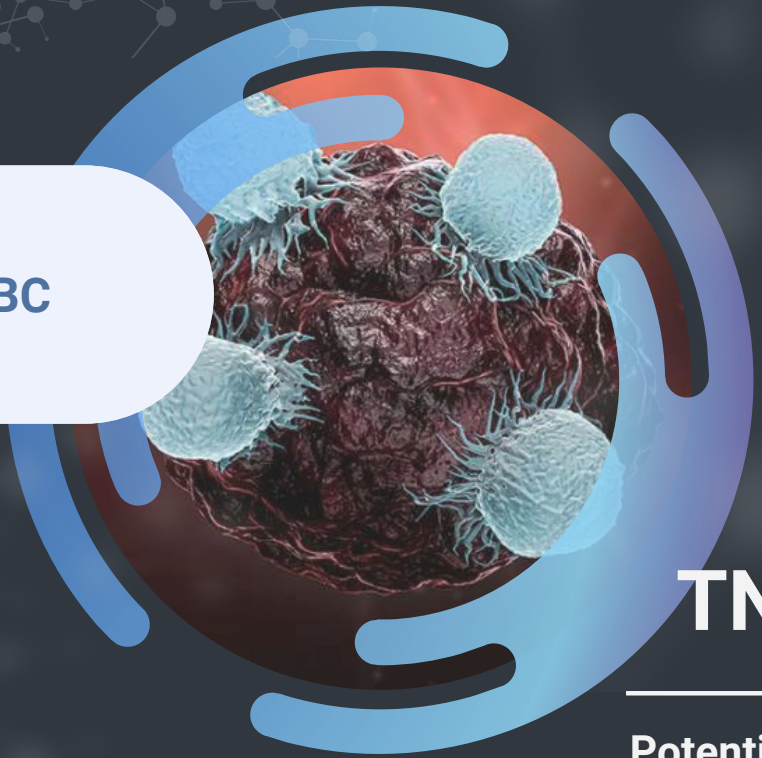
Vyuhpharma

TNBC



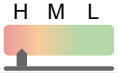
TNBC- Molecular subtypes

Potential response to I/Os

Anti-PD-1s showed better benefits vs chemo but multiple questions exists; Targeted treatment better prospects

Factors challenging broader utility of I/Os

- Currently, while TNBC are classified based on molecular & gene expression features (4 subtypes), it has not been clinically utilized in early or advanced disease setting. In addition, it not has been factored in major historical & upcoming trials. Need for transcriptomic analysis & lower patient accrual may have led to exclusion of these subtypes.
- Efficacy of Merck's Pembrolizumab (only approved immunotherapy in eTNBC) in all pts aren't fully clear, considering no major difference in EFS benefit among pCR achieved patients. In addition, benefits don't seem to be driven by PD-L1 expression. Other I/Os particularly PD-(L)1s regimens like Roche's atezolizumab failed in adjuvant setting trial recently. As such, mixed response of PD-1s questioned clinical utility in broader patients
- However, targeted treatments like PARPi has been shown to be beneficial in BRCAmut+ve setting as expected.

Key TNBC Subtypes (Lehman et al. 2016)	% of TNBC	Key features (expression pathways)	Key mutated genes	Tumor mutational Burden (Lehman et al. 2021)	% of immune cell infiltration (Lehman et al. 2016; Hanrano et al. 2018)	Potential response to I/Os
Basal like 1 (BL1)	35%	DNA damage response genes	*BRCA1/2, ATM,* TP53		48- 54%	(High)
Basal like 2 (BL 2)	22%	Growth factor (eg: EGFR, MET) and metabolic pathways (eg:glycolysis)	*TP63, MME*		30-65%	(moderate to high)
Mesenchymal (M)	25%	Cellular motility, differentiation (eg:ALK TGF-β signaling and Wnt/β-catenin)	*TGFB1L1, MMP2, CDH1*		0-20%	(low to moderate)
Luminal androgen receptor (LAR)	16%	Androgen receptor signaling & lipid kinases	*PIK3CA, AKT*		18 - 57%	(moderate to high)

Need more targeted treatment options

- TNBC is a more heterogeneous disease. Targeted therapeutic approaches like PARPi has been successful as expected. Molecular classification suggests certain subtypes like mesenchymal may be biologically different and have lower immune cell infiltration that may affect treatment response (although this is NOT clinically proven in a well controlled trial in eTNBC)
- Overall, responders to immunotherapies in eTNBC aren't well defined. There is a need for more targeted and identification of potential responders in future research. Note: NCCN guidelines suggested individualized adjuvant treatment approach. Pembrolizumab has NOT received category 1 recommendation yet.

Source: Company statements, Secondary sources

H - High; M- Moderate; L - Low

TNBC - NCCN & ESMO Guidelines

Anti-PD-1 + CT is recommended for 1L PD-L1+ve mTNBC; Anti-TROP2 ADC is category 1 recommendation for 2L+ mTNBC

Guidelines	Localized			Metastatic TNBC		
	Neoadjuvant	Adjuvant	Maintenance	1L	2L	3L+
NCCN Note: only preferred regimens included (exceptions are highlighted) (updated: V4 2024)	Pembrolizumab + CT[1] Doxorubicin + cyclophosphamide → Paclitaxel Docetaxel + cyclophosphamide Capecitabine	Pembrolizumab Olaparib[mut]	Capecitabine[#]	Pembrolizumab + CT[2] Olaparib or talazoparib Platinum CT (cisplatin or carboplatin) Doxorubicin/Paclitaxel /Capecitabine /Gemcitabine,/Vinorelbine/Eribulin	Sacituzumab govitecan Trastuzumab-Dxt	
ESMO Note: Included all recommended agents	Pembrolizumab + CT[1] Taxane + carboplatin - AC/EC	Pembrolizumab Olaparib[mut] Capecitabine[wt]		Pembrolizumab + CT[2] Atezolizumab + nab-pac[1] Olaparib/talazoparib Carboplatin Taxane/ anthracycline	Sacituzumab govitecan Trastuzumab-Dxt Eribulin, capecitabine and vinorelbine	

- Given aggressive nature of disease, almost all eTNBC patients are recommended to receive systemic chemotherapy as neo-adjuvant & adjuvant. cT1c-4 or N+ are candidates of systemic neo-adjuvant therapy as per NCCN & ESMO
- Among neoadjuvant therapies, Merck's pembrolizumab is recommended for "high risk" eTNBC (i.e. stage II–III TNBC). In adjuvant setting, NCCN & ESMO recommends pembrolizumab monotherapy for pts who had pembro containing neoadjuvant regimen, regardless disease factor after neoadjuvant setting (pCR or residual disease (ypT1–4,N0 or ypN≥1)
- Olaparib is only targeted therapy approved in eTNBC which is included for gBRCA1/2mut in both guidelines. Note: ~15 to 25 % TNBC pts are gBRCAmut positive

Note: Type of chemo regimens are specified wherever possible, otherwise listed with footnote. Also surgery & RT are not specified

gBRCA1/2 PD-L1 CPS >10 PD-L1 IC + HER2-low High-risk

mut - mutant wt - wild type #- Useful in certain circumstances

NCCN	Category 1	Others
ESMO	All recommendation (no category in latest guideline)	

1: Pembrolizumab + carboplatin + paclitaxel, followed by pembrolizumab + cyclophosphamide + doxorubicin or epirubicin
2:Albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin
AC : doxorubicin + cyclophosphamide; EC: Eribulin + cyclophosphamide

Source: Secondary sources, Vyuhpharma analysis