# The DCCC Brain Tumor Center

The Research Center is a member of DCCC and supported by The Danish Cancer Society

www.dcccbraintumor.dk

# Identifying targetable alterations predictive of distant progression in glioblastoma patients undergoing standard therapy

**Shivani Bangalore Chiranth[1], Vincent Fougner[1,2], Ib Jarle Christensen[1], Anouk Kirsten Trip[1,3], Terkel Christiansen[1,2], Dorte Schou Nørøxe[1,2], Christina Westmose Yde[4], Anne Kiil Berthelsen[2], Benedikte Hasselbalch[1,2], Ulrik Lassen[1,2], Hans Skovgaard Poulsen[1,2], and Thomas Urup[1,2]**

[1]The DCCC Brain Tumor Center, Rigshospitalet, Copenhagen, Denmark. [2]Department of Oncology, Rigshospitalet, Copenhagen, Denmark. [3]Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark. [4]Center for Genomic Medicine, Rigshospitalet, Copenhagen, Denmark.

## Background

Migratory growth is a hallmark of glioblastoma (GBM) and is a major factor in therapeutic failure.

**Hypothesis:** Genetic variants that predict distant progression (migratory growth) represent key treatment targets.

## AIM

Identify targetable genetic variants associated with distant progression

## Methods

**Patients**

All consecutive GBM *IDH wildtype (*wt) patients treated with standard therapy at Rigshospitalet (year 2016-21) were included.

**Genomic cohort**

Genomic tumor profiling (WES or WGS) was conducted in consenting patients.

**Definition of distant progression**

A new tumor lesion located more than 2 cm from the primary tumor.

**Candidate biomarkers**

Pathogenic or likely-pathogenic variants were grouped in i) gene alterations present in >5% of samples, and ii) the presence of alterations in four commonly altered signaling pathways.

**Statistics**

Cox regression analysis was used to model the association with time to distant progression.

## Results

**Table 1. Patient characteristics**

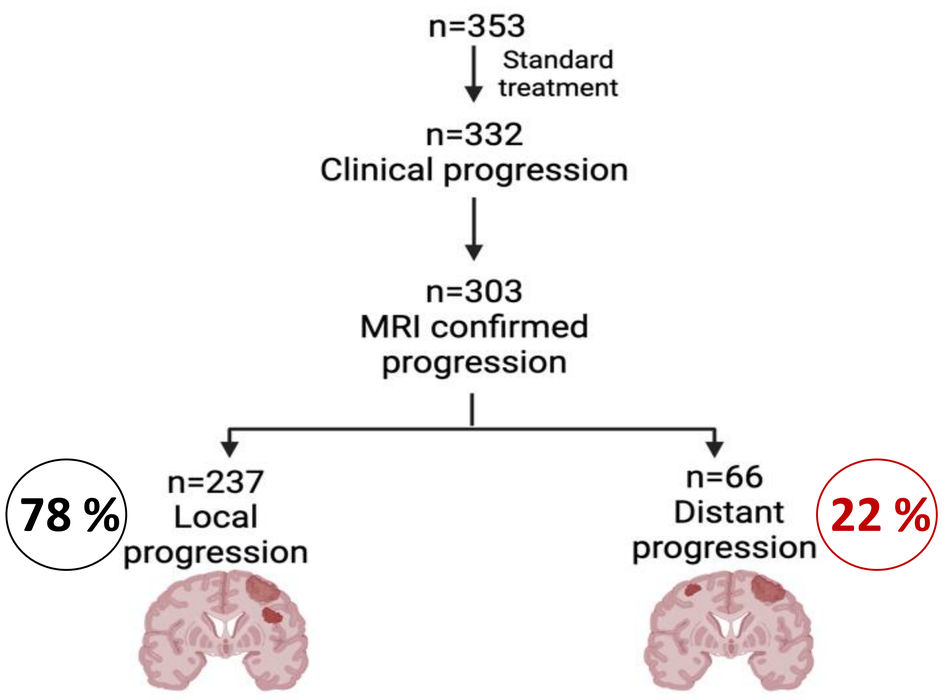
| | Total, n = 353 | Genomic, n =204 |
|---|---|---|
| Median age, years (range) | 59 (17 – 77) | 58 (18-77) |
| Female, n (%) | 134 (38) | 70 (34) |
| ECOG PS, n (%) | | |
| 0-1 | 332 (95) | 193 (96) |
| 2 | 17 (5) | 8 (4) |
| Subependymal involvement | 153 (43) | 85 (42) |
| Multicentric Disease, n (%) | 45 (13) | 17 (8) |
| Corticosteroid use, n (%) | 161 (46) | 82 (40) |
| Surgical resection, n (%) | 286 (81) | 180 (89) |
| Methylated MGMT, n (%) | 148 (42) | 91 (45) |
| Positive p53 expression, n (%) | 215 (68) | 129 (69) |
| Median PFS (95% CI), months | 7.5 (6-8 – 8.2) | 7.5 (7.0 – 8.0) |
| Resection at recurrence, n (%) | 115 (35) | 88 (46) |
| Second line treatment, n (%) | 240 (74) | 158 (84) |
| Median OS (95% CI), months | 17.2 (15.8 - 18.7) | 19.7 (17.0 - 22.5) |

