浜松オンコロジーフォーラム
2017年 9月16日 （土曜日）

がん内分泌療法
- 最近の疑問 -

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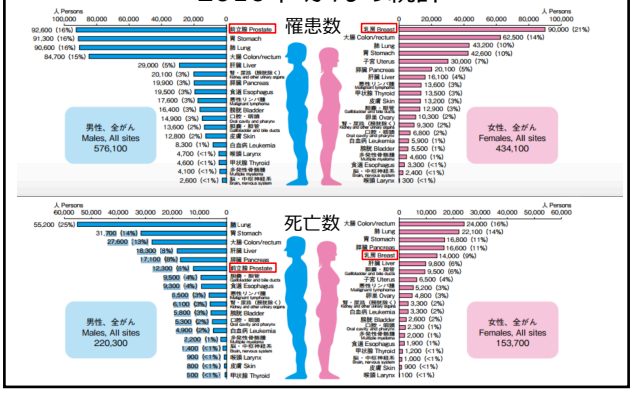
ホルモン依存性腫瘍の種類

発生母組織の正常機能がステロイドホルモンにより調節されているがん

＝　乳腺、前立腺、子宮内膜由来のがん

＝　乳がん　　前立腺がん　　子宮内膜がん

2016年 がんの統計



ホルモン依存性腫瘍と「餌」

乳がん	**閉経前**	**estrogens**
	閉経後	**estrogens**
前立腺がん		**androgens**

前立腺がんの治療
睾丸摘除術(除睾術)(去勢術)　castration

前立腺がんの治療

薬物療法（現在の主流）

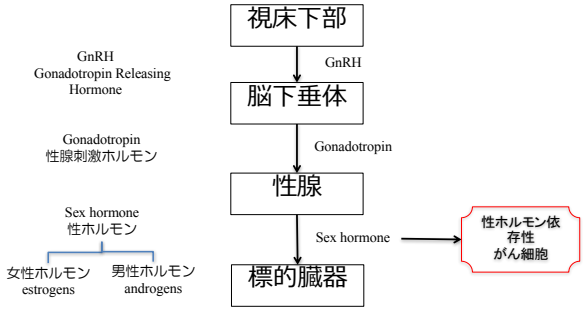
内分泌療法

男性ホルモン (=androgens)の血中濃度を下げる
男性ホルモンの作用を阻害する（受容体阻害）
がん組織内での男性ホルモン産生を抑制する

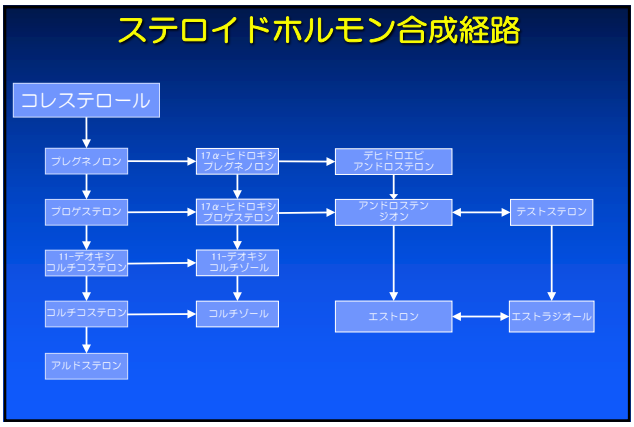
細胞毒性抗がん剤（がん細胞も正常細胞も痛める）

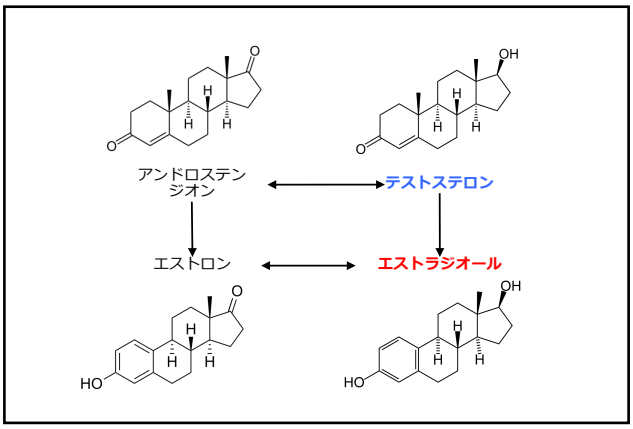
ドセタキセル、カバジタキセル

性ホルモン分泌の制御と性ホルモン依存性がんとの関係



ステロイドホルモン合成経路





ホルモン依存性腫瘍と「餌」

前立腺患者の血中アンドロゲンを低下させる治療 **(Androgen Deprivation Therapy)**
はがん細胞から「餌」を奪うことで増殖を抑制させる治療である。

