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Comprehensive molecular and phenotypic profiling of end-stage IV cancer identifies treatable targets and improves survival in individual patients

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BACKGROUND

Comprehensive profiling of patients' tumor tissue in cases with end-stage IV cancer of different tumor sites was conducted to identify mutations, proteins and activated cancer pathways potentially eligible for targeted therapies. Data evaluation included test results, clinical data, clinical trials and longitudinal follow-up data.

METHODS

Rapid tissue collection and processing was conducted under highly standardized conditions (ischemia time <10 min) to preserve the expression profile in tissue as it appears in the human body. Samples that passed the quality control (tumor content ≥ 50%) were analyzed using the following techniques: immunohistochemistry (IHC), next-generation sequencing (NGS) and simple western charge-based assays (NanoPro 1000 system). Expression of the major receptor proteins and phosphorylation of the signaling proteins ERK1/2, MEK1/2 and AKT of the MAP kinase pathway and the PI3K/AKT/mTOR-pathway were measured to infer targets on the (phospho-) proteomic level. On the genomic level DNA sequencing of "hotspot" regions covering 50 oncogenes and tumor suppressor genes was conducted using the Ion AmpliSeq™ Cancer Hotspot Panel v2.

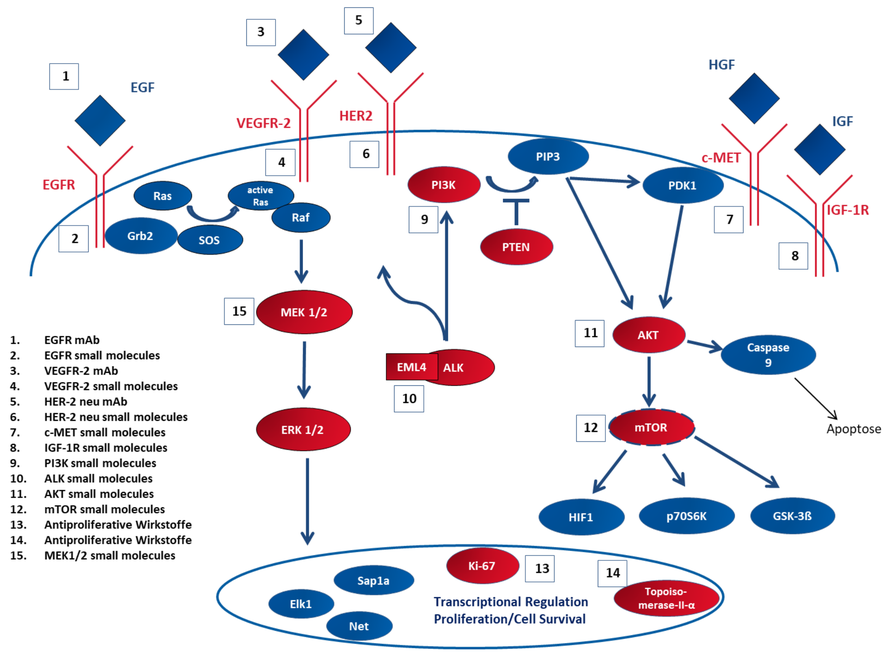

Figure 1: Overview of relevant pathways and molecular targets. Druggable receptor proteins and signaling proteins were analyzed for every case (red).

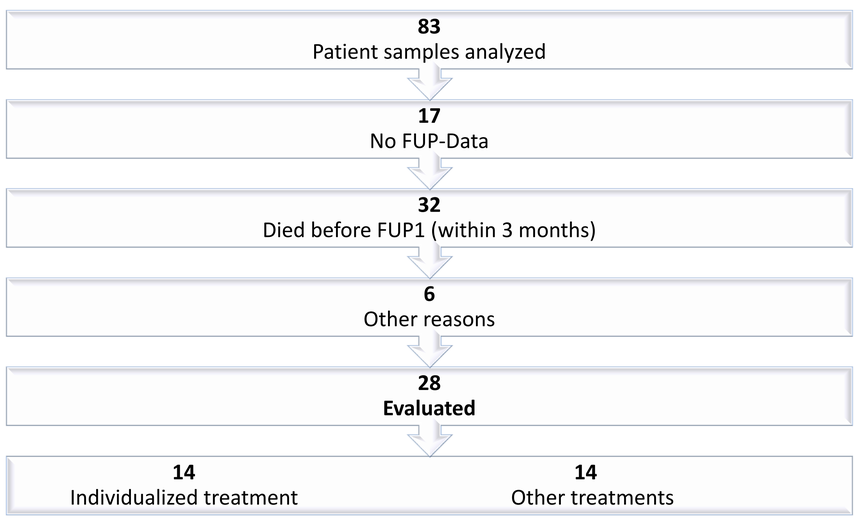

Figure 2: Overview of all patients whose tissue samples were analyzed and the applied selection criteria. The 28 patients who passed the filtering criteria and were finally evaluated in detail were divided into two groups according to their initial treatment.

