Educational session

Emerging systemic treatment in TNBC

How can we personalise treatment options for patients with TNBC ?

Kenji Tamura, MD and PhD.

Department of Breast and Medical Oncology

National Cancer Center Hospital Tokyo, JP

SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

Disclosure

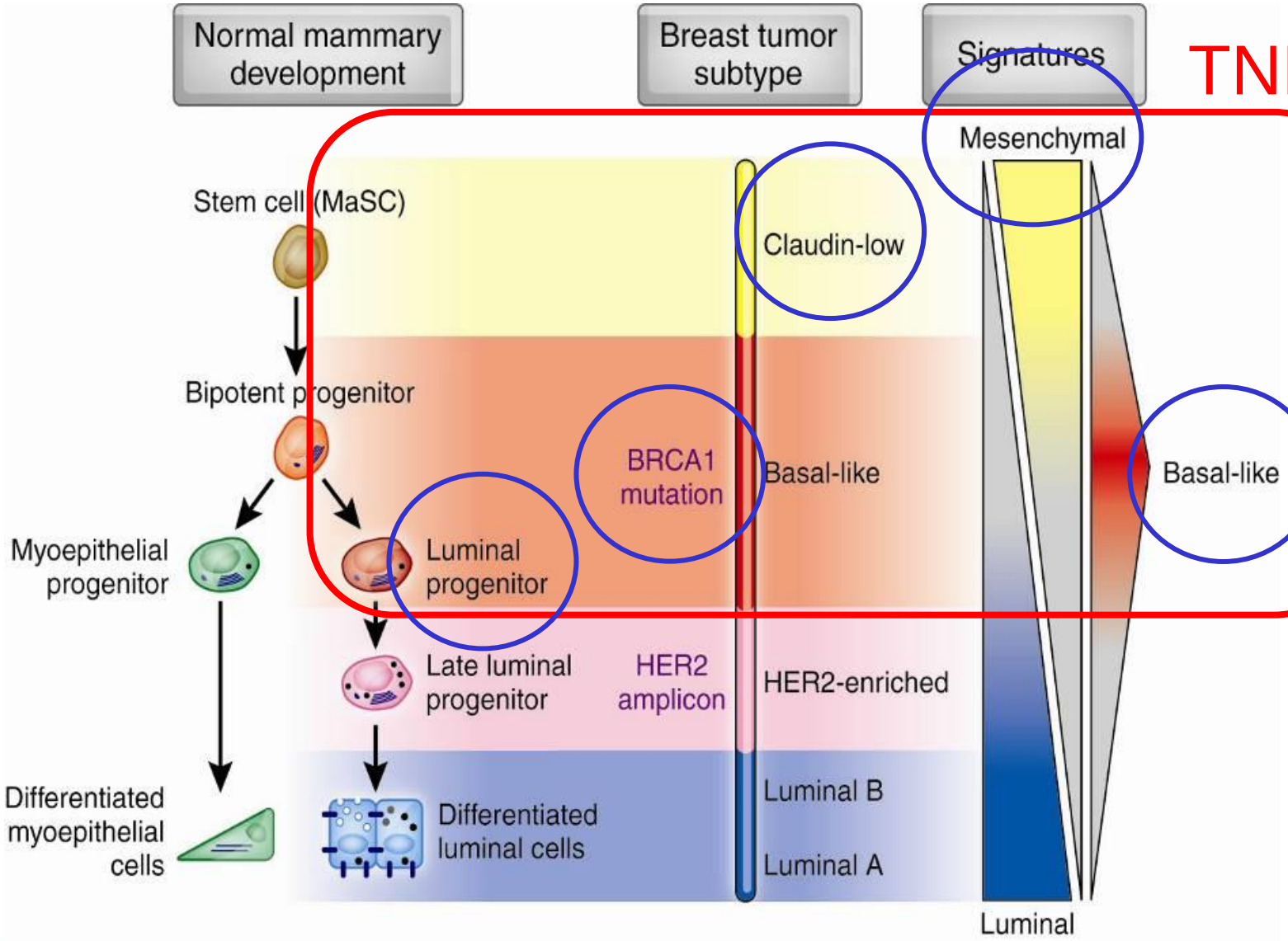
- Receipt of grants/research supports from AstraZeneca Co., Eisai Co. and MSD.

- I am also a primary investigator of different investigator initiated trials (IITs) which donated by AstraZeneca Co. or Eisai Co. respectively.

TNBC: background

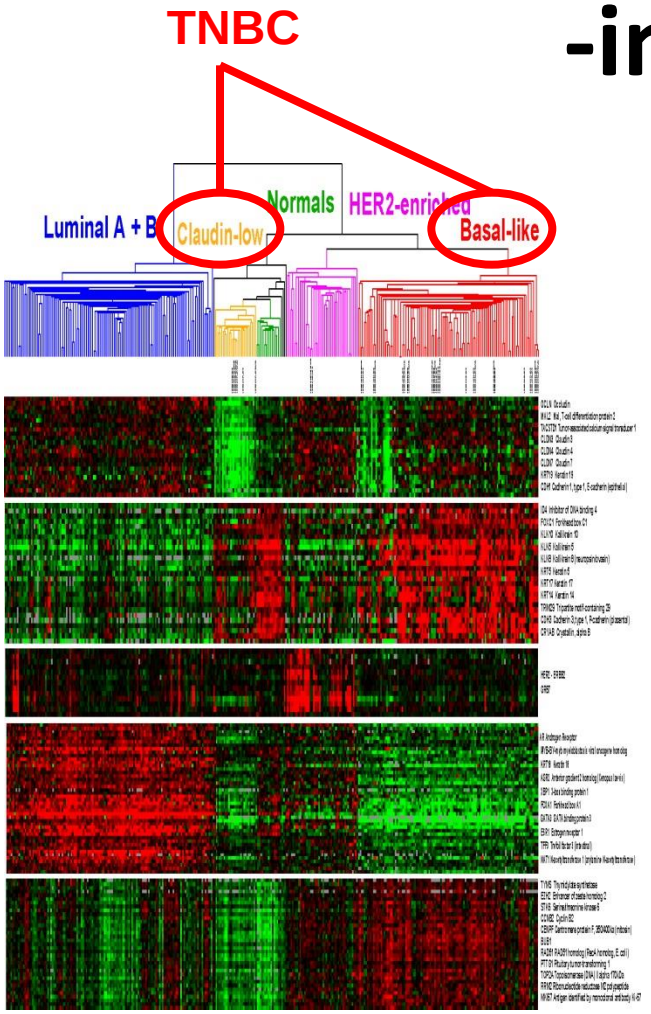
- ER (-), PGR (-), HER2 amplification (-)
- 15-20% in total BC.
- Recurrences occur usually within the first 2-3 years.
- Visceral metastases.
- Worse prognosis.
- Heterogeneity; Different response to chemotherapy.

Mammary development meets genomics



Plat A, Perou CM,
Nature Medicine, 15:842-844, 2009

Gene expression-clustering -intrinsic subtype-

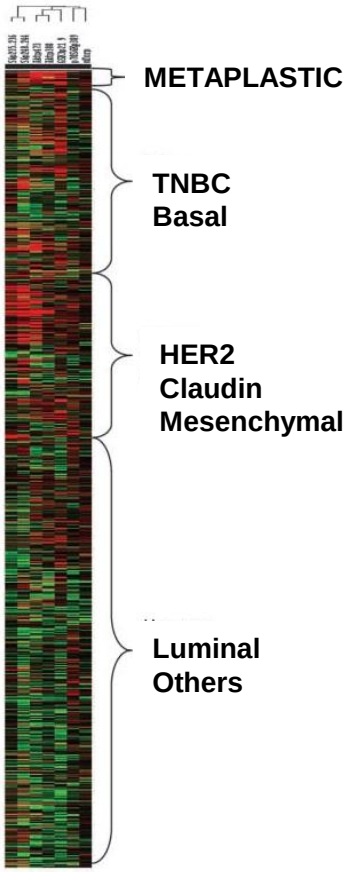


	ER	Her2	
Luminal A	+++	-	HR positive, HER negative
Luminal B	++	+	Double Positive, or high Ki67
Claudin-low	-	-	**TNBC**, **chemo-resistant** Mesenchymal-stem like
Normal-like	+	-	in definitive
HER2-enriched	+/-	+++	Her2 overexpression
Basal-like	-	-	**TNBC**, **chemo-sensitive** CK5/6(+) EGFR(+)

Herschkowitz et al: Genome Biol. 2007;8(5):R76;

Intrinsic Subtype in TNBC by pCR

TNBC



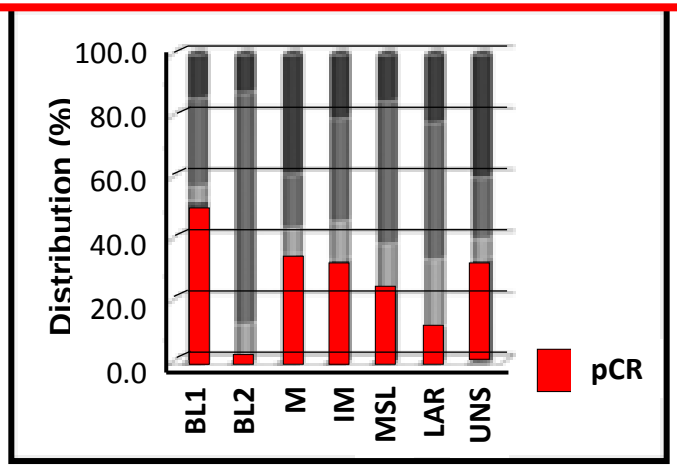
Functional proteomics of MBC

Hennessy et al: Cancer Res. 2009 May 15;69(10):4116-24

TNBC

6 Groups And UNS

1) Luminal androgen receptor (LAR)
2) Basal-like-1 (BL1)
3) Basal-like-2 (BL2)
4) Immunomodulatory (IM)
5) Mesenchymal (M)
6) Mesenchymal stem–like (MSL)
7) UNS