**Table 2. Multivariate analysis of the clinical cohort modelling time to distant progression**

| Covariate | HR (95%CI) p-value |
|---|---|
| **MGMT, un-methylated vs. methylated** | **2.69 (1.70-4.25) <0.001** |
| Corticosteroid use, yes vs. no | 0.93 (0.60 – 1.45) 0.75 |
| Age, per 10-year increase | 1.02 (0.85 – 1.22) 0.81 |
| **Multicentric vs. single lesion** | **2.54 (1.42 – 4.54) 0.002** |
| ECOG PS, 1-2 vs 0 | 0.90 (0.57 – 1.43) 0.67 |
| Biopsy vs. resection | 1.48 (0.80 – 2.76) 0.21 |

**Table 3. Multivariate analysis of the genomic cohort modelling time to distant progression**

| Covariate | HR (95%CI) p-value |
|---|---|
| **NF1 alteration vs. NF1 wildtype** | **3.22 (1.37-7.61) 0.008** |
| **MGMT, un-methylated vs. methylated** | **2.82 (1.28-6.21) 0.01** |
| Multicentric vs. single lesion | 1.95 (0.58 – 6.61) 0.28 |



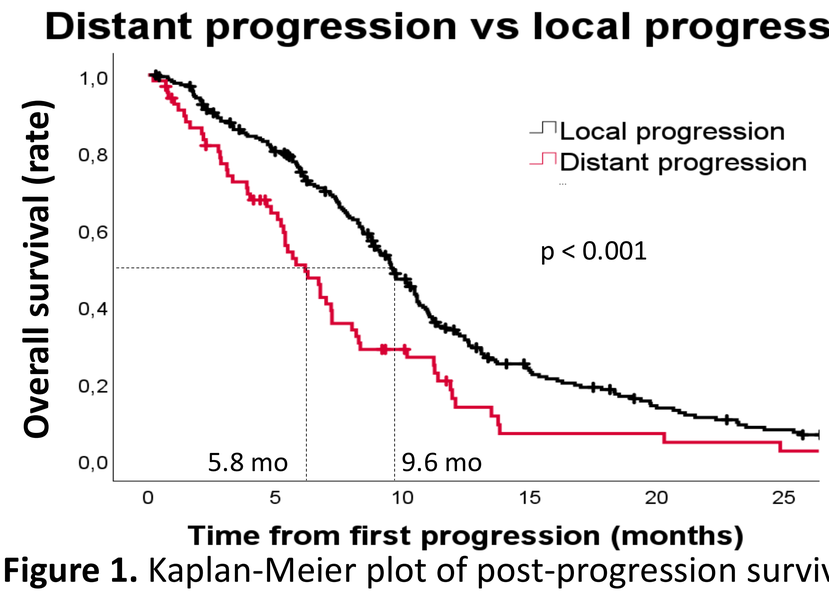