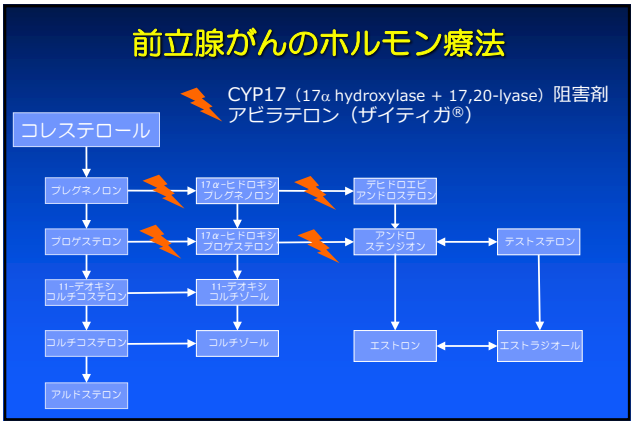
前立腺がん治療の落とし穴

Castration Sensitive PC 患者にAndrogen Depriving Therapyを行うと

血中androgen は98%抑制されるが、前立腺組織中のandrogenは75%程度しか抑制されない。

これは前立腺内でandrogenが産生されているためである。これを抑えないと前立腺がんの増殖は抑制しきれないのではないか・・・？

前立腺がんのホルモン療法



The STAMPEDE trial

James ND, de Bono JS, Spears MR, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med 2017;377:338-51.

The LATITUDE trial

Fizazi K, Tran N, Fein L, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med 2017;377:352-60.

The NEW ENGLAND JOURNAL of MEDICINE

LATITUDE: A phase 3, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebos in newly diagnosed high-risk metastatic hormone-naïve prostate cancer patients

Karim Fizazi,[1] NamPhuong Tran,[2] Luis Fein,[3] Nobuaki Matsubara,[4] Alfredo Rodriguez-Antolin,[5] Boris Y. Alekseev,[6] Mustafa Özgüroğlu,[7] Dingwei Ye,[8] Susan Feyerabend,[9] Andrew Protheroe,[10] Peter De Porre,[11] Thian Kheoh,[12] Youn C. Park,[13] Mary B. Todd,[14] Kim N. Chi,[15] on behalf of the LATITUDE Investigators

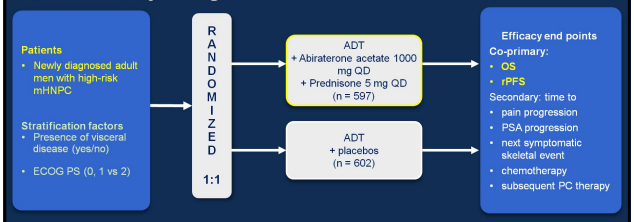
[1]Gustave Roussy, University of Paris-Sud, Villejuif, France; [2]Janssen Research & Development, Los Angeles, CA; [3]Instituto de Oncologia de Rosário, Rosário, Argentina; [4]National Cancer Center Hospital East, Chiba, Japan; [5]12 de Octubre University Hospital, Madrid, Spain; [6]P.A. Hertsen Moscow Cancer Research Institute, Moscow, Russian Federation; [7]Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey; [8]Fudan University Shanghai Cancer Center, China; [9]Studienpraxis Urologie, Nürtingen, Germany; [10]Oxford University Hospitals Foundation NHS Trust, Oxford, UK; [11]Janssen Research & Development, Beerse, Belgium; [12]Janssen Research & Development, San Diego, CA; [13]Janssen Research & Development, Raritan, NJ; [14]Janssen Global Services, Raritan, NJ; [15]BC Cancer Agency, Vancouver, BC, Canada

Objective

To evaluate the addition of AA + P to ADT on clinical benefit in men with newly diagnosed, high-risk, mCNPC

