|     |               |          |    | -              |                      | of the incl |               | [              |                |
|-----|---------------|----------|----|----------------|----------------------|-------------|---------------|----------------|----------------|
| Nu  | Clinical      | Refer    | Ye | Target         | Treatment(s)         | Primary     | Patients      | Median OS      | Median         |
| mbe | trial/Phase/S | ence     | ar | population     |                      | endpoint    | on            |                | PFS            |
| r   | tudy design   |          |    |                |                      | of          | treatmen      |                |                |
|     |               |          |    |                |                      | efficacy/   | t(s),n        |                |                |
|     |               |          |    |                |                      | Seconda     |               |                |                |
|     |               |          |    |                |                      | ry          |               |                |                |
|     |               |          |    |                |                      | outcome     |               |                |                |
|     |               |          |    |                |                      | s           |               |                |                |
| 1   | NCT0069030    | Ettric   | 20 | Patients with  | 75 mg/m <sup>2</sup> | Primary     | 44            | 10.1           | 1.82           |
|     | 0, DocOx      | h et al. | 16 | chemo-         | docetaxel for        | endpoint    |               | months         | months         |
|     | (AIO-         | [35]     |    | refractory     | 60 minutes on        | : tumor     |               |                |                |
|     | PK0106)       |          |    | advanced       | day 1 and <b>80</b>  | response    |               |                |                |
|     |               |          |    | pancreatic     | mg/m <sup>2</sup>    | accordin    |               |                |                |
|     | Phase II      |          |    | ductal         | oxaliplatin          | g to        |               |                |                |
|     |               |          |    | adenocarcino   | for 120              | RECIST      |               |                |                |
|     | An open       |          |    | ma with        | minutes on           | 1.0.        |               |                |                |
|     | label,        |          |    | previous       | day 2 in 21-         | Seconda     |               |                |                |
|     | multicenter,  |          |    | chemotherap    | day cycles.          | ry          |               |                |                |
|     | single arm,   |          |    | y experience   | The                  | endpoint    |               |                |                |
|     | study.        |          |    | (for example   | treatment            | s: PFS,     |               |                |                |
|     | study.        |          |    | gemcitabine    | period was           | OS,         |               |                |                |
|     |               |          |    | as first line  | scheduled for        | safety/to   |               |                |                |
|     |               |          |    | therapy for    | up to 8 cycles.      | xicity,     |               |                |                |
|     |               |          |    |                | up to o cycles.      | 2           |               |                |                |
|     |               |          |    | metastatic     |                      | quality     |               |                |                |
|     |               |          |    | pancreatic     |                      | of life     |               |                |                |
|     |               |          |    | cancer).       |                      | and         |               |                |                |
|     |               |          |    |                |                      | clinical    |               |                |                |
|     |               |          |    |                |                      | benefit.    |               |                |                |
| 2   | JapicCTI-     | Ueno     | 20 | Patients with  | Patients were        | Primary     | 140 (69       | 6.3 months     | 3.8            |
|     | 111554        | et al.   | 16 | gemcitabine-   | randomly             | endpoint    | patients      | for S-1 plus   | months         |
|     |               | [36]     |    | refractory     | assigned to          | : PFS       | in <b>S-1</b> | leucovorin     | for <b>S-1</b> |
|     | Phase II      |          |    | advanced       | receive S-1 at       |             | plus          | group and      | plus           |
|     |               |          |    | pancreatic     | 40, 50 or 60         | Seconda     | leucovor      | 6.1 months     | leucovor       |
|     | An open-      |          |    | cancer (first- | <b>mg</b> according  | ry          | in group      | for <b>S-1</b> | in group       |
|     | labeled,      |          |    | line treatment | to body              | endpoint    | and 71        | group.         | and 2.7        |
|     | multicenter,  |          |    | was with       | surface area         | s: OS,      | patients      |                | months         |
|     | randomized    |          |    | gemcitabine).  | plus 25 mg           | response    | in <b>S-1</b> |                | for <b>S-1</b> |
|     | study.        |          |    |                | leucovorin,          | rate        | group).       |                | group.         |
|     |               |          |    |                | both given           | (RR),       |               |                |                |
|     |               |          |    |                | orally twice         | disease     |               |                |                |

Supplementary Table 1. Characteristics of the included studies.

|   | 1             |        |    |                            |                      |                   |                        |                |                       |
|---|---------------|--------|----|----------------------------|----------------------|-------------------|------------------------|----------------|-----------------------|
|   |               |        |    |                            | daily for 1          | control           |                        |                |                       |
|   |               |        |    |                            | week,                | rate              |                        |                |                       |
|   |               |        |    |                            | repeated             | (DCR),            |                        |                |                       |
|   |               |        |    |                            | every 2              | duration          |                        |                |                       |
|   |               |        |    |                            | weeks; or S-1        | of                |                        |                |                       |
|   |               |        |    |                            | monotherap           | response          |                        |                |                       |
|   |               |        |    |                            | <b>y</b> at the same | , time to         |                        |                |                       |
|   |               |        |    |                            | dose as the S-       | treatmen          |                        |                |                       |
|   |               |        |    |                            | 1-leucovorin         | t failure         |                        |                |                       |
|   |               |        |    |                            | group for 4          | (TTF),            |                        |                |                       |
|   |               |        |    |                            | weeks,               | time to           |                        |                |                       |
|   |               |        |    |                            | repeated             | progress          |                        |                |                       |
|   |               |        |    |                            | every 6              | ion               |                        |                |                       |
|   |               |        |    |                            | weeks.               | (TTP),            |                        |                |                       |
|   |               |        |    |                            |                      | dose              |                        |                |                       |
|   |               |        |    |                            |                      | intensity         |                        |                |                       |
|   |               |        |    |                            |                      | , and             |                        |                |                       |
|   |               |        |    |                            |                      | adverse           |                        |                |                       |
|   |               |        |    |                            |                      | events.           |                        |                |                       |
| 3 | Phase II      | Tai et | 20 | Patients with              | Conventiona          | Primary           | 59 (28                 | 7 months       | 3                     |
| 5 | i nase n      | al.    | 16 | histological               | 1 group              | endpoint          | patients               | for            | months                |
|   | А             | [39]   | 10 | or                         | received             | : OS              | in                     | convention     | for                   |
|   | retrospective | [00]   |    | cytologically              | conventional         | .05               | conventi               | al group       | conventi              |
|   | , tow-armed   |        |    | confirmed                  | therapy              | Seconda           | onal                   | and 10         | onal                  |
|   | study.        |        |    | pancreatic                 | (leucovorin,         |                   |                        | months for     |                       |
|   | study.        |        |    | adenocarcino               | gemcitabine,         | ry                | <b>group</b><br>and 31 | targeted       | <b>group</b><br>and 9 |
|   |               |        |    |                            | cisplatin,           | endpoint          |                        | -              |                       |
|   |               |        |    | ma (locally<br>advanced or | -                    | s: PFS<br>and the | patients               | group.         | months<br>for         |
|   |               |        |    |                            | and<br>fluorouracil) |                   | in<br>torrected        | OS for         |                       |
|   |               |        |    | metastatic                 |                      | safety            | targeted               |                | targeted              |
|   |               |        |    | pancreatic                 | in two week          | profiles          | group).                | patients       | group.                |
|   |               |        |    | cancer) not                | intervals for        | of the            |                        | ≤60 years      | DEC (                 |
|   |               |        |    | amenable to                | 12 cycles.           | combine           |                        | <b>old</b> : 5 | PFS for               |
|   |               |        |    | curative                   | Targeted             | d                 |                        | months for     | patients              |
|   |               |        |    | treatment                  | group                | therapy.          |                        | convention     | ≤60                   |
|   |               |        |    | with surgery               | received             |                   |                        | al group       | years                 |
|   |               |        |    | or had been                | conventional         |                   |                        | and 12         | <b>old</b> : 3        |
|   |               |        |    | documented                 | therapy plus         |                   |                        | months for     | months                |
|   |               |        |    | or suspected               | bevacizumab          |                   |                        | targeted       | for                   |
|   |               |        |    | of metastases              | and                  |                   |                        | group.         | conventi              |
|   |               |        |    | to extra-                  | cetuximab in         |                   |                        |                | onal                  |
|   |               |        |    | pancreatic                 | each cycle           |                   |                        | There was      | group                 |
|   |               |        |    | sites. Patients            | (two week            |                   |                        | no             | and 10                |
|   |               |        |    | with no prior              |                      |                   |                        | difference     | months                |

|   |               |          |    | -l tl          | internal 6-1              |          |          | 1 t        | 6              |
|---|---------------|----------|----|----------------|---------------------------|----------|----------|------------|----------------|
|   |               |          |    | chemotherap    | intervals for             |          |          | between    | for            |
|   |               |          |    | y were         | 12 cycles).               |          |          | OS of two  | targeted       |
|   |               |          |    | included.      | Conventional              |          |          | treatment  | group.         |
|   |               |          |    |                | treatment                 |          |          | groups in  |                |
|   |               |          |    |                | arm: <b>1000</b>          |          |          | patients   | PFS for        |
|   |               |          |    |                | mg/ m <sup>2</sup>        |          |          | >60 years  | patients       |
|   |               |          |    |                | gemcitabine,              |          |          | old.       | >60            |
|   |               |          |    |                | 50 mg/ m <sup>2</sup>     |          |          |            | years          |
|   |               |          |    |                | cisplatin for             |          |          |            | <b>old</b> : 3 |
|   |               |          |    |                | the days 1, 8             |          |          |            | months         |
|   |               |          |    |                | and 15. The               |          |          |            | for            |
|   |               |          |    |                | treatment                 |          |          |            | conventi       |
|   |               |          |    |                | interval for              |          |          |            | onal           |
|   |               |          |    |                | each cycle                |          |          |            | group          |
|   |               |          |    |                | was 21 days.              |          |          |            | and 7          |
|   |               |          |    |                | Targeted                  |          |          |            | months         |
|   |               |          |    |                | group:                    |          |          |            | for            |
|   |               |          |    |                | gemcitabine               |          |          |            | targeted       |
|   |               |          |    |                | and cisplatin             |          |          |            | group.         |
|   |               |          |    |                | on day 1                  |          |          |            |                |
|   |               |          |    |                | similar to the            |          |          |            |                |
|   |               |          |    |                | conventional              |          |          |            |                |
|   |               |          |    |                | group, 5                  |          |          |            |                |
|   |               |          |    |                | mg/kg                     |          |          |            |                |
|   |               |          |    |                | bevacizumab               |          |          |            |                |
|   |               |          |    |                | (at 8 mg/kg in            |          |          |            |                |
|   |               |          |    |                | the first                 |          |          |            |                |
|   |               |          |    |                | cycle) with               |          |          |            |                |
|   |               |          |    |                | 200 mg/ m <sup>2</sup>    |          |          |            |                |
|   |               |          |    |                | cetuximab (at             |          |          |            |                |
|   |               |          |    |                | 350 mg/ m <sup>2</sup> in |          |          |            |                |
|   |               |          |    |                | the first                 |          |          |            |                |
|   |               |          |    |                |                           |          |          |            |                |
|   |               |          |    |                | cycle) and                |          |          |            |                |
|   |               |          |    |                | did not                   |          |          |            |                |
|   |               |          |    |                | receive                   |          |          |            |                |
|   |               |          |    |                | gemcitabine               |          |          |            |                |
|   |               |          |    |                | on the day 8              |          |          |            |                |
|   |               |          |    |                | or 15.                    |          |          |            |                |
| 4 | JASPAC 01     | Uesak    | 20 | Patients with  | Gemcitabine               | Primary  | 377 (190 | 25.5       | NA             |
|   | Phase III     | a et al. | 16 | histologically | (1000                     | endpoint | to the   | months for |                |
|   | Randomized    | [11]     |    | proven         | mg/m(2),                  | : OS in  | gemcita  | gemcitabin |                |
|   | , open-label, |          |    | invasive       | intravenousl              | the two  | bine     | e group;   |                |
|   | multicentre,  |          |    | ductal         | у                         |          | group    | 46.5       |                |

