Convegno Regionale AIOM Liguria 2018

La Biologia del Carcinoma Mammario (TN) e le Future Implicazioni Terapeutiche

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AIRC ASSOCIAZIONE ITALIANA PER LA RICERCA SUL CANCRO

INSTITUT JULES BORDET INSTITUUT

European School of Oncology Learning to care

ESMO

Disclosure Information

Relationship Relevant to this Session

Lambertini, Matteo:

- Consultant or advisor: Teva
- Honoraria: Theramex

Plan of the Talk

- Introduction
- Main biological features with clinical relevance
    1. High cell proliferation
    2. BRCAness/HRD/genomic scars
    3. Increased immune-infiltrate
    4. Androgen receptors
    5. Other potential targets
- Conclusions

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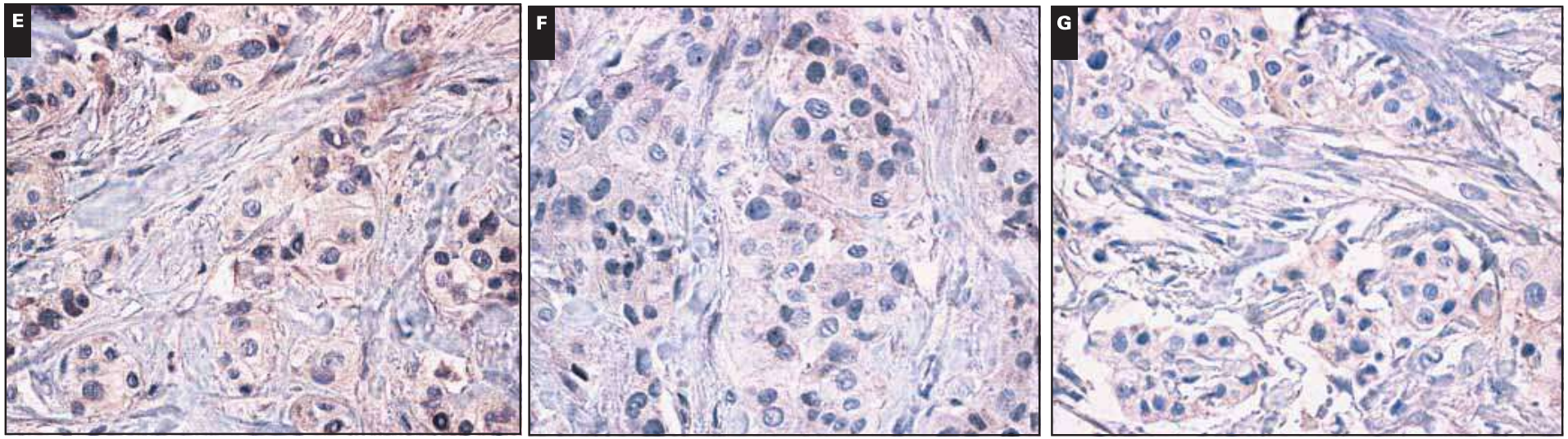
What is Triple Negative Breast Cancer (TNBC) ?

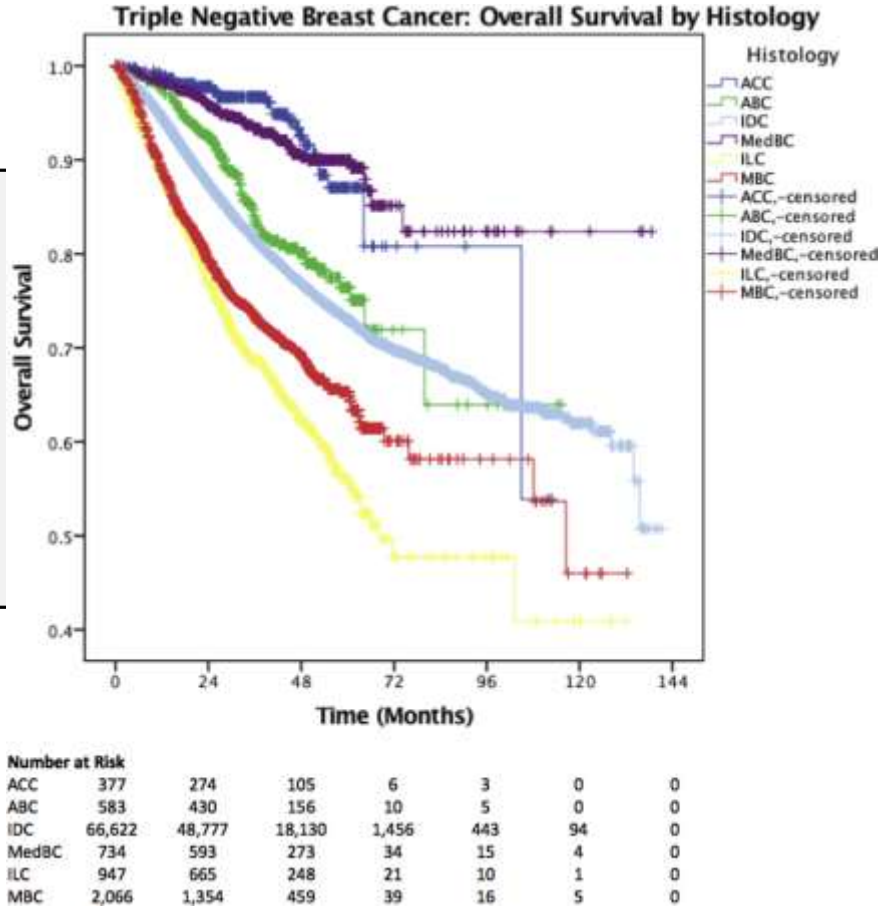
Estrogen receptor **Progesterone receptor** **HER2**



Schmadeka R et al, Am J Clin Pathol 2014;141:462-77

TNBC: Histological Features

Poor prognosis
Invasive ductal carcinoma NOS – high grade
Invasive lobular carcinoma – high grade
Metaplastic carcinoma – high grade
Myoepithelial carcinoma
High grade neuroendocrine (oat-cell) carcinoma
Good prognosis
Apocrine carcinoma – low grade
Medullary carcinoma
Secretory breast carcinoma
Adenoid cystic carcinoma
Metaplastic carcinoma – low grade (adenosquamous and fibromatosis-like)

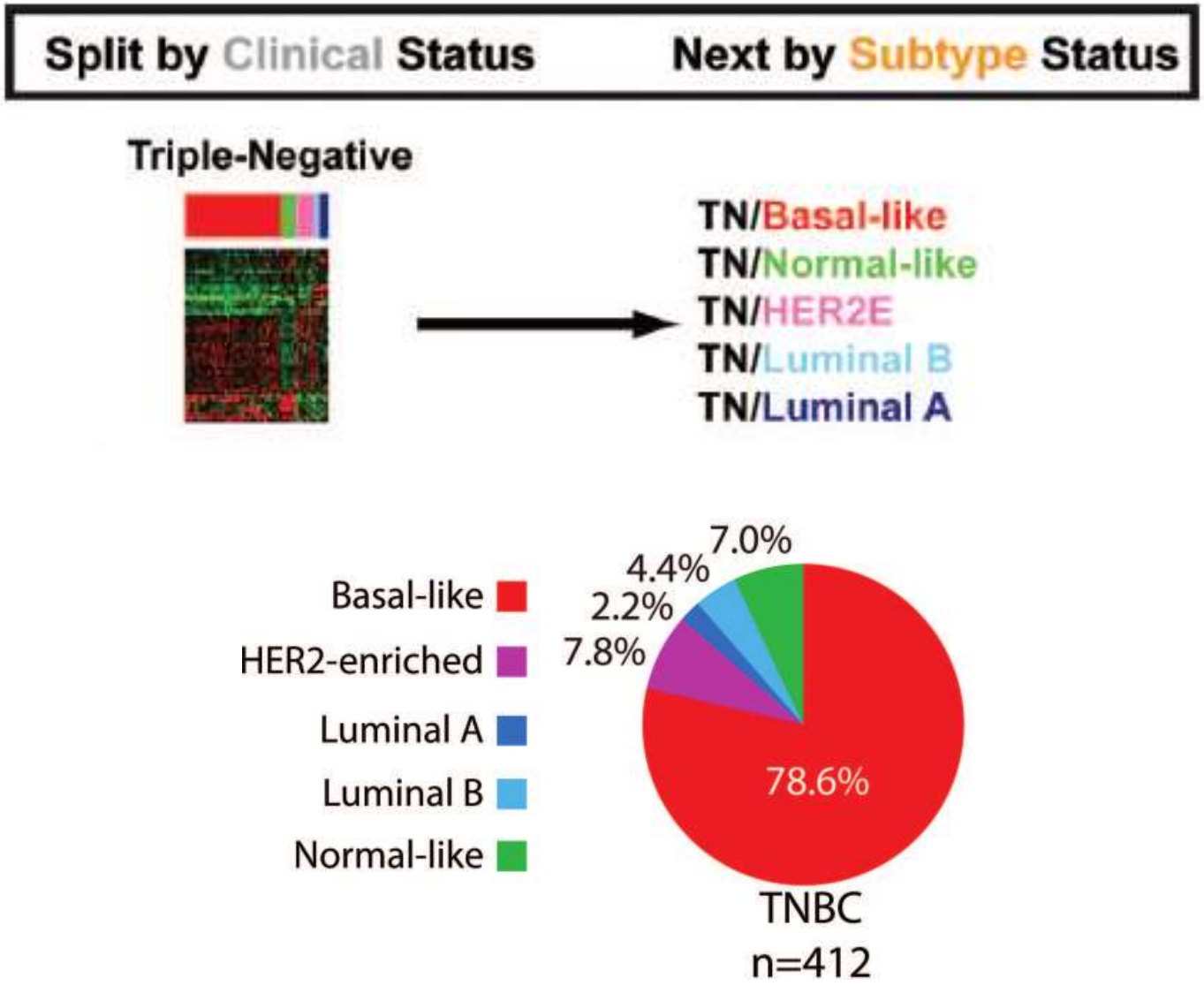


'**Triple negative (ductal)**' Cytotoxics

Medullary and adenoid cystic carcinomas may not require any adjuvant cytotoxics (if node negative).