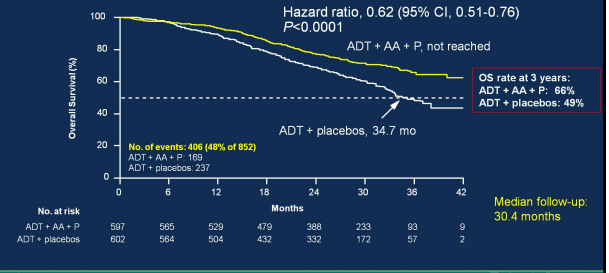
High-risk defined as meeting at least 2 of 3 high-risk criteria:
- Gleason score of ≥ 8
- Presence of ≥ 3 lesions on bone scan
- Presence of measurable visceral lesion

Overall study design of LATITUDE



- Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada
- Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results

Statistically significant 38% risk reduction of death



Median follow-up: 30.4 months

OS benefit consistently favorable across subgroups

Summary of adverse events

	ADT + AA + P (n = 597)	ADT + placebos (n = 602)
Adverse Events (AE)	n (%)	n (%)
Any AE	558 (93)	557 (93)
Grade 3 or 4 AE	374 (63)	287 (48)
Any Serious AE	165 (28)	146 (24)
Any AE leading to treatment discontinuation	73 (12)	61 (10)
AE leading to death	28 (5)	24 (4)

Presented By Karim Fizazi at 2017 ASCO Annual Meeting

Conclusions

- In the phase 3 LATITUDE, addition of AA + P to ADT led to:
  - Significantly improved OS with a 38% reduction in the risk of death
  - Significantly prolonged rPFS (53% reduction) and all secondary end points
- The overall safety profile of ADT + AA + P was consistent with prior studies in patients with mCRPC

Conclusions

- These findings indicate that the addition of AA + P to ADT can potentially be considered a new standard of care for patients with high-risk, newly diagnosed mCNPC

IMPORTANT: Listing of a study on this site does not reflect endorsement by the National Institutes of Health. Talk with a trusted healthcare professional before volunteering for a study. Read more...

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Home > Study Record Detail

Abiraterone Acetate in Treating Postmenopausal Women With Advanced or Metastatic Breast Cancer

This study has been completed.

Sponsor:
Cancer Research UK

Information provided by (Responsible Party):
Cancer Research UK

ClinicalTrials.gov Identifier:
NCT00755885

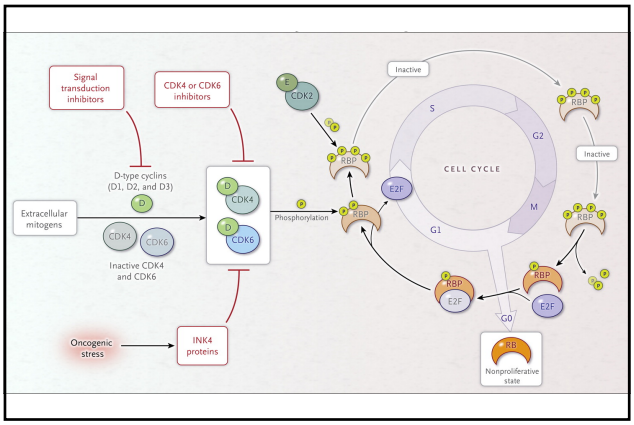
First received: September 18, 2008
Last updated: January 25, 2017
Last verified: January 2017
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

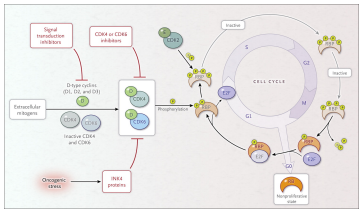
Tracking Information	
First Received Date ICMJE	September 18, 2008
Last Updated Date	January 25, 2017
Start Date ICMJE	October 2008
Primary Completion Date	June 4, 2016 (Final data collection date for primary outcome measure)
Current Primary Outcome Measures ICMJE (submitted: September 18, 2008)	• Causality of each adverse event and grading severity as measured by NCI CTCAE v3.0 (Phase I) • Maximum tolerated dose (MTD) of abiraterone acetate (Phase I) • Proportion of patients with stable disease for ≥ 24 weeks or objective response as measured by RECIST criteria (Phase II)
Original Primary Outcome Measures ICMJE	Same as current
Change History	Complete list of historical versions of study NCT00755885 on ClinicalTrials.gov Archive Site
Current Secondary Outcome Measures ICMJE (submitted: September 18, 2008)	• Plasma levels of abiraterone acetate as measured by liquid chromatography/tandem mass spectrometry assay (Phase I) • Relationship between dose and endocrine response (Phase I)

