IMMUTACE: A biomarker-orientated Phase II single-arm, open-label AIO study of transarterial chemoembolization (TACE) in combination with nivolumab performed for intermediate stage hepatocellular carcinoma (HCC) (AIO-HEP-0217) – Updated efficacy results

A.Saborowski1, D. Waldschmidt2, J. Hinrichs1, T. Ettrich3, U. Martens4, A. Mekolli5, E. De Toni6, T. Berg7, M. Geißler8, G. Hausner, 9, M.Maenz10, L. Maciolek11, U. Ehmer12, M. Kirstein13, S. Lehnerts14, E. Raschke15, A. Vogel1

1Hannover Medical School, Hannover, Germany; 2University Hospital Cologne, Cologne, Germany; 3Ulm University Hospital, Department of Internal Medicine I, Ulm, Germany; 4SLK-Kliniken Heilbronn, Clinic for Internal Medicine, Heilbronn, Germany; 5Göttingen Medical School, Göttingen, Germany; 6Department of Medicine II, University Hospital, LMU Munich, Munich, Germany; 7University of Leipzig, Section of Hepatology, Department of Gastroenterology and Rheumatology, Leipzig, Germany; 8Municipal Hospital Karlsruhe, Karlsruhe, Germany; 9Esslingen Hospital, Esslingen, Germany; 10Corbin GmbH, Berlin, Germany; 11Klinische Studien, AIO-Studien-gGmbH, Berlin, Germany; 12Internal Medicine II, Klinikum rechts der Isar, Technical University Munich, Munich, Germany; 13UKSH Schleswig-Holstein, Lübeck, Germany; 14Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, Frankfurt, Germany; 15Precision for Medicine, Redwood City, CA, USA

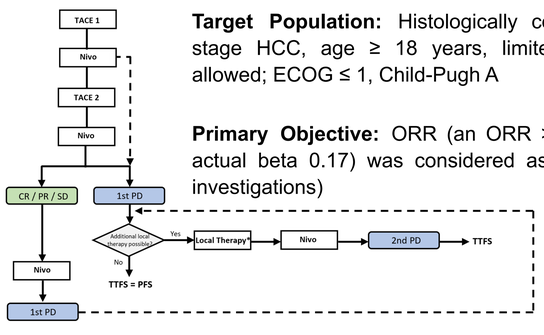
Background

Immunotherapy-based combinations recently revolutionized the treatment of patients (pts) with advanced HCC, but the efficacy of checkpoint inhibitors in earlier stages remains to be determined. TACE is commonly used as first line treatment in intermediate HCC, but outcome of patients treated with TACE in real-world cohorts is still poor with a median overall survival (OS) below 20 months. The aim of this study was to determine the safety and efficacy of TACE combined with nivolumab.

Methods

59 patients were enrolled at 10 sites in Germany between 06/2018 and 06/2020. Pts received up to two TACE treatments followed by nivolumab (240 mg/ Q2W), initiated on day 2-3 after the first TACE session and continued until progression for a maximum treatment duration of two years. After 8 weeks of treatment, a second TACE has been performed. Primary endpoint was ORR (mRECIST; with ORR exceeding 55% (power = 80%; actual beta 0.17) as promising for further investigations). Secondary endpoints include mPFS, mTTFS (median time to failure of strategy), mOS, QoL, and safety/tolerability. Tumor tissue was obtained at baseline and blood samples were collected longitudinally for translational research.

Study Design



Target Population: Histologically confirmed, intermediate stage HCC, age ≥ 18 years, limited metastatic disease allowed; ECOG ≤ 1, Child-Pugh A

Primary Objective: ORR (an ORR > 55% (power = 80%; actual beta 0.17) was considered as promising for further investigations)

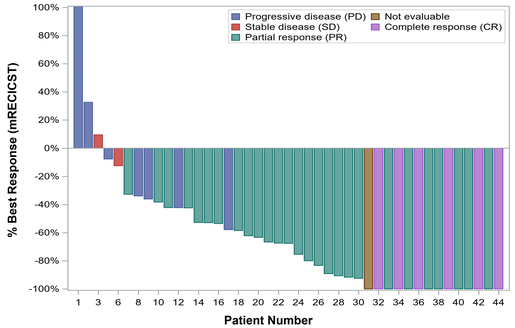
*Additional local therapy (including further TACE, radiofrequency ablation/microwave ablation or resection)

Conclusion

The study met its primary endpoint and provides evidence for the efficacy of TACE in combination with nivolumab without new safety signals in pts with intermediate HCC and no prior systemic therapy. Our findings support further evaluation of nivolumab-based combinations for the treatment of intermediate HCC.

