

ELMED219-2022

Project (team-based)

“Precision medicine and quantitative imaging in glioblastoma”

Arvid Lundervold (UiB) and Alexander S. Lundervold (HVL)



Høgskulen
på Vestlandet



The open call:

You are member of a group of established successful scientists that will team up to tackle an important biomedical and medical challenge.

There is an open call for research proposals under a new umbrella program entitled

“Artificial intelligence and computational (bio)medicine”,

where your multidisciplinary group are aiming for a project on

“Precision medicine and quantitative imaging in glioblastoma - a multiscale approach”.

Precision medicine and quantitative imaging in glioblastoma - a multiscale approach

The focus of the assignment is

- (i) description of relevant imaging technologies and modalities - possibly at different scales,
- (ii) proposal of imaging-derived biomarkers for glioblastoma,
- (iii) machine learning techniques for classification, treatment stratification and prediction,
- (iv) the novelty and expected impact of your approach, and
- (v) the evaluation of the ethics of your project and data management plans

Fig. 6: A precision medicine approach to the treatment and management of patients with brain tumours.

[Aldape et al.](#) Nat Rev Clin Oncol 2019

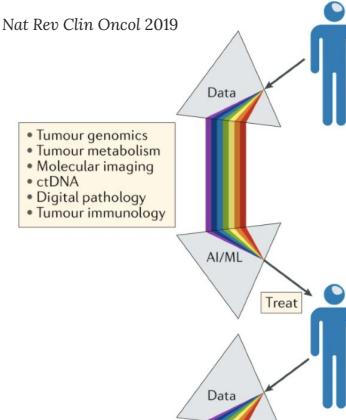
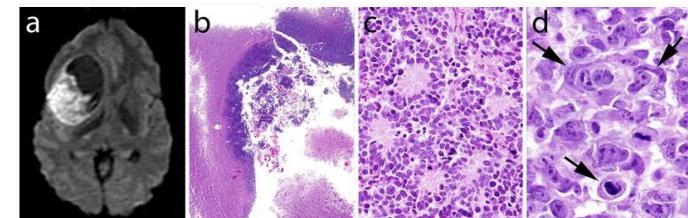


Fig. 3 Glioblastomas with primitive neuronal components (GBM-PNC)

[Louis et al.](#) Acta Neuropathol 2016



Organization of your team report:

Research plan

(3-5 pages incl. figures and bibliography)

- A brief background to the field
- Objectives and expected impact
- Material and methods
- Evaluation

Data management plan and ethical considerations

(1 1/2-2 1/2 pages incl. graphics / links)

- Description of generated data and code
- Sharing of data and code
- Ethical considerations

<https://github.com/MMIV-ML/ELMED219-2022/blob/main/project/README.md>

Grupper (6)

▼ Team1 Full 6 / 6 studenter

Maria Mathea Kehler Aarh...	Amalie Austgulen	Ingrid Aase Cowles
Borghild Tednes Larsen	Maria Olsen	Jens Andreas Thuestad

▼ Team2 Full 6 / 6 studenter

Enya Noor Akhtar	Malene Saelensminde Berg...	Ben René Bjørsvik
Odd Kasper Ekre	Oluokoya David Peter	Marius Eldevik Rusaas

▼ Team3 5 / 6 studenter

Mari Maaløy Alsaker	Linnea Frang	Hanna Marie Thorbjørnsen...
Ingeborg Bryne Retterstøl	Heris Sivanesarajah	

▼ Team4 Full 6 / 6 studenter

Ingrid Kleive Andersen	Oscar Alm Harestad	Håvard Mikkelsen
Sangeeta Roopan	Amalie Storesund	Olivia Winson

▼ Team5 Full 6 / 6 studenter

Hedda Johanne Askheim	Muhammad Eid	Caroline Pernille Syljeset H...
Jens Long Nguyen	Erica Sande Teige	Henrik Lippert Thue

▼ Team6 Full 6 / 6 studenter

Haldis Tuva Tolås Boge	Tuva Fløysvik	Osman Goni
Øyvind Grutle	Marte Hordnes	Karina Herland Nilsen

You should all have got an invite to your Team's document

Collaborative writing and publishing tool

The screenshot shows the Overleaf LaTeX editor interface. At the top, there is a navigation bar with links for Features & Benefits, Templates, Plans & Pricing, Help, Register, and Log In. Below the navigation bar, the main title "REPORT using LaTeX, Evolved" is displayed in large white letters, with "REPORT using" in bold. A subtitle "The easy to use, online, collaborative LaTeX editor" is also present. On the left side, there is a sidebar with a file tree showing "main.tex" as the selected file. The main workspace displays the LaTeX code for "main.tex". The code includes sections like "Introduction" and "Conclusion", and a figure inclusion for "universe.jpg". The right side of the interface shows the rendered output of the LaTeX document, which includes the title "The Universe", the date "May 2019", an introduction section with text and a small image of a galaxy, and a caption "Figure 1: The Universe". At the bottom, there are registration options for "email@example.com", "Register", "Register using Google", and "Register using ORCID".