|   | non-          |        |    | carcinoma of            | administered             | treatmen            | and 187           | months for   |    |
|---|---------------|--------|----|-------------------------|--------------------------|---------------------|-------------------|--------------|----|
|   | inferiority   |        |    | the pancreas,           | on days 1, 8,            | t groups.           | to the <b>S-1</b> | S-1 group.   |    |
|   | trial.        |        |    | pathologicall           | -                        | t groups.           |                   | 5-1 group.   |    |
|   | tildi.        |        |    |                         | and 15, every            |                     | group).           |              |    |
|   |               |        |    | y<br>                   | 4 weeks [one             |                     |                   |              |    |
|   |               |        |    | documented              | cycle], for up           |                     |                   |              |    |
|   |               |        |    | stage I-III,            | to six cycles)           |                     |                   |              |    |
|   |               |        |    | and no local            | or S-1 (40 mg,           |                     |                   |              |    |
|   |               |        |    | residual or             | 50 mg, or 60             |                     |                   |              |    |
|   |               |        |    | microscopic             | <b>mg</b> according      |                     |                   |              |    |
|   |               |        |    | residual                | to body-                 |                     |                   |              |    |
|   |               |        |    | tumor, and              | surface area,            |                     |                   |              |    |
|   |               |        |    | were aged 20            | orally                   |                     |                   |              |    |
|   |               |        |    | years or older          | administered             |                     |                   |              |    |
|   |               |        |    | were eligible.          | twice a day              |                     |                   |              |    |
|   |               |        |    | Patients with           | for 28 days              |                     |                   |              |    |
|   |               |        |    | resected                | followed by a            |                     |                   |              |    |
|   |               |        |    | pancreatic              | 14 day rest,             |                     |                   |              |    |
|   |               |        |    | cancer with             | every 6                  |                     |                   |              |    |
|   |               |        |    | no history of           | weeks [one               |                     |                   |              |    |
|   |               |        |    | chemotherap             | cycle], for up           |                     |                   |              |    |
|   |               |        |    | y or                    | to four                  |                     |                   |              |    |
|   |               |        |    | radiotherapy            | cycles).                 |                     |                   |              |    |
|   |               |        |    | within the              |                          |                     |                   |              |    |
|   |               |        |    | past 3 years.           |                          |                     |                   |              |    |
| 5 | LAP07         | Ham    | 20 | Patients with           | 1000 mg/m2               | Primary             | 449 (442          | 13.6         | NA |
|   |               | mel et | 16 | locally                 | weekly of                | endpoint            | in first          | months       |    |
|   | Phase III     | al.    |    | advanced                | gemcitabine              | :                   | randomi           | from the     |    |
|   |               | [12]   |    | pancreatic              | alone or 1000            | OS from             | zation            | date of the  |    |
|   | An            | _      |    | cancer. In              | <b>mg/m2</b> of          | the date            | and 269           | first        |    |
|   | international |        |    | second                  | gemcitabine              | of the              | in                | randomizat   |    |
|   | , open-label, |        |    | randomizatio            | plus 100                 | first               | second            | ion for the  |    |
|   | randomized    |        |    | n: patients             | mg/d of                  | randomi             | randomi           | 223 patients |    |
|   | trial.        |        |    | with                    | erlotinib.               | zation.             | zation).          | receiving    |    |
|   |               |        |    | progression-            | In second                |                     |                   | gemcitabin   |    |
|   |               |        |    | free disease            | randomizatio             | Seconda             |                   | e. 11.9      |    |
|   |               |        |    | after 4                 | n: patients              | ry                  |                   | months for   |    |
|   |               |        |    | months.                 | received 2               | outcome             |                   | the 219      |    |
|   |               |        |    | Patients had            | months of the            | s: effect           |                   | patients     |    |
|   |               |        |    |                         | same                     | of                  |                   | receiving    |    |
|   |               |        |    | no prior<br>chemotherap | chemotherap              | erlotinib           |                   | gemcitabin   |    |
|   |               |        |    | y or radiation          | y or                     | and                 |                   | e plus       |    |
|   |               |        |    |                         | v Uf                     | ana                 | 1                 | e pius       |    |
|   |               |        |    | -                       | -                        | analit-             |                   | -            |    |
|   |               |        |    | therapy.                | underwent<br>chemoradiot | quality<br>assuranc |                   | erlotinib.   |    |

|   |               |        |    |                 | -             |           |         |                   | []        |
|---|---------------|--------|----|-----------------|---------------|-----------|---------|-------------------|-----------|
|   |               |        |    |                 | herapy (54    | e of      |         | OS from           |           |
|   |               |        |    |                 | Gy plus       | radiothe  |         | the date of       |           |
|   |               |        |    |                 | capecitabine) | rapy on   |         | the first         |           |
|   |               |        |    |                 |               | OS, PFS   |         | randomizat        |           |
|   |               |        |    |                 |               | of        |         | ion was not       |           |
|   |               |        |    |                 |               | gemcitab  |         | significantl      |           |
|   |               |        |    |                 |               | ine-      |         | y different       |           |
|   |               |        |    |                 |               | erlotinib |         | between           |           |
|   |               |        |    |                 |               | and       |         | chemothera        |           |
|   |               |        |    |                 |               | erlotinib |         | py at 16.5        |           |
|   |               |        |    |                 |               | mainten   |         | months and        |           |
|   |               |        |    |                 |               | ance      |         | chemoradi         |           |
|   |               |        |    |                 |               | with      |         | otherapy at       |           |
|   |               |        |    |                 |               | gemcitab  |         | 15.2              |           |
|   |               |        |    |                 |               | ine alone |         | months.           |           |
|   |               |        |    |                 |               | at the    |         | monuis.           |           |
|   |               |        |    |                 |               | second    |         |                   |           |
|   |               |        |    |                 |               | randomi   |         |                   |           |
|   |               |        |    |                 |               |           |         |                   |           |
|   |               |        |    |                 |               | zation,   |         |                   |           |
|   |               |        |    |                 |               | and toxic |         |                   |           |
|   |               |        |    |                 |               | effects.  |         |                   |           |
| ( | Phase II      | Chain  | 20 | Dation to suith | Modified      | Decision  | 75 (21  | T                 | In        |
| 6 | Phase II      | Stein  | 20 | Patients with   |               | Primary   | 75 (31  | In                |           |
|   |               | et al. | 16 | untreated       | FOLFIRINO     | endpoint  | with    | metastatic        | metastat  |
|   | An open       | [28]   |    | metastatic      | X (irinotecan | :         | LAPC,   | pancreatic        | ic        |
|   | label single  |        |    | pancreatic      | and bolus 5-  | response  | 44 with | cancer            | pancreat  |
|   | arm multi-    |        |    | cancer (MPC)    | fluorouracil  | rate      | MPC).   | group: 10.2       | ic cancer |
|   | institutional |        |    | or locally      | reduced by    | (RR),     |         | months.           | group:    |
|   | study.        |        |    | advanced        | 25%).         | median    |         | In <b>locally</b> | 6.1       |
|   |               |        |    | pancreatic      |               | PFS and   |         | advanced          | months.   |
|   |               |        |    | cancer          |               | median    |         | pancreatic        | In        |
|   |               |        |    | (LAPC).         |               | OS of     |         | cancer            | locally   |
|   |               |        |    | No prior        |               | modified  |         | group: 26.6       | advance   |
|   |               |        |    | therapy of      |               | FOLFIRI   |         | months.           | d         |
|   |               |        |    | any type for    |               | NOX.      |         |                   | pancreat  |
|   |               |        |    | advanced        |               |           |         |                   | ic cancer |
|   |               |        |    | disease was     |               | Adverse   |         |                   | group:    |
|   |               |        |    | allowed.        |               | events    |         |                   | 17.8      |
|   |               |        |    | Prior           |               | were      |         |                   | months.   |
|   |               |        |    | adjuvant        |               | compare   |         |                   |           |
|   |               |        |    | chemotherap     |               | d with    |         |                   |           |
|   |               |        |    | y or            |               | full-dose |         |                   |           |
| 1 |               |        |    |                 |               |           |         |                   |           |
|   |               |        |    | radiotherapy    |               |           |         |                   |           |

|   |               |        |    | <i>( ) )</i>   |                       |             |            |                    |                  |
|---|---------------|--------|----|----------------|-----------------------|-------------|------------|--------------------|------------------|
|   |               |        |    | for resected   |                       | FOLFIRI     |            |                    |                  |
|   |               |        |    | pancreatic     |                       | NOX.        |            |                    |                  |
|   |               |        |    | adenocarcino   |                       |             |            |                    |                  |
|   |               |        |    | ma was         |                       |             |            |                    |                  |
|   |               |        |    | allowed if     |                       |             |            |                    |                  |
|   |               |        |    | more than 6    |                       |             |            |                    |                  |
|   |               |        |    | months had     |                       |             |            |                    |                  |
|   |               |        |    | elapsed since  |                       |             |            |                    |                  |
|   |               |        |    | completion of  |                       |             |            |                    |                  |
|   |               |        |    | prior therapy  |                       |             |            |                    |                  |
|   |               |        |    | and            |                       |             |            |                    |                  |
|   |               |        |    | registration.  |                       |             |            |                    |                  |
| 7 | JapicCTI-     | Ueno   | 20 | Japanese       | 125 mg/m(2)           | Overall     | 34         | 13.5               | 6.5              |
|   | 121987        | et al. | 16 | patients with  | nab-                  | response    | 01         | months             | months           |
|   | 121707        | [15]   | 10 | metastatic     | paclitaxel            | rate        |            | montris            | monuis           |
|   | Phase I/II    | [10]   |    | pancreatic     | followed by           | accordin    |            |                    |                  |
|   | 1 11050 1/11  |        |    | cancer.        | 1000 mg/m(2)          |             |            |                    |                  |
|   | A             |        |    | Patients with  | -                     | 0           |            |                    |                  |
|   | A non-        |        |    |                | gemcitabine           | Respons     |            |                    |                  |
|   | randomized,   |        |    | no prior       | on day 1, 8,          | e<br>E l vi |            |                    |                  |
|   | open-label,   |        |    | therapy        | and 15 every          | Evaluati    |            |                    |                  |
|   | multicenter   |        |    | excluding      | 4 weeks.              | on          |            |                    |                  |
|   | trial.        |        |    | surgery.       |                       | Criteria    |            |                    |                  |
|   |               |        |    |                |                       | In Solid    |            |                    |                  |
|   |               |        |    |                |                       | Tumors      |            |                    |                  |
|   |               |        |    |                |                       | (RECIST     |            |                    |                  |
|   |               |        |    |                |                       | ) in        |            |                    |                  |
|   |               |        |    |                |                       | phase II.   |            |                    |                  |
| 8 | GEST study    | Imao   | 20 | Elderly        | Gemcitabine           | Primary     | 261 (90    | 10.2               | 6.9              |
|   |               | ka et  | 16 | patients (≥ 70 | plus S-1 (GS)         | endpoint    | for        | months for         | months           |
|   | Phase III     | al.    |    | years) with    | (1000 mg/m2           | : OS        | gemcitab   | gemcitabin         | in the           |
|   |               | [10]   |    | un-resectable  | IV                    |             | ine plus   | e plus S-1         | gemcita          |
|   | Subgroup      |        |    | pancreatic     | gemcitabine           | Seconda     | S-1        | <b>group</b> , 8.0 | bine             |
|   | analysis of a |        |    | cancer.        | on days 1 and         | ry          | group,     | months for         | plus S-1         |
|   | randomized    |        |    |                | 8 plus S-1            | endpoint    | 85 for S-1 | S-1 group          | group,           |
|   | trial.        |        |    |                | orally twice          | s: PFS,     | group,     | and 8.5            | 4.2              |
|   |               |        |    |                | daily), or <b>S-1</b> | objective   | and 86     | months for         | months           |
|   |               |        |    |                | alone (at a           | response    | for        | gemcitabin         | in the <b>S-</b> |
|   |               |        |    |                | dose                  | rate and    | gemcitab   | e group.           | 1 group          |
|   |               |        |    |                | calculated            | safety.     | ine        | ~ *                | and 4.5          |
|   |               |        |    |                | according to          | ,           | group).    |                    | months           |
|   |               |        |    |                | the body              |             | 0 1/-      |                    | in the           |
|   |               |        |    |                | surface area          |             |            |                    | gemcita          |
|   |               |        |    |                | (BSA)) or             |             |            |                    | oundra           |
|   |               |        |    |                | (1007)) 01            |             |            |                    |                  |

