New and emerging agents in HER2-negative mBC: Implications for current and future practice

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Agenda

- Treatment for HER2-negative mBC: Where do we go from here?
- Current ADCs for HER2-negative mBC: Considerations for use
- Emerging ADCs for HER2-negative mBC: Future trends

ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer

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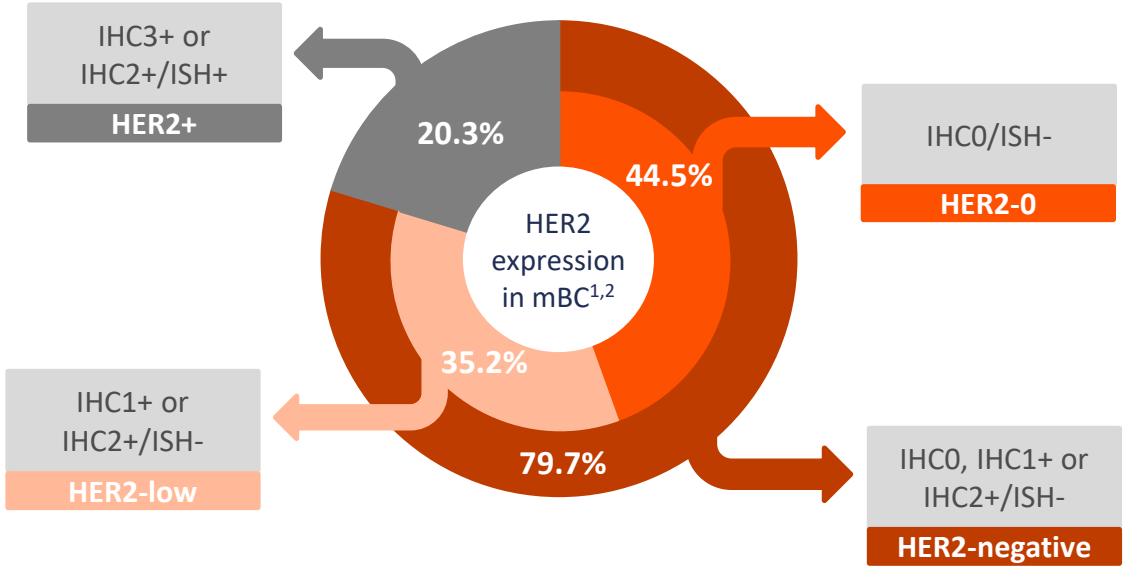
Treatment for HER2-negative mBC: Where do we go from here?

HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer.

HER2-negative BC encompasses HER2-0 and HER2-low



- **Patients with BC are often stratified and treated according to HR and HER2 status[3]**
- HR status includes[3]
  - HR+: Presence of ER or PR or both
  - HR-: Absence of ER and PR
- HER2-negative includes HER2-0 and HER2-low subtypes[3]
- Patients with HER2-negative BC can be HR+ or HR- (TNBC)[3,4]

Introducing a definition for HER2-low has the potential to expand access to certain treatments for patients with BC[2]

BC, breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic BC; PR, progesterone receptor; TNBC, triple negative BC.

1. Gampenrieder SP, et al. *Breast Cancer Res.* 2021;23:112; 2. Corti C, et al. *Curr Treat Options Oncol.* 2023;24:468–78; 3. Kay C, et al. *Future Oncol.* 2021;17:1665–81; 4. Zhang H, Peng Y. *Cancers*. 2022;15:126.

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Expanding treatment options for HER2-negative mBC

	Targeted agent[1–3]	Mechanism of action
Endocrine therapy	SERMs	Competes with estrogen for the ER, acting as an antagonist or partial agonist[3]
	Aromatase inhibitors	Suppresses plasma estrogen levels by inactivating aromatase enzyme[3]
	SERD	Pure ER antagonist that competitively binds to ER[3]
	CDK4/6 inhibitors	Inhibits CDK4/6 enzymes, which phosphorylate and inactivate Rb[3]
	PI3K/Akt/mTOR inhibitors	Inhibits PI3K/Akt/mTOR cell cycle pathways, which are often overactive in BC[3]
	PARP inhibitors	Prevents repair of persistent SSBs, which is essential for cell survival[4]
	ADCs	A mAb conjugated to a toxic payload via a linker that releases cytotoxic agent in target cells[5]

Endocrine therapy is the mainstay of treatment for HR+/HER2-negative mBC.[6] However, intrinsic and acquired resistance is common, prompting research into alternative therapeutic options.[7]

ADC, antibody–drug conjugate; Akt, protein kinase B; BC, breast cancer; CDK4/6, cyclin-dependent kinase 4 and 6; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mAb, monoclonal antibody; mBC, metastatic BC; mTOR, mechanistic target of rapamycin; PARP, poly-ADP ribose polymerase; PI3K, phosphoinositide 3-kinases; Rb, retinoblastoma protein; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; SSBs, single-strand breaks.