For
Writing
Teaching
Universities
Templates

ELMED219_2022_project_team_k

Source Rich Text Ω Recompile Review Share Submit History Chat

ELMED219_2022 project tea... elmed219_dummy_fig.png main.tex

File outline

Research plan

- A brief background to the field
- Objectives and expected impact
- Material and methods
- Evaluation

Data management plan and ethical consi...

- Description of generated data and co...
- Sharing of data and code
- Ethical considerations

1 \documentclass[11pt]{article}
2 \usepackage[utf8]{inputenc}
3 \usepackage{graphicx}
4 \usepackage[left=2.5cm,top=2.5cm,right=2.5cm,bottom=2.5cm]{geometry}
5 \usepackage{times} % font type
6 \usepackage[url] % for clickable web addresses in PDF document
7 \usepackage[graphicx] % for figures
8 \usepackage{float} % to force figure or table here [H]
9 \usepackage[multirow] % For tables with different rows and columns
10 \usepackage{lipsum} % for placeholder text (lorem ipsum ...)
11 %\usepackage[biblalex]
12
13 \title{Precision medicine and quantitative imaging in glioblastoma}
14 \author{ELMED219 (Artificial Intelligence and Computational Medicine),
January 3-28, 2022}\
15 \footnotesize \url{https://github.com/MMIV-ML/ELMED219-2022}}
16
17 \date{Team #k}
18 \begin{document}
19
20 \maketitle
21
22 \begin{scriptsize}
23 \begin{verbatim}
24 Team #k members:
25
26 Name, Category, E-mail
27 NN, MED, nn@student.uib.no
28 MM, TEK, mm@student.uib.no
29 KK, ING, kk@student.hvl.no
30
31 \end{verbatim}
32 \end{scriptsize}
33
34 \vspace{3mm}
35 \section{Research plan} % 3-5 pages incl. figures and bibliography
36
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Your team

Precision medicine and quantitative imaging in glioblastoma
ELMED219 (Artificial Intelligence and Computational Medicine), January 3-28, 2022
<https://github.com/MMIV-ML/ELMED219-2022>
Team #k
Team #k members:
Name, Category, E-mail
NN, MED, nn@student.uib.no
MM, TEK, mm@student.uib.no
KK, ING, kk@student.hvl.no

1 Research plan

1.1 A brief background to the field

Glioblastoma is ... [1] ... Aladape et al. [2] ... DUMMY TEXT: Fusce mauris. Vestibulum luctus nibh at lectus. Sed bibendum, nulla a faucibus semper, leo velit ultricies tellus, ac venenatis arcu wisi vel nisl. Vestibulum diam. Aliquam pellentesque, augue quis sagittis posuere, turpis lacinia congue quam, in hendrerit risus eros eget felis. Maecenas eget erat in sapien mattis porttitor. Vestibulum porttitor. Nulla facilisi. Sed a turpis eu lacus commodo facilisis. Morbi fringilla, wisi in dignissim interdum, justo luctus sagittis dui, et vehicula libero dui cursus dui. Mauris tempor ligula sed lacus. Duis cursus enim ut augue. Cras ac magna. Cras nulla. Nulla egestas. Curabitur a leo. Quisque egestas wisi eget nunc. Nam feugiat lacus vel est. Curabitur consectetur.

1.2 Objectives and expected impact

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1.3 Material and methods

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Tables

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Table is given in Tab. 1 ...

header 1	header 2	header 3
cell1	cell2	cell3
cell4	cell5	cell6
cell7	cell8	cell9

Table 1: This is an ELMED219 dummy table.

Data is illustrated in Fig. 1 ...

