



# How to select the most appropriate adjuvant treatment after neoadjuvant treatment and resection for locally advanced pancreatic cancer?

Elena Rangelova<sup>1,2^</sup>, Svein Olav Bratlie<sup>1,2</sup>

<sup>1</sup>Section for Upper Abdominal Surgery at Department of Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden; <sup>2</sup>Department of Surgery at The Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

*Contributions:* (I) Conception and design: E Rangelova; (II) Administrative support: Both authors; (III) Provision of study material or patients: Both authors; (IV) Collection and assembly of data: E Rangelova; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

*Correspondence to:* Elena Rangelova, MD, PhD, FACS. Department of Upper Abdominal Surgery, Sahlgrenska University Hospital, Blå Stråket 5, floor 2, 413 45 Gothenburg, Sweden. Email: elena.rangelova@gu.se.

**Abstract:** Adjuvant chemotherapy (ACT) significantly improves survival of patients undergoing upfront surgery for resectable pancreatic cancer. After introducing the concept of neoadjuvant therapy (NAT) with potent chemotherapy regimens, long term survival has been achieved even in patients with borderline and locally advanced pancreatic cancer (BR/LAPC) following radical resection. The observed pathologic tumor response is strongly predictive of survival and provides a unique opportunity to visualize to what extent the cancer has been sensitive to the administered chemotherapy regimen and may potentially give hint how to personalize further oncologic treatment. Current literature provides only limited and heterogeneous data as to whether and what type of ACT is beneficial after NAT and resection for BR/LAPC. Larger studies suggest that ACT may bring survival advantage and should be attempted particularly in node-positive disease and preferably with more potent regimen such as FOLFIRINOX, if tolerable. In case of complete pathologic response, particularly after FOLFIRINOX, it does not seem beneficial to deescalate the treatment during ACT, but whether continuation on the same regimen is worthwhile needs to be further examined. In case of gemcitabine-based treatment as NAT, continuation with more cycles seems to be of value unless tumor biology proves to be too aggressive, with high lymph node ratio. Whether switch to a different regimen should be sought, if tolerability allows it, needs to be further studied. Whether it is the exact treatment sequence (NAT, ACT or both) of the potent chemotherapy regimens like FOLFIRINOX and gemcitabine-nab-paclitaxel or the total dose of chemotherapy that has impact on survival in BR/LAPC, is unknown.

**Keywords:** Locally advanced pancreatic cancer (LAPC); borderline; resection; adjuvant therapy; neoadjuvant therapy

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<sup>^</sup> ORCID: 0000-0003-3844-7265.

## Introduction

Surgical resection is the treatment modality that must be involved if long-term survival of pancreatic cancer (PC) is to be achieved (1). Even after resection, about 30% of patients will develop recurrence within the first year of surgery and further up to 75–85% within 5 years, with fatal outcome (2,3). That implies that even smaller resectable tumors may give rise to indolent systemic spread that cannot be addressed solely by the local treatment that surgery is. The addition of adjuvant chemotherapy (ACT) after surgery, to address the problem of occult residual systemic metastatic disease, has almost cut in half the risk for recurrence and thus improved the survival of patients with resectable PC (4,5). The series of ESPAC trials established gemcitabine and, later on, gemcitabine in combination with capecitabine as the standard of adjuvant therapy, particularly in Europe (4,6). In Asian population, S-1 has been applied as an alternative of choice (7). As for borderline (BR) and locally advanced pancreatic cancer (LAPC), the same treatment sequence of upfront surgery followed by gemcitabine-based ACT, had not proven to give the same survival advantage (8). Thus, the skepticism towards the benefit of surgery in BR and LAPC has for long ruled the surgical opinion.

