



Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Systemic Therapy of Primary Early Breast Cancer – Triple-negative

Systemic Therapy of Primary Early Breast Cancer – Triple-negative



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- **Version 2025:**

Banys-Paluchowski / Loibl

Strategies for Differentiated Systemic Treatment in the Curative Situation

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If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred; study participation recommended

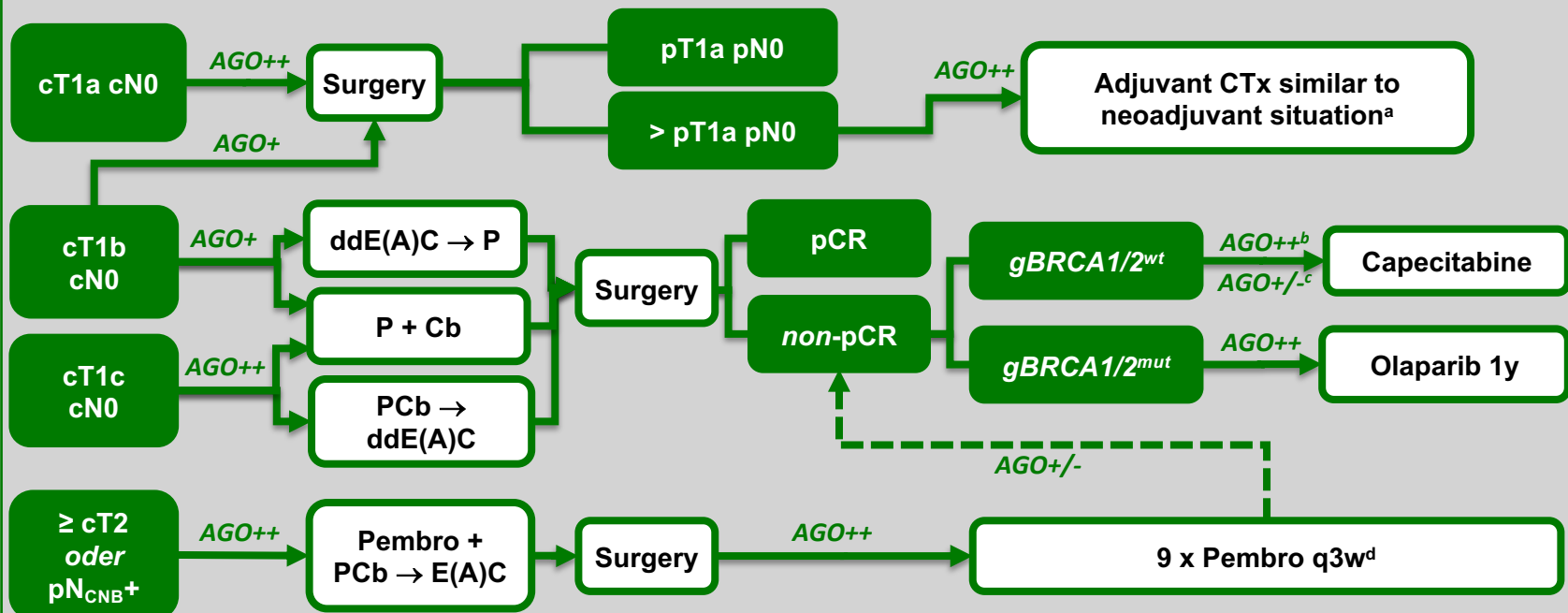
- | | |
|--|--------------------|
| <ul style="list-style-type: none"> ▪ HR+ / HER2- and „low recurrence-risk“ <ul style="list-style-type: none"> ▪ Endocrine therapy without chemotherapy | ++ |
| <ul style="list-style-type: none"> ▪ HR+ / HER2- and „high recurrence-risk“ <ul style="list-style-type: none"> ▪ endocrine therapy ▪ endocrine-based therapy (abemaciclib or ribociclib) ▪ Patients with indication for chemo-endocrine therapy* <ul style="list-style-type: none"> ▪ Conventionally dosed AT-based chemotherapy (q3w) ▪ Dose dense chemotherapy (including weekly schedule) | ++
+
+
++ |
| <ul style="list-style-type: none"> ▪ gBRCA1/2mut (HR+ / HER2- or TNBC respectively) <ul style="list-style-type: none"> ▪ Olaparib +/- endocrine therapy | ++ |
| <ul style="list-style-type: none"> ▪ Triple-negative (TNBC) <ul style="list-style-type: none"> ▪ Conventional dosed AT-based chemotherapy (q3w) ▪ Sequential AT-based chemotherapy (incl. weekly schedule) ▪ Neoadjuvant platinum-containing chemotherapy ▪ Neoadjuvant platinum-containing chemotherapy with ICPI (Pembrolizumab) | +
++
+
++ |
| <ul style="list-style-type: none"> ▪ HER2+ <ul style="list-style-type: none"> ▪ Trastuzumab (plus Pertuzumab in N+ or NACT) <ul style="list-style-type: none"> ▪ Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy ▪ Anthracycline-free, chemotherapy + anti-HER2 therapy | ++
++
++ |

