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Immunotherapy and Multiplex Genomic Evaluation in Triple Negative Breast Cancer

Disclosures

Advisory Committee and Consulting Agreements	Amgen Inc, AstraZeneca Pharmaceuticals LP, Celgene Corporation, Eisai Inc, Genentech BioOncology, Lilly, Merck, Novartis, Pfizer Inc, Roche Laboratories Inc, Sanofi Genzyme, Takeda Oncology
Contracted Research	Merck

Case presentation: Dr Ma

69-year-old woman

- 2015: Metastatic TNBC (ER was 2%) → AC x 1 (toxicity)
  - Positive for AR; started BRE203 trial with orteronel 300 mg BID x 5 months → PD → capecitabine
- 2017: Androgen deprivation trial, PD on first restaging scan → *nab* paclitaxel → PD → eribulin
- FoundationOne testing showed mutations in HER2, DNMT3A, p53, ZNF, SF3B1

Case presentation: Dr Agrawal

- **36-year-old woman with clinical Stage II ER/PR-negative, HER2-negative BC**
  - Neoadjuvant therapy: Weekly paclitaxel/carboplatin followed by dose-dense AC + pegfilgrastim
  - Complete clinical response
- Lumpectomy, with bilateral nipple-sparing mastectomy
  - Residual disease, with 10/13 nodes involved
- Underwent radiation therapy
- Discussion of adjuvant capecitabine

Case presentation: Dr Hart

51-year-old woman

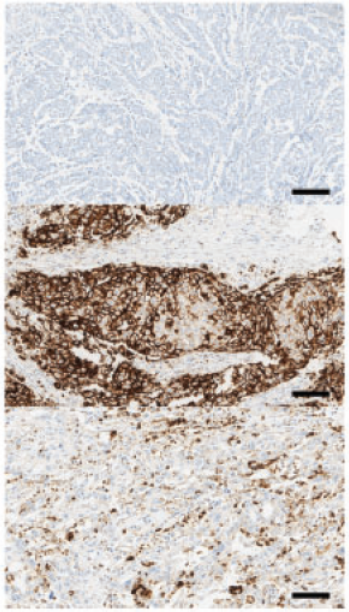
- Metastatic TNBC with liver involvement
- 2016: *Nab* paclitaxel ± atezolizumab trial (unblinded: Received *nab* paclitaxel alone) x 4 months → PD → AC x 4 then palliative MRM
- 2017: Eribulin for 6 months → CR maintained off therapy; patient feels well except mild neuropathy

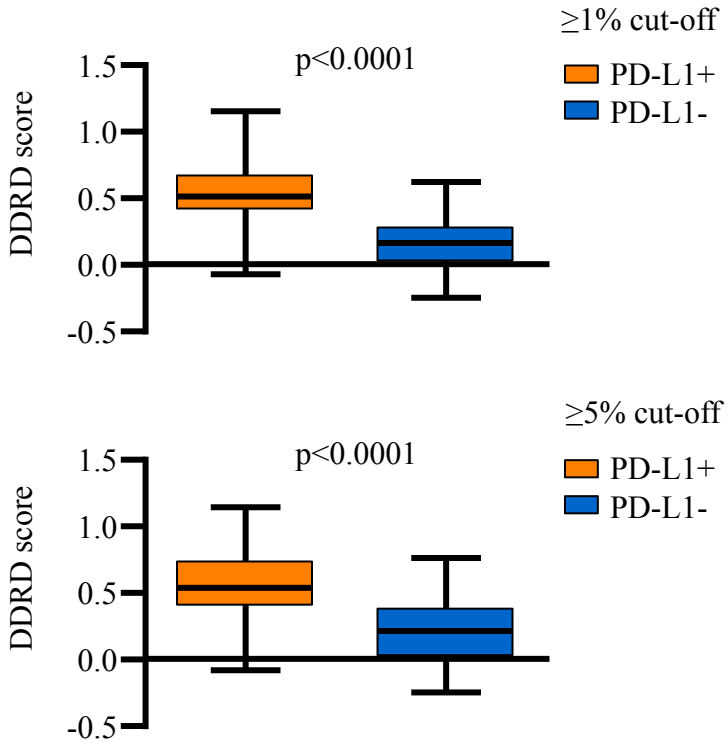
Expression of PD-L1 is associated with tumours deficient in DNA damage response

DDRD-negative

DDRD-positive tumour (CD8+ and CD4+ lymphocytes by IHC)

DDRD-positive immune (CD8+ and CD4+ lymphocytes by IHC)

