Neoadjuvant therapy in pancreatic cancer: what is the true oncological benefit?

Lei Ren 1,2 · Carmen Mota Reyes 1 · Helmut Friess 1,3,4 · Ihsan Ekin Demir 1,3,4,5

Received: 19 July 2020 / Accepted: 22 July 2020 / Published online: 10 August 2020
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Abstract

Background Neoadjuvant therapies (neoTx) have revolutionized the treatment of borderline resectable (BR) and locally advanced (LA) pancreatic cancer (PCa) by significantly increasing the rate of R0 resections, which remains the only curative strategy for these patients. However, there is still room for improvement of neoTx in PCa.

Purpose Here, we aimed to critically analyze the benefits of neoTx in LA and BR PCa and its potential use on patients with resectable PCa. We also explored the feasibility of arterial resection (AR) to increase surgical radicality and the incorporation of immunotherapy to optimize neoadjuvant approaches in PCa.

Conclusion For early stage, i.e., resectable, PCa, there is not enough scientific evidence for routinely recommending neoTx. For LA and BR PCa, optimization of neoadjuvant therapy necessitates more sophisticated complex surgical resections, machine learning and radiomic approaches, integration of immunotherapy due to the high antigen load, standardized histopathological assessment, and improved multidisciplinary communication.

Keywords Pancreatic cancer · Neoadjuvant therapy · Arterial resection · Immunotherapy

Introduction

The introduction of neoTx has led to a remarkable increase in the rate of surgical resections in PCa patients with LA or BR tumors, which were initially deemed inoperable at the time of diagnosis. However, two-thirds of these patients will develop local recurrences shortly after the operation [1]. In order to avoid disease relapse, surgeons have struggle to find ways to maximize R0 resections that still remain the only curative alternative for long-term survival in PCa. Although the first attempts of arterial resections (AR) in advanced tumors did not show the expected success, improved perioperative management and the integration of neoTx into multimodal therapy approaches have resulted in significantly reduced perioperative mortality and have proven the safety and feasibility of these radical approaches. Although neoTx is the standard of care for BR and LA tumors, its application on upfront resectable patients in order to downstage tumors and to increase surgical radicality is still subject of investigation. Furthermore, the introduction of immunotherapy to reactivate the pancreatic tumor microenvironment (TME) specially in neadjuvant settings constitutes a promising strategy for future multimodality PCa treatments (Fig. 1) [2, 3].

NeoTx in borderline resectable and locally advanced PCa

Upfront surgery in BR and LA tumors has not elicited the expected survival benefit and is associated with high morbidity, low R0 resection rate, and high early-systemic recurrences...
The introduction of neoadjuvant approaches enabling the tumor downstaging has led to successful surgical resection in up to 60% of these patients [5]. However, neoTx not only decreases tumor size and facilitates surgical resection but also enables the selection of patients with a favorable tumor biology, who will benefit from radical resections [6]. A multicenter phase III randomized controlled trial (RCT) validated the use of neoTx in BR PCa patients. The initial analysis showed that neoTx resulted in increased R0 resection rates and prolonged disease-free survival (DFS) [7]. However, the final results showed that the neoTx protocol (preoperative gemcitabine-based chemotherapy combined with 15×2.4 Gy radiotherapy) did not improve the overall survival [7]. After neoTx, PCa patients with LA tumors demonstrate favorable histopathological features with higher R0 resection rates and decreased frequency of lymph node metastasis and perineural and lymphatic vessel invasion [8]. These encouraging results have led to an increasing number of neoadjuvantly treated patients; however, not all of these patients ultimately undergo surgical exploration. Mellon et al. reported that 46 of 110 patients with BR PCa became unresectable due to local/distant progression or due to poor performance status that precluded resection after neoTx [9]. Importantly, therapeutic response to neoTx is not reliably reflected by the current imaging techniques. This highlights the need for multidisciplinary communications between surgeons and oncologists to ensure an unbiased selection of patients for surgical exploration and an optimized patient management in PCa.