The introduction of FOLFIRINOX and gemcitabine-nab-paclitaxel significantly prolonged the survival of patients with unresectable and metastatic disease (9,10). Furthermore, pretreatment with these potent regimens of patients with BR and LAPC, followed by surgical resection, resulted in the observation of long-term survivors and revived the interest towards neoadjuvant treatment (NAT) (11–14). The concept of NAT in PC has been widely picked up now, irrespective of local resectability status, and multiple trials are ongoing worldwide (15,16). NAT has the potential advantages of not only increasing the pool of patients receiving systemic therapy, since tolerability may be impaired after preceding major surgery, but also selecting the better surgical candidates, having more favorable tumor biology and responding to the applied oncologic therapy (11,12,17,18). FOLFIRINOX has also proved to be superior to gemcitabine in the adjuvant setting after resection, with 3-year survival of 63.4% versus 48.6%, respectively, thus becoming the new adjuvant gold standard, whenever tolerable (19). The question remains whether ACT still carries the same survival benefit in the context of preceding NAT and resection. Is it the timing, the potency or the personalized choice of chemotherapy that plays the decisive role for survival?

Most of the factors predictive of prognosis of BR and LAPC are attained from the final histological assessment of the resected specimen (20–24). The observed tumor regression provides a unique opportunity to practically evaluate to which extent patients have been responsive to the given oncologic treatment and potentially could hint what drugs should be more appropriate in the postoperative setting. In case of the most common partial pathologic response, it is unclear whether the optimal drug choice should be the one that has proven effective, as reflected by the presence of destructed tumor areas, or an alternative should be sought in order to address the residual non-responsive viable tumor. There are theoretical advantages to both scenarios. When radiotherapy comes into context, though, it becomes even more cumbersome to interpret histologic regression as guidance to further treatment. The regression grade reflects the potency of radiation itself but does not guarantee that potential systemic spread has not occurred already and hint which drug would best approach it.

The purpose of this review is to summarize the available evidence for the utility of ACT after preceding NAT for borderline and locally advanced pancreatic cancer. A systemic literature search in PubMed was performed to identify series reporting on the outcome of resected patients with pancreatic adenocarcinoma after NAT. Of these, articles reporting on series that included only BR/LAPC or where these were part of the cohorts were reviewed in detail, while series reporting solely on primary resectable PC were excluded. Of the relevant publications, only articles that reported survival outcome after ACT were assessed and summarized in *Table 1* in order to attempt to answer four clinical questions—whether there is benefit of ACT after NAT, particularly for patients with BR/LAPC; is there a subgroup of patients having (larger) benefit and which type of ACT should be chosen.

## Is there benefit of ACT after NAT?

The interest in NAT started to escalate exponentially recently, since 2011, after the report on the effectiveness of FOLFIRINOX in unresectable PC was published (9). Naturally, the studies investigating the usage of ACT after NAT are falling behind and data on its effectiveness has not always been reported in them (25–27). Currently, there are no randomized controlled trials assessing the utility of ACT after NAT and resection for PC. All evidence comes from retrospective studies, mostly published in 2019–

**Table 1** Overview of the studies reporting the effect of adjuvant therapy on survival of resected patients with PC pretreated with NAT

Author, year	Country	Study period	No. centers	NCCN category	NAT Chemo Type	NAT RT	AT after NAT	ACT type	Pathologic regression and AT	OS with and without ACT	Results	Comments
Roland (2015)	USA	1990–2008	Single	All	in 49%: Gem/ Cap 92% (Gem/cis in 72%)	100%	14% (36/263)	Gem-based (Gem mono 44%)	nr	72 vs. 33 mo	ACT beneficial after CRT if LNR <0.15	When pre- and postoperative chemotherapy is similar, additional ACT beneficial in LNR <0.15
Pietrasz (2015)	France	11/2010–12/2013	Multi (n=20)	BR/ LAPC	FFX 100%	65%	54% (43/80)	Gem 77%, FFX 9%, Other 14%	Reported, not correlated	nr	ACT not predictive of survival	26% with major pathologic response. ACT did not differ between BR and LAPC
Luffi (2016)	USA	2006–2012	NCDB	nr*	nr	65%	33% (386/1188)	nr	nr	27.8 vs. 23.6 mo	Additional ACT after NAT beneficial over “NAT only”.	*stage I and II PC. “NAT + ACT” beneficial also over “ACT only”. “NAT only” with marginal benefit over “ACT only.”
Epelboym (2017)	USA	2008–2015	Single	All	Gem-based 73%, 5-FU-based 21%	35%	70% (165/237)	Gem-based 86%, 5-FU 8%	nr	nr	Duration of ChT more important than timing	Survival after NAT ± ACT not reported separately. NAT was combination in 66%, AT in 25%. ACT of ≥6 cycles as beneficial as NAT +AT with same duration
Franko (2017)	USA	2006–2011	NCDB	All	nr	73%	nr	nr	nr	nr	ACT beneficial for survival	cT4 part of the cohort. No effect of adjuvant RT