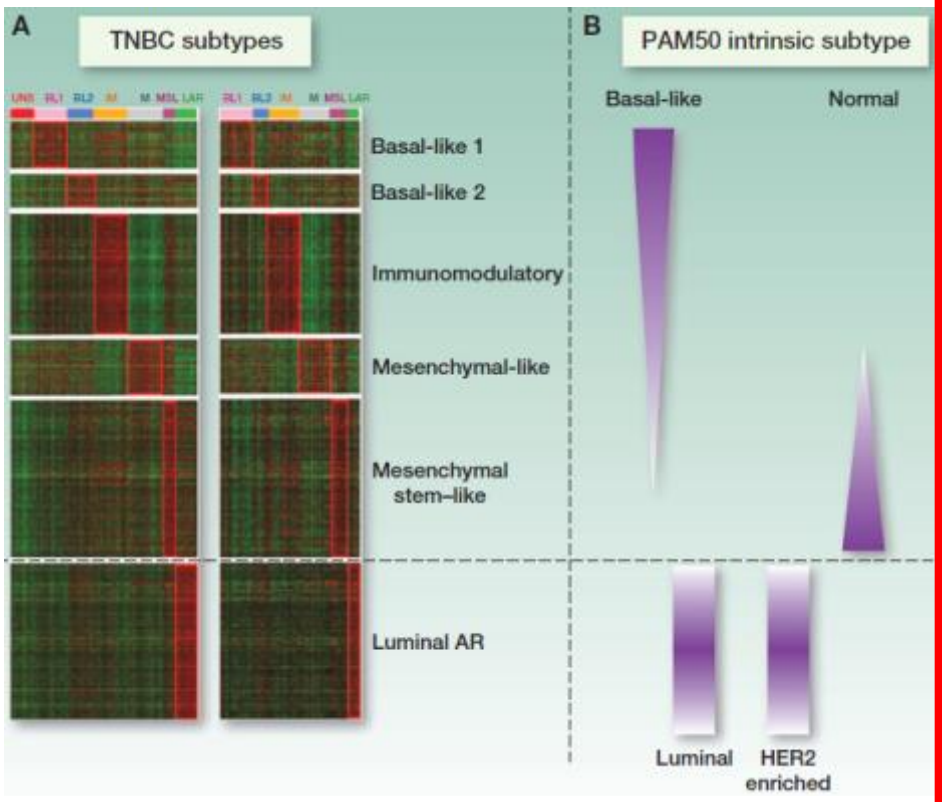


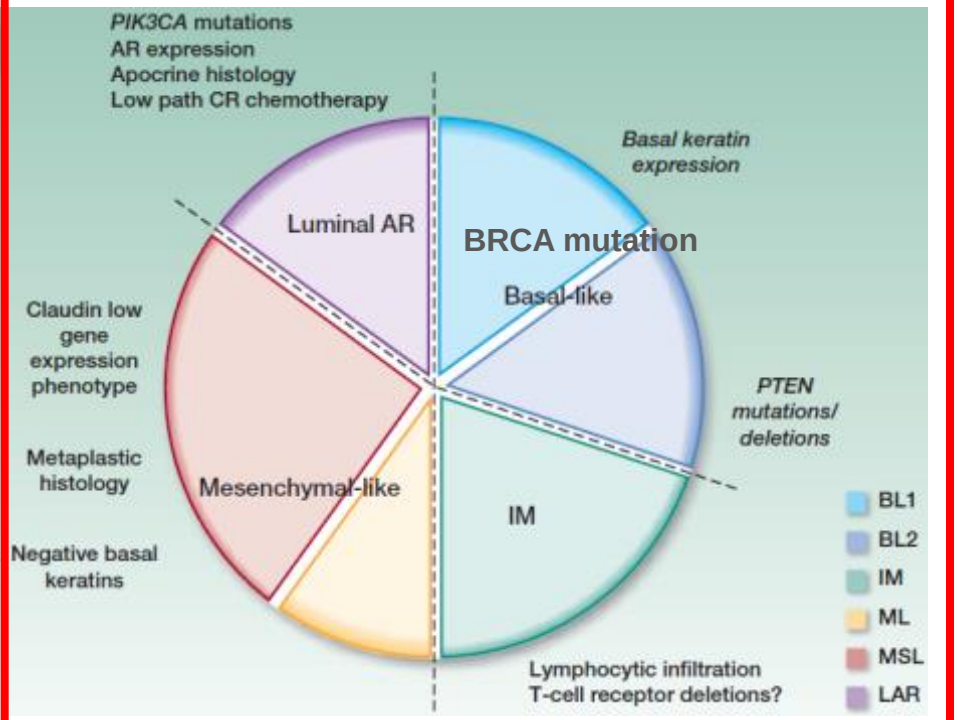
PAM 50
Affymetrix® U133 plus 2.0

Masuda H, Ueno NT et al:
Clin Cancer Res. 5533-5540, 2013

Microarray based gene-cluster analyses identified six distinct TNBC subtype.

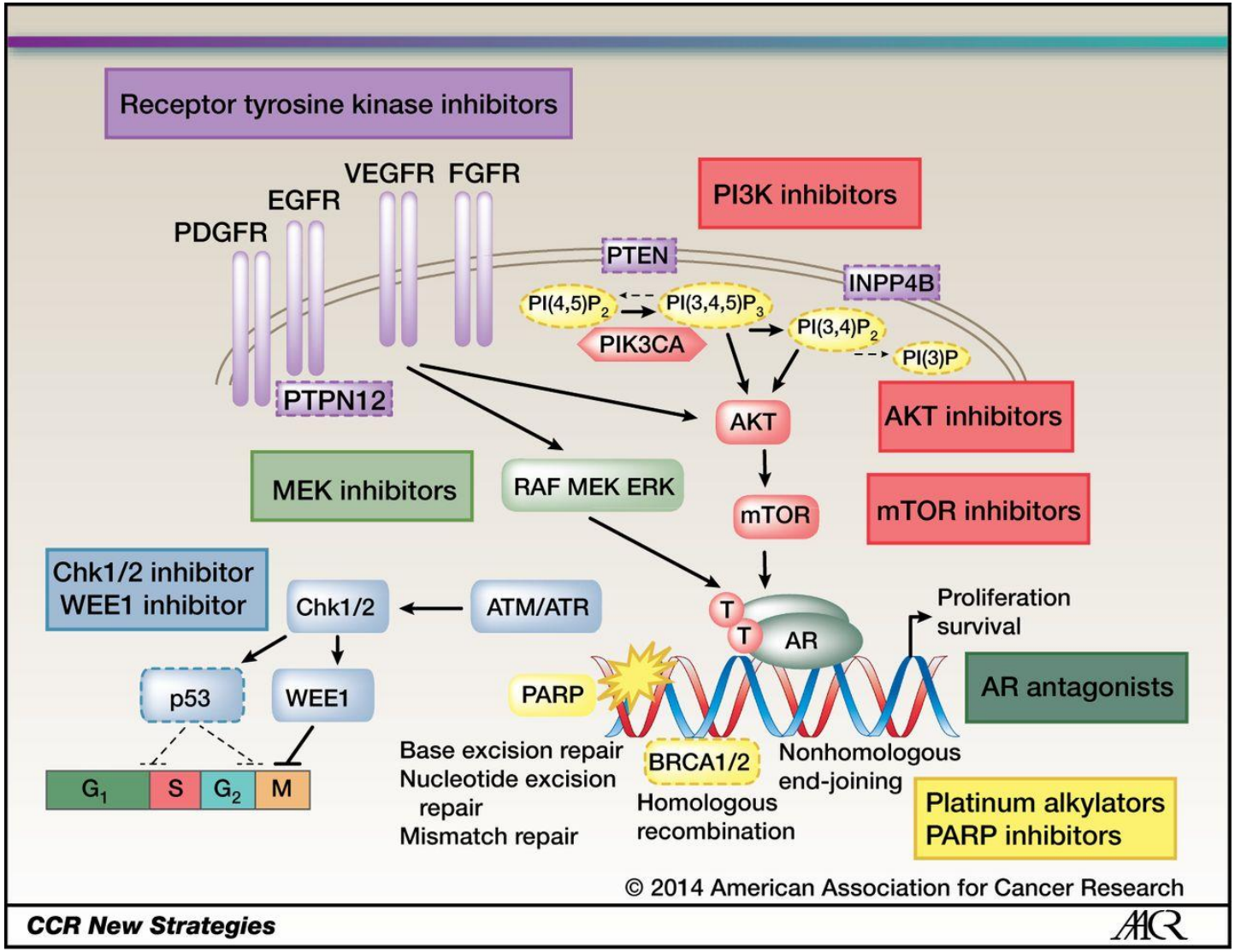
- TNBC; heterogeneous disease.
- Platinum agents, signal transduction inhibitors, PARP inhibitor, Eribulin as a novel tubulin inhibitor, immuno-checkpoint inhibitor or AR inhibitor *etc.*