|    |              |        |    |                | gemcitabine    |            |           |                    | bine      |
|----|--------------|--------|----|----------------|----------------|------------|-----------|--------------------|-----------|
|    |              |        |    |                | alone (1000    |            |           |                    |           |
|    |              |        |    |                |                |            |           |                    | group.    |
|    |              |        |    |                | mg/m2 on       |            |           |                    |           |
|    |              |        |    |                | days 1, 8, and |            |           |                    |           |
|    |              |        |    |                | 15 of a 28-day |            |           |                    |           |
|    |              |        |    |                | cycle).        |            |           |                    |           |
| 9  | Phase II     | Belli  | 20 | Patients with  | Trabectedin    | Primary    | 25        | 5.2 months         | 1.9       |
|    |              | et al. | 16 | metastatic     | 1.3 mg/m(2)    | endpoint   |           | (range 1.1-        | months    |
|    | A single-    | [29]   |    | pancreatic     | as a 3-h       | : PFS rate |           | 24.3).             | (range    |
|    | center,      |        |    | adenocarcino   | intravenous    | at 6       |           |                    | 0.8-7.4). |
|    | prospective, |        |    | ma             | continuous     | months     |           |                    |           |
|    | single-arm   |        |    | (gemcitabine-  | infusion       | (PFS-6).   |           |                    |           |
|    | study.       |        |    | resistant      | every 3        |            |           |                    |           |
|    |              |        |    | disease) after | weeks for a    | Seconda    |           |                    |           |
|    |              |        |    | gemcitabine-   | maximum of     | ry         |           |                    |           |
|    |              |        |    | based first-   | 6 months.      | outcome:   |           |                    |           |
|    |              |        |    | line           |                | to         |           |                    |           |
|    |              |        |    | chemotherap    |                | identify   |           |                    |           |
|    |              |        |    | у.             |                | inflamm    |           |                    |           |
|    |              |        |    |                |                | atory      |           |                    |           |
|    |              |        |    |                |                | biomark    |           |                    |           |
|    |              |        |    |                |                | ers        |           |                    |           |
|    |              |        |    |                |                | predictiv  |           |                    |           |
|    |              |        |    |                |                | e for      |           |                    |           |
|    |              |        |    |                |                | response   |           |                    |           |
|    |              |        |    |                |                | to         |           |                    |           |
|    |              |        |    |                |                | trabecte   |           |                    |           |
|    |              |        |    |                |                | din.       |           |                    |           |
| 10 | NAPOLI-1     | Wang   | 20 | Eligible       | Nanoliposo     | Primary    | 417 (117  | In                 | NA        |
| 10 |              | 0      |    | 0              | -              | -          | -         |                    | NA        |
|    | (NCT014945   | -      | 16 | patients with  | mal            | endpoint   | patients  | nanoliposo         |           |
|    | 06)          | Gilla  |    | metastatic     | irinotecan     | : OS       | in<br>    | mal                |           |
|    |              | m et   |    | pancreatic     | monotherap     |            | nanolipo  | irinotecan         |           |
|    | Phase III    | al.    |    | ductal         | y (120         | Safety     | somal     | plus               |           |
|    |              | [30]   |    | adenocarcino   | mg/m(2)        | was        | irinoteca | fluorouraci        |           |
|    | A global,    |        |    | ma             | every 3        | assessed   | n plus    | 1 and              |           |
|    | randomized,  |        |    | previously     | weeks,         | in all     | fluorour  | folinic acid       |           |
|    | open-label   |        |    | treated with   | equivalent to  | patients   | acil and  | <b>group</b> : 6.1 |           |
|    | trial.       |        |    | gemcitabine-   | 100 mg/m(2)    | who had    | folinic   | months             |           |
|    |              |        |    | based          | of irinotecan  | received   | acid      |                    |           |
|    |              |        |    | therapy.       | base) or       | study      | group,    | In                 |           |
|    |              |        |    |                | fluorouracil   | drug.      | 151       | fluorouraci        |           |
|    |              |        |    |                | and folinic    |            | patients  | l and              |           |
| 1  |              |        |    | 1              | 1              |            | 1         | folinic acid       |           |

|    |                        |         |    |               | arm                    |          | nanolipo  | <b>group</b> : 4.2 |                |
|----|------------------------|---------|----|---------------|------------------------|----------|-----------|--------------------|----------------|
|    |                        |         |    |               | consisting of          |          | somal     | months             |                |
|    |                        |         |    |               | nanoliposom            |          | irinoteca |                    |                |
|    |                        |         |    |               | al irinotecan          |          | n         | In                 |                |
|    |                        |         |    |               | (80 mg/m(2),           |          | monothe   | nanoliposo         |                |
|    |                        |         |    |               | equivalent to          |          | rapy      | mal                |                |
|    |                        |         |    |               | 70 mg/m(2) of          |          | group,    | irinotecan         |                |
|    |                        |         |    |               | irinotecan             |          | and 149   | monothera          |                |
|    |                        |         |    |               | base) with             |          | patients  | py group:          |                |
|    |                        |         |    |               | fluorouracil           |          | in        | 4.9 months.        |                |
|    |                        |         |    |               | and folinic            |          | fluorour  |                    |                |
|    |                        |         |    |               | acid every 2           |          | acil and  |                    |                |
|    |                        |         |    |               | weeks was              |          | folinic   |                    |                |
|    |                        |         |    |               | added later            |          | acid      |                    |                |
|    |                        |         |    |               | (1:1:1), in a          |          | group).   |                    |                |
|    |                        |         |    |               | protocol               |          |           |                    |                |
|    |                        |         |    |               | amendment.             |          |           |                    |                |
| 11 | Phase II               | Postle  | 20 | Patients with | 1000 mg/m <sup>2</sup> | Primary  | 22        | 35.5               | NA             |
|    |                        | wait    | 16 | resected      | gemcitabine            | outcome  |           | months             |                |
|    | А                      | et al.  |    | pancreatic    | plus 50                | s:       |           |                    |                |
|    | prospective            | [22]    |    | adenocarcino  | mg/m <sup>2</sup>      | recurren |           |                    |                |
|    | trial which            |         |    | ma which      | cisplatin.             | ce-free  |           |                    |                |
|    | assesses               |         |    | was           | Tumor                  | survival |           |                    |                |
|    | outcomes of            |         |    | previously    | ERCC1                  | (RFS)    |           |                    |                |
|    | patients               |         |    | treated with  | expression             | and OS.  |           |                    |                |
|    | treated with           |         |    | gemcitabine   | was                    |          |           |                    |                |
|    | adjuvant               |         |    | alone.        | evaluated by           |          |           |                    |                |
|    | gemcitabine/           |         |    | alone         | immune-                |          |           |                    |                |
|    | cisplatin,             |         |    |               | histo-                 |          |           |                    |                |
|    | stratifying            |         |    |               | chemistry              |          |           |                    |                |
|    | results by             |         |    |               | and                    |          |           |                    |                |
|    | tumor                  |         |    |               | dichotomize            |          |           |                    |                |
|    | excision               |         |    |               | d into low or          |          |           |                    |                |
|    | repair cross-          |         |    |               | high                   |          |           |                    |                |
|    | complementi            |         |    |               | expression.            |          |           |                    |                |
|    | -                      |         |    |               | expression.            |          |           |                    |                |
|    | ng group-<br>1 (ERCC1) |         |    |               |                        |          |           |                    |                |
|    |                        |         |    |               |                        |          |           |                    |                |
| 12 | expression.            | Cator   | 20 | Patients with | Vismodegib             | Drimorry | 106       | 6.9 and 6.1        | 4.0 and        |
| 12 | NCT0106462             | Caten   |    |               | -                      | Primary  |           |                    | 4.0 and<br>2.5 |
|    | 2                      | acci et | 15 | pancreatic    | plus                   | outcome: | patients  | months for         |                |
|    |                        | al.     |    | cancer not    | gemcitabine            | PFS.     | in phase  | GV and GP          | months         |
|    | Phase Ib/II            | [16]    |    | amenable to   | (GV) or                |          | II (53 in | arms,              | for GV         |
|    |                        |         |    | curative      | gemcitabine            |          |           |                    | and <b>GP</b>  |

|    | А                         |        |    | therapy who    | plus placebo       |                 | each       | respectivel       | arms,    |
|----|---------------------------|--------|----|----------------|--------------------|-----------------|------------|-------------------|----------|
|    |                           |        |    |                |                    |                 |            | -                 |          |
|    | multicenter,              |        |    | had received   | (GP).              |                 | arm).      | у.                | respecti |
|    | randomized                |        |    | no prior       |                    |                 |            |                   | vely.    |
|    | trial and                 |        |    | therapy for    |                    |                 |            |                   |          |
|    | preclinical               |        |    | metastatic     |                    |                 |            |                   |          |
|    | pancreatic                |        |    | disease.       |                    |                 |            |                   |          |
|    | cancer                    |        |    |                |                    |                 |            |                   |          |
|    | models.                   |        |    |                |                    |                 |            |                   |          |
| 13 | Phase II                  | Wu et  | 20 | Patients with  | Lapatinib          | Primary         | 17         | 5.2 months        | 2.6      |
|    |                           | al.    | 15 | metastatic,    | 1250 mg PO         | endpoint        |            |                   | months   |
|    | An open-                  | [24]   |    | un-resectable  | daily 1 h          | : median        |            |                   |          |
|    | label, single-            |        |    | pancreatic     | before or          | OS              |            |                   |          |
|    | arm study.                |        |    | cancer whose   | after meals,       |                 |            |                   |          |
|    | 5                         |        |    | disease had    | and                | Seconda         |            |                   |          |
|    |                           |        |    | progressed     | capecitabine       | ry              |            |                   |          |
|    |                           |        |    | on first-line  | 1000 mg/m(2)       | endpoint        |            |                   |          |
|    |                           |        |    | gemcitabine-   | PO twice           | s:              |            |                   |          |
|    |                           |        |    | based          | daily on days      | s.<br>objective |            |                   |          |
|    |                           |        |    |                |                    | -               |            |                   |          |
|    |                           |        |    | therapy.       | 1-14 of the 21-    | response        |            |                   |          |
|    |                           |        |    |                | day cycle.         | rate, PFS       |            |                   |          |
|    |                           |        |    | Patients were  |                    | and the         |            |                   |          |
|    |                           |        |    | required to    |                    | safety          |            |                   |          |
|    |                           |        |    | have an        |                    | profile of      |            |                   |          |
|    |                           |        |    | adequate       |                    | the             |            |                   |          |
|    |                           |        |    | performance    |                    | combina         |            |                   |          |
|    |                           |        |    | status (ECOG   |                    | tion            |            |                   |          |
|    |                           |        |    | 0-2) and       |                    | therapy.        |            |                   |          |
|    |                           |        |    | normal         |                    |                 |            |                   |          |
|    |                           |        |    | hepatic and    |                    |                 |            |                   |          |
|    |                           |        |    | renal function |                    |                 |            |                   |          |
|    |                           |        |    | prior to being |                    |                 |            |                   |          |
|    |                           |        |    | enrolled.      |                    |                 |            |                   |          |
| 14 | NCT0142360                | Hurw   | 20 | Patients with  | Ruxolitinib        | Primary         | 127 (64 in | 4.5 months        | NA       |
|    | 4                         | itz et | 15 | metastatic     | (15 mg twice       | endpoint        | ruxolitin  | in                |          |
|    |                           | al.    |    | pancreatic     | daily) <b>plus</b> | : OS            | ib plus    | ruxolitinib       |          |
|    | Phase II                  | [25]   |    | cancer who     | capecitabine       | -               | capecita   | plus              |          |
|    |                           |        |    | had            | (1,000             | Seconda         | bine       | capecitabin       |          |
|    | Randomized                |        |    | experienced    | mg/m(2)            | ry              | group,     | e group           |          |
|    | , Double-                 |        |    | treatment      | twice daily)       | endpoint        | 63 in      | - Browk           |          |
|    | , Double-<br>Blind Study. |        |    | failure with   | -                  | -               |            | 4.3 months        |          |
|    | Dinia Stuay.              |        |    |                | -                  |                 | placebo    |                   |          |
|    |                           |        |    | gemcitabine.   | plus               | clinical        | plus<br>   | in <b>placebo</b> |          |
|    |                           |        |    |                | capecitabine.      | benefit         | capecita   | plus              |          |
|    |                           |        |    |                |                    | response        |            |                   |          |

