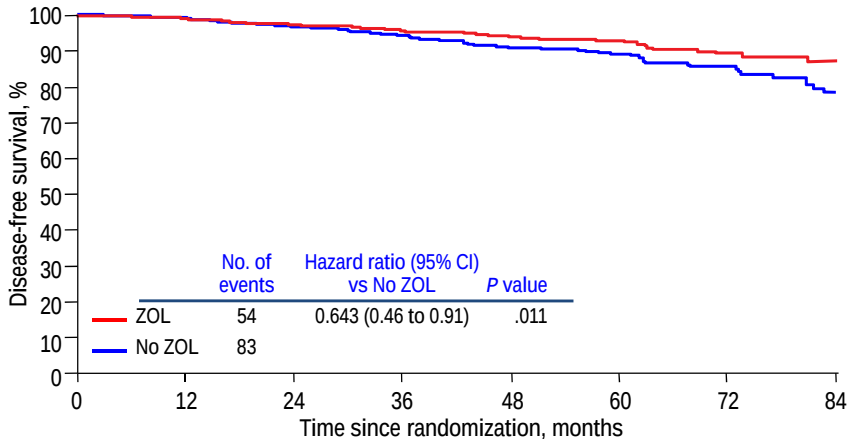
Endocrine Therapy plus Zoledronic Acid in Premenopausal Breast Cancer

Michael Gnant, M.D., Brigitte Mlineritsch, M.D., Walter Schippinger, M.D., Gero Luschin-Ebengreuth, M.D., Sabine Pöstlberger, M.D., Christian Menzel, M.D., Raimund Jakesz, M.D., Michael Seifert, M.D., Michael Hubalek, M.D., Vesna Bjelic-Radisic, M.D., Hellmut Samonigg, M.D., Christoph Tausch, M.D., Holger Eidtmann, M.D., Günther Steger, M.D., Werner Kwasny, M.D., Peter Dubsky, M.D., Michael Fridrik, M.D., Florian Fitzal, M.D., Michael Stierer, M.D., Ernst Rücklinger, Ph.D., and Richard Greil, M.D., for the ABCSG-12 Trial Investigators*

Gnant M et al. N Engl J Med 2009;360:679-691

Primary Endpoint: Disease-Free Survival

Zoledronic Acid Significantly Improves DFS Compared With Endocrine Therapy Alone



Number at risk

No ZOL	904	838	735	565	441	265	161	60
ZOL	899	851	744	573	434	270	131	59

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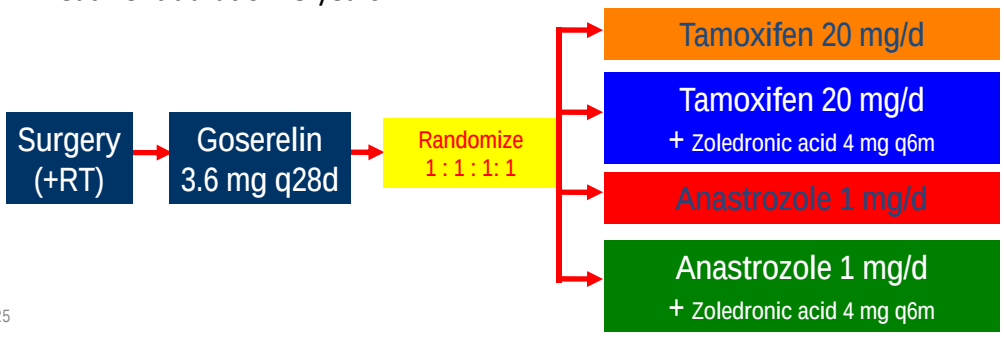
ABCSG-12 Trial Design

- Accrual 1999-2006
- 1,803 premenopausal breast cancer patients
- Endocrine-responsive (ER and/or PR positive)
- Stage I&II, <10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years



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Characteristic	Tamoxifen (N=451)	Tamoxifen plus Zoledronic Acid (N=449)	Anastrozole (N=453)	Anastrozole plus Zoledronic Acid (N=450)
Age at study entry				
Median — yr	45.5	45.3	45.0	44.5
Range — yr	27.6–56.5	27.5–56.3	25.9–56.3	28.8–56.4
≤40 yr — no. (%)	80 (17.7)	67 (14.9)	88 (19.4)	91 (20.2)
>40 yr — no. (%)	370 (82.0)	382 (85.1)	364 (80.4)	358 (79.6)
Cancer stage — no. (%)				
T1	338 (74.9)	335 (74.6)	348 (76.8)	339 (75.3)
≥T2	99 (22.0)	98 (21.8)	93 (20.5)	97 (21.6)
Unknown	13 (2.9)	16 (3.6)	11 (2.4)	13 (2.9)
Nodal status — no. (%)				
Negative	301 (66.7)	295 (65.7)	303 (66.9)	302 (67.1)
Positive	136 (30.2)	138 (30.7)	139 (30.7)	135 (30.0)
Unknown	13 (2.9)	16 (3.6)	10 (2.2)	12 (2.7)
Histologic grade — no. (%)				
1 or 2	344 (76.3)	344 (76.6)	344 (75.9)	339 (75.3)
3	93 (20.6)	89 (19.8)	97 (21.4)	98 (21.8)
Unknown	13 (2.9)	16 (3.6)	11 (2.4)	12 (2.7)