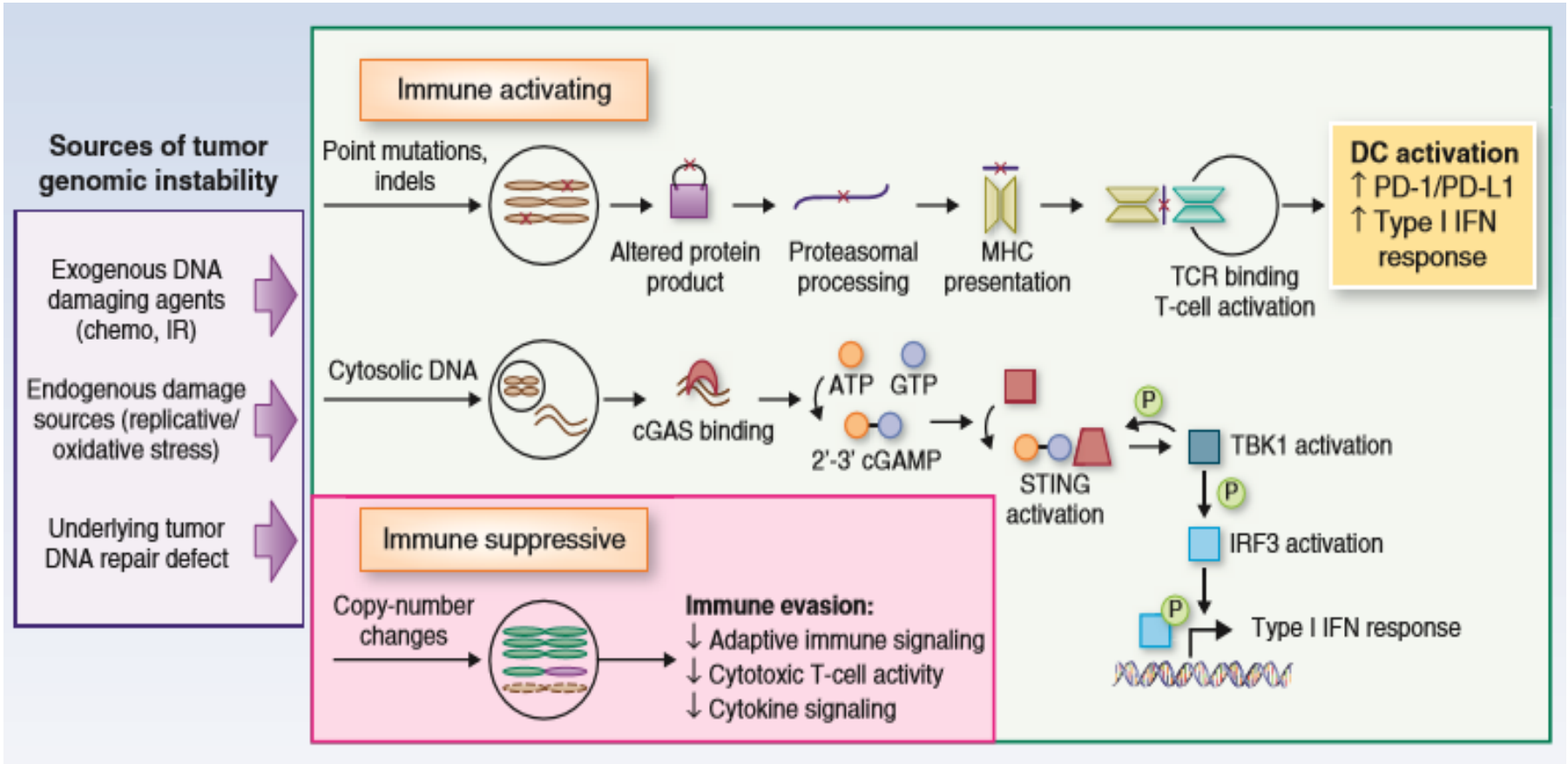




DDRD, DNA-damage response deficient; IHC, immunohistochemistry; PD-L1, programmed death-ligand 1

