MOUNTAINEER-02: PHASE 2/3 STUDY OF TUCATINIB, TRASTUZUMAB, RAMUCIRUMAB, AND PACLITAXEL IN PREVIOUSLY TREATED HER2+ GASTRIC OR GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA (TRIAL IN PROGRESS)

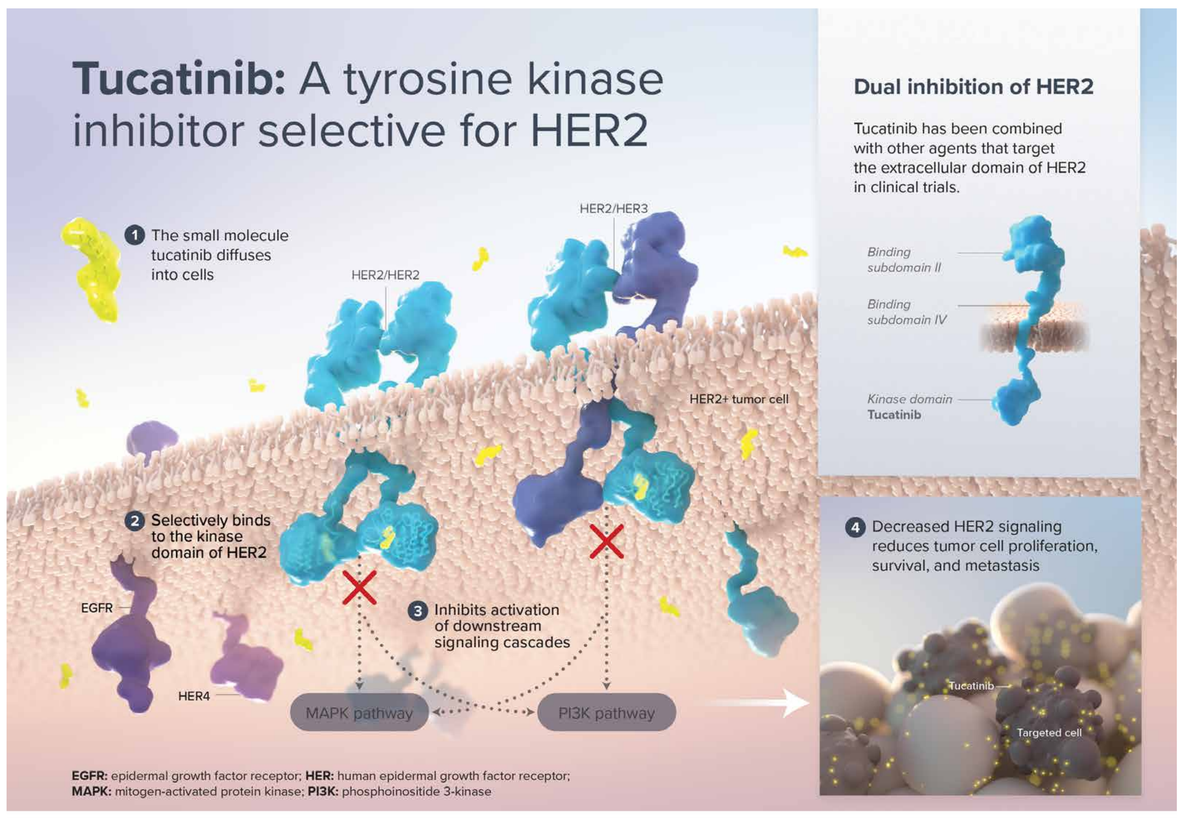
Josep Tabernero[1], John H. Strickler[2], Yoshiaki Nakamura[3], Kohei Shitara[3], Yelena Y. Janjigian[4], Afsaneh Barzi[5], Tanios S. Bekaii-Saab[6], Heinz-Josef Lenz[7], Takayuki Yoshino[3], Salvatore Siena[8], JoAl Garrido Mayor[9], Michelle Ubowski[9], Diqiong Xie[9], John Marshall[10]

[1]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [2]Duke University Medical Center, Durham, NC, USA; [3]National Cancer Center Hospital East, Kashiwa, Japan; [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [6]Mayo Clinic, Scottsdale, AZ, USA; [7]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [8]Grande Ospedale Metropolitano Niguarda, and Università degli Studi di Milano, Milan, Italy; [9]Seagen Inc., Bothell, WA, USA; [10]Georgetown University, Washington, DC, USA