|    |  |                                  |          |   |   | ,<br>objective<br>response<br>rate, and<br>safety.  | bine<br>group).                   | capecitabin<br>e group.                       |   |
|----|--|----------------------------------|----------|---|---|---|-----------------------------------|---|---|
| 15 | Phase I/II<br>An open-<br>label, multi-<br>center,<br>single-arm<br>study. | Goji <i>et</i><br><i>al.</i> [9] | 20       | Patients with<br>unresectable<br>pancreatic<br>cancer<br>confined to<br>the pancreatic<br>region with<br>no earlier<br>treatment for<br>pancreatic<br>cancer. | Fixed-dose-<br>rate<br>gemcitabine<br>(FDR-gem)<br>(300-400<br>mg/m(2), 5<br>mg/m(2)/min<br>) on days 1, 8,<br>22, and 29<br>and 60<br>mg/m(2) of S-<br>1 orally on<br>days 1-14, 22-<br>35. A total<br>radiation<br>dose of 50.4<br>Gy (1.8<br>Gy/day, 28<br>fractions)<br>was<br>delivered<br>concurrently. | Primary<br>endpoint<br>in the<br>dose<br>escalatio<br>n phase<br>(step 1):<br>to<br>establish<br>the<br>recomm<br>ended<br>phase II<br>dose.<br>Seconda<br>ry<br>objective<br>s:<br>severity<br>of<br>adverse<br>events,<br>PFS, and<br>OS. | 17<br>patients<br>in phase<br>II. | 16.0<br>months                                | 11.0<br>months                                |
| 16 | Phase II<br>A<br>multicenter<br>study.                                     | Maki<br>elski<br>et al.<br>[26]  | 20<br>15 | Patients who<br>had no more<br>than one<br>previous<br>chemotherap<br>y regimen for<br>their<br>pancreatic<br>adenocarcino<br>ma.                             | Sorafenib<br>200 mg orally<br>twice daily<br>along with<br>oxaliplatin<br>85 mg/m(2)<br>IV on days 1<br>and 15,<br>followed by<br>capecitabine<br>2250 mg/m(2)  | Primary<br>objective<br>:<br>response<br>rate.<br>Seconda<br>ry<br>objective<br>s: PFS,   | 24                                | 8.1 months<br>(range 1.5-<br>13.6<br>months). | 6.0<br>months<br>(range<br>1.5-13<br>months). |

|    |             |        | 1  |             |                 |           |          |              |           |
|----|-------------|--------|----|-------------|-----------------|-----------|----------|--------------|-----------|
|    |             |        |    |             | orally every 8  | OS, and   |          |              |           |
|    |             |        |    |             | h for six       | safety.   |          |              |           |
|    |             |        |    |             | doses starting  |           |          |              |           |
|    |             |        |    |             | on days 1 and   |           |          |              |           |
|    |             |        |    |             | 15 of a 28-day  |           |          |              |           |
|    |             |        |    |             | cycle.          |           |          |              |           |
| 17 | NCT0160884  | Wang   | 20 | Chemotherap | Gemcitabine     | Primary   | 88 (44   | 7.2 months   | 3.8       |
|    | 1           | et al. | 15 | y-naïve     | (1000 mg/m2     | endpoint  | patients | in           | months    |
|    |             | [13]   |    | metastatic  | as 30 minutes   | : disease | in each  | gemcitabin   | in        |
|    | Phase II    |        |    | pancreatic  | infusion on     | control   | group).  | e plus       | gemcita   |
|    |             |        |    | cancer      | days 1, 8, 15,  | rate.     |          | erlotinib    | bine      |
|    | A single-   |        |    | patients.   | 22, 29, 36 and  |           |          | group.       | plus      |
|    | center,     |        |    |             | 43 followed     |           |          | 4.4 months   | erlotini  |
|    | randomized, |        |    |             | by a 1-week     |           |          | in           | b group.  |
|    | open-label, |        |    |             | rest in cycle 1 |           |          | gemcitabin   | 2.4       |
|    | prospective |        |    |             | and on days     |           |          | e alone      | months    |
|    | trial.      |        |    |             | 1, 8, and 15 in |           |          | group.       | in        |
|    |             |        |    |             | all             |           |          | In           | gemcita   |
|    |             |        |    |             | subsequent 4-   |           |          | gemcitabin   | bine      |
|    |             |        |    |             | week cycles)    |           |          | e group OS   | alone     |
|    |             |        |    |             | or              |           |          | was similar  | group.    |
|    |             |        |    |             | gemcitabine     |           |          | regardless   | In        |
|    |             |        |    |             | plus            |           |          | of the       | gemcita   |
|    |             |        |    |             | erlotinib       |           |          | presence of  | bine      |
|    |             |        |    |             | (gemcitabine    |           |          | EGFR         | group     |
|    |             |        |    |             | like            |           |          | mutations.   | PFS was   |
|    |             |        |    |             | gemcitabine     |           |          | In           | similar   |
|    |             |        |    |             | alone,          |           |          | gemcitabin   | regardle  |
|    |             |        |    |             | erlotinib       |           |          | e plus       | ss of the |
|    |             |        |    |             | orally 100 mg   |           |          | erlotinib    | presence  |
|    |             |        |    |             | once a day).    |           |          | group,       | of EGFR   |
|    |             |        |    |             |                 |           |          | patients     | mutatio   |
|    |             |        |    |             |                 |           |          | with EGFR    | ns.       |
|    |             |        |    |             |                 |           |          | mutations    | In        |
|    |             |        |    |             |                 |           |          | had a        | gemcita   |
|    |             |        |    |             |                 |           |          | significantl | bine      |
|    |             |        |    |             |                 |           |          | y longer OS  | plus      |
|    |             |        |    |             |                 |           |          | (8.7 months  | erlotini  |
|    |             |        |    |             |                 |           |          | vs. 6.0      | b group,  |
|    |             |        |    |             |                 |           |          | months).     | patients  |
|    |             |        |    |             |                 |           |          |              | with      |
|    |             |        |    |             |                 |           |          |              | EGFR      |
|    |             |        |    |             |                 |           |          |              | mutatio   |
| L  | L           | L      | 1  | 1           | 1               | l         | l        |              |           |

|    |             |       |    |                |                    |           |               |                | ns had a<br>significa |
|----|-------------|-------|----|----------------|--------------------|-----------|---------------|----------------|-----------------------|
|    |             |       |    |                |                    |           |               |                | ntly                  |
|    |             |       |    |                |                    |           |               |                | longer                |
|    |             |       |    |                |                    |           |               |                | PFS (5.9              |
|    |             |       |    |                |                    |           |               |                | months                |
|    |             |       |    |                |                    |           |               |                | vs. 2.4               |
|    |             |       |    |                |                    |           |               |                | months).              |
| 18 | NCT0092329  | Assen | 20 | Advanced       | Weekly             | Primary   | 39            | 4.6 months     | 1.8                   |
|    | 9           | at et | 15 | pancreatic     | cetuximab          | objective | patients      |                | months                |
|    |             | al.   |    | cancer         | (400mg/m²,         | :         | in phase      |                |                       |
|    | Phase I/II  | [31]  |    | patients after | then               | Objectiv  | 2.            |                |                       |
|    |             |       |    | first-line     | 250mg/m²).         | e         |               |                |                       |
|    | A single-   |       |    | gemcitabine-   | They were          | response  |               |                |                       |
|    | arm, non-   |       |    | based          | sequentially       | rate,     |               |                |                       |
|    | randomized, |       |    | chemotherap    | included in        | safety,   |               |                |                       |
|    | multicenter |       |    | y failure.     | two                | progress  |               |                |                       |
|    | trial.      |       |    |                | trastuzumab        | ion-free  |               |                |                       |
|    |             |       |    |                | dose levels:       | survival  |               |                |                       |
|    |             |       |    |                | 3.0 or             | (PFS)     |               |                |                       |
|    |             |       |    |                | 4.0mg/kg,          | and       |               |                |                       |
|    |             |       |    |                | then <b>1.5 or</b> | overall   |               |                |                       |
|    |             |       |    |                | 2.0mg/kg/we        | survival  |               |                |                       |
|    |             |       |    |                | ekly.              | (OS).     |               |                |                       |
| 19 | Japic CTI-  | Ohka  | 20 | Patients with  | S-1                | Primary   | 271 (135      | 6.9 months     | 2.8                   |
|    | 090685      | wa et | 15 | confirmed      | (80/100/120 m      | endpoint  | patients      | for <b>S-1</b> | months                |
|    |             | al.   |    | progressive    | <b>g</b> day (-1)  | : PFS     | in <b>S-1</b> | group.         | for <b>S-1</b>        |
|    | Phase II    | [32]  |    | disease        | based on           |           | group,        | 7.4 months     | group.                |
|    |             |       |    | following the  | body surface       | Seconda   | 136           | for <b>SOX</b> | 3.0                   |
|    |             |       |    | first-line     | area (BSA),        | ry        | patients      | group.         | months                |
|    | А           |       |    | treatment      | orally, days       | endpoint  | in SOX        |                | for SOX               |
|    | randomized, |       |    | with a         | 1-28, every 6      | s: OS,    | group).       |                | group.                |
|    | open-label, |       |    | gemcitabine-   | weeks) or          | time to   |               |                |                       |
|    | multicenter |       |    | based          | SOX (S-1           | treatmen  |               |                |                       |
|    | study.      |       |    | regimen.       | 80/100/120 m       | t failure |               |                |                       |
|    |             |       |    |                | <b>g</b> day (-1)  | (TTF),    |               |                |                       |
|    |             |       |    |                | based on           | response  |               |                |                       |
|    |             |       |    |                | BSA, orally,       | rate      |               |                |                       |
|    |             |       |    |                | days 1-14,         | (RR),     |               |                |                       |
|    |             |       |    |                | plus               | disease   |               |                |                       |
|    |             |       |    |                | oxaliplatin        | control   |               |                |                       |
|    |             |       |    |                | 100 mg m(-2),      | rate      |               |                |                       |
|    |             |       |    |                | intravenousl       | (DCR),    |               |                |                       |