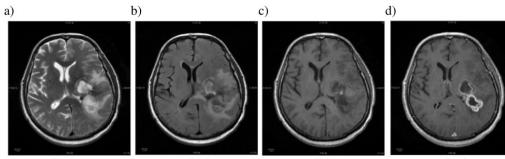


Figure 1: This is an ELMED219 dummy figure. (a) T2w, (b) FLAIR, (c) T1w, (d) T1wGd. (Image taken from study TCGA-06-1802 in the TCGA-GBM data collection [ref [1] in Section 2])

1.4 Evaluation

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References

- [1] Louis DN, Perry A, Reifenberger G et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016;131:803–820.
<https://doi.org/10.1007/s00401-016-1545-1>
- [2] Akdoge K, Brindle KM, Chesler L et al. Challenges to curing primary brain tumours. Nat Rev Clin Oncol 2019;16:509–520.
<https://doi.org/10.1038/s41571-019-0177-5>

2 Data management plan and ethical considerations

2.1 Description of generated data and code

We will be using data from the TCGA-GBM data collection [1] ... DUMMY TEXT: Pellentesque habitant morbi tristique senectus et netus et malesuada fames ac turpis egestas. Donec odio elit, dictum in, hendrerit sit amet, egestas sed, leo. Praesent feugiat sapien aliquet odio. Integer vitae justo. Aliquam vestibulum fringilla lorem. Sed neque lectus, consecetur at, consecetur sed, eleifend ac, lectus. Nulla facilisi. Pellentesque eget lectus. Proin eu metus. Sed porttitor. In hac habitasse platea dictumst. Suspendsisse eu lectus. Ut mi mi, lacinia sit amet, placerat et, mollis vitae, dui. Sed ante tellus, tristique ut, taculis eu, malesuada ac, dui. Mauris nibh leo, facilisis non, adipiscimus quis, ultricies a, dui.

2.2 Sharing of data and code

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2.3 Ethical considerations

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References

- [1] The TCGA-GBM data collection. Accessed on 28/12/2020.
<https://wiki.cancerimagingarchive.net/display/Public/TCGA-GBM>
- [2] Vollmer S, Mateo BA, Bohar G et al. Machine learning and artificial intelligence research for patient benefit: 20 critical questions on transparency, replicability, ethics, and effectiveness. BMJ 2020;368:m1927.
<https://www.bmjjournals.com/content/368/bmjj.1927>

Ad “level of detail”: https://github.com/MMIV-ML/ELMED219-2022/blob/main/project/latex-template/Seili_2020_examples/Seili_2020_project_template.pdf

Precision medicine and quantitative imaging in glioblastoma - a multiscale approach

OERCompBiomed Summer School, 10-14 August 2020
<https://github.com/oercombiomed/Seili-2020>

Template based on the report from Group#1 at the previous 2019 Seili Summer School
(for which PROSTATE CANCER was the topic)

Group members:
NN, KI (n.n@stud.ki.se)
NN, SDU (nn@student.sdu.dk)
NN, SDU (nn@student.sdu.dk)
NN, UEF (nn@student.uef.fi)

1 Research plan

1.1 A brief background to the field

Prostate cancer (PCA) is the most common form of cancer for men. Usually it grows slowly and rarely causes any symptoms on its early stage. However, in latest stages PCA can lead to urinary difficulties, blood in urine and pain in the pelvis, back and during urinating (Smith et al. 2017, Pientala et al., 2016). Reason for lack of symptoms can be e.g. that malignancies start to grow in the peripheral portion of the prostate away from the prostatic urethra. PSA is commonly used marker in PCA screening. PSA ratio increases during cancer development due to increased epithelial cell proliferation as PSA is secreted by the epithelial cells of the prostate gland (Pientala et al., 2016).

Test that are now used might lead to false positive and negative diagnosis. Because of this, multiparametric MRI (mpMRI) potential as a diagnostic tool. mpMRI gives the best anatomic imaging of the prostate gland. mpMRI has two anatomic sequences, T1 and T2 weighted. T1 weighting is useful for detecting hemorrhage of the biopsy. T2 in turn provides the highest soft tissue resolution for tumor visualization (zonal anatomy, capsule, neurovascular bundles, anterior fibrous stroma, and seminal vesicles). Decision to undergo active surveillance or treatments is based on multiple factors, like serum PSA, Gleason score and PSA density. However, mpMRI can be used when aggressiveness and risk stratification is made. (Turkbey and Choyke, 2012) Also, prostate specific membrane antigen (PSMA) can be used as a marker during prostate cancer diagnosis. PSMA is one of the most specific cell surface markers for prostate cancer diagnosis and targeted treatment. It plays important roles in many physiological processes like signal transduction, receptor function, nutrient uptake and cell migration. PSMA expression increases while androgen receptor is down regulated. This increased expression can be associated with tumor grade, pathologic state, high Gleason score and PSA recurrence. Development of PSMA-targeted protein, like ProCA32, MRI contrast agents are expected to have applications in the molecular imaging in early stages of prostate cancer and further with drug treatment effects by noninvasive evaluation of the PSMA level using MRI. (Pu et al., 2016)

