A Systematic Review on Efficiency & Effectiveness of Combined drug and therapy with Bevacizumab in Glioblastoma

By

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DECLARATION

It is hereby declared that

1. The thesis submitted is my/our own original work while completing the degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material that has been accepted or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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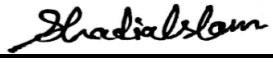

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APPROVAL

The thesis titled "Efficiency & Effectiveness of Combined drug and therapy With Bevacizumab in Glioblastoma" submitted by Shadia Islam Shommo (17146036) of Spring, 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on 15th June 2022.

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ETHICS STATEMENT

This study comprises no animal or human trials.

Abstract

The most frequent and deadly primary malignant cerebral tumor in adults is glioblastoma (GBM). The U.S. Food and Drug Administration has licensed Bevacizumab (BEV) for the treatment of recurrent GBM as it has been shown to increase progression-free survival (PFS). However, the treatment of glioblastoma with the use of combination regimens has been also explored. The aim of this review is to highlight the published data of current literatures and clinical trial researches on the efficacy, safety and toxicity of two or three combination of drug and therapy with Bevacizumab in the treatment of patients with recurrent and newly diagnosed GBM and analyze the outcomes. In this systematic review, through a search of PubMed and Google Scholar, published data for the most recent five years were collected. Progression free survival rate, overall survival rate, time on treatment, adverse effects and death rates were reported accordingly. A total of 15 studies (3 non-randomized (phase II) trial, 6 of randomized (phase I, II and III) trials, 3 of (phase I and II) trials, 11 of (phase II) trials, 1 (phase III) trial were retrieved for a total of 2,007 patients. Based on the available information, bevacizumab and temozolomide are known as first line treatment for glioblastoma multiform. However, there is still a shortage of relevant and sufficient information and data, bevacizumab and temozolomide based treatments are still debatable, despite the fact that certain drug combinations are frequently used in the treatment of glioblastoma.

DEDICATION

Dedicated to my Beloved Parents and My Respected Supervisor Dr. Mohd. Raeed Jamiruddin Sir.

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First and foremost, I am grateful to my Almighty Allah for the sound health and wellbeing during the project which was vital to complete the project work on time. Without the blessing, I would not be able enough to finish my project paper and submit it for my Bachelor's degree in Pharmacy.

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LIST OF ACRONYMS

WHO	World Health Organization
USFDA	United States Food and Drug Administration
NCI	National Cancer Institute
EMA	European Medicines Agency
GBM	Glioblastoma
BEV	Bevacizumab
TMZ	Temozolomide
VEGF	Vascular endothelial growth factor
VEGF-R	Vascular Endothelial Growth Factor Receptor
VEGF-A	Vascular Endothelial Growth Factor Alpha
VEGF-B	Vascular Endothelial Growth Factor B
VEGF-C	Vascular endothelial growth factor C
VEGF-D	Vascular endothelial growth factor C
PFS	Progression Free Survival
OS	Overall Survival
TT	Time on Treatment
RT	Radiotherapy
AE	Adverse Effect
TRAE	Treatment related Adverse Effect
MTD	Maximum Tolerated Dose
RP2D	Recommended Phase 2 Dose
DLT	Dose Limiting Toxicity

Chapter 1: Introduction

1.1 Cancer:

Cancer is a state when some cells in the body become uncontrollably proliferate and spread to other parts of the body. This condition can be started in any of the billions of cells which build up a human body. A process that is called cell division by which the cells of human body start to proliferate and reproduce. When cells get old or wounded, they die and are replaced by new cells. This well-ordered mechanism can occasionally fail, resulting in the growth and multiplication of abnormal or damaged cells. As a result, these cells can develop into tumors, which are detected as lumps in the tissue. Tumors can be benign or cancerous. (*What Is Cancer? - National Cancer Institute*, n.d.).

1.2 Brain cancer:

Brain cancer is a condition when the abnormal or damaged cells of brain starts to proliferate as cancerous cells. Brain cancer may develop from a variety of brain cells or when the cancerous cells begin to expand to the brain (metastasize) from other organs. Brain malignancies that grow within the brain are known as true brain cancers. It is a brain disorder where cancerous cells develop in brain's tissue. Malignant cells expand to develop a tumor, which obstructs brain functions like muscular power, remembrance, consciousness, and various functions of the human body. Cancerous cells form the majority of malignant tumors, whereas noncancerous cells form the majority of benign tumors. Cancerous cells that develop from brain tissue are known as primary brain tumors, however, cancerous cells that migrate from other organ to the brain are known as metastatic or secondary brain tumors. (Davis C.P, 2020.).

According to the National Cancer Institute (NCI) and the American Cancer Society, brain cancer is uncommon (1.4% of all new cancer patients per year), as a result, it is not seen as a frequent ailment. The National Cancer Institute (NCI) and the American Cancer Society estimate that

23,770 new people will be diagnosed with brain cancer each year, with 16,050 deaths. Neurofibromatosis, tuberous sclerosis, and some other inherited genetic illnesses may account for only approximately 5% of brain tumors (Davis C.P, 2020).

Bangladesh is the world's ninth most populous country, with 142 million people. In Bangladesh, there are about 13 to 15 lac cancer patients, with roughly 2 lakh new cancer patients diagnosed each year whereas brain tumors constitute about 2-5% (Hussain, 2013).

There are five types of tumors are known as brain cancers. They are meningiomas, gliomas, pituitary adenomas, vestibular schwannomas, and medulloblastomas. The classification of tumor depends on the appearance of the cell in the microscopy experiment. The rate of cell proliferation is also influenced by the class of the tumor. The National Cancer Institute assigns the following classes:

Class I: In this class, the tissue of the cell appears to be in decent shape. The cells resemble typical brain cells in appearance and form gradually.

Class II: The tissue is infected with cancerous cell. A class I tumor's cells appear normal cells less than a class II tumor's cells.

Class III: In this aggressive class, the appearance of cells in cancerous tissue differs from that of normal cells. The abnormal or damaged cells proliferate at a rapid rate with a distinct appearance (anaplastic).

Class IV: This is the most aggressive class where cells in cancerous tissue appear anomalistic and develop quickly. (Davis C.P, 2020)

1.3 Key Terms in the Treatment of Brain Cancer:

PFS: It is a period of time includes during and after any therapy for a patient lives with a disorder

state, for an example, a patient have cancer, and during that period of time the condition of patient does not worsen. This period of time is called progression free survival.

OS: Overall survival rate indicates that the number of alive patients after a specific period of time who have a disease such as cancer in the trial after any diagnosis or beginning of a treatment. For an example, the seven-year survival rate indicates the number or percentage of participants in a trial who are still alive for seven years after administrating the treatment.

Follow up Time: After any therapy or diagnosis, the certain time when the condition of a patient is being observed is known as follow up time. In a clinical trial for a longer period of time, not only during the therapy but also after the therapy, follow up is needed to track the health state of the participants.

Adverse Effect: The unanticipated medical condition that arises during the course of any medication or other therapy treatment is known as adverse effect. The types of adverse effect can be minor, moderate and severe.

1.4 Glioblastoma:

Glioblastoma (GBM), a brain disease or condition that is appertained to as the astrocytoma of grade IV, is a promptly expanding and invasive cerebral rash. It is a brain disorder where surrounding brain tissues get infiltrated but seldom expands to the other organs. It is a collection of tumors originating from glia of the central nervous system or their progenitor cells. GBM is called glioblastoma because it is a series of tumors that are a mixture of different types of "glial" brain cells and "multiform" means "very diverse." The cell types of these tumors differentiate and they interact closely with normal brain cells such as astrocytes, granulosa cells, microglia, and vascular cells (Holland, 2000). Glioblastoma is the most prevalent kind of primary malignant brain tumor in adults. This is a grade 4 brain tumor and has been graded by the World Health Organization (WHO) based on their histology (microscopic appearance) of the tumor sample (biopsy) (*Glioblastoma Multiforme - Brain Tumour Research*, n.d.). The appearance of tumors on

brain scans can also indicate the type and grade of tumor, but it is not as reliable as examining the cells themselves. Recent studies suggest that GBM originates from self-evolving immature cells rather than from full-blown brain cells or, DNA-damaged stem cells at some point in life during development from stem cells to progenitor cells, or to adult brain cells. The convolution, variety, and prompt growth of GBM tumors mean that it is difficult for researchers to develop effective treatments for patients with this diagnosis (*Glioblastoma Multiforme - Brain Tumour Research*, n.d.)

Glioblastoma is responsible for more than 60% of all adult brain tumors (Hanif et al., 2017). GBMs can strike at any age, however they are most common between the ages of 50 and 70. GBM most typically occurs in the cerebral hemispheres, with 95 percent of cases occurring in the supratentorial region, and less frequently in the brain stem, cerebellum, and spinal cord (Nakada et al., 2011).

GBM is known to be one of the most vascularized human tumors10, with GBM cells producing proangiogenic agents such as VEGF. The VEGF family is developed from the glycoproteins such as VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placenta growth factor. They bind to their tyrosine kinase receptors. The receptors are VEGFR-1, VEGFR-2, and VEGFR-3 which trigger angiogenesis, enhanced vascular permeability, and lymph angiogenesis. VEGF-A (or simply VEGF) is the most significant glycoprotein in tumor angiogenesis, with higher levels in cancer patient (Gil-Gil et al., 2013).

Glioblastoma (GBM) is being treated with a multimodality method that comprises maximal surgical reapportion and radiation as well as concurrent Temozolomide and tributary chemotherapy regimens. A median survival of only 14 to 16 months with a 2-year survival rate of 26–33% has been suggested by the latest clinical trials, despite multimodality therapy. As a result, new therapeutic options to better patient prognosis are urgently needed (Ren et al., 2021). Due to the poor results of current GBM treatments and the disease's widespread nature, a number of ingenious attempts at innovative therapeutic techniques have lately been launched with the goal

of eliminating neoplastic cells far from the tumor itself (Holland, 2000). The intention of this study was by following a meta-analysis of the synchronous or ongoing literatures to investigate the efficacy of the two or three medications or therapies with the drug “Bevacizumab” in combination treatment of GBM in order to assist settle the continuing issue.

1.5 The Drug “Bevacizumab”

Bevacizumab, a humanized monoclonal antibody that fights against the vascular endothelial growth factor (VEGF). The injection of bevacizumab gained expedited endorsement from the US Food and Drug Administration on May 5, 2009. Glioblastoma multiform patients are treated with a single treatment with relapsing disease despite past treatment. For the testing purpose in two trials, the dose of Bevacizumab was 10 mg/kg that was given by intravenous infusion in every 2 weeks. In one study, around 78 patients with GBM were included. In 25.9% of the patients, partial responses were reported (95% CI: 17.0% to 36.1%). The average of feedback time was 4.2 months (95% CI: 3.0 to 5.7 months). In another study, the number of total enrolled GBM patients was about 56. In 19.6% of the patients (95% CI: 10.9% to 31.3%), partial feedbacks were detected with the average counter time of 3.9 months (95% CI: 2.4 to 17.4 months) (Cohen et al., 2009). Since then, bevacizumab has been increasingly used in the treatment of recurrent glioblastoma, with a high response rate on early radiographs and good disease control of the disease. Bevacizumab has also been found in animal models to disrupt glioblastoma cell motility, suggesting that it has direct anti-tumor effect against gliomas that produce VEGF (Li et al., 2017). However, due to a lack of evidence, the European Medicines Agency (EMA) denied that instruction. BEV is popular in part because of this reason. In the United States, the conventional treatment for recurrent GBM is currently being used, however, not is used in Europe; yet, in several European states, off-label usage of bevacizumab as a monotherapy or in combination with other medicines and therapies is frequent. (Yu et al., 2016).

Chapter 2: Methodology

2.1 Search Strategy:

At first, a search of clinical trial was conducted through the year-round from 2015 to 2020. After that another search was conducted though PubMed and Google Scholar to locate the original studies of the clinical trials for this review. In the search bar, the keywords were "Bevacizumab or Avastin for Glioblastoma" or "Bevacizumab drug in the treatment of glioblastoma multiform" or "Different drugs combination or therapy with Bevacizumab in the treatment of glioblastoma" or "adverse effects of different drug combination with Bevacizumab "safety and efficacy of combination of other drugs, therapies with Bevacizumab in glioblastoma treatment". However, the search was limited to clinical trials with results (randomized or not randomized controlled trials), review articles, and articles brought out in English. Data and relevant information were collected from the clinical trials. The percentage of the most common adverse effects and mortality rate of the combination of drugs with bevacizumab were also taken for the consideration from the clinical trials and original articles. Moreover, abstracts from noticeable cancer conferences which found in PubMed and Google Scholar search results were taken into consideration to collect the relevant data. If the duplicate publications were found then only the most recent, complete and updated one was taken to the consideration.

2.2 Inclusion Criteria:

The inclusion criteria of this study were as follows: (i) The patients with glioblastoma or glioblastoma multiform (ii) Clinical trials which are randomized controlled, non-randomized or interventional study type from Phase I to Phase III (iii) Clinical trials which are completed with result (iv) Clinical trials that reported progression free survival rate (PFS), overall survival rate (OS) and the time on treatment or follow up time. (v) Participants who administered Bevacizumab in the treatment of glioblastoma (vi) Participants exposed to various combination of drugs or

therapies associated with Bevacizumab.

2.3 Exclusion criteria:

Exclusion criteria for this study included the following: (i) Clinical trials which are not being completed yet and have not results (ii) If any study or trial that did not provide outcomes for PFS, OS and follow up time or time to progression were undertaken the exclusion because of the insufficiency of the data and information. (iii) Only the latest publications from the same laboratory for several years were included in the analysis to rule out patient duplication. (iv) if the article was not published in English.

2.4 Selection of Trials:

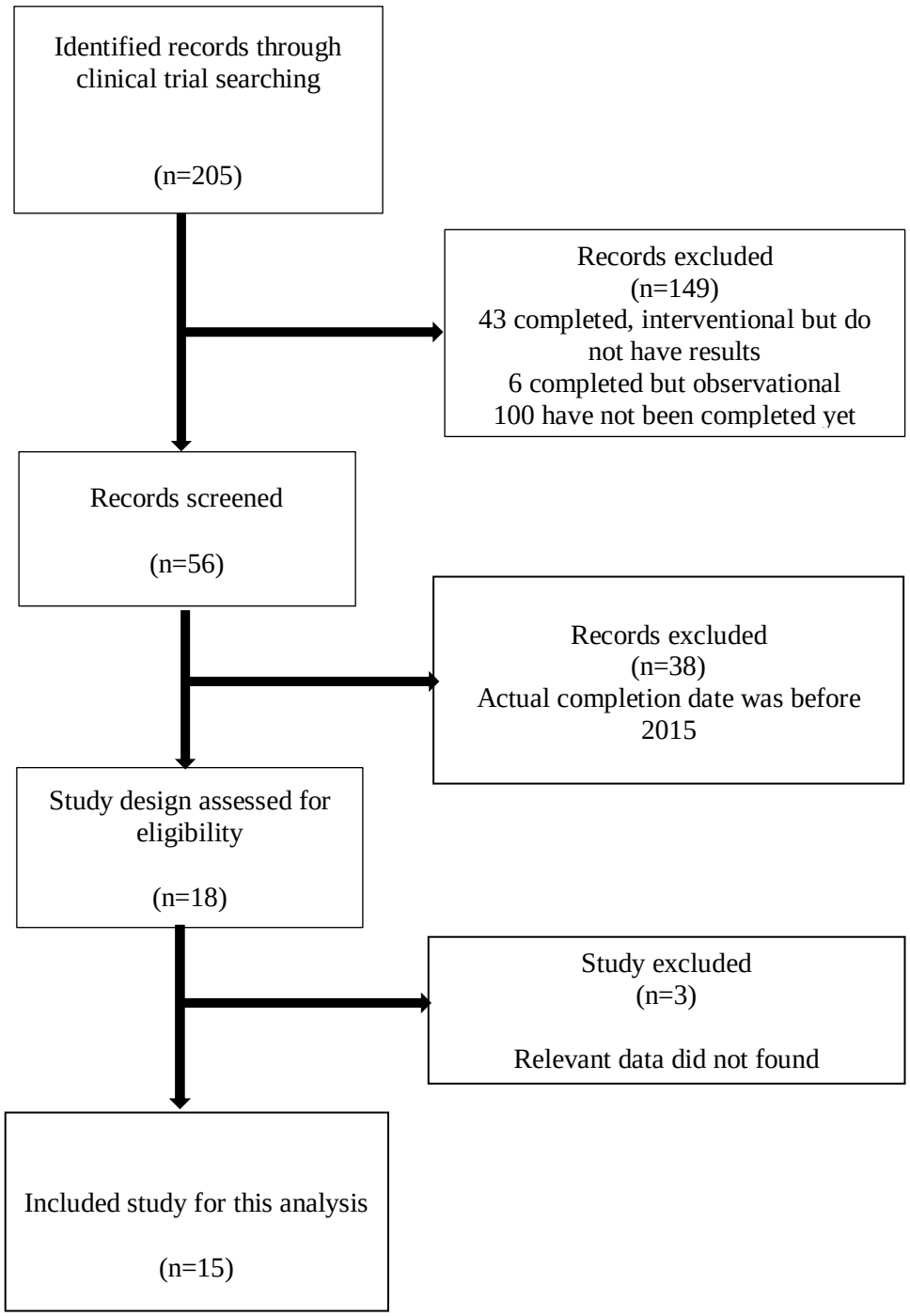
In this study, a total of 15 studies were finally selected that linked several combinations of drugs or therapy with Bevacizumab for glioblastoma treatment. (Bevacizumab + BKM120 (oral inhibitor of PI3 kinase), Bevacizumab + Vorionstat, Bevacizumab + TRC 105, Bevacizumab + TH- 302 (Evofosfomide), Bevacizumab + Dasatinib (Placebo), Bevacizumab + Magnetic Radiosurgery, Bevacizumab + Lomustine, Bevacizumab +/- Pembrolizumab, Bevacizmumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy, Bevacizumab + Erlotinib Hydrochloride, Bevacizumab + Vorionstat, Bevacizumab + Durvalumab + Standard Radiotherapy, Bevacizumab + AMG 102, Bevacizumab + Temozolomide + Hypofractionated RT, Bevacizumab + RT + Temozolomide + Placebo).

2.5 End Points:

This study or analysis included two forms of end points. One is major end point and other one is minor end point. The major ending of this analysis was the cumulation and summarization of median (PFS) progression free survival rate, median of overall survival rate (OS), reclaiming these data and the most common adverse effects of different combination of drugs and therapies from

the published article. Evaluation and contrasting the safety and efficacy of multiple combinations of treatment and scrutinize the reported toxicities such as diarrhea, vomiting, wound infection, urinary tract infection etc incorporated with bevacizumab was the secondary end point.

2.6 Flowchart for the included trials:



Chapter 3: Result:

Out of 205 studies, 56 studies were eligible as these studies were completed with results. After screening the full text study description, study design and result, only 18 studies were eligible for this systematic review article. In the meantime, 3 of studies were not considered because of the lack of sufficient relevant information. Therefore, finally, a total of 15 studies were selected for this systematic review article.

3.1 Characteristics of Included Trials:

Table. 1 Combinations of Drug & Therapy and Characteristics of Included Trials:

SL NO	Combinations	Phase	Study Purpose	Study Allocation	Actual Completion Date/Year	No. of patient/Age/ Sex	ClinicalTrials.gov Identifier
1.	Bevacizumab + BKM120 (oral inhibitor of PI3 kinase)	Phase 1 Phase 2	Treatment	N/A	29-Dec-18	88 participants /18 Years and older/All sex	NCT01349660
2.	Bevacizumab + Vorionstat	Phase 1 Phase 2	Treatment	Randomized	31-Jan-17	96 participants /18 Years to 99 Years/All sex	NCT01266031
3.	Bevacizumab + TRC 105	Phase 1 Phase 2	Treatment	Randomized	15-Apr-17	116 participants /18 Years and older/All sex	NCT01648348
4.	Bevacizumab + TH-302 (Evofosfomide)	Phase 2	Treatment	N/A	4-Dec-19	35 participants /18 Years	

						and older/All sex	NCT02342379
5.	Bevacizumab + Dasatinib (Placebo)	Phase 2	Treatment	Randomized	1-Jul-19	144 participants /18 Years and older/All sex	NCT00892177
6.	Bevacizumab + Magnetic Radiosurgery	Phase 2	Treatment	Non-Randomized	31-Mar-18	16 participants /18 Years and older/All sex	NCT02120287
7.	Bevacizumab + Lomustine	Phase 2	Treatment	Randomized	Oct-16	83 participants /18 Years and older/All sex	NCT01067469
8.	Bevacizumab +/- Pembrolizumab	Phase 2	Treatment	Randomized	14-Sep-20	80 participants /18 Years and older/All sex	NCT02337491
9.	Bevacizmumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation RT	Phase 2	Treatment	N/A	3-Feb-17	30 participants /18 Years and older/All sex	NCT01209442
10.	Bevacizumab + Erlotinib Hydrochloride	Phase 2	Treatment	N/A	5-Jul-18	115 participants /18 Years and older/All sex	NCT00720356

11.	Bevacizumab + Vorionstat	Phase 2	Treatment	Non-Randomized	Feb-16	48 participants /18 Years and older/All sex	NCT01738646
12.	Bevacizumab + Durvalumab + Standard Radiotherapy	Phase 2	Treatment	Non-Randomized	6-Jul-21	159 participants /18 Years and older/All sex	NCT02336165
13.	Bevacizumab + AMG 102	Phase 2	Treatment	N/A	Sep-15	36 participants /18 Years and older/All sex	NCT01113398
14.	Bevacizumab + Temozolomide + Hypofractionated RT	Phase 2	Treatment	N/A	Mar-17	40 participants /18 Years and older/All sex	NCT00782756
15.	Bevacizumab + RT + Temozolomide + Placebo	Phase 3	Treatment	Randomized	9-Sep-15	921 participants /18 Years and older/All sex	NCT00943826

Table 1 it depicted the characteristics of the included trials of this review. It showed that, 3 of non-randomized (phase II) trials, 6 of randomized (phase I, II and III) trials, 3 of (phase I and II) trials, 11 of (phase II) trials, 1 (phase III) trial were included in this analysis for 2,007 of total participants who were treated with bevacizumab and other drug and therapy combination for the treatment of

glioblastoma. The type of total 15 studies was interventional and the primary purpose was treatment. The number of patient in each trial was ranged from 16 to 921 and the age was ranged from 18 years to older. The clinical trial identifiers from which the data was collected were also showed in this table.

3.2 Efficacy of The Combined Regimens:

Table 2: Responses to The Treatments

Author, Year	Combinations	Median Age	Median OS	Median PFS	Median Time on Treatment
(Hainsworth et al., 2019)	Bevacizumab + BKM120 (oral inhibitor of PI3 kinase)	57 years (19–82) Female 48 (55%) Male 40 (45%)	10.8 months (95% CI 9.2, 13.5)	4.0 months (95% CI 3.4, 5.4)	10 months
(ClinicalTrials.gov, n.d.) (Beer et al., 2019)	Bevacizumab + Vorionstat	N/A	8.11 months (95% CI: 6.18, 9.63)	3.71 months (95% CI: 2.79, 4.21)	19.84 months
(Curry et al., 2015) (Liu et al., 2021)	Bevacizumab + TRC 105	N/A	N/A	1.81 months (95% CI: 1.25—2.07)	N/A
(Briskin et al., 2015)	Bevacizumab + TH- 302 (Evofosfomide)	56 years and 14 (61%) were male	4.6 months	3.8 months	4.41 months
(Galanis et al., 2019) (Cloughesy et al., 2017)	Bevacizumab + Dasatinib	57 years (18.0-79.0)	7.7 months [95% CI, 0.64-1.43]	3.2 months [95% CI, 0.53-1.19]	16.3 months
(Ml, 2016)	Bevacizumab + Magnetic Radiosurgery	N/A	18.1months (95% CI: (17.0,19.6)	15 months	12 months
(Weathers et al., 2016) (Brandes et al., 2019)	Bevacizumab + Lomustine	N/A	9.6 months (95% CI 6.26–16.73)	4.3 months, CI 2.96, 8.34)	N/A
(Nayak et al., 2021)	Bevacizumab +/- Pembrolizumab	52 years (42, 59)	8.8 months (95% CI: 7.7; 14.2)	4.1 months (95% CI:	48.6 months (95% CI:

				2.8; 5.5)	48.6)
(Ney et al., 2015)	Bevacizmumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy RT	57 years (31–78)	16.3 months (95.0 % CI, 12.4–15.8)	14.3 months (95.0 % CI, 13.2–17.2)	24.0 months (10.5–34.7) months
(Raizer et al., 2016)	Bevacizumab + Erlotinib Hydrochloride	55.5 years (29–75)	13.2 months [95 % CI (10.8, 19.6)	9.2 months [95 % CI (6.4, 11.3)	33 months
(Ghiaseddin et al., 2018)	Bevacizumab + Vorionstat	52.4 years (32–74 years)	10.4 months (95% CI 7.6–12.8)	3.7 months (95% CI 2.9-4.8)	23.3 months (95% CI 21.0–32.0)
(Autoridad Nacional del Servicio Civil, 2021)	Bevacizumab + Durvalumab + Standard Radiotherapy	57.0 years [40–74]	15.1 (95% CI: 12.0, 18.4)	N/A	24.5 months
(Affronti et al., 2018)	Bevacizumab + AMG 102	55.5 years (27–74)	11.2 months (95% CI: 7–17.5)	4.8 months (95% CI: 2.7–7.1)	65.0 months
(Omuro et al., 2014)	Bevacizumab + Temozolomide + Hypofractionated RT	55 years (17–75)	19 months (95% CI, 15–23)	10 months (95% CI, 8–11)	42 months
(Chinot et al., 2014) (Taphoorn et al., 2015)	Bevacizumab + RT + Temozolomide + Placebo	57 years (20-84)	16.8 months	10.6 months	16.3 months

Table 2 depicted the efficacy of the combined regimens which were included in this review. The responses such as median OS (overall survival rate), median PFS (progression free survival rate), median follow up time or time on treatment of the patients to the treatment of all the trials were extracted if they were available.

3.2.1 Median Overall Survival Rate:

Patients who received the treatment of Bevacizumab + Temozolomide + Hypofractionated RT combination, they had the highest median OS among the total 15 of trials which was 19 months (95% CI, 15–23) in comparison to other drug and therapy combinations. In contrast, patients who was under the treatment of the combination of Bevacizumab + TH- 302 (Evofosfomide) had the lowest median OS of 4.6 months. Moreover, in this analysis, patients who received other combination of drug and therapy also showed significant OS which were taken to the consideration. For the combinations of Bevacizumab+BKM120 (oral inhibitor of PI3 kinase), Bevacizumab + Vorionstat, Bevacizumab + Dasatinib (Placebo), Bevacizumab + Magnetic Radiosurgery, Bevacizumab + Lomustine, Bevacizumab +/- Pembrolizumab, Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy, Bevacizumab + Erlotinib Hydrochloride, Bevacizumab + Vorionstat, Bevacizumab + Durvalumab + Standard Radiotherapy, Bevacizumab + AMG 102, and Bevacizumab + RT + Temozolomide + Placebo, the median OS were 10.8 months (95% CI 9.2 to 13.5), 8.11 months (95% CI: 6.18, 9.63), 7.7 months (95% CI, 0.64-1.43), 18.1 months (95% CI: 17.0,19.6), 9.6 months (95% CI 6.26–16.73), 8.8 months (95% CI: 7.7; 14.2), 16.3 months (95.0 % CI, 12.4–15.8), 13.2 months [95 % CI (10.8, 19.6), 10.4 months (95% CI 7.6–12.8), 15.1 months (95% CI: 12.0, 18.4), 11.2 months (95% CI: 7–17.5), 16.8 months respectively. However, it would be worth to mention that for the combination of Bevacizumab + TRC 10, the median OS was not found.

