Navigating the evolving treatment landscape in mTNBC: What are the key considerations for clinical practice today?

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How are checkpoint inhibitors changing the treatment paradigm in mTNBC?

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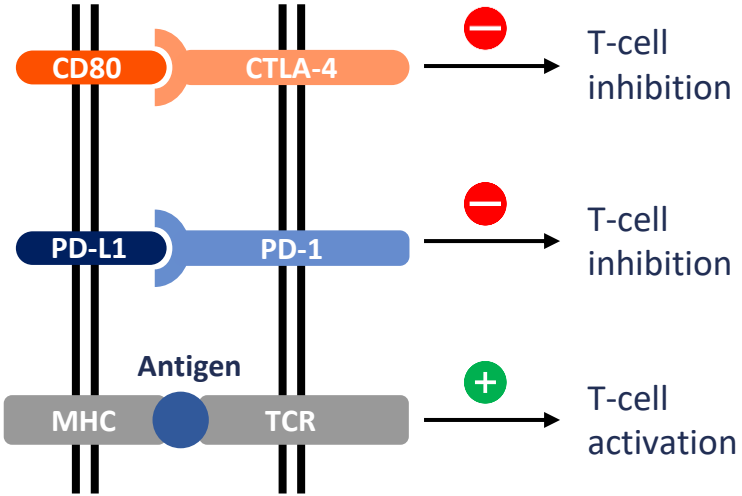
mTNBC, metastatic triple negative breast cancer.

Checkpoint inhibitors block T-cell inactivation[1]

CTLA-4 inhibitors
- Ipilimumab
- Tremelimumab

PD-1 inhibitors
- **Pembrolizumab**
- Nivolumab

PD-L1 inhibitors
- **Atezolizumab**
- Durvalumab



Adapted from de Mello, et al. 2017.

Pembrolizumab and **atezolizumab** have demonstrated efficacy in phase III trials and are approved for use in mTNBC[2,3]

CTLA-4, cytotoxic T-lymphocyte antigen 4; MHC, major histocompatibility complex; mTNBC, metastatic triple negative breast cancer; PD-1, programmed cell death protein; PD-L1, programmed death-ligand 1; TCR, T-cell receptor.

1. De Mello R, et al. *OncoTargets and Therapy*. 2017;10:21–30; 2. Schmid P, et al. *N Engl J Med*. 2018;379:2108–21; 3. Cortes J, et al. *Lancet*. 2020;396:1817–28.

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Efficacy data for ICIs in mTNBC

Trial	Patient population	Intervention	Results
IMpassion130[1]	Untreated mTNBC	**Atezolizumab** + nab-paclitaxel or placebo + nab-paclitaxel	**Significantly prolonged PFS** in the ITT population (7.2 vs 5.5 months [HR 0.80; 95% CI 0.69–0.92; p=0.002]) and PD-L1-positive subgroup (7.5 vs 5.0 months [HR 0.62; 95% CI 0.49–0.78; p<0.001]) with atezolizumab + nab-paclitaxel vs placebo + nab-paclitaxel, respectively; no significant OS benefit
IMpassion131[2]	Locally advanced or mTNBC No prior systemic therapy and no neo(adjuvant) ChT in the 12 months before randomization	**Atezolizumab** + paclitaxel or placebo + paclitaxel	**No significant benefit in PFS or OS** with atezolizumab + paclitaxel vs placebo + paclitaxel
KEYNOTE-355[3,4]	Untreated locally recurrent inoperable or mTNBC	**Pembrolizumab** + ChT or placebo + ChT	**Significantly prolonged PFS** (9.7 months vs 5.6 months [HR 0.65; 95% CI 0.49–0.86; p=0.0012]), and **OS** (23.0 months vs 16.1 months [HR 0.73; 95% CI 0.55–0.95; p=0.0093]) with pembrolizumab + ChT vs placebo + ChT, respectively, in patients with PD-L1 CPS ≥10 (NS for CPS ≥1 for both measures)

ChT, chemotherapy; CI, confidence interval; CPS, combined positivity score; HR, hazard ratio; ICI, immune checkpoint inhibitor; ITT, intention to treat; mTNBC, metastatic triple negative breast cancer; NS, not significant; OS, overall survival; PD-L1, programmed death-ligand; PFS, progression free survival.