Some additional guidelines

- We do not expect any coding or real experiments
- Only sketching a project idea (according to the template)
- Build on, extend, or combine previous research reported in the literature (start brainstorming early with your teammates)
- For those of you that have limited knowledge about biology and pathology of brain or want to refresh their knowledge, we recommend the free Coursera course <https://www.coursera.org/learn/neurobiology>, especially the lecture on brain tumors.
- Suggested links to start with:
 - Aldape K et al. Challenges to curing primary brain tumors. Nat Rev Clin Oncol 2019;16:509-520. [[link](#)]
 - Louis DN et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: A Summary. Acta Neuropathol 2016;131(6):803-820. [[link](#)]
- Then, browse <https://github.com/MMIV-ML/ELMED219-2022/blob/main/project/README.md>
- Report due: Monday, January 24th in the afternoon

Challenges to curing primary brain tumours

K. Aldape et al.

A precision medicine approach to the treatment and management of patients with brain tumours

Serving as a ‘biological prism’, the use of artificial intelligence (AI) and machine learning (ML) approaches should enable the integration of separate data streams at critical points in the patient journey, providing an unprecedented level of comprehensive decision-making to guide the selection of the most appropriate treatment and support the management of patients with brain tumours.

The knowledge gained through the management of each patient should be analysed iteratively over time, enabling constant refinement and improvements in clinical decision-making.

ctDNA = circulating tumour DNA

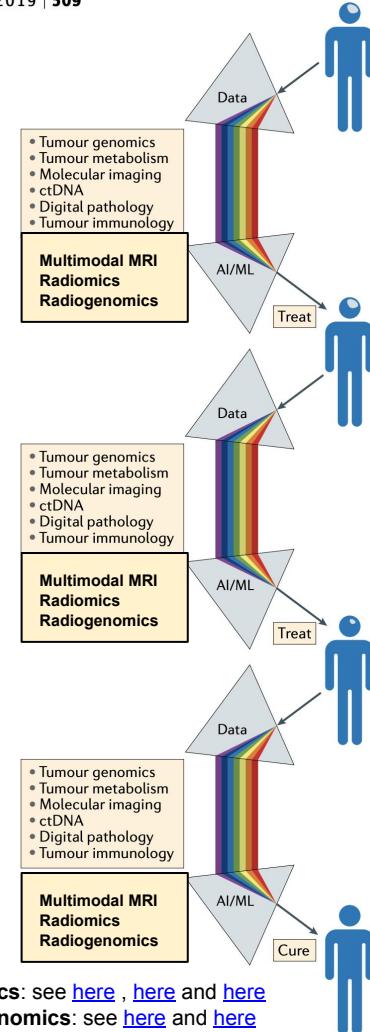
In addition to developing advanced diagnostic approaches, we must also learn how best to integrate these rich data streams if they are to revolutionize the treatment of patients with cancer.

Continual, iterative and integrated analysis of these complementary and complex data streams should be made possible by machine learning, artificial intelligence and/or other mathematical and computational approaches.

This will require a concerted effort to invent and deploy new analytical approaches and visualization technologies in order to generate a single flow of information that travels with a patient throughout his or her treatment journey, enabling better-informed management decisions and guiding the patient towards the maximum opportunity for cure (Fig. right).

Reporting the clinically relevant findings from such large-scale data sets to health-care professionals and patients will require a multidisciplinary approach, supported by appropriate information technology infrastructure, genetic counsellors, medical geneticists and clinical scientists.

This longitudinal and integrated approach will also enable the development of the next generation of adaptive precision medicine clinical trials.