Conventional computed tomography (CT), the most commonly used imaging modality for the initial determination of tumor stage and resectability of PCa, has striking limitations in the evaluation of vessel involvement after neoTx [10]. The recent introduction of whole-tumor radiomic analysis has opened a range of possibilities to assess therapy response and resectability in PCa in a quantitative and non-invasive manner. A supervised machine learning algorithm from diffusion-weighted magnetic resonance imaging allowed overall survival (OS) prediction with a high diagnostic accuracy as well as histopathological sub-stratification of PCa patients [11]. Recent reports also pointed out that the combination of radiomic features such as reduced tumor stiffness in endosonographic elastography or reduced intensity on PET-CT is able to assess therapy response in PCa after neoTx [12]. While still in need of validation studies, the large-scale implementation of such tools has the potential to revolutionize image interpretation and individualized patient care [11].

**NeoTx in resectable PCa: illusion versus reality**

Although upfront surgery followed by adjuvant chemotherapy is still the recommendation for resectable PCa, this treatment fails to discriminate patients with undetected metastatic dissemination or aggressive tumor biology that may not benefit from surgical resection [13]. Furthermore, due to the high postoperative morbidity associated with pancreatic resections, up to 30% fail to receive or complete adjuvant chemotherapy [14]. The success of neoTx in BR/LA tumors has raised the question whether neoTx can improve prognosis in resectable...
patients, and clinical trials addressing to this matter are increasingly emerging.

The potential risk for patients with resectable PCa to develop local or distant tumor progression during neoTx, which might not have occurred in the setting of upfront resection, has been a recurrent argument against the use of neoTx in resectable tumors. The therapeutic paradigm of PCa is constantly evolving, and the focus has now turned toward the ability of the surgeon to remove the tumor radically. In this regard, neoTx may reduce surgical complexity by reducing the tumor bulk, the proportion of viable tumor cells, and the involvement of nearby vascular structures, resulting in an increased R0 resection rate [15].

Two early studies comparing the efficacy of gemcitabine-based neoTx with upfront surgery for resectable PCa determined its safety and feasibility but were terminated early due to slow recruitment and did not achieve statistically significant results [6, 16, 17]. Accordingly, two RCTs reported recently that neoTx is safe and effective without increased risk of surgical complications and was associated with favorable R0 resection rates in patients with resectable PCa [18]. In a large retrospective study, Mockdad et al. described prolonged survival in neoadjuvant-treated patients with early-stage PCa compared with upfront resected patients and thus provided further support for the use of neoTx as a patient selection tool in the management of resectable PCa [14]. Moreover, grade 3/4 toxicity in resectable PCa patients treated with neoTx was lower than in patients with BR/LA disease [19, 20]. In contrast, the recently published PREOPANC trial failed to any benefit in overall survival of patients with borderline or upfront resectable PCa (16.0 months with preoperative chemoradiotherapy versus 14.3 months with upfront surgery $P = .096$). Therefore, for early-stage, i.e., resectable, PCa, there is not enough scientific evidence for routinely recommending neoTx [7]. NeoTx in resectable PCa remains a matter of controversy and awaits the results of ongoing RCTs [21].

**Radical resection in PCa: “the holy grail”**

Curative R0 resection remains the only chance for long-term survival in PCa [22, 23]; however, approximately half of the resections are microscopically incomplete and two-thirds of initially R0-diagnosed patients will develop local recurrence [24]. Despite the prognostic relevance of the pathological resection rate, a standard definition for R0 resection is still lacking, which leads to high variability on R0 resection rates that range between 15% and 92% [1, 24–26]. After the introduction of a standardized pathology protocol consisting of axial slicing technique, multicolor margin staining and extended sampling, and a circumferential resection margin (CRM) > 1 mm, the R1 rate significantly increased from 14 to 76% in a retrospective study carried out by Esposito et al. [27, 28]. These observations indicate that resection margin involvement is a common finding in PCa which is often underestimated due to the lack of a standardized pathological examination of all relevant margins [28] and insinuated the need to increase surgical radicality in other to obtain wider resection margins and higher R0 rates. In line with these results, a retrospective study with 360 patients revealed similar local recurrence rates of R0- and R1-staged PCa patients suggesting the widespread presence of undiagnosed microscopic residual disease. Further intercontinental discrepancy is reported on the definition of R0 status, which is 0-mm tumor distance from resection margin in the USA and > 1 mm in Europe and Australia [1, 24, 27, 29, 30]. In our recent meta-analysis assessing the importance of the resection status in PCa, we demonstrated that even with standardized pathology protocols, resection margin’s prognostic validity may be primarily confined to pancreatic head tumors [24].