Cyclin Dependent Kinase Inhibitor

name	brand name	price/month (28days)	
Palbociclib	Ibrance	$13155.66	(￥1,453,985)
Ribociclib	Kisqali	$13140.00	(￥1,452,255)
Abemaciclib			



風が吹けば桶屋が儲かる話から学ぶ Cyclin Dependent Kinase Inhibitor



Cell Cycle：細胞分裂周期

E2F：転写因子＝cell cycleを回す

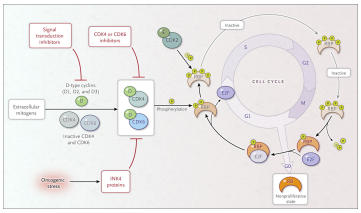
RBP：Retinoblastoma Protein
＝E2Fを抱きかかえて抑制する

Phosphate (リン)
Phosphorylation（リン酸化）

Cyclin D が増えると
Cyclin Dependent Kinase 4 とか
Cyclin Dependent Kinase 6 が活性化されて
RBPのリン酸化 が進む

RBP：Retinoblastoma Protein
がリン酸化されればされるほど
E2Fを抑制する力が落ちる
＝cell cycleが回る回る

風が吹けば桶屋が儲かる話から学ぶ Cyclin Dependent Kinase Inhibitor



Cyclin D1とCDK4は正常乳腺組織に特異的に発現している

Luminal typeの乳がんでも
Cyclin D1とCDK4の発現は高い

エストロゲン刺激をアロマターゼ阻害剤やフルベストラントなどのSERDで抑制すると

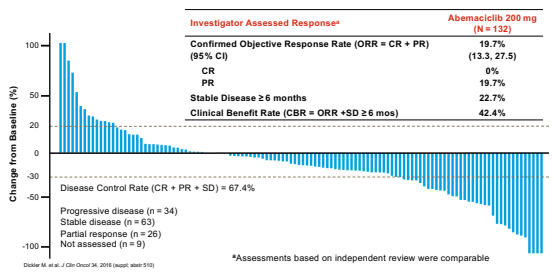
Estrogen Receptor (ER) 陽性乳がんではCyclin D1合成が抑制される

これがCDKIとホルモン剤併用効果のからくりである

CDK阻害剤のうち　出遅れているAbemaciclibは
CDK6/cyclin D3に対する抑制よりも14倍
CDK4/cyclin D1に対する抑制活性をもつ

Abemaciclibだけは単剤での活性が認められている

MONARCH 1: Response Summary



Investigator Assessed Response[a]	Abemaciclib 200 mg (N = 132)
Confirmed Objective Response Rate (ORR = CR + PR) (95% CI)	19.7% (13.3, 27.5)
CR	0%
PR	19.7%
Stable Disease ≥ 6 months	22.7%
Clinical Benefit Rate (CBR = ORR +SD ≥ 6 mos)	42.4%

*Assessments based on independent review were comparable

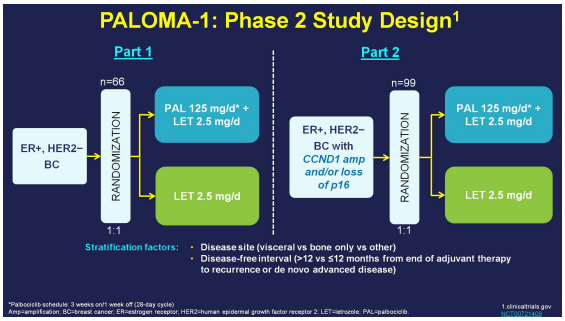
Dickler M. et al. J Clin Oncol 34, 2016 (suppl; abstr 510)

The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study

Richard S Finn, John P Crown, Istvan Lang, Katalin Boer, Igor M Bondarenko, Sergey O Kulyk, Johannes Ettl, Ravindranath Patel, Tamas Pinter, Marcus Schmidt, Yaroslav Shparyk, Anu R Thummala, Nataliya L Voytko, Camilla Fowst, Xin Huang, Sindy T Kim, Sophia Randolph, Dennis J Slamon

The Lancet Oncology 2015;16:25-35.