Background

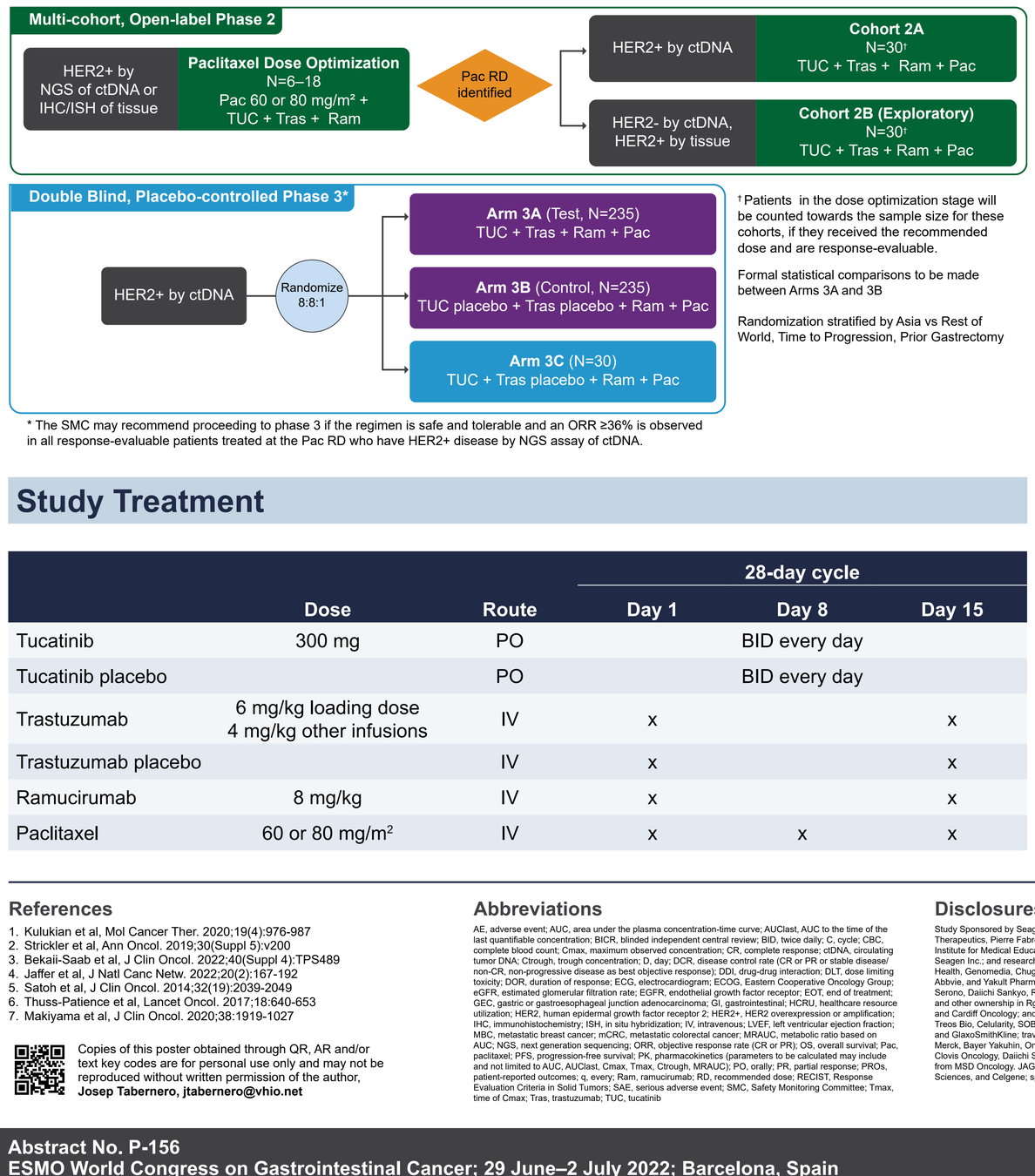
- Tucatinib (TUC) is a highly selective HER2-directed tyrosine kinase inhibitor with minimal EGFR inhibition[1], approved in multiple regions in combination with trastuzumab and capecitabine for HER2+ metastatic breast cancer (MBC)
- TUC is being investigated as a novel therapy for patients with HER2+ mCRC and other HER2+ GI tumors[2,3]
- Trastuzumab (Tras) with chemotherapy is standard in the 1st-line setting for metastatic HER2+ gastric or gastroesophageal junction adenocarcinoma (GEC)[4]
- However, no anti-HER2 therapy has demonstrated an OS benefit over chemotherapy in 2nd-line treatment[5,6,7], possibly due to loss of HER2 expression following Tras-based therapy
- In gastric and esophageal patient-derived and cell line-derived xenograft models, dual targeting of HER2 with TUC and Tras showed superior activity to either agent alone[1]
- Interim results from the MOUNTAINEER study have shown promising activity for TUC in combination with Tras in HER2+ mCRC[2]
- The MOUNTAINEER-02 study (NCT04499924) will combine the dual HER2-inhibition of TUC and Tras with standard of care therapy (ramucirumab + paclitaxel) in the 2nd-line setting for patients with HER2+ GEC