* see prognosis chapter

Therapy of Triple-negative Early Breast Cancer

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A, doxorubicin; C, cyclophosphamide; Cb, carboplatin; CNB, core needle biopsy; CTx, chemotherapy; dd, dose dense (every 2 weeks); E, epirubicin; *gBRCA1/2^{mut}*, germline *BRCA1/2* mutated; *gBRCA1/2^{wt}*, germline *BRCA1/2* wild type; pCR, pathological complete response; Pembro, pembrolizumab; P, paclitaxel; y, year; ^aif no change of prognostic factors after surgery; ^bafter A/T-containing chemotherapy; ^cafter chemotherapy with platinum and/or pembrolizumab; ^dif Pembrolizumab was started before surgery.

Indication for Chemotherapy +/- Immune Checkpoint Inhibitor Therapy (TNBC)

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Oxford		
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■ Clinical node-positive

- Neoadjuvant chemotherapy in combination with pembrolizumab

1b	A	++
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■ Clinical node-negative

- $\geq T2$ → Neoadjuvant chemotherapy in combination with pembrolizumab
- T1c → Neoadjuvant chemotherapy preferred
- T1b → Neoadjuvant or adjuvant chemotherapy
- T1a → Adjuvant chemotherapy

1b	A	++
----	---	----

2b	B	++
----	---	----

2b	B	+
----	---	---

2b	B	+/-
----	---	-----

General principles

	Oxford		
	LoE	GR	AGO
▪ Chemotherapy regimens can be administered in the neoadjuvant and adjuvant setting	1a	A	++
▪ Dose-dense regimens should be preferentially used (if pembrolizumab is not indicated)	1a	A	++
▪ Addition of platinum salts to anthracycline-/taxane-based chemotherapy (cT1 cN0) (irrespective of <i>gBRCA</i> status)	1b	B	+
▪ Addition of platinum salts to anthracycline-/taxane-based chemotherapy (\geq cT2 or cN+) (irrespective of <i>gBRCA</i> status)	1a	A	++
▪ Pembrolizumab in combination with carboplatin / paclitaxel \rightarrow 4 x EC q3w neoadjuvant and postoperative (\geq cT2 or cN+)	1b	A	++
▪ Olaparib in case of <i>gBRCA</i> ^m	1b	A	++

- Chemotherapy regimens can be administered in the neoadjuvant and adjuvant setting
- Dose-dense regimens should be preferentially used (if pembrolizumab is not indicated)
- Addition of platinum salts to anthracycline-/taxane-based chemotherapy (cT1 cN0) (irrespective of *gBRCA* status)
- Addition of platinum salts to anthracycline-/taxane-based chemotherapy (\geq cT2 or cN+) (irrespective of *gBRCA* status)
- Pembrolizumab in combination with carboplatin / paclitaxel \rightarrow 4 x EC q3w neoadjuvant and postoperative (\geq cT2 or cN+)
- Olaparib in case of *gBRCA*^m
 - Adjuvant: Tumor size \geq 2 cm or pN+
 - Post-neoadjuvant: non-pCR

ICPi therapy in the adjuvant only setting not recommended outside of clinical studies.