PALOMA-1: Phase 2 Study Design[1]



Presented By Richard Finn at 2017 ASCO Annual Meeting

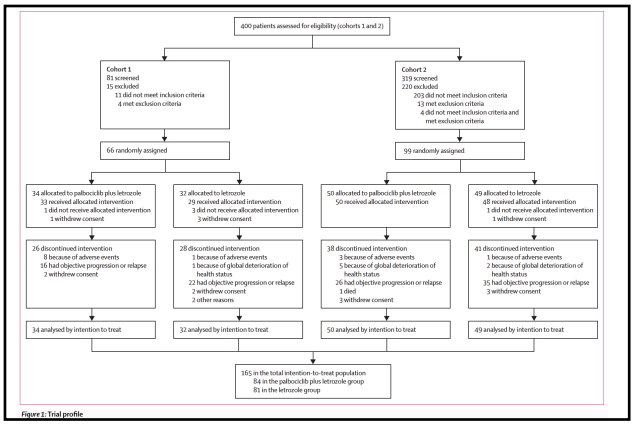
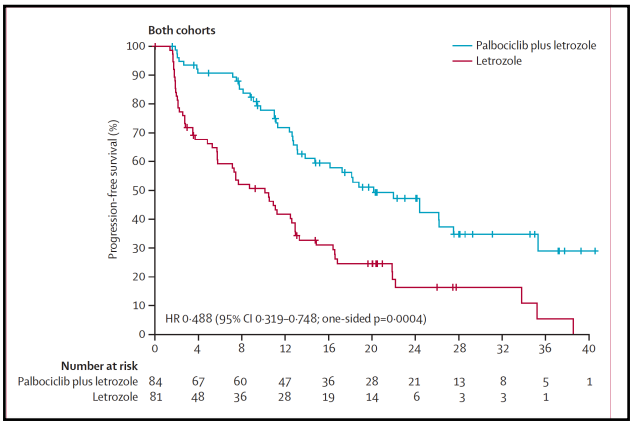


Figure 1: Trial profile



Overall Survival Results From the Randomized Phase 2 Study of Palbociclib in Combination With Letrozole vs Letrozole Alone for First-Line Treatment of ER+/HER2– Advanced Breast Cancer (PALOMA-1; TRIO-18)

Richard S. Finn,[1] John Crown,[2] Istvan Lang,[3] Katalin Boer,[4] Igor Bondarenko,[5] Sergey O. Kulyk,[6] Johannes Ettl,[7] Ravindranath Patel,[8] Tamas Pinter,[9] Marcus Schmidt,[10] Yaroslav V. Shparyk,[11] Anu Thummala,[12] Nataliya L. Voytko,[13] Camilla Fowst,[14] Xin Huang,[15] Sindy Kim,[15] Dennis J. Slamon[1]

[1]David Geffen School of Medicine, Los Angeles, CA, USA; [2]Irish Cooperative Oncology Research Group, Dublin, Ireland; [3]National Institute of Oncology, Budapest, Hungary; [4]Szent Margit Korhaz, Onkologia, Budapest, Hungary; [5]Dnepropetrovsk State Medical Center, Dnipropetrovsk, Ukraine; [6]Municipal Treatment-and-Prophylactic Institution, Donetsk, Ukraine; [7]Technical University of Munich, Munich, Germany; [8]Comprehensive Blood and Cancer Center, Bakersfield, CA, USA; [9]Petz Aladar Megyei Oktato Korhaz, Gyor, Hungary; [10]Johannes Gutenberg University, Mainz, Germany; [11]Lviv State Oncologic Regional Treatment and Diagnostic Center, Lviv, Ukraine; [12]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [13]Kyiv City Clinical Oncology Center, Kyiv, Ukraine; [14]Pfizer Inc, Milan, Italy; [15]Pfizer Inc, La Jolla, CA, USA

Presented at the 2017 ASCO Annual Meeting

Demographics and Baseline Characteristics

	PAL+LET (N=84)	LET (N=81)
Median (range) age, y	63 (41–89)	64 (38–84)
ECOG performance status, n (%)		
0	46 (55)	45 (56)
1	38 (45)	36 (44)
Disease stage, n (%)		
Stage III	3 (4)	1 (1)
Stage IV	81 (96)	80 (99)
Disease site, n (%)		
Visceral	38 (45)	43 (53)
Bone only	16 (19)	12 (15)
Other (nonvisceral)	30 (36)	26 (32)
Disease-free interval, n (%)		
>12 mo from adjuvant to recurrence	25 (30)	30 (37)
≤12 mo from adjuvant to recurrence or de novo advanced disease	59 (70)	51 (63)
(de novo advanced disease)	*[44 (52)*	*37 (46)]*
Prior systemic treatment, n (%)		
None	44 (52)	37 (46)
Chemotherapy	34 (40)	37 (46)
Hormonal	27 (32)	29 (36)
Tamoxifen	24 (29)	25 (31)
Anastrozole	8 (10)	12 (15)
Letrozole	2 (2)	1 (1)
Exemestane	4 (5)	2 (2)

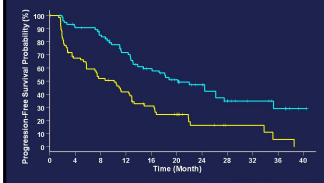
ECOG=Eastern Cooperative Oncology Group.