Characteristic	Tamoxifen (N=451)	Tamoxifen plus Zoledronic Acid (N=449)	Anastrozole (N=453)	Anastrozole plus Zoledronic Acid (N=450)
Estrogen-receptor status — no. (%)†				
Negative	16 (3.5)	19 (4.2)	15 (3.3)	17 (3.8)
Low expression	51 (11.3)	61 (13.6)	54 (11.9)	58 (12.9)
Medium expression	166 (36.8)	149 (33.2)	167 (36.9)	153 (34.0)
High expression	204 (45.2)	204 (45.4)	206 (45.5)	210 (46.7)
Unknown‡	14 (3.1)	16 (3.6)	11 (2.4)	12 (2.7)
Progesterone-receptor status — no. (%)†				
Negative	40 (8.9)	32 (7.1)	34 (7.5)	36 (8.0)
Low expression	52 (11.5)	64 (14.3)	58 (12.8)	59 (13.1)
Medium expression	160 (35.5)	142 (31.6)	149 (32.9)	131 (29.1)
High expression	185 (41.0)	195 (43.4)	200 (44.2)	212 (47.1)
Unknown‡	14 (3.1)	16 (3.6)	12 (2.6)	12 (2.7)
Preoperative chemotherapy — no. (%)				
No	406 (90.0)	404 (90.0)	408 (90.1)	405 (90.0)
Yes	24 (5.3)	23 (5.1)	24 (5.3)	26 (5.8)
Unknown	21 (4.7)	22 (4.9)	21 (4.6)	19 (4.2)

Events in the Intention-to-Treat Population

Table 2. **Events in the Intention-to-Treat Population.***

Event	Tamoxifen (N=900)	Anastrozole (N=903)	No Zoledronic Acid (N=904)	Zoledronic Acid (N=899)
			no. of events	
All events	65	72	83	54
Recurrence				
Locoregional	16	14	20	10
Distant	29	41	41	29
Bone metastases	18	21	23	16
Contralateral breast cancer	10	6	10	6
Secondary malignant condition	9	10	10	9
Death				
All	15	27	26	16
Without previous recurrence	1	1	2	0

* Only the first event per patient is included.

Gnant M et al. N Engl J Med 2009;360:679-691

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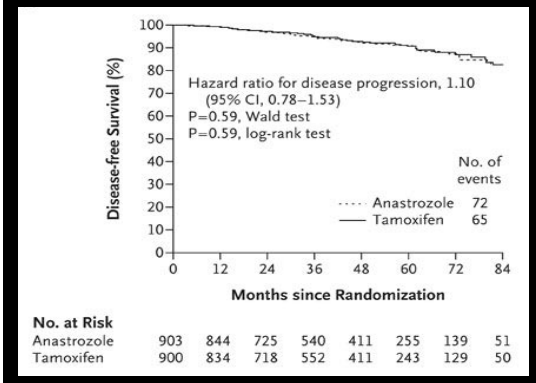
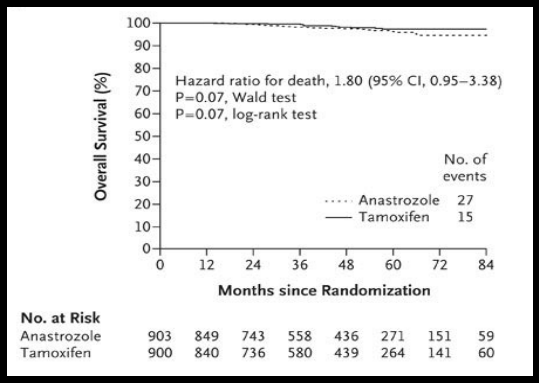
ABCSG-12 Trial

tamoxifen + goserelin vs. anastrozole + goserelin in premenopausal patients





Gnant M et al. N Engl J Med 2009;360:679-691

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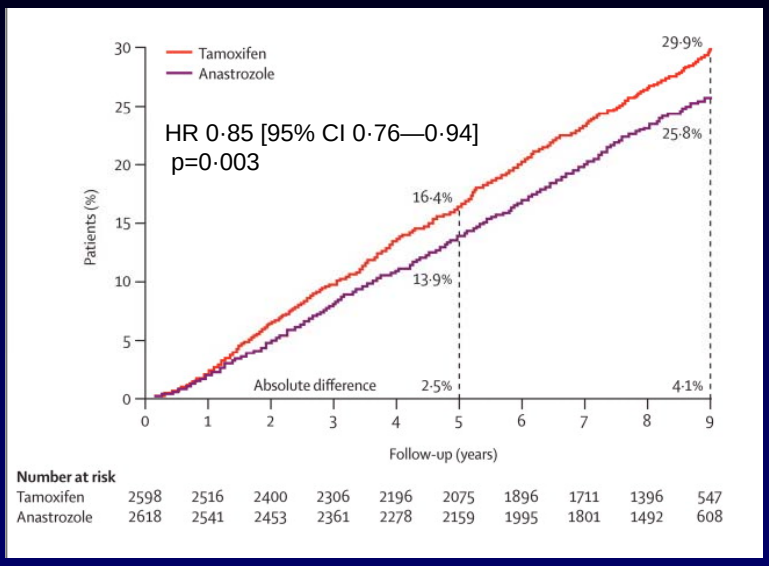
Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial

*The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group**

Forbes JF et al. Lancet Oncol 2008;9:45-53

100-month analysis of the ATAC trial
- ER positive patients -



ASCO Plenary Session
- 2009年の話題 -

卵巣癌
CA125の上昇に基づいて再発を早めにしても生存期間は延長しない

濾胞性リンパ腫
ワクチン治療は効果持続期間は延長するが生存期間は延長しない

乳癌
トリプルネガティブ乳癌にたいしてPARP阻害剤は有用である

結腸癌
病期II期、III期結腸癌術後、抗がん剤アバスチンを加えても効果ない

ASCO Annual '09 Meeting

PARP

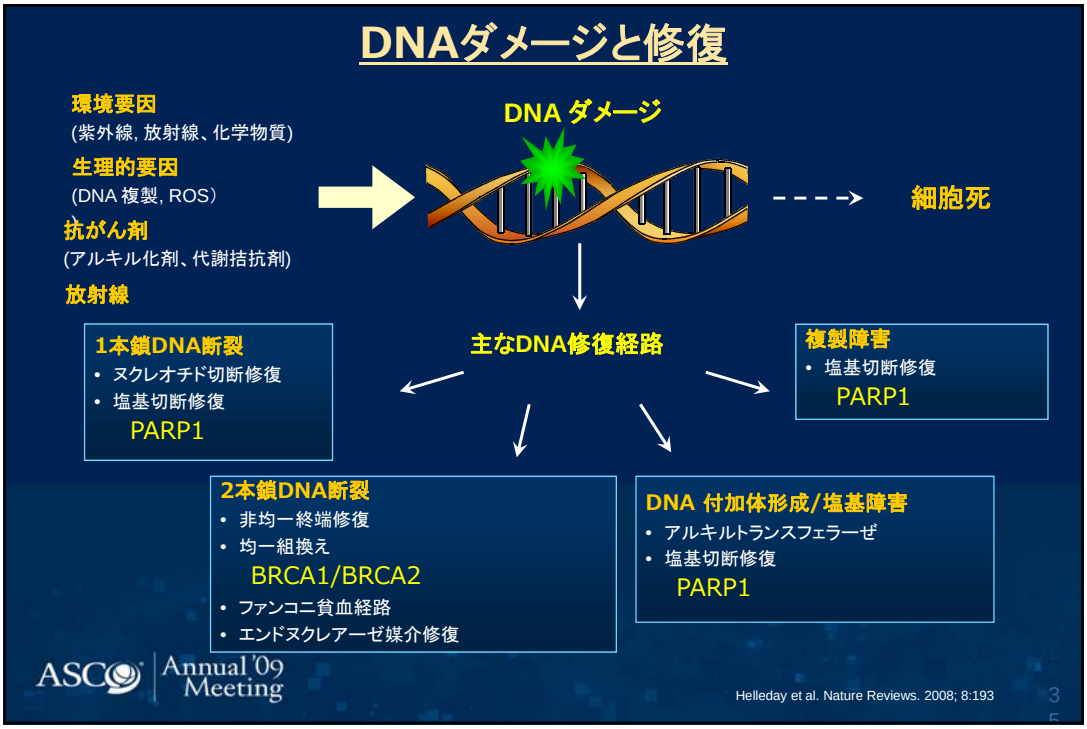
Poly(ADP-ribose) Polymerase

トリプルネガティブ乳癌におけるPARP阻害剤「BSI-201」の第II相試験

ゲムシタビン ＋ カルボプラチン
vs.
ゲムシタビン ＋ カルボプラチン+ BSI-201 (静注)

Presenter: Joyce O'Shaughnessy et al. (US Oncology)
Provider; BiPar Sciences

ASCO Annual '09 Meeting


DNAダメージと修復
環境要因
(紫外線, 放射線、化学物質)
生理的要因
(DNA 複製, ROS)
抗がん剤
(アルキル化剤、代謝拮抗剤)
放射線
DNA ダメージ
細胞死
主なDNA修復経路
1本鎖DNA断裂
• ヌクレオチド切断修復
• 塩基切断修復
PARP1
複製障害
• 塩基切断修復
PARP1
2本鎖DNA断裂
• 非均一終端修復
• 均一組換え
BRCA1/BRCA2
• ファンコニ貧血経路
• エンドヌクレアーゼ媒介修復
DNA 付加体形成/塩基障害
• アルキルトランスフェラーゼ
• 塩基切断修復
PARP1
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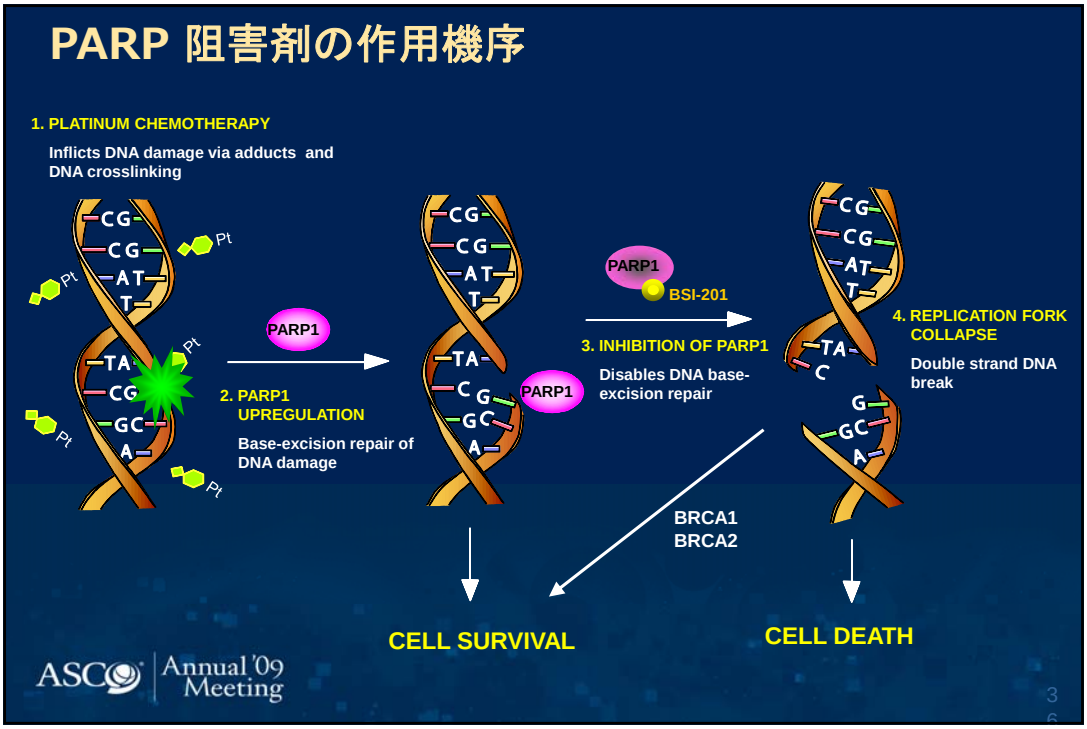
Helleday et al. Nature Reviews. 2008; 8:193