|    |                 |          |    |                       | y, day 1,             | and        |               |              |          |
|----|-----------------|----------|----|-----------------------|-----------------------|------------|---------------|--------------|----------|
|    |                 |          |    |                       | every 3               | safety.    |               |              |          |
|    |                 |          |    |                       | weeks).               |            |               |              |          |
| 20 | UMIN00000       | Shim     | 20 | Patients who          | Adjuvant              | Primary    | 57 (29        | 21.5         | NA       |
|    | 9118            | oda et   | 15 | had                   | chemotherap           | endpoint   | patients      | months in    |          |
|    |                 | al. [2]  |    | undergone             | y with <b>S-1</b> or  | : disease- | in <b>S-1</b> | S-1 group,   |          |
|    | Phase II        |          |    | resection of          | gemcitabine           | free       | group,        | 18.0         |          |
|    |                 |          |    | pancreatic            | after                 | survival   | 28            | months in    |          |
|    | А               |          |    | cancer.               | resection of          | (DFS).     | patients      | gemcitabin   |          |
|    | randomized      |          |    |                       | pancreatic            |            | in            | e group.     |          |
|    | clinical trial. |          |    |                       | cancer.               |            | gemcita       |              |          |
|    |                 |          |    |                       |                       |            | bine          |              |          |
|    |                 |          |    |                       |                       |            | group).       |              |          |
| 21 | NCT0107970      | Korde    | 20 | Patients with         | Capecitabine          | Primary    | 31            | 8.9 months   | 3.6 mont |
|    | 2               | s et al. | 15 | advanced              | 1000 mg/m(2)          | endpoint   | -             |              | hs       |
|    |                 | [27]     | -  | adenocarcino          | BID day 1-14          | :          |               |              | -        |
|    | Phase II        | ()       |    | ma of the             | and                   | response   |               |              |          |
|    |                 |          |    | pancreas              | everolimus            | rate       |               |              |          |
|    | An open-        |          |    | were                  | <b>10 mg</b> daily    | (RR).      |               |              |          |
|    | label, single-  |          |    | enrolled.             | ( <b>5 mg</b> BID) in | (iui).     |               |              |          |
|    | center study.   |          |    | Eligible              | a continuous          | Seconda    |               |              |          |
|    | center study.   |          |    | -                     |                       |            |               |              |          |
|    |                 |          |    | patients had a<br>WHO | 21-day<br>schedule.   | ry         |               |              |          |
|    |                 |          |    |                       | schedule.             | endpoint   |               |              |          |
|    |                 |          |    | performance           |                       | s: PFS,    |               |              |          |
|    |                 |          |    | status 0-2 and        |                       | OS and     |               |              |          |
|    |                 |          |    | adequate              |                       | 1-year     |               |              |          |
|    |                 |          |    | hepatic and           |                       | survival   |               |              |          |
|    |                 |          |    | renal                 |                       | rate.      |               |              |          |
|    |                 |          |    | functions.            |                       |            |               |              |          |
|    |                 |          |    | Also patients         |                       |            |               |              |          |
|    |                 |          |    | with prior            |                       |            |               |              |          |
|    |                 |          |    | chemotherap           |                       |            |               |              |          |
|    |                 |          |    | y in the              |                       |            |               |              |          |
|    |                 |          |    | adjuvant              |                       |            |               |              |          |
|    |                 |          |    | setting or for        |                       |            |               |              |          |
|    |                 |          |    | metastatic            |                       |            |               |              |          |
|    |                 |          |    | disease were          |                       |            |               |              |          |
|    |                 |          |    | eligible.             |                       |            |               |              |          |
| 22 | Phase II        | Cho et   | 20 | Patients with         | Two cycles of         | Primary    | 50 (29        | 17 months    | NA       |
|    |                 | al.      | 15 | pancreaticobi         | gemcitabine           | endpoint   | patients      | for patients |          |
|    | An open-        | [17]     |    | liary cancers         | and                   | :          | had           | with         |          |
|    | label, single-  |          |    | after a               | docetaxel             | incidenc   | pancreati     | pancreatic   |          |
|    | arm study.      |          |    | curative-             | followed by           | e of       | c cancer      | cancer.      |          |
| ı  | ·               | 1        | I  | I                     | ·                     | I          | 1             | 1            |          |

|   |  |  | intent         | 5FU-based      | severe     | and 21    | 23 months     |   |
|---|--|--|----------------|----------------|------------|-----------|---------------|---|
|   |  |  | resection and  | chemoradiati   | toxicities | patients  | for patients  |   |
|   |  |  | with no prior  | on. Four       | •          | had       | with          |   |
|   |  |  | chemotherap    | weeks after    |            | biliary   | resected      |   |
|   |  |  | y or radiation | completing     | Seconda    | tract or  | biliary tract |   |
|   |  |  | therapy.       | chemoradiati   | ry         | ampullar  | cancer.       |   |
|   |  |  |                | on, two cycles | endpoint   | у         |               |   |
|   |  |  |                | of             | s:         | cancers). |               |   |
|   |  |  |                | gemcitabine    | disease-   |           |               |   |
|   |  |  |                | and            | free       |           |               |   |
|   |  |  |                | docetaxel      | survival   |           |               |   |
|   |  |  |                | were           | (DFS)      |           |               |   |
|   |  |  |                | administered   | and OS.    |           |               |   |
|   |  |  |                |                |            |           |               |   |
|   |  |  |                | Gemcitabine    |            |           |               |   |
|   |  |  |                | was given at   |            |           |               |   |
|   |  |  |                | a dose of      |            |           |               |   |
|   |  |  |                | 1000 mg/m2     |            |           |               |   |
|   |  |  |                | as a 30-min    |            |           |               |   |
|   |  |  |                | intravenous    |            |           |               |   |
|   |  |  |                |                |            |           |               |   |
|   |  |  |                | (IV) infusion  |            |           |               |   |
|   |  |  |                | on days 1 and  |            |           |               |   |
|   |  |  |                | 8 with         |            |           |               |   |
|   |  |  |                | docetaxel at   |            |           |               |   |
|   |  |  |                | 35 mg/m2 IV    |            |           |               |   |
|   |  |  |                | on days 1 and  |            |           |               |   |
|   |  |  |                | 8 of a 21-day  |            |           |               |   |
|   |  |  |                | cycle for two  |            |           |               |   |
|   |  |  |                | cycles prior   |            |           |               |   |
|   |  |  |                | to radiation   |            |           |               |   |
|   |  |  |                | therapy.       |            |           |               |   |
|   |  |  |                | 5FU was        |            |           |               |   |
|   |  |  |                | given at       |            |           |               |   |
|   |  |  |                | 225 mg/m2      |            |           |               |   |
|   |  |  |                | per day as a   |            |           |               |   |
|   |  |  |                | continuous     |            |           |               |   |
|   |  |  |                | infusion       |            |           |               |   |
|   |  |  |                | throughout     |            |           |               |   |
|   |  |  |                | radiation      |            |           |               |   |
|   |  |  |                | starting       |            |           |               |   |
|   |  |  |                | 3 weeks after  |            |           |               |   |
|   |  |  |                | the second     |            |           |               |   |
| L |  |  |                |                |            |           | 1             | 1 |

|    |                |           |    |                         | 1 (                 |            |                  |                      |               |
|----|----------------|-----------|----|-------------------------|---------------------|------------|------------------|----------------------|---------------|
|    |                |           |    |                         | cycle of            |            |                  |                      |               |
|    |                |           |    |                         | gemcitabine.        |            |                  |                      |               |
| 23 | MPACT          | Golds     | 20 | Patients with           | Nab-                | Primary    | 861 (431         | 8.7 months           | NA            |
|    | (NCT008446     | tein et   | 15 | metastatic              | paclitaxel +        | endpoint   | patients         | for patients         |               |
|    | 49)            | al.       |    | pancreatic              | gemcitabine         | : OS.      | in <b>nab-</b>   | in <b>nab-</b>       |               |
|    |                | [14]      |    | cancer with             | (a 30- to 40-       |            | paclitaxe        | paclitaxel           |               |
|    | Phase III      |           |    | no prior                | minute              |            | l plus           | plus                 |               |
|    |                |           |    | chemotherap             | intravenous         |            | gemcita          | gemcitabin           |               |
|    | An             |           |    | y for                   | infusion of         |            | bine             | <b>e group</b> , 6.6 |               |
|    | international  |           |    | metastatic              | nab-paclitaxel      |            | <b>arm</b> , 430 | months for           |               |
|    | , multicenter, |           |    | disease.                | 125mg/m2,           |            | patients         | patients in          |               |
|    | open-label     |           |    |                         | followed by         |            | in               | gemcitabin           |               |
|    | study.         |           |    |                         | an infusion of      |            | gemcita          | e alone              |               |
|    |                |           |    |                         | gemcitabine         |            | bine             | group.               |               |
|    |                |           |    |                         | 1000mg/m2           |            | alone            |                      |               |
|    |                |           |    |                         | on days 1, 8,       |            | arm).            |                      |               |
|    |                |           |    |                         | 15, 29, 36, and     |            |                  |                      |               |
|    |                |           |    |                         | 43) or              |            |                  |                      |               |
|    |                |           |    |                         | gemcitabine         |            |                  |                      |               |
|    |                |           |    |                         | alone               |            |                  |                      |               |
|    |                |           |    |                         | (1000mg/m2          |            |                  |                      |               |
|    |                |           |    |                         | weekly for          |            |                  |                      |               |
|    |                |           |    |                         | seven of eight      |            |                  |                      |               |
|    |                |           |    |                         | weeks (cycle        |            |                  |                      |               |
|    |                |           |    |                         | 1)).                |            |                  |                      |               |
| 24 | Phase II       | Petrio    | 20 | Patients with           | The                 | Primary    | 67 (34           | 11.9                 | 6.8           |
| 21 | i nuse n       | li et al. | 15 | metastatic              | treatment in        | endpoint   | patients         | months in            | months        |
|    | А              | [18]      | 15 | pancreatic              | GEMOXEL             | : disease  | in               | GEMOXEL              | in            |
|    | randomized     | [10]      |    | cancer with             | arm                 | control    | GEMOX            | arm and 7.1          | GEMOX         |
|    | study.         |           |    |                         | (combination        | rate       | EL               | months in            | EL arm        |
|    | study.         |           |    | no prior<br>chemotherap |                     |            |                  |                      |               |
|    |                |           |    | -                       | of                  | (DCR).     | group,           | GEM arm.             | and 3.7       |
|    |                |           |    | у.                      | gemcitabine,        | <b>C</b> 1 | 33               |                      | months        |
|    |                |           |    |                         | oxaliplatin         | Seconda    | patients         |                      | in <b>GEM</b> |
|    |                |           |    |                         | and                 | ry         | in <b>GEM</b>    |                      | arm.          |
|    |                |           |    |                         | capecitabine)       | endpoint   | group).          |                      |               |
|    |                |           |    |                         | consisted of        | s: safety, |                  |                      |               |
|    |                |           |    |                         | gemcitabine         | PFS,       |                  |                      |               |
|    |                |           |    |                         | 1,000               | quality    |                  |                      |               |
|    |                |           |    |                         | <b>mg/m(2)</b> as a | of life,   |                  |                      |               |
|    |                |           |    |                         | 30-min              | and OS.    |                  |                      |               |
|    |                |           |    |                         | intravenous         |            |                  |                      |               |
|    |                |           |    |                         | infusion on         |            |                  |                      |               |
|    |                |           |    |                         | days 1, 8, 15,      |            |                  |                      |               |