Pancreatic surgeons are continuously developing new strategies to increase surgical radicality and improve R0 resection rates [4]. The feasibility of portomesenteric venous resection has been widely demonstrated. In contrast, extended arterial involvement remains a controversial issue in the management of PCa. Although tumor encasement of the superior mesenteric artery, common hepatic artery, or celiac artery defines local irresectability according to current guidelines, advances in the field of pancreatic surgery have turned the focus on redefining strategies that allow more radical approaches involving the resection and reconstruction of major peripancreatic arteries, to achieve R0 resection in patients without distant metastasis [4, 31].

In the first meta-analysis evaluating AR in patients undergoing pancreatectomy for PCa, AR was discouraged as standard of care and was associated with remarkably higher perioperative morbidity (OR = 2.17) and mortality (OR = 5.04) and poor survival (OR = 0.50) [4]. Conversely, in a recent study, Del Chiaro et al. demonstrated the feasibility and safety of AR in pancreatectomy, which was accompanied by increased survival compared with palliative procedures and showed no difference in postoperative mortality and morbidity, even though it was associated with longer operation time and higher blood loss [31, 32]. Consistent with these results, Sonohara et al. demonstrated that PCa patients with AR had marginally higher recurrence-free survival and longer overall survival without a significant increase in the incidence of severe postoperative complications [33]. Current studies evaluating celiac artery resection also showed that these procedures can be performed safely and with an encouraging median survival [32, 34]. Further analyses suggested the improvement to be a consequence of newly developed and more effective chemotherapeutical regimens used in neoadjuvant settings. The increasing use of neoTx has notably increased the rate of R0 resections in patients with initially suspected arterial infiltration [35] and has led to significantly higher survival.
| NCT identifier | Phase | Allo-cation | Arms | Target accrual | Primary endpoint | Recruitment status | Projected completion date | Disease status | neoTx |
|---------------|-------|-------------|------|----------------|------------------|--------------------|--------------------------|----------------|-------|
| NCT03114631   | III   | Non-R       | DCs pulsed with tumor lysate; DCs pulsed with MUC-1/WT-1 peptides; no intervention anti-PD-1 antibody | 30             | PR or CR at 1 year | Completed          | May 19                  | LAM            | no    |
| NCT03989310   | III   | N/A         | Manganese chloride; nab-paclitaxel, gemcitabine; anti-PD-1 antibody | 20             | AEs and DCR     | Recruiting         | Mar 21                  | LAM            | no    |
| NCT03323944   | I     | Non-R       | huCART-meso cells | 18             | AEs              | Recruiting         | Sep 21                  | NR/M           | no    |
| NCT03008304   | III   | R           | High-activity NK; no intervention | 20             | RECIST           | Completed          | Dec 19                  | M              | no    |
| NCT03165591   | III   | N/A         | V3-P | 30             | Tumor burden, CA19-9 | Recruiting         | Dec 20                  | NR/M           | no    |
| NCT03180437   | III   | R           | IRE surgery; IRE plus γδ T cells | 60             | PFS, OS          | Completed          | 43.617                  | LA             | no    |
| NCT03329248   | III   | N/A         | ALT-803; ETBX-011; GI-4000; nαNK; avelumab; bevacizumab; capcitabine; cyclophosphamide; fluorouracil; leucovorin, nab-paclitaxel; iovaza, oxalplatin, SBRT | 80             | RECIST, AEs      | Completed          | Dec 19                  | Progress after SoC | no    |
| NCT02718859   | III   | R           | NK cells; IRE | 60             | PFS, OS          | Completed          | Mar 19                  | NR/M           | no    |
| NCT03193190   | III   | R           | Nab-paclitaxel, gemcitabine, atezolizumab, selicrelumab, AB928, iragomab, cimitetib, PEGPH20, BL8040, RO6874281 | 260            | RECIST, AEs      | Recruiting         | Nov 21                  | NR/M, progress after SoC | no    |
| NCT02261714   | III   | N/A         | TGO1 | 32             | DTH responses and proliferative T cell responses | Completed          | May 19                  | ATx            | no    |
| NCT03941457   | I/II  | N/A         | BCAR-NK cells (ROBO1 CAR-NK cells) | 9              | CTCAE            | Active, not recruiting | May 20                  | M              | no    |
| NCT03168139   | I/II  | N/A         | Olaptespegol + pembrolizumab + combination therapy | 20             | AEs, ECG, vital signs | Complete           | Mar 20                  | M              | no    |
| NCT03153410   | I     | N/A         | Cyclophosphamide, GVAX, pembrolizumab, IMC-CS4 | 12             | OS, DFS, ORR, RECIST, resectability, pPR, PFS | Active, not recruiting | Sep 20                  | BR             | yes   |
| NCT03816358   | I/II  | Non-R       | Anetumab ravtansine, gemcitabine, ipilimumab, nivolumab | 64             | MTD              | Recruiting         | Apr 21                  | NR/M           | no    |
| NCT04050085   | I     | N/A         | Nivolumab, radiation Tx, TL9 agonist SD-101 | 6              | AE, clinical laboratory | Recruiting         | Aug 20                  | M, Progress after SoC | no    |