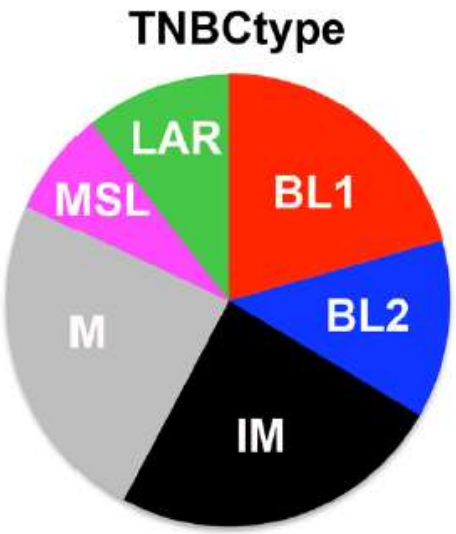
Oakman C et al, Breast 2010;19:312-21. Mills MN et al, Eur J Cancer 2018;98:48-58
Goldhirsch A et al, Ann Oncol 2011;22:1736-47

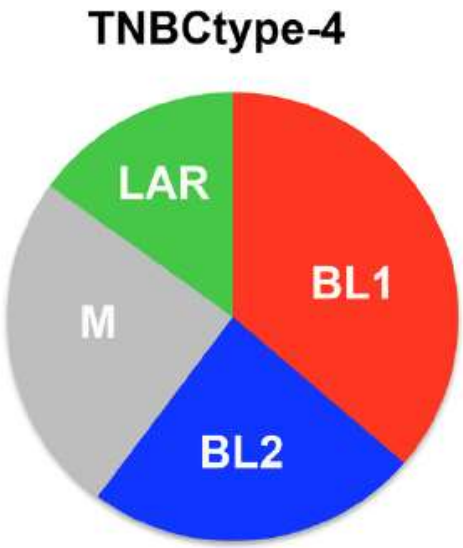
TNBC: Transcriptomic Landscape



Prat A et al, The Oncologist2013;18:123-33

TNBC: Transcriptomic Landscape





Subtype	"Driver pathways"	Possible sensitivity
Basal-like 1	high Ki-67; DNA damage response	PARP-I and Cisplatin
Basal-like 2	GF pathways	Anti-EGFR
Immunomodulatory	Immune genes	Immunotherapy
Mesenchymal	Cell motility	PI3K-mTOR Inh
Mesenchymal stem-like	Cell motility; claudin-low	Anti-angiogenetic
Luminal androgen receptor	Steroid pathways	AR antagonist

Lehmann BD et al, J Clin Invest 2011;121:2750-67. Lehmann BD et al, PLoS One 2016;11:e0157368

TNBC: Genomic Landscape

Substantial biological heterogeneity in the different TNBC molecular subtypes at the somatic mutation, copy number and gene expression levels

Gene involved in DNA repair mechanism are more deleted in BL1

BL1

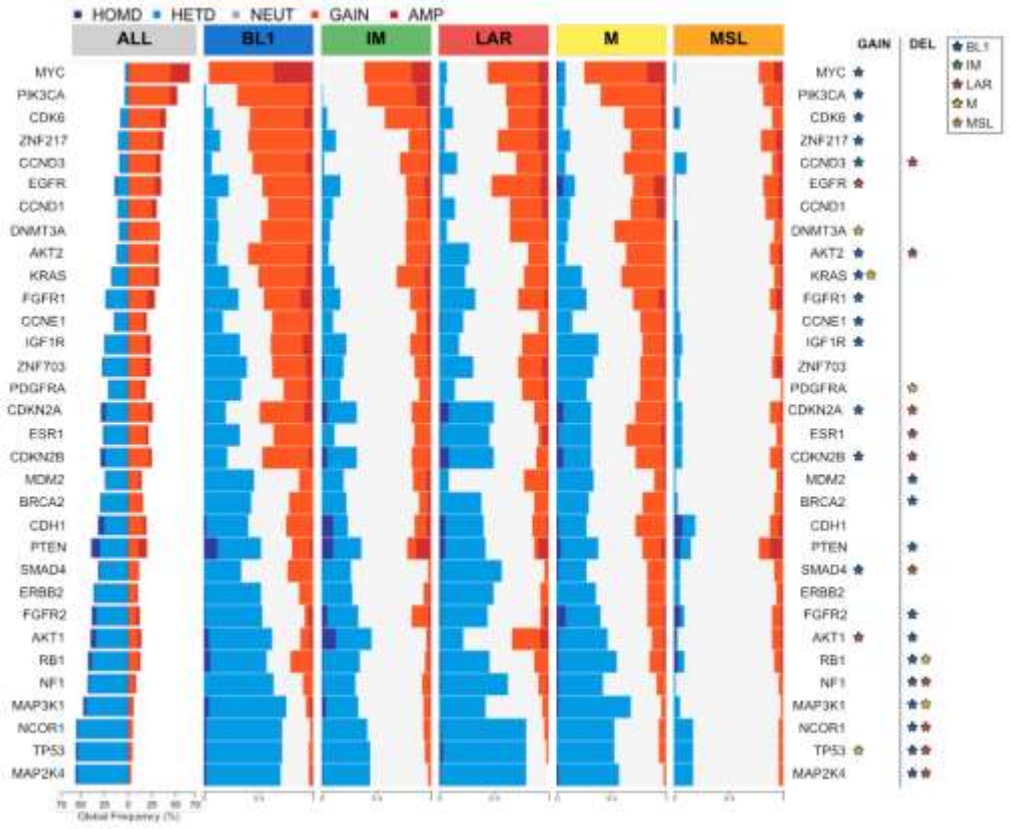
GAIN/AMP : *AKT2, CCND3, CCNE1, CDK6, CDKN2A/B, FGFR1, IGF1R, KRAS, MYC, PIK3CA, SMAD4 & ZNF217.*
HETD/HOMD : *AKT1, **BRCA2**, FGFR2, MAP2K4, MAP3K1, **MDM2**, NCOR1, NF1, **PTEN**, **RB1** & **TP53**.*

LAR

GAIN/AMP : *AKT1 & EGFR.*
HETD/HOMD : *AKT2, CDKN2A/B, ESR1, MAP2K4,* NCOR1, NF1, *SMAD4* & TP53

M

GAIN/AMP : *DNMT3A, KRAS & TP53.*
HETD/HOMD : *MAP3K1, PDGFRA & RB1.*



Bareche Y et al, Ann Oncol 2018;29(4):895-902

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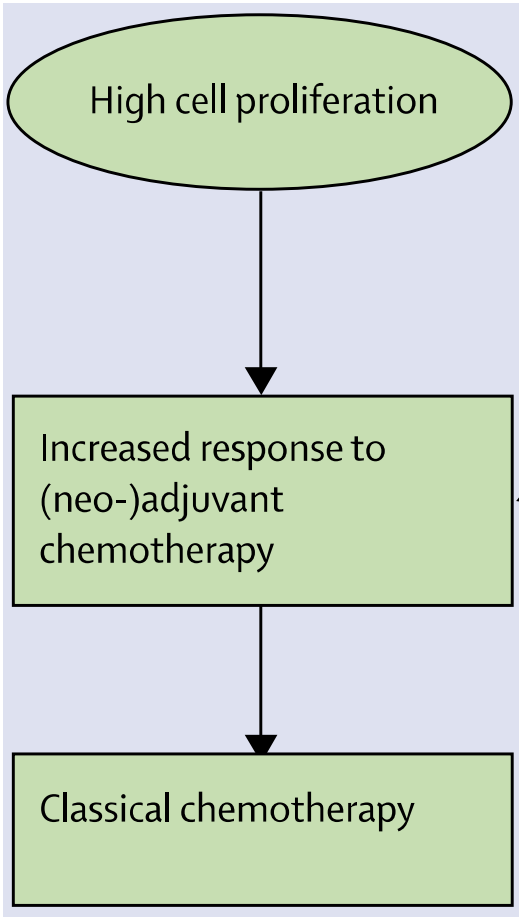
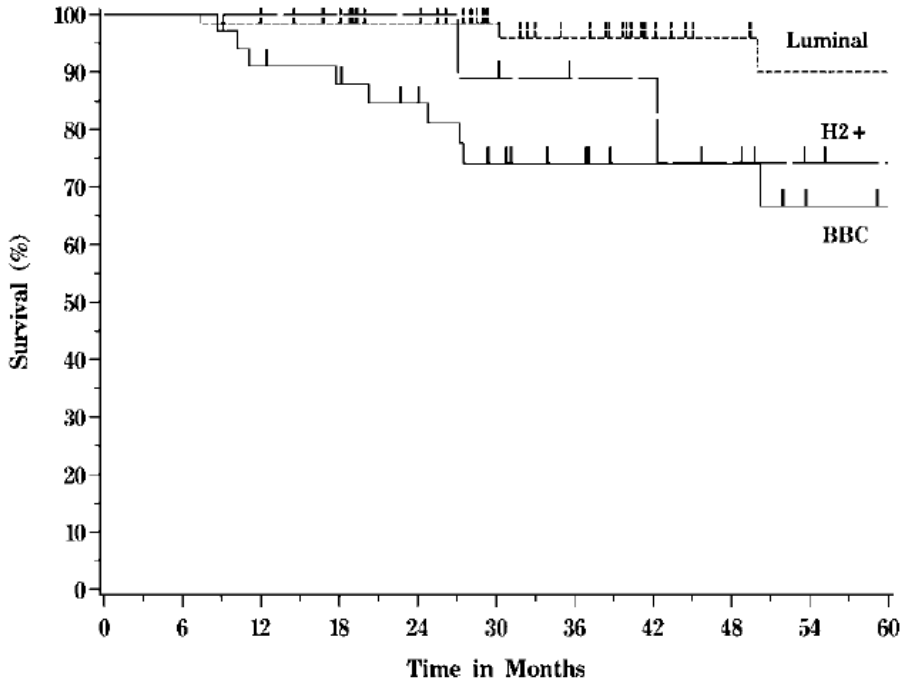
High Cell Proliferation: the TNBC Paradox



The Triple Negative Paradox: Primary Tumor Chemosensitivity of Breast Cancer Subtypes

	Entire population	Basal-like (n = 34)	HER2* (n = 11)	Luminal B (n = 26)	Luminal A (n = 36)	P
Clinical response to AC						
Complete response	15 (14%)	10 (29%)	1 (10%)	2 (8%)	2 (6%)	<0.0001
Partial response	50 (47%)	19 (56%)	6 (60%)	13 (50%)	12 (33%)	
Stable disease	40 (38%)	5 (15%)	3 (30%)	11 (42%)	21 (58%)	
Progressive disease	1 (1%)	0	0	0	1 (3%)	
Complete response + partial response	65 (61%)	29 (85%)	7 (70%)	15 (58%)	14 (39%)	<0.0001