Parkes, et al. J Natl Cancer Inst 2017

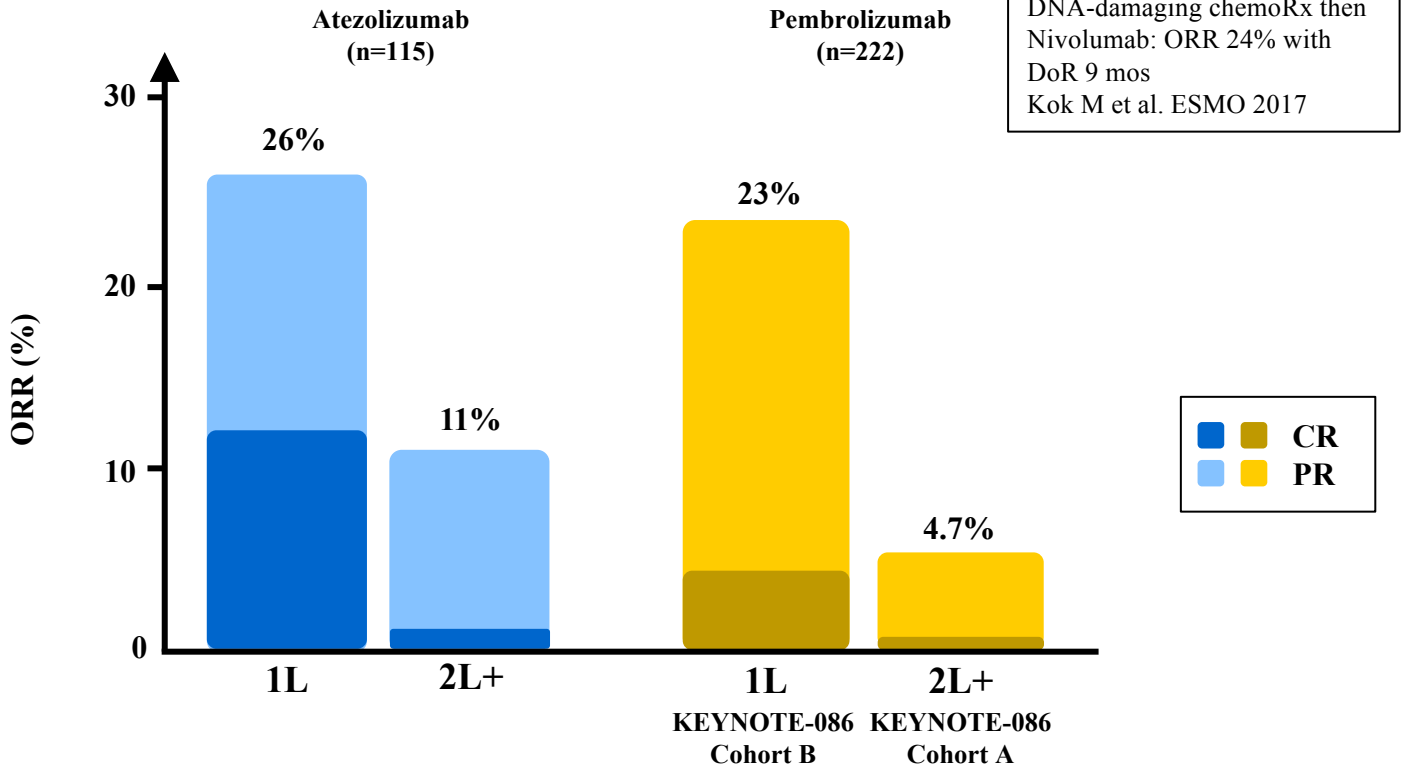
The Enlarging Intersection of DNA Repair Deficiency and Immunotherapy



Mouw KW, et al. Cancer Discovery, 2017

Response to single-agent anti-PD-L1/PD-1

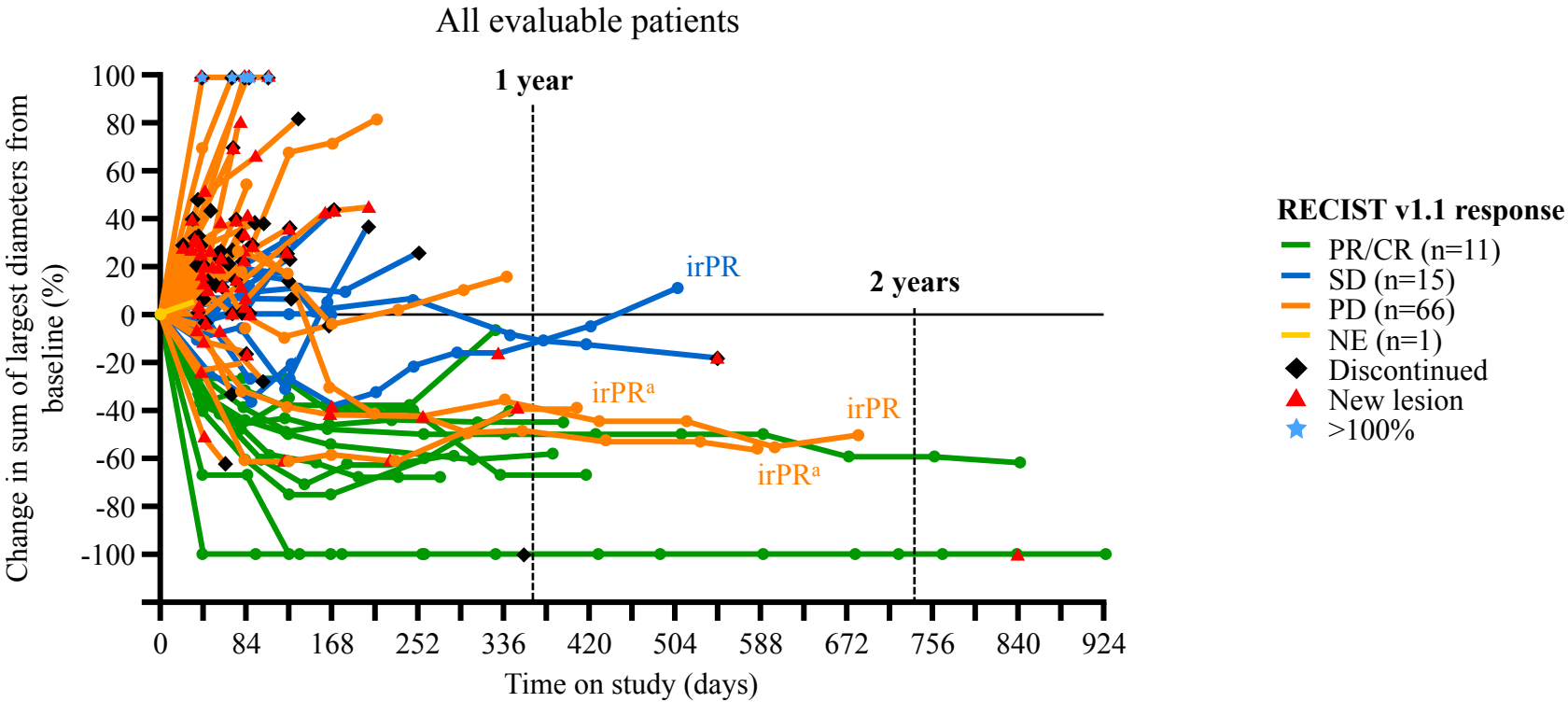
TONIC Phase II Trial
MetTNBC median 1 prior MBC regimen – priming with RT or DNA-damaging chemoRx then Nivolumab: ORR 24% with DoR 9 mos
Kok M et al. ESMO 2017



