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MEETING SUMMARY
ASCO GI 2019, San Francisco, USA

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CANCERS OF THE LIVER, LOWER INTESTINE AND PANCREAS TRACT

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This content is supported by an Independent Educational Grant from Bayer

EFFICACY AND SAFETY OF DABRAFENIB AND TRAMETINIB IN PATIENTS WITH *BRAF* V600E–MUTATED BILIARY TRACT CANCER (BTC): A COHORT OF THE ROAR BASKET TRIAL

Wainberg ZA, *et al.* ASCO GI 2019, Abst #187

ROAR STUDY
INTRODUCTION

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- This study was part of the basket study for rare tumors with *BRAF* V600E mutation. This abstract reported the data on the biliary tract cancers in this study (N=33 patients)
- Retrospective studies report incidence of about 5% of *BRAF* mutations in patients with biliary cancers, predominantly in intrahepatic tumors
- The combination of dabrafenib (*BRAF* inhibitor) and trametinib (MEK inhibitor) has demonstrated efficacy in *BRAF* V600E mutated cancers including melanoma, NSCLC
- The **ROAR study** evaluated 9 different rare tumors with *BRAF* V600E mutations, including biliary tract cancer
- This analysis focussed on the **biliary tract cancer cohort**

Wainberg ZA, *et al.* ASCO GI 2019, Abst #187
BRAF, B-Raf proto-oncogene, serine/threonine kinase; MEK, Mitogen-Activated Protein Kinase Kinase; N, number of patients; NSCLC, non-small-cell lung carcinoma

ROAR STUDY DESIGN

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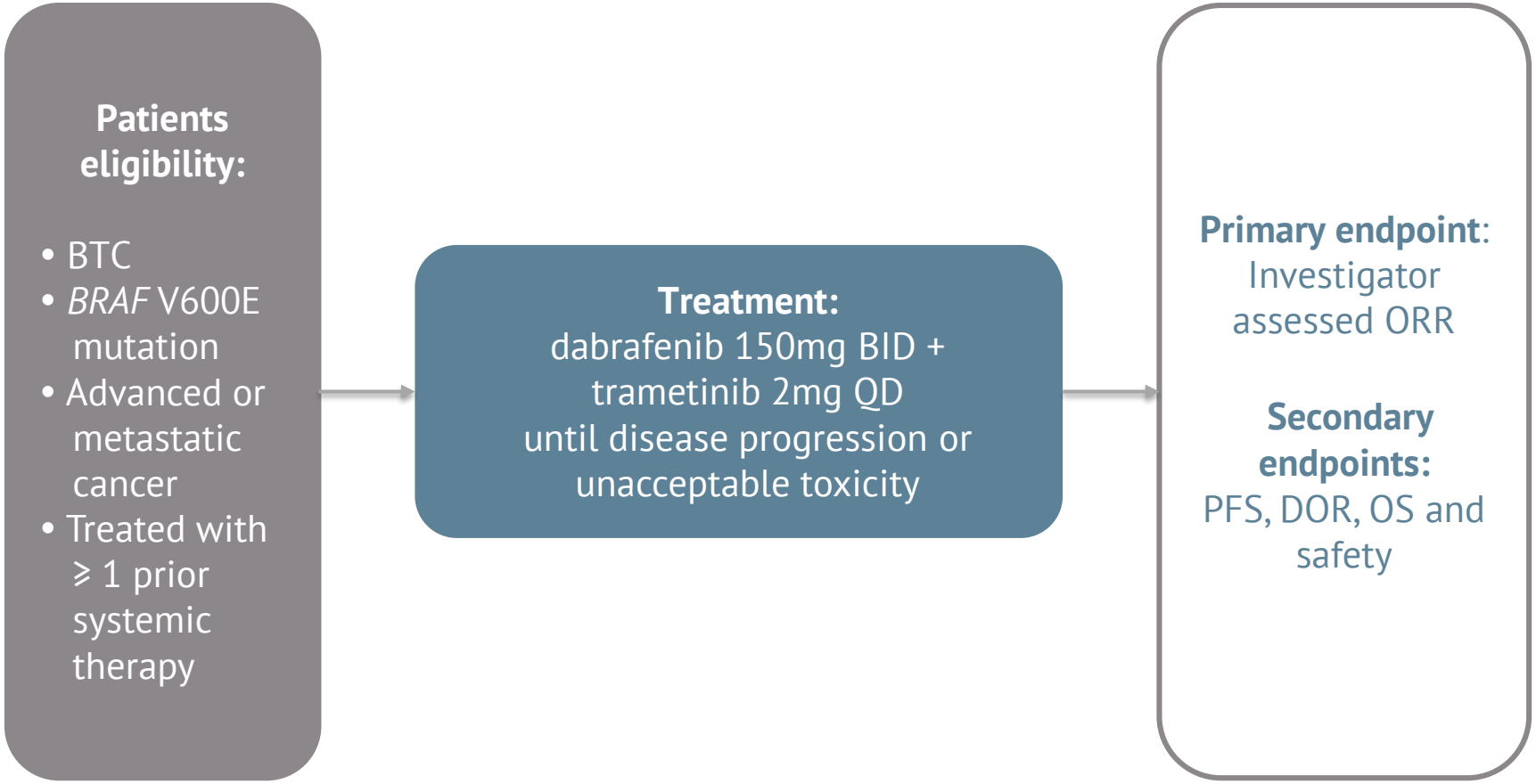
Phase II, open label, single-arm study (BTC cohort)