PARP 阻害剤の作用機序
1. PLATINUM CHEMOTHERAPY
Inflicts DNA damage via adducts and DNA crosslinking
PARP1
2. PARP1 UPREGULATION
Base-excision repair of DNA damage
PARP1
BSI-201
3. INHIBITION OF PARP1
Disables DNA base-excision repair
4. REPLICATION FORK COLLAPSE
Double strand DNA break
BRCA1
BRCA2
CELL SURVIVAL
CELL DEATH
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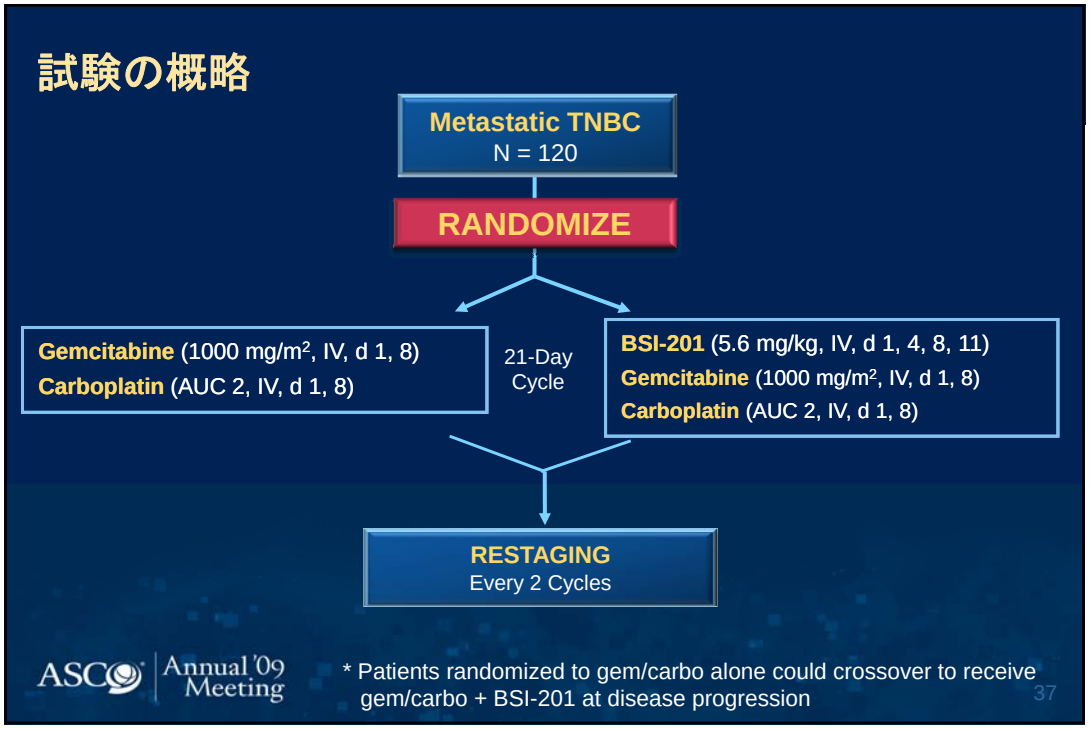
試験の概略
Metastatic TNBC
N = 120
RANDOMIZE
Gemcitabine (1000 mg/m², IV, d 1, 8)
Carboplatin (AUC 2, IV, d 1, 8)
21-Day Cycle
BSI-201 (5.6 mg/kg, IV, d 1, 4, 8, 11)
Gemcitabine (1000 mg/m², IV, d 1, 8)
Carboplatin (AUC 2, IV, d 1, 8)
RESTAGING
Every 2 Cycles
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* Patients randomized to gem/carbo alone could crossover to receive gem/carbo + BSI-201 at disease progression
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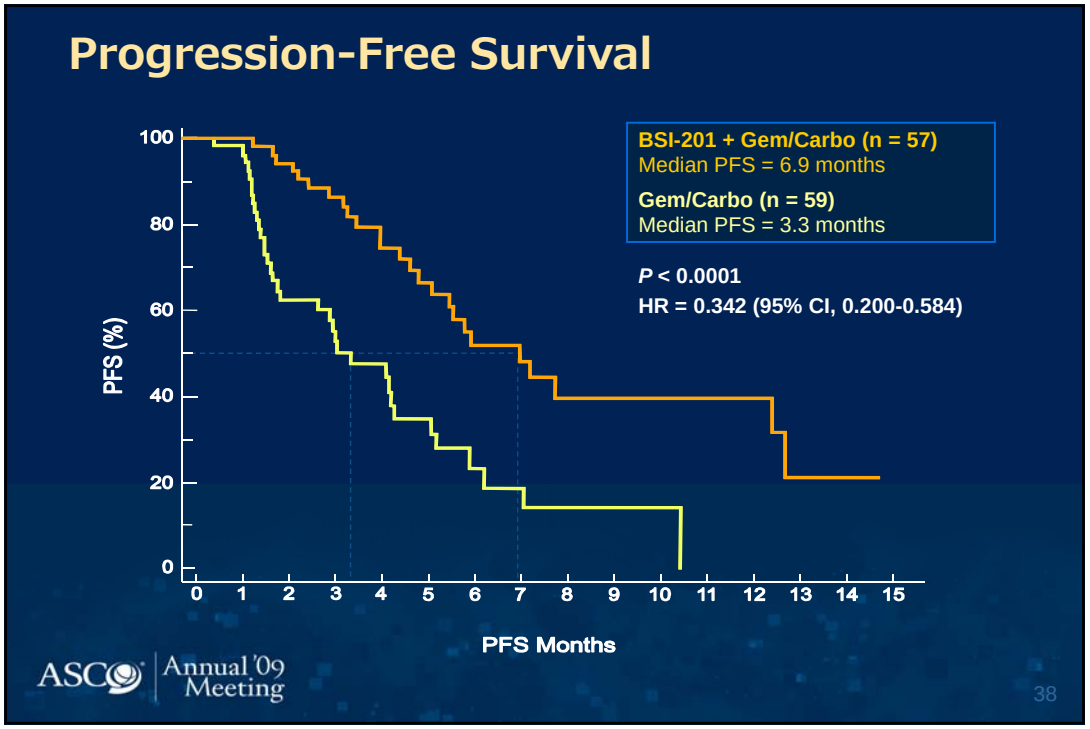
Progression-Free Survival
BSI-201 + Gem/Carbo (n = 57)
Median PFS = 6.9 months
Gem/Carbo (n = 59)
Median PFS = 3.3 months
P < 0.0001
HR = 0.342 (95% CI, 0.200-0.584)
PFS (%)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
PFS Months
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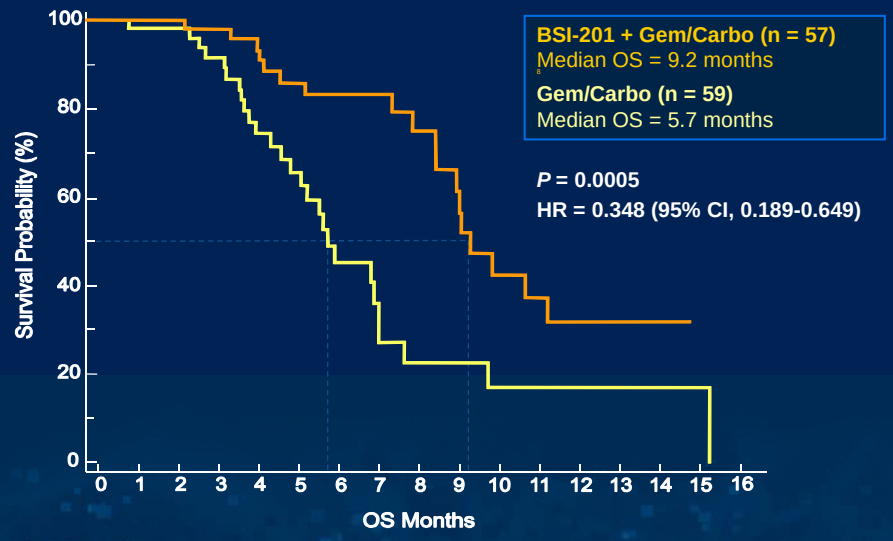
Overall Survival