1. NCCN. Breast cancer. V4.2023. Available at: https://bit.ly/3J8kZx2 (accessed 8 June 2023); 2. Gennari A, et al. *Ann Oncol*. 2021;32:1475–95; 3. Andrahennadi S, et al. *Curr Oncol.* 2021;28:1803–22; 4. Zheng F, et al. *Biomed Pharmacother.* 2020;123:109661; 5. Koster KL, et al. *Explor Target Antitumor Ther.* 2022;3:27–36; 6. Manohar PM, Davidson NE. *Cancer Biol Med*. 2021;19:202–12; 7. Lei JT, et al. *Breast.* 2019;28(Suppl. 1):S26–30.

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Current ADCs for HER2-negative mBC: Considerations for use

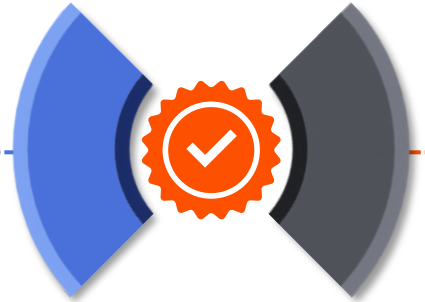
ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer.

Two ADCs are approved for HER2-negative mBC

Trastuzumab deruxtecan
HER2

Unresectable or **HER2-low mBC**
(IHC1+ or IHC2+/ISH-)[1,2]

Following prior chemotherapy for mBC or following disease recurrence during or within 6 months of completing adjuvant chemotherapy



Sacituzumab govitecan
TROP-2

Unresectable **LA/mTNBC**[3,4]

Following ≥2 prior systemic therapies (≥1 for advanced/mBC)

Unresectable **LA or HR+/HER2-negative mBC**
(IHC0, IHC1+ or IHC2+/ISH-)[3,5,6]

Following endocrine-based therapy and ≥2 additional systemic therapies for mBC

ADCs are approved as second- or third-line treatments for HER2-negative, HER2-low and TNBC mBC[1–4]

ADC, antibody–drug conjugate; BC, breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; LA, locally advanced; m, metastatic; TNBC, triple negative breast cancer.

1. FDA. Trastuzumab deruxtecan PI. Available at: https://bit.ly/3ONmHYa (accessed 12 July 2023) 2. EMA. Trastuzumab deruxtecan SmPC. Available at: https://bit.ly/3MMPBVK (accessed 12 July 2023); 3. FDA. Sacituzumab govitecan PI. Available at: https://bit.ly/45JgvH0 (accessed 12 July 2023); 4. EMA. Sacituzumab govitecan SmPC. Available at: https://bit.ly/3ILQLzN (accessed 12 July 2023); 5. EMA. 2023. Available at: https://bit.ly/3QhVWvT (accessed 02 August 2023); 6. Pharmaceutical technology. Available at: https://bit.ly/3YhfZMI (accessed 31 July 2023).

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Pivotal clinical trials for approved ADCs (efficacy data)

ADC	Trastuzumab deruxtecan[1]	Sacituzumab govitecan[2,3]	
Study	**DESTINY-Breast04** HER2-low mBC	**TROPiCS-02[2]** HR+/HER2–	**ASCENT[3]** mTNBC
Key efficacy results	**Trastuzumab deruxtecan vs TPC* (2:1), data cut-off 11 January 2022** **HR+ (n=494)** • **mPFS:** 10.1 vs 5.4 mo HR (95% CI), 0.51 (0.40–0.64); p<0.001 • **mOS:** 23.9 vs 17.5 mo HR (95% CI), 0.64 (0.48–0.86); p=0.003 • **ORR:** 52.6% vs 16.3% **HR- (n=58)** • **mPFS:** 8.5 vs 2.9 mo HR (95% CI), 0.46 (0.24–0.89) • **mOS:** 18.2 vs 8.3 mo HR (95% CI), 0.48 (0.24–0.95) • **ORR:** 50.0% vs 16.7%	**Sacituzumab govitecan vs TPC† (1:1), data cut-off 1 December 2022 (N=543)** • **mPFS:** 5.5 vs 4.0 mo HR (95% CI), 0.65 (0.53–0.81); p=0.0001 • **mOS:** 14.5 vs 11.2 mo HR (95% CI), 0.79 (0.65–0.95); p=0.0133 • **ORR:** 21% vs 14%	**Sacituzumab govitecan vs TPC† (1:1), data cut-off 11 March 2020 (n=468)** • **mPFS:** 5.6 vs 1.7 mo HR (95% CI), 0.41 (0.32–0.52); p<0.001 • **mOS:** 12.1 vs 6.7 mo HR (95% CI), 0.48 (0.38–0.59); p<0.001 • **ORR:** 35% vs 5%