**Table 1** (continued)

Table 1 (continued)

Author, year	Country	Study period	No. centers	NCCN category	NAT Chemo Type	NAT RT	AT after NAT	ACT type	Pathologic regression and AT	OS with and without ACT	Results	Comments
Chapman (2018)	USA	2012–2016	Single	BR/ LAPC	FFX 69%, GnP 31%	70%	72% (48/67)	nr	Reported, not correlated	nr	ACT not predictive of survival	Likelihood for resection bigger after FFX, but if resected no survival difference whether NAT was FFX or GnP
De Geus, (2018)	USA	2006–2013	NCDB	All	nr	nr	39% (524/1,357)	nr	nr	27.5 vs. 27.1 mo	ACT not predictive of survival	No difference in survival with ACT in sensitivity analysis for resection margins, LN status or LNR. No difference in survival if ACT was ChT- or CRT
Dhir (2018)	USA	06/2011–05/2017	Single	R/BR	GnP 62%, FFX 38%	yes	75% (144/193)	nr	Reported, not correlated	nr	ACT predictive of survival in all variable model (HR 0.24), but not in preoperative/clinical model survival	Similar number received ACT in the two NAT groups. In the preoperative variables/clinical model, the number of NAT/ACT cycles associated with survival
Swords (2019)	USA	2006–2014	NCDB	All	48.4% ChT only; type not reported	52%	45% (673/1,481)	nr	nr	42.8 vs. 33.4 mo in ChT NAT	ACT beneficial after NAT ChT in LNR 0.01–<0.15, but not in N0 or LNR >0.15	ACT given more often to N+ than N-. If NAT was CRT, ACT not beneficial stratified for LNR
Gemenetis (2019)	USA	1/2103–9/2017	Single	LAPC	FFX 63%, GnP 20%, Both 17%	96%	30% (25/84)	FFX 64%, GnP 20% Gem +/- Cap 44%	nr	36.1 vs. 28.6 mo	ACT not predictive of survival	ACT choice based on pathology and patient condition; details not specified

Table 1 (continued)