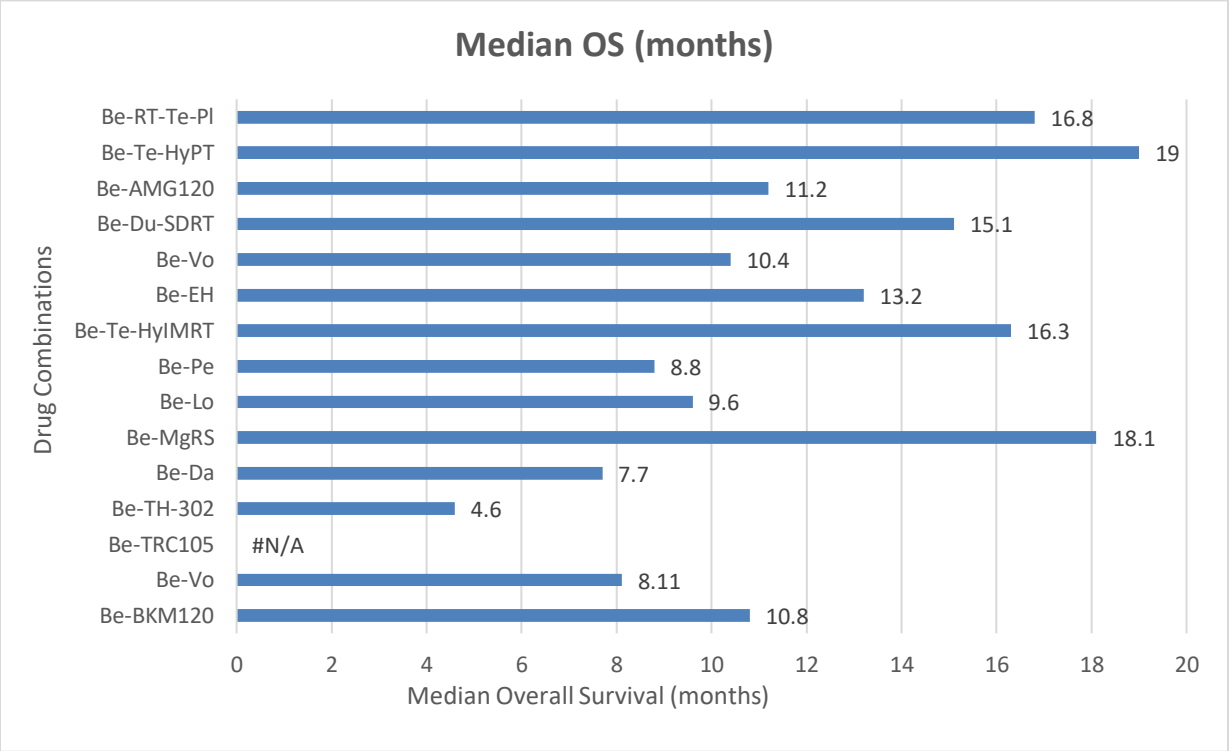


Figure 1: Median overall survival rates for different drug and therapy combinations with Bevacizumab. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). The values are presented as months in the graph.

3.2.2 Median Progression Free Survival Rate:

In terms of PFS, patients who administered the combined regimen of Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy, they showed highest median PFS which was 14.3 months (95.0 % CI, 13.2–17.2) in comparison to other combinations. On the other hand, another group of patients who administered the combinations of Bevacizumab + TRC 105 for the treatment they showed the lowest median PFS of 1.81 months (95% CI: (17.0,19.6) among the total 15 trials. However, patients who received other combination of drug and therapy also showed significant PFS which were also taken to the consideration. Likewise, for the combinations of Bevacizumab+BKM120 (oral inhibitor of PI3 kinase), Bevacizumab + Vorionstat, Bevacizumab + TH- 302 (Evofosfomide), Bevacizumab + Dasatinib (Placebo), Bevacizumab + Magnetic Radiosurgery, Bevacizumab + Lomustine, Bevacizumab +/- Pembrolizumab, Bevacizumab + Erlotinib Hydrochloride, Bevacizumab + Vorionstat, Bevacizumab + AMG 102, Bevacizumab + RT + Temozolomide + Placebo, the median PFS were 4.0 months (95% CI 3.4 to 5.4), 3.71 months (95% CI: 2.79, 4.21), 3.8 months, 3.2 months (95% CI, 0.53-1.19), 7 months, 4.3 months (95% CI 2.96, 8.34), 4.1 months (95% CI: 2.8; 5.5), 9.2 months (95 % CI: 6.4, 11.3), 3.7 months (95% CI: 2.9-4.8), 4.8 months (95% CI: 2.7–7.1) and 10.6 months respectively. Nevertheless, median PFS was not found for Bevacizumab + Durvalumab + Standard Radiotherapy combination.

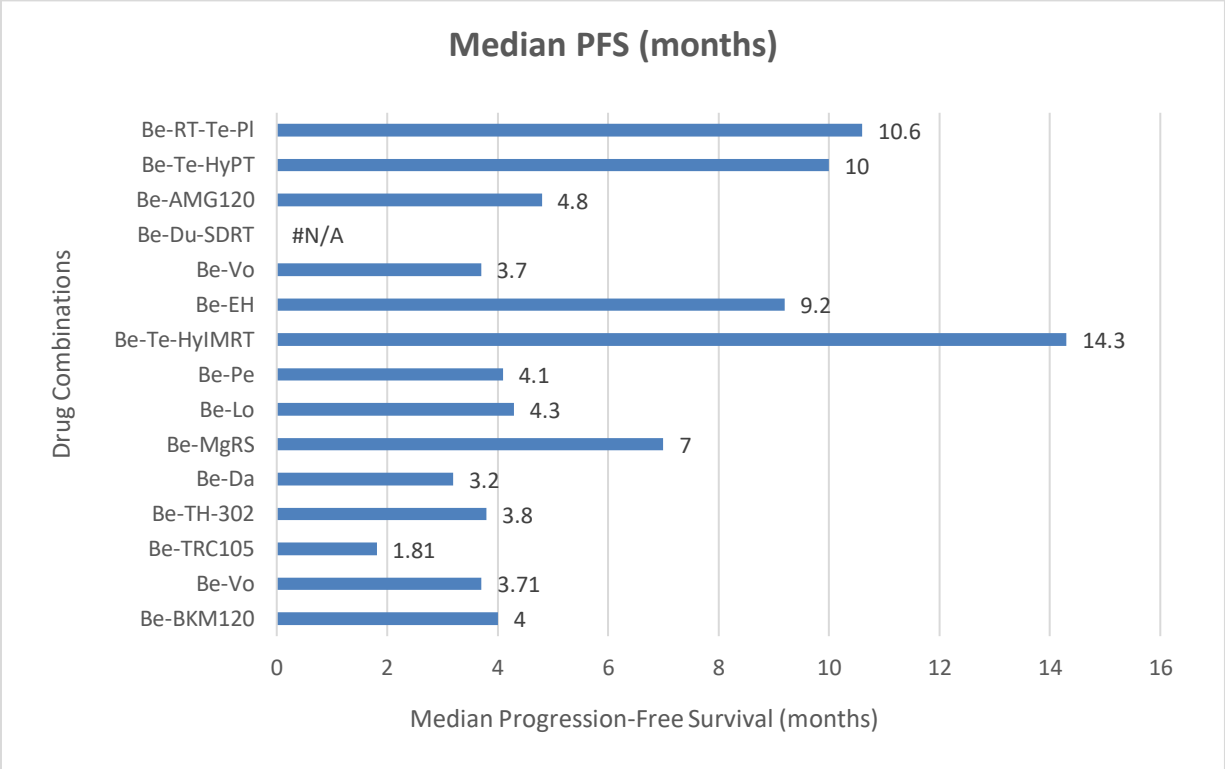


Figure 2: Median progression free survival rates for different drug and therapy combinations with Bevacizumab. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). The values are presented as months in the graph.

3.2.3 Median Time on Treatment:

In case of median time on treatment or follow-up time, the patients who administered the combined regimen of Bevacizumab + AMG 102 was longest which was 65 months and the patients who administered the combined regimen of Bevacizumab + TH- 302 (Evofosfomide) was shortest that was 4.41 months. Median follow up time of other combination of drug and therapy were also taken to the consideration in this analysis. For the combination of Bevacizumab + Lomustine and Bevacizumab + TRC, median time on treatment were not found.

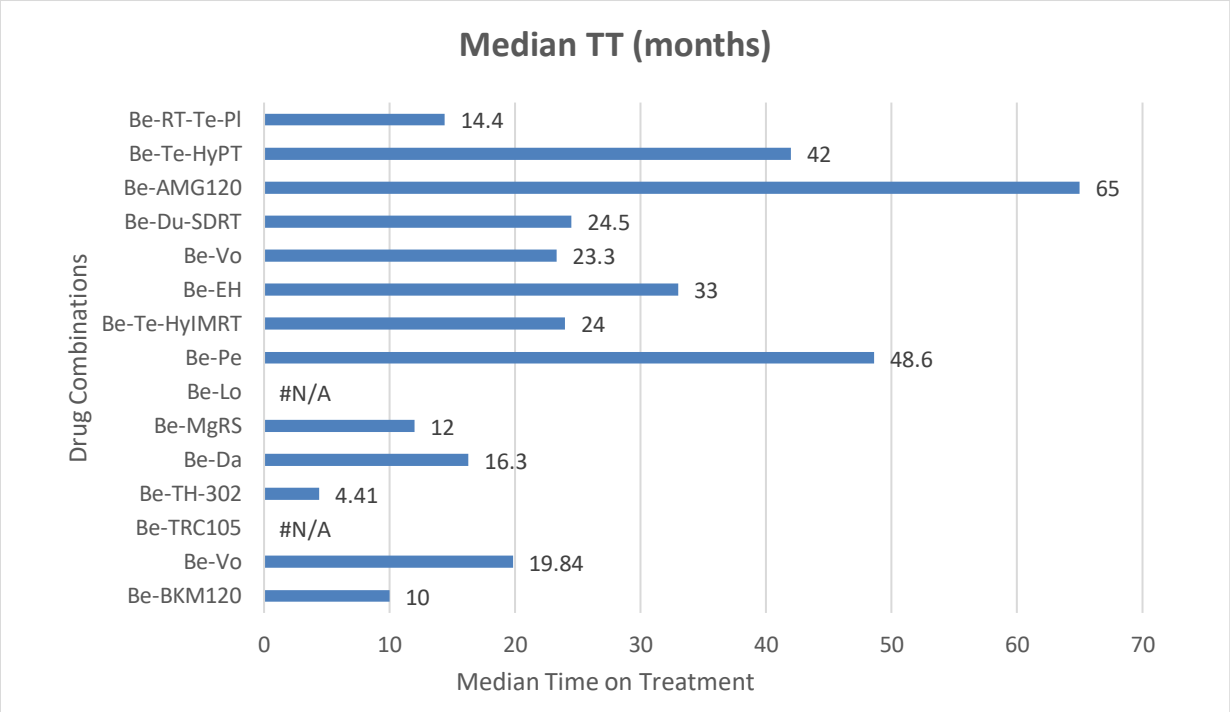


Figure 3: Median time on treatment for different drug and therapy combinations with Bevacizumab. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab +

Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). The values are presented as months in the graph.

3.3 Toxicity of The Treatments:

Table 3: Serious Adverse Effects Rate & Mortality Rate of the Combined Regimens

SL No	Combinations	Serious Adverse Effects Rate	Mortality Rate	ClinicalTrials.gov Identifier
1.	Bevacizumab + BKM120 (oral inhibitor of PI3 kinase)	2/6 (33.33%)	1/47 (2.13%)	NCT01349660
2.	Bevacizumab + Vorionstat	14/47 (29.79%)	2/49 (4.08%)	NCT01266031
3.	Bevacizumab + TRC 105	15/49 (30.61%)	0/35 (0.00%)	NCT01648348
4.	Bevacizumab + TH- 302 (Evofosfomide)	0/35 (0.00%)	N/A	NCT02342379
5.	Bevacizumab + Dasatinib (Placebo)	18/39 (46.15%)	14/16 (87.50%)	NCT00892177
6.	Bevacizumab + Magnetic Radiosurgery	7/16 (43.75%)	1/33 (3.03%)	NCT02120287
7.	Bevacizumab + Lomustine	9/35 (25.71%)	3/50 (6.00%)	NCT01067469
8.	Bevacizumab +/- Pembrolizumab	22/50 (44.00%)	N/A	NCT02337491
9.	Bevacizmumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy RT	3/30 (10.00%)	43/48 (89.58%)	NCT01209442
10.	Bevacizumab + Erlotinib Hydrochloride	15/48 (31.25%)	N/A	NCT00720356
11.	Bevacizumab + Vorionstat	12/40 (30.00%)	10/40 (25.00%)	NCT01738646

12.	Bevacizumab + Durvalumab + Standard Radiotherapy	26/40 (65.00%)	N/A	NCT02336165
13.	Bevacizumab + AMG 102	6/36 (16.67%)	40/40 (100.00%)	NCT01113398
14.	Bevacizumab + Temozolomide + Hypofractionated RT	19/40 (47.50%)	N/A	NCT00782756
15.	Bevacizumab + RT + Temozolomide + Placebo	179/461 (38.83%)	N/A	NCT00943826

Table 3 depicted the toxicities of the treatments. The serious adverse effect rate and the mortality rate of the included trials were illustrated in this table.

3.3.1 Serious Adverse Effect Rates:

Among the total of 15 trials, patients who received Bevacizumab + Durvalumab + Standard Radiotherapy combination had exhibited higher serious adverse events which was 65% (according to NCT02336165). The greatest widespread treatment-related adverse events (TRAEs, in ≥4 with 12.1% participants in each cohort): fatigue, dysphonia, increased ALT, AST, amylase, or lipase, diarrhea, hypertension, arthralgia, headache, and proteinuria (Autoridad Nacional del Servicio Civil, 2021). As well as patients receiving the combination of Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy had exhibited lower adverse events of 10% (according to NCT01209442).

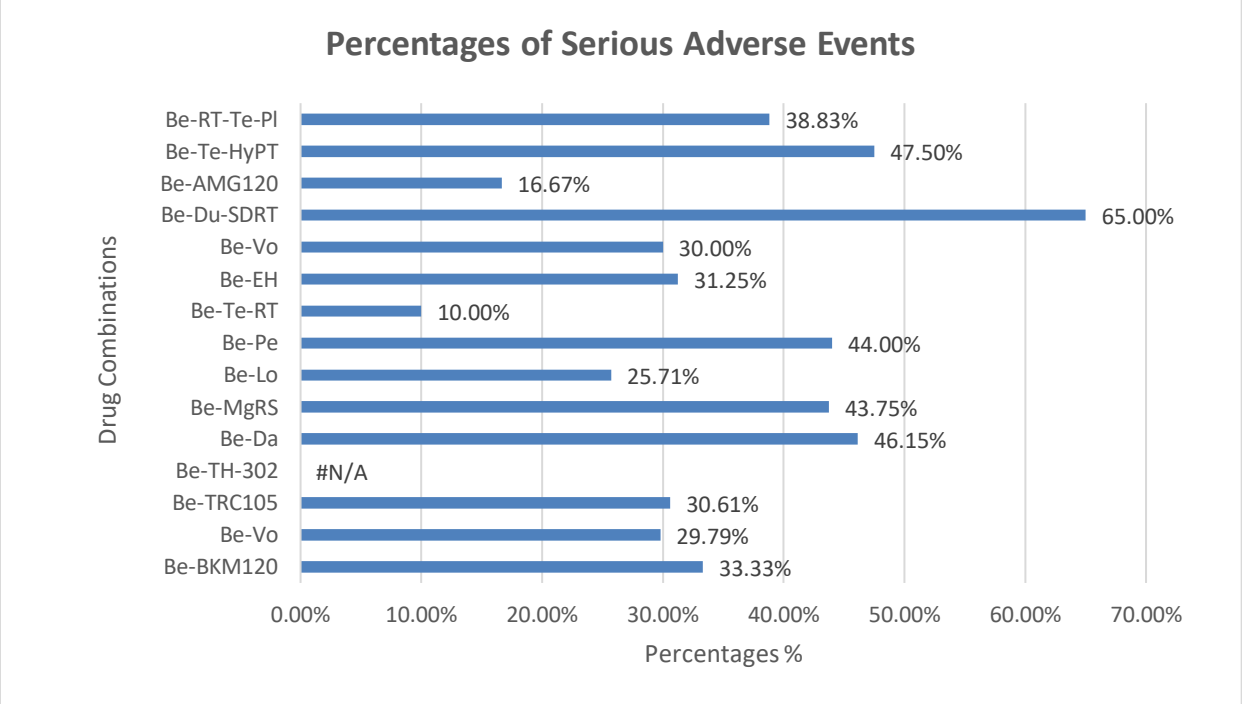
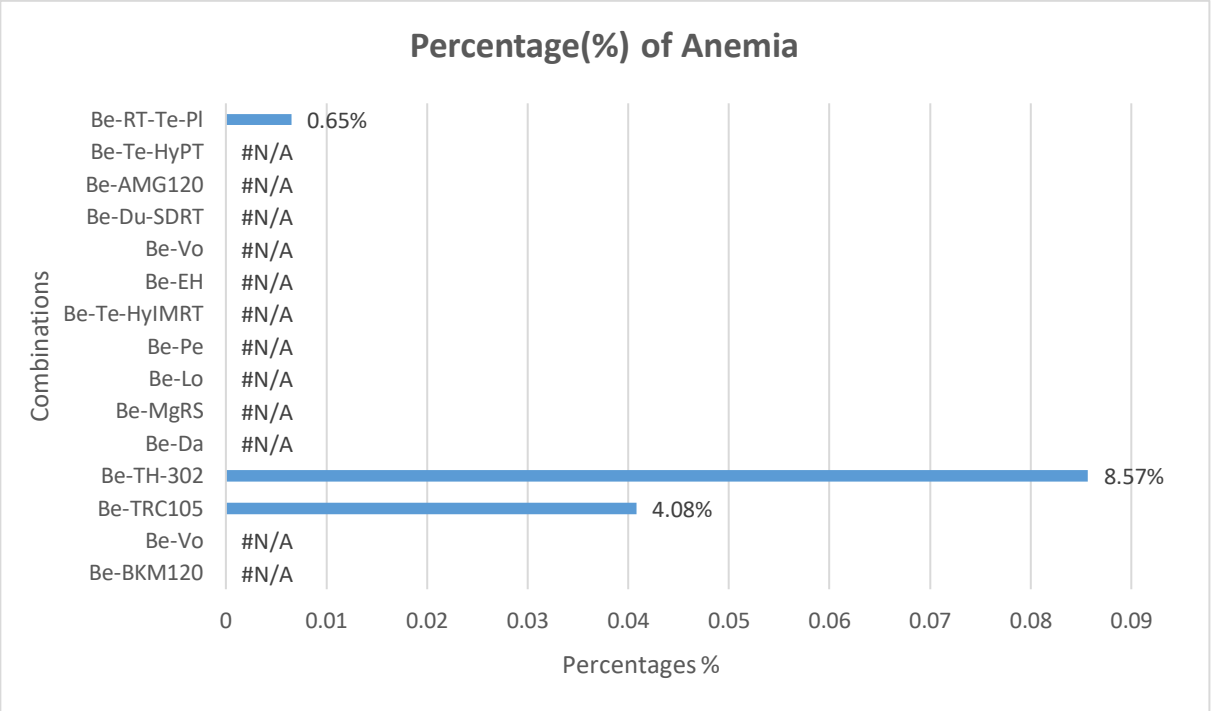


Figure 4: Percentages of serious adverse events for different drug and therapy combinations with Bevacizumab. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab

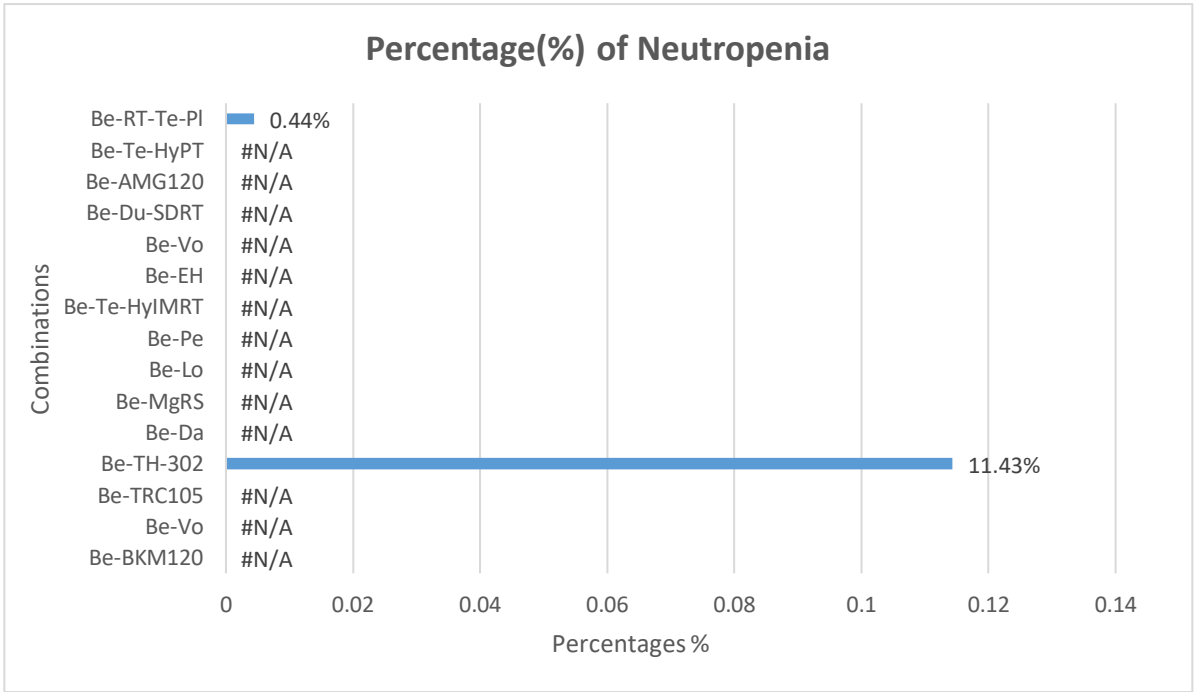
+ Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). The values are presented as percentage in the graph.

Blood and lymphatic system disorders are depicted by the following graphs:

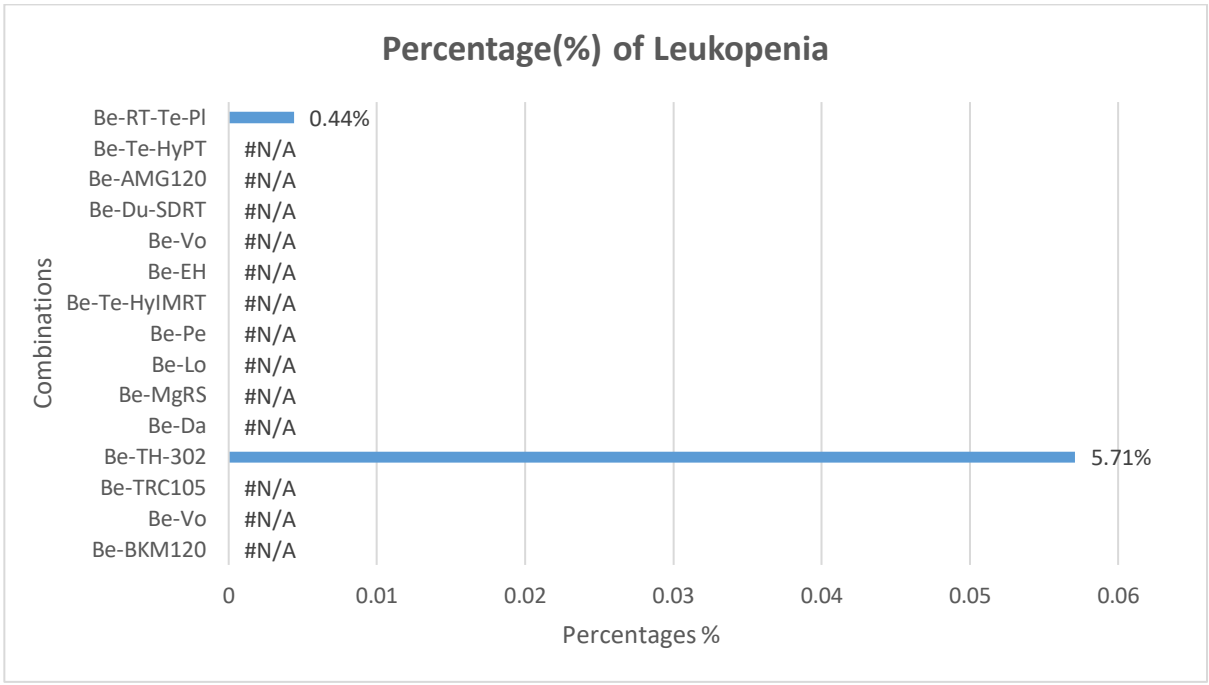
5(A)



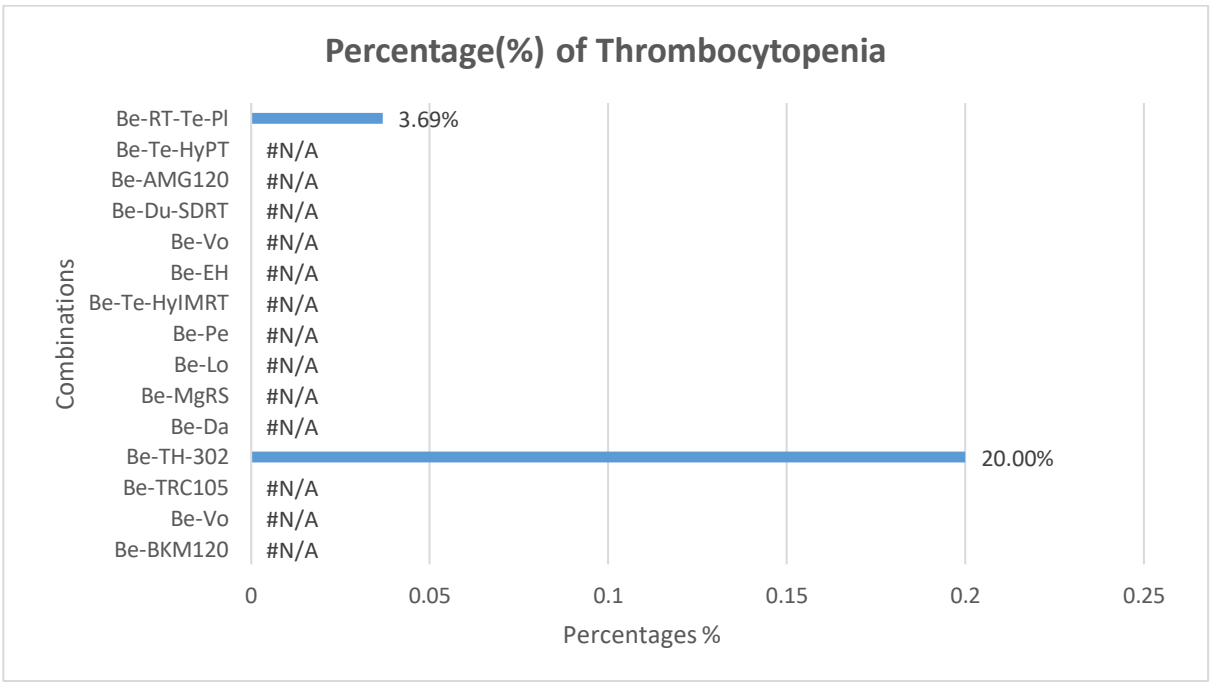
5(B)