Tucatinib Proposed Mechanism of Action



Tucatinib is an investigational agent, and its safety and efficacy have not been established. There is no guarantee that tucatinib will receive regulatory approval and become commercially available for uses being investigated.

Study Design



† Patients in the dose optimization stage will be counted towards the sample size for these cohorts, if they received the recommended dose and are response-evaluable.

Formal statistical comparisons to be made between Arms 3A and 3B

Randomization stratified by Asia vs Rest of World, Time to Progression, Prior Gastrectomy

* The SMC may recommend proceeding to phase 3 if the regimen is safe and tolerable and an ORR ≥36% is observed in all response-evaluable patients treated at the Pac RD who have HER2+ disease by NGS assay of ctDNA.

Study Treatment

	Dose	Route	28-day cycle Day 1	Day 8	Day 15
Tucatinib	300 mg	PO		BID every day	
Tucatinib placebo		PO		BID every day	
Trastuzumab	6 mg/kg loading dose 4 mg/kg other infusions	IV	x		x
Trastuzumab placebo		IV	x		x
Ramucirumab	8 mg/kg	IV	x		x
Paclitaxel	60 or 80 mg/m^2	IV	x	x	x

Key Eligibility Criteria

- Histologically or cytologically confirmed, locally-advanced, unresectable or metastatic GEC, excluding squamous cell or undifferentiated GEC
- HER2+ disease (performed or confirmed by central assessment):

Phase 2 Dose Optimization	HER2+ in NGS assay of ctDNA or IHC/ISH assay of tissue
Phase 2 Cohort 2A	HER2+ in NGS assay of ctDNA
Phase 2 Cohort 2B	HER2- in NGS assay of ctDNA, HER2+ in IHC/ISH assay of tissue
Phase 3	HER2+ in NGS assay of ctDNA

- Progression during or after 1st-line therapy and have received a HER2-directed antibody
- ≥18 years of age
- Measurable disease per RECIST v1.1 (phase 2 only)
- ECOG performance status ≤1
- Adequate hepatic, hematological, renal, and cardiac function

Phase 3 Sample Size

- The dual primary endpoints of PFS and OS will be evaluated using parallel testing, with α recycling if only one meets statistical significance
- Arm 3A and Arm 3B sample size of 470 patients maintains 90% power for PFS with an α of 0.02, and 88% power for OS with an α of 0.03
- An interim OS analysis is planned at the time of the final PFS analysis

Objectives and Endpoints – Phase 2

Phase 2 Primary Objectives	Endpoints
Determine the recommended dose of Pac	Frequency of DLTs during the first cycle of treatment
Safety and tolerability of phase 2 regimen	Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities; vital signs and other relevant safety variables; frequency of dose modifications
Secondary Objectives	**Endpoints**
Evaluate preliminary activity in Cohort 2A	ORR, confirmed ORR, PFS, DOR, and DCR per investigator
Evaluate PK of TUC, Pac, and their metabolites	PK parameters

- Exploratory objectives are preliminary activity in Cohort 2B, correlations between HER2 alterations detected by different assays, correlation between blood-based biomarkers and clinical outcomes, and PK in patients with gastrectomies.