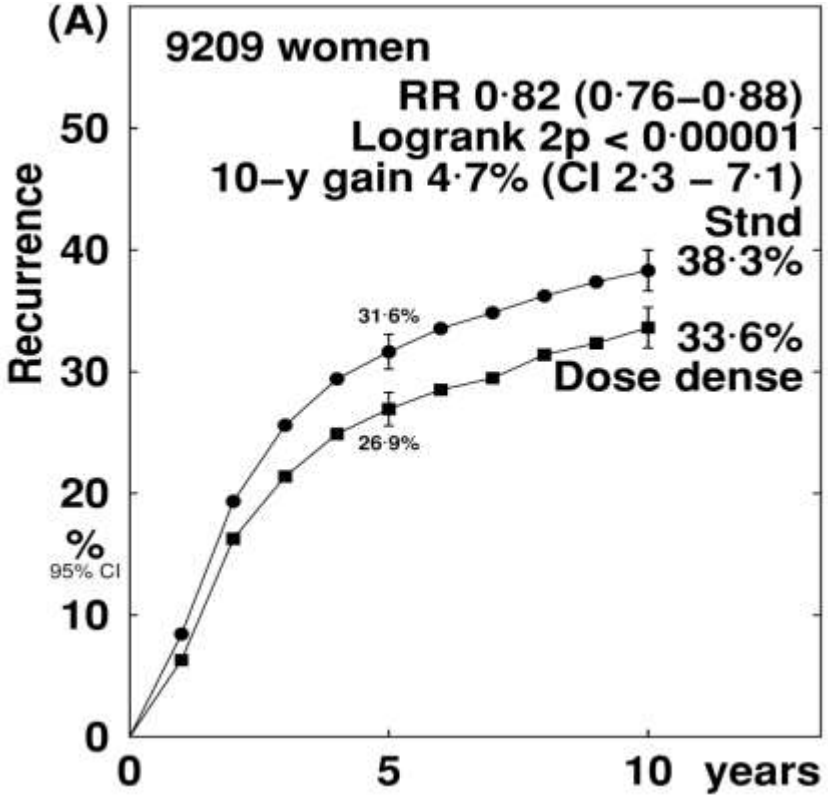


Denkert C et al, Lancet Oncol 2017;389:2430-42. Carey LA et al, Clin Cancer Res 2007;13(8):2329-34

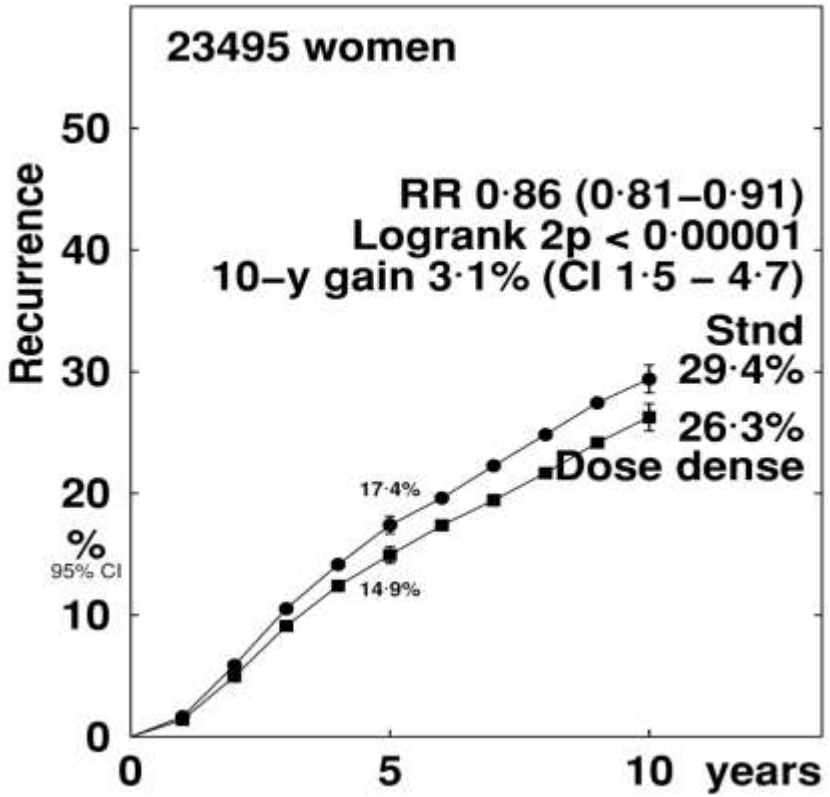
Therapeutic Implications: Dose-Dense CT

Pooled Analysis: Recurrence by ER Status

ER-Negative



ER-Positive



Gray R et al, SABCS 2017

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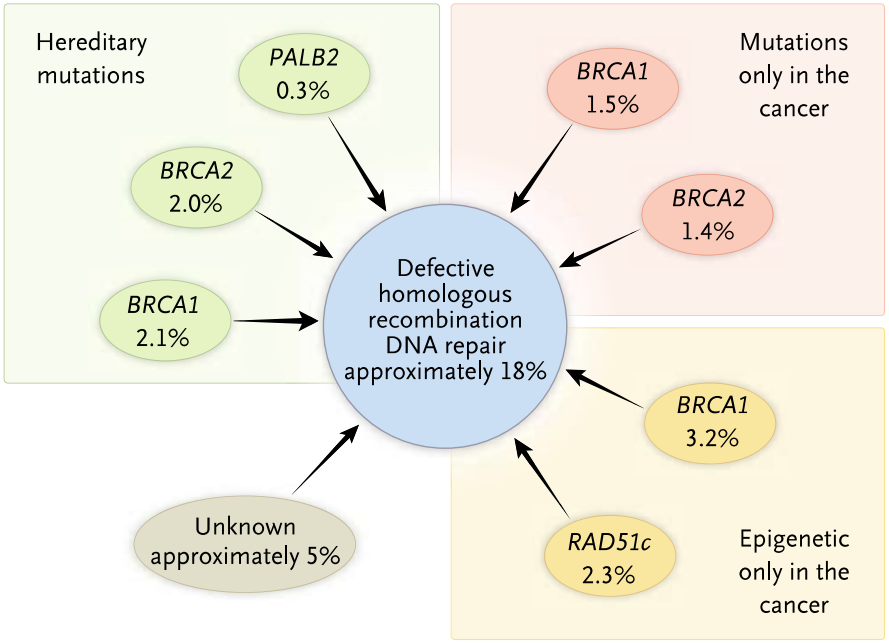
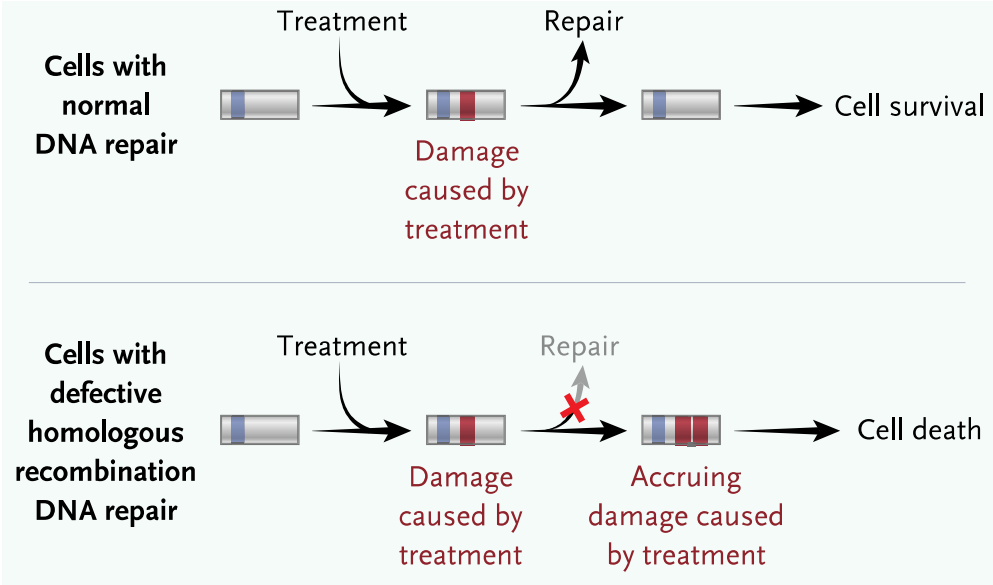
BRCAness/HRD/Genomic Scars





Turner NC. N Engl J Med 2017;377(25):2490-2

Therapeutic Implications: Platinum and PARPi

Platinum-based chemotherapy

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 1497–1508, 2018
doi:10.1093/annonc/mdy127
Published online 4 June 2018

REVIEW

Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis

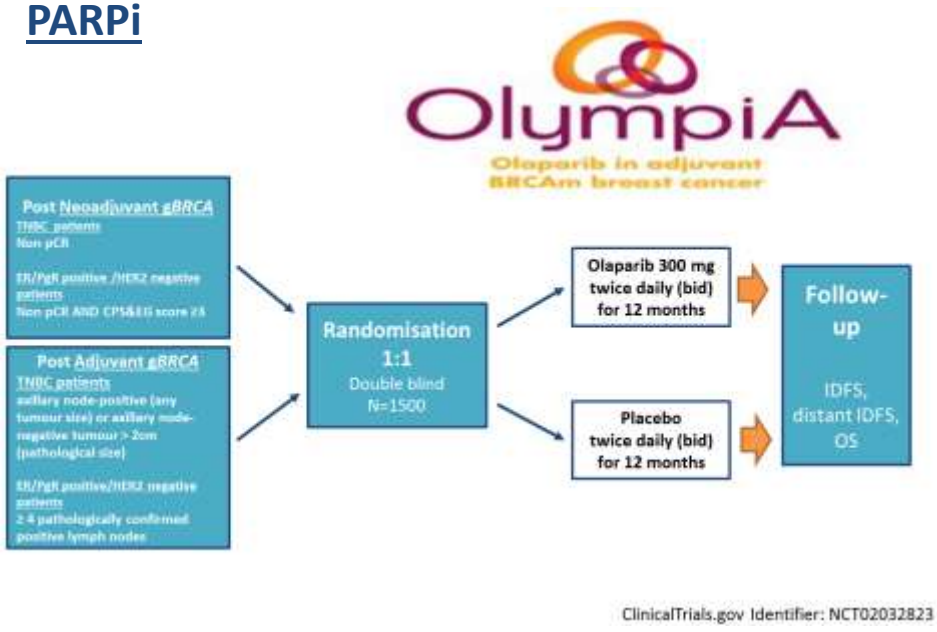
F. Poggio[1,2], M. Bruzzone[3], M. Ceppi[3], N. F. Pondé[1], G. La Valle[4], L. Del Mastro[5,6], E. de Azambuja[1] & M. Lambertini[1,7*]

nature medicine ARTICLES
https://doi.org/10.1038/s41591-018-0009-7

Carboplatin in *BRCA1/2*-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial

Andrew Tutt[1,2*], Holly Tovey[3], Maggie Chon U. Cheang[3], Sarah Kernaghan[3], Lucy Kilburn[3], Patrycja Gazinska[2], Julie Owen[4], Jacinta Abraham[5], Sophie Barrett[6], Peter Barrett-Lee[5], Robert Brown[7,8], Stephen Chan[9], Mitchell Dowsett[1,10], James M Flanagan[7], Lisa Fox[3], Anita Grigoriadis[2], Alexander Gutin[11], Catherine Harper-Wynne[12], Matthew Q. Hatton[13], Katherine A. Hoadley[14], Jyoti Parikh[15], Peter Parker[16,17], Charles M. Perou[14], Rebecca Roylance[18], Vandna Shah[2], Adam Shaw[19], Ian E. Smith[20], Kirsten M. Timms[11], Andrew M. Wardley[21], Gregory Wilson[22], Cheryl Gillett[4,23], Jerry S. Lanchbury[11], Alan Ashworth[24], Nazneen Rahman[25,26], Mark Harries[27], Paul Ellis[27], Sarah E. Pinder[4,23] and Judith M. Bliss[3]

PARPi



Open access Review

ESMO Open Cancer Horizons

Check for updates

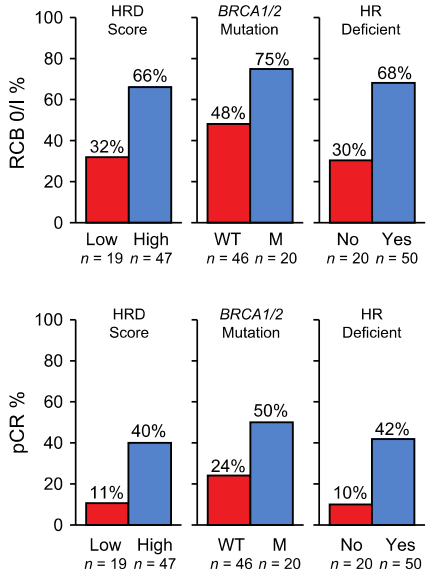
Single-agent PARP inhibitors for the treatment of patients with *BRCA*-mutated HER2-negative metastatic breast cancer: a systematic review and meta-analysis

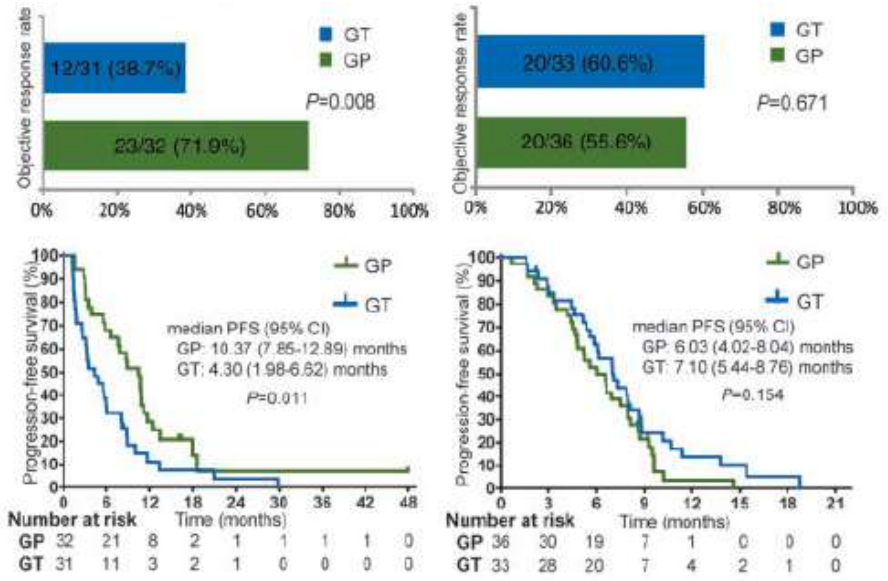
Francesca Poggio,[1,2] Marco Bruzzone,[3] Marcello Ceppi,[3] Benedetta Conte,[2] Samuel Martel,[4] Christian Maurer,[5] Marco Tagliamento,[2] Giulia Viglietti,[6] Lucia Del Mastro,[7] Evandro de Azambuja,[1] Matteo Lambertini[1,6]

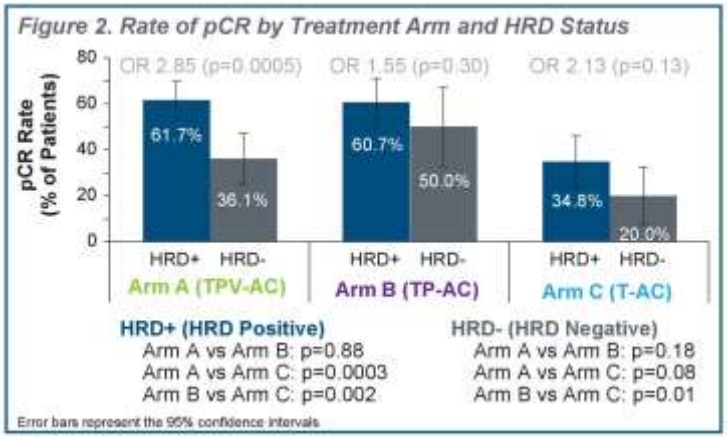
Poggio F et al, Ann Oncol 2018;29(7):1497-508

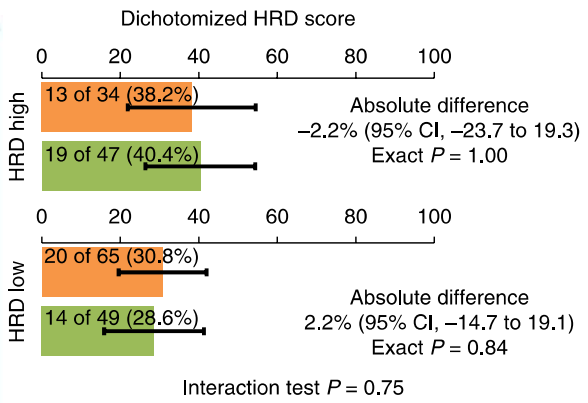
Poggio F et al, ESMO Open 2018;3(4):e000361. Tutt A et al, Nat Med 2018;24(5):628-37

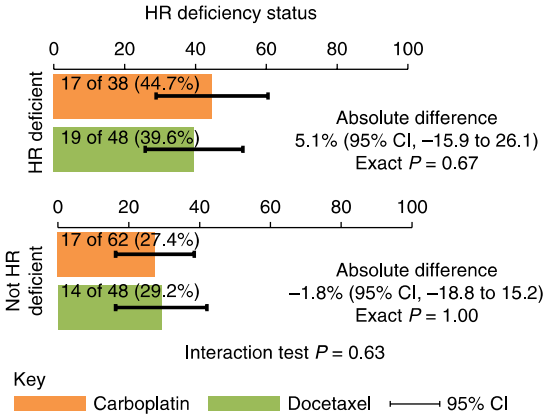
HRD Status to Predict Treatment Response: Conflicting Results !





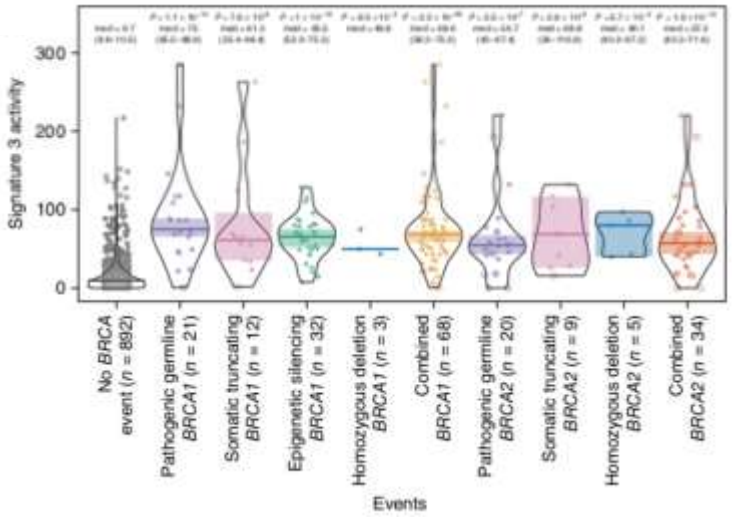


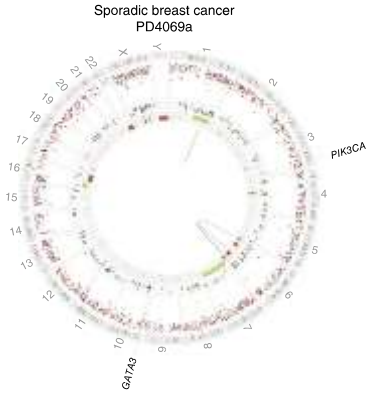


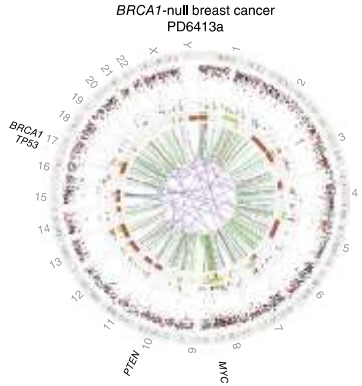


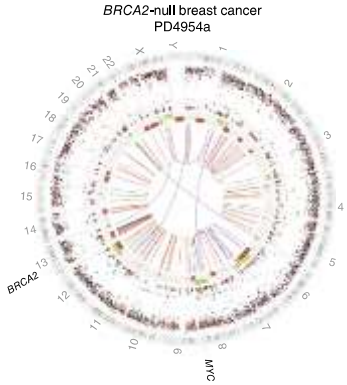
Telli ML et al, Clin Cancer Res 2016;22(15):3764-73. Zhang J et al, Ann Oncol 2018;29(8):1741-7
Telli ML et al, ASCO 2018. Tutt A et al, Nat Med 2018;24(5):628-37