1. Schmid P, et al. *N Engl J Med*. 2018;379:2108–21; 2. Miles D, et al. *Ann Oncol*. 2021;32:994–1004; 3. Cortés J, et al. *Lancet*. 2020;396:1817–28; 4. Cortés J, et al. *Ann Oncol*. 2021;32(Suppl. 5):S1289–S90.

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When and where should we consider ADCs in the mTNBC treatment journey?

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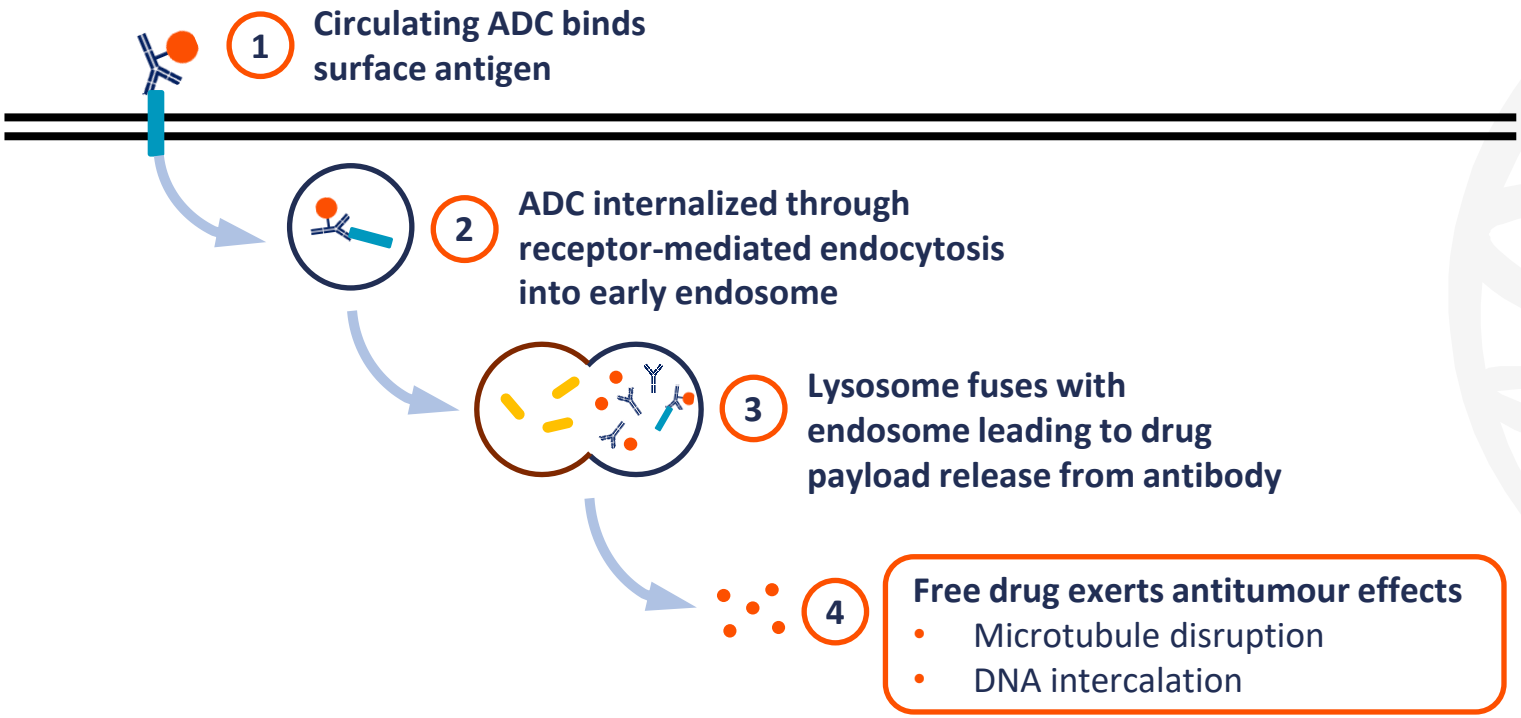
ADC, antibody–drug conjugate; mTNBC, metastatic triple negative breast cancer.