Radiomics: see [here](#), [here](#) and [here](#)
Radiogenomics: see [here](#) and [here](#)

Molecular biology / sequencing focus:

Cancer Cell

ARTICLE | VOLUME 35, ISSUE 4, P692-704.E12, APRIL 15, 2019

Evolutionary Trajectories of IDH^{WT} Glioblastomas Reveal a Common Path of Early Tumorigenesis Instigated Years ahead of Initial Diagnosis

Verena Körber • Jing Yang • Pankaj Barah • ... Guido Reifenberger • Thomas Höfer • Peter Lichter
Peter Lichter 17 Show all authors • Show footnotes

Open Archive • Published: March 21, 2019 • DOI: <https://doi.org/10.1016/j.ccr.2019.02.007>

Check for updates

[https://www.cell.com/cancer-cell/fulltext/S1535-6108\(19\)30102-3](https://www.cell.com/cancer-cell/fulltext/S1535-6108(19)30102-3)

Many tumors consist of genetically diverse subclones, which are thought to reflect cancer evolution. Indeed, we uncover large genetic diversity in primary and recurrent aggressive IDH-wild-type glioblastomas. Surprisingly, however, all these diverse tumors (which belong to four distinct DNA methylation subgroups) map onto a common path of early tumorigenesis where characteristic driver mutations are acquired by losses or gains of (parts of) chromosomes. Mutation rates suggest that these tumor-initiating events occur several years before diagnosis. Other common drivers, including TERT promoter mutations, often follow and may allow the tumor to grow to detectable size. Further genetic diversification may contribute little to the regrowth of the tumors after therapy.

We studied how intratumoral genetic heterogeneity shapes tumor growth and therapy response for isocitrate dehydrogenase (IDH)-wild-type glioblastoma, a rapidly regrowing tumor. We inferred the evolutionary trajectories of matched pairs of primary and relapsed tumors based on deep whole-genome-sequencing data. This analysis suggests both a distant origin of de novo glioblastoma, up to 7 years before diagnosis, and a common path of early tumorigenesis, with one or more of chromosome 7 gain, 9p loss, or 10 loss, at tumor initiation. TERT promoter mutations often occurred later as a prerequisite for rapid growth. In contrast to this common early path, relapsed tumors acquired no stereotypical pattern of mutations and typically regrew from oligoclonal origins, suggesting sparse selective pressure by therapeutic measures.

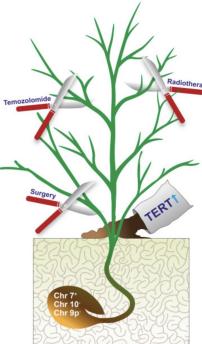
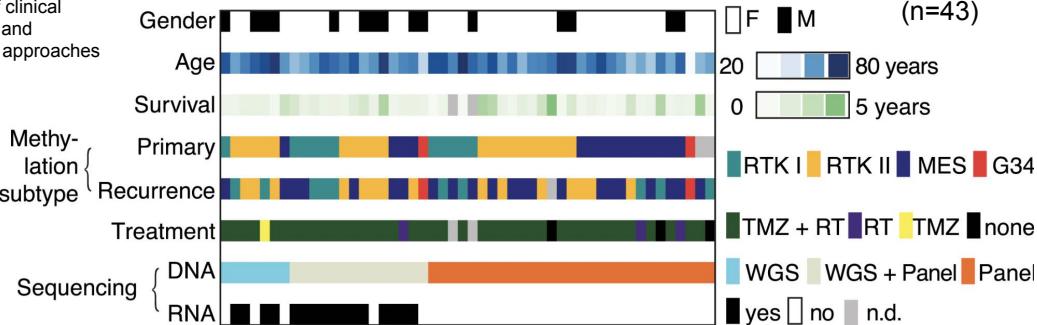
IDH^{WT} = [isocitrate dehydrogenase wild-type](#) glioblastoma

[STAR Methods](#) format (Structured, Transparent, Accessible Reporting)

TERT = [Telomerase reverse transcriptase](#)

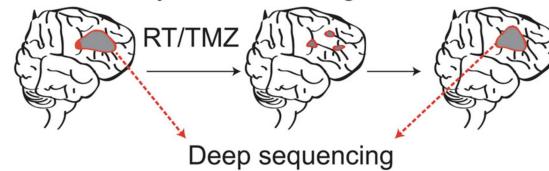
RT / TMZ = [radiotherapy](#) / [temozolomide](#)

Overview of clinical parameters and sequencing approaches

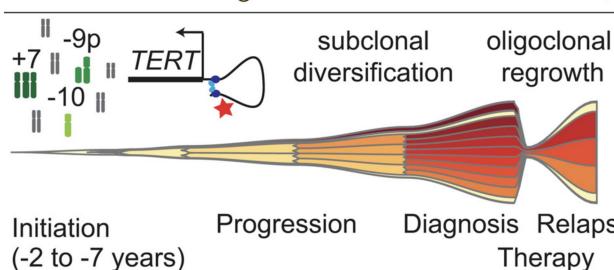
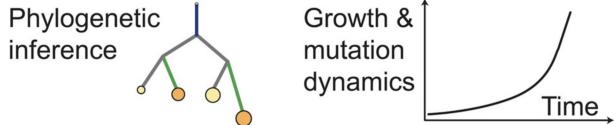