Mutational Signatures of HRD: Promising Data

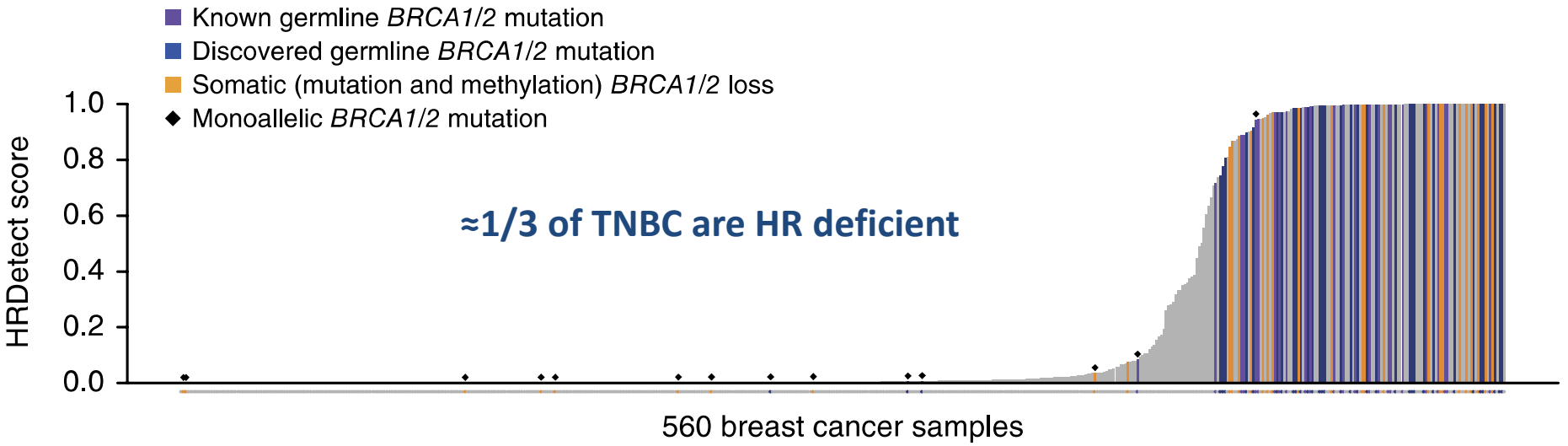








Combination of multiple HRD scars into HRDetect (somatic mutational signature)



Polak P et al, Nat Genet 2017;49(10):1476-86. Davies H et al, Nat Med 2017;23(4):517-25

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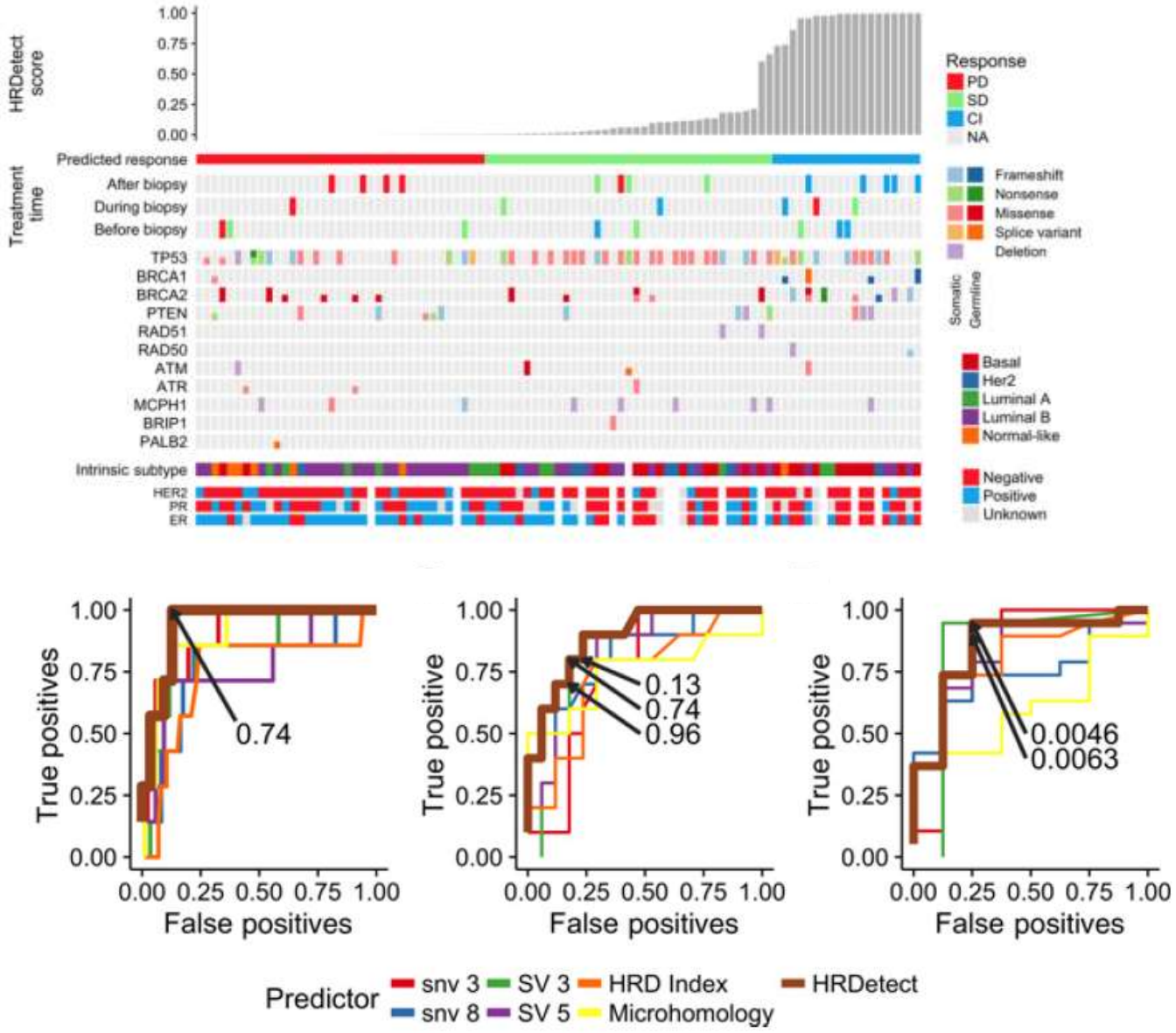

Zhao EY et al, Clin Cancer Res 2017;23(24):7521-30

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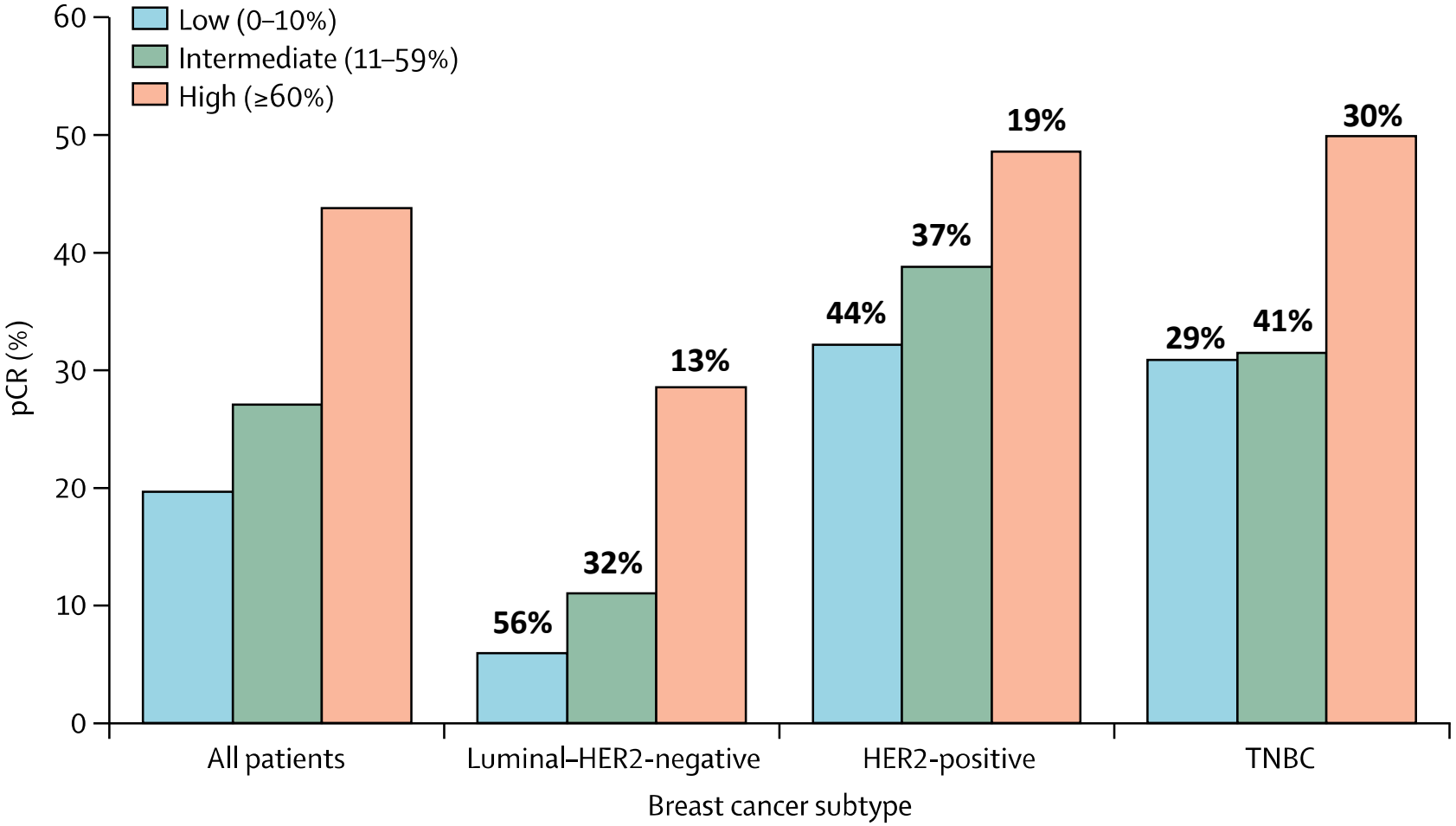
Increased Immune-Inflitrate: TILs