Direct comparisons between trials should not be made due to differences in trial design.

*Capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel; †Capecitabine, eribulin, gemcitabine or vinorelbine. ADC, antibody–drug conjugate; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR(+/-), hormone receptor (positive/negative); m, median; mBC, metastatic breast cancer; mo, month; mTNBC, metastatic triple negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TPC, treatment of physician's choice.

1. Modi S, et al. *N Eng J Med*. 2022;387:9–20; 2. Tolaney SM, et al. Presented at: ASCO Annual Meeting, Chicago, IL, USA. 2–6 June 2023. Presentation 1003;
3. Bardia A, et al. *N Eng J Med.* 2021;384:1529–41.

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Pivotal clinical trials for approved ADCs (safety data)

ADC	Trastuzumab deruxtecan[1]	Sacituzumab govitecan[2,3]	
Study	**DESTINY-Breast04** HER2-low mBC	**TROPiCS-02[2]** HR+/HER2–	**ASCENT[3]** mTNBC
Key safety results	**Trastuzumab deruxtecan vs TPC* (2:1), data cut-off 11 January 2022 (n=543)**	**Sacituzumab govitecan vs TPC† (1:1), data cut-off 1 December 2022 (n=517)**	**Sacituzumab govitecan vs TPC† (1:1), data cut-off 11 March 2020 (n=482)**
	• **Most common all-grade TEAEs: Nausea** (73% vs 24%), **fatigue** (48% vs 42%), **alopecia** (38% vs 33%) • **Grade ≥3 TEAEs:** 53% vs 67% • **ILD/pneumonitis**: 12% (grade ≥3, 2.2%) vs 0.6% • TEAEs leading to **death**: 3.8% vs 2.9%	• **Most common all-grade TEAEs: Neutropenia** (71% vs 55%), **diarrhoea** (62% vs 23%), **nausea** (59% vs 35%) • **Grade ≥3 TEAEs:** 74% vs 60% • TEAEs leading to **death**: 2% vs 0%	• **Most common all-grade TEAEs: Neutropenia** (63% vs 43%), **diarrhoea** (59% vs 12%), **nausea** (57% vs 26%) • **ILD/pneumonitis:** <1% vs 0% • TEAEs leading to **death**: <1% in both (n=3)

Direct comparisons between trials should not be made due to differences in trial design.

*Capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel; †Capecitabine, eribulin, gemcitabine or vinorelbine. ADC, antibody–drug conjugate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ILD, interstitial lung disease; mBC, metastatic breast cancer; mTNBC, metastatic triple negative breast cancer; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.

1. Modi S, et al. *N Eng J Med*. 2022;387:9–20; 2. Tolaney SM, et al. Presented at: ASCO Annual Meeting, Chicago, IL, USA. 2–6 June 2023. Presentation 1003;
3. Bardia A, et al. *N Eng J Med.* 2021;384:1529–41.

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Emerging ADCs for HER2-negative mBC: Future trends

ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer.

Emerging ADCs for HER2-negative mBC (1)