Clin Cancer Res 2013; 19: 6380-6388
Clin Cancer Res 2013; 19: 5533-5540

Potential therapeutic targets

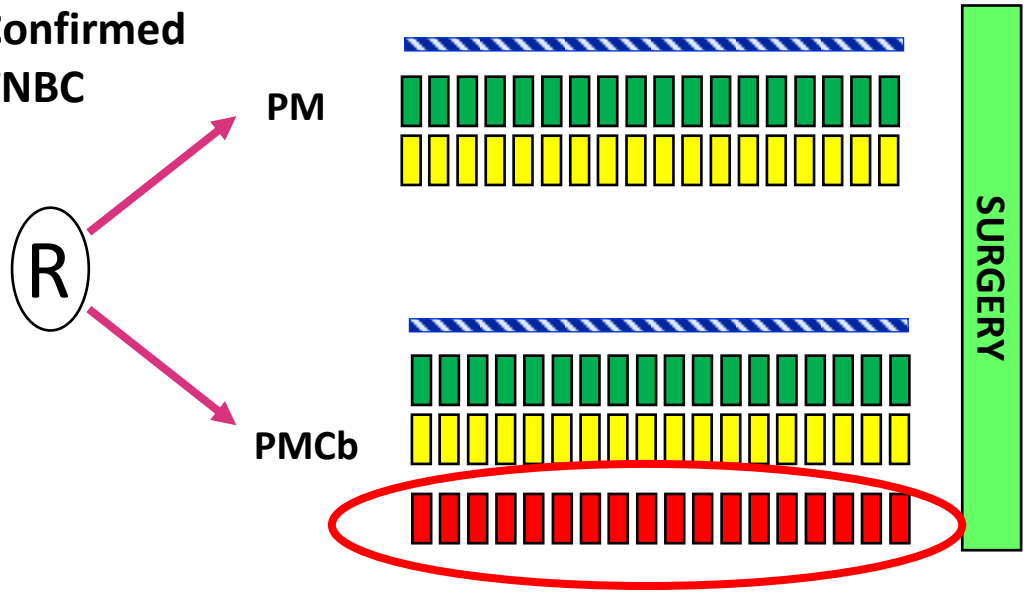


Ingrid A. Mayer et al.
Clin Cancer Res 2014;20:782-790

Therapies in TNBC subgroups

N=315

Centrally Confirmed TNBC



Paclitaxel 80 mg/m² q1w

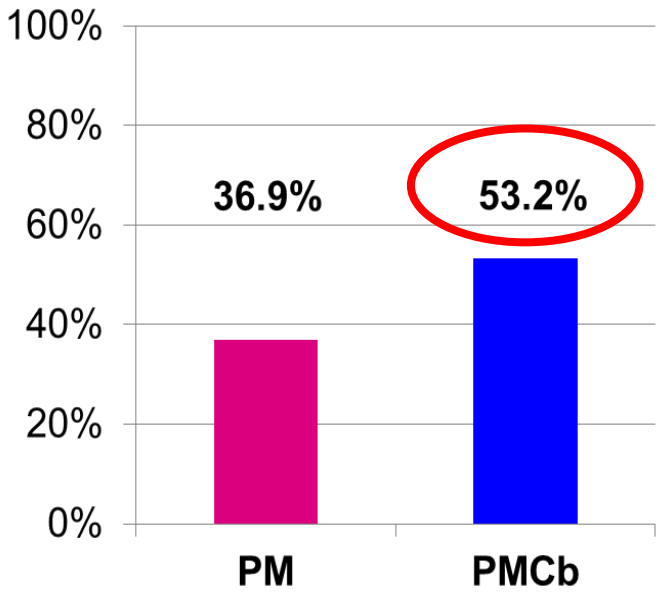
Non-pegylated liposomal doxorubicin (M) 20 mg/m² q1w

Carboplatin AUC 1.5-2 q1w

Bevacizumab 15 mg/kg q3w

TNBC

pCR Rates (ypT0 ypN0)