1L, first line; 2L, second line; CR, complete response; ORR, objective response rate; PD-1, programmed death -1; PD-L1, programmed death-ligand 1; PR, partial response

Schmid, et al. AACR 2017; Adams, et al ASCO 2017

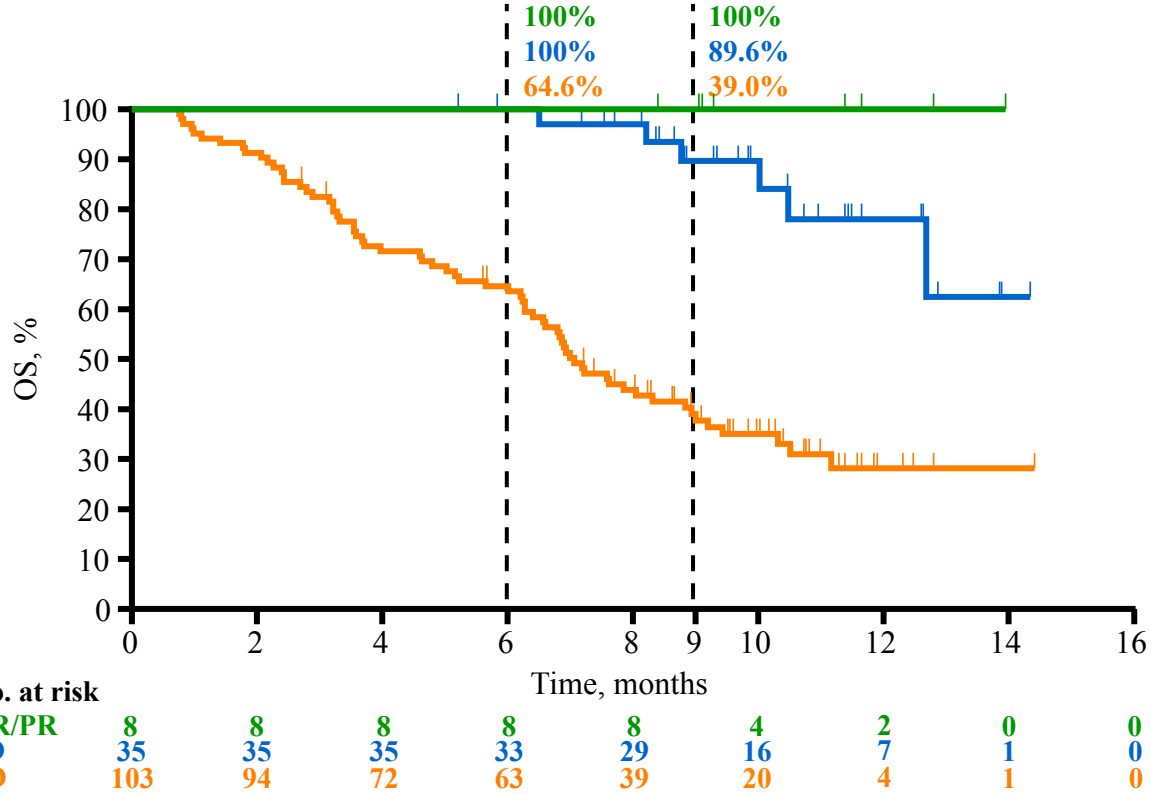
Durable responses with anti-PD-L1 mAb atezolizumab



Phase Ia atezolizumab in mTNBC. [a]Re-treatment period not plotted.
CR, complete response; irPR, PR per irRC; irRC, immune-related response criteria; NE, not evaluable; ORR, objective response rate; PR, partial response; PD, progressive disease; PD-L1, programmed death-ligand 1; SD, stable disease

Schmid, et al. AACR 2017

OS by best response to anti-PD-1 pembrolizumab in 2L+ metTNBC



	Events/ pts, n	Median (95% CI)
CR or PR	0/8	Not reached (NR–NR)
SD	6/35	Not reached (12.7–NR)
PD	66/103	7.1 mo (6.3–8.8)