ADC	Datopotamab deruxtecan			Disitamab vedotin
Study	**TROPION-PanTumor01** Phase I; NCT03401385 Relapsed/refractory unresectable advanced or mTNBC and HR+/HER2– unresectable or mBC[1–3]	**TROPION-Breast01** Phase III; NCT05104866 HR+/HER2– inoperable or mBC[4]	**TROPION-Breast02** Phase III; NCT05374512 Locally recurrent inoperable or mTNBC[5]	Phase III; NCT04400695 HER2-low LA or mBC[2]
Key results	**Data cut-off 22 July 2022[1,3]** **HR+/HER2– (n=41)[1]** • **ORR:** 27% • **mPFS:** 8.3 mo • **Most common all-grade TEAEs:** **Stomatitis** (83%) and **nausea** (56%) • **ILD/pneumonitis**: n=1 (grade 3) **TNBC (n=44)[3]** • **ORR:** 32% • **mOS:** 13.5 mo • **Most common all-grade TEAEs:** **Stomatitis** (73%) and **nausea** (66%) • **ILD/pneumonitis**: n=0	**Datopotamab deruxtecan vs ICC (1:1), N=~700[4]** **Expected study completion:[2]** August 2025	**First-line datopotamab deruxtecan vs ICC (1:1), N=~600[5]** **Expected study completion:[2]** December 2025	**Disitimab vedotin vs ICC N=366[2]** **Estimated study completion:[2]** December 2023
Combination trials	**+ Durvalumab (NCT03742102) Phase Ib/II[2]** Estimated completion: August 2024	**+ AZD5305 (NCT04644068) Phase I/IIa[2]** Estimated completion: January 2026		N/A

Direct comparisons between trials should not be made due to differences in trial design.

ADC, antibody–drug conjugate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICC, investigator's choice of chemotherapy; ILD, interstitial lung disease; LA, locally advanced; m, median; mBC, metastatic breast cancer; mo, month; mTNBC, metastatic triple negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression free survival; TEAE, treatment-emergent adverse event; TNBC, triple negative breast cancer.

1. Bardia A, et al. Presented at: 40th Annual Miami Breast Cancer Conference, Miami, FL, USA. 2–5 March 2023;37:14–15; 2. ClinicalTrials.gov. Available at: https://bit.ly/3P651qU searchable by specific trial number (accessed 7 June 2023); 3. Bardia A, et al. Presented at: 40th Annual Miami Breast Cancer Conference, Miami, FL, USA, 2–5 March 2023;37:13–14; 4. Bardia A, et al. *Cancer Res*. 2023;83(Suppl. 5):Abstr OT1-03-04; 5. Dent R, et al. *Cancer Res*. 2023;83(Suppl. 5):Abstr OT1-03-05.

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Emerging ADCs for HER2-negative mBC (2)

ADC	Ladiratuzumab vedotin[1]	Patritumab deruxtecan	
Study	Phase I; NCT01969643 LIV-1+ unresectable, LA or mBC	Phase II; NCT04699630 LA or mBC; HR+/HER2– or TNBC[3]	**ICARUS-BREAST01;** Phase II; NCT04965766 HR+/HER2– unresectable LA or mBC[2,4]
Key results	**Interim data (n=69)** **HR+/HER2– (n=18)** • **DCR:** 59% **TNBC (n=51)** • **DCR:** 64% • **ORR:** 32% • **mPFS:** 11.3 wks (95% CI: 6.1–17.1) • **Most common all-grade TEAEs:** **Fatigue** (59%) and **nausea** (51%) • Treatment-related **deaths**: n=1	**Part A data (n=60)** **HR+/HER2– (n=29)** • **ORR:** 41% (95% CI, 23.5–61.1) **TNBC (n=19)** • **ORR:** 21% (95% CI, 6.1–45.6) • **Most common all-grade TEAEs:** **Nausea** (50%) and **fatigue** (45%) • **ILD:** n=1 (1.7%)	**Data cut-off 23 January 2023 (n=56)** • **3-month RR:** 29% (95% CI, 18.4–41.5) • **Most common all-grade TEAE:** **Fatigue** (89%) and **nausea** (77%) • **ILD:** n=1 (1.8%; grade 1)
Combination trials	**+ Pembrolizumab,** phase Ib/II (NCT03310957)[2] Estimated completion: December 2024	N/A	

Direct comparisons between trials should not be made due to differences in trial design.

ADC, antibody–drug conjugate; BC, breast cancer; CI, confidence interval; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ILD, interstitial lung disease; LA, locally advanced; m, metastatic; mPFS, median progression free survival; ORR, objective RR; RR, response rate; TEAE, treatment-emergent adverse event; TNBC, triple negative breast cancer; wks, weeks.

1. Modi S, et al. *Cancer Research*. 2018;78(Suppl. 4):PD3-14; 2. ClinicalTrials.gov. Available at: https://bit.ly/3P651qU searchable by specific trial number (accessed 7 June 2023); 3. Hamilton EP, et al. Presented at: ASCO Annual Meeting, Chicago, IL, USA. 2–6 June 2023; 4. Pistilli B, et al. *Ann Oncol.* 2023;8(Suppl. 4): Abstr 1890.