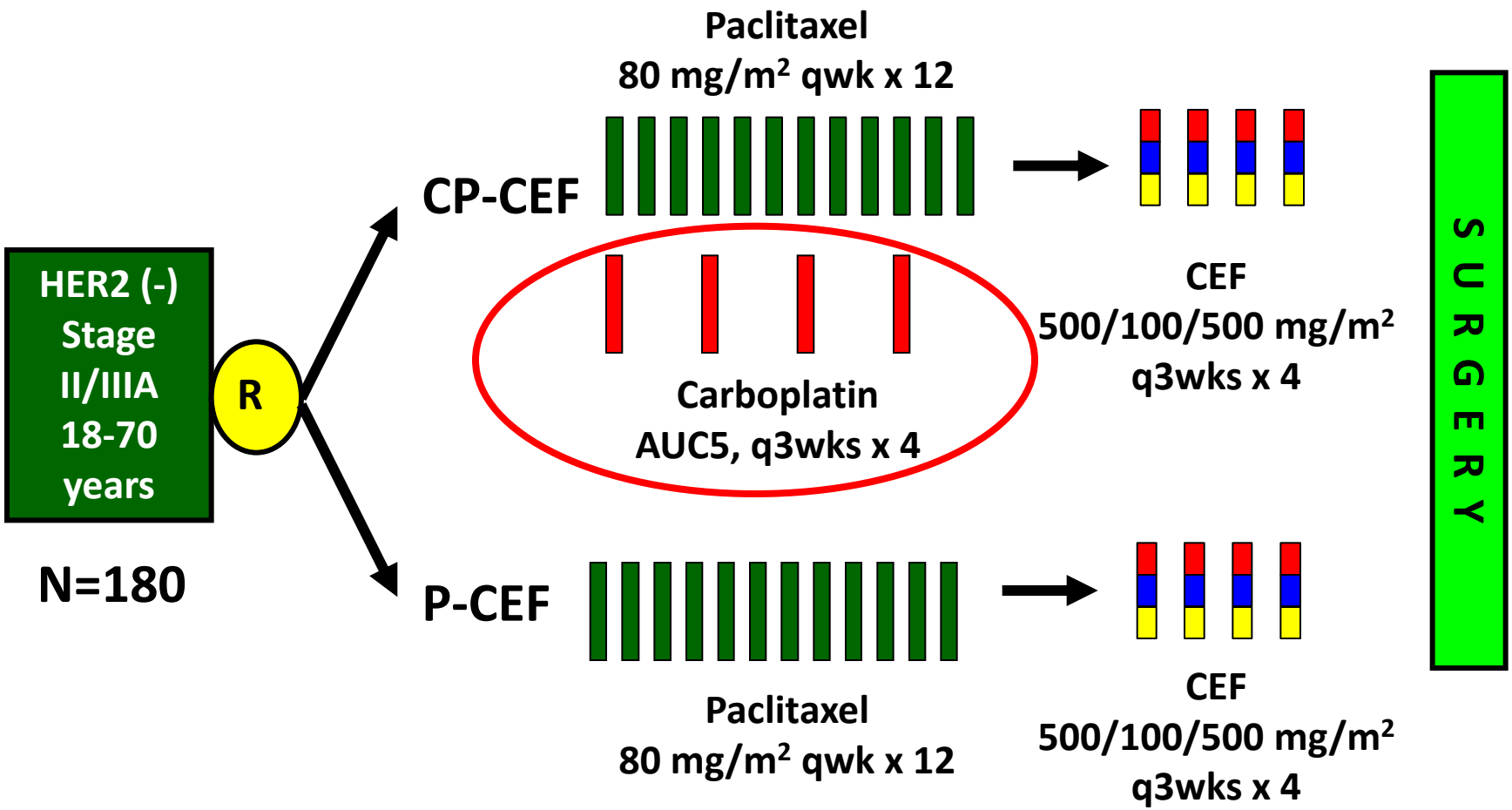


N=157 **N=158**

OR 1.94 (1.24 – 3.04)
P=0.005

von Minckwitz et al. Lancet Oncology, May 2014

Neoadjuvant in TNBC in JPN Pts

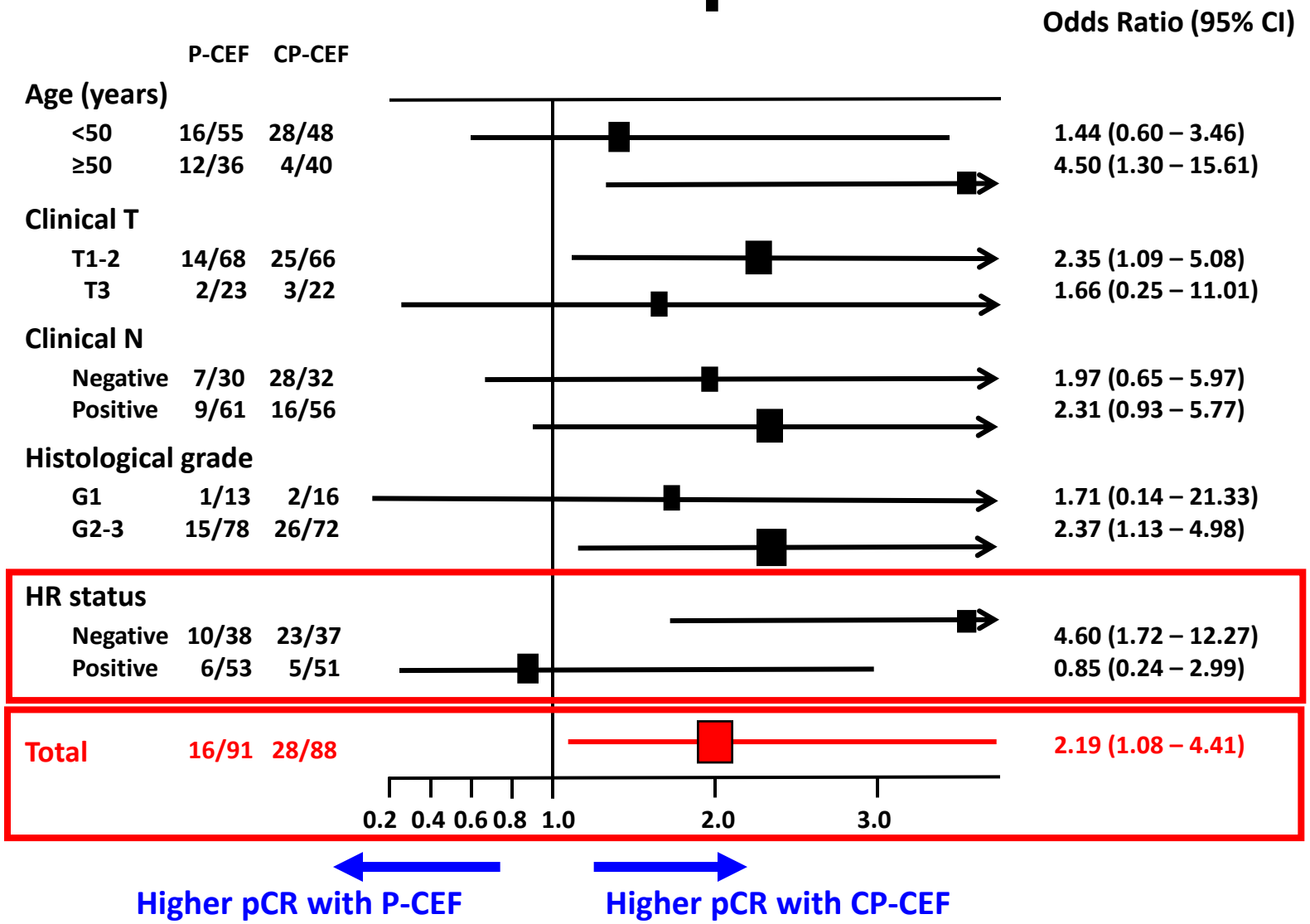


Primary Endpoint : pCR

Secondary Endpoint: RFS, Safety, Biomarker to predict CBDCA benefit

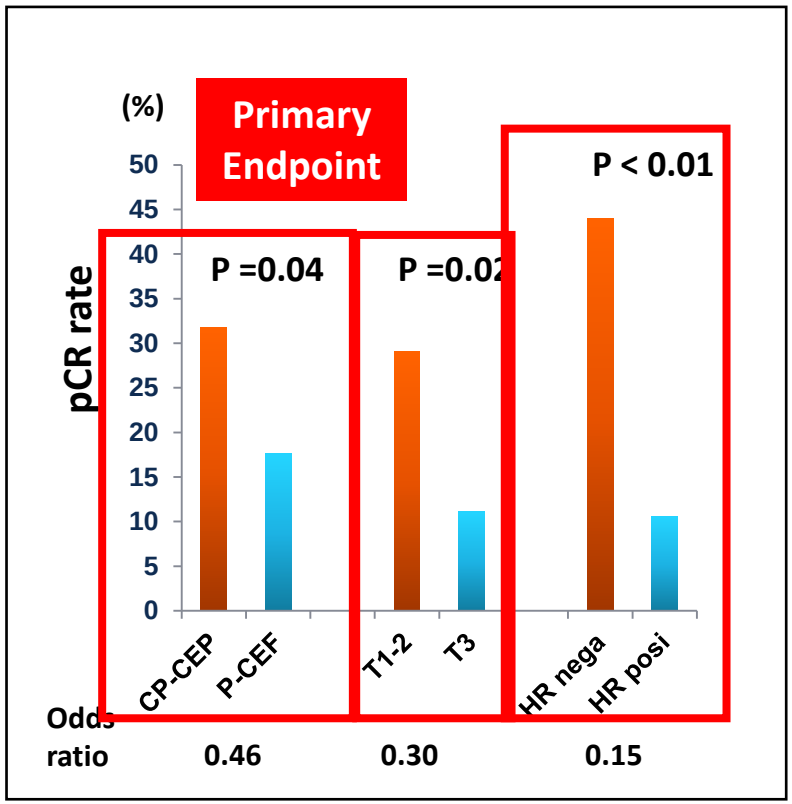
Ando M, Tamura K et al.
Breast Cancer Res Treat. 2014

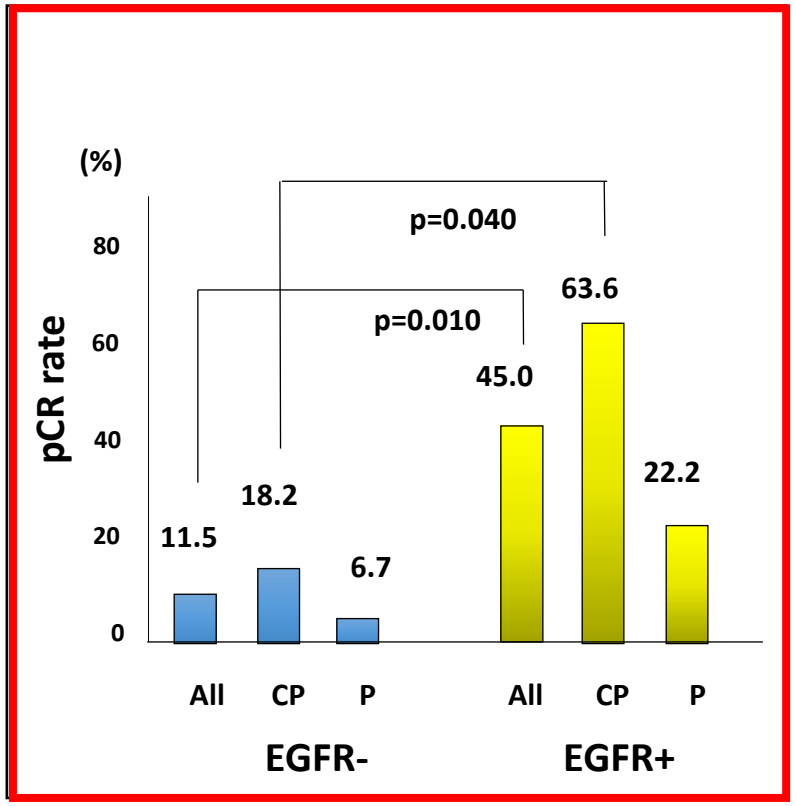
Forest plot



Ando M, Tamura K et al.
Breast Cancer Res Treat. 2014

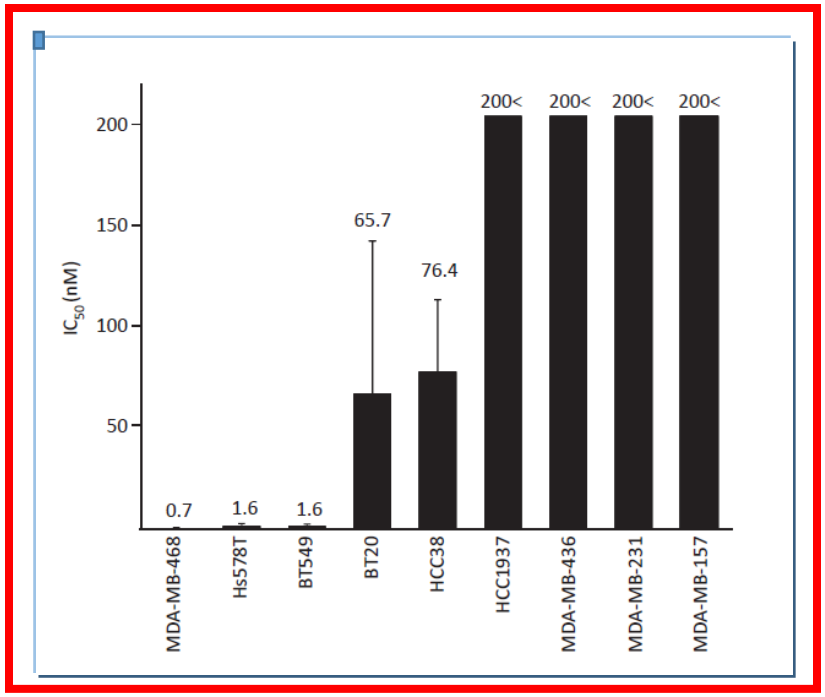
pCR according to sub subgroups



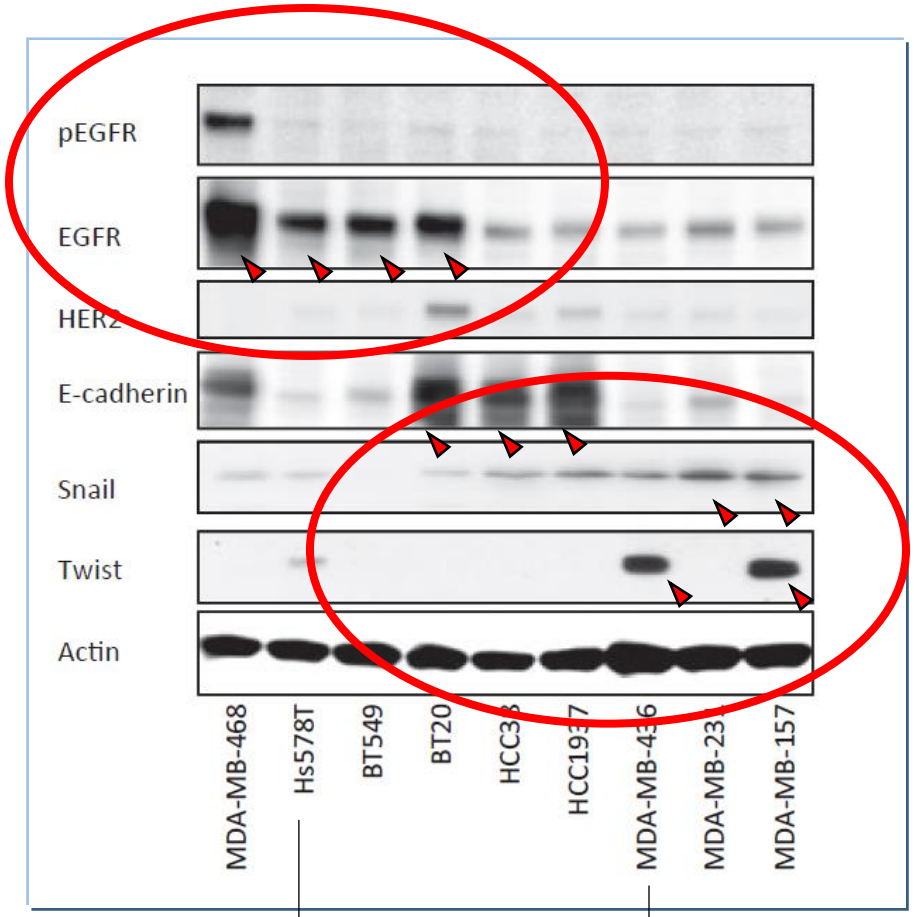


Protein expression in tissue sample by Immunohisto chemistry (IHC)

