

15130

Long-term follow-up GDFATHER-01 trial: GDF-15 neutralization combined with nivolumab can enable deep, long-term remission in heavily pretreated, anti-PD1/-L1 relapsed/refractory non-squamous non-small cell lung cancer (NSCLC), urothelial cancer (UC) and hepatocellular cancer (HCC)

L. Melero¹, M.J. De Miguel², E. Garraida³, G.A. De Velasco Oria⁴, M. Joerger⁵, J. Martin-Liberal⁶, M.E. Reig Monzon⁷, D. König⁸, J. Trojan⁹, M-E. Goebeler¹⁰, M.H.H. Schuler¹¹, G. Alonso Casal¹², M.E. Rodríguez-Ruiz¹³, E. Calvo², M. Liebig¹⁴, K. Klar¹⁵, P. Fettes¹⁴, F.S. Lichtenegger¹⁶, F. Hermann¹⁶, E. Leo¹⁶

¹ CIMA, IDISNA and CIBERONC, Clinica Universidad de Navarra, Pamplona, Spain, ² Centro Integral Oncologico Clara Campal, START Madrid-CIOCC, Madrid, Spain, ³ Hospital Universitari Vall d'Hebron, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, ⁴ Medical Oncology Department, Hospital 12 de Octubre, Madrid, Spain, ⁵ Department of Medical Oncology & Hematology, Cantonal Hospital, St. Gallen, Switzerland, ⁶ Medical Oncology Department, Catalan Institute of Oncology (ICO), L'Hospitalet de Llobregat, Barcelona, Spain, ⁷ BCLC-Liver Oncology Unit, Liver Unit, Hospital Clinic & Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, ⁸ Department of Medical Oncology, University Hospital Basel, Basel, Switzerland, ⁹ Department of Gastroenterology, Hepatology and Endocrinology, Goethe University Hospital, Frankfurt am Main, Germany, ¹⁰ Early Clinical Trial Unit, Medizinische Klinik 2 and Comprehensive Cancer Center Mainfranken, University Hospital Würzburg, Würzburg, Germany, ¹¹ Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Essen, Germany, ¹² NEXT Oncology Phase I Unit/IOB, Hospital Quironsalud Barcelona, Barcelona, Spain, ¹³ Department of Immunology and Oncology, Clinica Universidad de Navarra, Pamplona, Spain, ¹⁴ Clinical Operations, CatalYm GmbH, Planegg-Martinsried, Germany, ¹⁵ Translational Research, CatalYm GmbH, Planegg-Martinsried, Germany ¹⁶ Clinical Development, CatalYm GmbH, Planegg-Martinsried, Germany

Background

Growth and Differentiation Factor 15 (GDF-15) has emerged as resistance factor to immune checkpoint inhibition (ICI) [*Nat Commun* 2023;14,4253]. The GDFATHER-01 trial (NCT04725474) investigates visugromab (V; anti-GDF-15) in combination with nivolumab (N; anti-PD-1) in heavily pretreated, by strict criteria anti-PD1/PD-L1-relapsed/refractory (r/r) patients (pts) with locally advanced/metastatic non-squamous (nsq) NSCLC, UC and HCC, and reported notable response rates previously [*Nature Dec 11, 2024*]. This long-term follow-up analysis now reveals an unparalleled durability of response by V+N, including a substantially grown number of late-onset complete (CR) and complete metabolic responses (CMR).

Methods

V (10mg/kg) combined with N (240mg) was administered Q2W in ph1 and disease-specific ph2a expansion cohorts to a total of 77 pts with advanced/metastatic, by strict criteria anti-PD1/PD-L1 r/r nsq NSCLC (22), UC (27) and HCC (28).

Results

The Objective Response Rate (ORR) for V+N treatment was 18.2%, 18.5% and 14.3% in nsq-NSCLC, UC and HCC, respectively (data cut-off 30Apr2025). 61.5% (8/13) of responders achieved a confirmed CR (5/13) or CMR (3/13; as assessed by PET-CT). 8/13 (61.5%) experienced a deeper response level as compared with their initial, approved 1st or 2nd line ICI treatment regimen. The median duration of response (DoR) surpassed 28.4 and 26.3 mo. for nsq NSCLC and UC, and 15.6 mo. for HCC (protracted enrolment), respectively. 69.2% of responses (including all CR+CMR) are still ongoing and 46.2% continue with treatment. The safety profile of V+N was favorable, treatment-related adverse events > Grade 3 were reported in 10/77 (13.0%) pts, only.

Conclusions

In 77 heavily pre-treated, by strict criteria anti-PD-1/-L1 relapsed/refractory nsq NSCLC, UC and HCC pts, V+N treatment induced very durable and deep long-term response, with 61.5% (8/13) of responders achieving confirmed CR or CMR. GDF-15 neutralization by V may overcome ICI resistance and enable long-term immunologic tumor control in metastatic nsq NSCLC, UC and HCC.