ADCs enable targeted payload release



Adapted from Tong, et al. 2021.

ADC, antibody–drug conjugate.
Tong J, et al. *Molecules*. 2021;26:5847.

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Efficacy data for ADCs in mTNBC

Trial	Patient population	Intervention	Results
ASCENT[1]	mTNBC, relapsed or refractory to ≥2 previous standard ChT regimens; previous therapy had to include a taxane (for any indication)	**Sacituzumab govitecan** or ChT	Sacituzumab govitecan **prolonged PFS** (5.6 months vs 1.7 months [HR 0.41; 95% CI 0.32–0.52; p<0.001]) and **OS** (12.1 months vs 6.7 months [HR 0.48; 95% CI 0.38–0.59; p<0.001]) compared with ChT
Sacituzumab govitecan[2] (phase I/II trial)	Heavily pre-treated mTNBC refractory to or relapsed after ≥1 standard therapy	Single arm: **sacituzumab govitecan**	ORR 30%; median DOR 8.9 months; CBR 46%; median PFS 6.0 months (95% CI 5.0–7.3); median OS 16.6 months (95% CI 11.1–20.6)
SGNLVA-002[3] (phase Ib/II)	Previously untreated, unresectable locally advanced or mTNBC	Single arm: **ladiratuzumab vedotin** + pembrolizumab	*[Trial ongoing]*
BEGONIA[4] (phase Ib/II)	Untreated, locally advanced or mTNBC	Durvalumab + **trastuzumab deruxtecan** or durvalumab + paclitaxel	Durvalumab + trastuzumab deruxtecan: ORR 100%; durvalumab + paclitaxel: ORR 57%, median PFS 7.3 months (95% CI 5.4–13.8)
DESTINY-Breast04[5]	HER2-low unresectable metastatic BC, including 58 patients with TNBC	**Trastuzumab deruxtecan** or PCT	In the TNBC subgroup, trastuzumab deruxtecan **prolonged PFS** (8.5 months vs 2.9 months [HR 0.46; 95% CI 0.24–0.89]) and **OS** (18.2 months vs 8.3 months [HR 0.48; 95% CI 0.24–0.95]) vs PCT

ADC, antibody–drug conjugate; BC, breast cancer; CBR, clinical benefit rate; ChT, chemotherapy; CI, confidence interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mTNBC, metastatic TNBC; ORR, overall response rate; OS, overall survival; PCT, physician's choice therapy; PFS, progression free survival; TNBC, triple negative breast cancer.

1. Bardia A, et al. *N Engl J Med.* 2021;384:1529–41; 2. Bardia A, et al. *J Clin Oncol*. 2017;35:2141–48; 3. Meisel J, et al. *J Clin Oncol.* 2022;40(Suppl. 16):TPS1127; 4. Schmid P, et al. *J Clin Oncol*. 2021;39(Suppl. 15):1023; 5. Modi S, et al. *N Engl J Med*. 2022;387:9–20.

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What is the role of PARP inhibitors in mTNBC?