Sensitivity of Everolims with 9 kinds of TNBC cell line



Sensitivity of Everolims

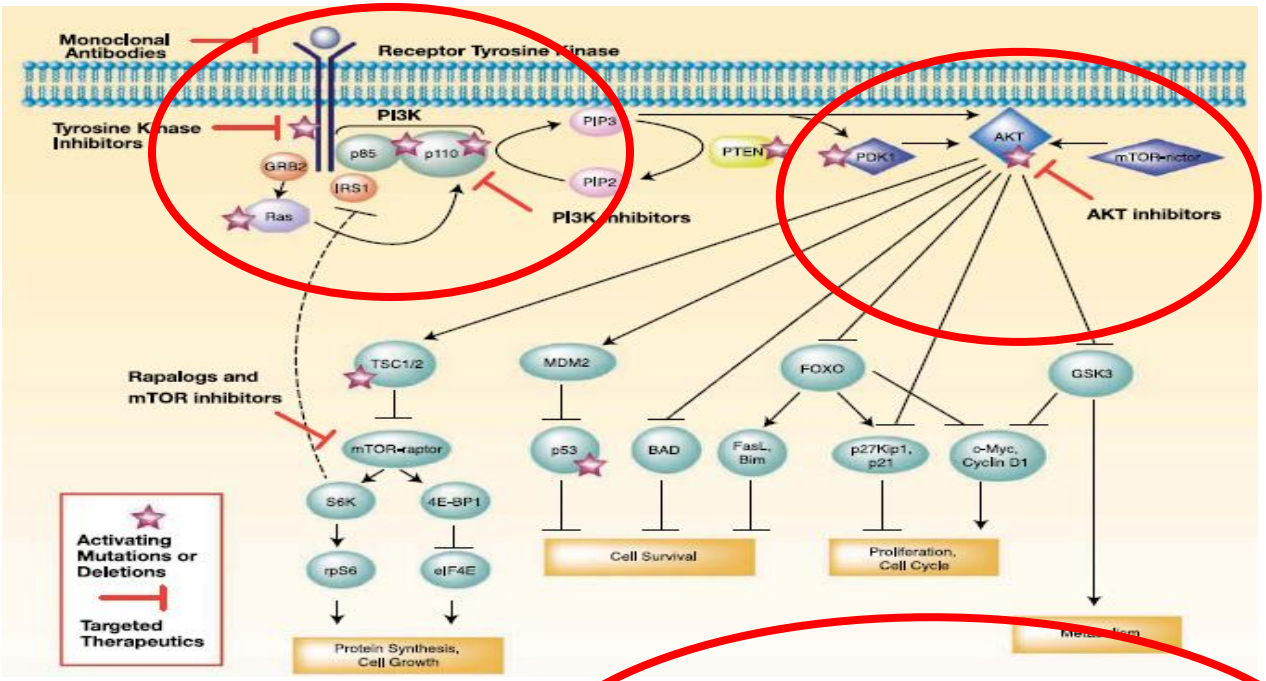


Yunokawa M, Tamura K etc
Cancer Sci. 2012 103:1665-71, 2012

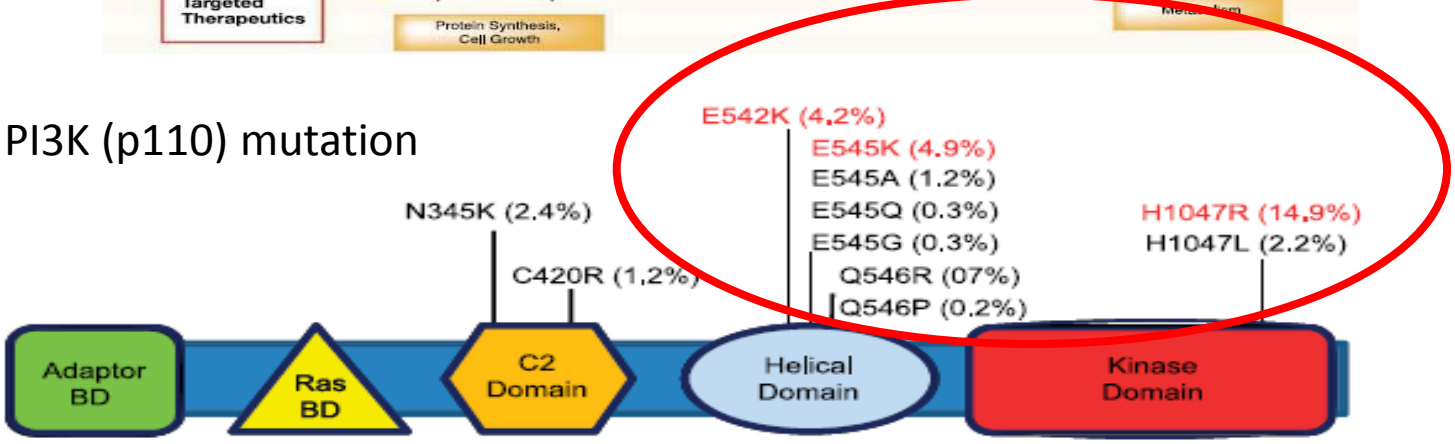
TSLC1 positive

BRCA
Germ Mu+

PIC3CA Mutation



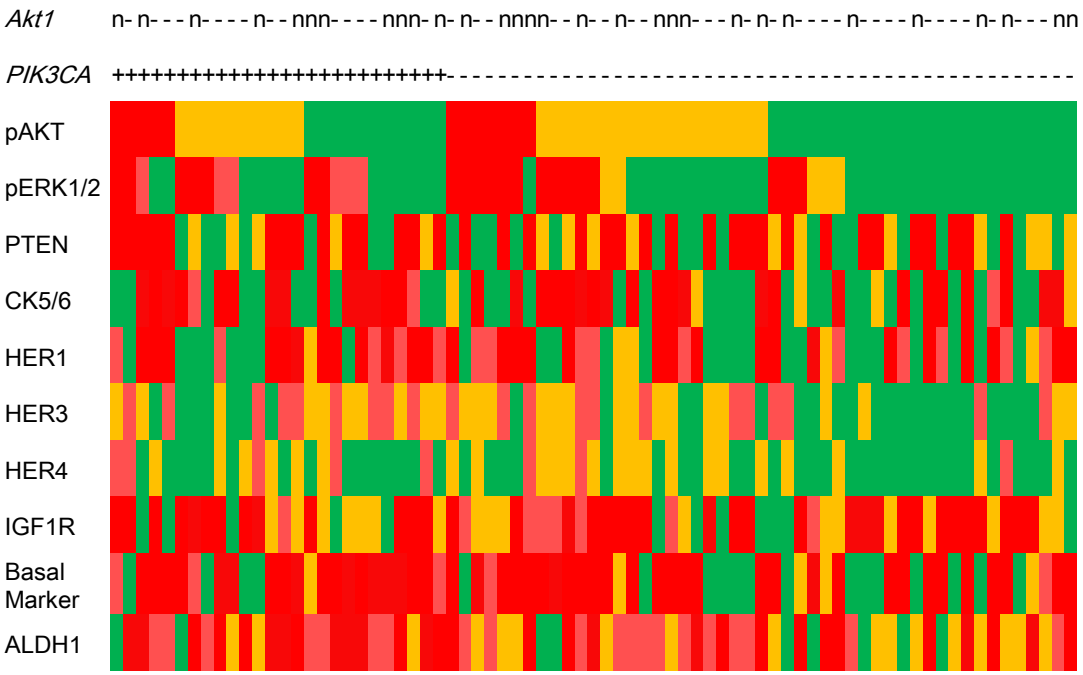
Class I PI3K (p110) mutation

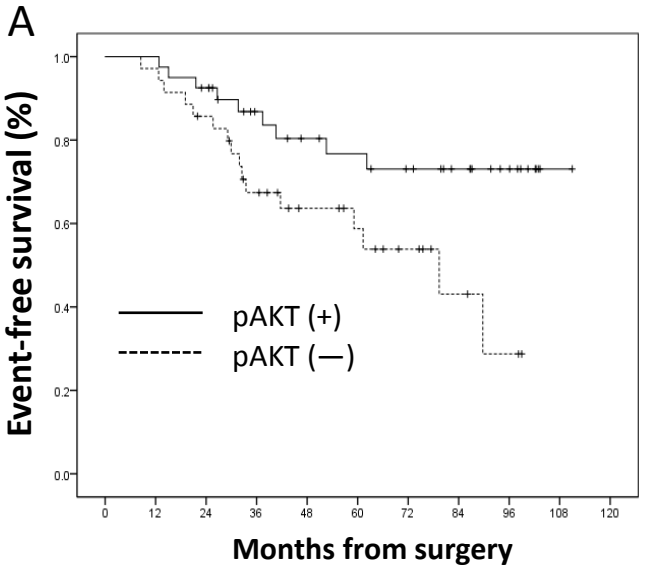


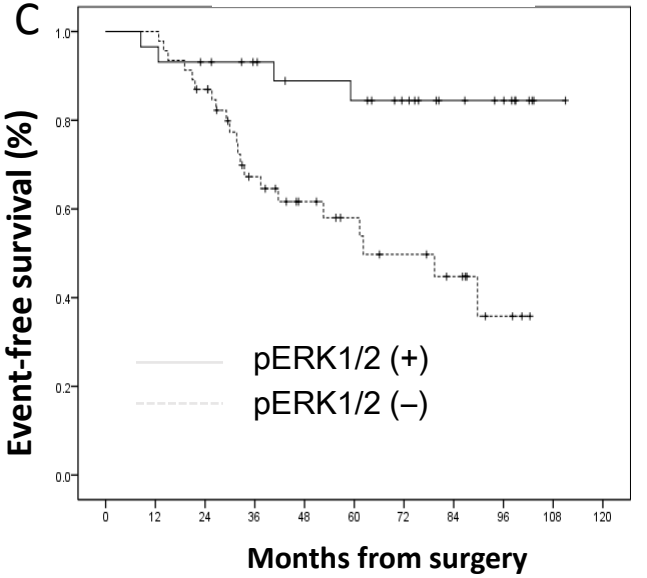
Clin Cancer Res 2009; 15: 5017,
Clin Cancer Res 2009; 15: 504