| NCT03373188   | I     | R           | Anti-SEMA4D monoclonal antibody, VX15/2503, ipilimumab, nivolumab | 32             | T cell infiltration | Recruiting         | Dec 22                  | Re             | yes   |
| NCT03970252   | I/II  | N/A         | Fluorouracil, irinotecan, leucovorin, nivolumab, oxalplatin | 36             | Pancreatic fistula, pCR | Recruiting         | Apr 22                  | BR             | yes   |
| NCT03252808   | I     | R           | TBI-1401 (HF10), gemcitabine, nab-paclitaxel, TS-1 | 36             | AEs, ORR, RECIST, PFS | Active, not recruiting | Mar 35                  | NR/M           | no    |
| NCT03269520   | I/II  | N/A         | EGFR BATs | 22             | AEs, OS          | Recruiting         | Mar 23                  | NR/M           | no    |
| NCT03767582   | I/II  | R           | SBRT | 30             | CTCAE, immune response | Recruiting         | Dec 22                  | NR              | no    |
| NCT03745326   | I/II  | Non-R       | Cyclophosphamide, fludarabine, aldesleukin, anti-KRAS G12D mTCR PBL | 70             | AEs, response rate | Recruiting         | Dec 22                  | NR/M           | no    |
| NCT03953235   | I/II  | Non-R       | GRT-C903, GRT-R904, nivolumab, ipilimumab | 144            | AEs, SAEs, DLT, ORR, RECIST, Rp2D | Recruiting         | Dec 23                  | NR/M           | no    |
| NCT01351103   | I     | Non-R       | LGK974, PDR001 | 184            | MTD, RDE        | Recruiting         | Mar 22                  | NR/M, progress after SoC | no    |
| NCT03058289   | I/II  | Non-R       | INT230-6, anti-PD-1 antibody, anti-CTLA-4 antibody | 110            | CTCAE           | Recruiting         | Oct 22                  | Progress after SoC | no    |
| NCT03611556   | I     | R           | Ocleumab, durvalumab, gemcitabine, nab-paclitaxel, oxalplatin, leucovorin, S-FU | 339            | AEs, ORR, RECIST, ECG, clinical laboratory | Active, not recruiting | Dec 21                  | M              | no    |
| NCT03336216   | I     | R           | Cabiralumab, nab-paclitaxel, onivyde, nivolumab, fluorouracil, gemcitabine, oxalplatin, leucovorin, irinotecan | 179            | PFS, RECIST     | Active, not recruiting | Dec 20                  | NR/M, progress after SoC | no    |
| NCT02907099   | I     | N/A         | CXCR4 antagonist BL-8040, pembrolizumab | 23             | ORR, RECIST     | Active, not recruiting | Dec 22                  | Progress after SoC | no    |
| NCT identifier | Phase | Allocation | Arms | Target accrual | Primary endpoint | Recruitment status | Projected completion date | Disease status | neoTx |
|----------------|-------|------------|------|----------------|-----------------|--------------------|--------------------------|----------------|-------|
| NCT03161379    | II    | N/A        | Cyclophosphamide, nivolumab, GVAX, SBRT | 50 | pCR            | Recruiting        | Jan 23                  | BR             | yes   |
| NCT03723915    | II    | N/A        | Pembrolizumab, wild-type reovirus     | 30 | ORR, RECIST    | Active, not recruiting | Jun 21                | NR/M, progress after SoC | no   |
| NCT02305186    | I/II  | R          | Pembrolizumab, NeoCRTx                | 56 | Number of TILs, DLT | Active, not recruiting | Dec 22                | Re/BR, BR       | yes   |
| NCT03563248    | II    | R          | FOLFI RINOX, lansartan, nivolumab, SBRT | 160 | R0-resection rate | Recruiting        | Dec 25                  | BR/LA, BR       | yes   |
| NCT01088789    | II    | R          | PAN C10.05 pcDNA-1:GM-Neo and PAN C 6.03 pcDNA-1 neo vaccine | 72 | DFS, CTCAE     | Recruiting        | Apr 23                  | Re/BR, BR       | yes   |
| NCT03190265    | II    | R          | Cyclophosphamide, nivolumab, ipilimumab, GVAX pancreas vaccine, CRS-207 | 63 | ORR, RECIST    | Recruiting        | Oct 23                  | M              | no    |
| NCT03006302    | II    | R          | Epacadostat, pembrolizumab, CRS-207, CY, GVAX | 70 | Recommended dose, 6-months survival | Recruiting        | Jun 23                  | NR/M, progress after SoC | no   |
| NCT01896869    | II    | R          | Ipilimumab, vaccine, FOLFI RINOX       | 83 | OS             | Completed         | May 19                  | M              | no    |
| NCT03250273    | II    | Non-R      | Entinostat, nivolumab                 | 54 | ORR, RECIST    | Recruiting        | Nov 20                  | NR/M, M         | no    |
| NCT03717298    | II    | N/A        | Oexin-Viusid®                         | 30 | EORTC QLQ-C30, | Recruiting        | Dec 20                  | NR/M, M         | no    |
| NCT03767582    | I/II  | R          | SBRT, nivolumab, CCR2/CCR5 dual antagonist, GVAX | 30 | CTCAE, immune response | Recruiting        | Mar 22                  | LA, M          | yes   |
| NCT02446093    | II    | R          | GMCI, CTx, radiation, surgery         | 38 | Resection rate, CTC | Recruiting        | Dec 22                  | BR/LA, BR       | yes   |
| NCT0372880     | II    | R          | Pembrolizumab, defactinib             | 36 | pCR            | Recruiting        | May 23                  | Re             | yes   |
| NCT03806309    | II    | R          | FOLFI R, OSE2102, nivolumab           | 156 | OS             | Recruiting        | Dec 23                  | LAM, M         | no    |
| NCT03977272    | III   | R          | Combination drug, CTx                 | 110 | OS             | Recruiting        | Mar 22                  | M              | no    |
| NCT03983057    | III   | R          | Anti-PD-1 monoclonal antibody          | 830 | PFS            | Recruiting        | Apr 22                  | BR/LA          | yes   |