Objectives and Endpoints – Phase 3

Phase 3 Primary Objectives	Endpoints
Compare efficacy of TUC and Tras (Arm 3A) vs placebo (Arm 3B), both with Ram + Pac	**Dual primary:** OS and PFS per RECIST v1.1 per investigator **Key secondary:** Confirmed ORR per investigator **Other secondary:** PFS, confirmed ORR, ORR, DOR, DCR per BICR; ORR, DOR, DCR per investigator
Secondary Objectives	**Endpoints**
Evaluate safety and tolerability of TUC + Tras + Ram + Pac	Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities; vital signs and other relevant safety variables; frequency of dose modifications
Evaluate anti-tumor activity of TUC + Ram + Pac (Arm 3C)	Confirmed ORR, DOR per investigator

- Other secondary and exploratory objectives are to evaluate PROs by arm, evaluate safety and tolerability of TUC + Ram + Pac, evaluate the PK of TUC, evaluate correlations between biomarkers and outcomes, and assess HCRU by arm.

Study Assessments

- Response per RECIST v1.1: q6 weeks for 36 weeks, then q9 weeks. After discontinuation, assessments are q9 weeks until disease progression, withdrawal of consent, death, or study closure
- Safety: AEs, SAEs, events of interest, treatment modifications, laboratory assessments (metabolic panel, CBC with differential, eGFR, and coagulation panel), vital signs, LVEF every 12 weeks, and ECG at baseline and EOT
- Phase 2 PK (blood draws on C1D1, C1D8, and C2D1):
  - Dose optimization stage: serial PK to assess TUC-Pac DDI
  - Dose expansion stage: serial PK in first 6 patients with gastrectomy to assess impact on TUC PK
- Biomarker: screening HER2 status by NGS of ctDNA and tissue and IHC/ISH of tissue; blood sample for other biomarkers at screening and EOT

Summary

- MOUNTAINEER-02 is a randomized, double-blind, placebo-controlled, active comparator phase 2/3 study investigating dual HER2-inhibition of TUC and Tras with standard of care therapy in the 2nd-line treatment of patients with HER2+ GEC
- Approximately 180 sites are planned in Europe, North America, and Asia-Pacific
- Enrollment to the phase 2 part of the study is ongoing

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Abbreviations

AE, adverse event; AUC, area under the plasma concentration-time curve; AUClast, AUC to the time of the last quantifiable concentration; BICR, blinded independent central review; BID, twice daily; C, cycle; CBC, complete blood count; Cmax, maximum observed concentration; CR, complete response; ctDNA, circulating tumor DNA; Ctrough, trough concentration; D, day; DCR, disease control rate (CR or PR or stable disease/non-CR, non-progressive disease as best objective response); DDI, drug-drug interaction; DLT, dose limiting toxicity; DOR, duration of response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; EGFR, endothelial growth factor receptor 2; HER2+, HER2 overexpression or amplification; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer; mCRC, metastatic colorectal cancer; MRAUC, metabolic ratio based on AUC; NGS, next generation sequencing; ORR, objective response rate (CR or PR); OS, overall survival; Pac, paclitaxel; PFS, progression-free survival; PK, pharmacokinetics (parameters to be calculated may include and not limited to AUC, AUClast, Cmax, Tmax, Ctrough, MRAUC); PO, orally; PR, partial response; PROs, patient-reported outcomes; q, every; Ram, ramucirumab; RD, recommended dose; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; SMC, Safety Monitoring Committee; Tmax, time of Cmax; Tras, trastuzumab; TUC, tucatinib