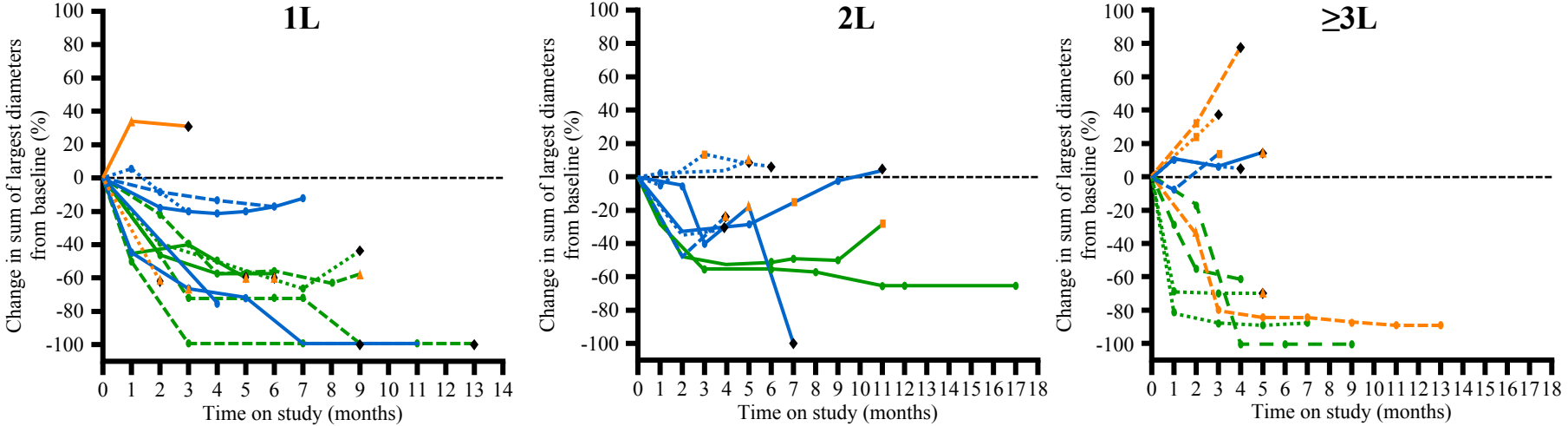
CR/PR
SD
PD

2L+ pembrolizumab

CR, complete response; NR, not reportable; OS, overall survival; PR, partial response; PD, progressive disease; PD-1, programmed death-1; SD, stable disease

Adams, et al ASCO 2017

Nab-paclitaxel + anti-PD-L1 (atezolizumab)



	1L n=13	2L n=9*	3L+ n=10†
Confirmed ORR (95% CI)*	46% (19–75)	22% (3–60)	40% (12–74)
SD	39%	67%	30%
PD	15%	0	30%
DCR	85%	89%	70%

Best confirmed response

PR/CR	SD	PD
IC1/2/3	IC1/2/3	IC1/2/3
IC0	IC0	IC0
Unknown	Unknown	Unknown

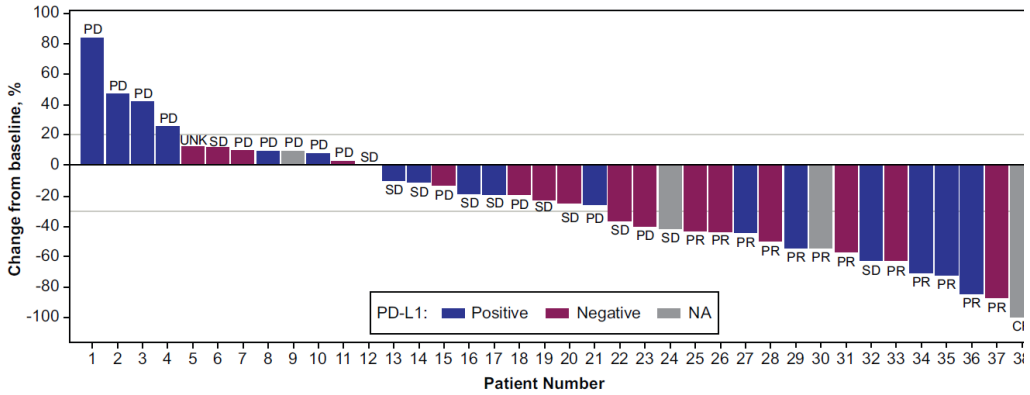
- ◆ Discontinued atezolizumab
- ▲ New lesion
- ■ Progressive disease

*Investigator-assessed confirmed response rate. †One tissue missing/unevaluable.1L, first line; 2L, second line; 3L, third line; CI, confidence interval; CR, complete response; DCR, disease control rate; IC, tumour-infiltrating immune cell; ORR, objective response rate; PD-L1, programmed death-ligand 1; PR, partial response; PD, progressive disease; SD, stable disease

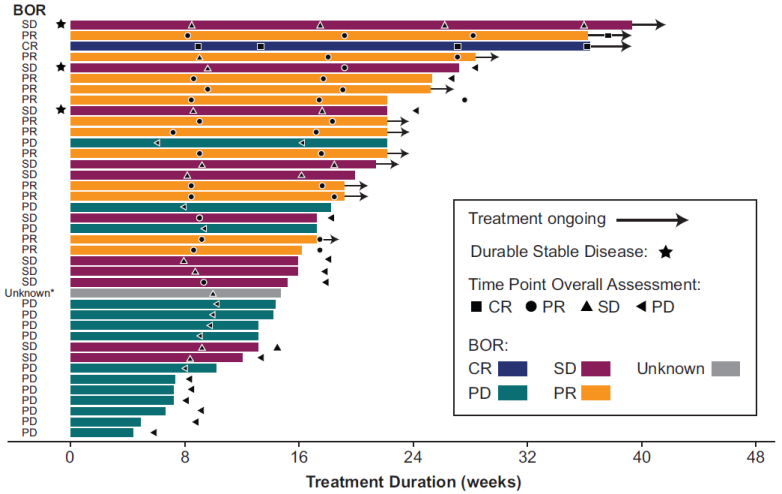
Adams, et al. ASCO 2016

Eribulin + anti-PD-1 (pembrolizumab)