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Author, year	Country	Study period	No. centers	NCCN category	NAT Chemo Type	NAT RT	AT after NAT	ACT type	Pathologic regression and AT	OS with and without ACT	Results	Comments
Groot (2019)	USA	2007–2015	Single	BR/ LAPC	FFX 42%, gem-based 39%, both 19%	78%	60% (138/231)	FFX-based 19%; GnP 11%, Gem- Cap 11%, Mono Tx 19%	Reported, not correlated	22.7 vs. 15.4 mo	ACT associated with improved RFS and OS	ACT associated with reduced multiple/liver recurrence
Blair (2019)	USA	2009–2017	Single	BR/ LAPC	FFX 38%, Gem comb 31%, Both 21%, Mono Tx 10%	100%	48% (14/29)	FFX 14% Gem comb 36% mono 36% Clinical trial 14%	pCR only	nr	ACT not predictive of survival in pCR after CRT	Even after pCR, 14/29 recurred and 70% of them had distant metastases
Kourie (2019)	France	2009–2017	Multi (n=9)	BR/ LAPC	FFX 100%	83%	30% (8/29)	Gem 50% FOLFIRI 25% FOLFOX 13% GemOx 13%	pCR only	nr	ACT not predictive of OS and DFS	
Pietrasz (2019)	France	11/2010–2015	Multi (n=23)	BR/ LAPC	FFX 100%	50%	57% (116/203)	Gem 67%, 5-FU+Ox/ Iri 23%, FFX 10%	Reported, not correlated	nr	ACT not predictive of OS.	More often administered after FFX chemo- than after chemoradiotherapy (73% versus 41%)
Perri (2020)	USA	2010–7/2017	Single	All	FFX 47%, GnP 15%, Other (gem- based) 38%	90%	63% (155/245)	Gem mono 56% Gem or Cap comb 25% FFX 10% GnP 6%	Reported, not correlated	42 vs. 32 mo	ACT marginally beneficial for OS in multivariate analysis in propensity- matched cohort (P=0.05)	Those receiving ACT had fewer NAT cycles or received chemoradiation only

Table 1 (continued)

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Author, year	Country	Study period	No. centers	NCCN category	NAT Chemo Type	NAT RT	AT after NAT	ACT type	Pathologic regression and AT	OS with and without ACT	Results	Comments
Liu (2020)	USA	2008–2016	Single	All	Gem-based 70%, 5-FU based 30%	20%	74% (178/241)	nr	nr	34.5 vs. 19.1 mo	ACT beneficial if CA19-9 not normalized or decreased <50%.	68% non-optimal CA19-9 responders. Same% received AT, with similar number of cycles. Optimal responders had more favorable histologic features
Weniger (2020)	Europe	1/2011–6/2017	Multi (n=7)	BR/LAPC	FFX 56%, GnP 16%, Gem mono 7%, Other 21%	12%	60% (107/179)	Gem 43%, GnP 16%, FFX 12%	Reported, not correlated	nr	ACT not predictive of OS and PFS.	59% of ACT treated had FFX before. Neither ACT as Gem, FFX nor GnP had impact on survival
van Roessel (2020)	Europe/USA	2012–2018	Multi (n=31)	All	FFX 100%	nr	66% (343/520)	Gem-based 59%, FFX 20%, Cap 4%, Comb/ others 13%, Unknown 4%	Reported, not correlated	29 vs. 29 mo OS, 26 vs. 13 mo in pN1	ACT not predictive of OS. ACT beneficial only in pN1 BR/LAPC, not pN0	BR/LAPC 49.8%. In R: ACT not beneficial irrespective if pN0 or 1. Both Gem and FFX beneficial, bigger for FFX
Drake (2020)	USA	2004–2015	NCDB	All**	nr	55%	34% (680/2,011)	nr	nr	23.6 vs. 20.5 mo in R1	ACT Improved survival in R1 propensity), not in R0	**T1-3 PDAC resected after NAT (T4 excluded). AT improved survival in R1 resection both on multivariate analysis and propensity matching

Table 1 (continued)

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Author, year	Country	Study period	No. centers	NCCN category	NAT Chemo Type	NAT RT	AT after NAT	ACT type	Pathologic regression and AT	OS with and without ACT	Results	Comments
Cloyd (2020)	USA	2004–2016	NCDB	All	nr	48%	35% (2,748/7,902)	nr	pCR reported, not correlated	nr	ACT beneficial for OS.	Known cT and pT. ACT more often in non-complete pathologic response
Okada (2020)	Japan	2008–2019	Single	BR	Gem/S-1 45%, GnP/S-1 42%, FFX 5%, Others 8%	0	67% (72/108)	nr	Reported, not correlated	nr	ACT beneficial for OS.	
Wittmann (2020)	USA	2009–2018	Single	R/BR	FFX 49%, GnP 18%, 5-FU/Gem-based comb 27%, Gem 4%	87%	nr	nr	Reported, not correlated	nr	ACT beneficial for OS.	Resectable PC treated with chemoradiation with gem or cap. BR treated with 2 months ChT followed by radiation. ACT more often in incomplete response, but type not reported
Tsai (2020)	USA	2009–2017	Single	R/BR	nr	81%	59% (77/131)	nr	nr	nr	ACT not predictive of OS.	Only patients with preoperatively elevated CA19-9. Patients with greatest decrease of Ca19-9—more likely to have lower pathologic disease stage