Denkert C et al, Lancet Oncol 2018;19(19):40-50

Therapeutic Implications: Available Data

Metastatic disease

Study	Phase	Checkpoint inhibitor	Combination	Population	Number of patients	PD-L1 selection	ORR (RECIST 1.1)
KEYNOTE-012[27]	1b	Pembrolizumab	Nil	TNBC; pre-treated	32	PD-L1 positive (expression in stroma or ≥1% tumour cells)	18.5%
KEYNOTE-086[29, 30]	2	Pembrolizumab	Nil	TNBC; Cohort A, pre-treated; Cohort B, first line	Cohort A: 170 Cohort B: 52	Cohort A, unselected; Cohort B, PD-L1 positive (combined positive score ≥1%)	Cohort A: 5% Cohort B: 23%
Emens et al.[31]	1a	Atezolizumab	Nil	TNBC; majority pre-treated	21	PD-L1 positive (≥5% of infiltrating immune cells)	24%
Schmid et al.[25]	1a	Atezolizumab	Nil	TNBC; first line or pre-treated	115	Unselected	10%
Tolaney et al.[32]	1b/2	Pembrolizumab	Eribulin	TNBC; first line or pre-treated	39	Unselected	33.3%
Adams et al.[34]	1b	Atezolizumab	Nab-paclitaxel	TNBC; first line or pre-treated	32	Unselected	42%
KEYNOTE-028[36]	1b	Pembrolizumab	Nil	ER+/HER2-; pre-treated	25	PD-L1 positive (expression in stroma or ≥1% tumour cells)	12%
JAVELIN[39]	1b	Avelumab	Nil	Unselected; pre-treated	168	Unselected	5.4%

Summary of recently presented studies of anti-PD1/PD-L1 therapy in metastatic breast cancer. *ORR* objective response rate, *TNBC* triple-negative breast cancer

Early disease

Study	Phase	Checkpoint inhibitor	Chemotherapy	Population	No. of patients	pCR (ypT0/is and ypN0)
I-SPY 2[43]	2	Pembrolizumab	Paclitaxel or paclitaxel/pembro followed by doxorubicin/cyclophosphamide	TNBC; HR+/HER2-; PD-L1 unselected; tumour size ≥ 2.5 cm; mammaprint high risk (nodal involvement in 37.7% pembro, 43.9% control)	69 pembro, 180 control	TNBC: 60% pembro vs. 20% control[a] HR+/HER2-: 34% pembro vs. 13% control[a]
KEYNOTE-173[41]	1b	Pembrolizumab	A: pembro followed by pembro + nab-paclitaxel followed by pembro + doxorubicin/cyclophosphamide. B: pembro followed by pembro + nab-paclitaxel + carboplatin followed by pembro + doxorubicin/cyclophosphamide	TNBC; PD-L1 unselected; locally advanced (primary tumour stage ≥T2 in 90%, nodal involvement in 75%)	20	Cohort A, 60%; Cohort B, 90%
Pusztai et al.[42]	1	MEDI4736	MEDI4736 + nab-paclitaxel followed by dose dense doxorubicin/cyclophosphamide	TNBC; PD-L1 unselected; stage I-III (primary tumour stage ≥T2 in 57%, nodal involvement in 57%)	7	71.4%

Recently presented studies of anti-PD1/PD-L1 agents in neoadjuvant breast cancer therapy. *pCR* pathological complete response. [a]Estimated pCR

Wein L et al, Br J Cancer 2018;119(1):4-11

Therapeutic Implications: Ongoing Trials

	Indication	Phase	Design
NCT02513472	Metastatic TNBC, (first-line to third-line)	Phase 1b/2	Eribulin plus pembrolizumab (single-arm study)
TONIC (NCT02499367)	Metastatic TNBC (second-line to fourth-line)	Phase 2	Nivolumab alone *vs* nivolumab plus doxorubicin *vs* nivolumab plus cyclophosphamide *vs* nivolumab plus radiation *vs* nivolumab plus cisplatin (five arms, open-label trial)
KEYNOTE-086 (NCT02447003)	Metastatic TNBC (all lines)	Phase 2	Pembrolizumab (single-arm study)
KEYNOTE-355 (NCT02819518)	..	..	..
Part 1	Locally recurrent inoperable or metastatic TNBC (first-line)	Phase 3	Pembrolizumab plus nab-paclitaxel *vs* pembrolizumab plus paclitaxel *vs* pembrolizumab plus gemcitabine and carboplatin
Part 2	Locally recurrent inoperable or metastatic TNBC (first-line)	Phase 3	Pembrolizumab plus chemotherapy *vs* pembrolizumab plus placebo
KEYNOTE-119 (NCT02555657)	Metastatic TNBC (second-line or third-line)	Phase 3	Pembrolizumab *vs* physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine)
IMpassion130 (NCT02425891)	Metastatic TNBC (first-line)	Phase 3	Nab-paclitaxel plus atezolizumab *vs* nab-paclitaxel plus placebo
NCT02489448	Early TNBC (neoadjuvant)	Phase 1/2	MEDI4736 plus weekly nab-paclitaxel followed by dose-dense doxorubicin and cyclophosphamide (single-arm study)
NCT02530489	Early TNBC (neoadjuvant)	Phase 2	Atezolizumab plus nab-paclitaxel
NeoTRIPaPDL1 (NCT02620280)	Early TNBC (neoadjuvant)	Phase 3	Carboplatin plus nab-paclitaxel plus atezolizumab *vs* carboplatin plus nab-paclitaxel (open-label study)
GeparNuevo (NCT02685059)	Early TNBC (neoadjuvant)	Phase 2	Epirubicin plus cyclophosphamide plus nab-paclitaxel plus durvalumab (MEDI4736) *vs* epirubicin plus cyclophosphamide plus nab-paclitaxel plus placebo

Media Release

Roche

Basel, 02 July 2018

Phase III IMpassion130 study showed Roche's Tecentriq plus Abraxane significantly reduced the risk of disease worsening or death in people with metastatic triple negative breast cancer

