AIO-STO-0417: Modified FOLFOX plus/minus Nivolumab and Ipilimumab vs. FLOT plus Nivolumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction – A randomized phase 2 trial. [MOONLIGHT]

<table>
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<tr>
<th>Study type</th>
<th>Randomized, open labelled, multicenter phase II trial followed by a non-randomized arm</th>
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| Objectives / Endpoints (efficacy, safety) | Primary endpoint:  
PFS based on the ITT population for patients treated with mFOLFOX plus Nivolumab plus Ipilimumab (Arm A) vs. patients treated with mFOLFOX alone (Arm B) and progression-free survival rate (PFS@6) for Arms A2 and C.  

Secondary endpoints:  
- Progression Free Survival acc. to RECIST v1.1 for Arms A1, A2 and C  
- Progression Free Survival rate at 6 months (PFS@6) for Arms A and B  
- Overall Response Rate (ORR) according to RECIST v1.1  
- Duration of response and disease stabilization  
- Overall survival (OS)  
- Subgroup analysis including PFS and OS by PD-L1 expression status |
- Safety (according to NCI-CTCAE V 4.03) and tolerability
- Quality of life (EORTC QLQ-C30). The QoL analyses will include QoL mean values, QoL response and time to symptom deterioration (TTSD)
- Translational research: correlation of biomarkers potentially associated with clinical efficacy (OS, PFS and ORR) from nivolumab plus ipilimumab by molecular quantitation of target gene expression and immune cell composition

**Background / Rationale**

Rationale for the currently recruiting FLOT arm: Emerging data from recent phase III trials indicate that immune checkpoint inhibitors such as Nivolumab and Pembrolizumab prolong OS and PFS when added to the doublet chemotherapy. However, the extent of improvement regarding PFS is smaller than expected and if administered as monotherapy, there is an increased early mortality with the checkpoint inhibitors as compared with chemotherapy (crossing survival curves) (Tabernero et al. 2019; Janjigian et al. 2021, Kato et al. 2020). This is most likely explained by the fact that patients need time to establish antitumoral immunity, while some patients with aggressive disease experience early disease progression and death. This provides a rationale to test whether the intensification of chemotherapy using a triplet (mFOLFOX plus Docetaxel = FLOT) instead of the doublet, while reducing immunotherapy to Nivolumab instead of Nivolumab and Ipilimumab would be more beneficial and safer. Therefore, Arm C is designed to evaluate the efficacy of the combination of FLOT plus Nivolumab in the same patient group of the other study arms and descriptively compare this treatment with mFOLFOX plus Nivolumab plus Ipilimumab (Arm A) and with mFOLFOX alone (Arm B).

As our study generally aims at gaining insights into the potentially most optimal chemo-immunotherapy regimen (therapy optimization) for a future trial, the implementation of Arm C fits well into the concept of the trial. With Arm C our trial evaluates three variations for the concept of immunochemotherapy: chemotherapy doublet plus immunotherapy doublet administered in parallel, chemotherapy doublet plus immunotherapy doublet administered sequentially, and chemotherapy triplet plus immune monotherapy administered in parallel. Because Arms A and B are fully recruited, it is not possible to perform a randomized comparison for Arm C. However, using the patients from Arms A and B as a comparator is still better than historical controls as these patients are treated by the same centres, under the same therapeutic and diagnostic guidelines, and in a close time period.

It is important to note that FLOT is a well-established standard of care triplet regime in both, the neoadjuvant and metastatic settings. Accordingly, according to current S3 guidelines, docetaxel-containing triplet therapy such as FLOT can be considered for patient treatment, based on numerous studies on this field (e.g. van Cutsem et al., 2006 and Wagner et al., 2017).

Approximately 20-30% of patients with mGC in the US (Davis et al NCCN Network Annual Conference and Abrams, ESMO GI 2016# PD-034) and a comparable proportion of patients in Germany receive a taxane-containing triplet as first-line therapy. Rationale for this in most cases is an expected faster and more frequent treatment response, which is crucial for the therapy choice especially for patients with a high remission pressure.

**Population**

Patients with advanced or metastatic adenocarcinoma of stomach or gastroesophageal junction are eligible for this study.