Signal transduction with TNBC

- **75 TNBC patients with lymph-node metastases who had received adjuvant chemotherapy.**
- **11 biomarkers, including PIK3CA and AKT1mutation**
- **PIK3CA Mu 35%, AKT1 Mu 3%**





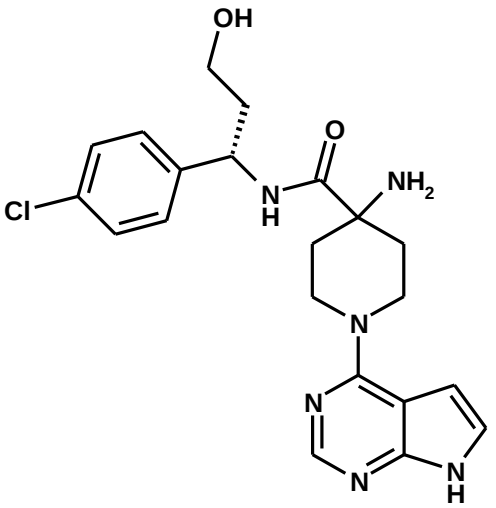


Hashimoto K, Tamura K, Fujiwara Y *et al*. Ann Oncol, July, 2014

AZD5363 is a potent inhibitor of AKT

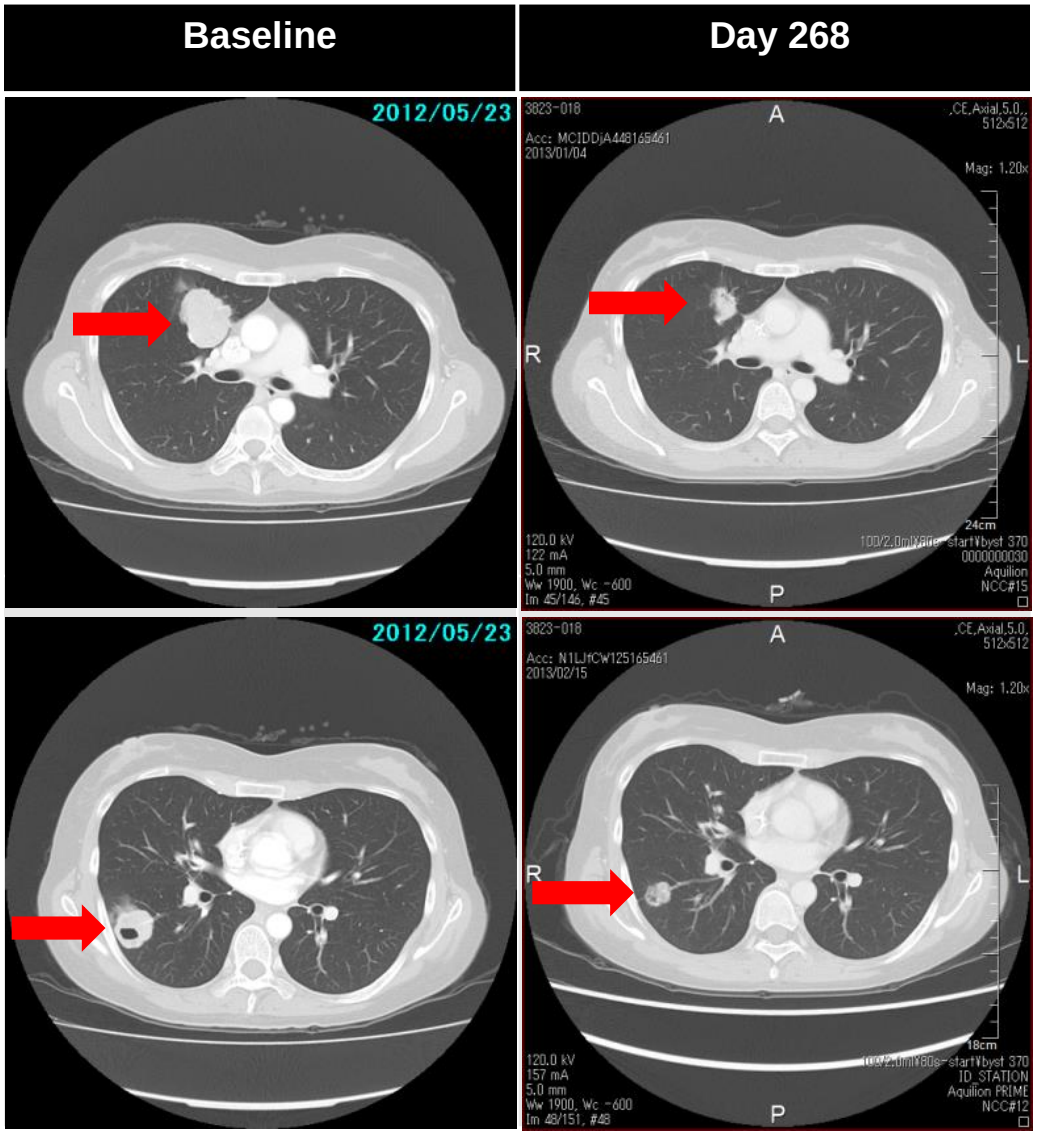
	Target	AZD5363 IC_{50} nM
Enzyme inhibition	Akt1	3
	Akt2	7
	Akt3	7
	ROCK1	470
	ROCK2	60
	PKA	7
	P70S6K	6
Cellular Akt substrate phosphorylation (cell type)	pPRAS40 (BT474c)	310
	pGSK3b (MDA MB468)	380
	FOXO3a nuclear translocation (BT474c)	690
	pS6 (RT4, TSC1-/-, TSC2 very low expression)	4800

AZD5363



Davies BR et al.
Mol Cancer Ther 2012: 11: 873–887

Super-responder by AKT inhibitor

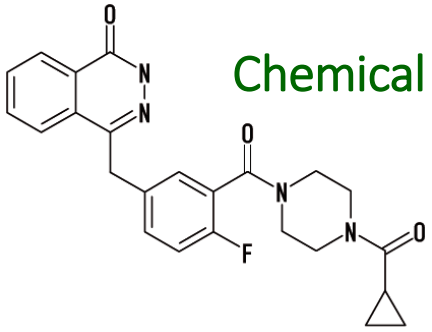


- A 38 year-old female, Asian patient with metastatic (lung), endometrioid cancer of the ovary
- $AKT1^{E17K}$ somatic mutation positive
- AZD5363 480 mg bid (4 days on / 3 days off) schedule
- 47% decrease in tumor size from baseline
- Eight previous lines of chemotherapy

Davies B, Tamura K et al, Mol Cancer Ther. 2015

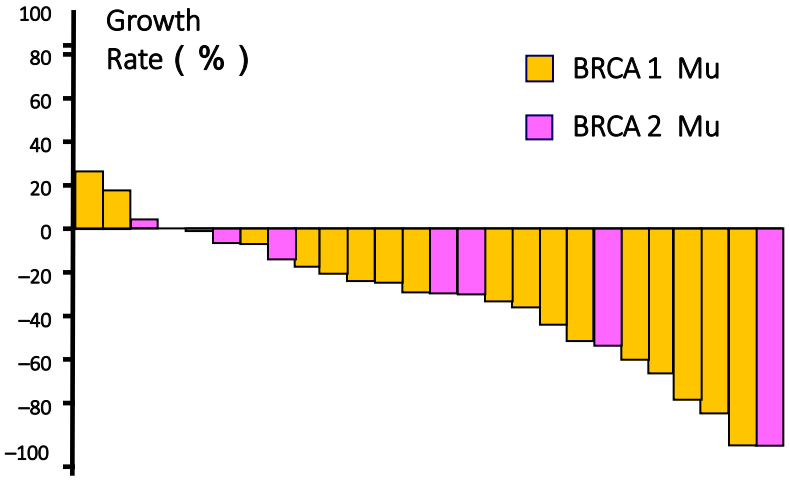
Olaparib

- A potent inhibitor of PARP (polyadenosine 5'-diphosphoribose polymerase).
- PARP inhibition is a novel approach for targeting tumors with deficiencies in DNA repair mechanisms.
- Previous studies indicate that olaparib can effectively inhibit the PARP enzyme, affecting the repair of damaged DNA, and may also enhance the DNA-damaging effects of other chemotherapy agents.