|    |             |       |    |               | 22,                 |            |    |        |        |
|----|-------------|-------|----|---------------|---------------------|------------|----|--------|--------|
|    |             |       |    |               | oxaliplatin         |            |    |        |        |
|    |             |       |    |               | 100 mg/m(2)         |            |    |        |        |
|    |             |       |    |               | i.v. on day 2,      |            |    |        |        |
|    |             |       |    |               | and                 |            |    |        |        |
|    |             |       |    |               | capecitabine        |            |    |        |        |
|    |             |       |    |               | 1,500               |            |    |        |        |
|    |             |       |    |               | mg/m(2)/day         |            |    |        |        |
|    |             |       |    |               | in two              |            |    |        |        |
|    |             |       |    |               | divided             |            |    |        |        |
|    |             |       |    |               | doses on days       |            |    |        |        |
|    |             |       |    |               | 1-14, every 21      |            |    |        |        |
|    |             |       |    |               | days (one           |            |    |        |        |
|    |             |       |    |               | cycle).             |            |    |        |        |
|    |             |       |    |               | In                  |            |    |        |        |
|    |             |       |    |               | gemcitabine         |            |    |        |        |
|    |             |       |    |               | alone group,        |            |    |        |        |
|    |             |       |    |               | gemcitabine         |            |    |        |        |
|    |             |       |    |               | was                 |            |    |        |        |
|    |             |       |    |               | administered        |            |    |        |        |
|    |             |       |    |               | weekly for          |            |    |        |        |
|    |             |       |    |               | seven               |            |    |        |        |
|    |             |       |    |               | consecutive         |            |    |        |        |
|    |             |       |    |               | weeks               |            |    |        |        |
|    |             |       |    |               | followed by         |            |    |        |        |
|    |             |       |    |               | 1-week rest         |            |    |        |        |
|    |             |       |    |               | for the first 8     |            |    |        |        |
|    |             |       |    |               | weeks, and          |            |    |        |        |
|    |             |       |    |               | thereafter,         |            |    |        |        |
|    |             |       |    |               | gemcitabine         |            |    |        |        |
|    |             |       |    |               | was                 |            |    |        |        |
|    |             |       |    |               | continued on        |            |    |        |        |
|    |             |       |    |               | days 1, 8, 15,      |            |    |        |        |
|    |             |       |    |               | every 28            |            |    |        |        |
|    |             |       |    |               | days.               |            |    |        |        |
| 25 | NCT0114605  | Herm  | 20 | Patients with | Gemcitabine         | Primary    | 49 | 13.9   | 7.8    |
|    | 4           | an et | 15 | locally       | (1000               | endpoint   |    | months | months |
|    |             | al.   |    | advanced      | <b>mg/m(2))</b> for | : the rate |    |        |        |
|    | Phase II    | [19]  |    | pancreatic    | up to three         | of late    |    |        |        |
|    | -           | с · л |    | cancer        | weeks               | (more      |    |        |        |
|    | A single-   |       |    | (LAPC) with   | followed by a       | than 3     |    |        |        |
|    | arm, multi- |       |    | no prior      | 1-week <b>break</b> | months     |    |        |        |
|    | , mand      |       |    | abdominal     | and                 | after      |    |        |        |
|    |             |       |    | abuominal     | anu                 | anei       |    |        |        |

| institu | ıtional | radiotherapy. | stereotactic   | SBRT)      |  |  |
|---------|---------|---------------|----------------|------------|--|--|
| study.  |         | Patients with | body           | gastritis, |  |  |
|         |         | more than 3   | radiotherapy   | fistula,   |  |  |
|         |         | doses of      | (SBRT) (33.0   | enteritis  |  |  |
|         |         | gemcitabine   | gray [Gy] in 5 | or ulcer   |  |  |
|         |         | before        | fractions).    | of grade   |  |  |
|         |         | stereotactic  | After SBRT,    | more       |  |  |
|         |         | body          | patients       | than 2     |  |  |
|         |         | radiotherapy  | continued to   | and any    |  |  |
|         |         | (SBRT) were   | receive        | other      |  |  |
|         |         | excluded.     | gemcitabine    | late       |  |  |
|         |         |               | until disease  | grade 3    |  |  |
|         |         |               | progression    | to 4 GI    |  |  |
|         |         |               | or toxicity.   | toxicity   |  |  |
|         |         |               | Ĩ              | attributa  |  |  |
|         |         |               |                | ble to     |  |  |
|         |         |               |                | gemcitab   |  |  |
|         |         |               |                | ine and    |  |  |
|         |         |               |                | SBRT.      |  |  |
|         |         |               |                |            |  |  |
|         |         |               |                | Seconda    |  |  |
|         |         |               |                | ry         |  |  |
|         |         |               |                | endpoint   |  |  |
|         |         |               |                | s:         |  |  |
|         |         |               |                | freedom    |  |  |
|         |         |               |                | from       |  |  |
|         |         |               |                | local      |  |  |
|         |         |               |                | disease    |  |  |
|         |         |               |                | progress   |  |  |
|         |         |               |                | ion        |  |  |
|         |         |               |                | (FFLP);    |  |  |
|         |         |               |                | acute      |  |  |
|         |         |               |                | gastritis, |  |  |
|         |         |               |                | fistula,   |  |  |
|         |         |               |                | enteritis, |  |  |
|         |         |               |                | or ulcer   |  |  |
|         |         |               |                | of grade   |  |  |
|         |         |               |                | more       |  |  |
|         |         |               |                | than 2     |  |  |
|         |         |               |                | and any    |  |  |
|         |         |               |                | other      |  |  |
|         |         |               |                | acute      |  |  |
|         |         |               |                | grade 3    |  |  |

| 1  |                              |               | 1  |  |   |  |  |  | I  |
|----|------------------------------|---------------|----|--|---|--|--|--|----|
|    |                              |               |    |  |   | to 4 GI  |  |  |    |
|    |                              |               |    |  |   | toxicity   |  |  |    |
|    |                              |               |    |  |   | attributa  |  |  |    |
|    |                              |               |    |  |   | ble to   |  |  |    |
|    |                              |               |    |  |   | gemcitab   |  |  |    |
|    |                              |               |    |  |   | ine and  |  |  |    |
|    |                              |               |    |  |   | SBRT;  |  |  |    |
|    |                              |               |    |  |   | OS; PFS;   |  |  |    |
|    |                              |               |    |  |   | usefulne   |  |  |    |
|    |                              |               |    |  |   | ss of  |  |  |    |
|    |                              |               |    |  |   | FDG-   |  |  |    |
|    |                              |               |    |  |   | PET  |  |  |    |
|    |                              |               |    |  |   |  |  |  |    |
|    |                              |               |    |  |   | images<br>for  |  |  |    |
|    |                              |               |    |  |   | for  |  |  |    |
|    |                              |               |    |  |   | estimatio  |  |  |    |
|    |                              |               |    |  |   | n of   |  |  |    |
|    |                              |               |    |  |   | survival   |  |  |    |
|    |                              |               |    |  |   | outcome;   |  |  |    |
|    |                              |               |    |  |   | and  |  |  |    |
|    |                              |               |    |  |   | quality  |  |  |    |
|    |                              |               |    |  |   | of life  |  |  |    |
|    |                              |               |    |  |   | (QoL).   |  |  |    |
| 26 | NCT0106587                   | Sher          | 20 | Pancreatic   | Patients in   | Primary  | 45 (34   | 32.5   | NA |
|    |                              |               |    |  |   |  |  |  |    |
|    | 0                            | man           | 15 | adenocarcino   | both arterial   | endpoint   | patients   | months for   |    |
|    | 0                            | man<br>et al. | 15 | adenocarcino<br>ma patients  | both arterial<br>and venous   | endpoint<br>: to   | patients<br>in   | months for<br>all 45   |    |
|    | 0<br>Phase II                |               | 15 |  |   |  |  |  |    |
|    |                              | et al.        | 15 | ma patients  | and venous  | : to   | in   | all 45   |    |
|    |                              | et al.        | 15 | ma patients<br>presenting  | and venous<br>arms were   | : to<br>achieve  | in<br><b>arterial</b>                                      | all 45<br>patients.  |    |
|    | Phase II                     | et al.        | 15 | ma patients<br>presenting<br>with locally  | and venous<br>arms were<br>treated with 3   | : to<br>achieve<br>resection   | in<br><b>arterial</b><br><b>arm</b> , 11                   | all 45<br>patients.<br>29 months   |    |
|    | Phase II<br>A                | et al.        | 15 | ma patients<br>presenting<br>with locally<br>advanced,   | and venous<br>arms were<br>treated with 3<br>week cycle   | : to<br>achieve<br>resection<br>in at  | in<br><b>arterial</b><br><b>arm</b> , 11<br>patients       | all 45<br>patients.<br>29 months<br>for <b>arterial</b>  |    |
|    | Phase II<br>A<br>prospective | et al.        | 15 | ma patients<br>presenting<br>with locally<br>advanced,<br>un-resectable  | and venous<br>arms were<br>treated with 3<br>week cycle<br>for 6 cycles of  | : to<br>achieve<br>resection<br>in at<br>least 50%   | in<br><b>arterial</b><br><b>arm</b> , 11<br>patients<br>in | all 45<br>patients.<br>29 months<br>for <b>arterial</b><br><b>arm.</b>   |    |
|    | Phase II<br>A<br>prospective | et al.        | 15 | ma patients<br>presenting<br>with locally<br>advanced,<br>un-resectable<br>disease   | and venous<br>arms were<br>treated with 3<br>week cycle<br>for 6 cycles of<br>GTX   | : to<br>achieve<br>resection<br>in at<br>least 50%<br>of the   | in<br>arterial<br>arm, 11<br>patients<br>in<br>venous      | all     45       patternel     100       29     months       for     arternel       arm.     For     the   |    |
|    | Phase II<br>A<br>prospective | et al.        | 15 | ma patients<br>presenting<br>with locally<br>advanced,<br>un-resectable<br>disease<br>because of                                       | and venous<br>arms were<br>treated with 3<br>week cycle<br>for 6 cycles of<br>GTX<br>(neoadjuvant<br>gemcitabine  | $\begin{array}{c} : & to \\ achiever \\ resection \\ in & at \\ least 50% \\ of & the \\ patients \end{array}$   | in<br>arterial<br>arm, 11<br>patients<br>in<br>venous      | all 45<br>patients.<br>29 months<br>for arterial<br>arm.<br>For the<br>venous  |    |
|    | Phase II<br>A<br>prospective | et al.        | 15 | ma patients<br>presenting<br>with locally<br>advanced,<br>un-resectable<br>disease<br>because of<br>arterial or                        | and venous<br>arms were<br>treated with 3<br>week cycle<br>for 6 cycles of<br>GTX<br>(neoadjuvant<br>gemcitabine<br>(750 mg/m2,   | : to<br>achiever resection in at least 50% of the patients in the arterial   | in<br>arterial<br>arm, 11<br>patients<br>in<br>venous      | all 45 patients 29 months for artertal arm. For 6the the the the the the the the the the   |    |
|    | Phase II<br>A<br>prospective | et al.        | 15 | ma patients<br>presenting<br>with locally<br>advanced,<br>un-resectable<br>disease<br>because of<br>arterial or<br>extensive<br>venous | and venous<br>arms were<br>treated with 3<br>week cycle<br>for 6 cycles of<br>GTX<br>(neoadjuvant<br>gemcitabine<br>(750 mg/m2,<br>days 4 and   | : to<br>achi=vertial to the test to the te | in<br>arterial<br>arm, 11<br>patients<br>in<br>venous      | all 45 patients. 29 months for arter14 For 6th venous arm, 6th median overall  |    |
|    | Phase II<br>A<br>prospective | et al.        | 15 | ma patients<br>presenting<br>with locally<br>advanced,<br>un-resectable<br>disease<br>because of<br>arterial or<br>extensive           | and venous<br>arms were<br>treated with 3<br>week cycle<br>for 6 cycles of<br>GTX<br>(neoadjuvant<br>gemcitabine<br>(750 mg/m2,<br>days 4 and<br>11), docetaxel   | : to<br>achieve<br>resection<br>in at<br>least 50%<br>of the<br>patients<br>in the<br>arterial<br>arm.   | in<br>arterial<br>arm, 11<br>patients<br>in<br>venous      | all     45       patients     nonthom       29     nonthom       for     artertal       arm.     the       arm.     the       overall     survival   |    |
|    | Phase II<br>A<br>prospective | et al.        | 15 | ma patients<br>presenting<br>with locally<br>advanced,<br>un-resectable<br>disease<br>because of<br>arterial or<br>extensive<br>venous | and venous<br>arms were<br>treated with 3<br>week cycle<br>for 6 cycles of<br>GTX<br>(neoadjuvant<br>gemcitabine<br>(750 mg/m2,<br>days 4 and<br>11), docetaxel<br>(30 mg/m2,   | : to<br>achiever resection in at least 50% of the patients in the $arterialarm$ .<br>Patients  | in<br>arterial<br>arm, 11<br>patients<br>in<br>venous      | all     45       patients     nonths       29     nonths       for     arturta       arm.     the       venous     arturta       arm.     the       overall     the       overall     the       has     not  |    |
|    | Phase II<br>A<br>prospective | et al.        | 15 | ma patients<br>presenting<br>with locally<br>advanced,<br>un-resectable<br>disease<br>because of<br>arterial or<br>extensive<br>venous | and venous<br>arms were<br>treated with 3<br>week cycle<br>for 6 cycles of<br>GTX<br>(neoadjuvant<br>gemcitabine<br>(750 mg/m2,<br>days 4 and<br>11), docetaxel<br>(30 mg/m2,<br>days 4 and   | : to<br>achiever<br>resection<br>in at<br>least 50%<br>of the<br>patients<br>in the<br>arterial<br>arm.<br>Patients<br>also  | in<br>arterial<br>arm, 11<br>patients<br>in<br>venous      | all     45       patients     1       29     months       for     attents       for     attents       For     the       for     the       arm.     the       overouts     the       arm.     the       survival     the       has     not       been     the |    |
|    | Phase II<br>A<br>prospective | et al.        | 15 | ma patients<br>presenting<br>with locally<br>advanced,<br>un-resectable<br>disease<br>because of<br>arterial or<br>extensive<br>venous | and venous<br>arms were<br>treated with 3<br>week cycle<br>for 6 cycles of<br>GTX<br>(neoadjuvant<br>gemcitabine<br>(750 mg/m2,<br>days 4 and<br>11), docetaxel<br>(30 mg/m2,<br>days 4 and<br>11), and   | : to<br>achiever<br>resection<br>in at<br>least 50%<br>of the<br>patients<br>in the<br>arterial<br>arm.<br>Patients<br>also<br>were  | in<br>arterial<br>arm, 11<br>patients<br>in<br>venous      | all     45       patients     1       29     months       for     artent       arm.     the       venous     4       arm.     the       arm.     the       overall     the       survival     not       been     at  |    |
|    | Phase II<br>A<br>prospective | et al.        | 15 | ma patients<br>presenting<br>with locally<br>advanced,<br>un-resectable<br>disease<br>because of<br>arterial or<br>extensive<br>venous | and venous<br>arms were<br>treated with 3<br>week cycle<br>for 6 cycles of<br>GTX<br>(neoadjuvant<br>gemcitabine<br>(750 mg/m2,<br>days 4 and<br>11), docetaxel<br>(30 mg/m2,<br>days 4 and<br>11), and<br>capecitabine                                 | : to<br>achi=v=<br>resection<br>in at<br>least 50%<br>of the<br>patients<br>in the<br>arterial<br>arm.<br>Patients<br>also<br>were<br>followed   | in<br>arterial<br>arm, 11<br>patients<br>in<br>venous      | all45patients:29monthsforattentarm.thevenousthearm.theoveraltsurvivatsurvivatthebeenteatmodientteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteat  |    |
|    | Phase II<br>A<br>prospective | et al.        | 15 | ma patients<br>presenting<br>with locally<br>advanced,<br>un-resectable<br>disease<br>because of<br>arterial or<br>extensive<br>venous | and venous<br>arms were<br>treated with 3<br>week cycle<br>for 6 cycles of<br>GTX<br>(neoadjuvant<br>gemcitabine<br>(750 mg/m2,<br>days 4 and<br>11), docetaxel<br>(30 mg/m2,<br>days 4 and<br>11), and<br>capecitabine<br>(1500 mg/m2,                 | <ul> <li>: to</li> <li>achiever</li> <li>resection</li> <li>in at</li> <li>least 50%</li> <li>of the</li> <li>patients</li> <li>in the</li> <li>arterial</li> <li>arterial</li> <li>arterial</li> <li>arterial</li> <li>arterial</li> <li>in the</li> </ul>  | in<br>arterial<br>arm, 11<br>patients<br>in<br>venous      | all     45       patients     1       29     months       for     artent       arm.     the       venous     4       arm.     the       arm.     the       overall     the       survival     not       been     at  |    |
|    | Phase II<br>A<br>prospective | et al.        | 15 | ma patients<br>presenting<br>with locally<br>advanced,<br>un-resectable<br>disease<br>because of<br>arterial or<br>extensive<br>venous | and venous<br>arms were<br>treated with 3<br>week cycle<br>for 6 cycles of<br>GTX<br>(neoadjuvant<br>gemcitabine<br>(750 mg/m2,<br>days 4 and<br>11), docetaxel<br>(30 mg/m2,<br>days 4 and<br>11), and<br>capecitabine<br>(1500 mg/m2,<br>days 1-14)). | : to<br>achiever<br>resection<br>in at<br>least 50%<br>of the<br>patients<br>in the<br>arterial<br>arm.<br>Patients<br>also<br>were<br>followed<br>for<br>survival   | in<br>arterial<br>arm, 11<br>patients<br>in<br>venous      | all45patients:29monthsforattentarm.thevenousthearm.theoveraltsurvivatsurvivatthebeenteatmodientteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteat  |    |
|    | Phase II<br>A<br>prospective | et al.        | 15 | ma patients<br>presenting<br>with locally<br>advanced,<br>un-resectable<br>disease<br>because of<br>arterial or<br>extensive<br>venous | and venous<br>arms were<br>treated with 3<br>week cycle<br>for 6 cycles of<br>GTX<br>(neoadjuvant<br>gemcitabine<br>(750 mg/m2,<br>days 4 and<br>11), docetaxel<br>(30 mg/m2,<br>days 4 and<br>11), and<br>capecitabine<br>(1500 mg/m2,                 | <ul> <li>: to</li> <li>achiever</li> <li>resection</li> <li>in at</li> <li>least 50%</li> <li>of the</li> <li>patients</li> <li>in the</li> <li>arterial</li> <li>arterial</li> <li>arterial</li> <li>arterial</li> <li>arterial</li> <li>in the</li> </ul>  | in<br>arterial<br>arm, 11<br>patients<br>in<br>venous      | all45patients:29monthsforattentarm.thevenousthearm.theoveraltsurvivatsurvivatthebeenteatmodientteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteatmodentteat  |    |