IMPASSION 130
NCT02425891

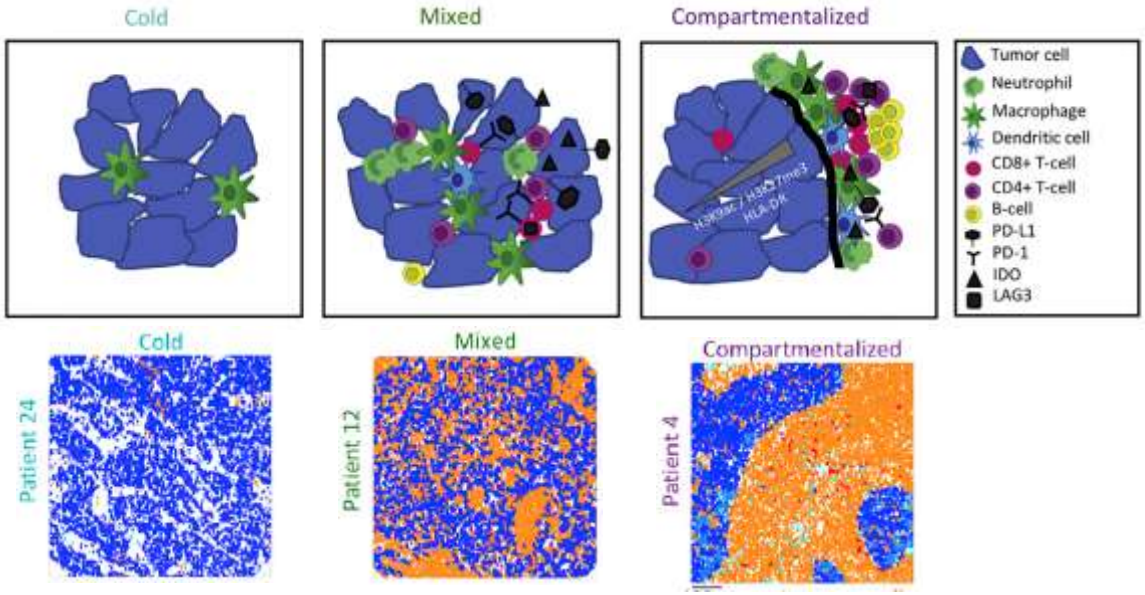
TNBC
1L

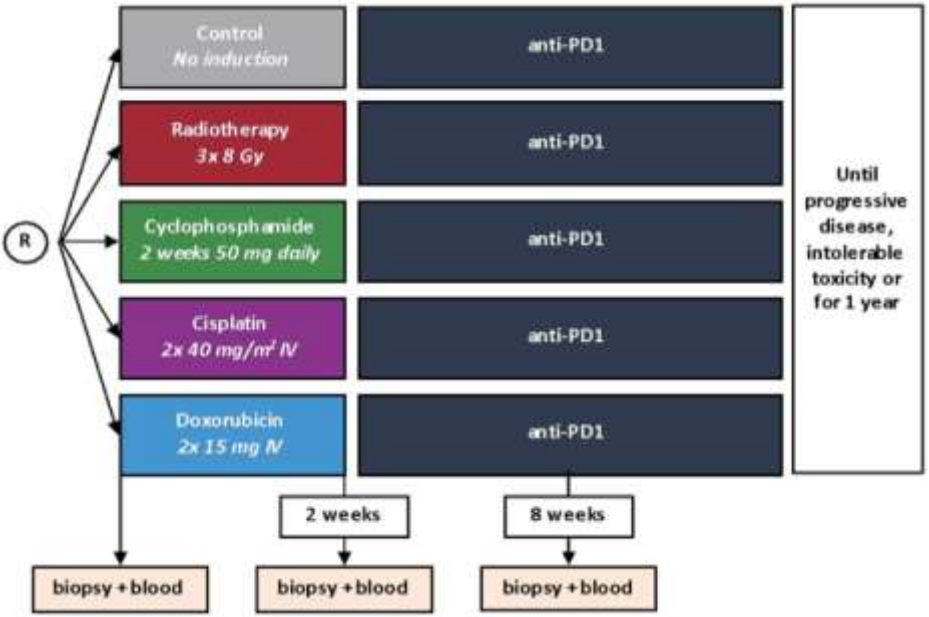
Nab-Paclitaxel + Atezolizumab

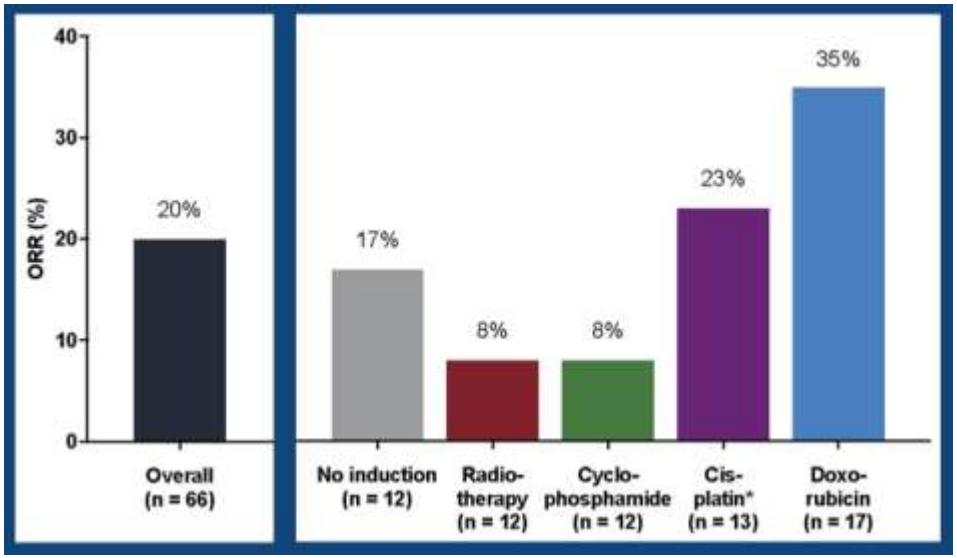
Nab-Paclitaxel + placebo

Denkert C et al, Lancet Oncol 2017;389:2430-42

Modulating the Immune-Infiltrate







Keren L et al, Cell 2018;174(6):1373-87. Kok M et al, ASCO 2018

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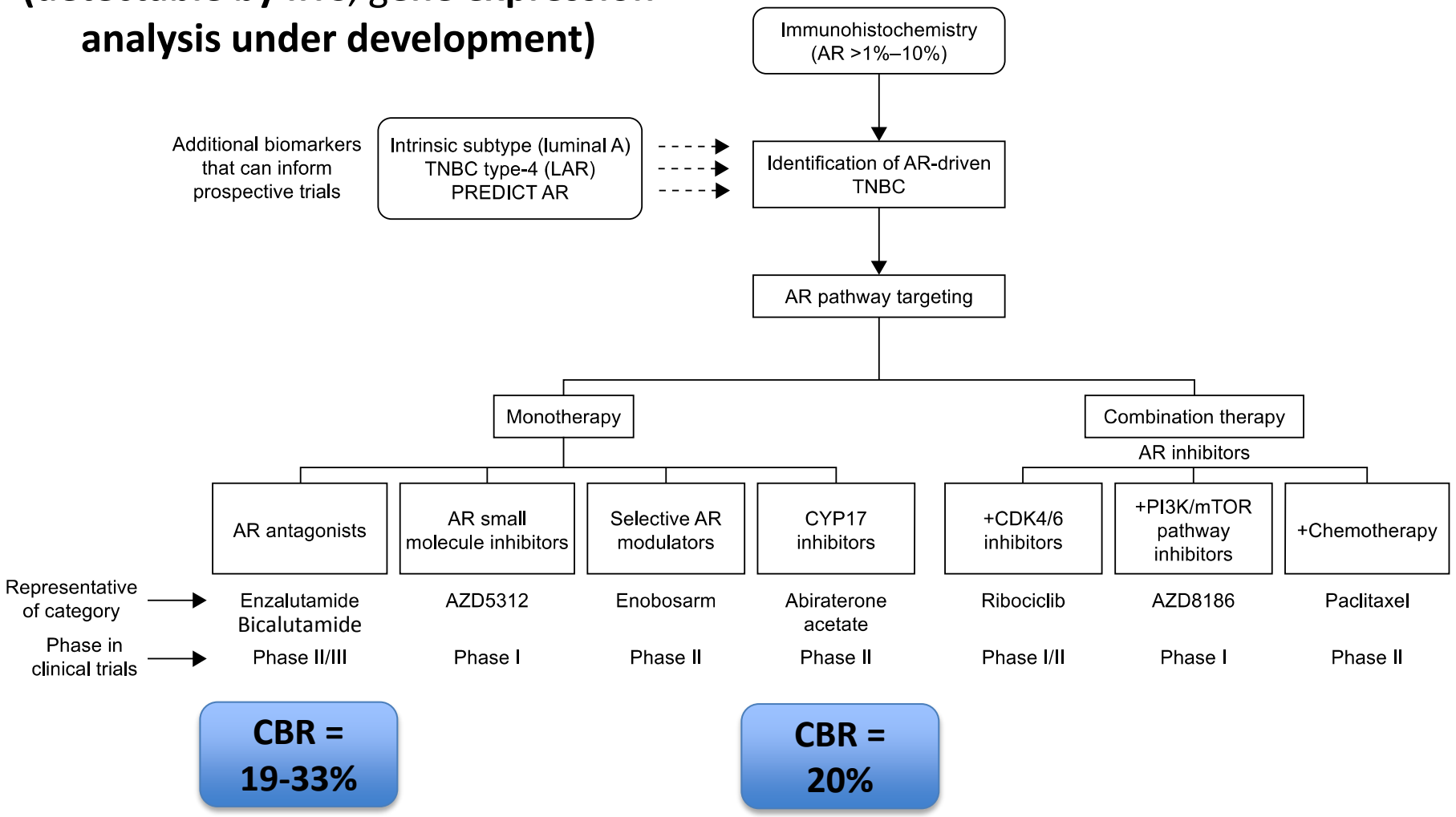
Androgen Receptors

AR is present in 12% to 38% of TNBC (detectable by IHC; gene expression analysis under development)

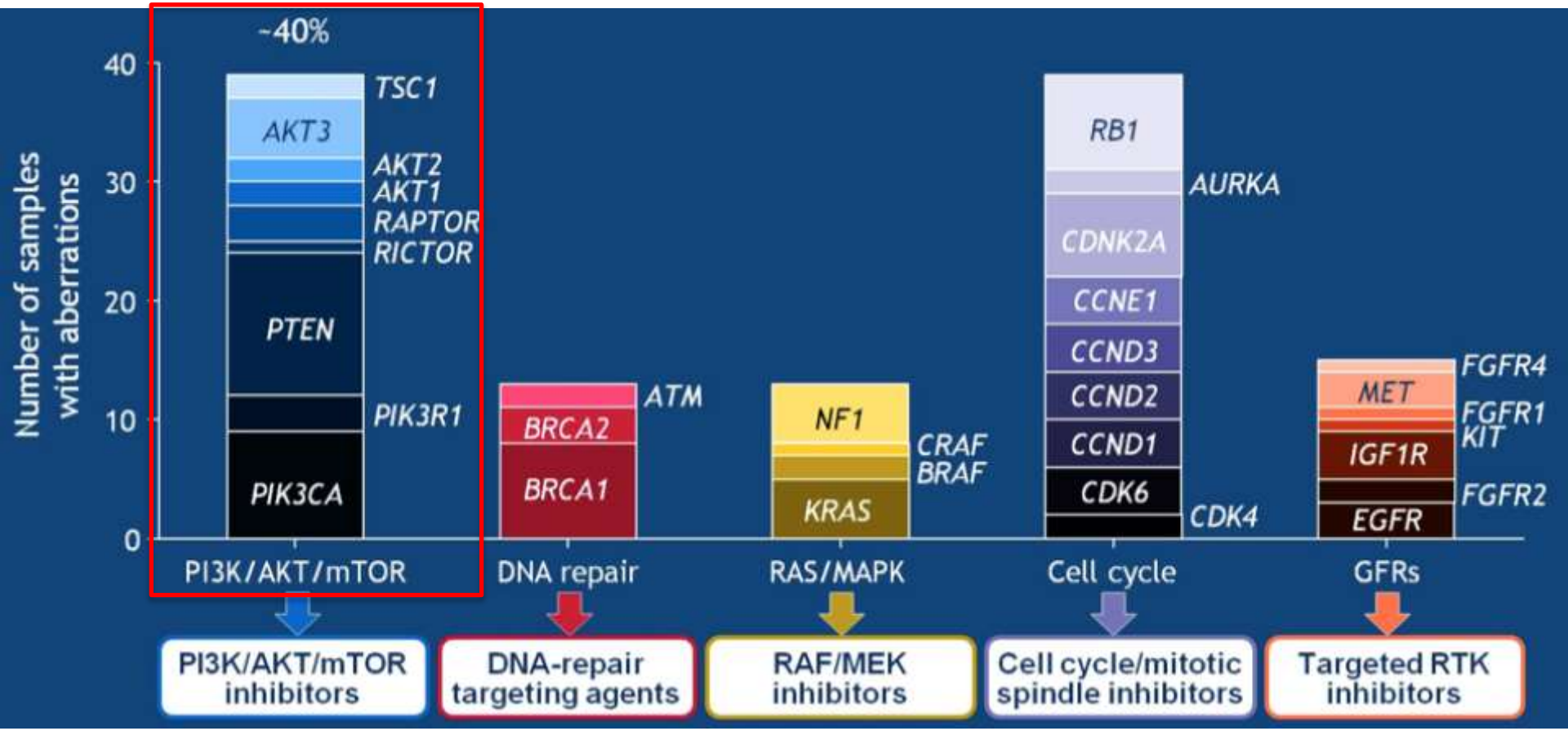


Gucalp A et al, Cancer Res 2013; 19:5505-12. Bonnefoi H et al, Ann Oncol 2016;27:812-8
Mina A et al, Onco Targets Ther 2017;10:4675-85. Traina TA et al, J Clin Oncol 2018;36(9):884-90

Plan of the Talk

- Introduction
- **Main biological features with clinical relevance**
    1. High cell proliferation
    2. BRCAness/HRD/genomic scars
    3. Increased immune-infiltrate
    4. Androgen receptors
    5. **Other potential targets**
- Conclusions

Other Potential Targets: Genomic Aberrations



Balko JM et al, Cancer Discov 2014;4:232-45. Dent R, ASCO 2018

Other Potential Targets: Genomic Aberrations

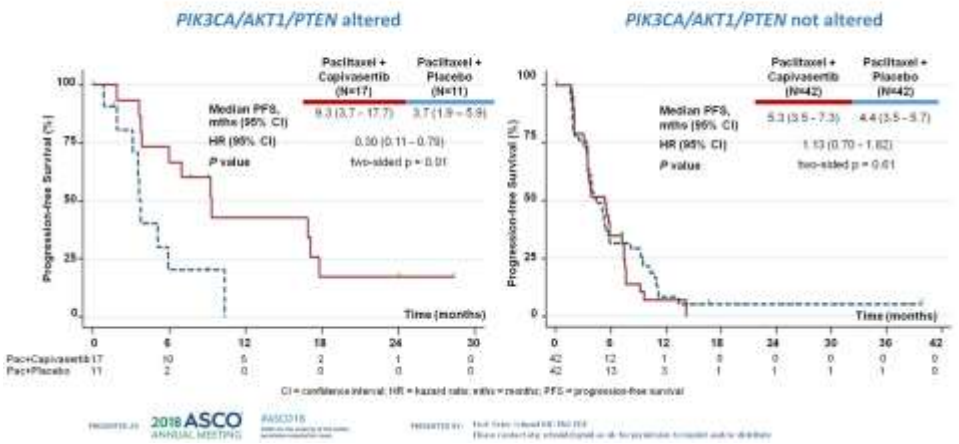
AZD5363 plus Paclitaxel versus Placebo plus Paclitaxel as first-line therapy for metastatic triple-negative breast cancer (PAKT): A randomised, double-blind, placebo-controlled, phase II trial.