**Figure 1.** Kaplan-Meier plot of post-progression survival for patients with distant vs. local progression.

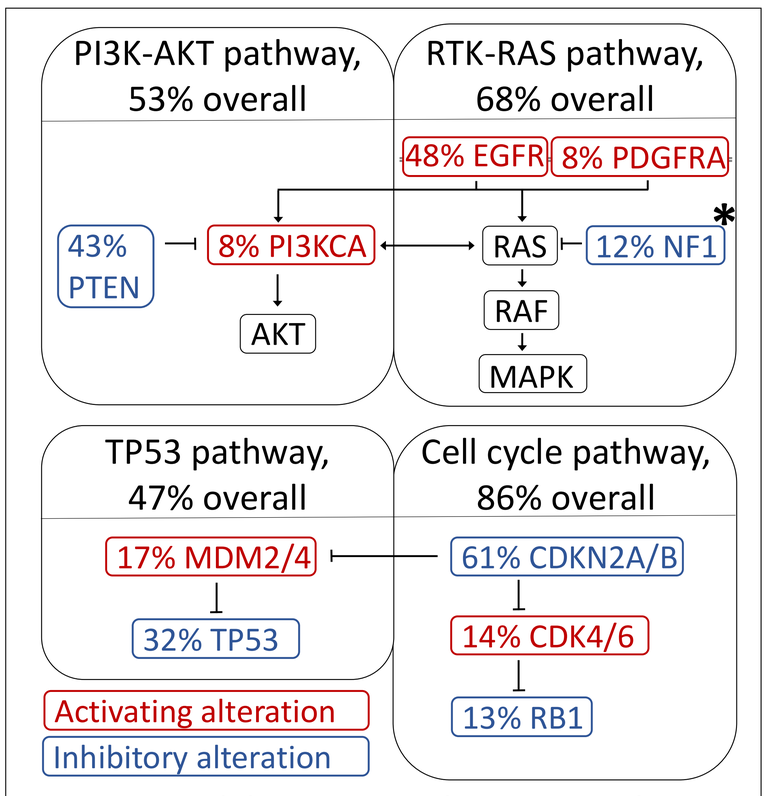



**Figure 2.** Candidate genetic alterations incl. frequency (%) analyzed by univariate analysis.

*_NF1_ alteration showed association with distant progression (HR=3.46, 95%CI: 1.51-7.94, p=0.003).

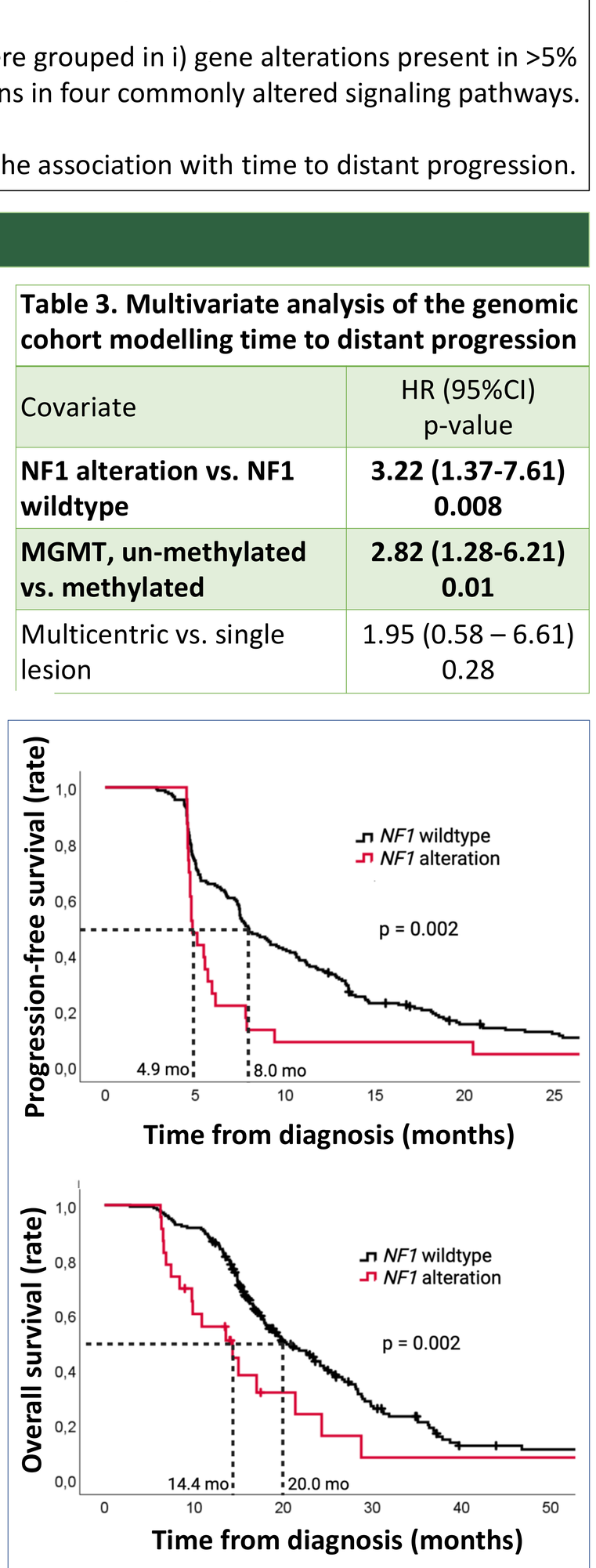



**Figure 3.** Kaplan-Meier plots of PFS and OS for *NF1* altered and *NF1*wt glioblastoma

## Conclusion

- Distant progression is an aggressive growth pattern associated with poor survival.
- Clinical predictors of distant progression:
  - Unmethylated MGMT
  - Multicentric tumor
- *NF1* alteration predicts distant progression (migratory growth).
- *NF1* alteration is an independent predictor of poor progression-free survival and overall survival.
- *NF1* alteration serves as a potential target for personalized therapy.

Correspondence: Thomas.Urup@regionh.dk