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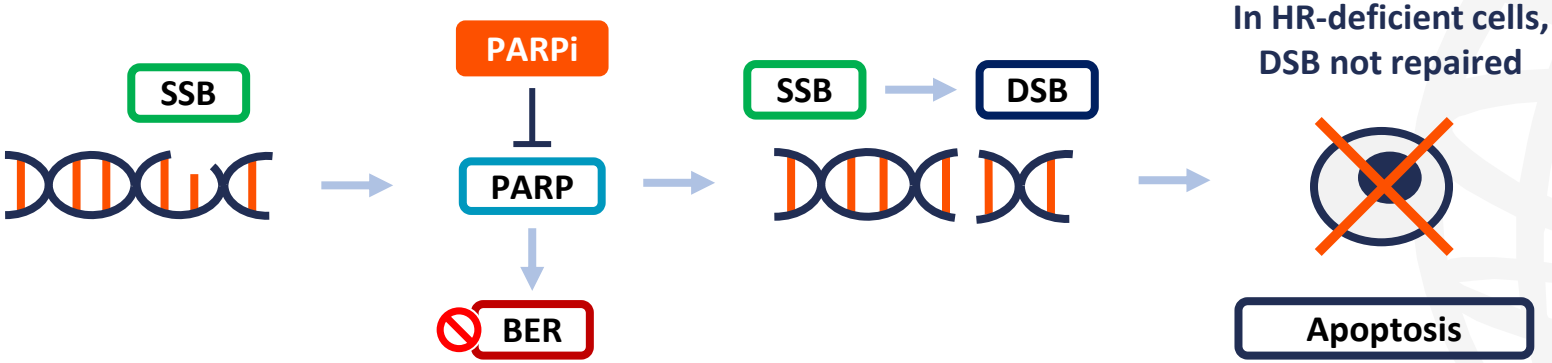
mTNBC, metastatic triple negative breast cancer; PARP, poly (ADP-ribose) polymerase.

PARP inhibitors prevent DNA repair to trigger apoptosis

Following PARP inhibition, DSBs that occur due the SSB accumulation cannot be repaired in HR-deficient cells, resulting in cell death



1. SSB occurs
2. PARPi prevents BER
3. SSBs accumulate, resulting in DSB
4. DSB not repaired, leading apoptosis

Adapted from Barchiesi, et al. 2021.

BER, base excision repair; DSB, double-strand break; HR, homologous recombination; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; SSB, single-strand break.
Barchiesi G, et al. *Front Oncol*. 2021;11:769280.

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PARPi therapy efficacy data in patients with TNBC

Trial	Patient population	Intervention	Results
OlympiAD[1,2]	HER2 negative BC with g*BRCA*m; ≤2 previous ChT regimens; 49.8% and 49.5% of patients in olaparib vs comparator arms, respectively, had TNBC	**Olaparib** or PCT	**Prolonged median PFS** with olaparib over PCT (7.0 vs 4.2 months [HR 0.58; 95% CI 0.43–0.80; p<0.001) **No significant difference in OS** between olaparib and PCT arms in TNBC subgroup (17.4 vs 14.9 months, respectively [HR 0.93; 95% CI 0.62–1.43; p=NS]); overall OS was not statistically different between treatment arms **Maintained QoL** with olaparib over PCT – prolonged time to clinically meaningful decrease in QLQ-C30 (median time not reached vs 15.3 months [HR 0.44; 95% CI 0.25–0.77; p=0.004]) with olaparib vs PCT, respectively
EMBRACA[3]	Locally advanced or metastatic BC with g*BRCA*m; ≤3 cytotoxic regimens; 45.3% and 41.7% of patients in talazoparib vs comparator arms, respectively, had TNBC	**Talazoparib** or PCT	**Prolonged median PFS** with talazoparib over PCT in overall population (8.6 vs 5.6 months [HR 0.54; 95% CI 0.41–0.71; p<0.001]) and in TNBC population (HR 0.60; 95% CI 0.41–0.87)

BC, breast cancer; ChT, chemotherapy; CI, confidence interval; g*BRCA*m, germline *BRCA* mutation; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NS, not significant; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PCT, physician's choice therapy; PFS, progression free survival; QoL, quality of life; TNBC, triple negative breast cancer.

1. Robson M, et al. *N Engl J Med.* 2017;377:523–33; 2. Robson M, et al. *Ann Oncol*. 2019;30:558–66; 3. Litton J, et al. *N Engl J Med.* 2018;379:753–63.

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