Table 1 (continued)

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Author, year	Country	Study period	No. centers	NCCN category	NAT Chemo Type	NAT RT	AT after NAT	ACT type	Pathologic regression and AT	OS with and without ACT	Results	Comments
Ren (2021)	USA	2008–2018	Single	All	In 92% FFX 79%	51%	53% (44/83)	nr	Reported, not correlated	nr	ACT beneficial for OS in postoperative model	92% with BR/LAPC according to AHPBA/SSAT/SSO. ACT varied dependent on dose, tolerability and tumor response
Truty (2021)	USA	2010–2017	Single	BR/LAPC	FFX 85%, GnP 65% (switch 19%)	100%	nr	nr	Reported, not correlated	nr	ACT not predictive of OS and PFS	192 pts. NAT >6 cycles, optimal Ca19-9 and major pathologic response (CAP 0/1) predictive of survival

AT, adjuvant therapy; ACT, adjuvant chemotherapy; BR, borderline resectable pancreatic cancer; Cap, capecitabine; ChT, chemotherapy; DFS, disease-free survival; FFX, FOLFIRINOX; Gem, gemcitabine; GnP, Gemcitabine with nab-paclitaxel; LAPC, locally advanced pancreatic cancer; LNR, lymph node ratio; NAT, neoadjuvant therapy; NCCN, National Comprehensive Cancer Network; NCDB, National Cancer Database; nr, not reported; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; RT, radiotherapy.



2020. Many of the series are reports from single centers, including longer periods of time, when varying NAT regimen have been prevalent (22,28-30). Others use data extracted from the National Cancer Database and therefore lack information on the particular type of NAT and ACT used (27,31-35). The studies reporting on the outcome in resected patients with PC receiving ACT after NAT are summarized in *Table 1*.

#### *Administration frequency and selection criteria for ACT*

The frequency with which ACT has been given varies among the studies between 14% and 75%. In the dominating part, less than half of the patients have received treatment. Notably, in the large-scale reports based on the National Cancer Database, only about one third of the patients have received additional ACT after NAT and resection for PC (31-35). That is considerably less than the frequency with which ACT is administered after upfront resection reported repeatedly to be about 60% (2,36). Barbas *et al.* found that ACT is particularly spared to the elderly, above 75 years of age, despite that they received NAT to the same extent as younger patients (37). The criteria for the application of ACT after NAT, beside tolerability, are seldom revealed, but few studies point out it is more often administered in patients with less favorable tumor characteristics on histology, such as regional lymph node metastases, R1 resection, and incomplete pathologic response (27,35,38-40). Whether the reduced dose intensity or duration of NAT affects the decision to continue with ACT postoperatively has not been addressed.

#### *Survival outcome with ACT after NAT—matter of timing or total dose of chemotherapy*

The results whether ACT brings survival advantage after NAT in resected PC irrespective of resectability state preoperatively are contradictory. Eleven of the studies report no survival benefit (13,21,29,32,41-47), while other fourteen find it beneficial (22,28,30,31,33-35,38-40,48-51). The majority of the studies revealing advantage of ACT do not specify what the resectability status of the patients involved has been and only four of them (22,28,38,48) provide data on the type of ACT administered. Interestingly, in half of the studies proving benefit of ACT, positive impact on survival has been observed not in the whole cohort, but only in specific subgroups of patients, such as having lymph node metastases, lower lymph-node ratio, R1 resection, and non-

significant reduction of CA19-9 after NAT (28,30,33,34,48).