Wainberg ZA, *et al.* ASCO GI 2019, Abst #187

BID, twice daily; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; BTC, biliary tract cancer; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once daily

ROAR STUDY
PATIENT ENROLMENT AND CHARACTERISTICS

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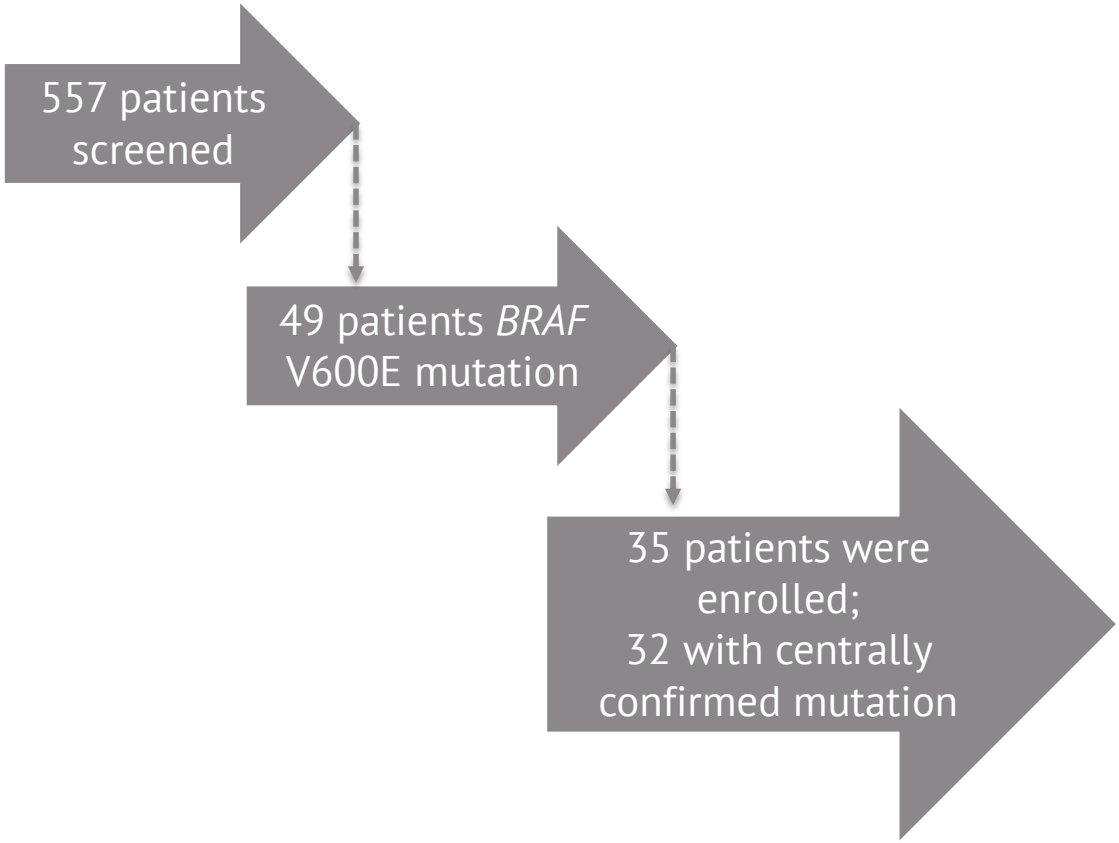
BTC cohort