RESULTS

Analyses of 83 patients were performed. 28 patients met the determined evaluation criteria. These patients were divided into two groups. In one group (n = 14) targets for available therapeutics could be identified and patients were treated accordingly. In the other group (n=14) targets could not be found or were not regarded as useful by the oncologist. These patients were treated with conventional, palliative therapies. The 6-months follow-up revealed a better outcome when patients were treated according to an identified target. 49% of patients responded to targeted treatment. 14% of patients had a complete remission (CR), 14% had a stable disease (SD) and another 21% had a partial remission (PR). 36% progressed under targeted therapy and 14% died. In contrast, only 21% responded under conventional, palliative therapy by showing a stable disease, 64% of patients progressed (PD) and 14% died. No complete or partial remission was observed in patients treated by conventional approaches.

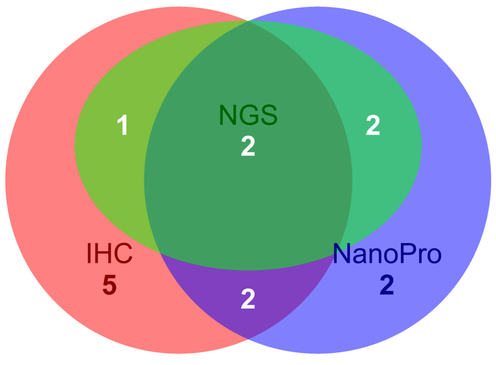

Figure 3: Venn diagram of the amount of detected targets via the different measurement techniques (IHC, NGS and NanoPro) on which a therapy decision was based in the subgroup of 14 patients who were initially treated according to their molecular profile.

OVERVIEW OF FOLLOW-UP AND TREATMENT RESPONSE

No.	Tumor entity	Analysed tissue
28	colon carcinoma	liver metastasis
27	pancreatic cancer	liver metastasis
26	CUP	ovary
25	desmoid (abdominal wall)	primary tumor
24	non-small-cell lung cancer (NSCLC)	bone metastasis
23	renal cell carcinoma (RCC)	liver metastasis
22	acinic cell carcinoma of the parotid gland	chest wall metastasis
21	colon carcinoma	primary tumor
20	cholangiocarcinoma (CCC)	liver metastasis
19	rectal carcinoma	liver metastasis
18	gastric cancer	primary tumor
17	triple negative breast cancer (TNBC)	cutaneous metastasis
16	CUP	peritoneal carcinosis
15	CUP	lymph node metastasis
14	SETTLE tumor	liver metastasis
13	neuroendocrine pancreatic carcinoma	liver metastasis
12	rectal carcinoma	lung metastasis
11	tube carcinoma	liver metastasis
10	cecum carcinoma	liver metastasis
9	breast cancer	cutaneous metastasis
8	rectal carcinoma	brain metastasis
7	esophagus carcinoma	primary tumor
6	gastric cancer	primary tumor
5	anal cancer	liver metastasis
4	triple negative breast cancer (TNBC)	cutaneous metastasis
3	CUP	lymph node metastasis
2	cholangiocarcinoma (CCC)	liver metastasis
1	gastric cancer	primary tumor

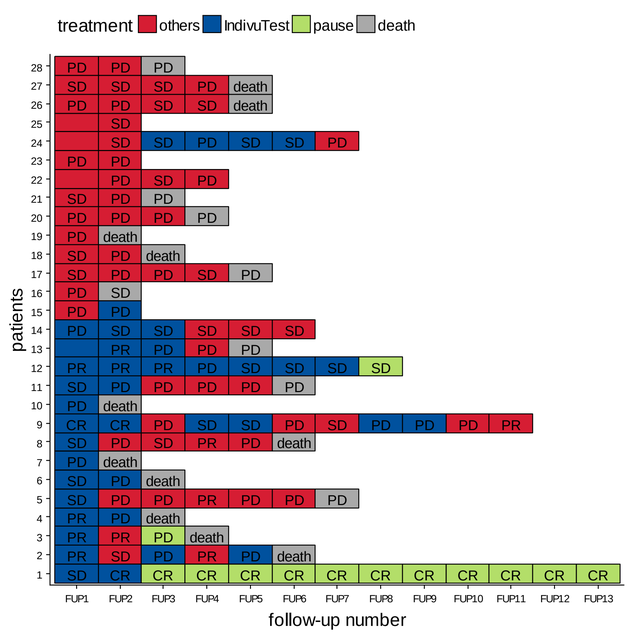

Figure 4: Diagram and overview of all 28 evaluated patients in relation to their follow-up frequency. The first follow-up (FUP1) was raised three months after molecular analyses and was requested in three months intervals. **Blue bars:** Recommended drugs were considered during follow-up interval. **Red bars:** Patient was treated with other drugs than recommended. **Green bars:** Therapy was interrupted. **Grey bars:** Patient died. Response to treatment in each interval is described by abbreviations: Stable disease / Minor response (SD), Partial Response (PR), Complete Response (CR) and Progressive Disease (PD).

