Preliminary results from the NCT02770378 proof-of-concept clinical trial assessing the safety of the Coordinated Undermining of Survival Paths by 9 repurposed drugs (version 3) combined with metronomic temozolomide (CUSP9v3) protocol for recurrent glioblastoma

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Introduction:

Despite refinements of neurosurgical techniques and emerging adjuvant therapies, patients with recurrent glioblastoma continue to face a dismal prognosis. We report preliminary results of a clinical trial evaluating a protocol of 9 repurposed drugs (aprepitant, minocyclin, disulfiram, celecoxib, sertraline, captopril, itraconazole, ritonavir, auranofin) and low-dose metronomic temozolomide in patients with recurrent glioblastoma.

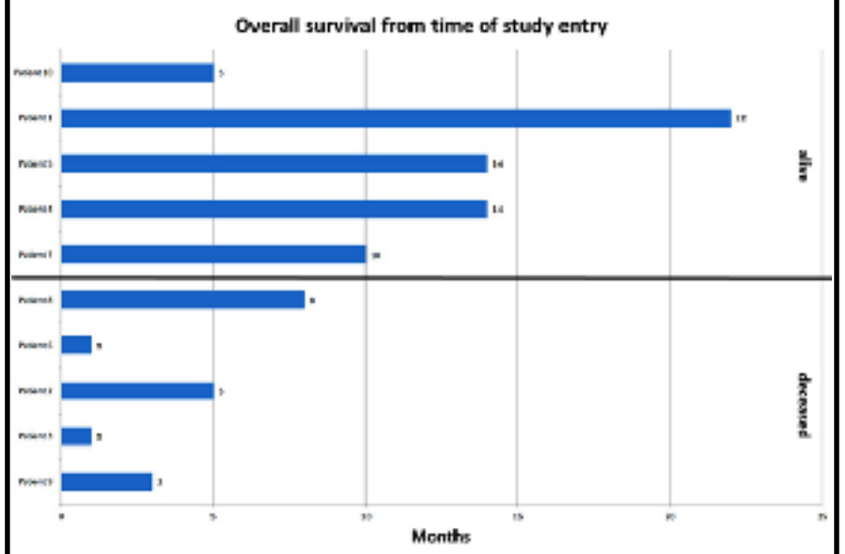
Methods:

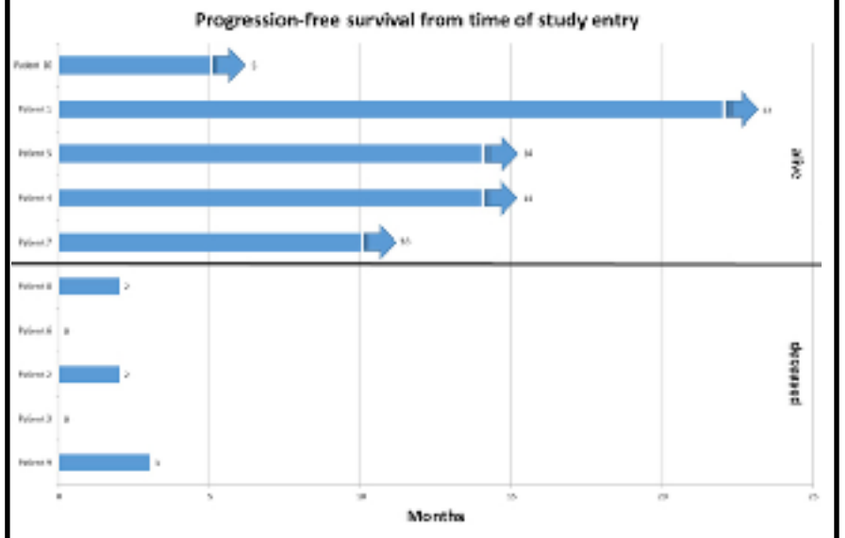
Between November 2016 and October 2018, 10 patients (age ≥ 18 years, KPS ≥ 70%) with glioblastoma recurrence after standard therapy were included in the CUSP9v3 single-arm proof-of-concept clinical trial. The primary endpoint was dose-limiting toxicity during the first 12 weeks of treatment. Secondary endpoints were overall survival and best tumor response during the 12-month medication period according to RANO criteria.

Baseline characteristics:

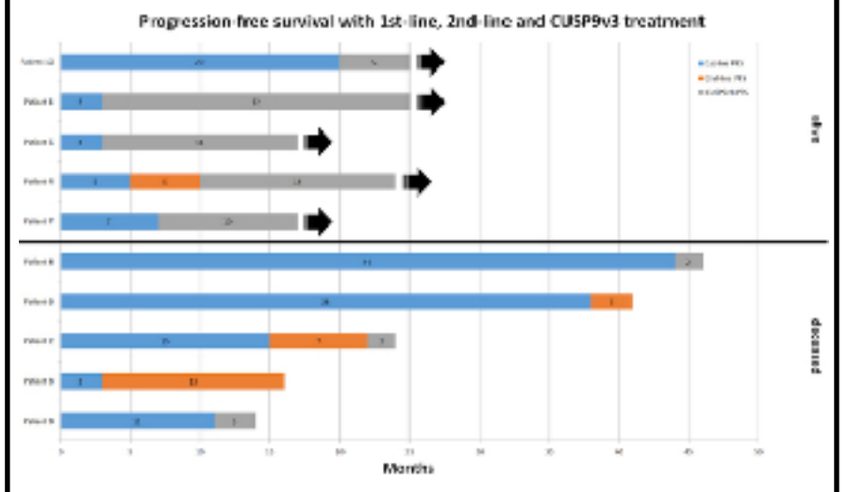
Characteristic	Patients (n=10)
Sex – no. (%)	
Female	6 (60)
Male	4 (40)
Age – years	
Median	41
Range	25-60
Karnofsky performance status – no. (%)	
100	5 (50)
90	4 (40)
70	1 (10)
Year of diagnosis	
Median	2016
Range	2013-2017
Glioblastoma WHO grade IV – no. (%)	
Primary	8 (80)
Secondary	2 (20)
Recurrences or progressions - no. (%)	
First	6 (60)
Second	4 (40)
Tumor location – no. (%)	
Frontal lobe	2 (20)
Temporal lobe	2 (20)
Parietal lobe	1 (10)
Disseminated - basal ganglia	1 (10)
Disseminated - midbrain and brainstem	2 (20)
Disseminated - callosal	2 (20)
Extent of resection – no. (%)	
Gross total	7 (70)
Subtotal	3 (30)
MGMT promoter status - no. (%)	
Methylated	5 (50)
Unmethylated	4 (40)
Intermediate	1 (10)
Previous treatment - no. (%)	
Radiation therapy with temozolomide	10 (100)
Time between first diagnosis and start of CUSP9v3 – days	
Median	490
Range	131-1412