5(C)


Percentage(%) of Leukopenia
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
0.44%
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
5.71%
#N/A
#N/A
#N/A
0
0.01
0.02
0.03
0.04
0.05
0.06
Percentages %

5(D)


Percentage(%) of Thrombocytopenia
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
3.69%
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
20.00%
#N/A
#N/A
#N/A
0
0.05
0.1
0.15
0.2
0.25
Percentages %

5(E)

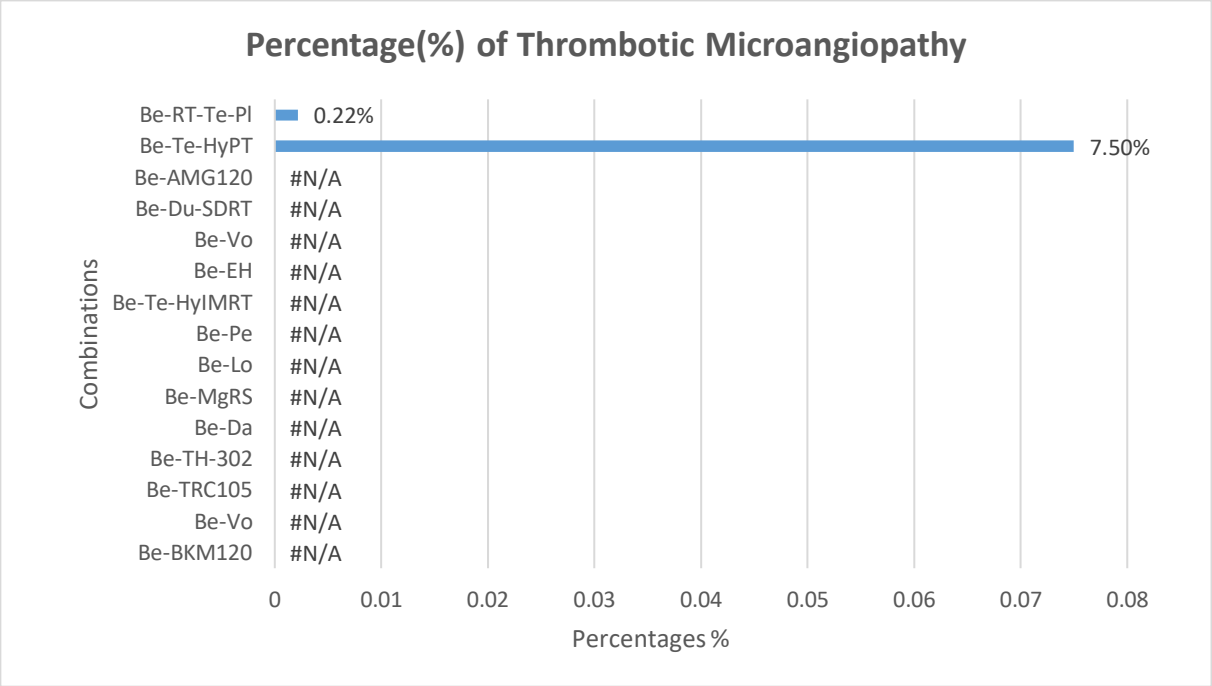
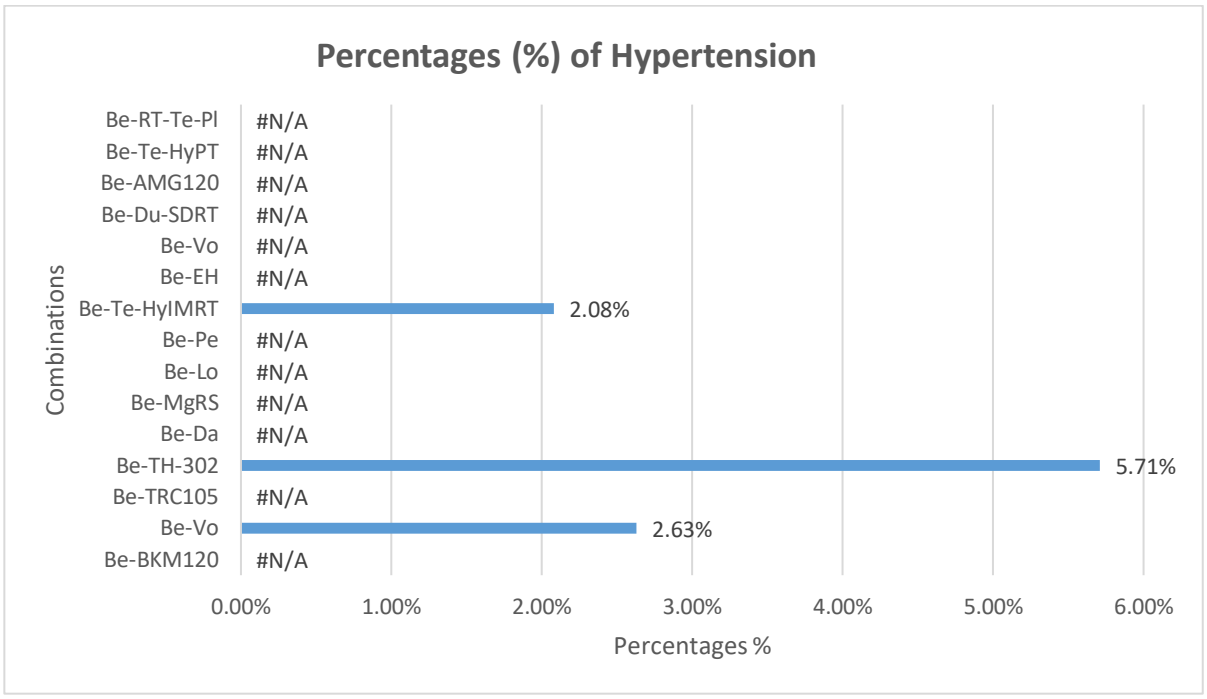


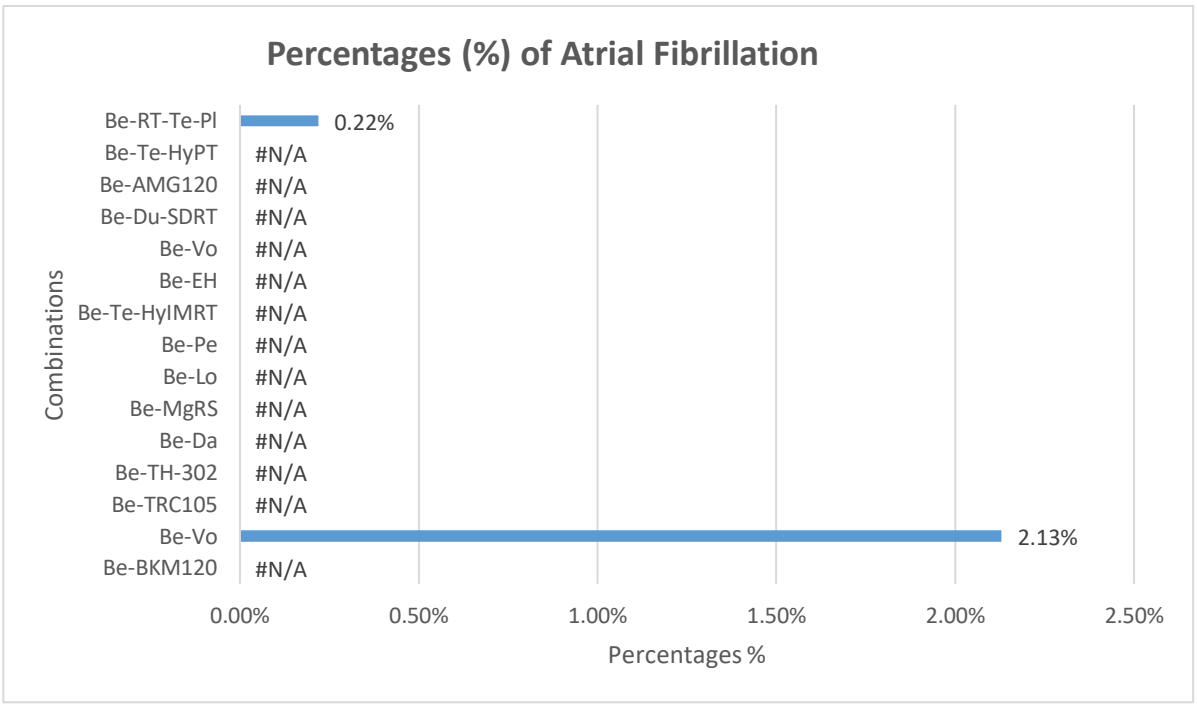
Figure 5: Percentage of blood and lymphatic system disorders in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizmumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Anemia; (B) Neutropenia; (C) Leukopenia; (D) Thrombocytopenia; (E) Thrombotic Microangiopathy. The values are presented as percentages in the graphs.

Cardiac disorders are depicted by the following graphs:

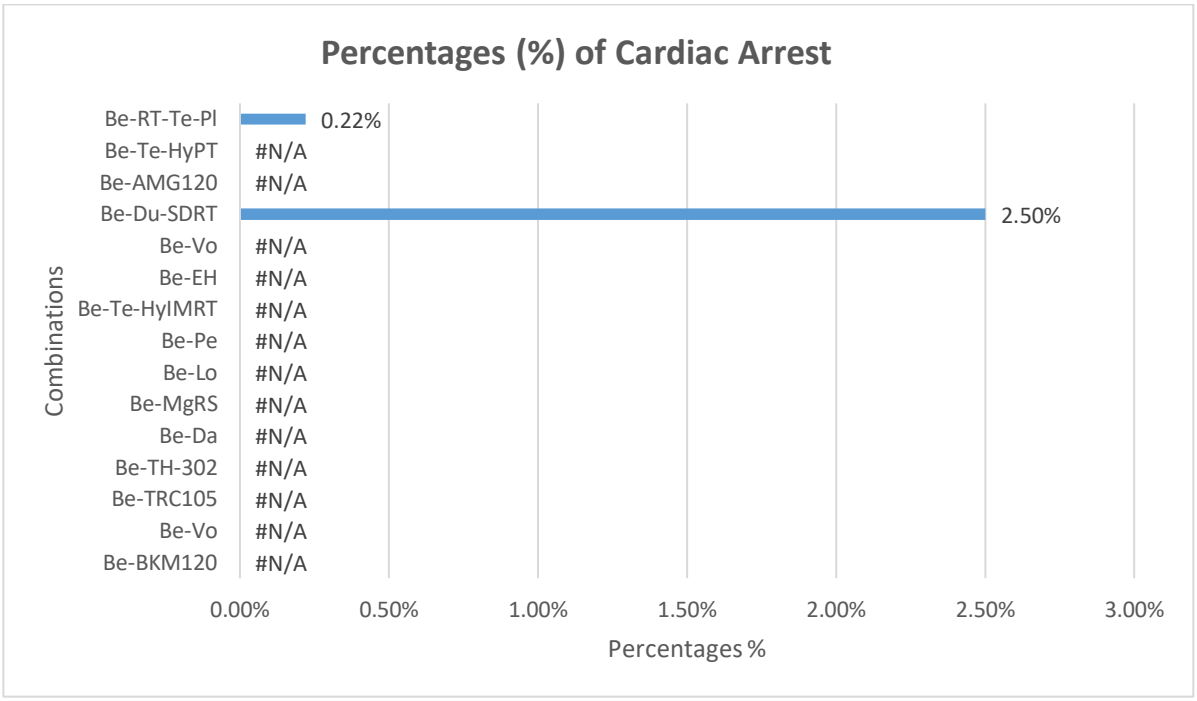
6(A)



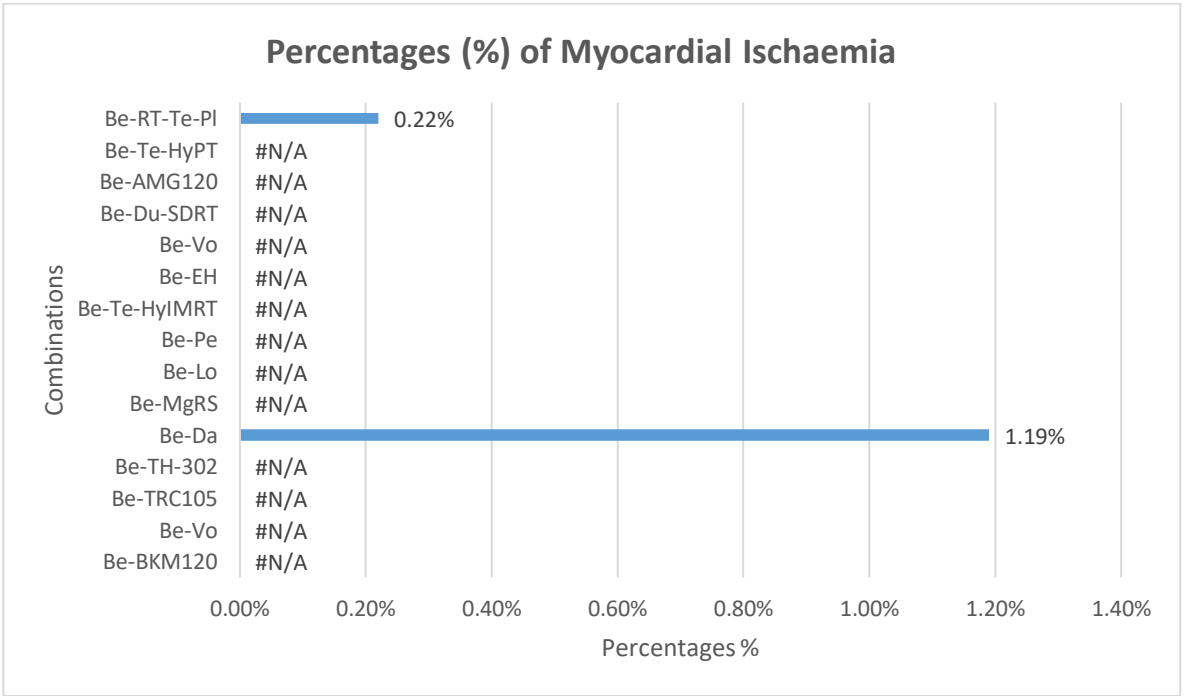
6(B)



6(C)


Percentages (%) of Cardiac Arrest
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
0.22%
#N/A
#N/A
2.50%
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
Combinations
0.00%
0.50%
1.00%
1.50%
2.00%
2.50%
3.00%
Percentages %

6(D)


Percentages (%) of Myocardial Ischaemia
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
0.22%
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
1.19%
#N/A
#N/A
#N/A
#N/A
Combinations
0.00%
0.20%
0.40%
0.60%
0.80%
1.00%
1.20%
1.40%
Percentages %

6(E)

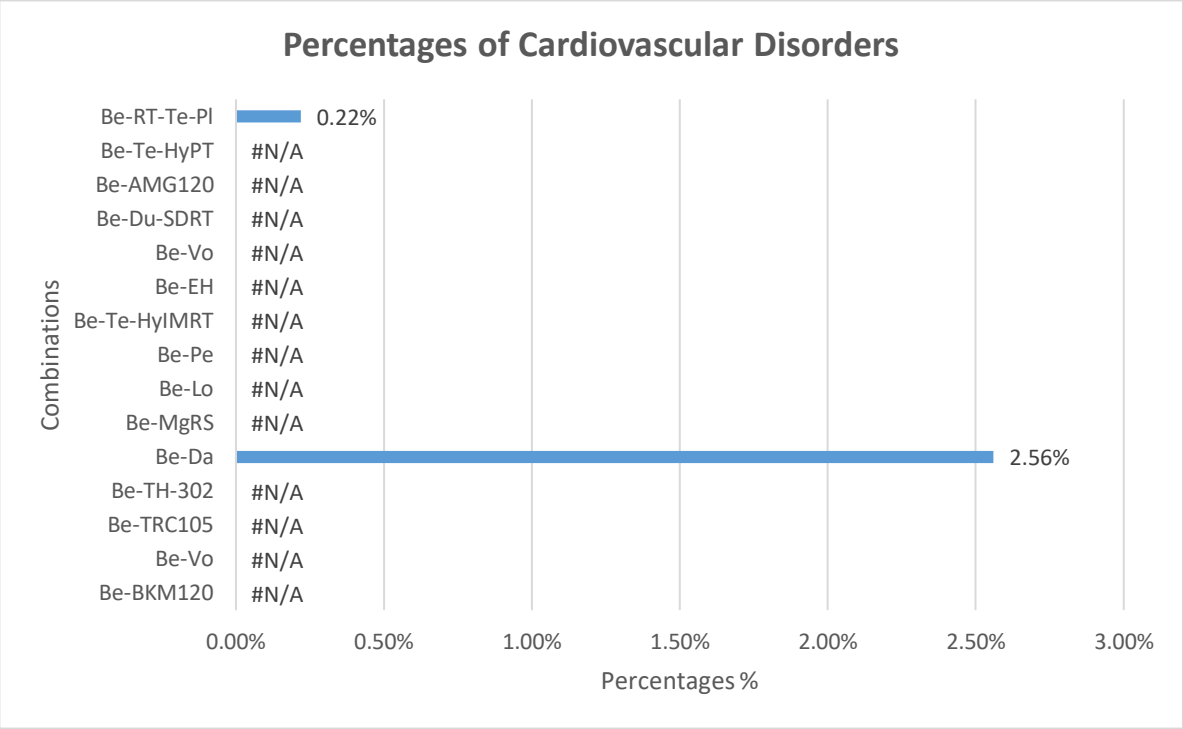


Figure 6: Percentage of cardiac disorders in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Hypertension; (B) Atrial Fibrillation; (C) Cardiac Arrest; (D) Myocardial Ischemia; (E) Cardiovascular Dosprders. The values are presented as percentages in the graphs.

Eye disorder is depicted by the following graph:

7(A)

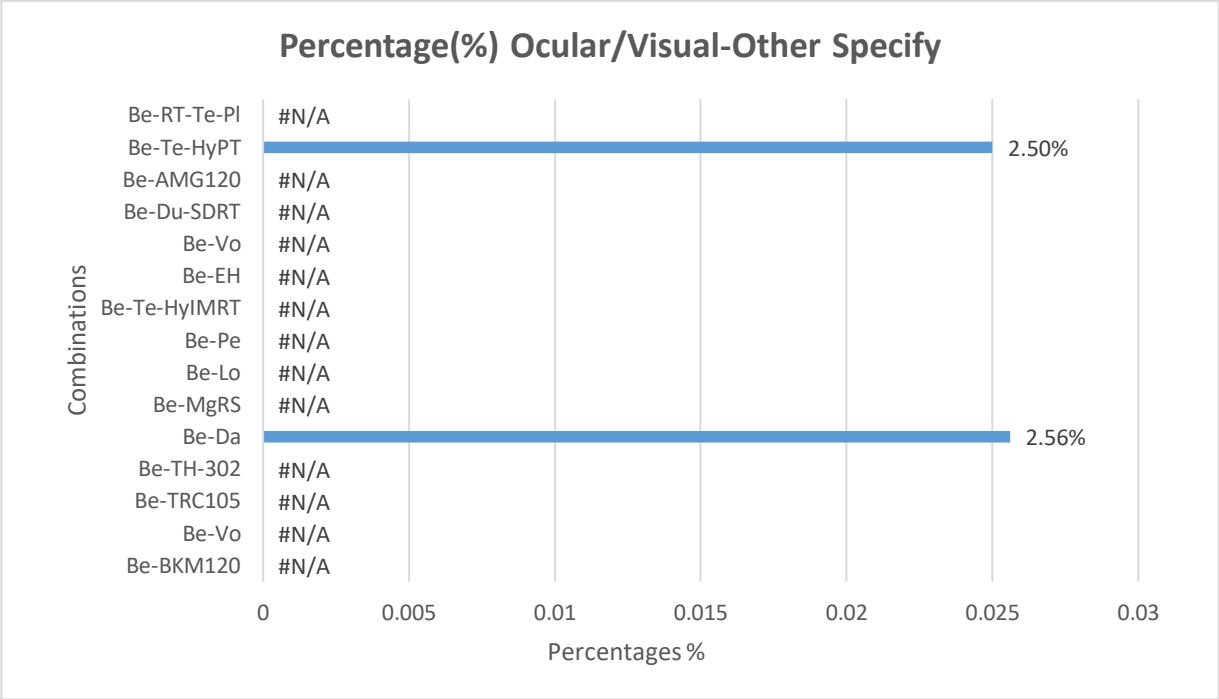
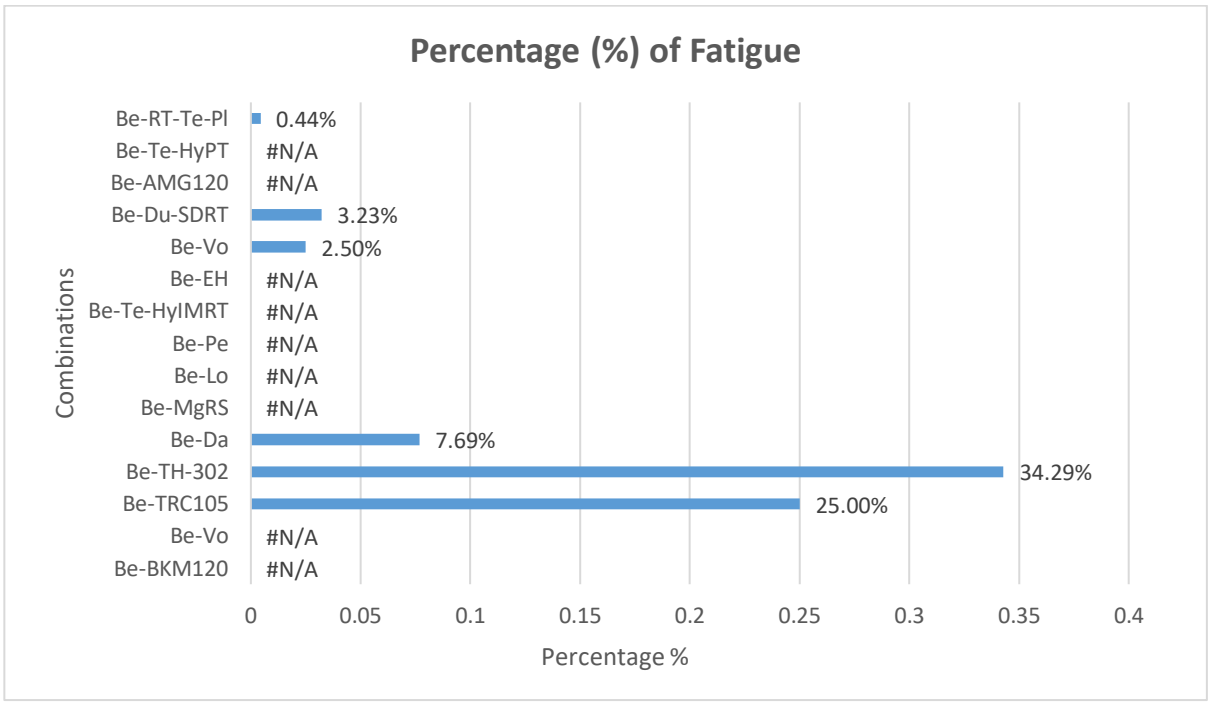


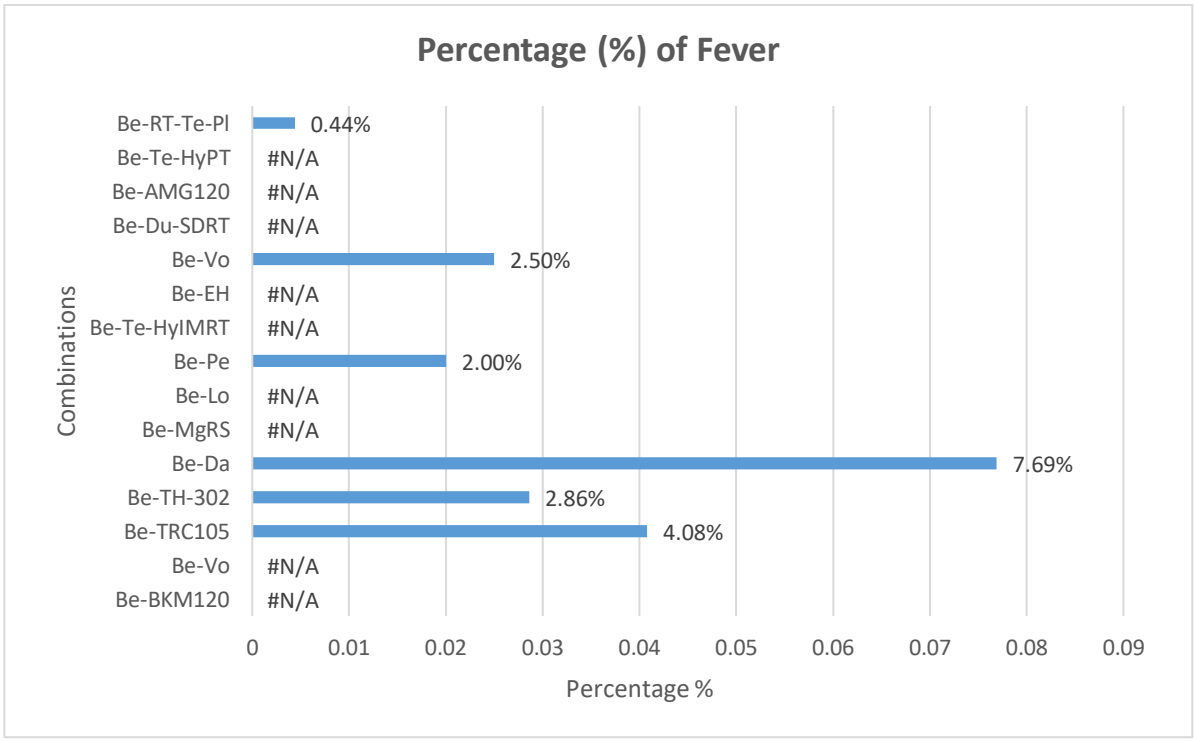
Figure 7: Percentage of eye disorders in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Ocular/Visual - Other (specify). The values are presented as percentages in the graphs.