Neoadjuvant Chemotherapy Treatment Strategies Based on Clinical Response

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In case of early response

- Completion of neoadjuvant chemotherapy

1b A ++

In case of no change:

- Completion of neoadjuvant chemotherapy (NACT) followed by surgery
- Continuation of NACT with non-cross-resistant regimen
 - AC or EC x 4 → D x 4 or Pw x 12
 - Paclitaxel / carboplatin → EC (q2w or q3w) x 4

2b C ++

2b B +

2b B +

1b B +

In case of disease progression

- Re-evaluation of tumorbiological factors
- Stop NACT and proceed to surgery or radiotherapy
- Additional adjuvant chemotherapy with non-cross-resistant regimen

5 D +/-

4 D ++

4 D +/-

Preferred Regimens in Triple-negative Breast Cancer

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Non-platinum-containing regimens

- ddEC x 4 → Paclitaxel₈₀ q1w x 12 (T1 N0)

1b B ++

Platinum-containing regimens

- Paclitaxel₈₀ / Carbo_{AUC 1,5} q1w x 12 → ddEC x 4

1b B ++

- Paclitaxel₈₀ q1w x 12 / Carbo_{AUC 5} q3w x 4 → ddAC / ddEC x 4

1b B ++

- Paclitaxel/Carbo_{AUC 1,5} q1w x 18 (T1 N0)

2b B ++

Checkpoint inhibitors

- Pembro₂₀₀ q3w + Pac₈₀ / Carbo_{AUC 1,5} q1w x 12 → E₉₀C q3w x 4

1b B ++

- Pembro₂₀₀ q3w + Pac₈₀ q1w x 12 / Carbo_{AUC 5} q3w → E₉₀C q3w x 4

1b B ++

Post-neo/Adjuvant Therapy in Triple-negative Breast Cancer

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pCR

- Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)

Non-pCR

- Capecitabine (q3w up to 8 courses)¹
 - In case of non-pCR after A-T-containing chemotherapy¹
 - In case of non-pCR after platinum +/- pembrolizumab-containing therapy
- Platinum salts (carboplatin or cisplatin) q3w after AT-pretreatment
- Olaparib (*gBRCA^{MUT}*)²
- Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)

Oxford

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	LoE	GR	AGO
Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+
Capecitabine (q3w up to 8 courses) ¹			
In case of non-pCR after A-T-containing chemotherapy ¹	1a	A	++
In case of non-pCR after platinum +/- pembrolizumab-containing therapy	5	D	+/-
Platinum salts (carboplatin or cisplatin) q3w after AT-pretreatment	1b	B	-
Olaparib (<i>gBRCA^{MUT}</i>) ²	1b	A	++
Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	++

¹ in stage II-III without platinum/pembrolizumab-based pretreatment

² according to inclusion criteria of OlympiA trial

Gray R et al., Lancet 2019

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Early Breast Cancer Trialists' Cooperative Group (EBCTCG)

Increasing the dose-density of adjuvant chemotherapy: an EBCTCG meta-analysis

Same chemotherapy drugs and doses (**n = 10,004**)

Recurrence-free survival: 10-y Gain 4.3% (95%-CI 2.2-6.5)

(RR = 0.83; 95%-CI 0.76-0.91; p < 0.0001)

Overall survival: 10-y Gain 2.8% (95%-CI 0.8-4.8)

(RR = 0.86; 95%-CI 0.77-0.96; p = 0.0054)

ER negative: **10-y Gain 4.7%** (95%-CI 2.3-7.1)

ER positive: **10-y Gain 3.1%** (95%-CI 1.5-4.7)