Whether it is the exact timing (NAT, ACT or both) or it is the amount of chemotherapy delivered that has larger impact on survival is not quite clear. Epelboym *et al.* addressed particularly this issue in a single-institution series where the administered NAT and ACT were similar—gemcitabine-based in 73% and 85.5%, respectively, and 5-FU based in 21% and 8.3% (29). In this situation with the same NAT and ACT, the entire duration of the oncologic treatment was found to be more important than the timing itself. ACT of at least 6 cycles had similar benefit as combination of NAT and ACT with the same duration. On the contrary, van Roessel *et al.* reported that similar number of NAT cycles were administered to patients with and without ACT and still additional ACT had no benefit in the common cohort (48). The type of chemotherapy in NAT and ACT, though, was not specified and matched. They found, however, in a subgroup of patients with node-positive BR/LAPC in which ACT was beneficial, that the effect modification was dependent of fewer number of NAT cycles. Dhir *et al.* investigated the value of ACT in patients who received NAT in form FOLFIRINOX or GnP and found that ACT was predictive of survival in one multivariate model, while in another model, the total number of NAT/ACT cycles to be associated with improved survival (50). The type of ACT administered was not reported. In a series of patients with only early-stage PC (IA-IB), Vega *et al.* found that any sequence of chemotherapy given (NAT, ACT or perioperative NAT/ACT) lead to improved survival compared to if not chemotherapy was given at all (52). They did not provide data on the type of chemotherapy applied either (52). Thus, the question whether the total dose or the time-point of chemotherapy is more important, remains to be answered.

#### **Is there benefit of ACT after NAT in BR and LAPC?**

Only three of the eleven studies focusing specifically on BR/LAPC, and being the largest ones, revealed survival advantage of ACT (22,48). Groot *et al.* reported the largest single-center series of BR/LAPC where 138 of 231 patients received ACT and also the only one showing ACT is advantageous both for the overall and recurrence-free survival. ACT was associated with reduced number of liver and multiple-site recurrence (22). van Roessel *et al.* found in a multi-institutional cohort that ACT, given to 159 of 259 BR/LAPC patients, was beneficial for survival only in lymph-node positive, but not in node-negative BR/

LAPC patients (48). Okada *et al.* who reported the only study on purely BRPC and the only study coming from the East, where S-1 was used as part of gemcitabine-based combination therapy in NAT in 87% of the patients (51). They found ACT to improve the survival of resected BR patients. Although the type of ACT was not specified, reference to previous publications reveals that the adjuvant regimen was probably similar—combination of gemcitabine/S-1. The total number of cycles of chemotherapy in NAT/ACT were not reported. The remaining smaller studies did not show any additional survival benefit of ACT, but might as well have been underpowered to detect a difference.

### ***ACT after FOLFIRINOX in BR/LAPC***

Four studies reported data where only FOLFIRINOX was used as NAT. In two of them, reporting multicenter data from France, ACT was dominated by gemcitabine in 67 and 77%, respectively, while FOLFIRINOX was very seldom continued—in about 9% of patients (41,45). ACT was not found to play a role for the overall survival. No subgroup analysis was performed to correlate pathologic response and the value of additional treatment. A third study, also from France, looked only at patients with complete pathologic response (pCR) after FOLFIRINOX. Only 30% of patients received ACT (gemcitabine in 50% and no FOLFIRINOX) and it had no impact on survival (44). In the fourth already mentioned study by van Roessel *et al.*, ACT was also dominated by gemcitabine-based treatment in 59% while FOLFIRINOX was applied in 20% of cases, but it was not reported whether specifically the BR/LAPC group received ACT with the same proportion of drugs (48). Both gemcitabine and FOLFIRINOX showed advantage given as ACT, particularly the latter.