General disorders are depicted by the following graphs:

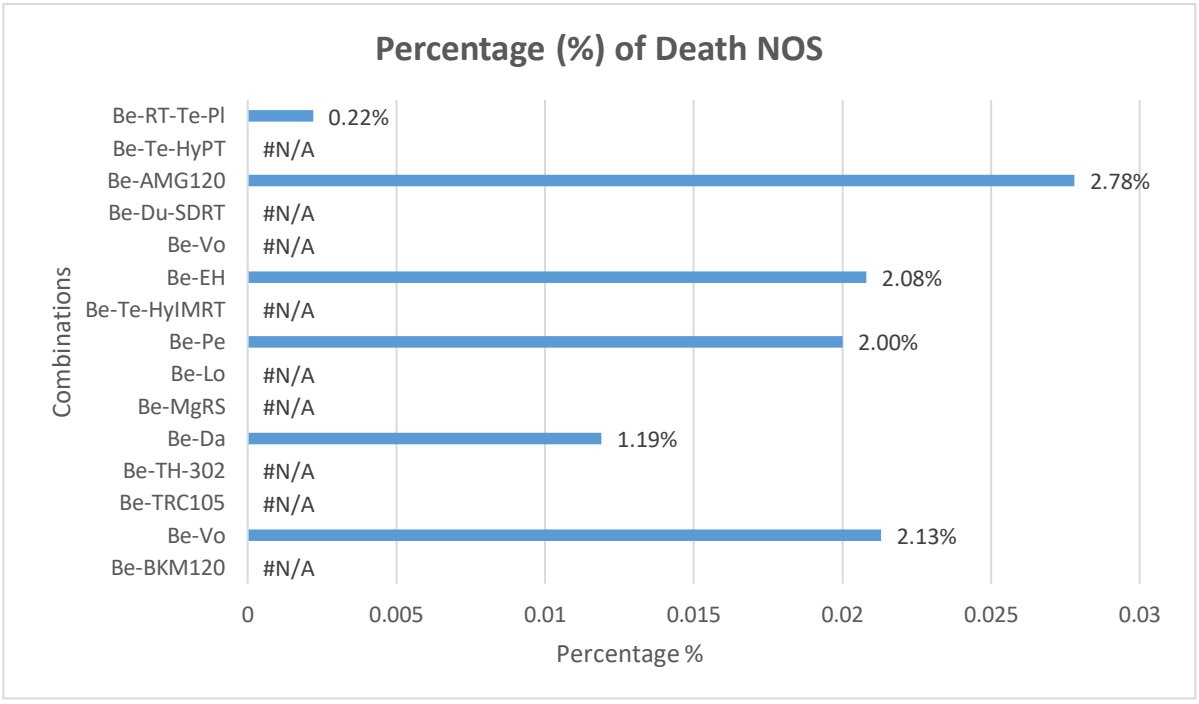
8(A)



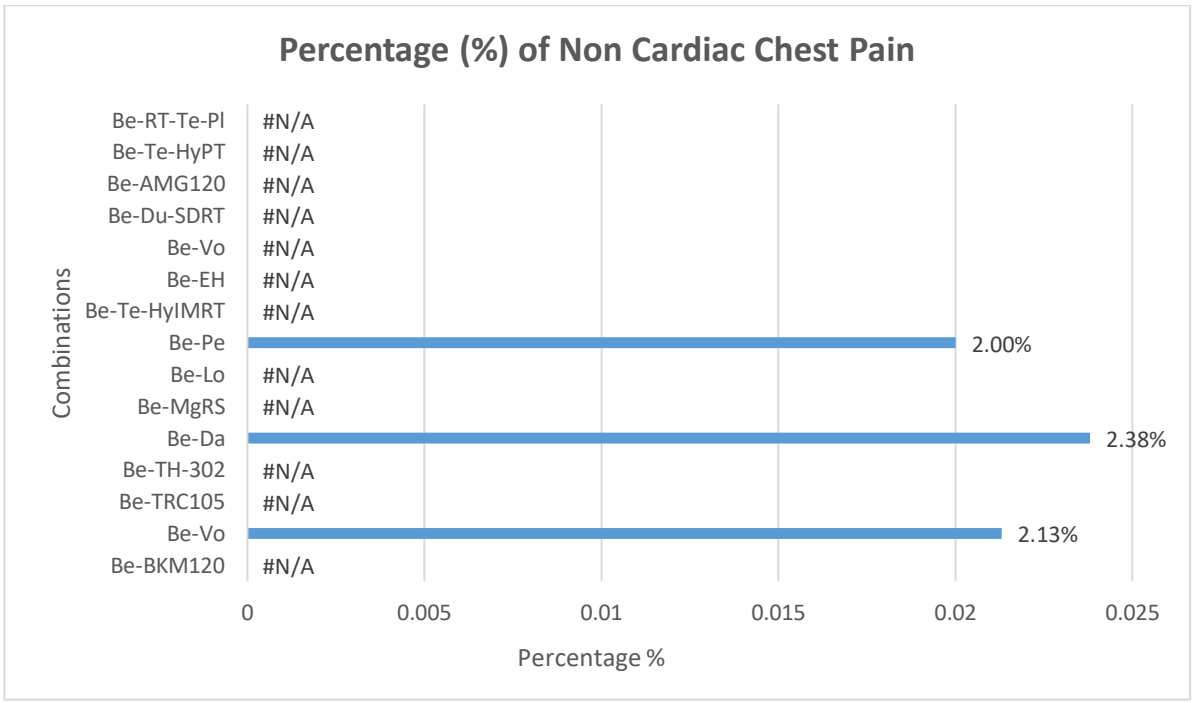
8(B)



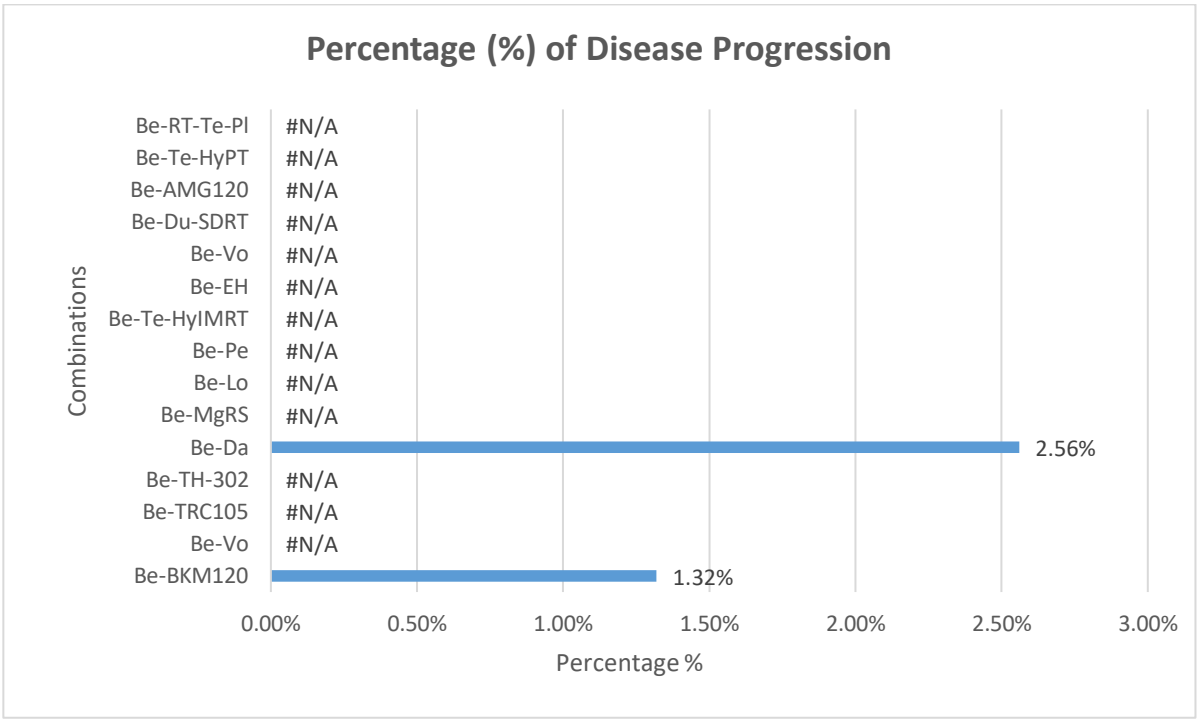
8(C)


Percentage (%) of Death NOS
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
0.22%
#N/A
2.78%
#N/A
#N/A
2.08%
#N/A
2.00%
#N/A
#N/A
1.19%
#N/A
#N/A
2.13%
#N/A
0
0.005
0.01
0.015
0.02
0.025
0.03
Percentage %

8(D)


Percentage (%) of Non Cardiac Chest Pain
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
2.00%
#N/A
#N/A
2.38%
#N/A
#N/A
2.13%
#N/A
0
0.005
0.01
0.015
0.02
0.025
Percentage %

8(E)



8(F)

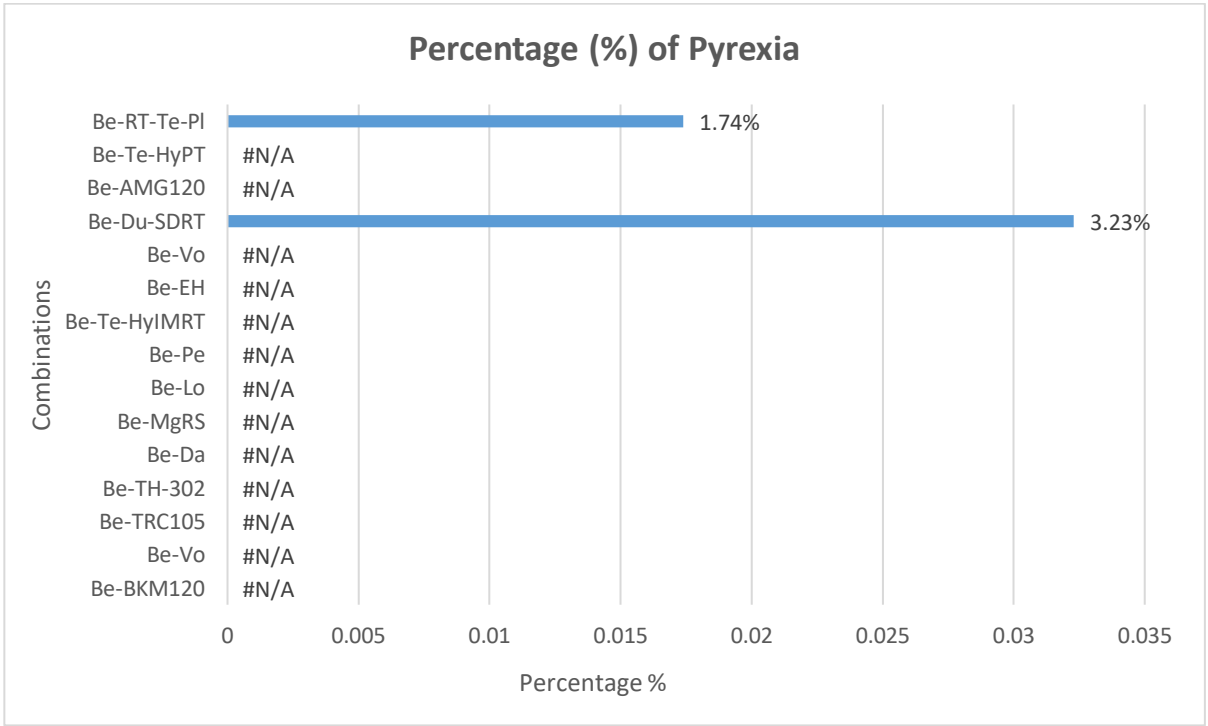
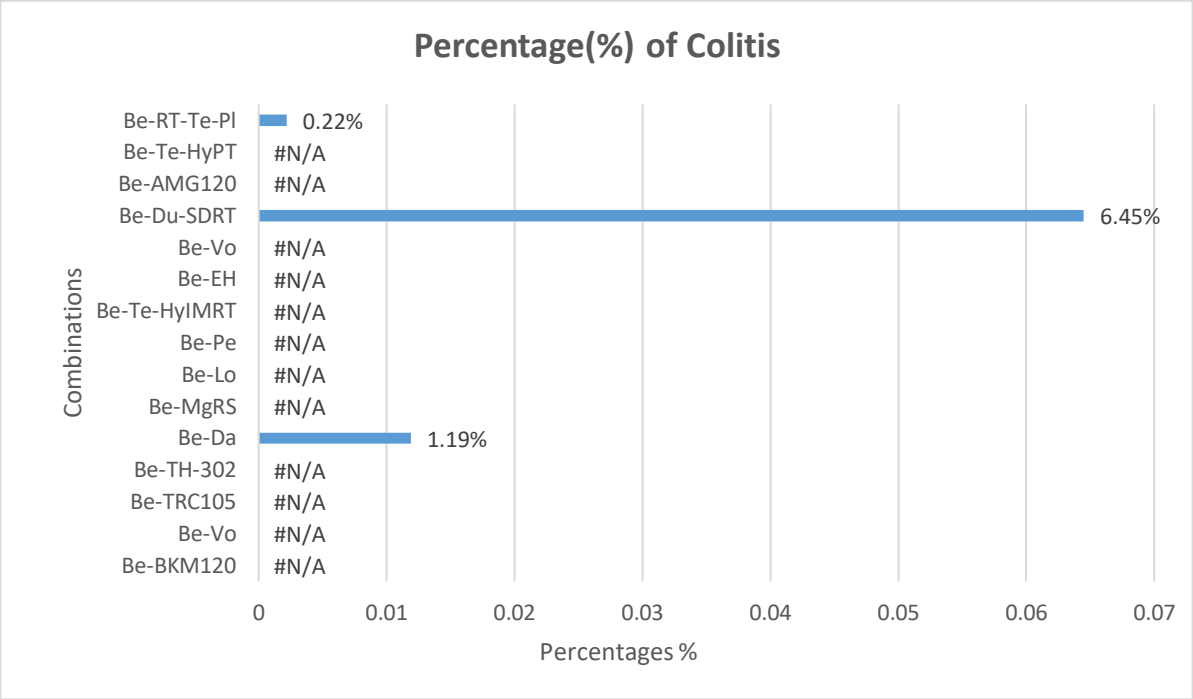


Figure 8: Percentage of general disorders in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat

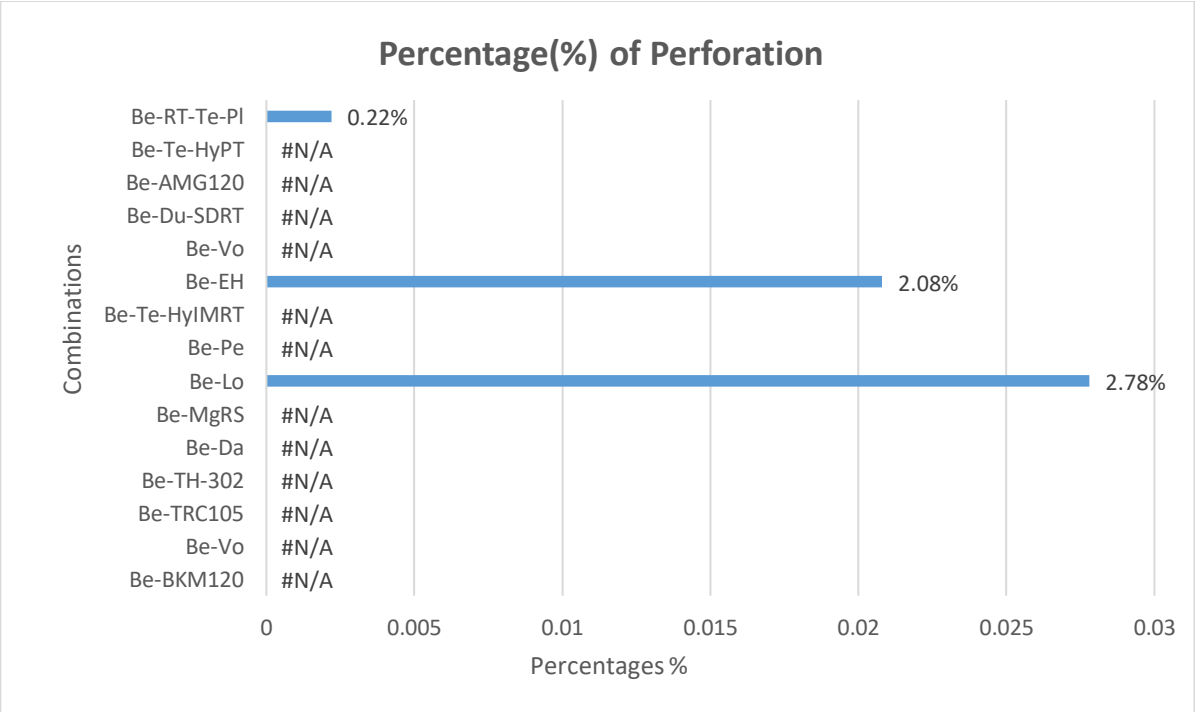
(Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Fatigue; (B) Fever; (C) Death NOS; (D) Non Cardiac Chest Pain; (E) Disease Progression; (F) Pyrexia. The values are presented as percentages in the graphs.

Gastrointestinal disorders are depicted by following graphs:

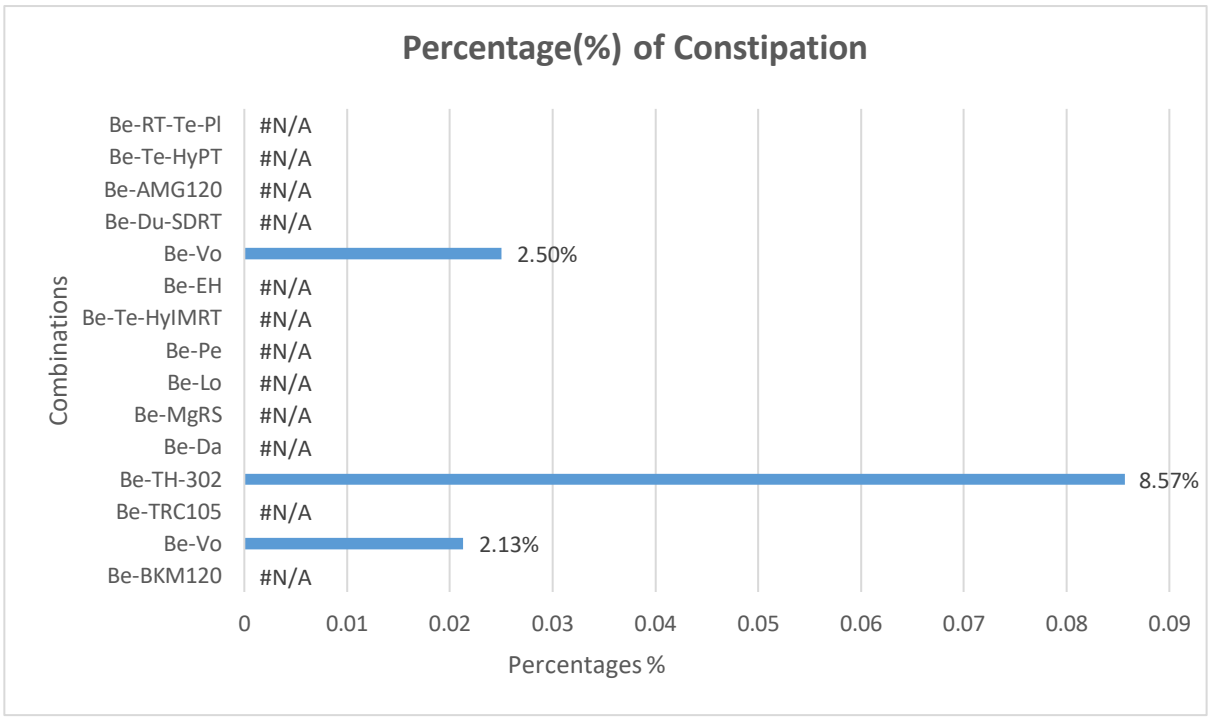
9(A)



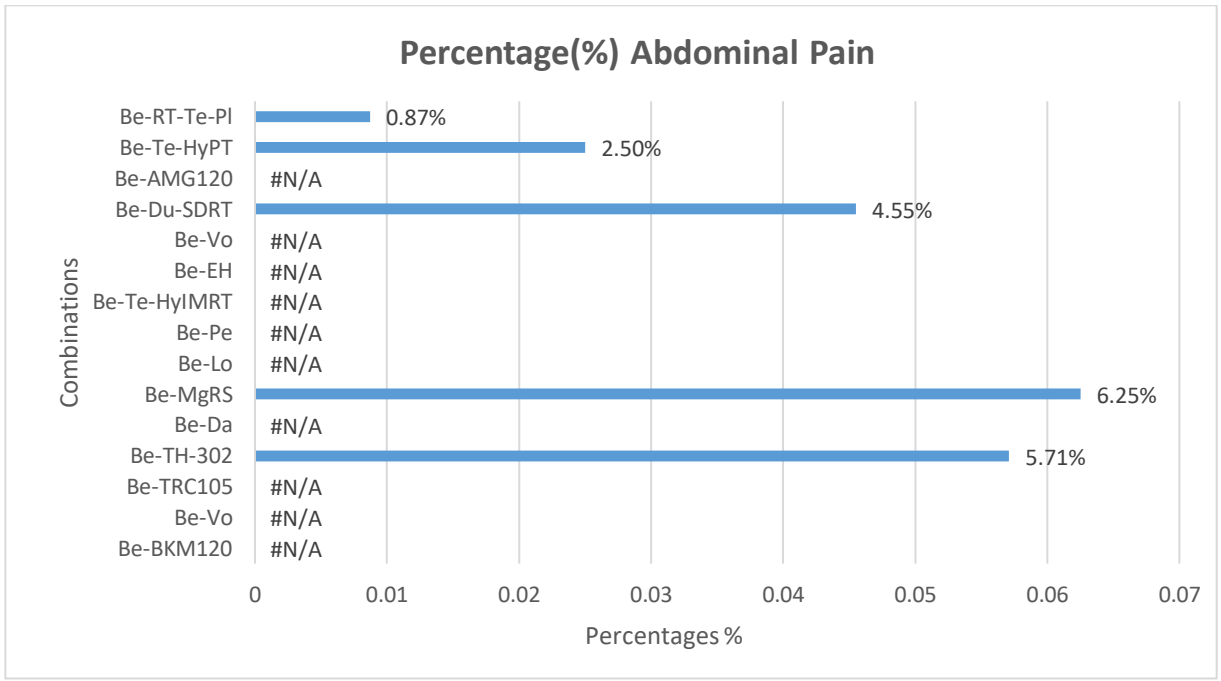
9(B)



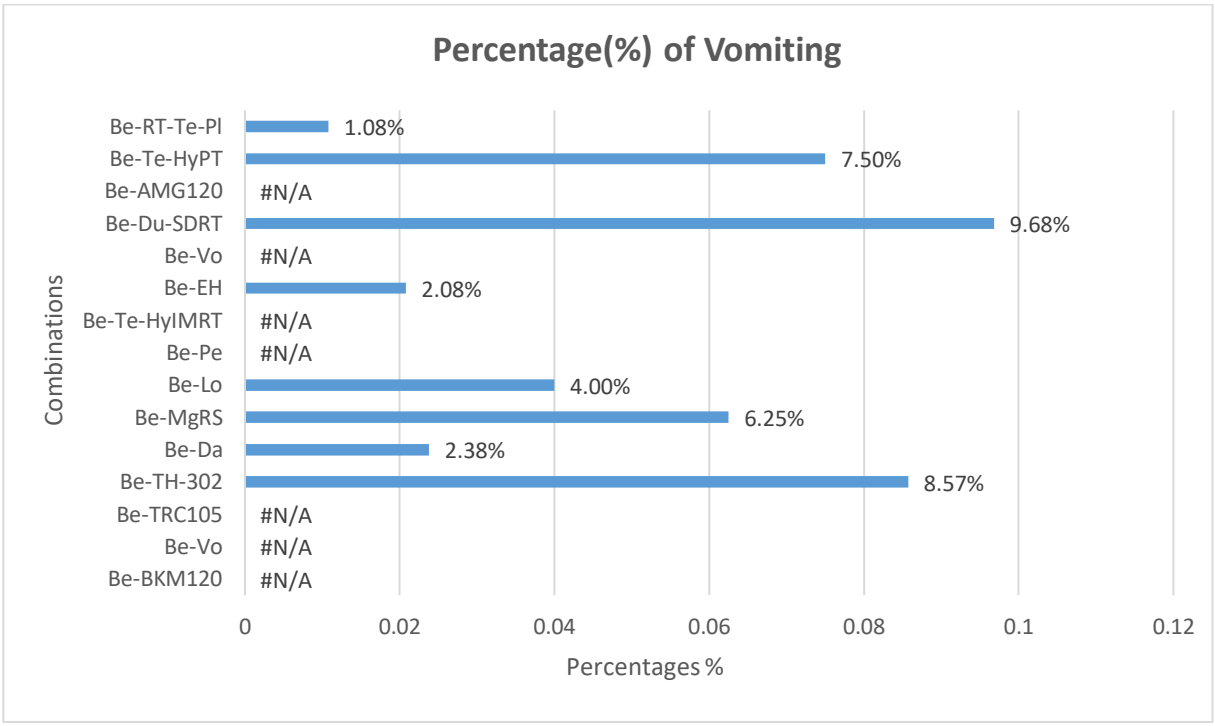
9(C)


Percentage(%) of Constipation
Combinations
Be-RT-Te-Pl #N/A
Be-Te-HyPT #N/A
Be-AMG120 #N/A
Be-Du-SDRT #N/A
Be-Vo 2.50%
Be-EH #N/A
Be-Te-HyIMRT #N/A
Be-Pe #N/A
Be-Lo #N/A
Be-MgRS #N/A
Be-Da #N/A
Be-TH-302 8.57%
Be-TRC105 #N/A
Be-Vo 2.13%
Be-BKM120 #N/A
0 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09
Percentages %

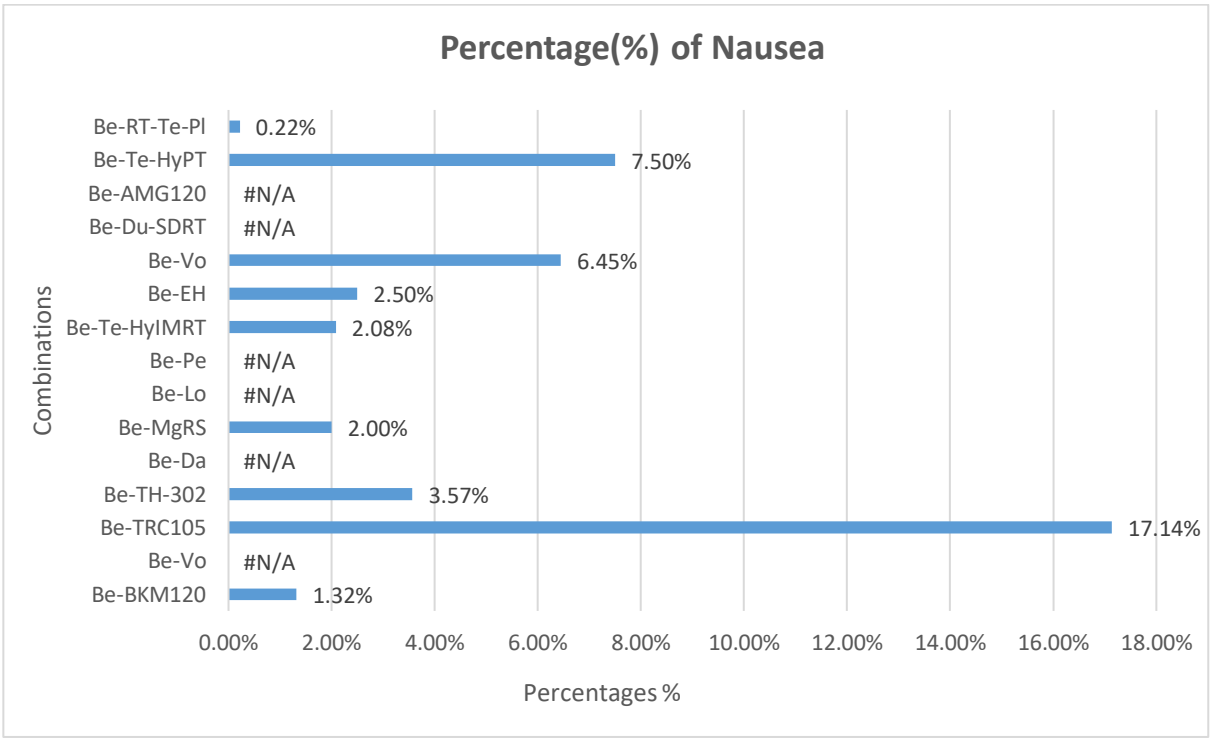
9(D)