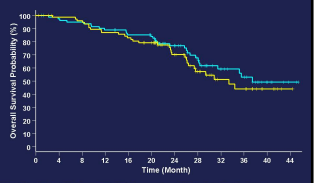
Presented By Richard Finn at 2017 ASCO Annual Meeting

PFS and OS (ITT)
(Data Cut-Off: Nov 29, 2013)

PFS	PAL+LET (N=84)	LET (N=81)
Patients with events, n (%)	41 (49)	59 (73)
Median PFS, months (95% CI)	20.2 (13.8, 27.5)	10.2 (5.7, 12.6)
Hazard Ratio (95% CI)	0.488 (0.319, 0.748)	
P value	0.0004	

OS	PAL+LET (N=84)	LET (N=81)
Patients with events, n (%)	30 (36)	31 (38)
Median OS, months (95% CI)	37.5 (28.4, NR)	33.3 (26.4, NR)
Hazard Ratio (95% CI)	0.813 (0.492, 1.345)	
P value	0.42	





- Median duration of follow-up: PAL+LET, 29.6 months (95% CI: 27.9, 36.0); LET, 27.9 months (95% CI: 25.5, 31.1)

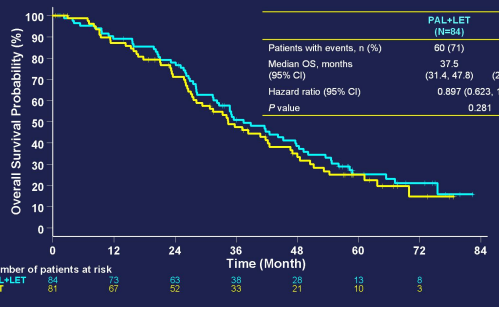
Finn RS, et al. *Lancet Oncol* 2015;16:25-35. NR=not reached.

Presented By Richard Finn at 2017 ASCO Annual Meeting

Final Overall Survival Analysis
(Data Cut-Off: Dec 30, 2016)

Presented By Richard Finn at 2017 ASCO Annual Meeting

OS: Phase 2 (ITT)

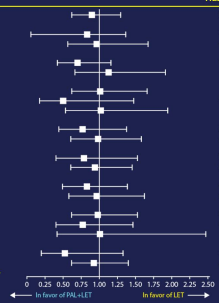


	PAL+LET (N=84)	LET (N=81)
Patients with events, n (%)	60 (71)	56 (69)
Median OS, months (95% CI)	37.5 (31.4, 47.8)	34.5 (27.4, 42.6)
Hazard ratio (95% CI)	0.897 (0.623, 1.294)	
P value	0.281	

Presented By Richard Finn at 2017 ASCO Annual Meeting

Subgroup Analysis of OS

Subgroup		n (%)	Hazard Ratio (95% CI)
All randomized patients		165 (100)	0.90 (0.62, 1.29)
Age	<65 y	89 (54)	0.83 (0.51, 1.36)
	≥65 y	76 (46)	0.97 (0.57, 1.67)
ECOG Status	0	91 (55)	0.70 (0.42, 1.16)
	1	74 (45)	1.12 (0.66, 1.91)
Disease site	Visceral	81 (49)	1.01 (0.62, 1.66)
	Bone only	28 (17)	0.50 (0.17, 1.47)
	Other	56 (34)	1.02 (0.53, 1.94)
Prior chemotherapy	Yes	71 (43)	0.77 (0.43, 1.36)
	No	94 (57)	0.98 (0.61, 1.57)
Prior hormonal therapy	Yes	56 (34)	0.78 (0.40, 1.52)
	No	109 (66)	0.94 (0.61, 1.45)
Prior systemic therapy	Yes	84 (51)	0.83 (0.49, 1.38)
	No	81 (49)	0.96 (0.57, 1.62)
Time from end of adjuvant treatment to disease recurrence	≤12 mo or de novo	110 (67)	0.98 (0.62, 1.52)
	>12 mo	55 (33)	0.77 (0.40, 1.46)
	≤12 mo	29 (18)	1.01 (0.42, 2.46)
Region	North America	36 (22)	0.52 (0.20, 1.33)
	Europe	123 (75)	0.93 (0.62, 1.39)