Patient characteristics:

- Median age 57
- 43% male
- ECOG 0-1 (1 patient was ECOG 2)
- Most patients with adenocarcinoma
- Most with stage IV
- 80% receiving 2 prior lines of therapy

Wainberg ZA, *et al.* ASCO GI 2019, Abst #187
BRAF, B-Raf proto-oncogene, serine/threonine kinase; BTC, biliary tract cancer; ECOG, Eastern Cooperative Oncology Group; Perf, performance

ROAR STUDY
RESULTS: EFFICACY

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- Median duration of treatment was 6 months (range, 2-32 months)
- At the data cut off 67% of patients discontinued treatment mostly due to progression (60%)
- **ORR 42% (95%CI, 25.5-60.8) by investigator review**, 36% (95%CI, 20.4-54.9) by independent review
- Duration of response at 6 months was 66% (95%CI, 32-86%)
- 15 patients (45%) had durable stable disease
- Median PFS 9.2 (95%CI, 5.4-10.1) months
- Median OS 11.7 (95%CI, 7.5-17.7) months

Wainberg ZA, *et al.* ASCO GI 2019, Abst #187
ORR, overall response rate; OS, overall survival; PFS, progression-free survival

ROAR STUDY
RESULTS: ADVERSE EVENTS

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- Adverse events were as expected with the combination, mostly (n=35):
  - Pyrexia (40%)
  - Rash (29%)
  - Nausea (23%)
  - Diarrhoea (23%)
  - Fatigue (23%)
  - Chills (20%)

ROAR STUDY
CONCLUSIONS

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- *BRAF* V600E mutation occur in about 5% of patients with biliary cancers
- This is the first prospective study analysing the benefit of dabrafenib and trametinib in biliary cancer
- Efficacy was comparable to first line chemotherapy in this disease
- ORR of 42% and median PFS of 9.2 months and median OS of 11.7 months
- This is one of several actionable mutations in this disease and should be evaluated for all patients with biliary cancers
- **Based on these results, tumors harbouring this mutation should receive treatment with dabrafenib and trametinib**

Wainberg ZA, *et al.* ASCO GI 2019, Abst #187
BRAF, B-Raf proto-oncogene, serine/threonine kinase; ORR, overall response rate; OS, overall survival; PFS, progression free survival

RANDOMIZED, OPEN LABEL, PERIOPERATIVE PHASE II STUDY EVALUATING NIVOLUMAB ALONE VERSUS NIVOLUMAB PLUS IPILIMUMAB IN PATIENTS WITH RESECTABLE HCC

Kaseb AO, et al. ASCO GI 2019, Abst #185

PERIOPERATIVE IMMUNOTHERAPY FOR RESECTABLE HCC: INTRODUCTION

- No data are available for neoadjuvant or adjuvant therapy in HCC
- HCC is a very immunogenic tumor, with activity of PD-1 inhibitors which are currently approved for treatment of metastatic disease
- This is the first perioperative study in this patient population

Kaseb AO, et al. ASCO GI 2019, Abst #185
HCC, hepatocellular carcinoma; PD-1, programmed cell death protein 1