**Inclusion/exclusion criteria**

**Inclusion Criteria:**

1. All subjects must have inoperable, advanced or metastatic GC or GEJ adenocarcinoma.
2. Subjects must have HER2-negative disease defined as either IHC 0 or I+ or IHC 2+, the latter in combination with ISH-, as assessed locally on a primary or metastatic tumour.
3. Subject must be previously untreated with systemic treatment given as primary therapy for advanced or metastatic disease.
4. Prior adjuvant or neoadjuvant chemotherapy, radiotherapy and/or chemoradiotherapy are permitted as long as the last administration of the last regimen (whichever was given last) occurred at least 6 months prior to randomization.
5. Palliative radiotherapy is allowed and must be completed 2 weeks prior to randomization.
6. Subjects must have measurable or evaluable non-measurable disease as assessed by the investigator, according to RECIST v1.1 (Appendix D).
7. ECOG performance status score of 0 or 1 (Appendix B).
8. Life expectancy > 12 weeks
9. Screening laboratory values must meet the following criteria (using NCI CTCAE v.4.03):
   a. WBC ≥ 2000/uL
   b. Neutrophils ≥ 1500/µL
   c. Platelets ≥ 100x10^3/µL
   d. Hemoglobin ≥ 9.0 g/dL
   e. Serum creatinine ≤ 1.5 x ULN
   f. AST ≤ 3.0 x ULN (or ≤ 5.0X ULN if liver metastases are present)
   g. ALT ≤ 3.0 x ULN (or ≤ 5.0X ULN if liver metastases are present)
   h. Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN)
10. Males and Females* ≥ 18 years of age
    *There are no data that indicate special gender distribution. Therefore patients will be enrolled in the study gender-independently.
11. Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.
12. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.
13. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug. Women must not be breastfeeding.
14. WOCBP must agree to follow instructions for method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo 5 half-lives. The terminal half-lives of nivolumab and ipilimumab are approximately 25 days and 15 days, respectively. WOCBP should use an adequate method to avoid pregnancy for approximately 5 months (30 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of investigational drug.
15. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo 5 half-lives. The terminal half-lives of nivolumab and ipilimumab are approximately 25 days and 15 days, respectively. Males who are sexually active with WOCBP must continue contraception for approximately 7 months (90 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of investigational drug. In addition, male subjects must be willing to refrain from sperm donation during this time.

Exclusion Criteria:
1. Malignancies other than disease under study within 5 years prior to inclusion, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
2. Subjects with untreated symptomatic CNS metastases. Subjects are eligible if CNS metastases are asymptomatic (this includes patients with unknown CNS metastatic status who have no clinical signs of CNS metastases) or those with asymptomatic or symptomatic CNS who are adequately treated and are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization. Patients with unknown CNS metastatic status and any clinical signs indicative of CNS metastases are eligible if CNS metastases are excluded using CT and/or MRI scans, or CNS metastases are confirmed but adequately treated as described above.

3. Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll. For any cases of uncertainty, it is recommended that the medical monitor be consulted prior to signing informed consent.

4. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

5. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

6. All toxicities attributed to prior anti-cancer therapy other than hearing loss, alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4.03) or baseline before administration of study drug.

7. > Grade 1 peripheral neuropathy according to CTCAE version 4.03

8. Known Dihydropyrimidine dehydrogenase (DPD) deficiency

9. Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive study drug.

10. Ascites which cannot be controlled with appropriate interventions.

11. Unstable cardiac disease despite treatment, myocardial infarction within 6 months prior to study entry; congestive heart failure NYHA grade 3 and 4

12. Significant acute or chronic infections including, among others:
   a. Positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
   b. Any positive test result for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.

13. History of allergy or hypersensitivity to study drugs or any constituent of the products

14. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.

15. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].

<table>
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<tr>
<th>Investigational and control drugs</th>
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<tr>
<td>Study drugs: Nivolumab and Ipilimumab</td>
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<tr>
<td>Study treatment: FOLFOX + Nivolumab and Ipilimumab; sequential therapy with FOLFOX + Nivolumab and Ipilimumab; FLOT + Nivolumab</td>
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<th>Investigational and Control Arm, Dose, regimen, treatment cycle</th>
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<tr>
<td><strong>Treatment:</strong> Arm A/A1* (this therapy arm is already closed)</td>
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<tr>
<td>FOLFOX: Oxaliplatin 85 mg/m², leucovorin 400 mg/m² and fluorouracil 400 mg/m² administered IV on Day 1 of each treatment cycle, and fluorouracil</td>
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</table>
2400 mg/m² IV continuous infusion over 44 hours (day1+2) every 2 weeks until disease progression or unacceptable toxicity or end of study treatment. Chemotherapy can also be administered per local standard.