R randomized, Non-R non randomized, LA locally advanced, NR not resectable, M metastatic, Re resectable, PR partial response, CR complete response, pCR pathological complete response, pRR pathological response rate, DCR disease control rate, AE adverse events, CAR T cells chimeric antigen receptor modified T cells, IRE irreversible electroporation, PFS progression-free survival, OS overall survival, RECIST response evaluation criteria in solid tumors, SoC standard of care, CTx chemotherapy, ATx adjuvant therapy, DHT delayed hypersensibility, CTCAE common terminology criteria for adverse events, ECG electrocardiogram, PFS progression-free survival, MTD maximum tolerated dose, STBR stereotactic body radiation, ORR objective response rate, RP2D recommended phase 2 dose, RDE recommended dose for expansion, DCR disease control rate, TIL tumor-infiltrating lymphocytes, DLT dose-limiting toxicity
rates (78.8%) compared with patients who underwent upfront surgery (26.7%) [36]. In line with these results, Bachellier et al. reported remarkably prolonged survival in neoadjuvantly treated patients (23 months) compared with upfront resected PCa patients (13.7 months) after extended pancreatectomies involving AR [37]. Therefore, neoTx appears to provide an additional benefit to AR in patients with BR and LA PCa undergoing extended pancreatectomy by decreasing tumor burden and arterial invasion [33, 38]. In the case of adequate therapeutic response and good performance status, resectability should be re-assessed via surgical exploration, as cross-sectional images often fail to identify the extent of the remaining viable tumor. Combining AR with pancreatectomy in these cases increases the feasibility of R0 resection, which is still the only option to achieve long-term survival [39]. Here, neoTx should be performed rather than upfront surgery. Clinical trials analyzing the superiority of combined chemotherapeutical regimes and radical surgical resections are still needed and ongoing [4, 40–42].