Results - OS and PFS:

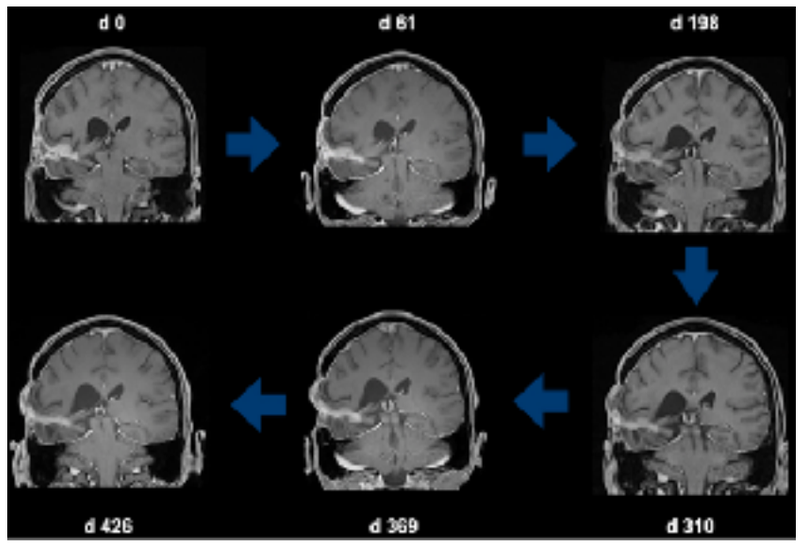


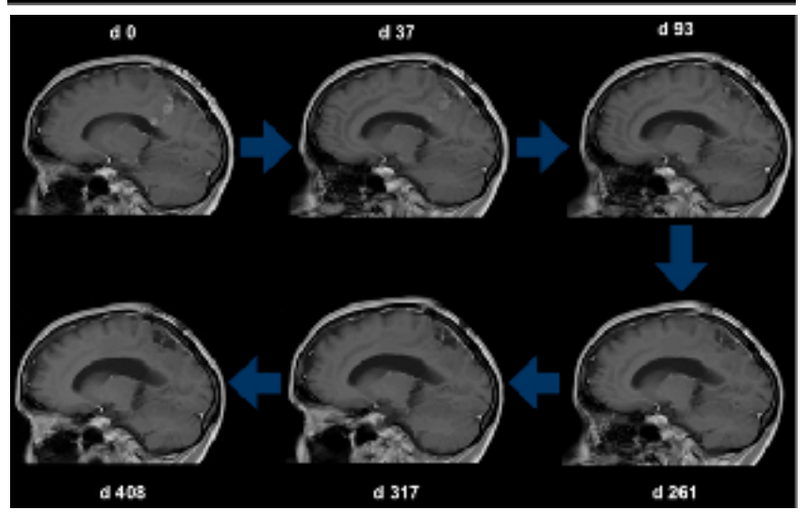


PFS comparison with previous therapies:

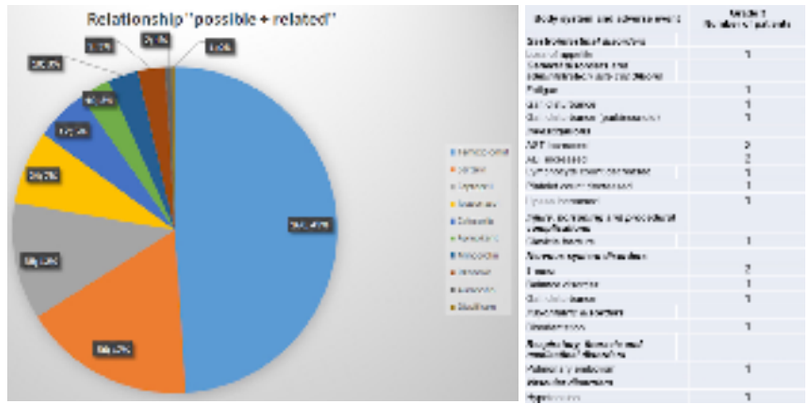


Case illustrations:





Adverse events:



Conclusion:

With close ambulatory monitoring and drug schedule adaptations according to individual side effects, CUSP9v3 appears to be a safe protocol. Assessment of efficiency is preliminary but suggests good tolerability. The six-month progression-free survival of recurrent disease in this study is 50%.

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