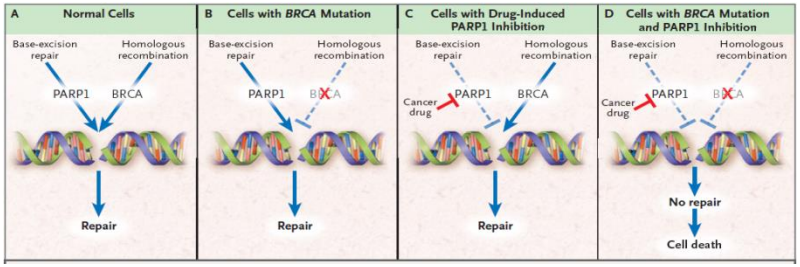


Chemical Structure

Phase II Trial of Olaparib in BRCA Mu Breast Ca



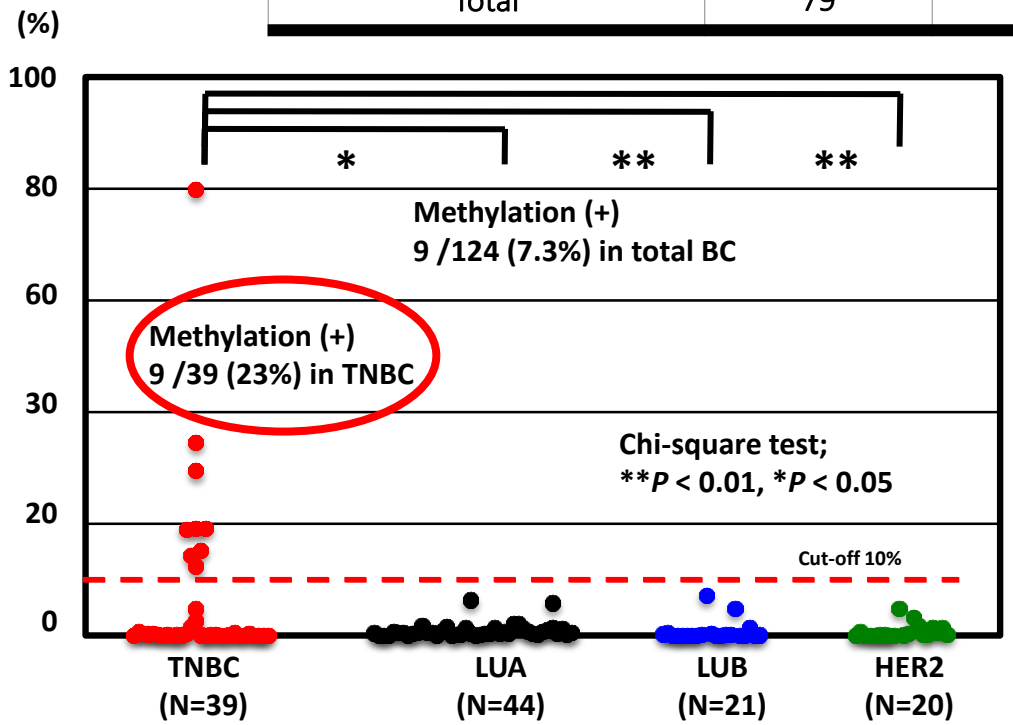
Synthetic Lethality Theory



Keith A. et al.
J. Med. Chem. 2008, 51, 6581–6591

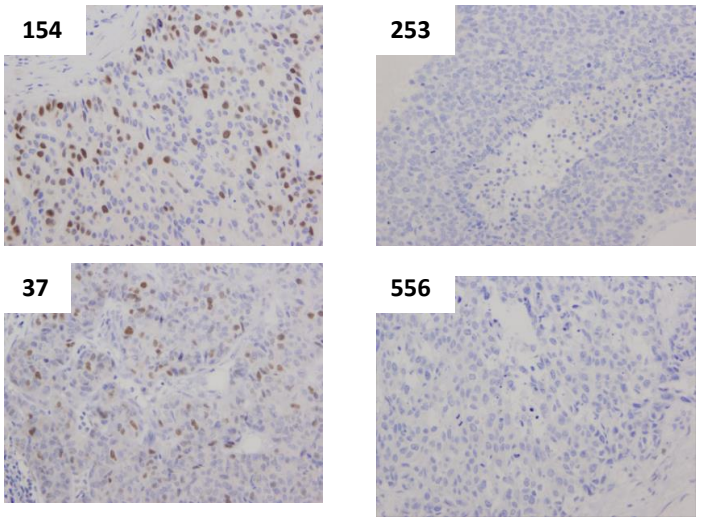
Metylation of BRCA in TNBC

Surgical specimen	Frozen specimens	Acetone-fixed paraffin embedded specimens	Total
TNBC (ER-, HER2-)	19	19	39
Luminal A (ER+, HER2-)	29	14	44
Luminal B (ER+, HER2+)	17	4	21
HER2 (ER-, HER2+)	14	5	20
Total	79	42	124



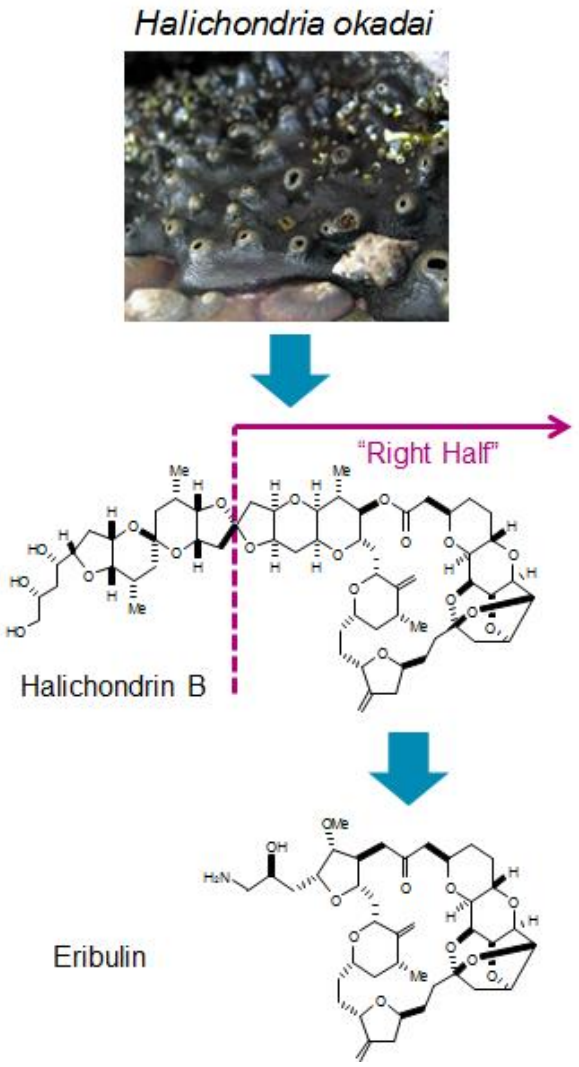
BRCA1 Protein Expression by IHC (x 200)

BRCA1 methylation (–) *BRCA1* methylation (+)



Kawachi, Tamura K *et al.*
ESMO Asia SINGAPORE, 2015

Eribulin, Analog of Halichondrin B



1986:	***Halichondria okadai* discovered in Japan; anticancer activity first reported**
1991:	**Tubulin-based mechanism proposed by US NCI**
1992:	**Synthesized at Harvard by Yoshito Kishi and colleagues**
1992:	**Kishi's synthetic materials tested at Eisai, leading to discovery that biological activity resides in 'Right Half'**
1993–1999:	**200+ right half analogs synthesized at Eisai and Harvard**
1998:	**Eribulin selected as final drug candidate**
1998:	**NCI collaboration begins**
2002:	**Phase I clinical trials begin**
2004:	**Phase II clinical trials begin**
2006:	**Phase III clinical trials begin**
2010:	**First regulatory approval (USA)**

Hirata Y. *Pure Appl Chem.* 1986;58:701–710;
Ledford H. *Nature*. 2010;468:608–609;

Eribulin vs. Capecitabine in Ad BC

Randomized, Global, Open-label Phase III

Eligibility

N=1,102

- **Locally Advanced or Metastatic Breast Cancer**
- **No. of Pre- Antitumor Treatments ≤ 3 regime**
- **History of Anthra- and Taxane Based Treatments**

R

Randomization 1:1

Eribulin
1.4 mg/m², 2-5 min IV bolus
Day 1, 8, q21 days

capecitabine
1,250 mg/m², twice/daily, PO,
Day 1-21, q21 days

Primary Endpoint

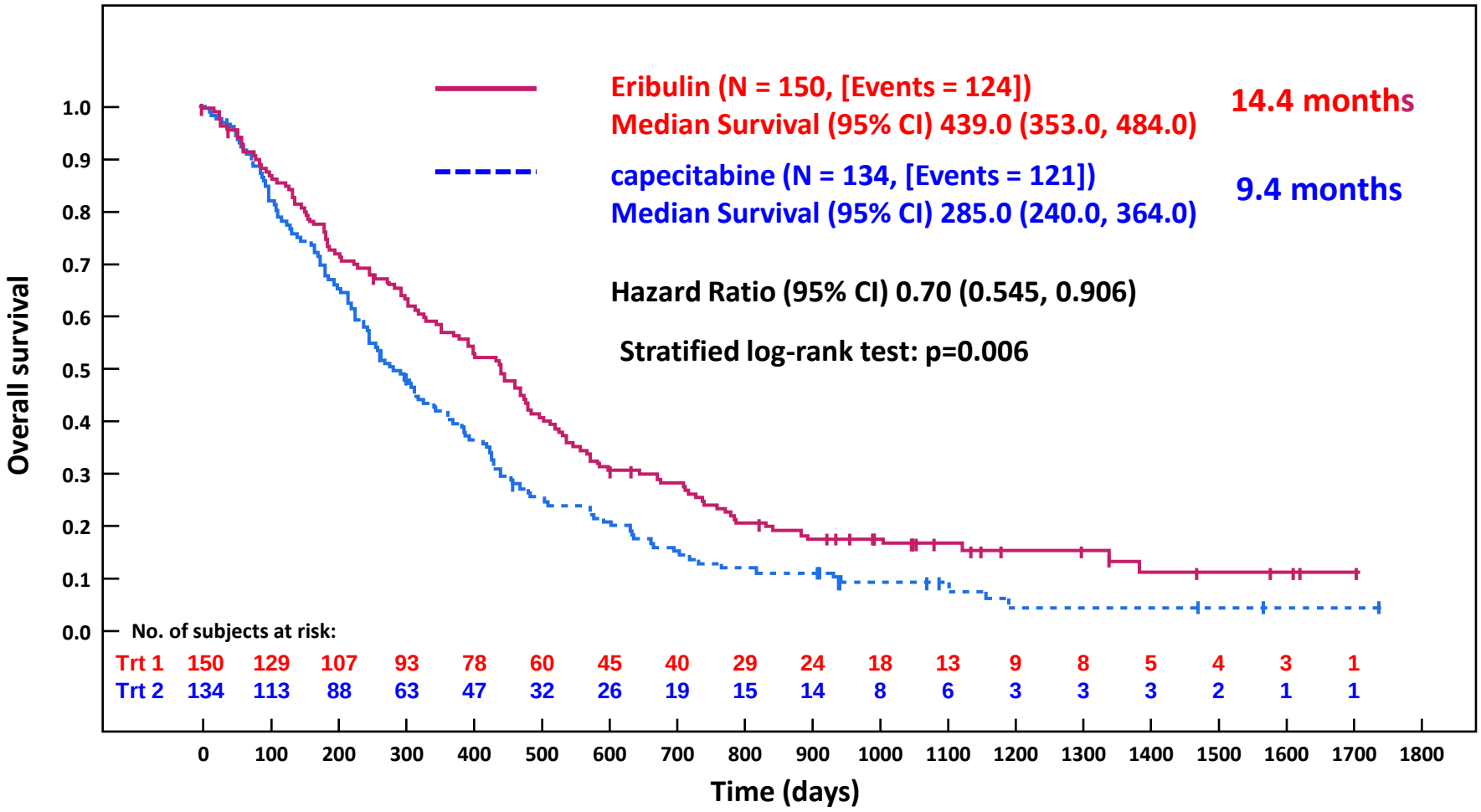
- **OS and PFS**

Secondary Endpoints

- **QOL**
- **Response rate**
- **Duration of response**
- **Safety**
- **Biomarker**