**Immunotherapy as a novel neoadjuvant approach in PCa**

Cancer immunotherapy has demonstrated remarkable therapeutic efficacy in many solid malignancies [43]. Due to low tumor mutational burden and the presence of a highly immunosuppressive TME, immunotherapies have consistently failed to elicit the expected outcomes in PCa [44]. This limitation may be circumvented by the application of immunotherapy in a neoadjuvant setting, with the primary tumor serving as an antigen source for in situ T cell priming that may unleash a more potent antitumor immune response compared with adjuvant approaches [45]. Current neoTx in PCa mostly relies on classical chemotherapy regimens such as FOLFIRINOX and does not make use of immune-based and molecular-targeted therapies. Surprisingly, we observed an immunological shift toward more cytotoxic inflammation in the TME of PCa after conventional neoTx. This was mainly due to the depletion of immunosuppressive cells like regulatory T cells (Treg cells) [46] and myeloid-derived suppressor cells (MDSCs) [45, 47]. These results suggested that neoTx is able to prime the TME and potentiate the effect of immunotherapy by boosting the local antitumor immune response in PCa.

Ongoing trials on PCa are now focusing on combinatorial approaches exploiting the ability of cancer vaccines to promote T cell recruitment followed by the subsequent activation of cytotoxic cells by checkpoint inhibitors (ICIs) or immunomodulatory agents [48]. The inhibition of T cell checkpoints such as T lymphocyte protein 4 (CTLA4) and programmed cell death protein 1 (PD-1) has shown enormous promise in a number of cancer types [49, 50] by unleashing tumor-specific cytotoxic T cells that already reside in TME before treatment [51]. So far, none of these antagonists has proven effective in PCa [48]. However, the combination of a CD40 agonist with nab-paclitaxel plus gemcitabine resulted in partial response in 4 of 21 patients with PCa, and a clinical trial for its use as a neoadjuvant is underway (NCT02588443). Adoptive immunotherapy involves the injection of tumor reactive immune cells into patients and has increasingly gained attention over the past years. Although the first clinical trials with chimeric antigen receptor (CAR) T cells or tumor-pulsed dendritic cells in advanced PCa have shown promise [48], adoptive approaches have yet not been tested in neoadjuvant settings in PCa. The number of clinical trials evaluating the use of neoadjuvant immunotherapy is limited compared with its use within palliative approaches (Table 1).

In low mutational tumors such as PCa, neoTx may be particularly beneficial to potentiate the antitumor immune response compared with adjuvant approaches, as the tumor epithelium itself remains an essential source for the release of tumor antigens and cross-priming of tumor-directed T cell responses. This important reservoir for induction of tumor-directed immune responses is no longer available after tumor resection [52]. Liu et al. administrated various combination immunotherapies in either neoadjuvant or adjuvant setting and discovered that regardless of the type of immunotherapy used, neoadjuvant approaches were superior to adjuvant treatments in primary breast tumors [53]. In line with these observations, Brooks et al. demonstrated that only the combination of neoadjuvantly applied gemcitabine and a PD-1 inhibitor, but not adjuvant treatment, effectively suppressed local tumor recurrence and improved survival in a transgenic mouse model of PCa [52].

**Conclusion**

NeoTx leads to an immunologic shift toward a more effective antitumor immune response in the pancreatic TME, which recently provided impetus for studying the possibility of combining neoTx with immunotherapy in patients with PCa. Furthermore, neoTx leads to increased R0 resection rates and reduces the complexity of pancreatic surgical resections in LA/BR PCa patients. After neoTx, the postoperative morbidity associated with AR in pancreatectomy was similar to less radical approaches, leading the way to more sophisticated and radical surgical strategies in PCa. However, for resectable PCa, the overall survival benefit through neoTx does not exist in a convincing extent. Optimal drug regimens, timing of surgery with regard to therapy, and the role of additional immunotherapy still need to be defined. Balancing the optimal therapy for PCa will be complex and will require correct patient stratification, the use of combination strategies, and improved interdisciplinary cooperation.
Funding information Open Access funding provided by Projekt DEAL. IED was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)—project ID 329628492-SFB 1321.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors. The article does not contain any animal experiments.

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