+ Nivolumab 240mg “Flatdose” i.v. d1 every 2 weeks
+ Ipilimumab 1mg/kg i.v. d1 every 6 weeks

**Treatment: Arm A2 (“sequential”)** (this therapy arm is already closed)
Three cycles of induction chemotherapy with FOLFOX:
Oxaliplatin 85 mg/m², leucovorin 400 mg/m2 and fluorouracil 400 mg/m² administered IV on Day 1 followed by fluorouracil 2400 mg/m² IV continuous infusion over 44 hours of each treatment cycle. Cycles are repeated every 2 weeks. Chemotherapy can also be administered per local standard.

Followed by immunotherapy consisting of 4 administrations of Nivolumab at 240mg “Flatdose” i.v. d1 every 2 weeks
and 2 administrations of Ipilimumab at 1mg/kg i.v. d1 every 6 weeks

Repetition of chemotherapy and immunotherapy:
The above described therapy sequence consisting of 3 cycles of FOLFOX followed by immunotherapy may be repeated starting two weeks after last administration of immunotherapy once, or, if medically reasonable, for an unlimited number of repetitions upon investigator decision. However, repetition of chemotherapy after the first 3 cycles is optional and may be skipped.

After completion or discontinuation of chemotherapy, immunotherapy will be continued consisting of:
Nivolumab at 240mg “Flatdose” i.v. d1 every 2 weeks
and Ipilimumab at 1mg/kg i.v. d1 every 6 weeks

**Standard Treatment Arm B** (this therapy arm is already closed)
FOLFOX (Oxaliplatin 85 mg/m², leucovorin 400 mg/m2 and fluorouracil 400 mg/m² administered IV on Day 1 of each treatment cycle, and fluorouracil 2400 mg/m² IV continuous infusion over 44 hours (day1+2) every 2 weeks until disease progression or unacceptable toxicity or end of study treatment. Chemotherapy can also be administered per local standard.

**Treatment Arm C** (currently recruiting)
Nivolumab 240mg “Flatdose” i.v. d1 every 2 weeks
+ FLOT: Docetaxel 50mg/2, Oxaliplatin 85 mg/m², leucovorin 200 mg/m² on day 1 and fluorouracil 2600 mg/m² IV continuous infusion over 24 hours of each treatment cycle.
Cycles are repeated every 2 weeks until disease progression or unacceptable toxicity or end of study treatment. After completion or discontinuation of chemotherapy, immunotherapy may be continued consisting of:
Nivolumab at 240mg “Flatdose” i.v. d1 every 2 weeks
Chemotherapy can also be administered per local standard.
Therapy can also be splitted, administering nivolumab on day one and FLOT starting at day two of the cycle.

**Duration of treatment**
Treatment with each of the components FOLFOX, FLOT, nivolumab and/or ipilimumab will be administered until progression (according to RECIST v1.1), intolerable toxicity, patient’s request, or end of study treatment phase (24 months). The study treatment will be limited to a maximum of 24 months. If one component of the treatment is stopped for any cause, the other components can be continued.
**Arm A1** is identical to Arm A. Patients are randomized concurrently with Arm A2 after recruitment of the first 118 patients into Arm A and B is completed. A1 will comprise 30 patients. **Arm C** will recruit 50 patients.

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<th>Statistical considerations</th>
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| Arm A vs. B: PFS analysed according to the ITT principle is the primary efficacy endpoint. The expected median PFS in the standard arm is 5.5 months; the expected median PFS in the experimental arm is 8.5 months. We hypothesize that the experimental therapy is associated with clinically relevant improvement according to a HR of 0.68. In the frame of a phase II testing, the use of a one-sided significance level of 10% is justified. Based on this, 118 randomized subjects (59 in the control and 59 in the experimental treatment group) will be enrolled to provide 80% power for detecting an average HR of 0.68 using the log rank test at a one-sided type I error of 10% and assuming a 5% drop out rate. The sample size calculation is based on 2 years recruitment time and 1 year follow up time after last patient-in. So the minimum follow-up time is 3 years.