|    |              |        |    |                   | involvement        | of       |          |           |           |
|----|--------------|--------|----|-------------------|--------------------|----------|----------|-----------|-----------|
|    |              |        |    |                   | were treated       | relapse. |          |           |           |
|    |              |        |    |                   | with GX/RT         |          |          |           |           |
|    |              |        |    |                   | (gemcitabine       |          |          |           |           |
|    |              |        |    |                   | and                |          |          |           |           |
|    |              |        |    |                   | capecitabine/      |          |          |           |           |
|    |              |        |    |                   | radiation          |          |          |           |           |
|    |              |        |    |                   | therapy) after     |          |          |           |           |
|    |              |        |    |                   | chemotherap        |          |          |           |           |
|    |              |        |    |                   | у.                 |          |          |           |           |
| 27 | NCT0101012   | Hobd   | 20 | Patients with     | Temsirolimu        | Co-      | 56       | 34 months | 13.2      |
|    | 6            | ay et  | 15 | well or           | s 25 mg            | primary  |          |           | months    |
|    |              | al.    |    | moderately        | intravenousl       | end      |          |           |           |
|    | Phase II     | [33]   |    | differentiated    | y (IV) once        | points:  |          |           |           |
|    |              |        |    | pancreatic        | per week (on       | tumor    |          |           |           |
|    | A two-stage  |        |    | neuroendocri      | days 1, 8, 15,     | response |          |           |           |
|    | multicenter  |        |    | ne tumors         | and 22) and        | rate and |          |           |           |
|    | single-arm   |        |    | (PNETs) and       | bevacizumab        | 6-month  |          |           |           |
|    | open-label   |        |    | progressive       | <b>10 mg/kg</b> IV | PFS.     |          |           |           |
|    | trial.       |        |    | disease.          | once every 2       |          |          |           |           |
|    |              |        |    | Prior             | weeks (on          |          |          |           |           |
|    |              |        |    | systemic          | days 1 and 15      |          |          |           |           |
|    |              |        |    | treatments        | of a 28-day        |          |          |           |           |
|    |              |        |    | for metastatic    | cycle).            |          |          |           |           |
|    |              |        |    | disease were      | 5                  |          |          |           |           |
|    |              |        |    | permitted.        |                    |          |          |           |           |
| 28 | RAD001 in    | Lomb   | 20 | Patients with     | Patients were      | Primary  | 410 (207 | NA        | For       |
|    | Advanced     | ard-   | 15 | advanced,         | prospectively      | endpoint | in       |           | chemo-    |
|    | Neuroendoc   | Bohas  | -  | progressive,      | stratified by      | : PFS    | everolim |           | naïve     |
|    | rine Tumors, | et al. |    | low- or           | prior              | -        | us       |           | patients: |
|    | Third Trial  | [34]   |    | intermediate-     | chemotherap        |          | group,   |           | 11.4      |
|    | (RADIANT-    | r. =1  |    | grade             | y use and          |          | 203 in   |           | months    |
|    | 3)           |        |    | pancreatic        | World Health       |          | placebo  |           | with      |
|    | Phase III    |        |    | neuroendocri      | Organization       |          | group).  |           | everoli   |
|    | A            |        |    | ne tumors         | performance        |          | 5-3"F).  |           | mus and   |
|    | prospective, |        |    | (pNET) with       | status and         |          |          |           | 5.4       |
|    | double-      |        |    | no prior          | were               |          |          |           | months    |
|    | blind,       |        |    | cytotoxic         | randomly           |          |          |           | with      |
|    | randomized,  |        |    | chemotherap       | assigned (1:1)     |          |          |           | placebo.  |
|    | parallel-    |        |    | _                 | to                 |          |          |           | For       |
|    | group,       |        |    | y,<br>immunothera | everolimus         |          |          |           | patients  |
|    | placebo-     |        |    |                   | <b>10 mg/d</b> or  |          |          |           | with      |
|    | -            |        |    | py, or            | -                  |          |          |           |           |
|    | controlled,  |        |    | radiotherapy      | placebo.           |          |          |           | prior     |