PERIOPERATIVE IMMUNOTHERAPY FOR RESECTABLE HCC: DESIGN

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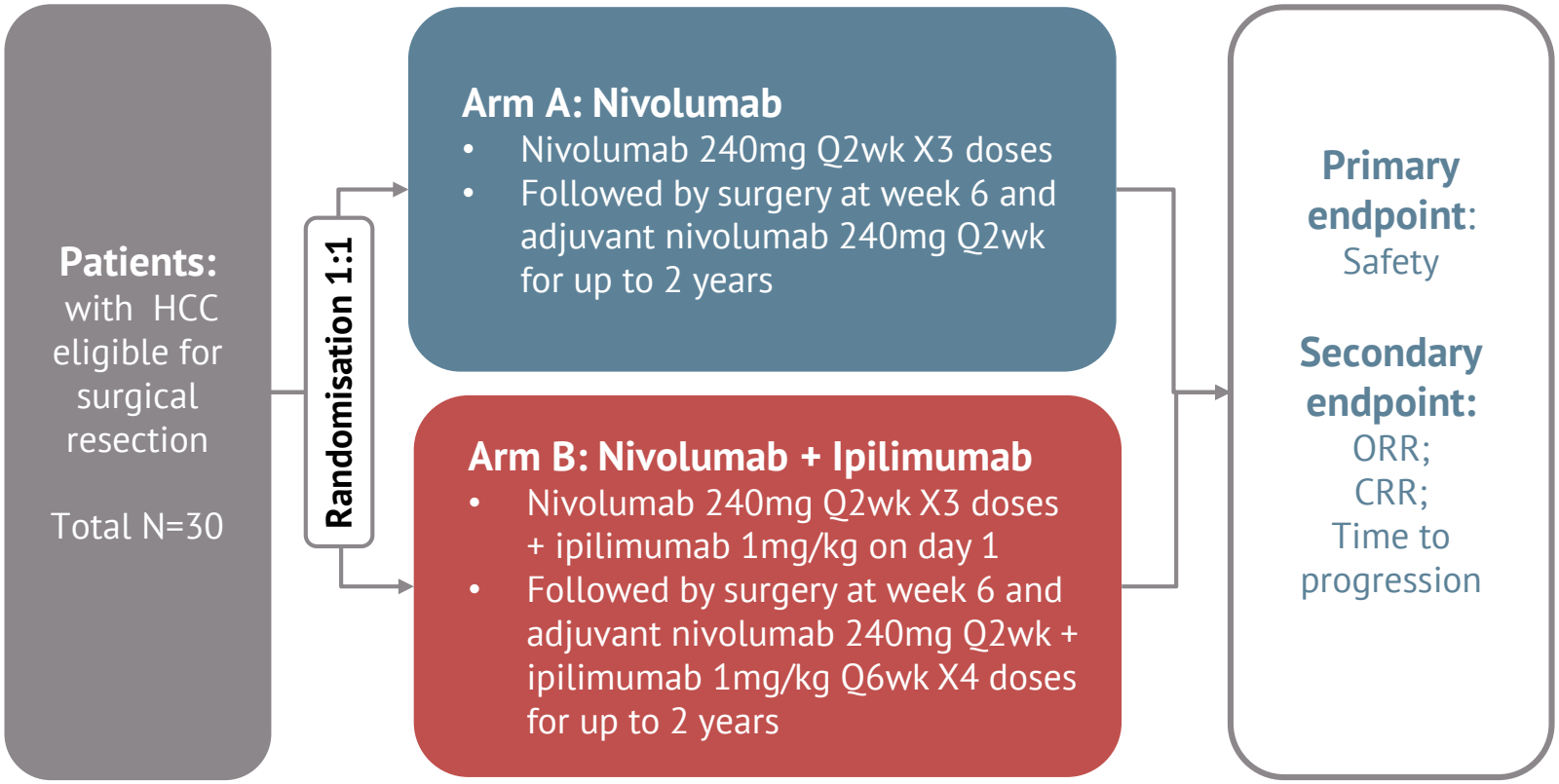
Phase II, randomised study

Neoadjuvant immunotherapy, surgical resection, followed by adjuvant immunotherapy



Kaseb AO, et al. ASCO GI 2019, Abst #185
CRR, complete response rate; HCC, hepatocellular carcinoma; ORR, overall response rate; Q, every; wk, week

PERIOPERATIVE IMMUNOTHERAPY FOR RESECTABLE HCC: RESULTS (1)

- Report of the first interim analysis of 8 evaluable patients
- **3/8 patients showed pathologic CR following surgery**

Results	Arm A: Nivolumab (N=5)	Arm B: Nivolumab + Ipilimumab (N=3)	Arms: A and B (N=8, %)
Safety: Grade 3 Adverse event	1*	2*	3 (37.5%)
Efficacy: pCR	2	1	3 (37.5%)

* Did not affect resectability of tumour

- Results show overall good tolerance to the regimen without any affect on the surgical complications
- Further evaluation of their tissue showed significant increase in lymphocyte infiltration and immune reaction