Kaufman PA et. al.
J Clin Oncol. 33:594-601. 2015

Extend OS in TNBC subset



Kaufman PA et. al.
J Clin Oncol. 33:594-601. 2015

Olaparib with eribulin in patients with advanced or metastatic TNBC

Phase I Part（Dose escalation cohort）

N =24

TNBC
（ER-, PgR-, HER2 -）

→

Eribulin 1.4mg/m² d1, 8
Olaparib twice, daily
q3w, until PD

Dose escalation of Olaparib

↓

Estimated Recommended Dose

Phase II Part

N =24

TNBC
（ER-, PgR-, HER2 -）

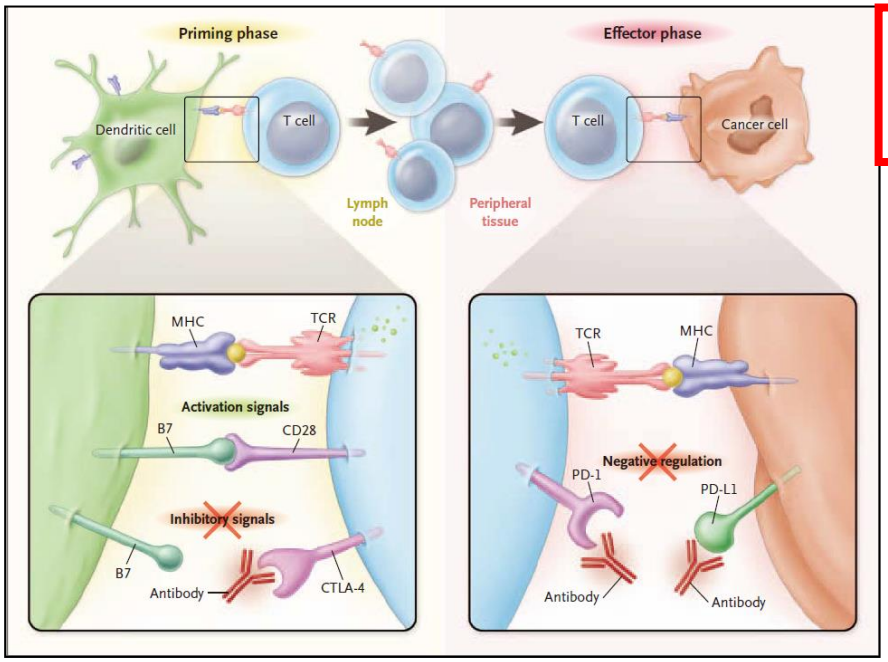
→

Eribulin 1.4mg/m² d1, 8
Olaparib RD twice, daily
q3w, until PD

Assess the Efficacy and Safety of Olaparib with Recommended Dose

Response rate, PFS and OS data will be opened in ASCO Meeting 2016

Immuno-checkpoint inhibitors



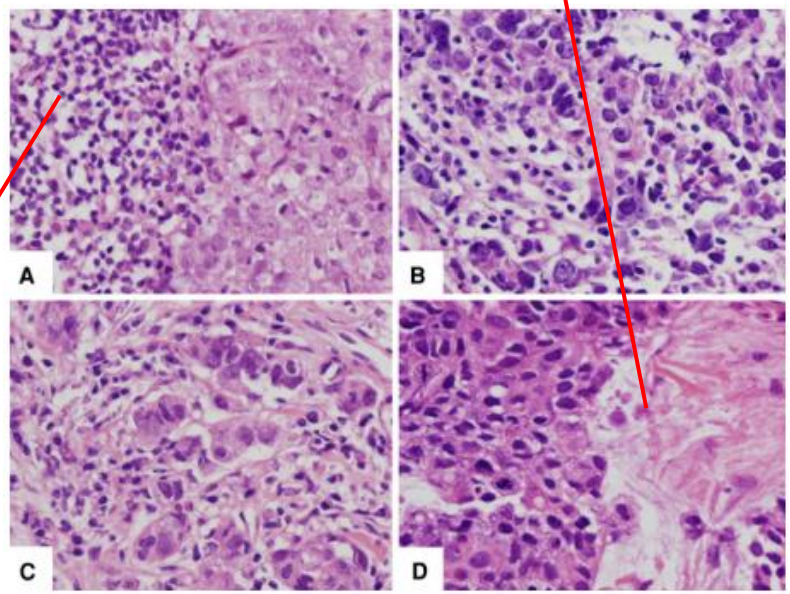
***MK-3475* (pembrolizumab; PD1 antibody)**
For TNBC, PII, PIII

TIL(tumor infiltrated lymphocytes)

(H.E)

low (0 + 0 = 0)

high (3+ 2 = 5)



- **Intensity Score**
  (intensity of lymphatic infiltration)

	Marked	Mild	absent
score	2	1	0

- **Proportional Score**
  (area of stroma infiltrated by lymphocytes)

	> 50%	> 10-50%	≤ 10%	absent
score	3	2	1	0

TILs score = Proportional score + Intensity Score (0-5)

0-2 : low

3-5 : high

PD-1 expression on TILs

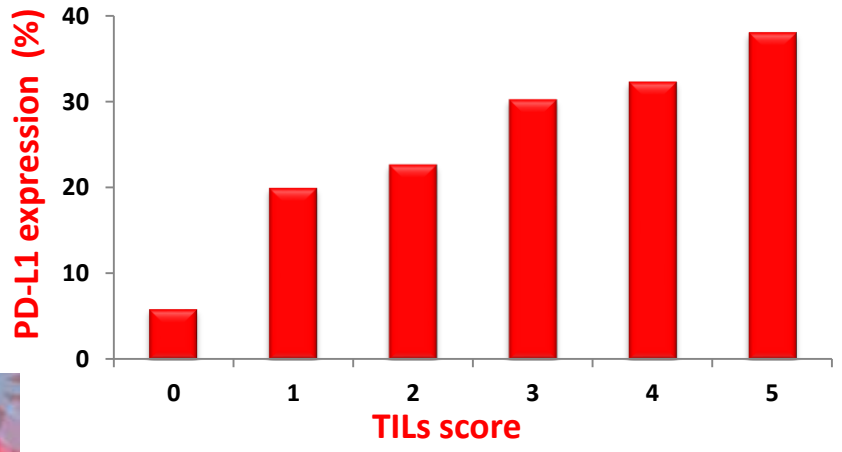
Tumor-infiltrating lymphocytes are correlated with response to neo-adjuvant chemotherapy in triple-negative breast cancer.

Ono M, Tamura K, *et al*. Breast cancer Res Treat, 132: 793-805, 2012

	N=180	PD-1 expression in TILs Positive Negative		P value
Age	≤50 >50	15 (27) 25 (24)	41 (73) 83 (79)	0.61
TILs	High Low	29 (33) 11 (14)	59 (67) 65 (86)	**0.006**
Sub type	**TNBC** HER2-enriched Luminal	26 (32) 8 (20) 6 (14)	56 (68) 32 (80) 36 (86)	**0.08**
Grade	1 or 2 3	9 (17) 31 (28)	43 (83) 81 (72)	0.15
Stage	2 3	26 (25) 14 (23)	76 (75) 48 (77)	0.67

		PD-1 expression on TILs		
		Positive	Negative	
PD-L1 expr. on tumor cell	Positive	21 (13.0)	40 (24.6)	61 (37.6)
	Negative	19 (11.7)	82 (50.6)	101 (62.4)
		40 (24.7)	122 (75.3)	162

P=0.03



Subtypes and Targeted Drugs

- BL1 (chemo-sensitive)
  BRCA deficient
- BL2 (chemo-resistant)
  PIC3CA Mu+, AKT Mu+
- Immunomodulatory (IM)

- Luminal AR
  AR expression +
- Mesenchymal (M)
- Mesenchymal-stem like (MSL)

- Platinum agents
  PARP inhibitor
  EGFR inhibitor, mTOR inhibitor
  PI3K inhibitor, AKT-inhibitor

- PD1/PDL1 antibody (pembrolizumab etc.)
- AR inhibitor

- Eribulin

Summary

- TNBC is a heterogeneous disease.
- Microarray based gene-cluster analyses identified six distinct TNBC subtype.
- Platinum agents, signal transduction inhibitors, PARP inhibitor, Eribulin as a novel tubulin inhibitor, immuno-checkpoint inhibitor or AR inhibitor *etc.* are potential therapeutic drugs.
- Predictive biomarker for response are crucial needed for personalize treatment in TNBC.