### ***ACT after other NAT in BR/LAPC***

The remaining studies used various NAT regimens as the proportion of FOLFIRINOX in them varied between 38% and 85%. In four them the ACT type was reported, mostly dominated by gemcitabine except for one (13,22,41,43). In the only series selectively performed in LAPC, Gemenetzi *et al.* reported similar proportion of FOLFIRINOX to be given both as NAT and ACT, 63% and 64%, yet, proving no advantage of ACT (13). It was not reported whether patients tended to be kept on the same NAT and ACT regimens or not. Radiotherapy was part of NAT in more than half of the patients and up to 100% in all the series,

but whether its application would modify the efficacy of ACT has not been addressed.

How to interpret the data on ACT in BR/LAPC from the current reports is somehow ambiguous. The studies are relatively small to address this particular issue. The patients undergoing surgery after NAT are already a selected cohort that carries the common feature of response to particular regimen by showing stabilization or regression during treatment. To look further for effectiveness of various ACT, one should probably look into subgroups of patients stratified according to treatment response to NAT and the type of additional treatment, which would demand much larger cohorts. This information on the treatment sequence in each patient is lacking in the literature—whether the type of NAT and ACT administered was similar or not and whether the pathologic response to NAT have influenced the choice and efficiency of ACT. So, would it be fair to generalize in favor or not of ACT when so many important variables are not taken into consideration?

### **To whom should ACT be given after NAT?**

Data from the focused BR/LAPC studies was inconclusive whether ACT might have a benefit for the whole cohort of patients or only for a certain subgroup. Therefore, we looked broader for further details in the remaining studies reporting ACT after NAT for all categories of resected PC (*Table 1*) in which BR and LAPC were at least part of the cohorts. Of the ten studies reporting definitive beneficial effect of ACT, in five advantage was observed only in a subgroup of the patients.

### ***ACT in the presence of lymph node metastases***

The most studied correlation is the efficacy of ACT in respect to the lymph node status after resection. Lymph node metastases and lymph node ratio (LNR) are negative prognostic factors for survival and can be referred to as signs of tumor aggressiveness and/or relative insensitivity to the administered NAT (22,38). Respectively, additional potent chemotherapy might presumably be of benefit. ACT has more often been administered to N1 patients after NAT (33,40,48). Roland *et al.* and Swords *et al.* reported that patients with lower LNR <0.15 were the ones who benefit from additional ACT (28,33). In the study by Roland *et al.* both NAT and ACT were similar - gemcitabine/capecitabine-based (28). That could point out that whenever tumor aggressiveness is greater or the tumor

is not responsive to the administered lower-potency NAT, as reflected by higher LNR, continuous treatment with similar chemotherapy might not be beneficial. In van Roessel's study, node-positive patients with BR/LAPC had benefit of ACT irrespective if it was gemcitabine-based or FOLFIRINOX (48). Interestingly, the same study did not find ACT to improve survival in N1 primary resectable cancer, but details on the profile of the administered NAT and ACT in this case were not provided. Other studies did not find correlation between lymph node status and benefit of ACT (32).

### ***ACT and pathologic regression***

While it is more difficult to assume what the lymph node status has initially been before NAT, the pathologic regression of the primary tumor gives a more quantitative impression of the therapeutic response. It describes the proportions of post-treatment fibrosis and the remaining viable tumor and has been clearly associated with survival. Two studies looked at patients with pCR after NAT. Kourie *et al.* did not find additional benefit of ACT after FOLFIRINOX and pCR (44). None of the patients in the study received FOLFIRINOX as ACT. Blair *et al.* evaluated 29 patients with pCR all of whom received radiotherapy. Despite that about half of the patients developed recurrence after pCR (n=14/29), and of them 70% had distant metastases, indicating that the systemic control of disease was failing, no benefit of ACT was seen (43). In this study, FOLFIRINOX represented only 38% of NAT and 14% of ACT, the latter being dominated by gemcitabine and monotherapy in 2/3 of the cases. Thus, in case of pCR, whether FOLFIRINOX given as ACT would provide additional survival benefit, particularly if it has been the regimen in the induction chemotherapy, remains to be investigated. As for the most common scenario, when incomplete pathologic response is observed, there are no studies that correlated it with the efficacy of the administered ACT.