Kaseb AO, et al. ASCO GI 2019, Abst #185
CR, complete response; HCC, hepatocellular carcinoma; N, number of patients

PERIOPERATIVE IMMUNOTHERAPY FOR RESECTABLE HCC: CONCLUSIONS

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- This is the first study evaluating peri-operative approach in resectable HCC showing encouraging results with about a third of the patients with pathologic CR
- **The study is ongoing, and if this rate of response continues may result in a shift in the way we approach resectable HCC**

Kaseb AO, et al. ASCO GI 2019, Abst #185
CR, complete response; HCC, hepatocellular carcinoma; N, number of patients

RANDOMIZED PHASE II/III TRIAL OF NEOADJUVANT CHEMOTHERAPY WITH GEMCITABINE AND S1 VERSUS UPFRONT SURGERY FOR RESECTABLE PANCREATIC CANCER (PREP-02/JSAP05)

Unno M, et al. ASCO GI 2019, Abst #189

NEOADJ CHEMOTHERAPY IN PANCREATIC CANCER: INTRODUCTION

- This trial was based on a phase II single arm study completed in Japan using neoadjuvant gemcitabine and S1 which showed a 2 year overall survival of 55.9%[1]
- This data led to the current study[2]

1. Motoi, et al. J Gastroenterol (2018). https://doi.org/10.1007/s00535-018-1506-7 ; 2. Unno M, et al. ASCO GI 2019, Abst #189
Neoadj, neoadjuvant; S1, Tegafur/gimeracil/oteracil

NEOADJ CHEMOTHERAPY IN PANCREATIC CANCER: DESIGN

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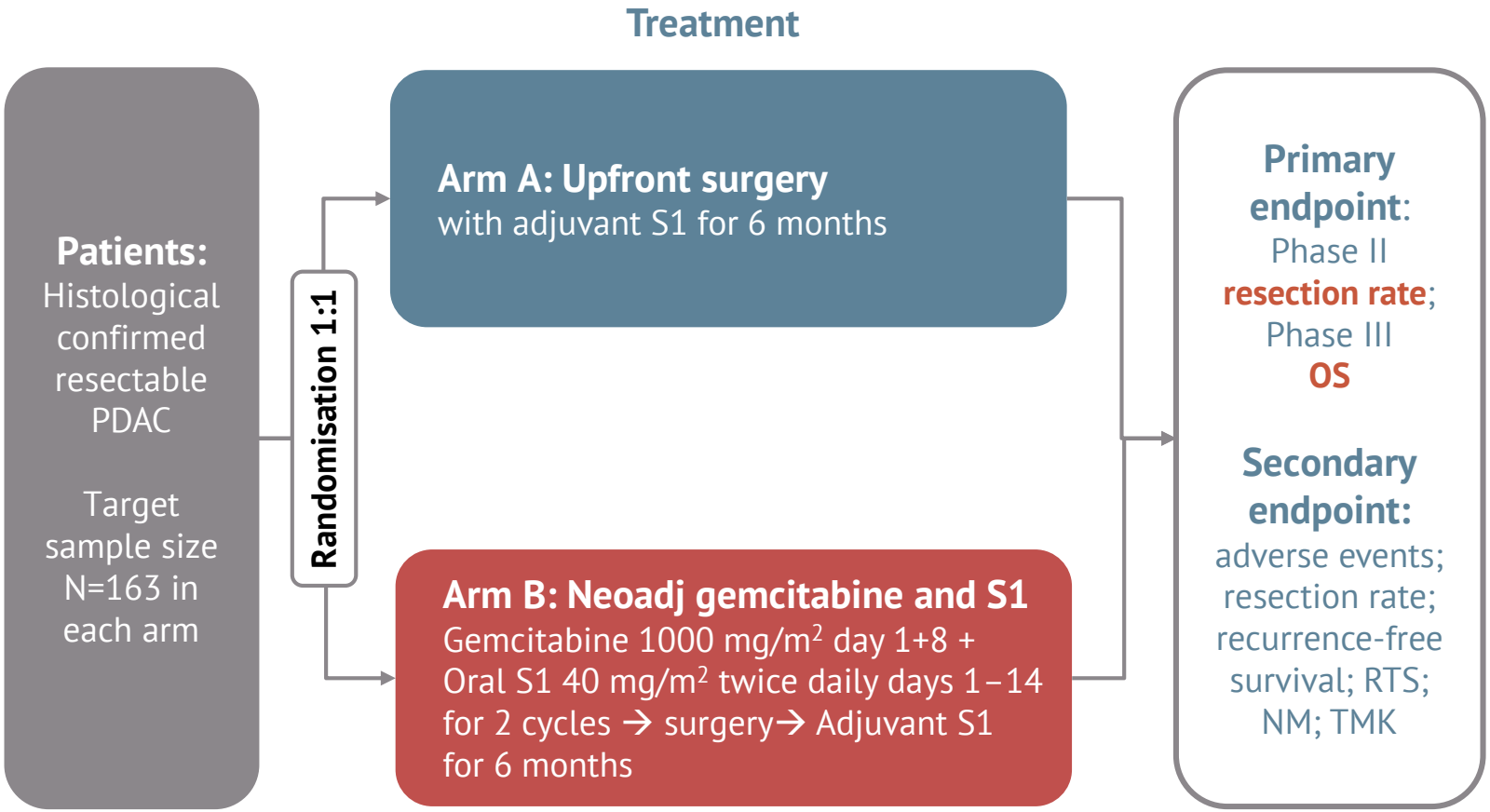
Phase II/III, multicentre, randomised study