Original Article

Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer

Gabriel N. Hortobagyi, M.D., Salomon M. Stemmer, M.D., Howard A. Burris, M.D., Yoon-Sim Yap, M.D., Gabe S. Sonke, M.D., Ph.D., Shani Paluch-Shimon, M.D., Mario Campone, M.D., Ph.D., Kimberly L. Blackwell, M.D., Fabrice André, M.D., Ph.D., Eric P. Winer, M.D., Wolfgang Janni, M.D., Ph.D., Sunil Verma, M.D., Pierfranco Conte, M.D., Ph.D., Carlos L. Arteaga, M.D., David A. Cameron, M.D., Katarina Petrakova, M.D., Ph.D., Lowell L Hart, M.D., Cristian Villanueva, M.D., Arlene Chan, M.D., Erik Jakobsen, M.D., M.P.H., Arnd Nusch, M.D., Olga Burdaeva, M.D., Eva-Maria Grischke, M.D., Emilio Alba, M.D., Ph.D., Erik Wist, M.D., Ph.D., Norbert Marschner, M.D., Anne M. Favret, M.D., Denise Yardley, M.D., Thomas Bachelot, M.D., Ph.D., Ling-Ming Tseng, M.D., Sibel Blau, M.D., Fengjuan Xuan, Ph.D., Farida Souami, M.Sc., Michelle Miller, M.D., Caroline Germa, M.D., Samit Hirawat, M.D., and Joyce O'Shaughnessy, M.D.

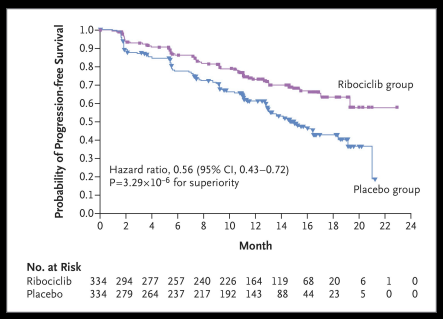
N Engl J Med
Volume 375(18):1738-1748
November 3, 2016
The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- In patients with advanced HR-positive, HER2-negative breast cancer, the addition of the cyclin-dependent kinase inhibitor ribociclib to letrozole was associated with a significantly higher rate of progression-free survival than placebo.

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Analysis of Progression-free Survival.



Hortobagyi GN et al. N Engl J Med 2016;375:1738-1748

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Conclusions

- Among patients receiving initial systemic treatment for HR-positive, HER2-negative advanced breast cancer, the duration of progression-free survival was significantly longer among those receiving ribociclib plus letrozole than among those receiving placebo plus letrozole, with a higher rate of myelosuppression in the ribociclib group.

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MONARCH 2: Abemaciclib in Combination with Fulvestrant in Patients with HR+/HER2- Advanced Breast Cancer Who Progressed On Endocrine Therapy

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Study Design

N=669

- HR+/HER2- ABC
- Pre/peri-[a] or postmenopausal
- ET resistant:
  - Relapsed on neoadjuvant or on/within 1 yr of adjuvant ET
  - Progressed on first-line ET
- No chemo for MBC
- No more than 1 ET for MBC
- ECOG PS ≤ 1

2:1 Randomization

- abemaciclib: 150 mg[b] BID (continuous schedule) fulvestrant: 500 mg[c]
- placebo: BID (continuous schedule) fulvestrant: 500 mg[c]

Primary endpoint:
Investigator-assessed PFS

Secondary endpoint:
OS, Response, Clinical Benefit Rate, Safety

Stratification factors:
- Metastatic site
- ET resistance (primary vs secondary)[4,5]

- **Statistics: 378 events for 90% power at one-sided α of .025 assuming a true HR of .703**
- Patients enrolled in 142 centers in 19 countries

[a]Required to receive GnRH agonist
[b]Dose reduced by protocol amendment in all new and ongoing patients from 200 mg to 150 mg BID after 178 patients enrolled
[c]Fulvestrant administered per label