Tumor initiation occurs several years before diagnosis with one of three key chromosome-level mutations, but a detectable GBM does not form until a survival-promoting mutation fuels tumor growth. Standard treatment of surgery, radiotherapy, and temozolamide does not produce a clear evolutionary bottleneck causing it to slow progression rather than to provide curative effects. This is analogous to a plant in which the seed is sowed but does not become observable until the conditions are suitable to enable growth above the earth, at which point current therapeutic interventions act only to prune rather than to eradicate.

Primary and recurrent glioblastomas



Phylogenetic inference



[https://www.cell.com/cancer-cell/fulltext/S1535-6108\(19\)30154-0](https://www.cell.com/cancer-cell/fulltext/S1535-6108(19)30154-0)



FLAIR

cT1-w

aparc+aseg (T1-w)

4chn HD-GLIO

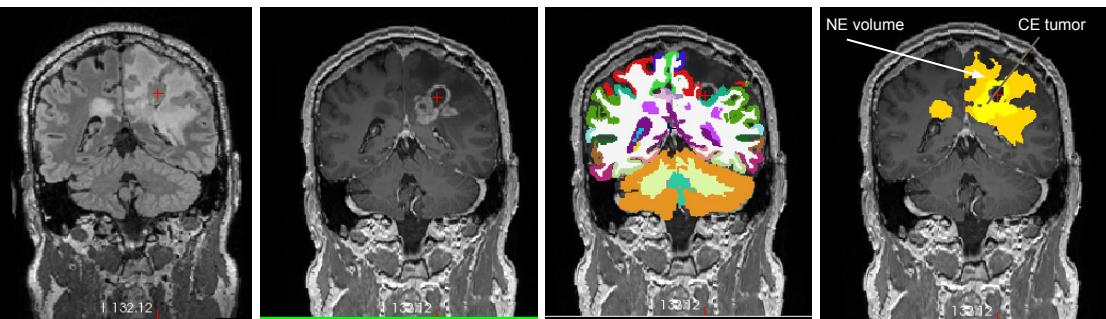
Sequential bortezomib and temozolomide treatment promotes immunological responses in glioblastoma patients with positive clinical outcomes: A phase 1B study

Mohummad A. Rahman¹ | Jorunn Brekke^{1,2} | Victoria Arnesen¹ |
Marianne H. Hannisdal² | Andrea G. Navarro¹ | Andreas Waha³ |
Lars Herfindal⁴ | Cecilie B. Rygh⁵ | Eirik Bratland⁶ | Petter Brandal⁷ |
Judit Haasz⁵ | Leif Oltedal⁵ | Hrvoje Miletic⁸ | Arvid Lundervold^{1,5} |
Stein A. Lie⁹ | Dorota Goplen² | Martha Chekenya¹

<https://onlinelibrary.wiley.com/doi/10.1002/iid3.315>

Background: Glioblastoma (GBM) is an aggressive malignant brain tumor where median survival is approximately 15 months after best available multimodal treatment. Recurrence is inevitable, largely due to O6 methylguanine DNA methyltransferase (MGMT) that renders the tumors resistant to temozolomide (TMZ). We hypothesized that pretreatment with bortezomib (BTZ) 48 hours prior to TMZ to deplete MGMT levels would be safe and tolerated by patients with recurrent GBM harboring unmethylated MGMT promoter. The secondary objective was to investigate whether 26S proteasome blockade may enhance differentiation of cytotoxic immune subsets to impact treatment responses measured by radiological criteria and clinical outcomes.

Methods: Ten patients received intravenous BTZ 1.3 mg/m² on days 1, 4, and 7 during each 4th weekly TMZ-chemotherapy starting on day 3 and escalated from 150 mg/m² per oral 5 days/wk via 175 to 200 mg/m² in cycles 1, 2, and 3, respectively. Adverse events and quality of life were evaluated by CTCAE and EQ-5D-5L questionnaire, and immunological biomarkers evaluated by flow cytometry and Luminex enzyme-linked immunosorbent assay.