Unno M, et al. ASCO GI 2019, Abst #189

N, number of patients; NM, nodal metastases; Neoadj, neoadjuvant; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; RTS, residual tumor status; S1, Tegafur/gimeracil/oteracil; TMK, tumor marker kinetics

NEOADJ CHEMOTHERAPY IN PANCREATIC CANCER: PATIENT ENROLMENT

- 182 patients were enrolled on the neoadjuvant therapy arm of which 140 underwent resection
- 180 patients were enrolled on the upfront surgery arm of which 129 underwent resection
- Patient's characteristics were well-balanced between the two arms

Unno M, et al. ASCO GI 2019, Abst #189
Neoadj, neoadjuvant

NEOADJ CHEMOTHERAPY IN PANCREATIC CANCER: RESULTS – EFFICACY (1)

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Results	Arm A: Upfront surgery	Arm B: Neoadj gemcitabine + S1	Statistical analysis
Phase II:			
Resection rate	82%	93%	
Phase III:			
Median OS	26.6 months	36.7 months	HR, 95% CI; 0.72 (0.55-0.94, P=0.015)
2-year OS rate	52.5%	63.7%	

Unno M, et al. ASCO GI 2019, Abst #189

CI, confidence interval; HR, hazard ratio; Neoadj, neoadjuvant; OS, overall survival; P, probability; S1, Tegafur/gimeracil/oteracil

NEOADJ CHEMOTHERAPY IN PANCREATIC CANCER: RESULTS – EFFICACY (2)

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The phase III study portion:

- Subgroup analysis showed improved survival in most subgroups
- Pathologic evaluation showed higher lymph node positivity in the upfront surgery arm versus the neoadjuvant arm
- Recurrence patterns showed higher liver recurrence in the upfront surgery arm versus the neoadjuvant arm

Unno M, et al. ASCO GI 2019, Abst #189
Neoadj, neoadjuvant

NEOADJ CHEMOTHERAPY IN PANCREATIC CANCER: RESULTS, ADVERSE EVENTS

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- Adverse events of neoadjuvant therapy showed expected rate of haematological toxicities
- There was **no** effect on ability to perform surgery or surgical complications

Unno M, et al. ASCO GI 2019, Abst #189
Neoadj, neoadjuvant

NEOADJ CHEMOTHERAPY IN PANCREATIC CANCER: CONCLUSIONS

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- This is the first prospective study to prove the feasibility and benefit of **neoadjuvant therapy in resectable PDAC tumors**
- Results of multiple ongoing studies in this area, using agents that are available in US and Europe, are eagerly awaited
- **This is likely to become the recommended approach for the management of resectable PDAC tumors**

Unno M, et al. ASCO GI 2019, Abst #189
Neoadj, neoadjuvant; PDAC, pancreatic ductal adenocarcinoma

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