1:1 Randomization will be performed according to the following stratification criteria:
- ECOG PS (0 vs 1)
- Tumor status (prior resection vs. no prior resection)

Arm A1 vs. A2
To evaluate if a sequential treatment of mFOLFOX plus Nivolumab plus Ipilimumab (Arm A2) is less toxic but equally effective as parallel treatment of mFOLFOX plus Nivolumab plus Ipilimumab (Arm A and A1) 57 patients are needed using a one-stage Fleming design (Fleming 1982) with following assumptions:
- The sequential therapy would be rated as unacceptable, if the actual PFS rate at 6 months (PFS@6) was only 47% or lower (corresponding to the median PFS of Arm B of 5.5 months)
- The sequential therapy would be considered to be a promising candidate for further development, if the true PFS@6 amounted to 61% or higher (corresponding to the expected median PFS of Arm A of 8.5 months)
- Probability to accept the sequential therapy as effective, in spite of a true PFS@6 of <47%: 10% (type I error)
- Probability to reject the sequential therapy as ineffective (<47%), although the true PFS@6 is promising (>61%): 20% (type II error, corresponding to a power of 80%)

Allowing for two non-informative drop-outs, 59 patients have to be recruited into Arm A2. 30 patients are to be allocated to the reference arm A1, according to the 1:2 randomization. The same stratification factors (ECOG PS and tumor status) as in the randomization of arms A and B are applied.

The final conclusion for the sequential treatment will depend on the definite PFS rate and its confidence interval, the respective findings in the reference arm, as well as the information on type, frequency and severity of toxicities.

Arm C:
Based on emerging data from recent phase III trials, immune checkpoint inhibitors such as Nivolumab and Pembrolizumab added to the doublet chemotherapy prolong OS and PFS, but the extent of improvement regarding PFS is smaller than expected and if administered as monotherapy, there is an increased early mortality (crossing survival curves) with the checkpoint inhibitors as compared with chemotherapy (Tabernero et al. 2019; Janjigian et al. 2021; Kato et al. 2020). This is most likely explained by the fact that patients need time to establish antitumoral immunity, while some patients with aggressive disease experience early disease progression and death. This provides a rationale to test whether the intensification of chemotherapy using a
triplet (mFOLFOX plus Docetaxel = FLOT) instead of the doublet, reducing immunotherapy to Nivolumab instead of Nivolumab and Ipilimumab would be more beneficial and safer. Therefore, Arm C is designed to evaluate the efficacy of the combination of FLOT plus Nivolumab in the same patient group and descriptively compare this treatment with mFOLFOX plus Nivolumab plus Ipilimumab (Arm A) and with mFOLFOX alone (Arm B). The sample size is chosen according to clinical reasoning. No statistical hypothesis testing is planned. A sample size of 50 patients to be treated with FLOT plus Nivolumab is regarded sufficient to get a first sight into the efficacy and to obtain data on the feasibility, safety and toxicity of the study treatment. As our study generally aims at gaining insights into the potentially most optimal chemo-immunotherapy regimen (therapy optimization) for a future trial, the implementation of Arm C fits well into the concept of the trial. With Arm C our trial evaluates three variations for the concept of immunochemotherapy: chemotherapy doublet plus immunotherapy doublet administered in parallel, chemotherapy doublet plus immunotherapy doublet administered sequentially, and chemotherapy triplet plus immune monotherapy administered in parallel. Because Arms A and B are fully recruited, it is not possible to perform a randomized comparison for Arm C. However, using the patients from Arms A and B as a comparator is still better than historical controls as these patients are treated by the same centres, under the same therapeutic and diagnostic guidelines in a close time period. The KEYNOTE-062 study (Tabernero et al. 2019) reported a median PFS of 6.9 months for the combination of Pembrolizumab plus chemotherapy while the Checkmate 649 (Janjigian et al. 2021) reported a median PFS of 7.7 months for the combination of Nivolumab plus mFOLFOX. Therefore, we expect the true median PFS of FLOT plus Nivolumab to be between 8 and 9 months corresponding to PFS rates at 6 months of about 59% and 63%. The final conclusion for the combination of FLOT plus Nivolumab will depend on the definite PFS rate at 6 months (and its confidence interval), the respective findings in the arms A and B, as well as the information on type, frequency and severity of toxicities. The precision of the estimation of the PFS@6 is provided by confidence intervals (CIs) in the following table, for different actual PFS@6 findings:

<table>
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<th>PFS@6</th>
<th>Exact 95% CI</th>
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<tr>
<td>29/50 (58%)</td>
<td>43.2% ... 71.8%</td>
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<tr>
<td>30/50 (60%)</td>
<td>45.2% ... 73.6%</td>
</tr>
<tr>
<td>31/50 (62%)</td>
<td>47.2% ... 75.4%</td>
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<tr>
<td>32/50 (64%)</td>
<td>49.2% ... 77.1%</td>
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Key dates

FFPV: Q2 2018
Planned time for recruitment: 45 months
Follow-up: every 2 months for up to 1 year after last patient-in.