<https://surfer.nmr.mgh.harvard.edu>

<https://github.com/NeuroAI-HD/HD-GLIO>

(A)

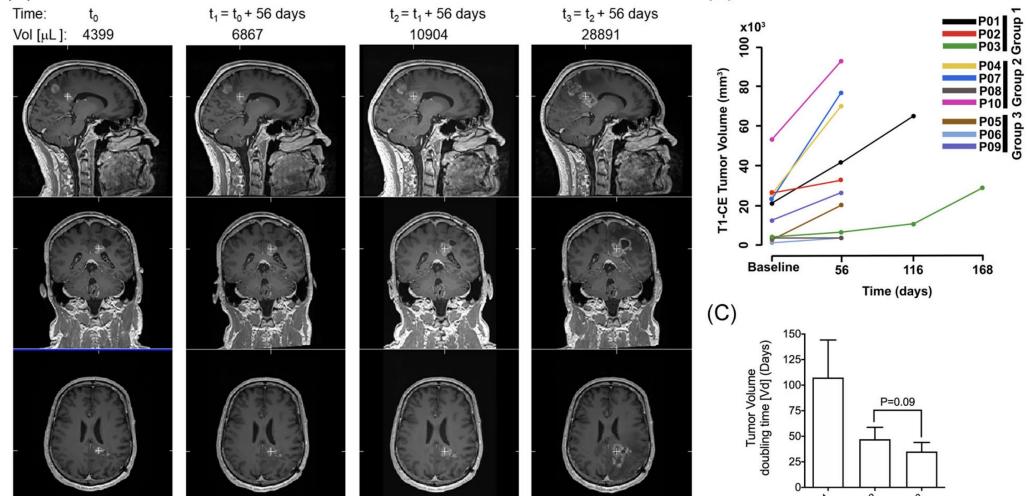


FIGURE 3 Tumour growth and population doubling time. A, Coregistered 3D T1 weighted gadolinium contrast enhanced serial MR image of patient-03 (*IDHwt; MGMT UM, 54 years male*) treated for 6 months, time indicated in days and tumour volume in μL . B, Mean of 3D measured tumour volumes in mm^3 from T1-weighted MR images with contrast of all patients, and (C) tumor population doubling time (in days) for group 1, 2, and 3 patients

K-means clustering of MRI data set from TCGA-GBM

We will be using a four-channel multispectral image (an axial slice from a multispectral 3D recording is shown below), downloaded from the TCGA-GBM data collection - i.e. study TCGA-06-1802. The DICOM images were converted to NIFTI using the [dcm2niix](#) software.

```
1 from IPython.display import Image
2 Image(filename='./assets/TCGA-GBM-dataset.png', width=900)
```

Data Access Detailed Description Citations & Data Usage Policy | Versions

Version 4 (Current): Updated 2020/05/29

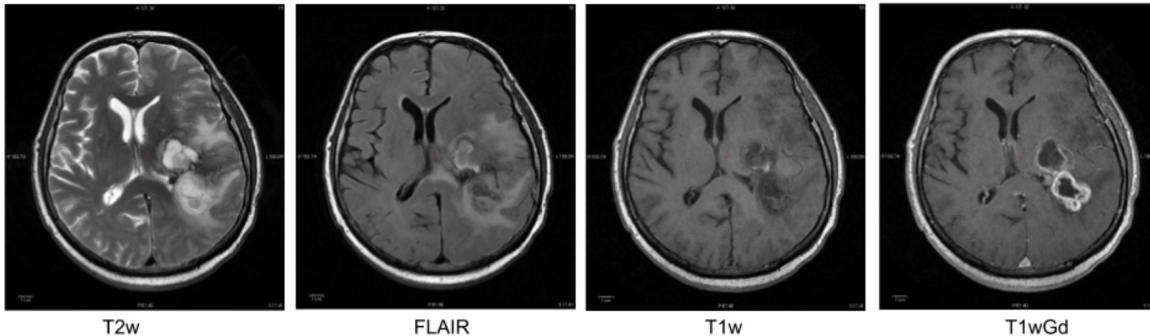
Data Type	Download all or Query/Filter
Images (DICOM, 73.5GB)	<input type="button" value="Download"/> <input type="button" value="Search"/>
Tissue Slide Images (web)	<input type="button" value="Search"/>
Clinical Data (TXT)	<input type="button" value="Download"/>
Biomedical Data (TXT)	<input type="button" value="Download"/>
Genomics (web)	<input type="button" value="Search"/>

Image Statistics

Modality	MR
Number of Participants	262
Number of Studies	575
Number of Series	5,412
Number of Images	481,158
Image Size (GB)	73.5