Clinical trial identification

NCT04725474.

Legal entity responsible for the study

Catalym GmbH.

Funding

Catalym GmbH.

Disclosure

I. Melero: Financial Interests, Personal, Advisory Board: Agneus, Alligator Bioscience, AstraZeneca, BMS, BioLineRx, Boehringer Ingelheim, Boston Pharma, CRISPR Therapeutics, CatalYm GmbH, Crescendo Biologics, Curon Blopharmaceutical, EMD Serono, F-Star, Genentech, Genmab, Highlight Therapeutics, Hookipa Pharma, HotSpot Therapeutics, Inc., ImmuneSensor Therapeutics, Inc., Janssen, MSD, Merus N.V., Monopteros Therapeutics, NOXXON Pharma AG, Numab, Phenomic Bio, Pieris Pharmaceuticals GmbH, Pierre Fabre, Roche, Sanofi, Senti Biosciences, Servier, Shattuck Labs, Third Rock Ventures, ModeX, Mestag, Compugen, Asgard Therapeutics AB, QBiotics; Financial Interests, Personal, Other, Consultant: Pharma Mar, Pioneering Medicines; Financial Interests, Institutional, Coordinating PI: AstraZeneca, Roche, BMS, Genmab, Alligator. M.J. De Miguel: Financial Interests, Institutional, Invited Speaker: Janssen; Financial Interests, Institutional, Advisory Board: MSD; Financial Interests, Personal, Invited Speaker: HFiBio; Financial Interests, Personal, Other, award committe: Pharmamar; Non-Financial Interests, Principal Investigator: Janssen, MSD, Roche, Pharmamar, Replimune, Novartis, AbbVie, Achilles, Amunix, Arcus, Furmo, BioNTech, Catalym, Dizal, Genentech, Loxo, Numab, Seagen, HiFiBio, D3Bio, Bayer. E. Garralda: Financial Interests, Personal, Advisory Board: Roche, Ellipses Pharma, Boehringer Ingelheim, Janssen Global Services, Seattle Genetics, Anaveon, Hengrui, Sanofi, Incyte, Medscape, Skypta, Sotio, AbbVie, Astex Therapeutics, Alentis Therapeutics, Marengo Therapeutics, Medpace, Pfizer, Amgen, GenMab, GreyWolf, Gilead, Daiichi Sankyo; Financial Interests, Personal, Invited Speaker: MSD, Roche, Novartis, Seagen, PPD, Aran, The Ricky Rubio Foundation, ESMO, Fundación SEOM, CDDF, Springer Nature, Karger, Doctaforum, Tactics, AEFI, Fundación ECO, ESO (European School of Oncology), MeetingPharma, AstraZeneca, Alcura, Horizon CME; Financial Interests, Personal, Full or part-time Employment: NEXT Oncology; Financial Interests, Personal, Stocks/Shares: 1TRIALSP; Financial Interests, Institutional, Research Grant: Novartis, Roche, Thermo Fisher, AstraZeneca, Taiho, BeiGene, Janssen, Anaveon. G.A. De Velasco Oria: Financial Interests, Personal, Advisory Board: Pfizer, astellas, BMS, MSD, Ipsen, Bayer, AstraZeneca, EISAI, Arcus; Financial Interests, Personal, Invited Speaker: Pfizer, astellas, BMS, MSD, Roche, Ipsen, Merck, Novartis, Janssen, Bayer; Financial Interests, Institutional, Research Grant: Roche. M. Joerger: Financial Interests, Institutional, Coordinating PI, Clinical study activity: Basilea, Bayer, BMS, Immunophotonics, MSD, Novartis, Roche; Financial Interests, Institutional, Other, Clinical study activity: DaiichySankyo; Financial Interests, Institutional, Local PI, Clinical study activity: Innomedica; Financial Interests, Institutional, Coordinating PI: Anaveon; Non-Financial Interests, Advisory Role: Novartis, AstraZeneca, Basilea, Bayer, BMS, Debiopharm, MSD, Roche, Sanofi. J. Martin-Liberal: Financial Interests, Personal, Invited Speaker: Astellas, Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Sanofi; Financial Interests, Personal, Advisory Board: Bristol Myers Squibb, Novartis, Pierre Fabre, Roche, Sanofi, Highlight Therapeutics, Trialing Health, Ipsen; Financial Interests, Personal, Other, Travel grant: Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Ipsen, Merck. M.E. Reig Monzon: Financial Interests, Personal, Advisory Board: AstraZeneca, Bayer, BMS, Ipsen, Eli Lilly, Roche, Merck, Universal DX, Boston Scientific, Engitix Therapeutics, Parabilis Medicines Inc; Financial Interests, Personal, Invited Speaker: AstraZeneca, BMS, Eli Lilly, Bayer, Gilead, Roche, Biotoscana Farma; Financial Interests, Personal, Other, Consultancy: Geneos; Financial Interests, Institutional, Research Grant: Bayer, Ipsen. D. König: Financial Interests, Institutional, Advisory Board: AstraZeneca, MSD, Merck, Novartis, MSD, AstraZeneca, PharmaMar, Impulze, Merck, Bristol Myers Squibb International, Iaculis, Johnson and Johnson, Roche; Financial Interests, Institutional, Other, Support for attending meetings and/or travel: Roche, Amgen, Sanofi; Financial Interests, Institutional, Invited Speaker: Mirati Therapeutics, Amgen, Sanofi, Swiss Oncology in Motion, Bristol Myers Squibb International, Roche, AstraZeneca. J. Trojan: Financial Interests, Personal, Invited Speaker: Amgen, Eisai, Merck Serono, Merck Sharp & Dome; Financial Interests, Personal, Advisory Board: AstraZeneca, Bayer Healthcare, Bristol Myers Squibb, Insitute for Quality and Efficiency in Health Care (IQWiG), Ipsen, Lilly Imclone, onkowissen.de, Roche, Oncolytics Biotech Inc; Financial Interests, Institutional, Research Grant: Roche. M. Goebeler: Financial Interests, Personal, Advisory Board, Participation in CML Master Class: Novartis; Financial Interests, Institutional, Invited Speaker, Symposium on adverse event management in IO: BMS; Non-Financial Interests, Principal Investigator, responsibility for a number of Phase I/II trials sponsored by several pharmaceutical companies: University Hospital. M.H.H. Schuler: Financial Interests, Personal, Invited Speaker: Amgen, Bristol Myers Squibb, Janssen, Roche, GSK, MSD; Financial Interests, Personal, Advisory Board: Amgen, AstraZeneca, Bristol Myers Squibb, GSK, Janssen, Novartis, Roche, Sanofi, Takeda, MSD, Regeneron, Immunocore; Financial Interests, Institutional, Research Grant: Bristol Myers Squibb, AstraZeneca, Janssen; Non-Financial Interests, Principal Investigator, Member, Study Steering Board: Janssen; Non-Financial Interests, Principal Investigator, Member, Study Steering Committee: Amgen. G. Alonso Casal: Financial Interests, Personal, Advisory Board: Ellipses Pharma, Boehringer Ingelheim. E. Calvo: Financial Interests, Personal, Advisory Board: Adcendo, Amunix, Anaveon, AstraZeneca, BMS, Boehringer-Ingelheim, Chugai, Diaccurate, Elevation Oncology, Ellipses Pharmacy, Genmab, Grey Wolf, Incyte, Janssen, MSD, Merus, MonTa, Nanobiotix, Nouscom, Novartis, Servier, SyneosHealth, T-knife, TargImmune, iTeos, Debio; Financial Interests, Personal, Invited Speaker: OncoDNA, PharmaMar, Roche/Genentech; Financial Interests, Personal, Full or part-time Employment, Director, Clinical Research: HM Hospitales Group; Financial Interests, Personal, Full or part-time Employment, Medical Oncologist. Clinical Investigator. Director, Clinical Research: START Madrid - CIOCC (Centro Integral Oncológico Clara Campal); Financial Interests, Personal, Member of Board of Directors, External Independent member of Board of Directors: PharmaMar; Financial Interests, Personal, Ownership Interest: START, Oncoart Associated; Financial Interests, Personal, Steering Committee Member, Member of Data Monitoring Committee: BeiGene, Sanofi, Merus, Shionogi; Financial Interests, Personal, Steering Committee Member: Novartis; Non-Financial Interests, Other, Non-for-profit Foundation. President and co-founder: INTHEOS (Investigational Therapeutics in Oncological Sciences) non-for-profit Foundation; Non-Financial Interests, Advisory Role: PsiOxus; Non-Financial Interests, Other, Chair of the Independent Data Monitoring Committee: EORTC

IDMC; Non-Financial Interests, Member of Board of Directors, Non-for-profit Foundation, trustee member: Non-for-profit Foundation PharmaMar; Non-Financial Interests, Advisory Role, Non-for-profit foundation: CRIS Cancer Foundation, non-for-profit ; Non-Financial Interests, Member: ASCO, ESMO, SEOM, EORTC. M. Liebig, K. Klar, P. Fettes, F.S. Lichtenegger: Financial Interests, Personal, Full or part-time Employment: CatalYm. F. Hermann: Financial Interests, Personal, Financially compensated role: CatalYm; Financial Interests, Personal, Full or part-time Employment: Thermosome. E. Leo: Financial Interests, Personal, Full or part-time Employment, CMO: CatalYm GmbH; Financial Interests, Institutional, Stocks/Shares: Catalym GmbH. All other authors have declared no conflicts of interest.

© *European Society for Medical Oncology*