Percentage(%) Abdominal Pain
Combinations
Be-RT-Te-Pl 0.87%
Be-Te-HyPT 2.50%
Be-AMG120 #N/A
Be-Du-SDRT 4.55%
Be-Vo #N/A
Be-EH #N/A
Be-Te-HyIMRT #N/A
Be-Pe #N/A
Be-Lo #N/A
Be-MgRS 6.25%
Be-Da #N/A
Be-TH-302 5.71%
Be-TRC105 #N/A
Be-Vo #N/A
Be-BKM120 #N/A
0 0.01 0.02 0.03 0.04 0.05 0.06 0.07
Percentages %

9(E)


Percentage(%) of Vomiting
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
1.08%
7.50%
#N/A
9.68%
#N/A
2.08%
#N/A
#N/A
4.00%
6.25%
2.38%
8.57%
#N/A
#N/A
#N/A
0
0.02
0.04
0.06
0.08
0.1
0.12
Percentages %

9(F)


Percentage(%) of Nausea
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
0.22%
7.50%
#N/A
#N/A
6.45%
2.50%
2.08%
#N/A
#N/A
2.00%
#N/A
3.57%
17.14%
#N/A
1.32%
0.00%
2.00%
4.00%
6.00%
8.00%
10.00%
12.00%
14.00%
16.00%
18.00%
Percentages %

9(G)

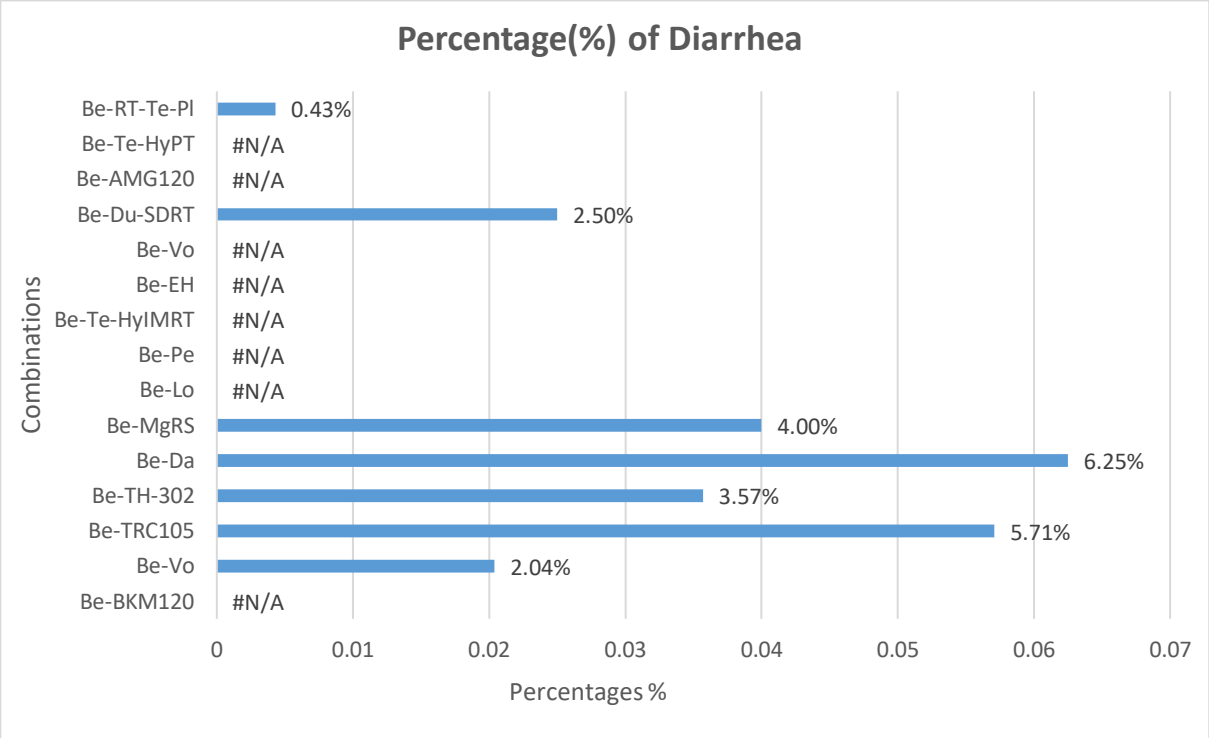


Figure 8: Percentage of gastrointestinal disorders in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Colitis; (B) Perforation; (C) Constipation; (D) Abdominal Pain; (E) Vomiting; (F) Nausea; (G) Diarrhea. The values are presented as percentages in the graphs.

Hepatobiliary disorder is depicted by the following graph:

10(A)

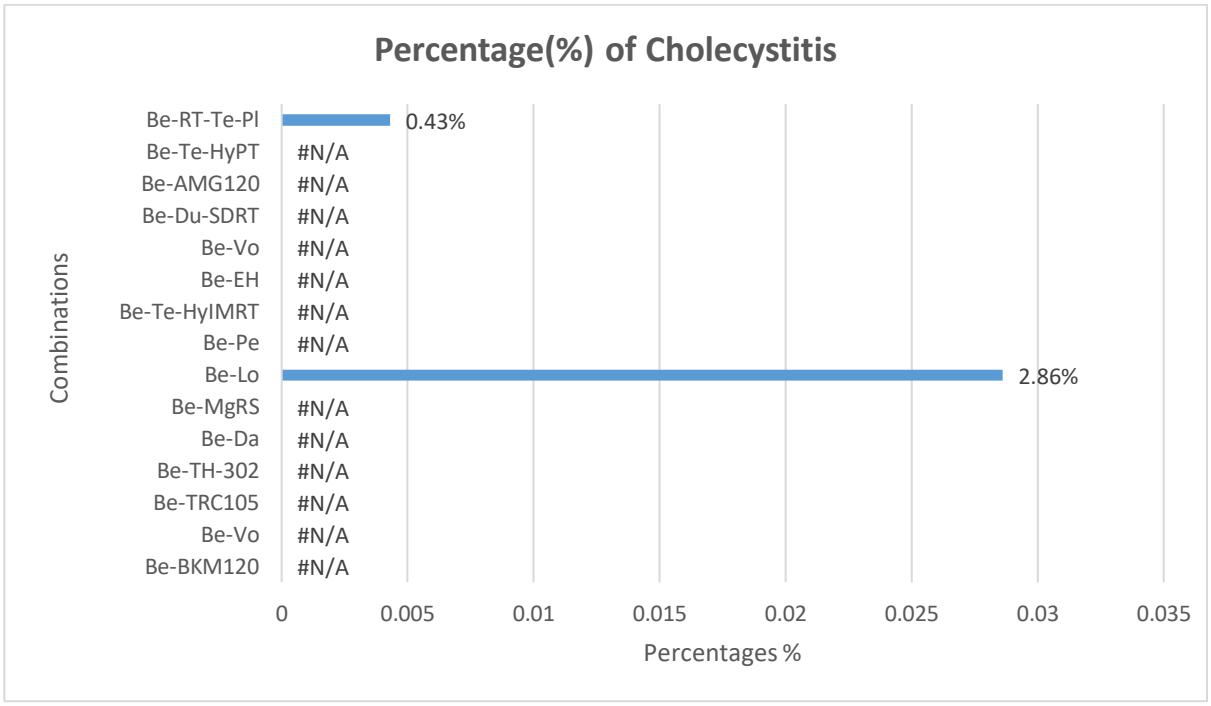
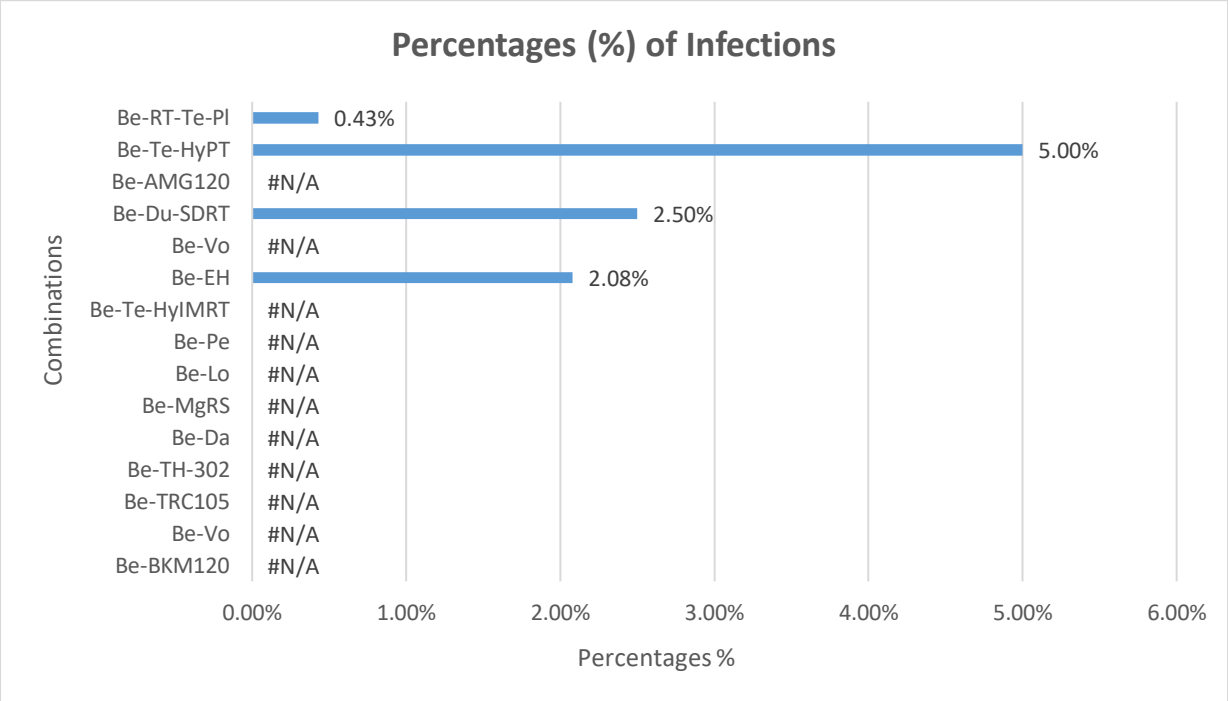


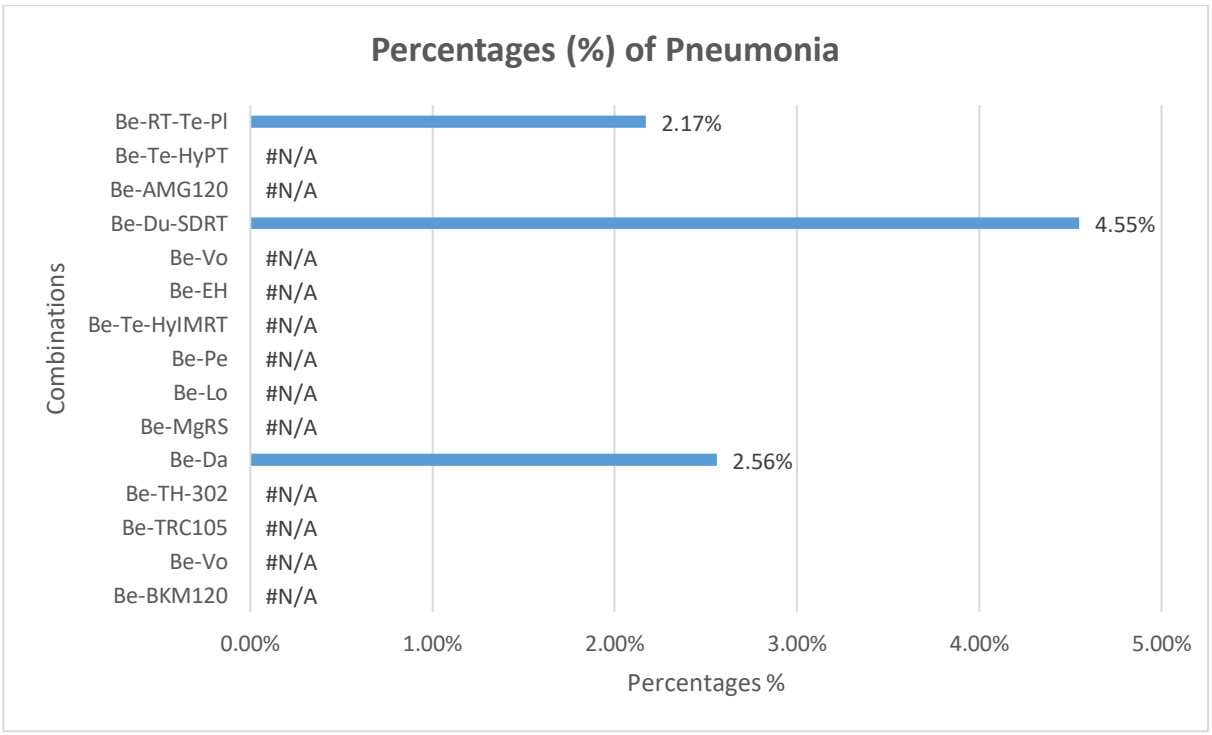
Figure 10: Percentage of hepatobiliary disorder in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Cholecystitis. The values are presented as percentages in the graphs.

Infections and infestations are depicted by the following graphs:

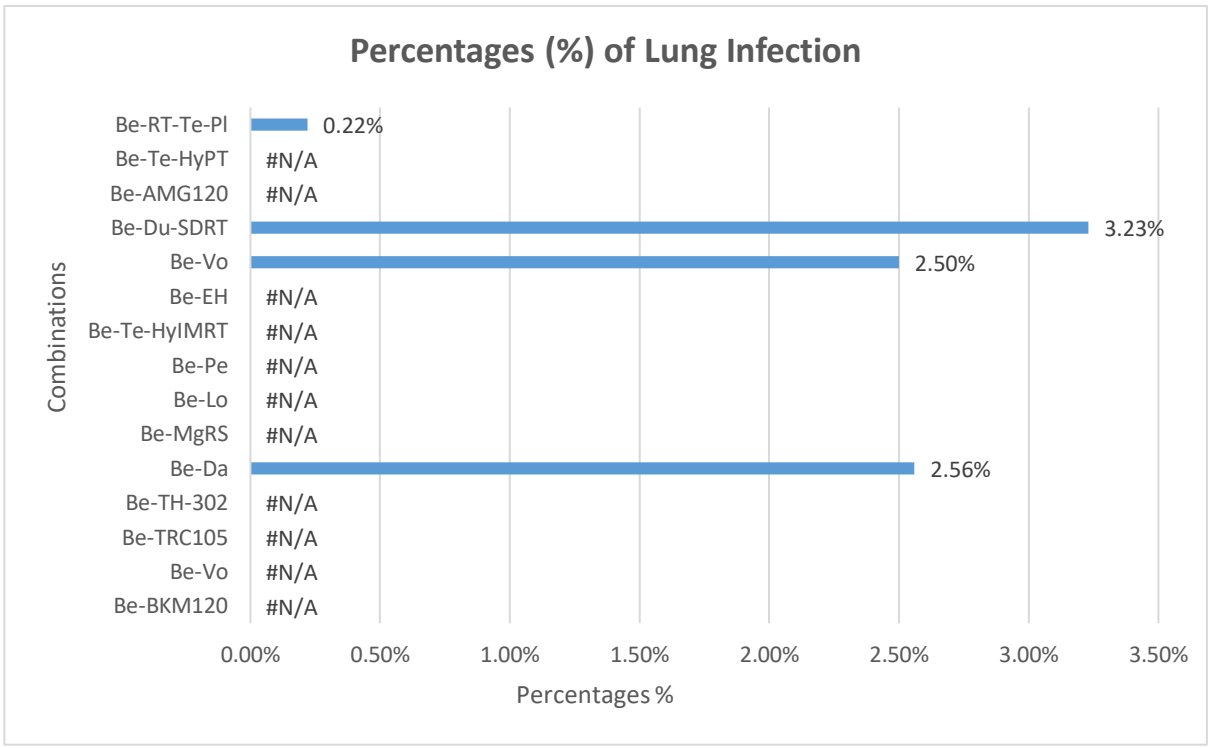
11(A)



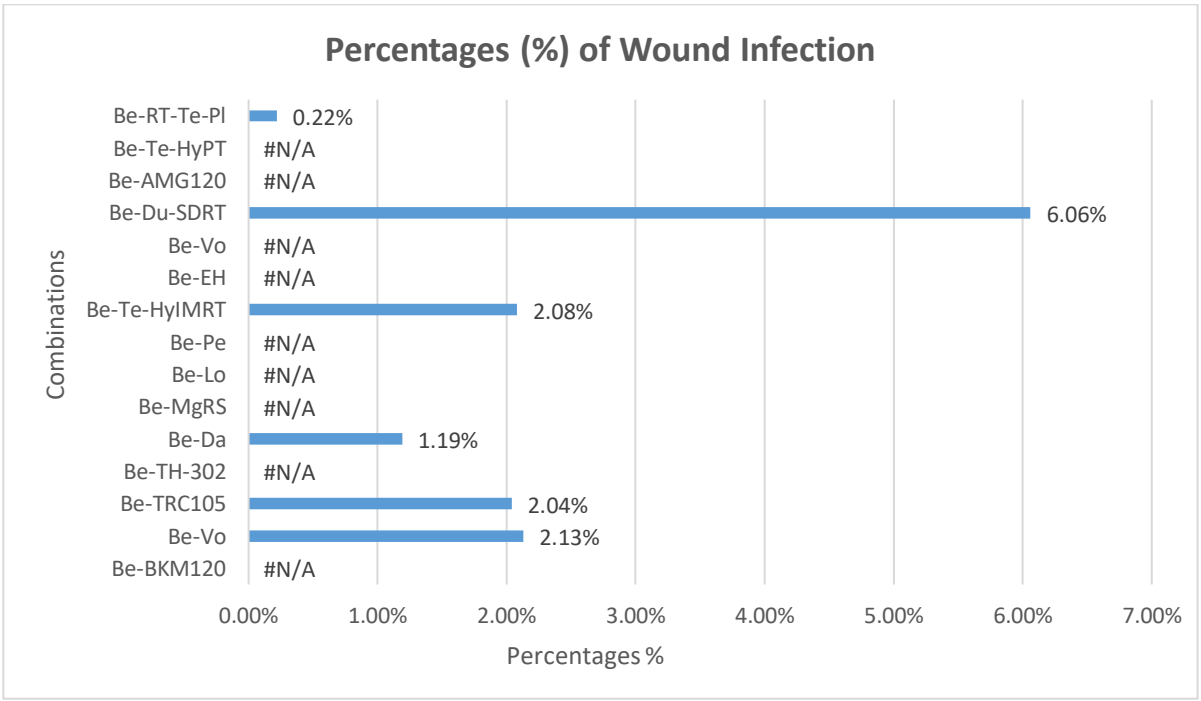
11(B)



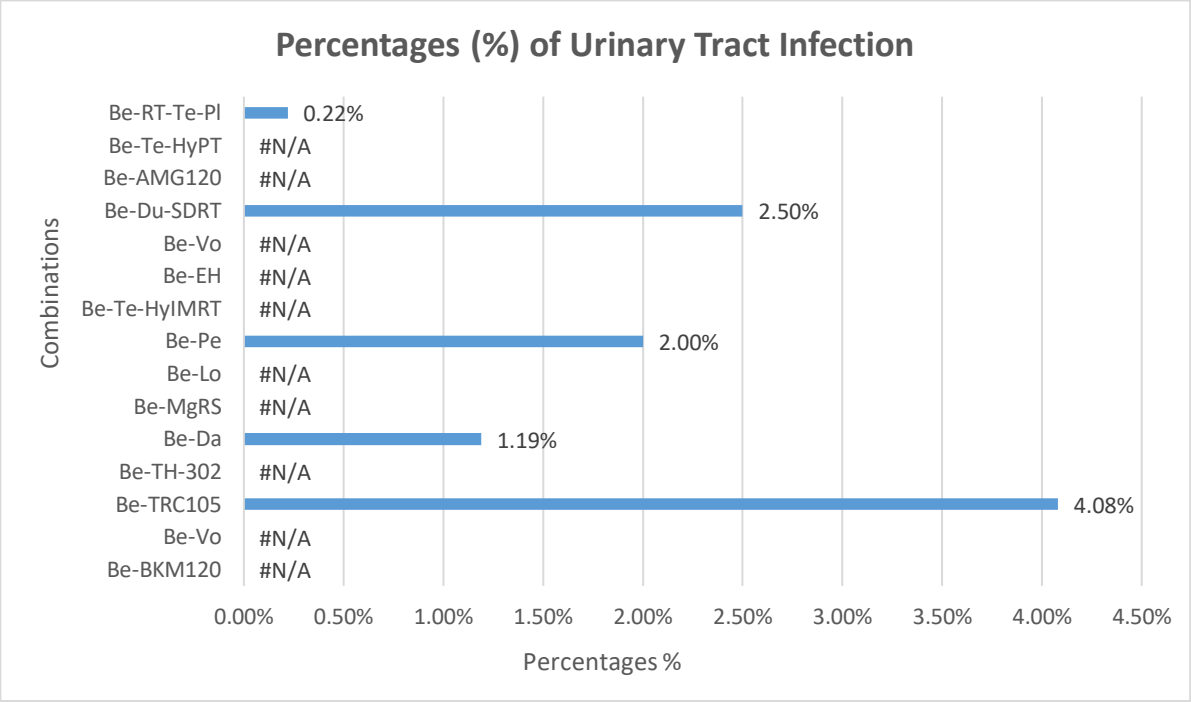
11(C)


Percentages (%) of Lung Infection
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
0.22%
#N/A
#N/A
3.23%
2.50%
#N/A
#N/A
#N/A
#N/A
#N/A
2.56%
#N/A
#N/A
#N/A
#N/A
0.00%
0.50%
1.00%
1.50%
2.00%
2.50%
3.00%
3.50%
Percentages %

11(D)


Percentages (%) of Wound Infection
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
0.22%
#N/A
#N/A
6.06%
#N/A
#N/A
2.08%
#N/A
#N/A
#N/A
1.19%
#N/A
2.04%
2.13%
#N/A
0.00%
1.00%
2.00%
3.00%
4.00%
5.00%
6.00%
7.00%
Percentages %

11(E)



11(F)

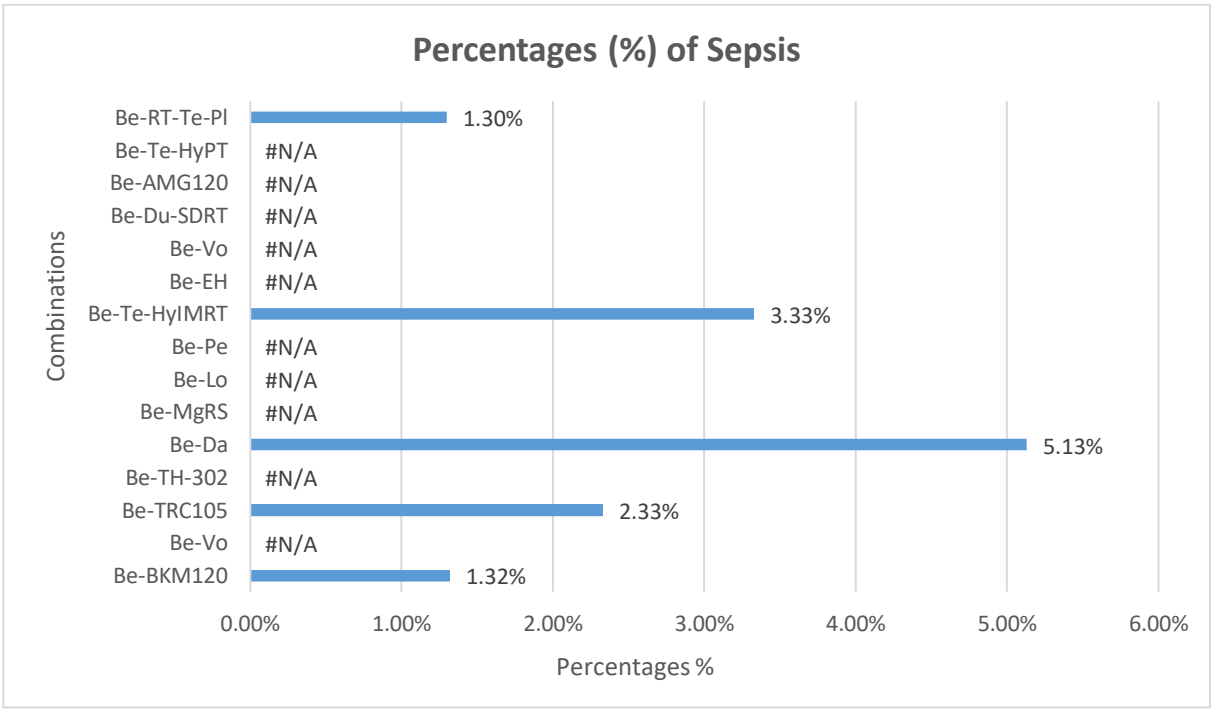
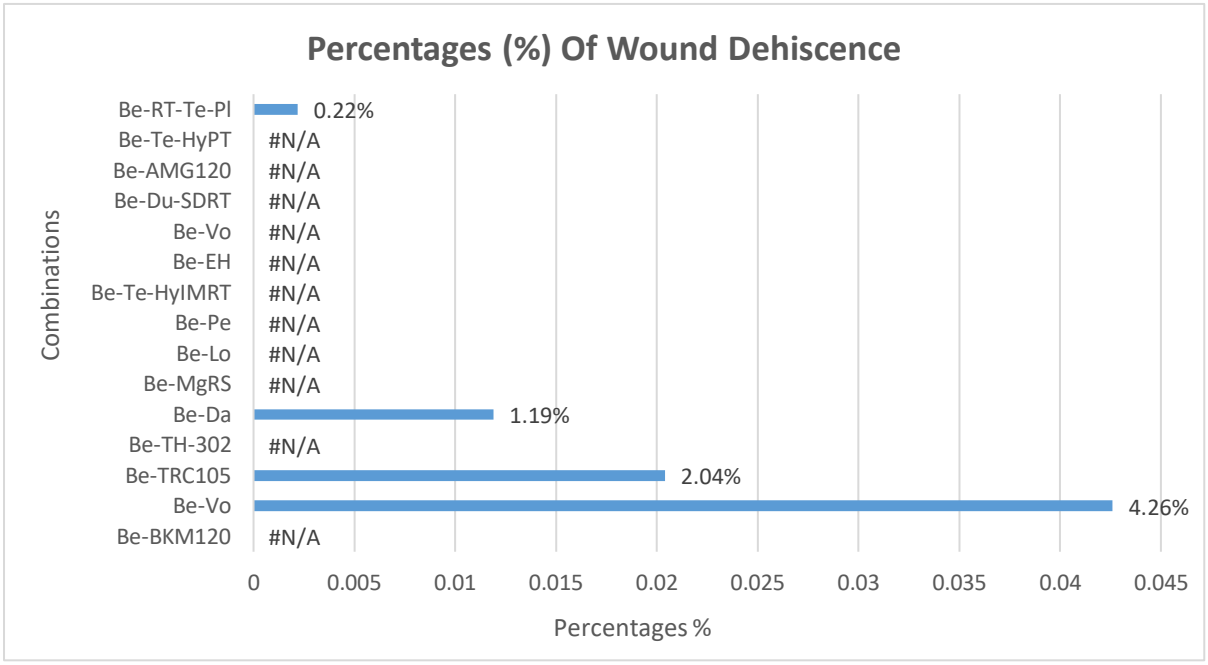


Figure 11: Percentage of infections and infestations in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-

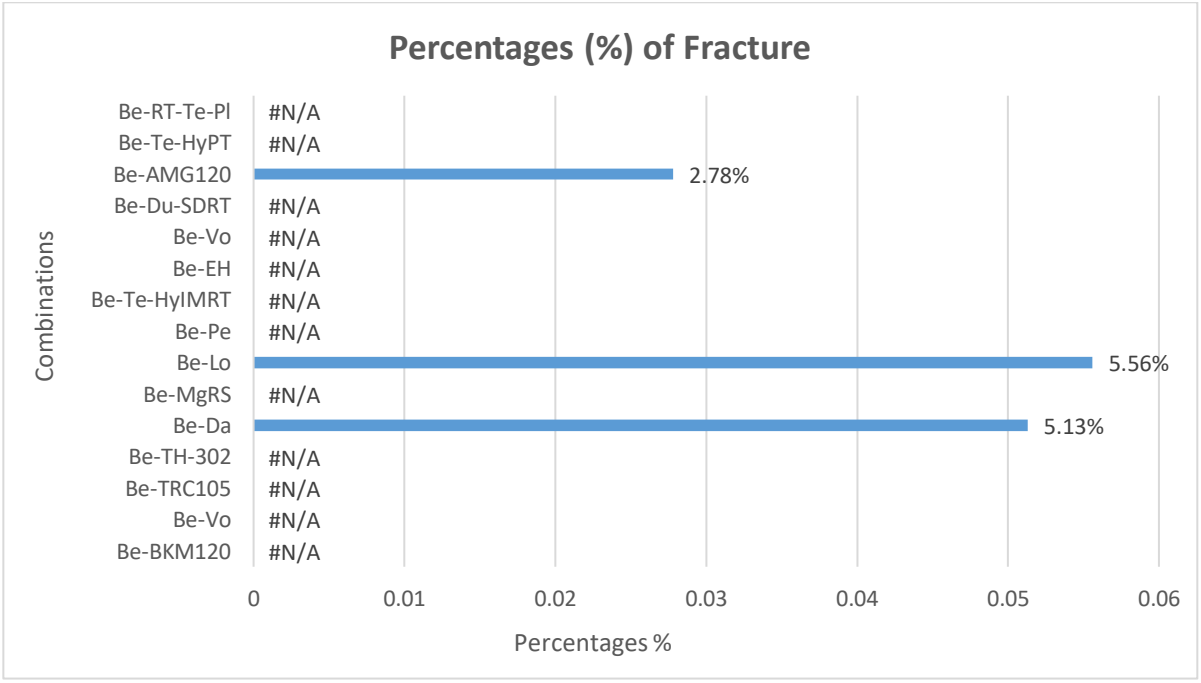
TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Infection; (B) Pneumonia; (C) Lung Infection; (D) Wound Infection; (E) Urinary Tract Infection; (F) Sepsis. The values are presented as percentages in the graphs.