4. Cardoso F et al. *The Breast* 6:489-502, 2014; 5. Cardoso F et al. *Ann Oncol* 25:1871-88, 2014.

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Accrual and Analysis

- 669 patients (ITT*) randomized from Aug 2014 to Dec 2015
- Data cut-off: 14-Feb-2017
- Median follow-up: 19.5 months

abemaciclib + fulvestrant N = 446		placebo + fulvestrant N = 223
	ITT population	
n = 441	Received treatment (safety population)	n = 223
n = 222	PFS events (ITT population)	n = 157
n = 170	On treatment (ITT population)	n = 45

*ITT population includes patients who started at 200 mg and 150 mg

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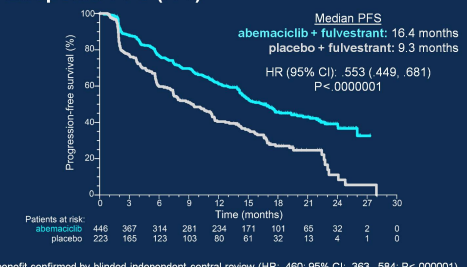
Primary Endpoint: PFS (ITT)



PFS benefit confirmed by blinded independent central review (HR: .460; 95% CI: .363, .584; P<.000001)

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TEAE (Safety Population)

	abemaciclib + fulvestrant n = 441			placebo + fulvestrant n = 223		
≥ 20% in either arm, n (%)	All	G3	G4	All	G3	G4
Any	435 (98.6)	241 (54.6)	26 (5.9)	199 (89.2)	46 (20.6)	5 (2.2)
Diarrhea[a]	381 (86.4)	59 (13.4)	0	55 (24.7)	1 (0.4)	0
Neutropenia[b]	203 (46.0)	104 (23.6)	13 (2.9)	9 (4.0)	3 (1.3)	1 (0.4)
Nausea	199 (45.1)	12 (2.7)	-	51 (22.9)	2 (0.9)	-
Fatigue	176 (39.9)	12 (2.7)	-	60 (26.9)	1 (0.4)	-
Abdominal pain	156 (35.4)	11 (2.5)	-	35 (15.7)	2 (0.9)	-
Anemia	128 (29.0)	31 (7.0)	1 (0.2)	8 (3.6)	2 (0.9)	0
Leukopenia	125 (28.3)	38 (8.6)	1 (0.2)	4 (1.8)	0	0
Decreased appetite	117 (26.5)	5 (1.1)	0	27 (12.1)	1 (0.4)	0
Vomiting	114 (25.9)	4 (0.9)	0	23 (10.3)	4 (1.8)	0
Headache	89 (20.2)	3 (0.7)	-	34 (15.2)	1 (0.4)	-

[a]Grade 2 diarrhea: abemaciclib + fulvestrant n=140 (31.7%); placebo + fulvestrant n=11 (4.9%).
[b]Febrile neutropenia was uncommon [6 patients in the abemaciclib arm (1 incorrectly coded, 1 post-chemotherapy)] and was not associated with severe infection

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Conclusions

- Abemaciclib at 150 mg BID plus fulvestrant was an effective treatment for women with HR+/HER2- ABC whose disease progressed on prior endocrine therapy
- Abemaciclib plus fulvestrant significantly improved PFS (16.4 vs 9.3 months; HR: .553) and ORR (48.1% vs 21.3% in patients with measurable disease)
- Abemaciclib dosed on a continuous schedule was generally well-tolerated
  - Grade 3 & 4 neutropenia was 26.5%
  - Diarrhea typically occurred early and was managed with dose adjustment and antidiarrheal medication

Based on these results, abemaciclib in combination with endocrine therapy as adjuvant treatment of HR+/HER2- high-risk breast cancer will begin recruitment 3Q2017 (monarchE)

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Presented By George Sledge at 2017 ASCO Annual Meeting

がん内分泌療法
- 最近の疑問 -

乳がんと前立腺がんは内分泌依存性という共通特性を有し治療も極めて類似性が高い。これらを乳腺外科医と泌尿器科医という異質の医師集団によってマネージしていてよいのか？
もっとよい医師集団がここにいるだろー！！！

CDK阻害剤は極めて魅力的な作用機序で注目されている。確かに副作用は軽いがOSの延長効果はなく薬価は超高額である。
CDK阻害剤が果たして本当に有効な薬剤として定着するのだろうか？　熱に浮かされたような現在の開発合戦は果たして患者に真に幸せをもたらすのだろうか？

天竜川と飯田線無人駅を望む