**Supplementary Table S3. Summary of Included Multi-Group Observational Studies of 2L Treatments for Advanced BTC**

| **Author, year** | **Study period** | **N** | **1L chemo** | **Drug** | **Groups, n** | **ORR, %** | **Median OS, months** | **Median PFS,** | **6-month OS, %** | **6-month PFS, %** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Adhikaree and Madhusudan  2014 | 2008-2012 | 18 | GEM-CIS | Grp1: GEM/GEM+CIS/5FU+CIS | 18 | NR | 29 (measured from 1L) | 13.3 (measured from 1L) | NR | NR |
| Brieau 2015 | 2002-2013 | 196 | GEM-OX, GEM-CIS | Grp 1: Mixed (FLUOR+/TGT/  Other[NS])  Grp 2: FOLFIRI/XELIRI  Grp 3: FOLFOX/XELOX  Grp 4: Mixed (GEM+/PLT+/  TGT/Other)  Grp 5: LV5FU2+CIS  Grp 6: Mono Tx (5FU/CAP)  Grp 7: Mono Tx (FLUOR)  Grp 8: Mono Tx (SUN)  Grp 9: Combo Tx (FLUOR+) | Grp 1: 196  Grp 2: 64  Grp 3: 21  Grp 4: 23  Grp 5: 38  Grp 6: 40  Grp 7: 123  Grp 8: 10  Grp 9: 40 | Grp 1: 11.8  Grp 2: 11.5  Grp 3: 10  Grp 4: 12  Grp 5: 13.5  Grp 6: 10.8  Grp 7: NR  Grp 8: 11.1  Grp 9: NR | Grp 1: 6.7  Grp 2: 6.1  Grp 3: NR  Grp 4: 6.8  Grp 5: NR  Grp 6: NR  Grp 7: 5.6  Grp 8: 8.4  Grp 9: 6.3 | Grp 1: 3.2  Grp 2: 2.6  Grp 3: NR  Grp 4: 4.2  Grp 5: 3.3  Grp 6: 3.3  Grp 7: 3.3  Grp 8: 4.6  Grp 9: 3 | NR | NR |
| Croitoru 2012 | 2004-2008 | 46 | GEM±CIS, FLUOR+  CIS | Grp 1: Mixed (FLUOR±)  Grp 2: Mixed (GEM±) | Grp 1: 17  Grp 2: 29 | NR | NR | Grp 1: 3.2  Grp 2: 6.1 | NR | NR |
| Fiteni 2014 | 1998-2010 | 16 | GEMOX | Grp 1: FOLFIRI/  FOLFOX  Grp 2: Mono Tx  (5FU-LV/CAP) | Grp 1: 5  Grp 2: 11 | NR | Grp 1: 6.1  Grp 2: 5.2 | Grp 1: 4.4  Grp 2: 3.8 | NR | NR |
| Fornaro 2014  *Related publication: Fornaro 2015* | 2004-2013 | 300 | GEM-PLT, GEM-FLUOR, MIX (GEM-based), GEM, other | Grp 1: Mixed (GEM±FLUOR/  GEM±Other[NS]/  Other[NS])  Grp 2: Combo Tx (GEM+FLUOR/  GEM+Other[NS]/  Other[NS])  Grp 3: Mono Tx (GEM/Other[NS])  Grp 4: Mixed (FLUOR±/GEM±/Other [NS]) | Grp 1: 300  Grp 2: NR  Grp 3: NR  Grp 4: 174 | Grp 1: 4  Grp 2: NR  Grp 3: NR  Grp 4: 3.4 | Grp 1: 7.2  Grp 2: 8.2  Grp 3: 5.2  Grp 4: 6.6 | Grp 1: 3.2  Grp 2: 3  Grp 3: 3.4  Grp 4: 3 | NR | NR |
| Kim 2017 | 2010-2015 | 321 | GEM-CIS | Grp 1: Combo Tx (FLUOR+PLT)  Grp 2: Mono Tx (FLUOR) | Grp 1: 66  Grp 2: 255 | Grp 1: 8.3  Grp 2: 1.2 | Grp 1: 6.2  Grp 2: 6.5 | Grp 1: 2.6  Grp 2: 1.8 | NR | NR |
| Kus 2017 | 2008-2016 | 29 | GEM-CIS,  5-FU-CIS,  FOLFIRINOX | Grp 1: FOLFIRINOX/  FOLFOX/XELIRI/XELOX  Grp 2: Mixed (GEM±) | Grp 1: 20  Grp 2: 7 | NR | NR | Grp 1: 2.77  Grp 2: 3.23 | NR | NR |
| Moik 2019 | 2003-2016 | 80 | GEM+CIS, GEM, other chemotherapy | Grp 1: BSC  Grp 2: Mixed (FLUOR±/Other [NS]) | Grp 1: 42  Grp 2: 38 | Grp 1: NR  Grp 2: 3 | Grp 1: 2.7  Grp 2: 12.1 | NR | Grp 1: 29  Grp 2: 77 | NR |
| Neuzillet 2020  *Related publication:* Neuzillet 2019 | 2003-2016 | 351 | GEMCIS, GEMOX | Grp 1: Combo Tx (FLUOR+IRI), French cohort  Grp 2: Combo Tx (FLUOR+PLT), French cohort  Grp 3: Mono Tx (FLUOR), French cohort  Grp 4: Combo Tx (FLUOR+IRI), Italian cohort  Grp 5: Combo Tx (FLUOR+PLT), Italian cohort  Grp 6: Mono Tx (FLUOR), Italian cohort | Grp 1: 194  Grp 2: 94  Grp 3: 63  Grp 4: 60  Grp 5: 16  Grp 6: 97 | NR | Grp 1: 6.7  Grp 2: 7.1  Grp 3: 5.6  Grp 4: 7.5  Grp 5: 6  Grp 6: 5.2 | NR | NR | NR |
| Ramaswamy 2016 | 2012- 2014 | 87 | GEMOX,  GEM-CIS,  GEM-CAR,  CET-GEMOX,  XELIRI | Combo Tx (FLUOR+/GEM+) | 87 | 21.8 | 8 | 6 | NR | NR |
| Rogers 2014 | 2009- 2012 | 56 | GEM-CIS,  GEM-CIS-ERL,  GEM,  Other (FOLFOX/ FOLFORINOX/  GEM-CAP/  CAR+PAC) | Mixed (FLUOR+/GEM+/TGT±) | 56 | NR | NR | 2.7 | NR | NR |
| Schweitzer 2018 | 2000-2015 | 142 | GEM based: GEM,  GEM-PLT  MIX (5FU): MIX (5FU/CAP), FOLFOX/  FOLFIRI  GEM+5-FU  Others | Mixed (FLUOR±/GEM±/Other [NS]) | 142 | 9.7 | 9.9 | NR | NR | NR |

1L, first-line; 2L, second-line; BTC, biliary tract cancer; chemo, chemotherapy; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial. See also *Treatment abbreviations* section.

“-“ or “+” indicates that combination treatment was received (eg, CAP-PBO, capecitabine plus placebo, CAP+CIS, capecitabine plus cisplatin). “±” indicates that a treatment was received either in combination with the next listed treatment or as a monotherapy (eg, FLUOR±PLT, fluoropyrimidine with or without a platinum). “/” indicates that either treatment listed was received (eg, GEM+CIS/S1, gemcitabine plus cisplatin *or* S1).