Injury, poisoning and procedural complications are depicted by the following graphs:

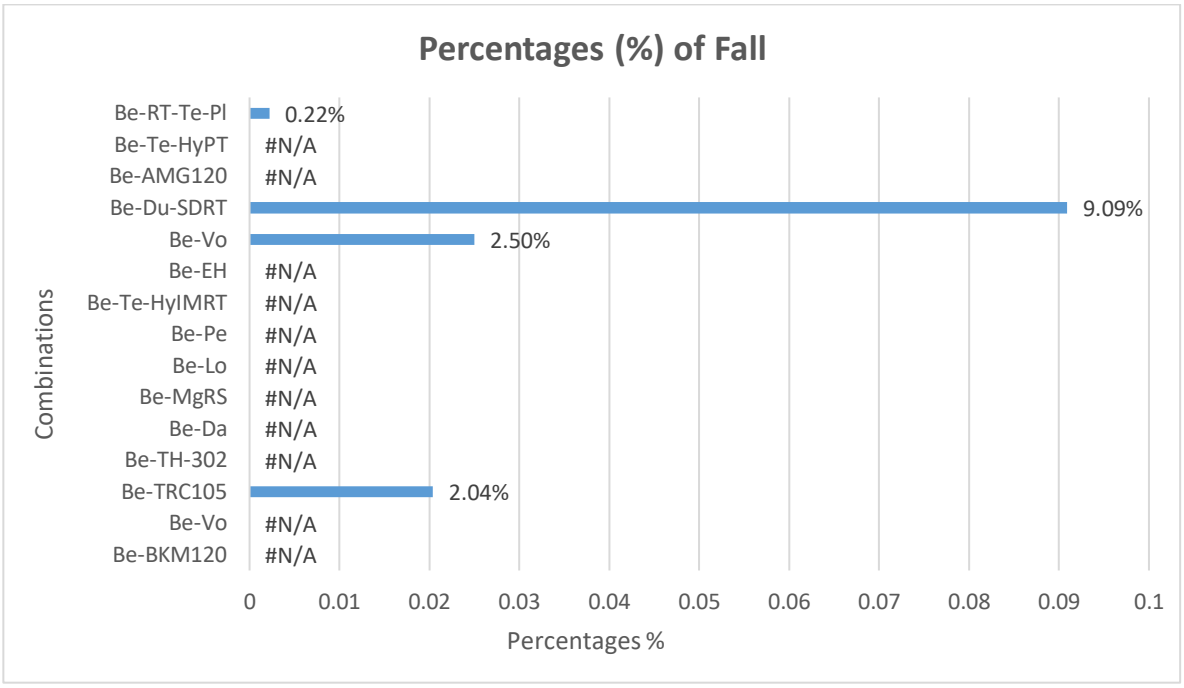
12(A)



12(B)



12(C)



12(D)

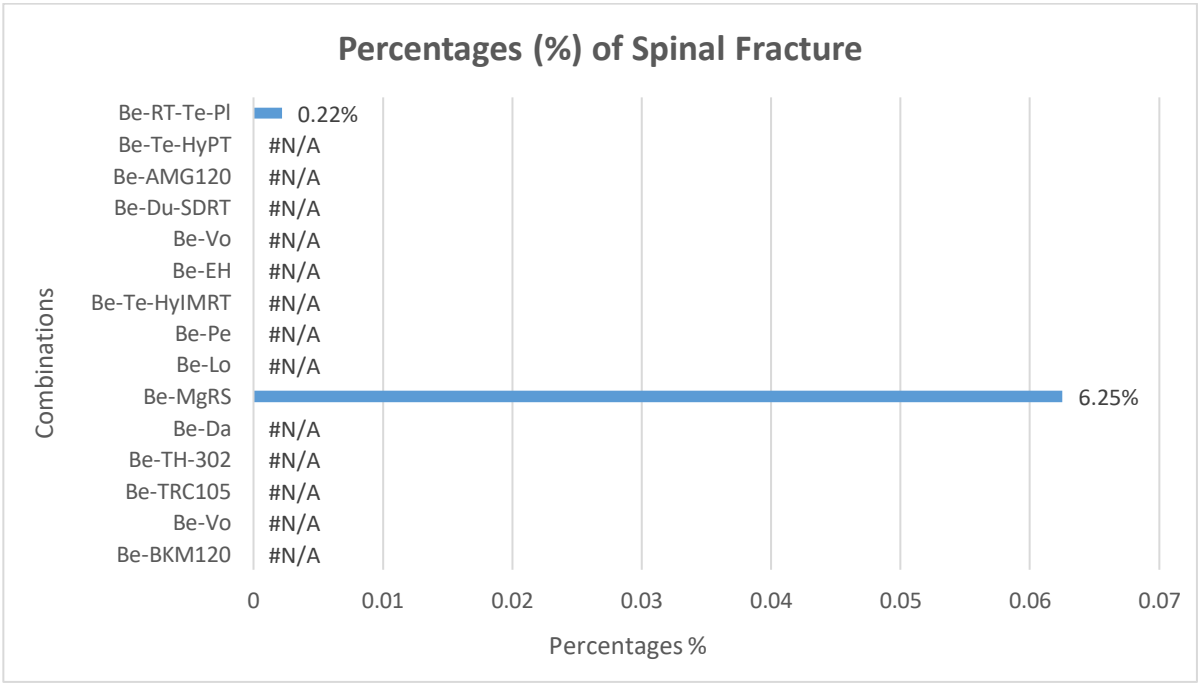
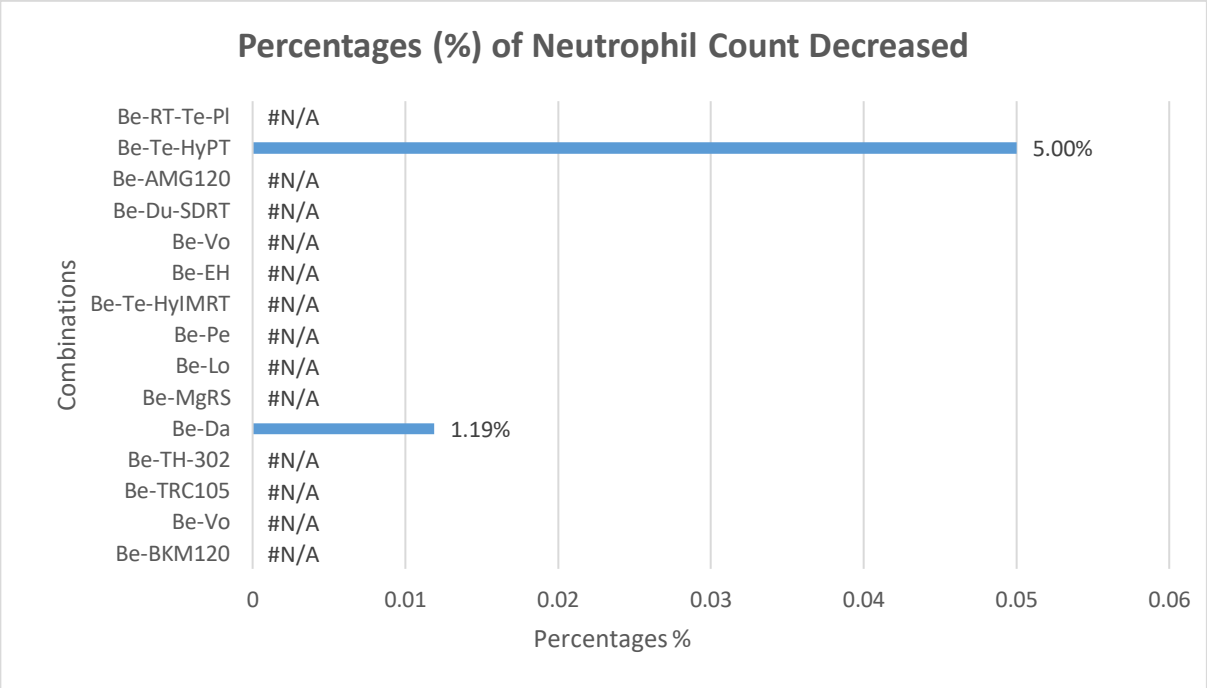


Figure 12: Percentage of injury, poisoning and procedural complications in patients receiving Bevcizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH-

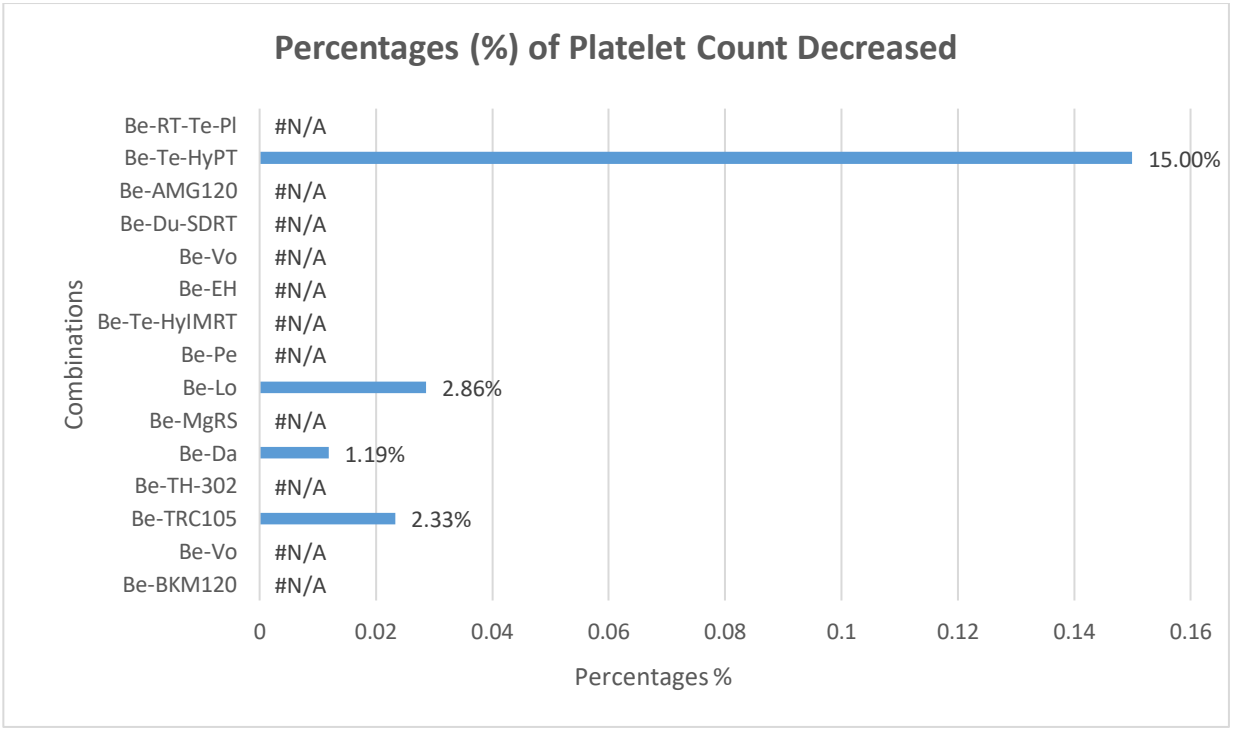
302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizmumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Wound Dehiscence; (B) Fracture; (C) Fall; (D) Spinal Fracture. The values are presented as percentages in the graphs.

Investigations are depicted by the following graphs:

13(A)



13(B)



13(C)

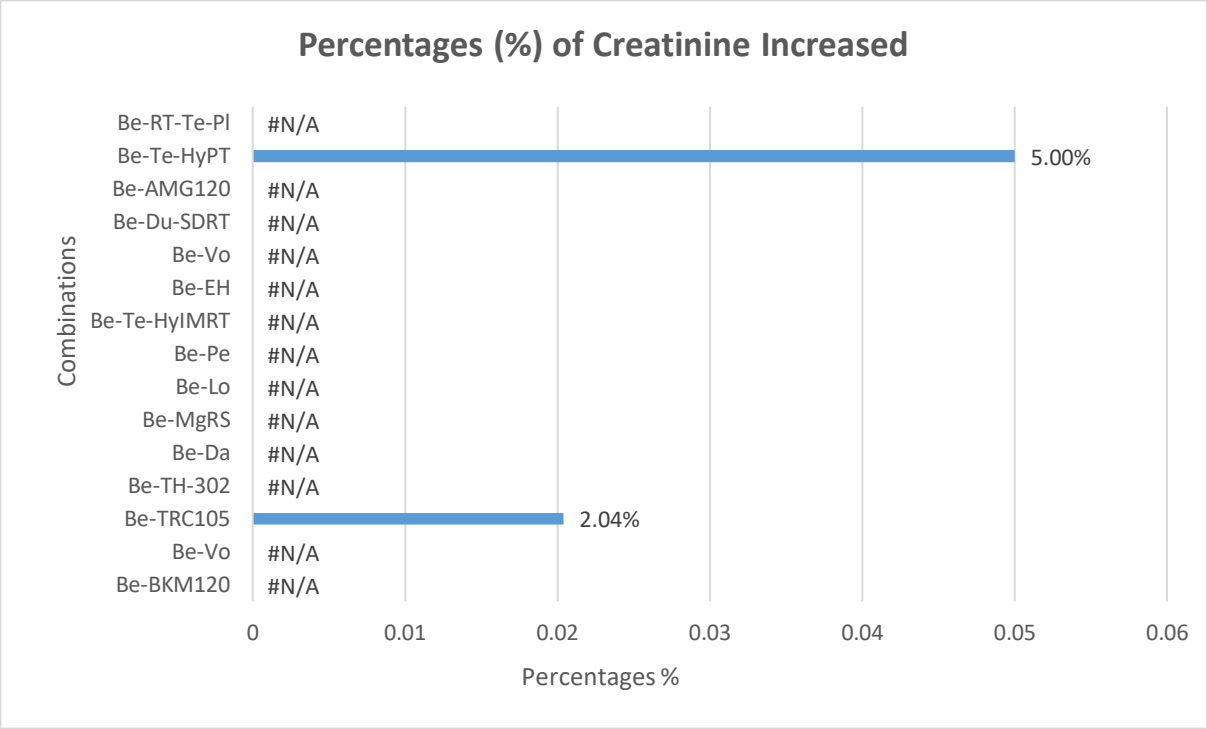
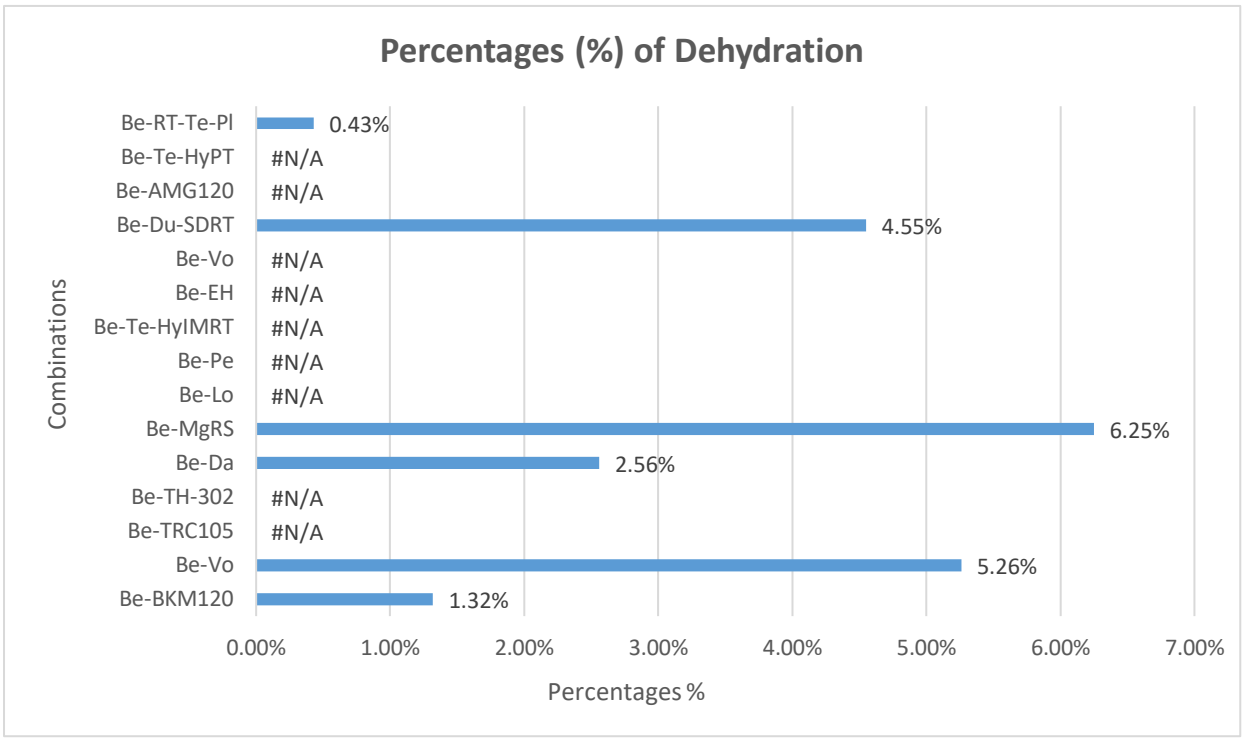


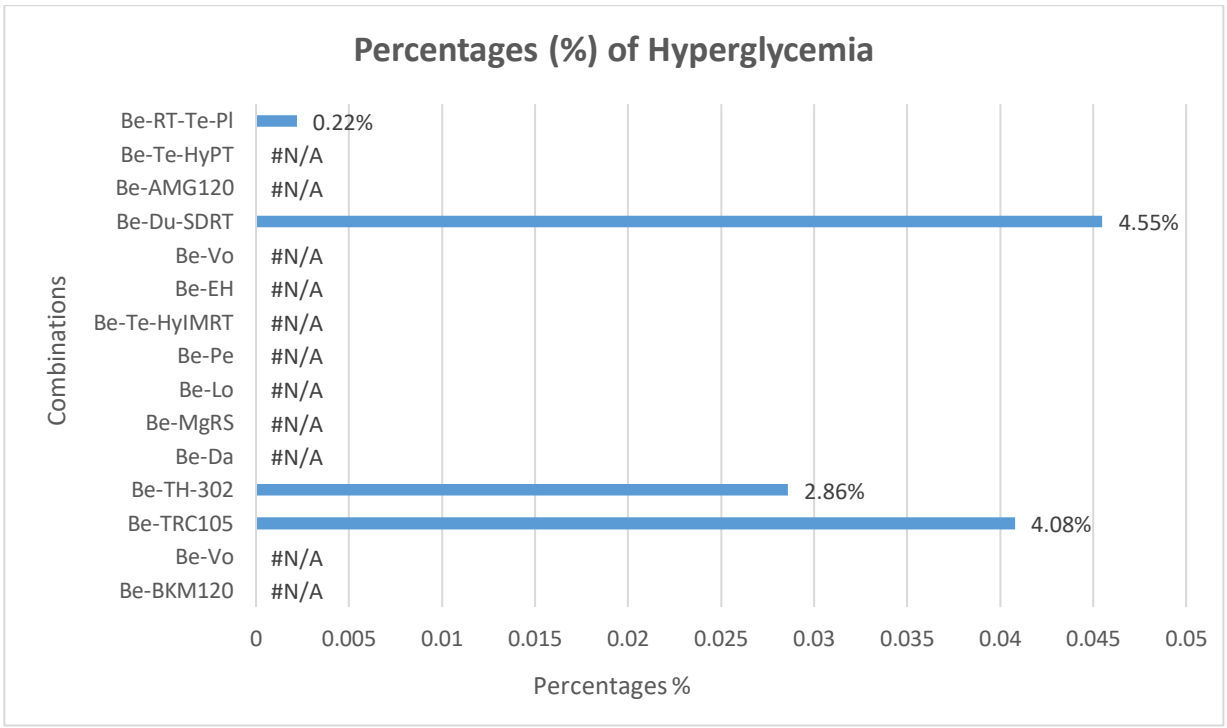
Figure 13: Percentage of investigations in patients receiving Bevcizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Neutrophil Count Decreased; (B) Platelet Count Decreased; (C) Creatinine Count Increased. The values are presented as percentages in the graphs.

Metabolism and nutrition disorders are depicted by the following graphs:

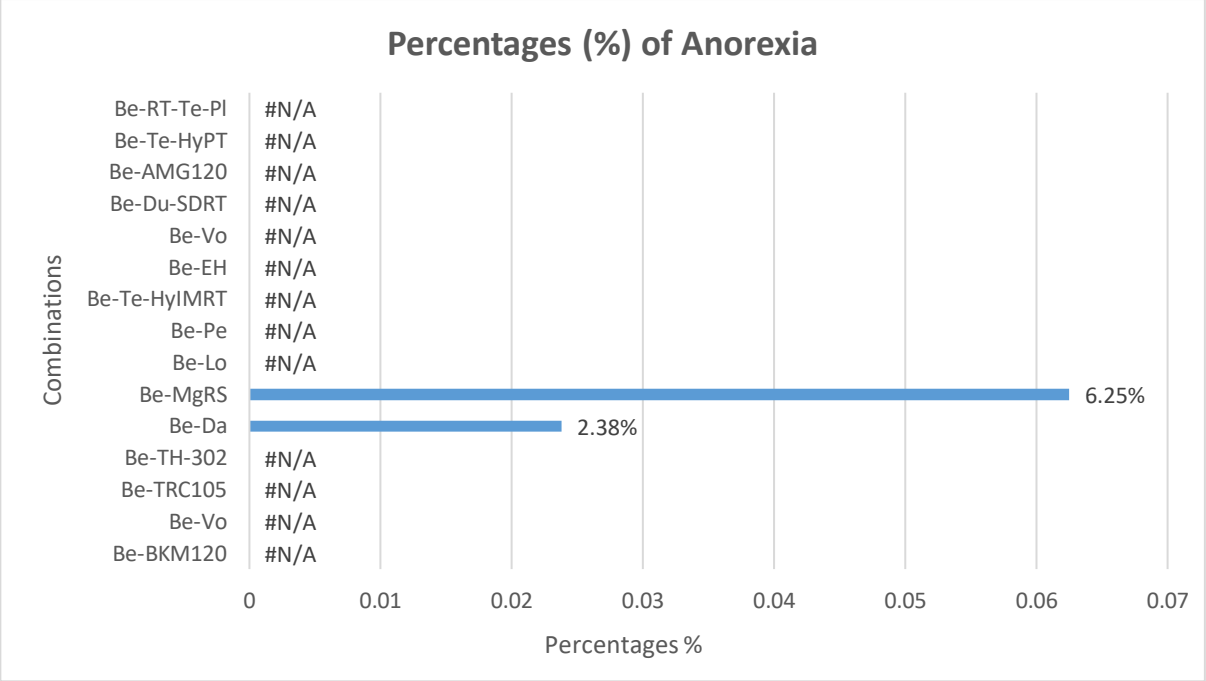
14(A)



14(B)



14(C)



14(D)