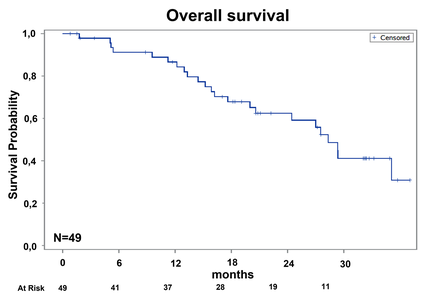
Results

49 pts (14.3% HCV and 8.2% HBV, 18,4 % ASH, 30,6% NASH) received at least one dose of nivolumab, median tumor size was 4.5 cm (0.9 – 15 cm) and median number 3 (1 – 12). ORR by mRECIST was 71.4% (CR: 16.3%, PR: 55.1%, SD 4.1%, PD: 14.3%). At a median follow-up of 20 mo, mPFS was 7.2 mo (95% CI; 5.3 – 11.2; 40 events), mTTFS was 11.2 mo (95% CI; 7.2, 13.5; 42 events) and mTTSST (median time to subsequent systemic therapy) was 24.9 mo (95% CI; 12.2, - ; 21 events). Median duration of nivolumab was 8.3 mo and mOS was 28.3 mo (95% CI; 20 – not estimable; 23 events). Grade ≥ 3 treatment-related adverse events occurred in 34.7% of patients.

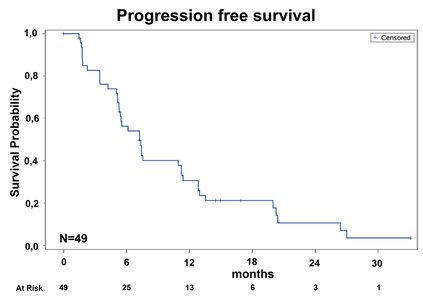


ORR according to mRECIST for HCC

Variable	Analysis (n=49)
ORR (95% CI), %	71.4 (56.8 – 83.4)
Best OR, n (%)	
CR	8 (16.3)
PR	27 (55.1)
SD	2 (4.1)
PD	7 (14.3)
Not evaluable	5 (10.2)



Provisional mOS (95% CI): 28.32 mo (19.98 – NE); 23 events



Median PFS (95% CI): 7.23 mo (5.29 – 11.24); 40 events

AIO-Studien-gGmbH
MHH Medizinische Hochschule Hannover
IKF Institut für Klinische Krebsforschung am Krankenhaus Nordwest

Conflict of Interest:
Amgen, Roche, Bayer, Sanofi, BMS, Lilly, Novartis, EISAI, AstraZeneca, Merck, Incyte, Ipsen, PierreFabre, MSD, Sirtex, BTG, Servier, Terumo, GSK- Speaker, consultancy and advisory role.
Servier: Research funding.
Onclive: Commercial medical-education provider

Study lead contact information:
Coordinating Investigator: Prof. Dr. med. Arndt Vogel
vogel.arndt@mh-hannover.de
@ArndtVogel

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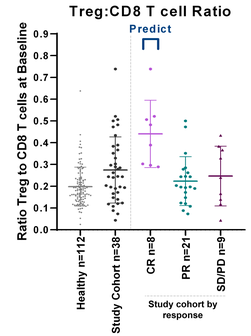
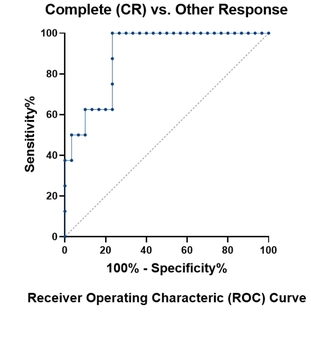
Study management contact information:
Sarah Lehnerts, lehnerts.sarah@ikf-khnw.de
Lea Maciolek, Lea.Maciolek@aio-studien-ggmbh.de

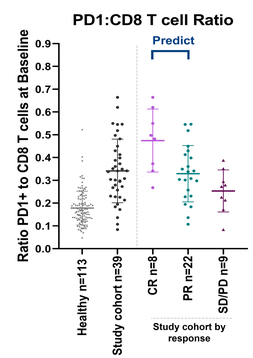
TR Analysis:
Precision for Medicine GmbH, Berlin, Germany

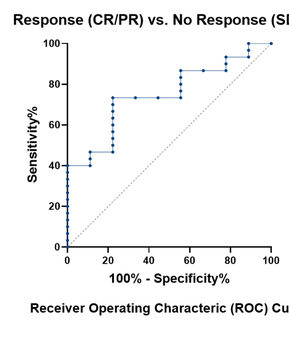
Translational Research

39 pts provided a whole blood sample pre-treatment that was analyzed with Epiontis ID, an immunophenotyping method that uses cell-specific epigenetic markers to quantify immune cells in blood and tissue samples (Baron et al., 2018, Sci Transl Med 2018:10). The pre-treatment levels of CD8 T cells, Regulatory T cells and PD1 positive cells were measured in a cohort of healthy donors and in the study cohort and evaluated for their portential to predict clinical response.









Translational Research- Results

A high pre-treatment ratio of Treg:CD8 T cells above 0.287 was observed in all 8 patients with CR, while only 23/30 patients with no CR response measured above 0.287 (prediction of CR with 100% sensitivity, 77% specificity, AUC 0.90). A high pre -treatment ratio of PD1:CD8 T cells above 0.2961 predicted any response (CR or PR) versus no response (SD/PD) (73% sensitivity, 78% specificity, AUC 0.75).