Percentage change in total sum of target lesion diameters from baseline



Duration of treatment



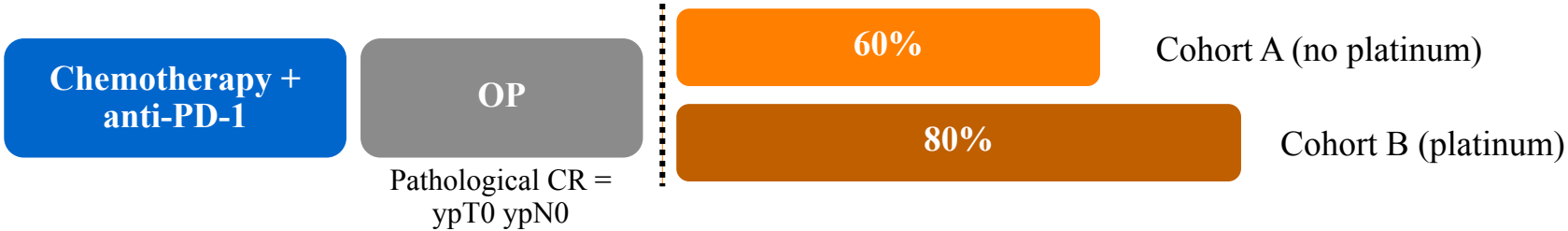
	All	1L (n=17)	2L/3L (n=18)	PD-L1+ (n=17)	PD-L1− (n=18)
ORR	34.4%	41.2%	27.3%	29.4%	33.3%
CBR	40.6%	47.1%	36.4%	35.8%	44.4%

1L, first line; 2L/3L, second/third line; BOR, best overall response; CBR, clinical benefit rate; CR, complete response; IC, tumour-infiltrating immune cell; ORR, objective response rate; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PR, partial response; PD, progressive disease; SD, stable disease

Tolaney, et al. SABCS 2016

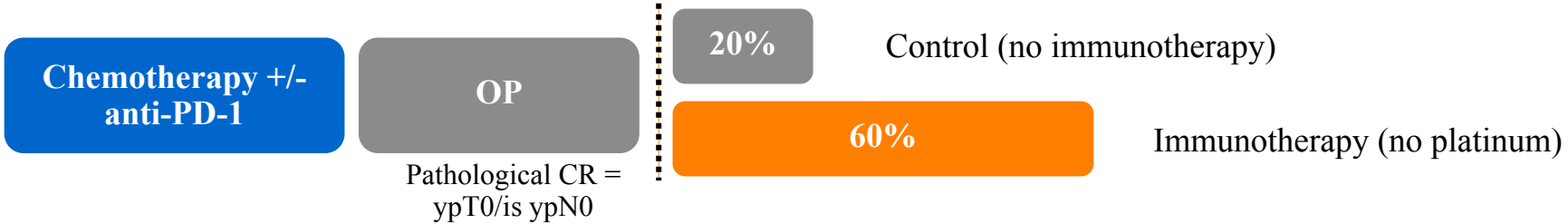
Neoadjuvant chemotherapy + anti-PD-L1/anti-PD-1

KEYNOTE-173 phase 1/2 trial



Paclitaxel Q1W x12 ± carboplatin Q1W x12 + pembrolizumab Q3W x4 → AC Q3W x4 + pembrolizumab Q3W x4

I-SPY 2 trial



Paclitaxel Q1W x12 + pembrolizumab Q3W x4 → AC Q3W x4

AC, doxorubicin + cyclophosphamide; CR, complete response; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; Q1W, every week; Q3W, every 3 weeks; ypT0/Tis ypN0, no invasive residual in breast or nodes - noninvasive breast residuals allowed; ypT0 ypN0, no invasive or noninvasive residual in breast or nodes

Schmid, et al. ASCO 2017;
Nanda, et al. ASCO 2017

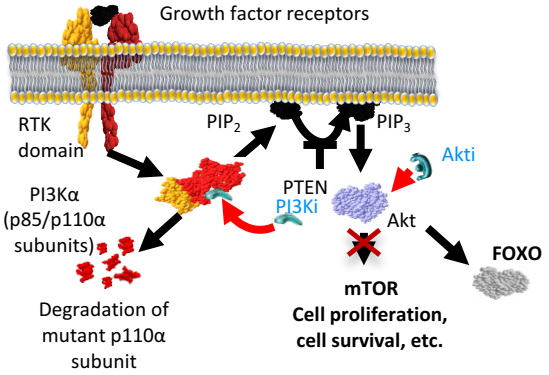
Multiplex Genomic Evaluation in TNBC: Evolving Clinical Utility