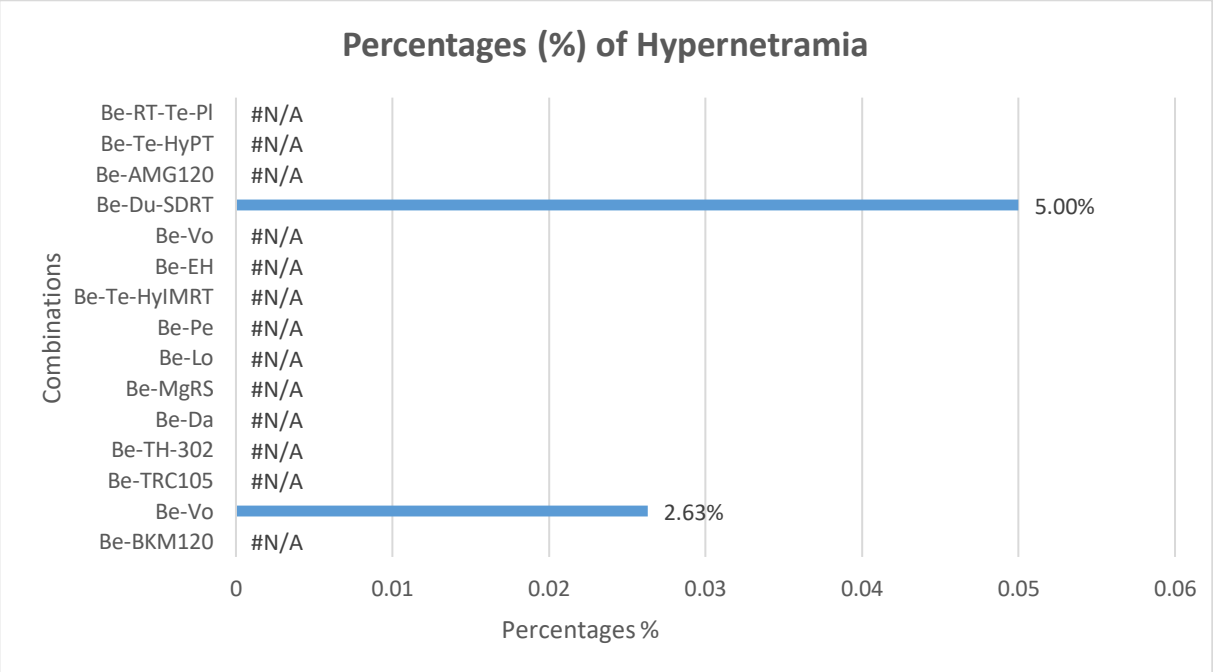
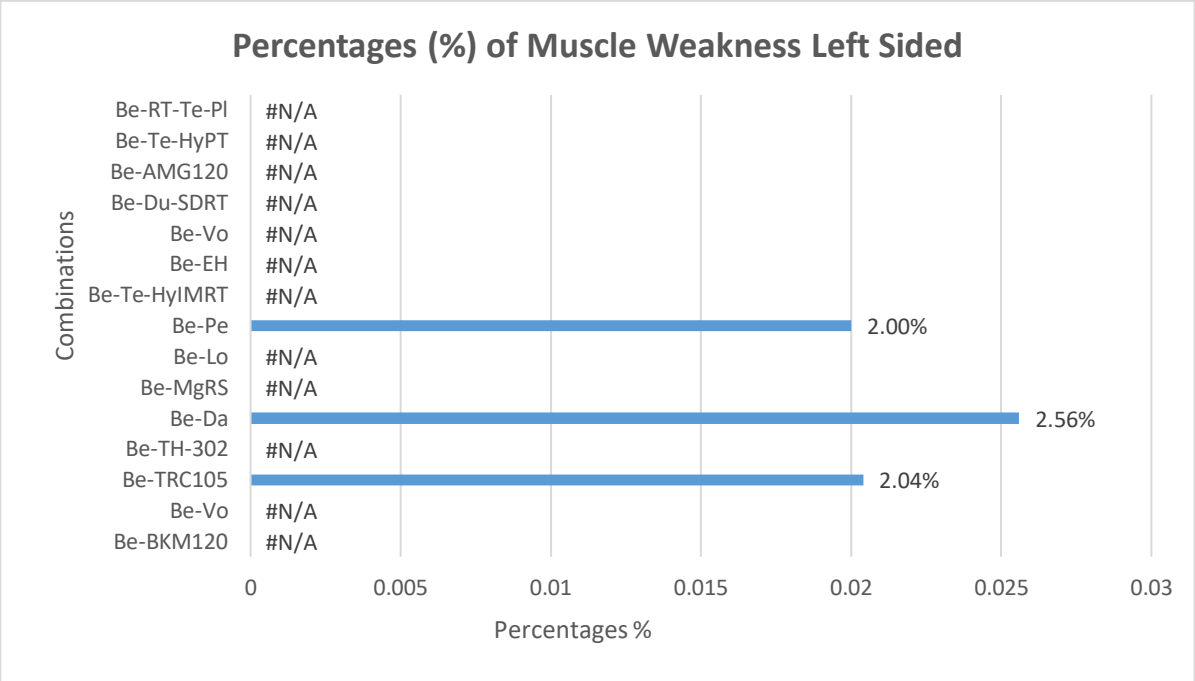


Figure 14: Percentage of metabolism and nutrition disorders in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat

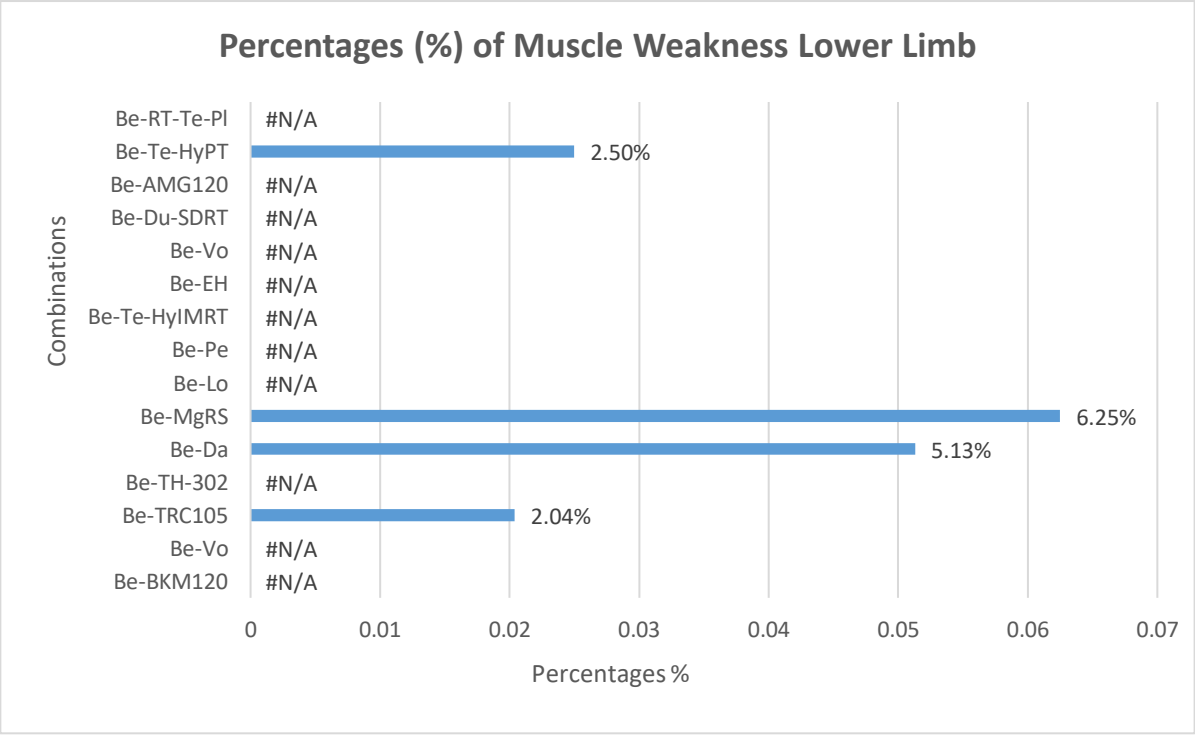
(Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizmumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Dehydration; (B) Hyperglycemia; (C) Anorexia; (D) Hypernatremia. The values are presented as percentages in the graphs.

Musculoskeletal and connective tissue disorders are depicted by the following graphs:

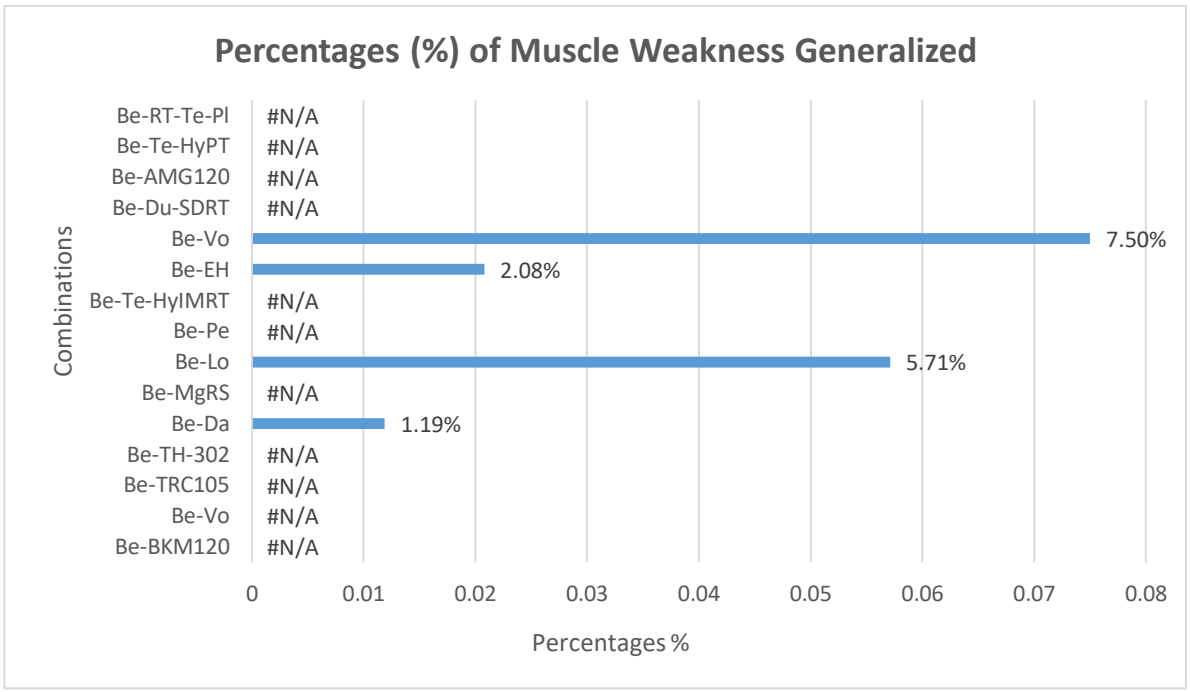
15(A)



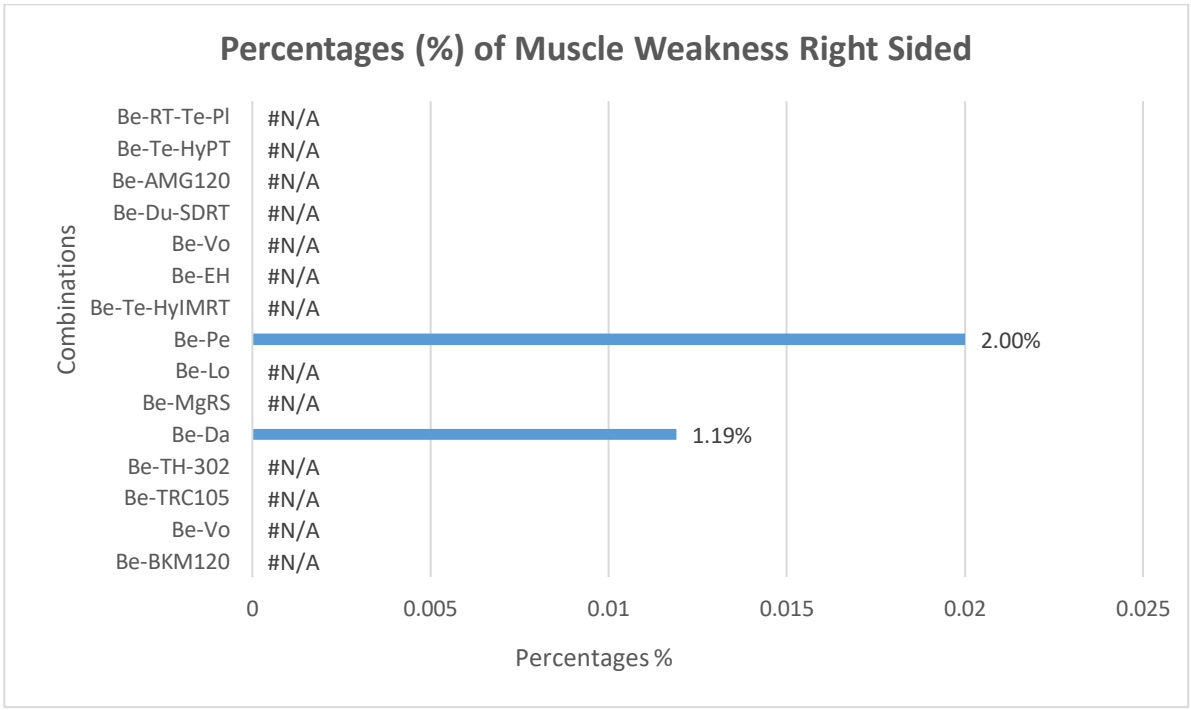
15(B)



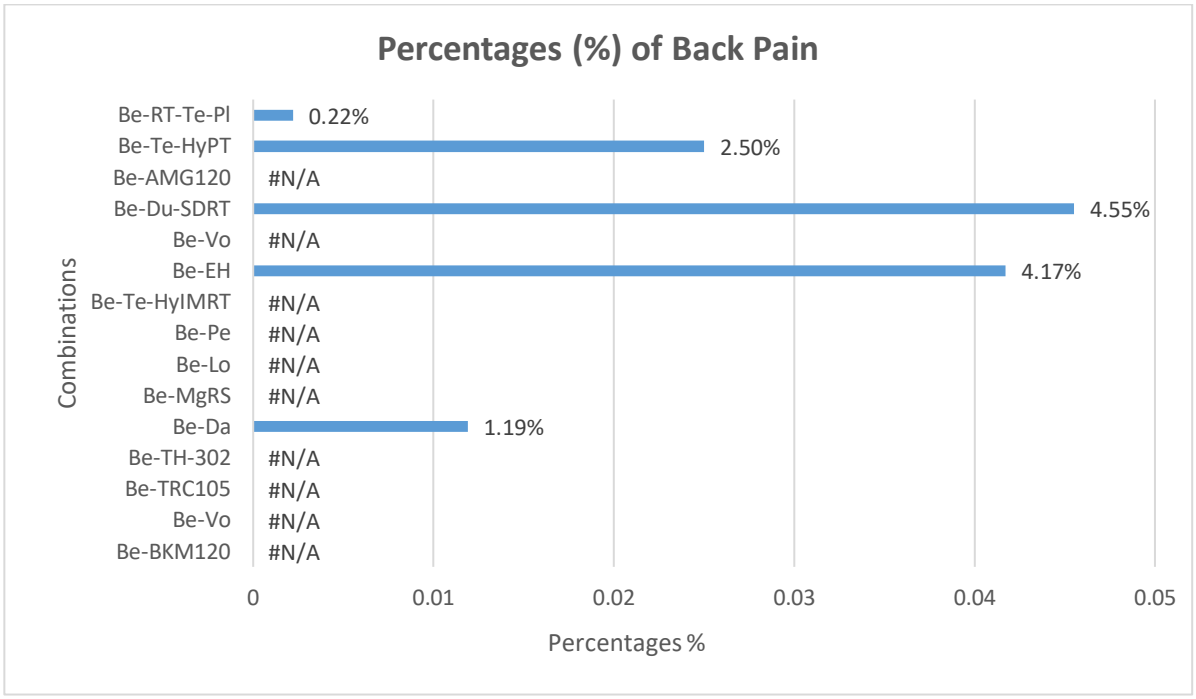
15(C)


Percentages (%) of Muscle Weakness Generalized
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
#N/A
7.50%
2.08%
5.71%
1.19%
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
Percentages %

15(D)


Percentages (%) of Muscle Weakness Right Sided
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
#N/A
2.00%
1.19%
0
0.005
0.01
0.015
0.02
0.025
Percentages %

15(E)



15(F)

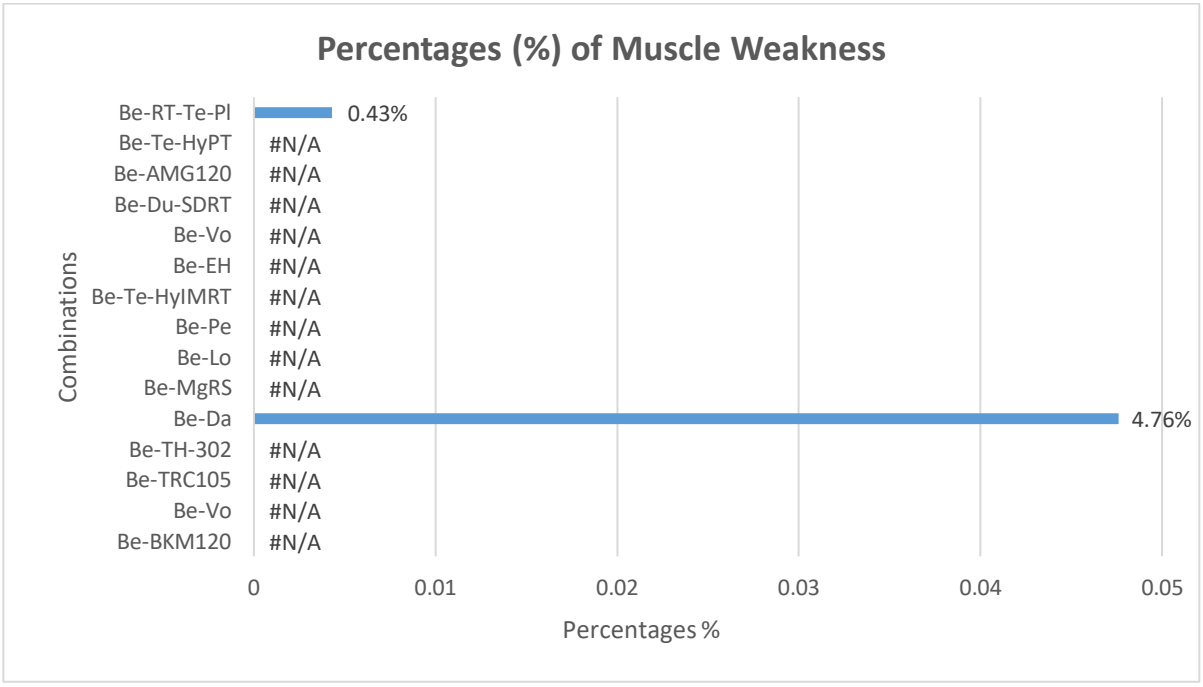


Figure 15: Percentage of musculoskeletal and connective tissue in patients receiving Bevcizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-

TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizmumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Muscle Weakness Left Sided; (B) Muscle Weakness Lowe Limb; (C) Muscle Weakness Generalized; (D) Muscle Weakness Right Sided; (E) Back Pain; (F) Muscle Weakness. The values are presented as percentages in the graphs.

Neoplasms benign, malignant and unspecified (cysts and polyps) is depicted by the following graph:

16(A)

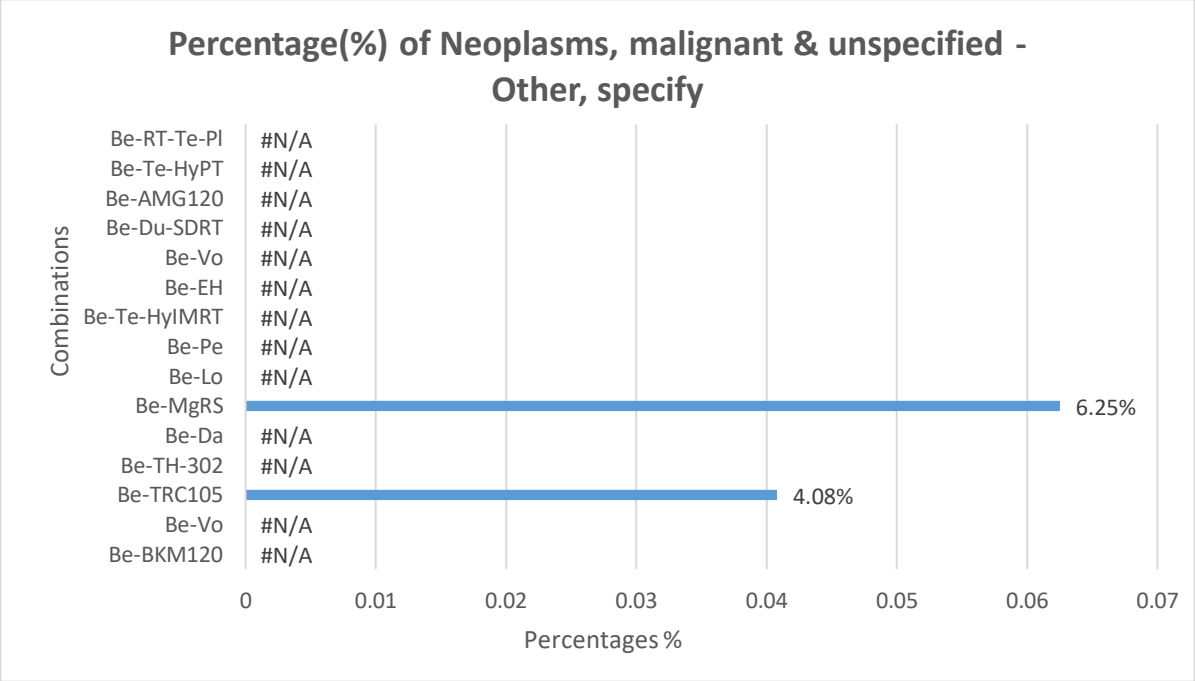
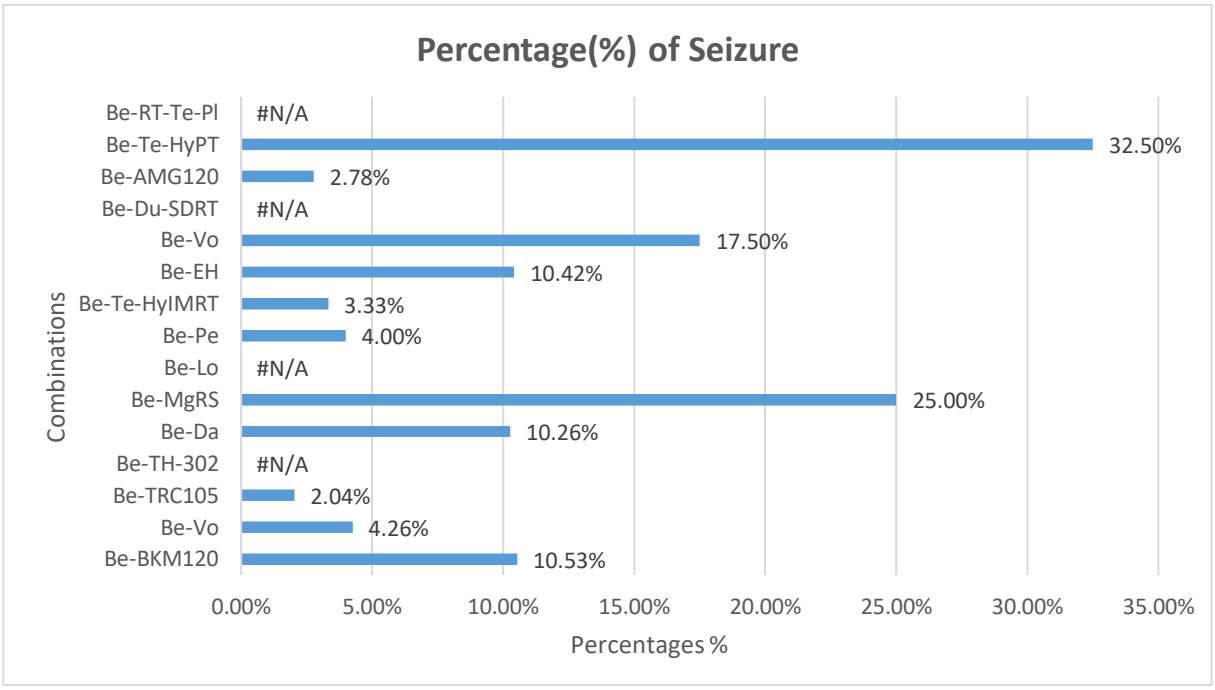


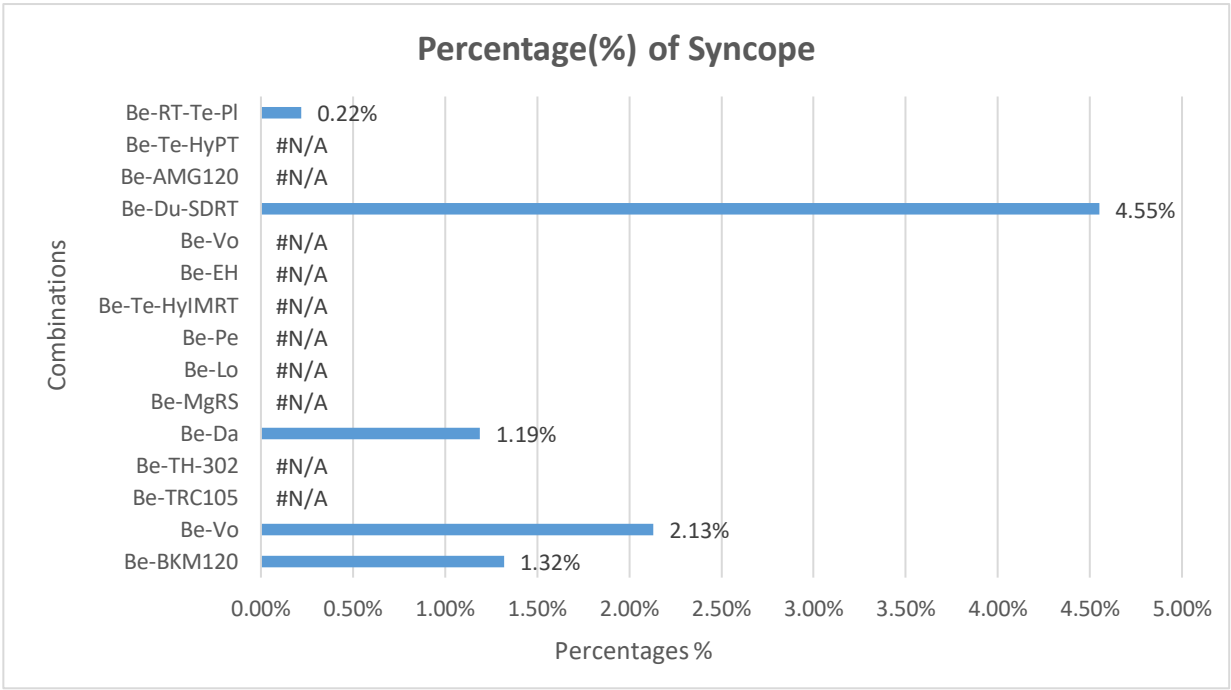
Figure 16: Percentage of neoplasms benign, malignant and unspecified (cysts and polyps) in patients receiving Bevcizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizmumab + Temozolomide + Radiotherapy (Be-Te-RT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Neoplasms benign, malignant and unspecified - Other, specify. The values are presented as percentages in the graphs.