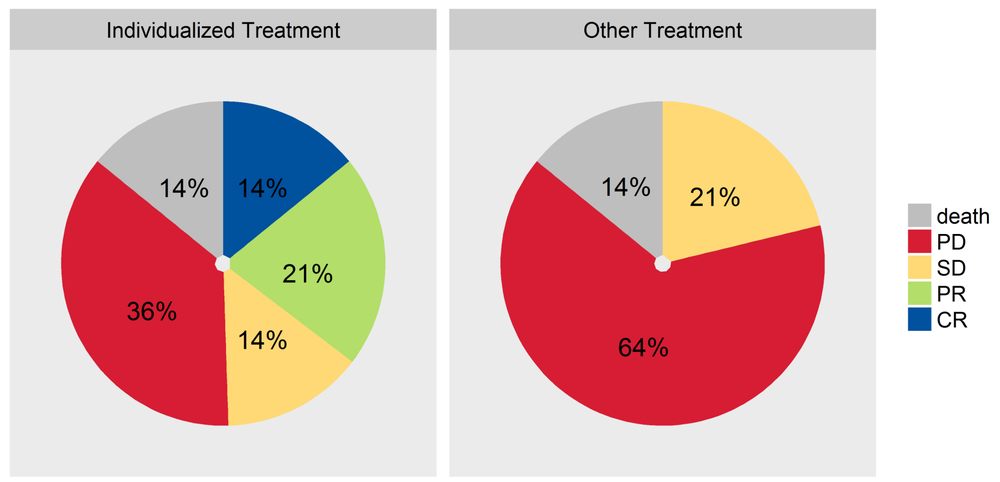

Figure 5: Pie chart of treatment response after six months in the second follow-up interval (FUP2). Pie chart of treatment response during the second follow-up interval (FUP 2). The left panel shows the response to individualized treatment of 14 patients, while the right panel shows response to other treatments of 14 patients. The following abbreviations were used: Progressive Disease (PD), Stable Disease / Minor Response (SD), Partial Response (PR), Complete Response (CR).

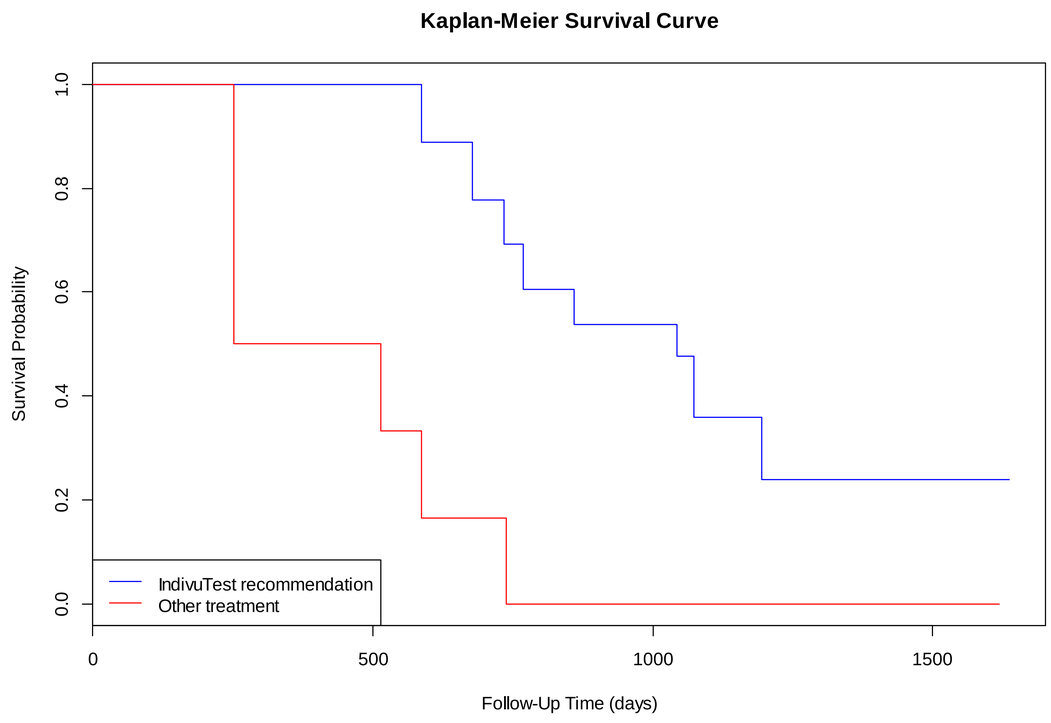

Figure 6: Kaplan-Meier survival curves. The red line indicates survival probability of the 14 patients who were initially not treated according to a specific molecular target. The blue line belongs to the 14 patients initially treated matched to a molecular target.

CONCLUSION

A comprehensive molecular and phenotypic tumor characterization can identify in individual patients - suffering from highly advanced cancer - targeted therapies that impact cancer growth and lead in single cases even to a complete remission.