### ***ACT and biochemical response***

Biochemical response after NAT and correlation with the efficacy of ACT has also been investigated. Liu *et al.* found that ACT improved the overall survival of patients who did not have normalized serum CA19-9 or in whom it was reduced by less than 50% after gemcitabine and 5-FU-based NAT (30). The type of ACT was not reported in the study.

### ***ACT and genetic profile of the tumor***

Finding a genetic signature that reveals sensitivity to chemotherapy is a long-tempted mean for personalized patient approach in order to fine-tune the treatment selection. The most widely addressed expression of hENT1 as a marker for sensitivity to gemcitabine, has been found to correlate with survival in patients with BR treated with gemcitabine-based neoadjuvant chemoradiotherapy (53). However, whether patients had further benefit of continuous ACT was not addressed in this study. Using the PC mutational profile could potentially identify responders to platinum (54) or other targetable drugs (55). Whether these correlated with the histologic response found post factum after NAT or whether targeted ACT to detected would have additional benefit has not been investigated.

### ***Which type of ACT is most efficient after NAT?***

Optimally, the clinical question would be whether the given NAT has sufficient effectiveness, as predicted by the observed pathologic and biochemical response, and whether treatment should continue postoperative with the same agent(s). Like addressed previously, there is no study that investigates this issue. van Roessel *et al.* are the only ones to address which type of ACT is more effective after single type of NAT (FOLFIRINOX), finding that both continuation of FOLFIRINOX as well as gemcitabine-based ACT was effective in N1 BR/LAPC (48). Further data was not presented on whether the same ACT or a therapy switch to gemcitabine may have had impact on survival depending on pathologic tumor response. Kourie *et al.* showed that in patients with pCR after FOLFIRINOX, gemcitabine and fewer-agents ACT do not further improve survival (44). No one in this series continued on FOLFIRINOX, so it is unclear whether further benefit could have been obtained from the same regimen.

The majority of the remaining studies report heterogeneous NAT and ACT, without correlation on what premise the choice of ACT has been made. Therefore, hardly any conclusions can be drawn on what the optimal choice of ACT should be. In the two studies where gemcitabine or 5-FU-based treatment was used both in the pre- and the postoperative setting, ACT seems worthwhile in case of more favorable histology—e.g., either if the tumor does not express very aggressive features (higher LNR) or whenever at least some tumor response to chemotherapy is present (28). The same might be true

even for FOLFIRINOX, as suggested by van Roessel *et al.* Further studies are needed to assess whether greater number of cycles bring additional benefit in responders and whether gemcitabine may still prove efficient in case tumor is fairly insensitive to FOLFIRINOX.

In summary, data on whether and what type of ACT is beneficial after NAT and resection for BR/LAPC are very limited and heterogeneous. Larger studies suggest that ACT may bring survival advantage and should be attempted particularly in node-positive disease and preferably with more potent regimen such as FOLFIRINOX, if tolerable. In case of complete pathologic response, particularly after FOLFIRINOX, it does not seem beneficial to deescalate the treatment during ACT, but whether continuation on the same regimen is worthwhile needs to be further examined. In case of gemcitabine-based treatment as NAT, continuation with more cycles seems to be of value unless tumor biology proves to be too aggressive, with high LNR. Whether switch to a different regimen should be sought, if tolerability allows it, needs to be further studied. Whether it is the exact timing of administration or the total dose of chemotherapy that impacts survival, especially for FOLFIRINOX and gemcitabine-Nab-paclitaxel, is unknown. Generally, there is a strong and calling need for further research assessing patient-level data on response to oncologic therapy and using this information to personalize ACT for the most effective postoperative treatment.

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### Footnote

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