Disclosures

Study Sponsored by Seagen Inc.; JT consultancy for Bayer, Boehringer Ingelheim, Lilly, MSD, Merck Serono, Novartis, Sanofi, Taiho Pharmaceutical, Peptomyc, Chugai Pharma, Pfizer, Seagen Inc., Array BioPharma, AstraZeneca, Genentech, Menarini, Servier, HalioDx, F. Hoffmann LaRoche, Mirati Therapeutics, Pierre Fabre, Tessa Therapeutics, TheraMyc, Daiichi Sankyo, Samsung Bioepis, IQVIA, Ikena Oncology, Merus, Neophore, Orion Biotechnology, Hutchison MediPharma, Avvinity, and Scandion Oncology; and other relationships with Imedex, Medscape, MJH Life Sciences, PeerView Institute for Medical Education, and Physicians' Education Resource (PER). JHS consultancy for Amgen, Bayer, Natera, Abbvie, Pfizer, Mereo Biopharma, AstraZeneca, Viatris, Seagen Inc., Roche/Genentech, Inivata, Silverback Therapeutics, and GlaxoSmithKline; travel accommodations from Seagen Inc.; and research funding from Abbvie, Roche/Genentech, Exelixis, Seagen Inc., Leap Therapeutics, Nektar, Amgen, Curegenix, A*STAR, Bayer, AstraZeneca/MedImmune, Sanofi, Daiichi Sankyo/Lilly, and Silverback Therapeutics. YN research funding from Taiho Pharmaceutical, Guardant Health, Genomedia, Chugai Pharma, and Seagen Inc. KS consultancy for Astellas Pharma, Lilly, Bristol-Myers Squibb, Takeda, Pfizer, Ono Pharmaceutical, MSD, Taiho Pharmaceutical, Novartis, Abbvie, GlaxoSmithKline, Daiichi Sankyo, Amgen, and Boehringer Ingelheim; honoraria from Novartis, Abbvie, and Yakult Pharmaceutical; and research funding from Sumitomo Dainippon Pharma, Lilly, MSD, Daiichi Sankyo, Taiho Pharmaceutical, Chugai Pharma, Ono Pharmaceutical, Astellas Pharma, Mediscience Planning, and Eisai. YYJ consultancy for Pfizer, Merck, Bristol-Myers Squibb, Merck Serono, Daiichi Sankyo, Rgenix, Bayer, Imugene, AstraZeneca, Lilly, Zymeworks, Basilea Pharmaceutical, Michael J. Hennessy Associates, Paradigm Medical Communications, and Seagen Inc.; other relationships with Clinical Care Options, Axis Medical Education, Research to Practice; stock and other ownership in Rgenix; and research funding from Bayer, Rgenix, Bristol-Myers Squibb, Merck, Lilly, NCI, Department of Defense, Cycle for Survival, Fred's Team, and Genentech/Roche. AB consultancy for Merrion, bioTheranostics, Bayer Technology System, Daiichi Sankyo/AstraZeneca, and Cardiff Oncology; and research funding from Bayer, and Merck. TSBS consultancy for Amgen, Ipsen, Lilly, Bayer, Roche/Genentech, Abbvie, Incyte, Immuneering, Seagen Inc., Pfizer, Boehringer Ingelheim, Janssen, Eisai, Daiichi Sankyo/UCB Japan, AstraZeneca, Exact Sciences, Natera, Treos Bio, Celularity, SOBI, BeiGene, and Foundation Medicine; patents for WO/2018/183488, and WO/2019/055687; and other relationships with Exelixis, Merck, AstraZeneca, Lilly, and Pancreatic Cancer Action Network. HJL consultancy for Merck Serono, Roche, Bayer, Bristol-Myers Squibb, and GlaxoSmithKline; travel accommodations from Merck Serono, and Bayer; and honoraria from Merck Serono, Roche, Bayer, Boehringer Ingelheim, Isofol Medical, GlaxoSmithKline, G1 Therapeutics, Jazz Pharmaceuticals, Oncocyte, and Fulgent Genetics. TY honoraria from Chugai Pharma, Merck, Bayer Yakuhin, Ono Pharmaceutical, Lilly, and Taiho Pharmaceutical; and research funding from Chugai Pharma, MSD, Daiichi Sankyo, PAREXEL, Ono Pharmaceutical, Taiho Pharmaceutical, Amgen, and Sanofi. SS consultancy for Amgen, Roche/Genentech, Bayer, Bristol-Myers Squibb, Clovis Oncology, Daiichi Sankyo, Incyte, Merck, Novartis, Seagen Inc., and CheckmAb; travel accommodations from Amgen, Bayer, and Roche; patents, royalties and other intellectual property from Amgen; stock and other ownership in Guardant Health, and Myriad Genetics; and research funding from MSD Oncology. JAGM and MU employment from Seagen Inc. and stock and other ownership in Seagen Inc. DX employment from Seagen Inc. JM employment from Caris Life Sciences, and Indivumed; consultancy for Genentech/Roche, Amgen, Bayer/Onyx, Taiho Pharmaceutical, Caris Life Sciences, and Celgene; speaker's bureau for Amgen, Bayer/Onyx, Taiho Pharmaceutical, and Merck; and honoraria from Amgen, Bayer/Onyx, Taiho Pharmaceutical, Caris Life Sciences, and Merck.

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