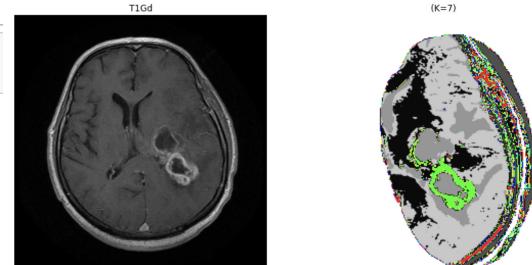
The TCGA-06-1802 data set including metadata
(DICOM images converted to NIFTI format using [dcm2niix](#))

TCGA-06-1802_5_AX_T2_FR-FSE.json
TCGA-06-1802_5_AX_T2_FR-FSE.nii.gz
TCGA-06-1802_6_AX_T2_FLAIR.json
TCGA-06-1802_6_AX_T2_FLAIR.nii.gz
TCGA-06-1802_7_AX_T1_pre_GD_FLAIR.json
TCGA-06-1802_7_AX_T1_pre_GD_FLAIR.nii.gz
TCGA-06-1802_8_AX_T1_POST_GD_FLAIR.json
TCGA-06-1802_8_AX_T1_POST_GD_FLAIR.nii.gz
TCGA-06-1802_clinical.tsv
TCGA-06-1802_exposure.tsv
TCGA-06-1802_family_history.tsv

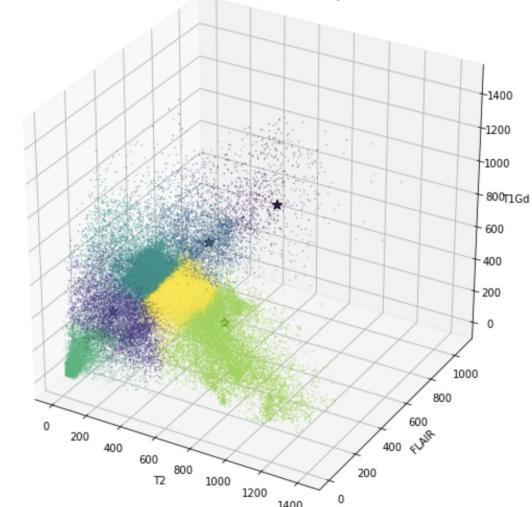


<https://github.com/MMIV-ML/ELMED219-2022/tree/main/project>

The multispectral MRI slice and K-means clustering



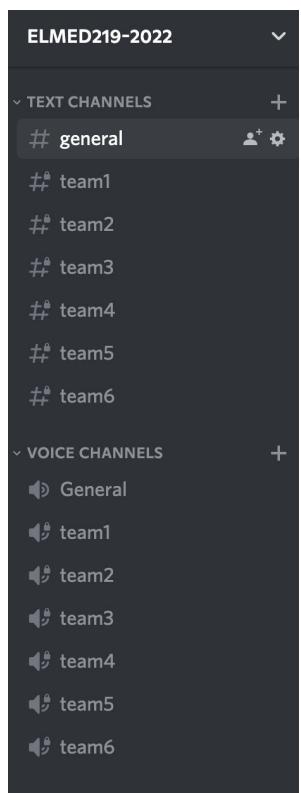
K-means (K=7), n=100000 samples



Good luck with your project and happy learning !



link on MittUiB



Welcome to
ELMED219-2022

This is a brand new, shiny server. Here are some steps to help you get started. For more, check out our [Getting Started guide](#).

- Invite your friends
- Personalize your server with an icon
- Send your first message

alundervold 12/30/2021 Velkommen til ELMED219-2022!

arvidl just slid into the server. 12/31/2021

Wave to say hi!

Yay you made it, Amalie! Yesterday at 1:42 PM

Wave to say hi!

Good to see you, AmalieA. Yesterday at 8:35 PM

Wave to say hi!

Maria O is here. Today at 9:43 AM

Wave to say hi!

ingeborgbry just slid into the server. Today at 10:25 AM

Wave to say hi!

Message #general

alundervold caro Enya Akhtar Gobbles sangi alundervold Amalie AmalieA Ben Bjorsvik Borghild T. Larsen Brodden David_Peter Haldis Tuva HannL herissiv ingeborgbry ingrid1191 Jens Long Nguyen Jencicus KarinaN

What's next?

Tomorrow:

LAB 0: Introduction to some theory and tools for machine learning

Preparatory work:
Watch this 19 minute
video some time today