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Safety Summary

- No differences in hematologic or non-hematologic toxicities
- No differences in gemcitabine/carboplatin dose reductions between study arms

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Phase III Metastatic TNBC Study

Open-Label, Randomized Safety and Efficacy Trial of Gemcitabine/Carboplatin ± BSI-201 in Metastatic TNBC

- **Primary Endpoints**
  - Overall Survival
  - Progression-Free Survival
- Patients randomized to chemotherapy alone may crossover to BSI-201 at disease progression
- **Planned Initiation: Late June 2009**
- **For more information: http://www.BiParSciences.com**

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BRCA欠損を伴う進行乳癌に対する経口PARP阻害剤「olaparib」の第II相試験

Presenter: Andrew Tutt (Guy's Hospital,London UK)

Sponsor: AstraZeneca

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 9, 2009 VOL. 361 NO. 2

Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from *BRCA* Mutation Carriers

Peter C. Fong, M.D., David S. Boss, M.Sc., Timothy A. Yap, M.D., Andrew Tutt, M.D., Ph.D., Peijun Wu, Ph.D., Marja Mergui-Roelvink, M.D., Peter Mortimer, Ph.D., Helen Swaisland, B.Sc., Alan Lau, Ph.D., Mark J. O'Connor, Ph.D., Alan Ashworth, Ph.D., James Carmichael, M.D., Stan B. Kaye, M.D., Jan H.M. Schellens, M.D., Ph.D., and Johann S. de Bono, M.D., Ph.D.