Targeting the PI3K pathway through AKT

PI3Ki, e.g. alpelisib, taselisib

- Targets the ATP-binding pocket in the p110α subunit of PI3K[4]
- Uniquely induces degradation of the mutant p110α subunit[5]
- Maintains PI3K pathway suppression

PI3K/Akt pathway activation frequently occurs in TNBC[1–3]



Akti, e.g. AZD5363, ipatasertib

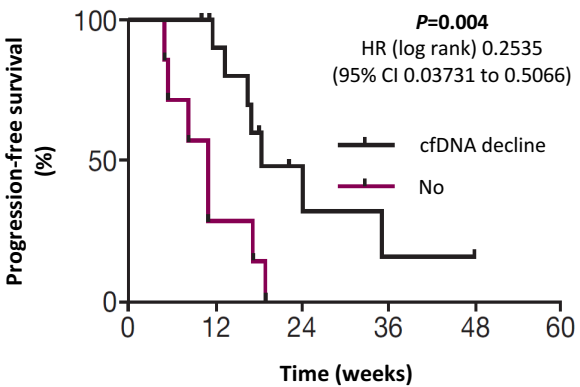
- Selectively binds all three isoforms of Akt[6]
- Inhibits signalling via mTOR and promotes FOXO-dependent apoptosis[7]
- Blocks the pathway even when activated downstream of PI3K

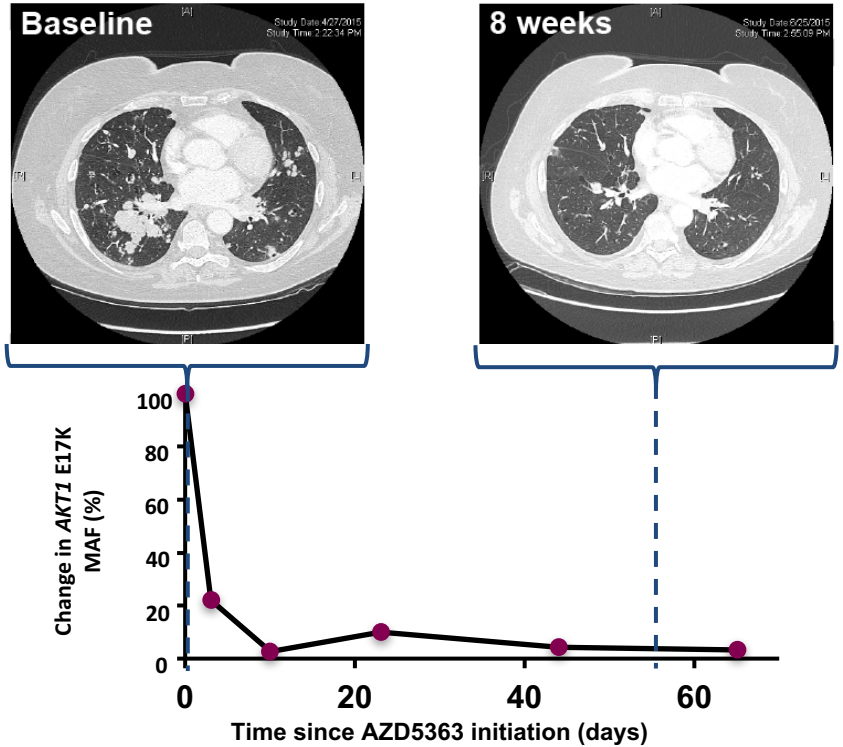
Inhibition by either mechanism prevents downstream events, including tumour cell proliferation, and sensitises cells to apoptosis

1. Koboldt DC, *et al*. *Nature* 2012; 2. Miller TW, *et al*. *Breast Cancer Res* 2011; 3. Cossu-Rocca P, *et al*. *PLOS One* 2015; 4. Biooncology. https://www.biooncology.com/pipeline-molecules/taselisib.html; 5. Freidman LS, *et al*. SABCS 2016; 6. Nitulescu GM, *et al*. *Int J Oncol*. 2016; 7. Lin J, *et al*. *Clin Cancer Res* 2013.

AKT1 E17K in plasma tumor ctDNA predicts response to AZD5363

- AKT mutation detectable in 21/23 patients at baseline by ddPCR and MSK-IMPACT
- Transient *AKT1* ctDNA decline observed in 20/21 (95%) patients, but persistent (≥21 days) decline* correlated with PFS and RECIST response