Peter Schmid[1], Jacinta Abraham[2], Stephen Chan[3], Duncan Wheatley[4], Adrian Murray Brunt[5], Gia Nemsadze[6], Richard Baird[7], Yeon Hee Park[8], Peter Hall[9], Timothy Perren[10], Rob Stein[11], Mangel László[12], Jean-Marc Ferrero[13], Melissa Phillips[14], John Conibear[14], Javier Cortes[15], Shah-Jalal Sarker[1], Aaron Prendergast[1], Hayley Cartwright[1], Kelly Mousa[1], Nick Turner[16]

[1]Barts Cancer Institute, St Bartholomew's Hospital, Queen Mary University of London, UK; [2]Velindre NHS Trust, UK; [3]Nottingham University Hospitals NHS Trust, UK; [4]Royal Cornwall Hospitals NHS Trust, UK; [5]University Hospitals of North Midlands NHS Trust, UK; [6]Institute of Clinical Oncology, Georgia; [7]Cambridge University Hospitals NHS Foundation Trust, UK; [8]Samsung Medical Centre, Republic of Korea; [9]NHS Lothian, UK; [10]Leeds Teaching Hospitals NHS Trust, UK; [11]University College London Hospitals NHS Foundation Trust, UK; [12]Medical University of Pécs, Hungary; [13]Centre Antoine Lacassagne, France; [14]Barts Health NHS Trust, UK; [15]Ramon Y Cajal University Hospital, Spain; [16]Royal Marsden NHS Foundation Trust, UK

Queen Mary · ECMC · Cancer Research UK · Barts Health NHS

PFS by tumour *PIK3CA/AKT1/PTEN* status

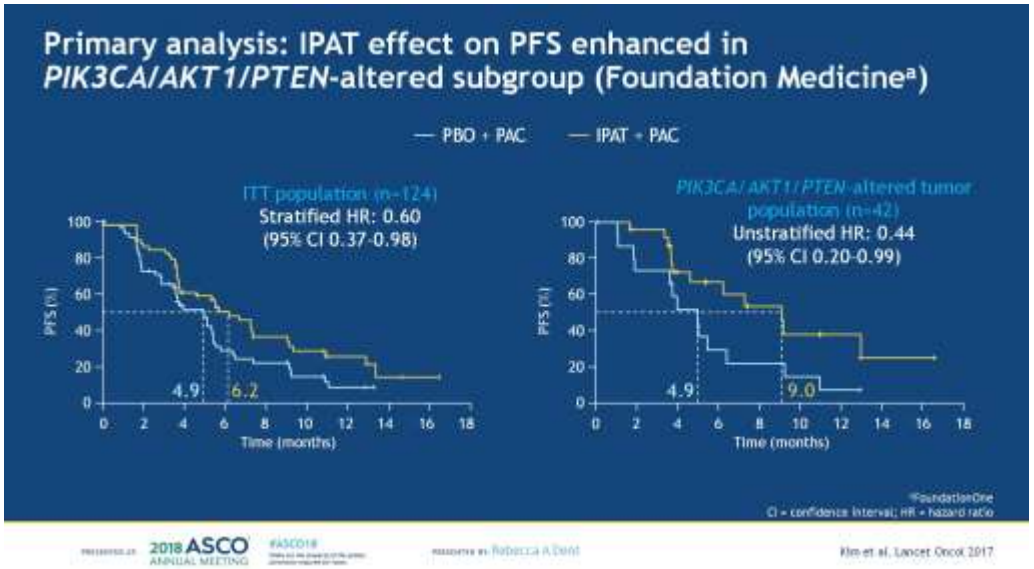


Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

Sung-Bae Kim, Rebecca Dent*, Seock-Ah Im, Marc Espié, Sibel Blau, Antoinette R Tan, Steven J Isakoff, Mafalda Oliveira, Cristina Saura, Matthew J Wongchenko, Amy V Kapp, Wai Y Chan, Stina M Singel, Daniel J Maslyar, José Baselga, on behalf of the LOTUS investigators†*

Overall survival update of the double-blind placebo-controlled randomized phase 2 LOTUS trial of first-line ipatasertib + paclitaxel for locally advanced/metastatic triple-negative breast cancer

Primary analysis: IPAT effect on PFS enhanced in *PIK3CA/AKT1/PTEN*-altered subgroup (Foundation Medicine[a])



Schmid P et al, ASCO 2018. Kim SB et al, Lancet Oncol 2017;18(10):1360-72. Dent R, ASCO 2018

Other Potential Targets: Epithelial Antigens

Surface Antigen	Antibody-Drug Conjugate	Status of Drug Development: Status	Trial Acronym	Trial No.
Trop-2	Sacituzumab govitecan (IMMU-132)	Phase I/II trial reported[51]		NCT01631552
		Phase III trial recruiting; FDA breakthrough therapy and fast-track designation	ASCENT	NCT02574455
Glycoprotein nonmetastatic B (gpNMB)	Glembatumumab vedotin (CDX-011)	Phase I/II trial reported[51a]		NCT00704158
		Phase II trial reported[52]	EMERGE	NCT01156753
		Phase IIb trial active, not recruiting	METRIC	NCT01997333
LIV-1	Ladiratuzumab vedotin (SGN-LIV1A)	Interim results of phase I trial reported		NCT01969643
		Phase Ib/2 trial in combination with pembrolizumab planned		NCT03310957
Mesothelin	Anetumab ravtansine (BAY94-9343)	Phase I trial (MTD) reported		NCT01439152
		Phase Ib multi-indication trial including TNBC recruiting		NCT03102320
Carbonic anhydrase 6 (CA6)	SAR566658	Phase I trial (MTD) reported		NCT01156870
		Phase II trial recruiting		NCT02984683
Protein tyrosine kinase 7 (PTK7)	PF-06647020	Interim results of phase I trial reported		NCT02222922
		Phase I trial in combination with gedatolisib planned		NCT03243331

Chan JJ et al, J Oncol Pract 2018;14(5):281-9

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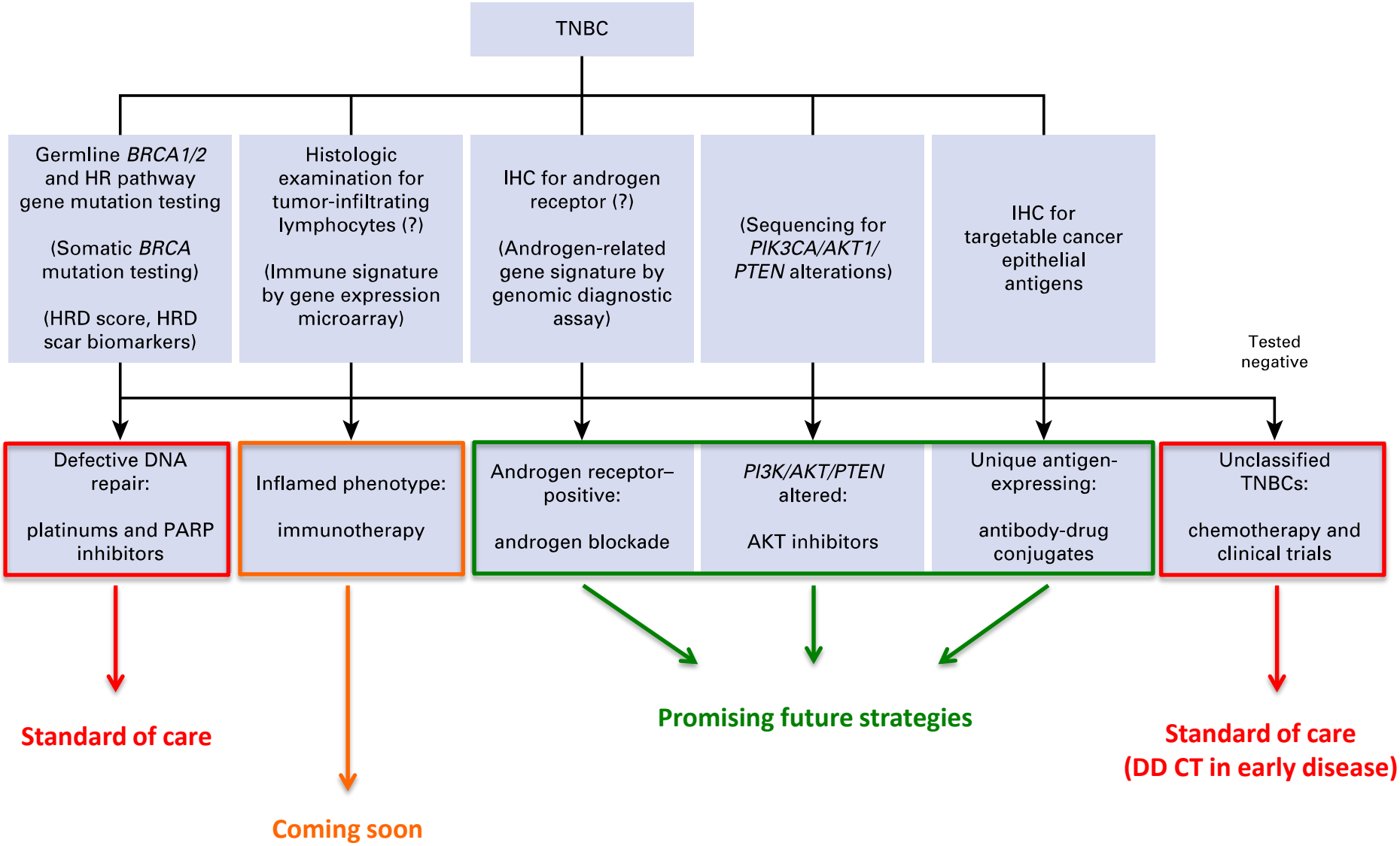
Conclusions



Chan JJ et al, J Oncol Pract 2018;14(5):281-9