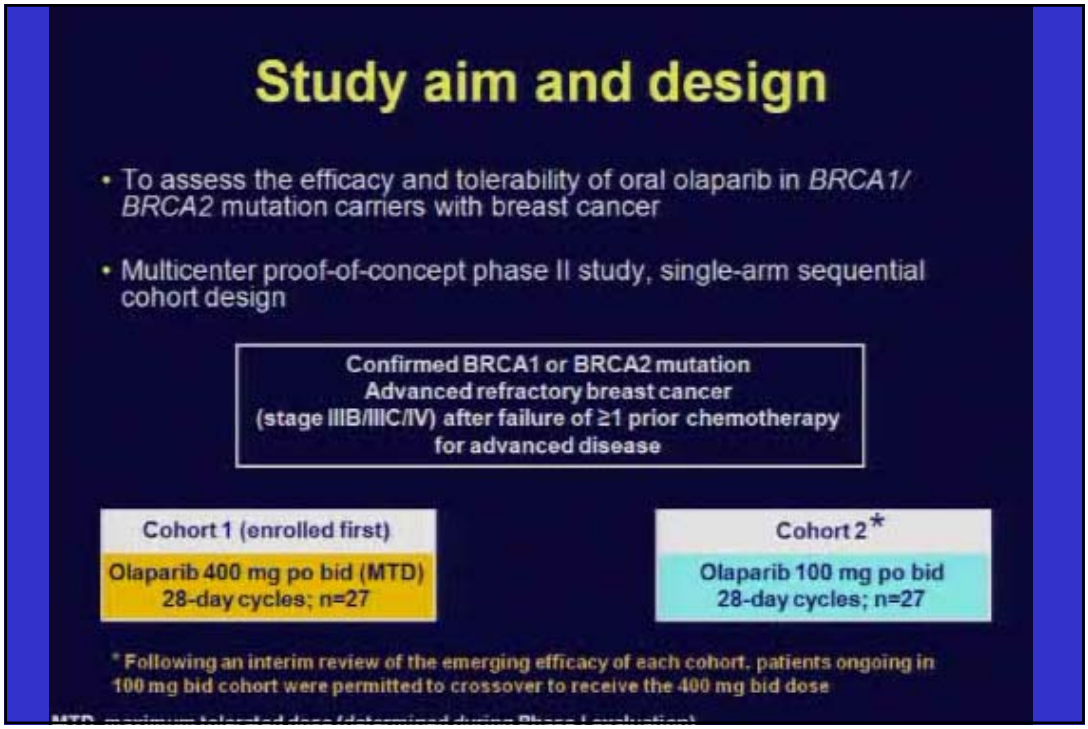
Olaparib 臨床第I相試験 有害事象の種類、頻度、程度

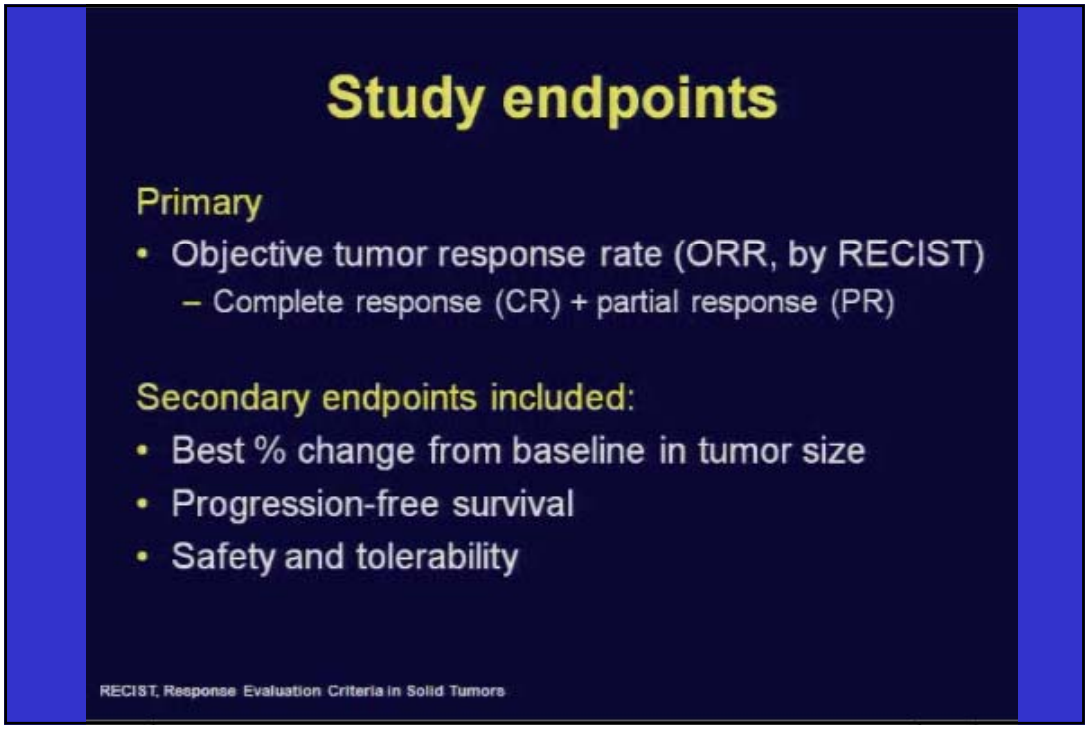
Table 3. Olaparib-Related Adverse Events Found in at Least 5% of the Safety Population, According to Olaparib Dose.*

Adverse Event	<100 mg, Daily or Twice Daily, 2 of Every 3 Wk (N=18)	100 mg, Twice Daily, 2 of Every 3 Wk (N=4)	100 mg, Twice Daily, Continuously (N=5)	200 mg Twice Daily, Continuously (N=20)	400 mg Twice Daily, Continuously (N=8)	600 mg Twice Daily, Continuously (N=5)	Total (N=60)
	number of patients/total number (percent)						
Anemia							
Grade 1–2	1 (6)	0	0	0	0	1 (20)	2 (3)
Grade 3–4	0	0	0	1 (5)	0	0	1 (2)
Lymphopenia							
Grade 1–2	0	0	0	0	0	0	0
Grade 3–4	0	0	0	2 (10)	1 (12)	0	3 (5)
Diarrhea							
Grade 1–2	0	0	0	2 (10)	1 (12)	0	3 (5)
Grade 3–4	0	0	0	0	0	0	0
Dyspepsia							
Grade 1–2	0	0	0	1 (5)	1 (12)	2 (40)	4 (7)
Grade 3–4	0	0	0	0	0	0	0
Nausea							
Grade 1–2	6 (33)	1 (25)	0	7 (35)	0	3 (60)	17 (28)
Grade 3–4	0	0	0	0	1 (12)	1 (20)	2 (3)
Stomatitis							
Grade 1–2	0	0	0	3 (15)	0	0	3 (5)
Grade 3–4	0	0	0	0	0	0	0
Vomiting							
Grade 1–2	2 (11)	1 (25)	0	5 (25)	0	3 (60)	11 (18)
Grade 3–4	0	0	0	0	1 (12)	0	1 (2)
Anorexia							
Grade 1–2	3 (17)	0	0	2 (10)	0	2 (40)	7 (12)
Grade 3–4	0	0	0	0	0	0	0
Dysgeusia							
Grade 1–2	0	2 (50)	0	2 (10)	1 (12)	3 (60)	8 (13)
Grade 3–4	0	0	0	0	0	0	0
Fatigue							
Grade 1–2	3 (17)	0	1 (20)	4 (20)	5 (62)	4 (80)	17 (28)
Grade 3–4	0	0	0	1 (5)	0	0	1 (2)
Dizziness							
Grade 1–2	0	0	0	1 (5)	0	1 (20)	2 (3)
Grade 3–4	0	0	0	0	1 (12)	0	1 (2)

* The listed adverse events were classified as being possibly, probably, or definitely related to olaparib in the safety population. No grade 5 adverse events related to olaparib were reported at the time of the analysis. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (version 3.0).