Van Mackelenbergh M et al., Eur J Cancer 2022

Effects of capecitabine as part of neo- / adjuvant chemotherapy

Meta-analysis of individual patient data from 12 randomized trials (n = 15,457)

HR for DFS overall 0.952 (95%-CI 0.895-1.012, p = 0.115)
X add. 0.888 (95%-CI 0.817-0.965, p = 0.005)
X instead 1.035 (95%-CI 0.945-1.134, p = 0.455)

HR for OS overall 0.892 (95%-CI 0.824-0.965, p = 0.005)
X add. 0.837 (95%-CI 0.751-0.933, p = 0.001)
X instead 0.957 (95%-CI 0.853-1.073, p = 0.450)

Significance only for TNBC overall DFS 0.886 (95%-CI 0.789-0.994, p = 0.040)
OS 0.828 (95%-CI 0.720-0.952, p = 0.008)
X add.: DFS 0.818 (95%-CI 0.713-0.938, p = 0.004)
OS 0.778 (95%-CI 0.657-0.921, p = 0.004)

ICPi plus Neoadjuvant Chemotherapy for Patients with Triple Negative Breast Cancer



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	GeparNuevo	IMpassion031	Keynote 522	neoTRIP	GeparDOUZE/NSABP-B59
Phase	II	III	III	II	III
n	174	333	602 (pCR) 1174 (EFS)	280	1550
Prim. endpoint	pCR	pCR	pCR + EFS	EFS	EFS
ICPi	Durvalumab (24 weeks)	Atezolizumab (1 y)	Pembrolizumab (1 y)	Atezolizumab (24 weeks)	Atezolizumab (1 y)
Chemo	NabPac ₁₂₅ q1w x 12 → EC q2w x 4	NabPac ₁₂₅ q1w x 12 → EC q2w x 4	Pac q1w x 12 + carbo q3w AUC 5 or q1w AUC 1,5 → AC/EC q3w x 4	NabPac ₁₂₅ + carbo AUC 2 q1w d1 and d8	Pac q1w x 12 + carbo q3w AUC 5 or q1w AUC 1.5 → AC/EC q2w/3w x 4
Inclusion criteria	cT1b-cT4a-d	cT2-cT4, cN0-cN3	cT1cN1-2 or cT2 N0-2	cT1cN1; cT2cN1; cT3cN0	cT1cN1-2 or cT2 cN0-2
pCR ITT	53.4% vs. 44.2% Δ 10.8% (n.s.)	57.6% vs. 41.2% Δ 16.5% (p < 0.01)	64.8% vs. 51.2% Δ 13.6% (p < 0.00055)	48.6% vs. 44.4% Δ 4.2% (n.s.)	63.3% vs. 57.0% Δ 6.3%
Follow up/EFS/iDFS (months)/HR EFS/iDFS	43.7 months 3y iDFS: 85.6% vs. 77.2%, HR 0.48 (p = 0.036)	24 months 2y EFS: 85% vs. 80%, HR 0.76 (n.s.)	75.1 months 5y EFS: 81.2% vs. 72.2%, HR 0.65	54 months 5y EFS: 70.6% vs. 74.9%, HR 1.076 (p = 0.76)	47 months 4y EFS: 85.2% vs. 81.9%, HR 0.8; p = 0.08
EFS/iDFS adjusted to pCR/non-pCR	pCR 95.5% vs. 86.1% non-pCR 76.3% vs. 69.7%	n.a.	pCR 92.2% vs. 88.2% non-pCR 62.6% vs. 52.3%	n.a.	pCR: 93% vs. 91% non-pCR: 70.5% vs. 68.9%
OS	3y OS: 95.2% vs. 83.5%; HR 0.24; p = 0.006	2y OS: 95% vs. 90%; HR 0.56	5y OS: 86.6% vs. 81.7%; HR 0.65; p = 0.002	n.a.	4y OS: 90.2% vs. 89.5%; HR: 0.86

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