**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/XELIRIGrp 3: FOLFOX/XELOXGrp 4: Mixed (GEM+/PLT+/TGT/Other)Grp 5: LV5FU2+CISGrp 6: Mono Tx (5FU/CAP)Grp 7: Mono Tx (FLUOR)Grp 8: Mono Tx (SUN)Grp 9: Combo Tx (FLUOR+) | Grp 1: 196Grp 2: 64Grp 3: 21Grp 4: 23Grp 5: 38Grp 6: 40Grp 7: 123Grp 8: 10Grp 9: 40 | Grp 1: 11.8Grp 2: 11.5Grp 3: 10Grp 4: 12Grp 5: 13.5Grp 6: 10.8Grp 7: NRGrp 8: 11.1Grp 9: NR | Grp 1: 6.7Grp 2: 6.1Grp 3: NRGrp 4: 6.8Grp 5: NRGrp 6: NRGrp 7: 5.6Grp 8: 8.4Grp 9: 6.3 | Grp 1: 3.2Grp 2: 2.6Grp 3: NR Grp 4: 4.2Grp 5: 3.3Grp 6: 3.3Grp 7: 3.3Grp 8: 4.6Grp 9: 3 | NR | NR |
| Croitoru 2012 | 2004-2008 | 46 | GEM±CIS, FLUOR+CIS | Grp 1: Mixed (FLUOR±)Grp 2: Mixed (GEM±) | Grp 1: 17Grp 2: 29 | NR | NR | Grp 1: 3.2Grp 2: 6.1 | NR | NR |
| Fiteni 2014 | 1998-2010 | 16 | GEMOX | Grp 1: FOLFIRI/FOLFOXGrp 2: Mono Tx (5FU-LV/CAP) | Grp 1: 5Grp 2: 11 | NR | Grp 1: 6.1Grp 2: 5.2 | Grp 1: 4.4Grp 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: 300Grp 2: NRGrp 3: NRGrp 4: 174 | Grp 1: 4Grp 2: NRGrp 3: NRGrp 4: 3.4 | Grp 1: 7.2Grp 2: 8.2Grp 3: 5.2Grp 4: 6.6 | Grp 1: 3.2Grp 2: 3Grp 3: 3.4Grp 4: 3 | NR | NR |
| Kim 2017 | 2010-2015 | 321 | GEM-CIS | Grp 1: Combo Tx (FLUOR+PLT)Grp 2: Mono Tx (FLUOR) | Grp 1: 66Grp 2: 255 | Grp 1: 8.3Grp 2: 1.2 | Grp 1: 6.2Grp 2: 6.5 | Grp 1: 2.6Grp 2: 1.8 | NR | NR |
| Kus 2017 | 2008-2016 | 29 | GEM-CIS,5-FU-CIS,FOLFIRINOX | Grp 1: FOLFIRINOX/FOLFOX/XELIRI/XELOXGrp 2: Mixed (GEM±) | Grp 1: 20Grp 2: 7 | NR | NR | Grp 1: 2.77Grp 2: 3.23 | NR | NR |
| Moik 2019 | 2003-2016 | 80 | GEM+CIS, GEM, other chemotherapy | Grp 1: BSCGrp 2: Mixed (FLUOR±/Other [NS]) | Grp 1: 42Grp 2: 38 | Grp 1: NRGrp 2: 3 | Grp 1: 2.7Grp 2: 12.1 | NR | Grp 1: 29Grp 2: 77 | NR |
| Neuzillet 2020*Related publication:* Neuzillet 2019 | 2003-2016 | 351 | GEMCIS, GEMOX | Grp 1: Combo Tx (FLUOR+IRI), French cohortGrp 2: Combo Tx (FLUOR+PLT), French cohortGrp 3: Mono Tx (FLUOR), French cohortGrp 4: Combo Tx (FLUOR+IRI), Italian cohortGrp 5: Combo Tx (FLUOR+PLT), Italian cohortGrp 6: Mono Tx (FLUOR), Italian cohort | Grp 1: 194Grp 2: 94Grp 3: 63Grp 4: 60Grp 5: 16Grp 6: 97 | NR | Grp 1: 6.7Grp 2: 7.1Grp 3: 5.6Grp 4: 7.5Grp 5: 6Grp 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-PLTMIX (5FU): MIX (5FU/CAP), FOLFOX/FOLFIRIGEM+5-FUOthers | 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).