Fong P et al. N Engl J Med 2009;10.1056/NEJMoa0900212


Study aim and design
• To assess the efficacy and tolerability of oral olaparib in *BRCA1/BRCA2* mutation carriers with breast cancer
• Multicenter proof-of-concept phase II study, single-arm sequential cohort design
Confirmed BRCA1 or BRCA2 mutation
Advanced refractory breast cancer
(stage IIIB/IIIC/IV) after failure of ≥1 prior chemotherapy for advanced disease
Cohort 1 (enrolled first)
Olaparib 400 mg po bid (MTD)
28-day cycles; n=27
Cohort 2*
Olaparib 100 mg po bid
28-day cycles; n=27
* Following an interim review of the emerging efficacy of each cohort, patients ongoing in 100 mg bid cohort were permitted to crossover to receive the 400 mg bid dose

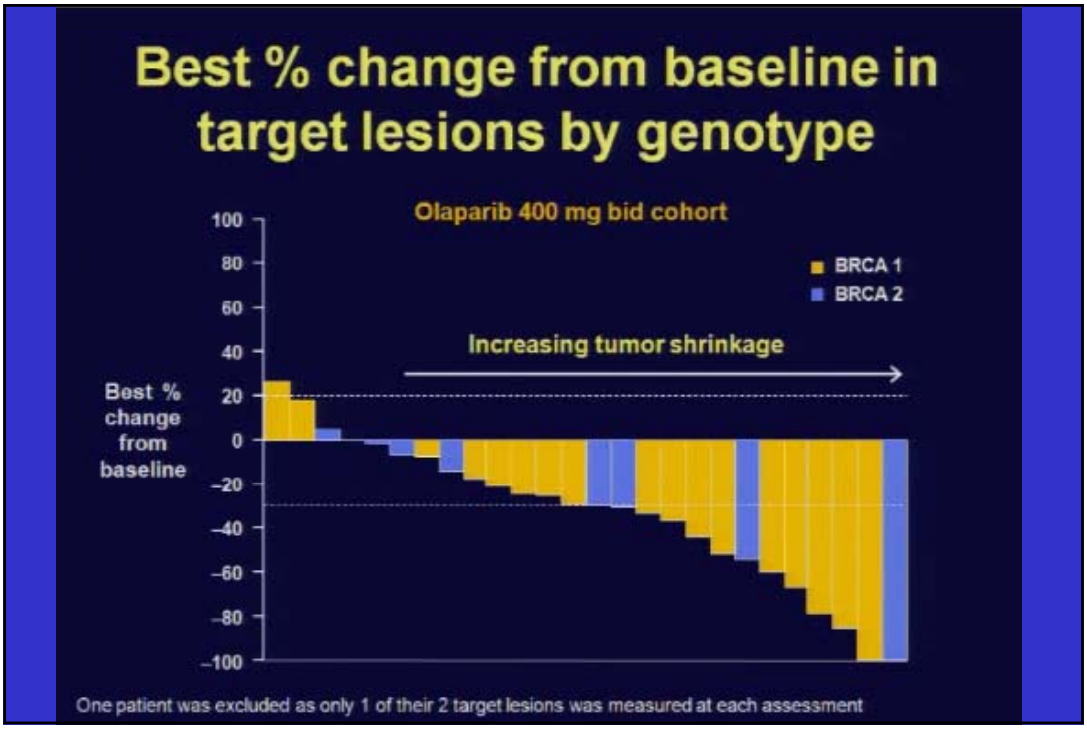

Study endpoints
Primary
• Objective tumor response rate (ORR, by RECIST)
– Complete response (CR) + partial response (PR)
Secondary endpoints included:
• Best % change from baseline in tumor size
• Progression-free survival
• Safety and tolerability
RECIST, Response Evaluation Criteria in Solid Tumors

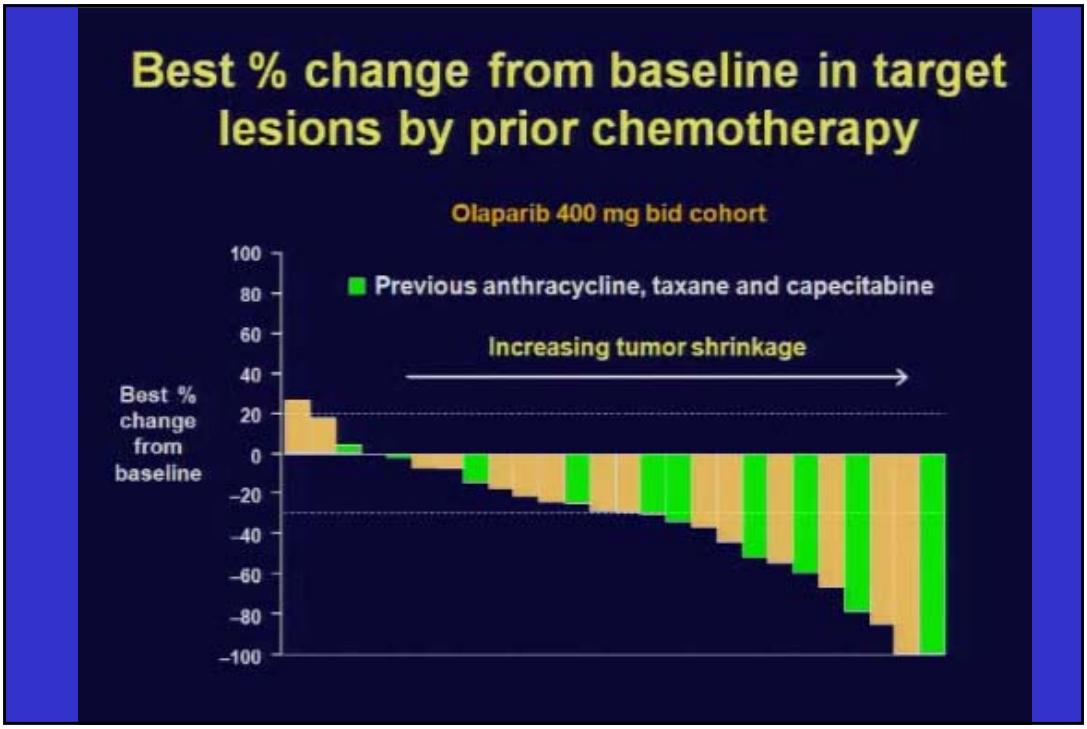
患者背景

	400 mg bid (n=27)	100 mg bid (n=27)
PS (0/1/2)	12/13/2	16/10/1
先行治療レジメン		
レジメン数　中央値（範囲）	3 (1-5)	3 (2-4)
タキサン･アンソラサイクリン･カペ	10 (37)	11 (41)
プラチナ	6 (22)	8 (30)
ターゲット状況		
トリプルネガティブ	13/26 (50)	16/25 (64)
ER+ HER2-	11/27 (41)	4/26 (15)
ER+ HER2+	1/27 (4)	4/26 (15)
ER- HER2+	1/27 (4)	1/26 (4)