|    | 1            |        |    |                |                      |          |          |             | 1 11           |
|----|--------------|--------|----|----------------|----------------------|----------|----------|-------------|----------------|
|    | multicenter  |        |    | within 4       |                      |          |          |             | chemoth        |
|    | study.       |        |    | weeks before   |                      |          |          |             | erapy:         |
|    |              |        |    | randomizatio   |                      |          |          |             | 11.0           |
|    |              |        |    | n.             |                      |          |          |             | months         |
|    |              |        |    |                |                      |          |          |             | with           |
|    |              |        |    |                |                      |          |          |             | everoli        |
|    |              |        |    |                |                      |          |          |             | <b>mus</b> and |
|    |              |        |    |                |                      |          |          |             | 3.2            |
|    |              |        |    |                |                      |          |          |             | months         |
|    |              |        |    |                |                      |          |          |             | with           |
|    |              |        |    |                |                      |          |          |             | placebo.       |
| 29 | CESAR        | Berg   | 20 | Patients with  | Gemcitabine          | Primary  | 61 (33   | 36.7 weeks  | 13.3           |
|    | (Central     | mann   | 15 | locally        | at a dosage of       | endpoint | patients | for the     | weeks          |
|    | European     | et al. |    | advanced,      | 1.000mg/m(2)         | : PFS.   | in       | GEM arm     | for GEM        |
|    | Society for  | [21]   |    | un-resectable  | d1, 8, 15 q28        |          | gemcita  | and 30.4    | arm and        |
|    | Anticancer   |        |    | or metastatic  | versus a             | Seconda  | bine     | weeks for   | 11.6           |
|    | Drug         |        |    | pancreatic     | combination          | ry       | group    | SUNGEM      | weeks          |
|    | Research-    |        |    | ductal         | of SUNGEM            | endpoint | and 28   | arm.        | for            |
|    | EWIV)        |        |    | adenocarcino   | (gemcitabine         | s: OS,   | patients |             | SUNGE          |
|    | Phase II     |        |    | ma (PDAC)      | plus                 | toxicity | in       |             | M arm.         |
|    | A            |        |    | without        | sunitinib) at        | and      | SUNGE    |             | ivi unit.      |
|    | prospective, |        |    | previous       | a dosage of          | overall  | M        |             |                |
|    | randomized,  |        |    | chemotherap    | GEM                  |          |          |             |                |
|    |              |        |    | -              |                      | response | group).  |             |                |
|    | open-label   |        |    | y for adjuvant | 1.000mg/m(2)         | rate     |          |             |                |
|    | trial.       |        |    | or metastatic  | d1+8 and             | (ORR).   |          |             |                |
|    |              |        |    | disease.       | sunitinib            |          |          |             |                |
|    |              |        |    |                | <b>50mg</b> p.o. d1- |          |          |             |                |
|    |              |        |    |                | 14, q21d.            |          |          |             |                |
| 30 | Phase III    | Lee et | 20 | Patients with  | Gemcitabine          | Primary  | 214 (108 | 10.3        | 6.2            |
|    | А            | al.    | 17 | advanced pa    | plus                 | endpoint | in       | months in   | months         |
|    | randomized,  | [23]   |    | ncreatic       | capecitabine         | : median | gemcita  | the         | in the         |
|    | multicenter  |        |    | cancer         | (oral                | OS       | bine     | gemcitabin  | gemcita        |
|    | study.       |        |    | without prior  | capecitabine         |          | plus     | e plus      | bine           |
|    |              |        |    | chemotherap    | 1660mg/m             | Seconda  | capecita | capecitabin | plus           |
|    |              |        |    | у.             | plus                 | ry       | bine     | e group.    | capecita       |
|    |              |        |    |                | gemcitabine          | endpoint | group    | 7.5 months  | bine           |
|    |              |        |    |                | <b>1000mg/m</b> by   | s: PFS,  | and 106  | in the      | group.         |
|    |              |        |    |                | 30-minute            | overall  | in       | gemcitabin  | 5.3            |
|    |              |        |    |                | intravenous          | response | gemcita  | e group.    | months         |
|    |              |        |    |                | infusion             | rate     | bine     |             | in the         |
|    |              |        |    |                | weekly for 3         | (ORR),   | alone    |             | gemcita        |
|    |              |        |    |                | weeks                | disease  | group).  |             | bine           |
|    |              |        |    |                | followed by a        | control  |          |             | group.         |
| L  | 1            | I      | I  | l              |                      |          | 1        |             | 0.1.           |

|    |              |        |    | 1             | 1                          | I              | I        | 1             |               |
|----|--------------|--------|----|---------------|----------------------------|----------------|----------|---------------|---------------|
|    |              |        |    |               | 1-week break               | rate, and      |          |               |               |
|    |              |        |    |               | every 4                    | toxicity.      |          |               |               |
|    |              |        |    |               | weeks) or                  |                |          |               |               |
|    |              |        |    |               | gemcitabine                |                |          |               |               |
|    |              |        |    |               | alone (by 30-              |                |          |               |               |
|    |              |        |    |               | minute                     |                |          |               |               |
|    |              |        |    |               | intravenous                |                |          |               |               |
|    |              |        |    |               | infusion                   |                |          |               |               |
|    |              |        |    |               | weekly for 3               |                |          |               |               |
|    |              |        |    |               | weeks every                |                |          |               |               |
|    |              |        |    |               | 4 weeks).                  |                |          |               |               |
| 31 | Phase II     | Ioka   | 20 | Patients with | S-1 (80-                   | Primary        | 127      | 6.8 months    | 3.5           |
|    | А            | et al. | 17 | gemcitabine-  | <b>120 mg</b> for 14       | endpoint       |          | in            | months        |
|    | randomized,  | [37]   |    | refractory pa | days every 4               | : PFS.         |          | irinotecan    | in            |
|    | multicenter, |        |    | ncreatic      | weeks) plus                |                |          | plus S-1      | irinotec      |
|    | controlled   |        |    | cancer.       | intravenous                |                |          | group.        | an plus       |
|    | trial.       |        |    |               | irinotecan                 |                |          | 5.8 months    | S-1           |
|    |              |        |    |               | ( <b>100 mg/m</b> on       |                |          | in <b>S-1</b> | group.        |
|    |              |        |    |               | days 1 and 15              |                |          | monothera     | 1.9           |
|    |              |        |    |               | every 4                    |                |          | py group.     | months        |
|    |              |        |    |               | weeks) or                  |                |          | 178-11        | in <b>S-1</b> |
|    |              |        |    |               | oral S-1 alone             |                |          |               | monoth        |
|    |              |        |    |               | (80-120 mg                 |                |          |               | erapy         |
|    |              |        |    |               | daily for 28               |                |          |               | group.        |
|    |              |        |    |               | days every 6               |                |          |               | Storb.        |
|    |              |        |    |               | weeks).                    |                |          |               |               |
| 32 | UMIN00000    | Satoi  | 20 | Chemotherap   | Paclitaxel                 | Primary        | 33 (22   | 16.3          | NA            |
| 02 | 9446         | et al. | 17 | y-            | administered               | endpoint       | with     | months        | 1111          |
|    | Phase II     | [38]   | 17 | naïve pancre  | intravenousl               | : 1-year       | peritone | monuis        |               |
|    | A            | [00]   |    | atic ductal   | y at <b>50mg/m</b>         | overall        | al       |               |               |
|    | multicenter  |        |    | adenocarcino  | and                        | survival.      | dissemin |               |               |
|    | study.       |        |    | ma patients   | intraperitone              | Survival.      | ation    |               |               |
|    | study.       |        |    | with          | al at <b>20mg/m</b>        | Seconda        | and 11   |               |               |
|    |              |        |    | peritoneal    | on days 1 and              |                | with     |               |               |
|    |              |        |    | metastasis.   | -                          | ry<br>endpoint |          |               |               |
|    |              |        |    | metastasis.   | 8. <b>S-1</b> administered | -              | positive |               |               |
|    |              |        |    |               |                            | s:             | peritone |               |               |
|    |              |        |    |               | at 80mg/m/d                | antitumo       | al       |               |               |
|    |              |        |    |               | for 14                     | r effect       | cytology |               |               |
|    |              |        |    |               | consecutive                | and            | ).       |               |               |
|    |              |        |    |               | days,                      | safety.        |          |               |               |
|    |              |        |    |               | followed by 7              |                |          |               |               |
|    |              |        |    |               | days of rest.              |                |          |               |               |

| Author       | Selection | Study    | Confounders | Blinding | Data       | Withdrawals | General  |
|--------------|-----------|----------|-------------|----------|------------|-------------|----------|
|              | bias      | design   |             | _        | collection | and         | rating   |
|              |           |          |             |          | methods    | dropouts    |          |
| Ettrich et   | Strong    | Weak     | NA          | Weak     | Strong     | Moderate    | Weak     |
| al. [35]     |           |          |             |          |            |             |          |
| Ueno et al.  | Strong    | Strong   | Strong      | Weak     | Strong     | Moderate    | Moderate |
| [36]         |           |          |             |          |            |             |          |
| Tai et al.   | Strong    | Weak     | Strong      | Weak     | Strong     | Weak        | Weak     |
| [39]         |           |          |             |          |            |             |          |
| Uesaka et    | Moderate  | Strong   | Strong      | Weak     | Strong     | Strong      | Moderate |
| al. [11]     |           |          |             |          |            |             |          |
| Hammel et    | Moderate  | Strong   | Strong      | Weak     | Strong     | Moderate    | Moderate |
| al. [12]     |           |          |             |          |            |             |          |
| Stein et al. | Strong    | Weak     | Weak        | Weak     | Strong     | Moderate    | Weak     |
| [28]         |           |          |             |          |            |             |          |
| Ueno et al.  | Strong    | Weak     | Moderate    | Weak     | Strong     | Strong      | Weak     |
| [15]         |           |          |             |          |            |             |          |
| Imaoka et    | Strong    | Strong   | Weak        | Weak     | Strong     | Strong      | Weak     |
| al. [10]     |           |          |             |          |            |             |          |
| Belli et al. | Strong    | Weak     | NA          | Weak     | Strong     | Strong      | Weak     |
| [29]         |           |          |             |          |            |             |          |
| Wang-        | Strong    | Moderate | Strong      | Weak     | Strong     | Strong      | Moderate |
| Gillam et    |           |          |             |          |            |             |          |
| al. [30]     |           |          |             |          |            |             |          |
| Postlewait   | Strong    | Weak     | Strong      | Weak     | Strong     | Moderate    | Weak     |
| et al. [22]  |           |          |             |          |            |             |          |
| Catenacci    | Strong    | Strong   | Strong      | Weak     | Moderate   | Moderate    | Moderate |
| et al. [16]  |           |          |             |          |            |             |          |
| Wu et al.    | Strong    | Weak     | NA          | Weak     | Strong     | Strong      | Weak     |
| [24]         |           |          |             |          |            |             |          |
| Hurwitz et   | Strong    | Moderate | Strong      | Strong   | Strong     | Strong      | Strong   |
| al. [25]     |           |          |             |          |            |             |          |
| Goji et al.  | Strong    | Weak     | Strong      | Weak     | Weak       | Moderate    | Weak     |
| [9]          |           |          |             |          |            |             |          |
| Makielski    | Strong    | Weak     | NA          | Weak     | Strong     | Strong      | Weak     |
| et al. [26]  |           |          |             |          |            |             |          |
| Wang et al.  | Strong    | Strong   | Strong      | Weak     | Strong     | Moderate    | Moderate |
| [13]         |           |          |             |          |            |             |          |
| Assenat et   | Strong    | Weak     | NA          | Weak     | Strong     | Strong      | Weak     |
| al. [31]     |           |          |             |          |            |             |          |
| Ohkawa et    | Strong    | Strong   | Strong      | Weak     | Strong     | Strong      | Moderate |
| al. [32]     |           |          |             |          |            |             |          |

| Shimoda                                 | Moderate | Strong   | Strong   | Weak   | Moderate | Strong   | Moderate |
|---|----------|----------|----------|--------|----------|----------|----------|
| et al. [2]<br>Kordes et                 | Strong   | Weak     | NA       | Weak   | Strong   | Strong   | Weak     |
| <i>al.</i> [27]<br>Cho <i>et al.</i>    | Strong   | Weak     | Weak     | Weak   | Strong   | Strong   | Weak     |
| [17]<br>Goldstein<br><i>et al.</i> [14] | Strong   | Moderate | Strong   | Weak   | Strong   | Strong   | Moderate |
| Petrioli <i>et al.</i> [18]             | Strong   | Moderate | Strong   | Weak   | Strong   | Strong   | Moderate |
| Herman <i>et</i><br>al. [19]            | Moderate | Weak     | NA       | Weak   | Moderate | Strong   | Weak     |
| Sherman<br>et al. [20]                  | Strong   | Weak     | Moderate | Weak   | Strong   | Moderate | Weak     |
| Hobday <i>et</i><br><i>al.</i> [33]     | Strong   | Weak     | NA       | Weak   | Strong   | Strong   | Weak     |
| Lombard-<br>Bohas <i>et al.</i><br>[34] | Strong   | Moderate | Strong   | Strong | Strong   | Strong   | Strong   |
| Bergmann<br>et al. [21]                 | Strong   | Moderate | Strong   | Weak   | Strong   | Strong   | Moderate |
| Lee <i>et al.</i><br>[23]               | Strong   | Strong   | Strong   | Weak   | Strong   | Moderate | Moderate |
| Ioka <i>et al.</i><br>[37]              | Strong   | Moderate | Strong   | Weak   | Strong   | Strong   | Moderate |
| Satoi <i>et al.</i><br>[38]             | Moderate | Weak     | NA       | Weak   | Strong   | Strong   | Weak     |