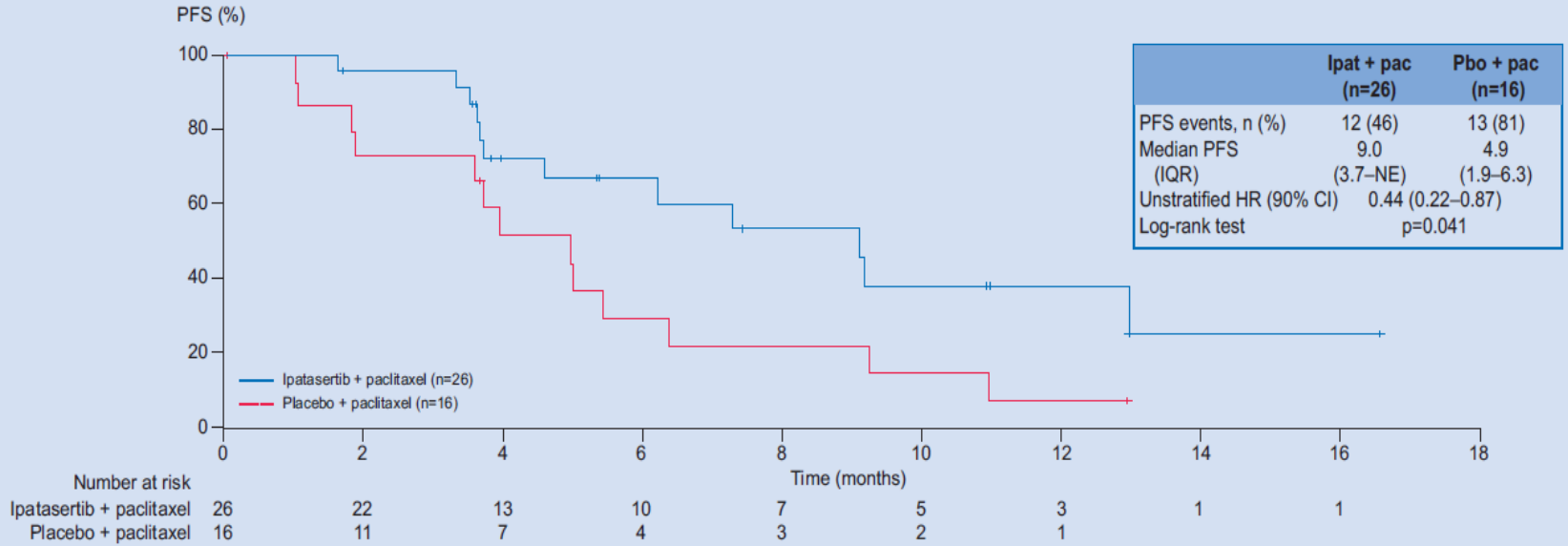


AKT1 E17K cfDNA decline* at day 21 predicts improved progression-free survival

*cfDNA decline is defined as reduction of *AKT1* E17K MAF to levels ≤50% vs baseline. MAF baseline set at 100%

Paclitaxel +/- Ipatasertib: AKT Inhibitor for PI3K altered MetTNBC

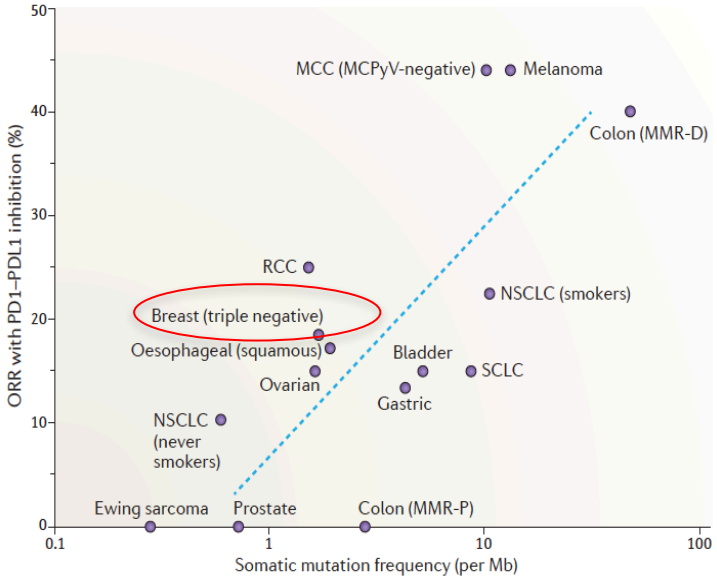
PI3K/AKT/PTEN Abn by NGS



	Ipat + pac (n=26)	Pbo + pac (n=16)
PFS events, n (%)	12 (46)	13 (81)
Median PFS (IQR)	9.0 (3.7–NE)	4.9 (1.9–6.3)
Unstratified HR (90% CI)	0.44 (0.22–0.87)	
Log-rank test	p=0.041	

NE = not evaluable.

Dent R et al. ASCO. 2017.



Pembrolizumab Response Rate by Tumor Type.

Tumor Type	No. of Tumors	Patients with a Response	Range of Response Duration
		no. (%)	*mo*
Colorectal cancer	90	32 (36)	1.6+ to 22.7+
Endometrial cancer	14	5 (36)	4.2+ to 17.3+
Biliary cancer	11	3 (27)	11.6+ to 19.6+
Gastric or gastroesophageal junction	9	5 (56)	5.8+ to 22.1+
Pancreatic cancer	6	5 (83)	2.6+ to 9.2+
Small-intestine cancer	8	3 (38)	1.9+ to 9.1+
Breast cancer	2	2 (100)	7.6 to 15.9
Prostate cancer	2	1 (50)	9.8+
Other cancers	7	3 (43)	7.5+ to 18.2+

Microsatellite Instability and Breast Cancer

Uncommon but Actionable

Lemery S, et al. New Engl J Med 2017