効　果

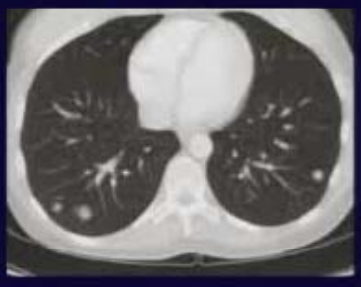
ITT コホート	Olaparib 400 mg bid (n=27)	Olaparib 100 mg bid (n=27)
ORR　n (%)	11 (41)	6 (22)
CR　n (%)	1 (4)	0
PR　n (%)	10 (37)	6 (22)
Per protocol コホート	(n=26)	(n=24)
ORR　n (%)	11 (42)	6 (25)
CR　n (%)	1 (4)	0
PR　n (%)	10 (39)	6 (25)


Best % change from baseline in target lesions by genotype
Olaparib 400 mg bid cohort
BRCA 1
BRCA 2
Increasing tumor shrinkage
Best % change from baseline
100
80
60
40
20
0
–20
–40
–60
–80
–100
One patient was excluded as only 1 of their 2 target lesions was measured at each assessment

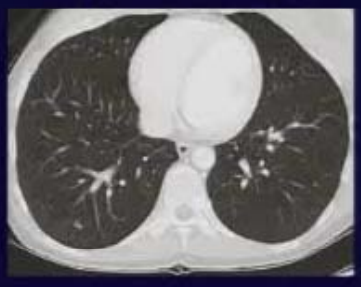

Best % change from baseline in target lesions by prior chemotherapy
Olaparib 400 mg bid cohort
Previous anthracycline, taxane and capecitabine
Increasing tumor shrinkage
Best % change from baseline
100
80
60
40
20
0
–20
–40
–60
–80
–100

RECIST response to olaparib 400 mg bid

Pre-dose



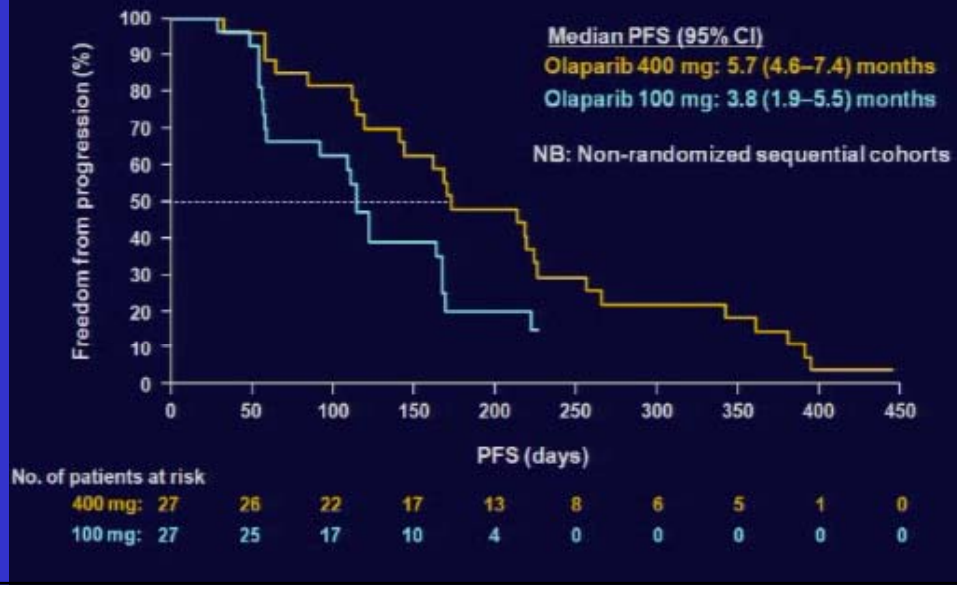
Day 180 on study



- BRCA1 carrier
- ER -ve, PR -ve, HER2 -ve
- Adjuvant dose dense AC-T, capecitabine/bevacizumab, vinorelbine/bevacizumab
- Olaparib commenced 12.6.07 – remains on olaparib

Courtesy of Mark Robson MSKCC

Progression-free survival



投与量減量・中止状況

	Olaparib 400 mg bid (n=27)	Olaparib 100 mg bid (n=27)
有害事象による中止	0	1 (4)
有害事象による中断	8 (30)	2 (7)
有害事象による減量	8 (30)	1 (4)

結　論

BRCA1/BRCA2変異を有する乳癌患者を対象として分子標的治療の有効性を検討した初の報告である。

経口PARP阻害剤「olaparib 400 mg bidは、濃厚な先行治療を受けたBRCA1/BRCA2変異を有する乳癌に対して十分な活性を示した。

- 奏効率　41%
- PFS(中央値）　5.7か月

経口olaparibは、副作用は、BRCA1/BRCA2変異の有無に関係なく軽度である。

乳癌、卵巣癌でPARP阻害剤の作用理論が臨床的に検証された。

St.Gallen 2009
治療選択の考え方
- ホルモン療法編 -

若年発症乳癌患者には、仕事、妊娠、出産など女性としての人生を有意義に生きることができるように配慮した効果的な治療を選択しなくてはいけない。

乳癌の生物学的特性（ターゲット）に基づいた治療薬剤の選択の流れは、ほぼ、完全に定着したといえる。

トリプルネガティブ乳癌に対して、PARP阻害剤の有用性が検証されつつある。一筋の光明を感じる。