Nervous system disorders are depicted by the following graphs:

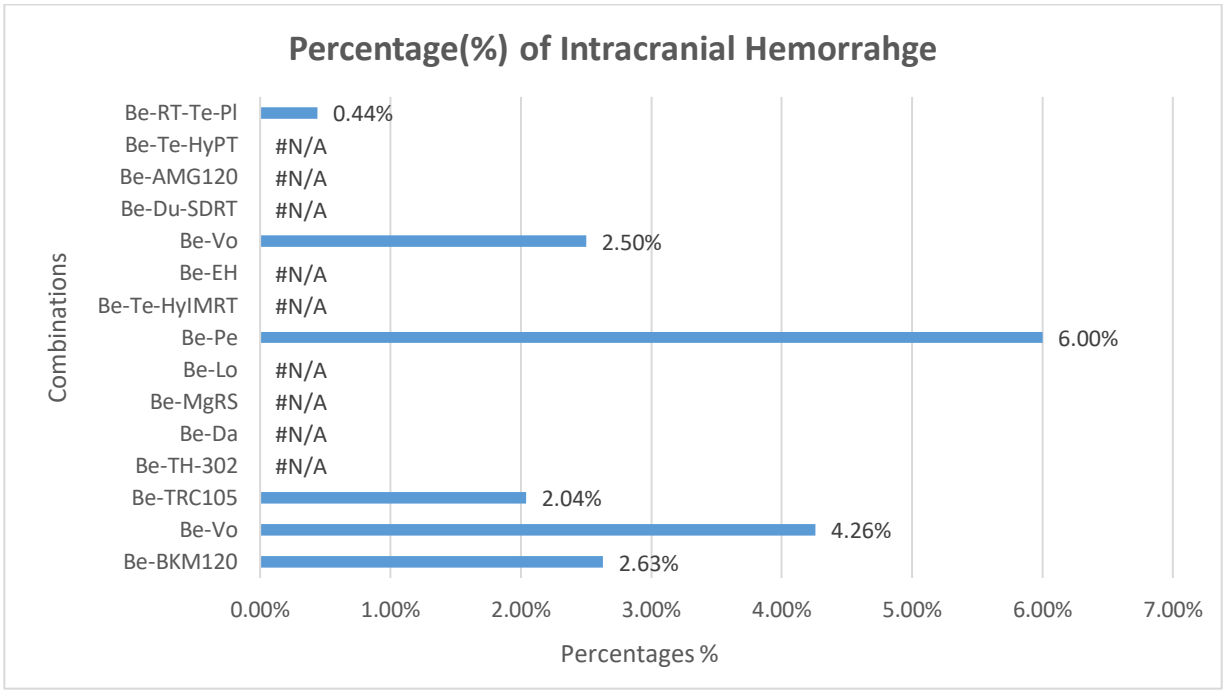
17(A)



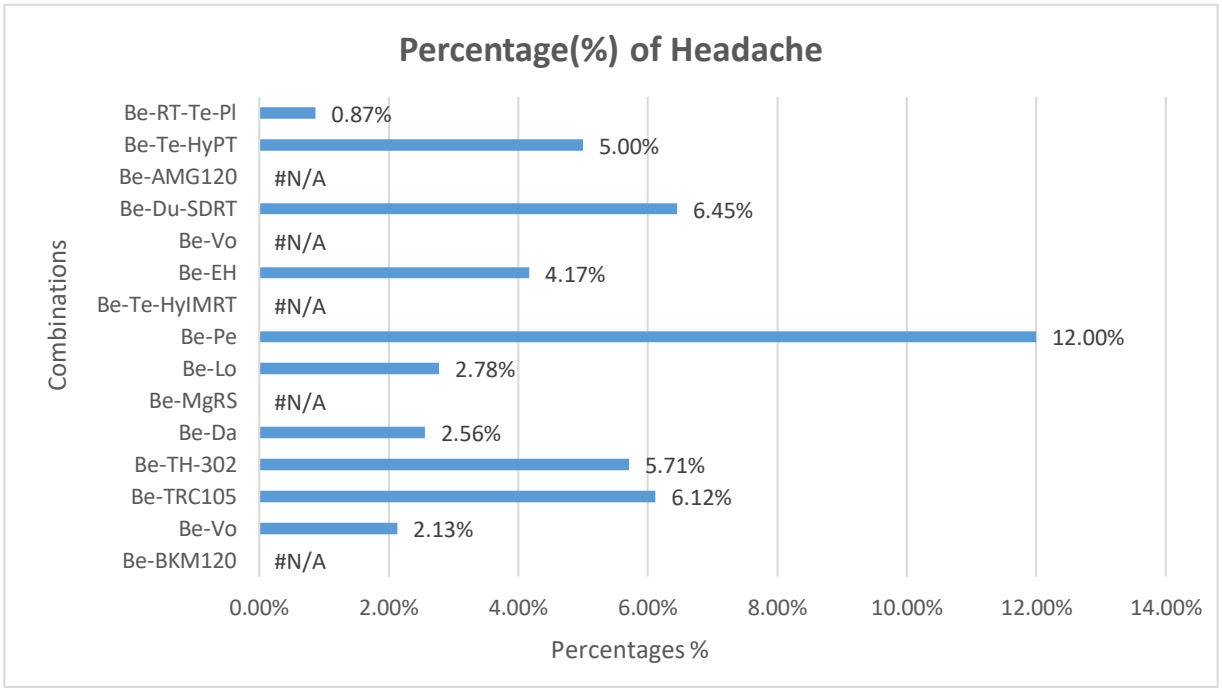
17(B)



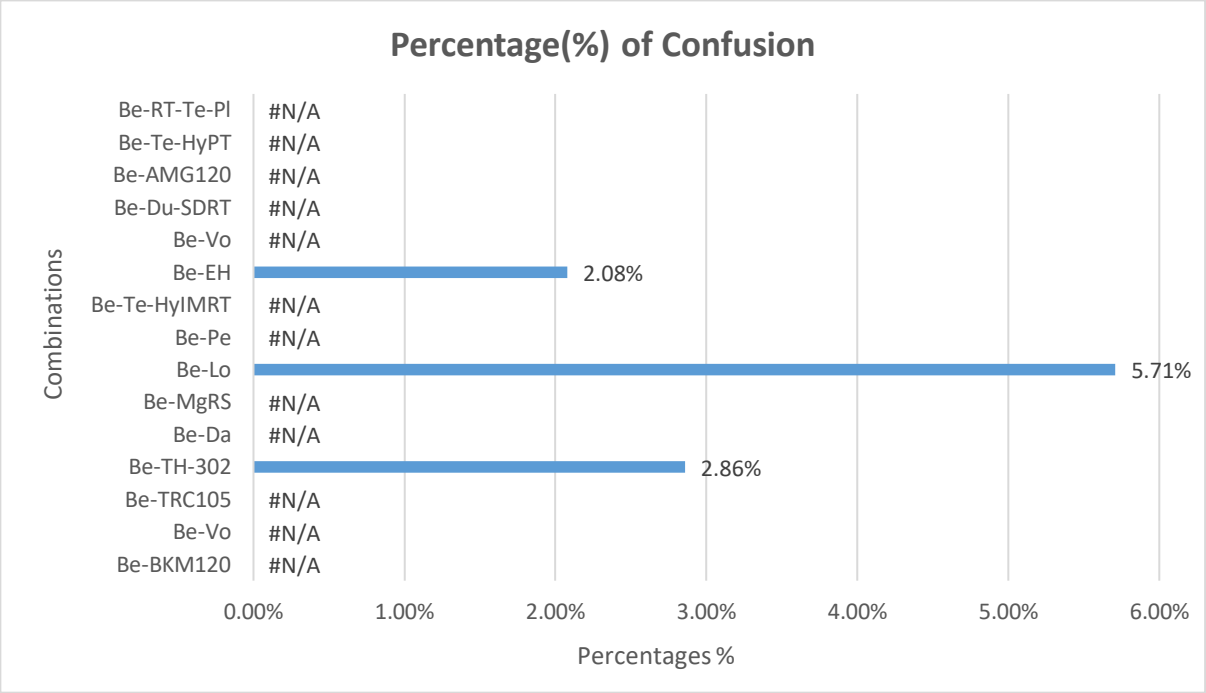
17(C)


Percentage(%) of Intracranial Hemorrahge
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
0.44%
#N/A
#N/A
#N/A
2.50%
#N/A
#N/A
6.00%
#N/A
#N/A
#N/A
#N/A
2.04%
4.26%
2.63%
Combinations
0.00%
1.00%
2.00%
3.00%
4.00%
5.00%
6.00%
7.00%
Percentages %

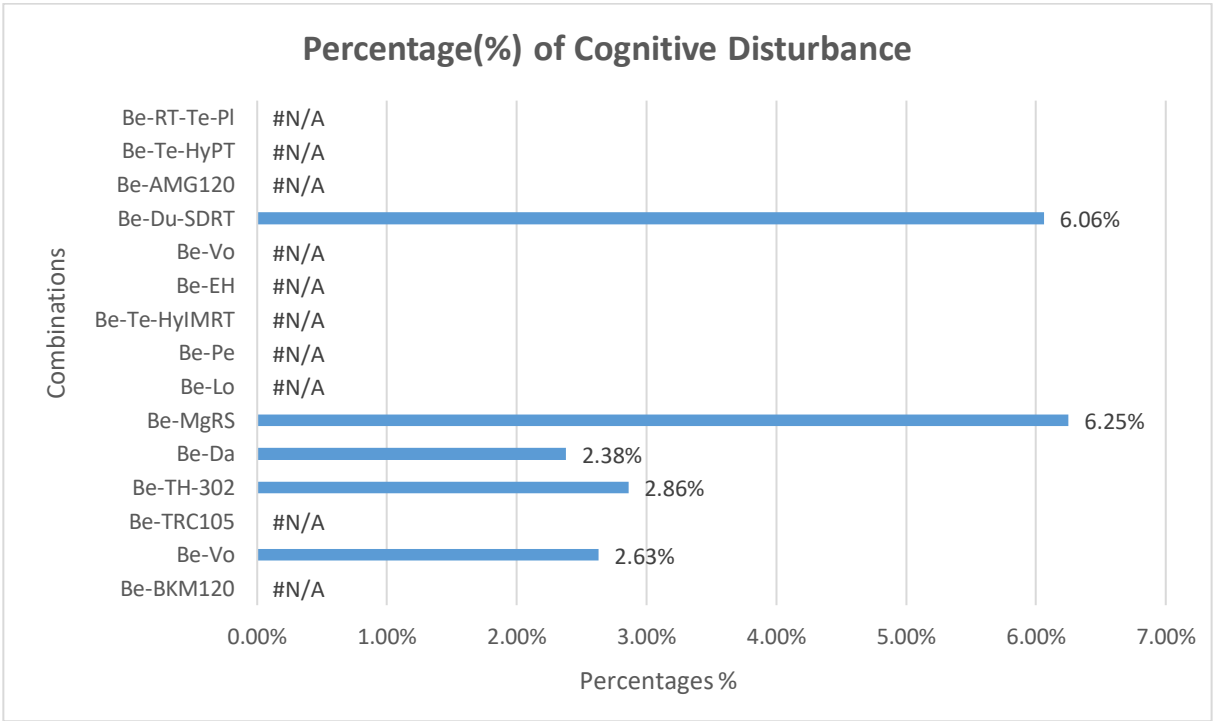
17(D)


Percentage(%) of Headache
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
0.87%
5.00%
#N/A
6.45%
#N/A
4.17%
#N/A
12.00%
2.78%
#N/A
2.56%
5.71%
6.12%
2.13%
#N/A
Combinations
0.00%
2.00%
4.00%
6.00%
8.00%
10.00%
12.00%
14.00%
Percentages %

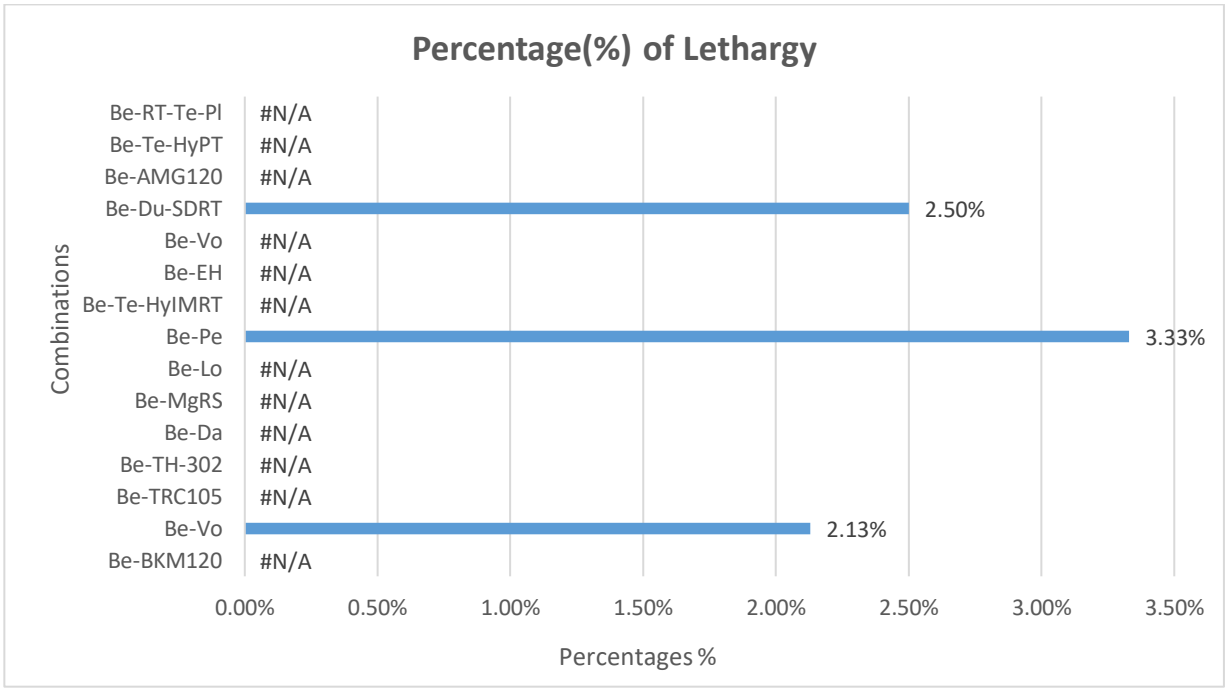
17(E)


Percentage(%) of Confusion
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
#N/A
2.08%
5.71%
2.86%
0.00%
1.00%
2.00%
3.00%
4.00%
5.00%
6.00%
Percentages %

17(F)


Percentage(%) of Cognitive Disturbance
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
#N/A
6.06%
6.25%
2.38%
2.86%
2.63%
0.00%
1.00%
2.00%
3.00%
4.00%
5.00%
6.00%
7.00%
Percentages %

17(G)



17(H)

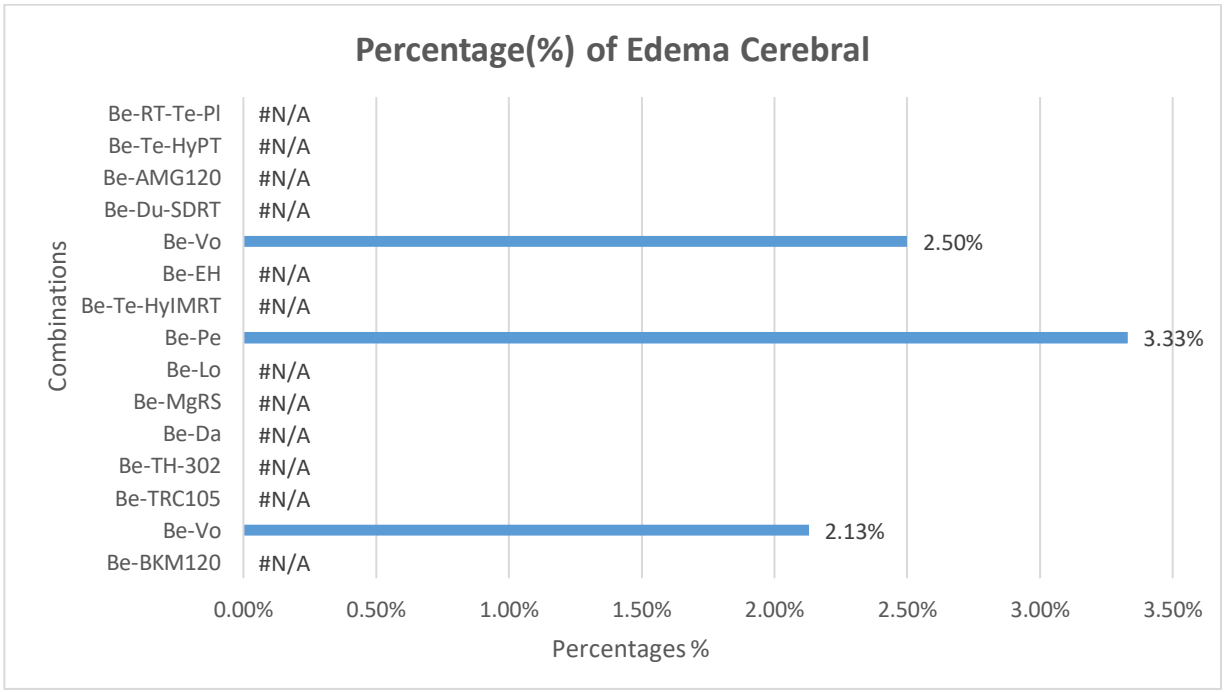
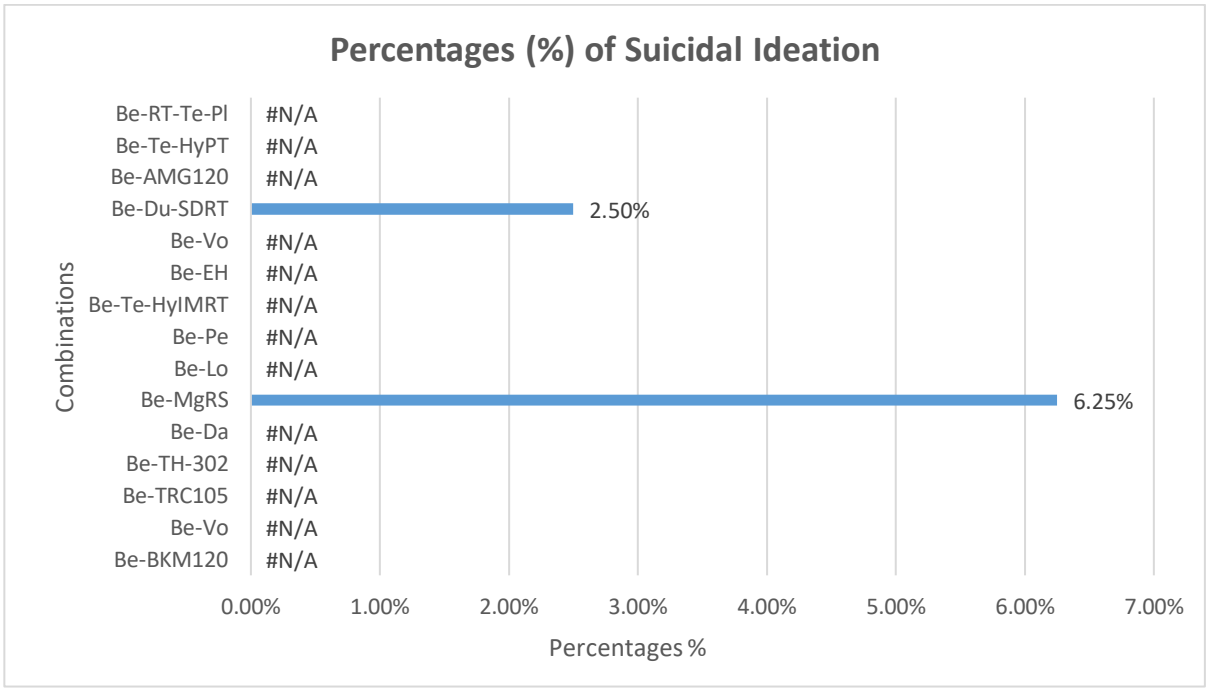


Figure 17: Percentage of nervous system disorders in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-

TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizmumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Seizure; (B) Syncope; (C) Intracranial Hemorrahge; (D) Headache; (E) Confusion; (F) Cognitive Disturbance. (G) Lethargy; (H) Edema Cerebral. The values are presented as percentages in the graphs.

Psychiatric disorders are depicted by the following graphs:

18(A)



18(B)

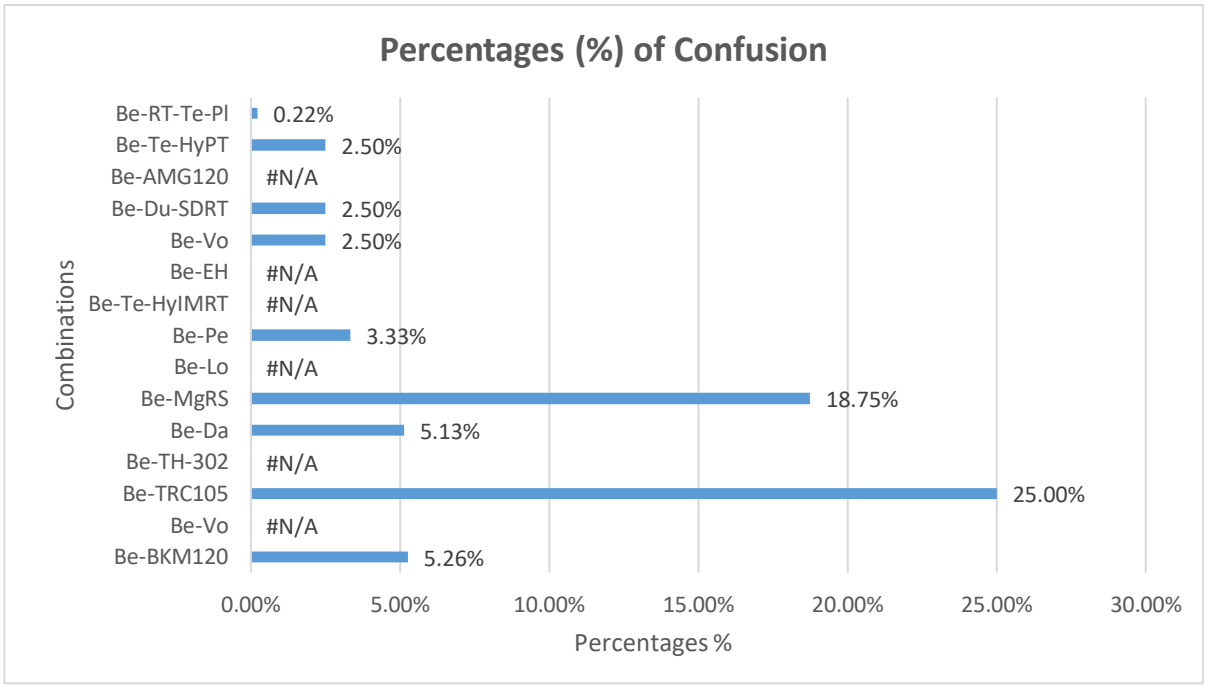
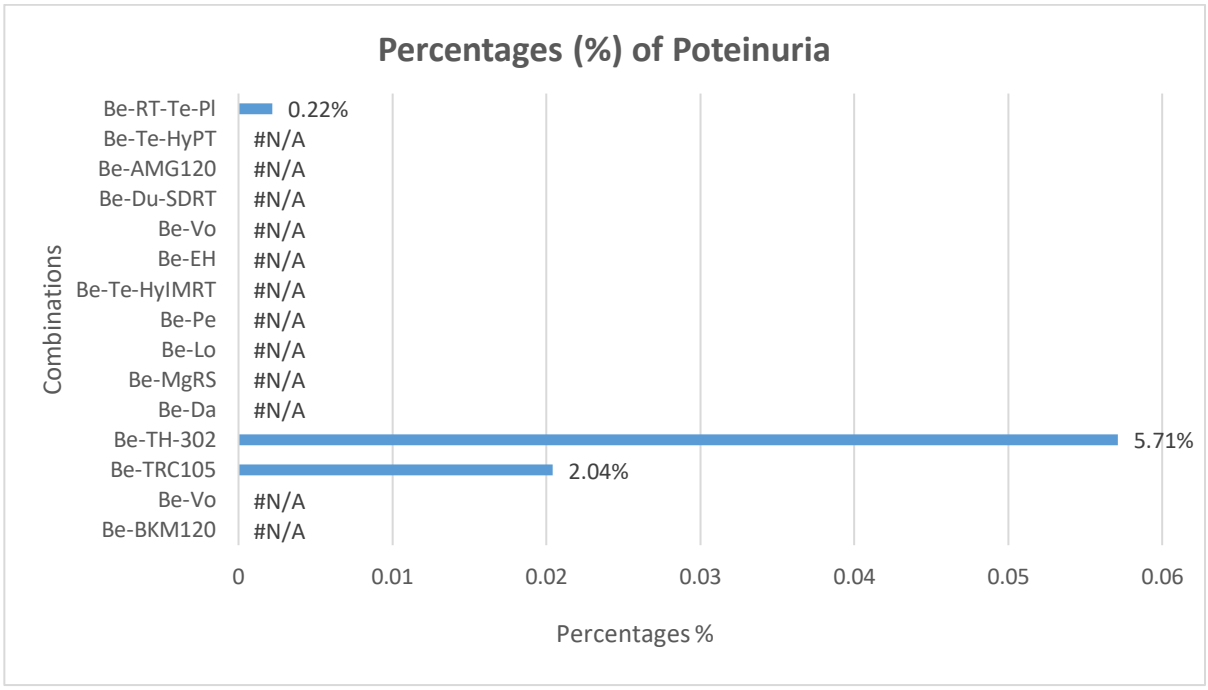


Figure 18: Percentage of psychiatric disorders in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are:

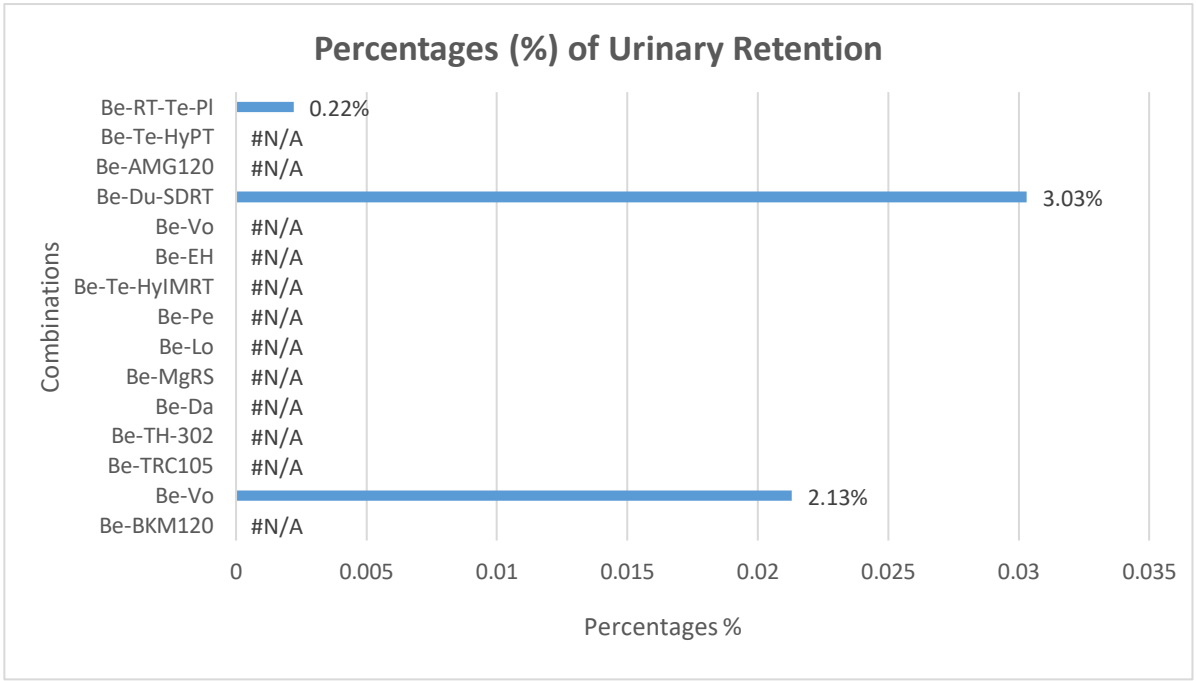
Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizmumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Suicidal Ideation; (B) Confusion. The values are presented as percentages in the graphs.

Renal and urinary disorders are depicted by the following graphs:

19(A)



19(B)



19(C)

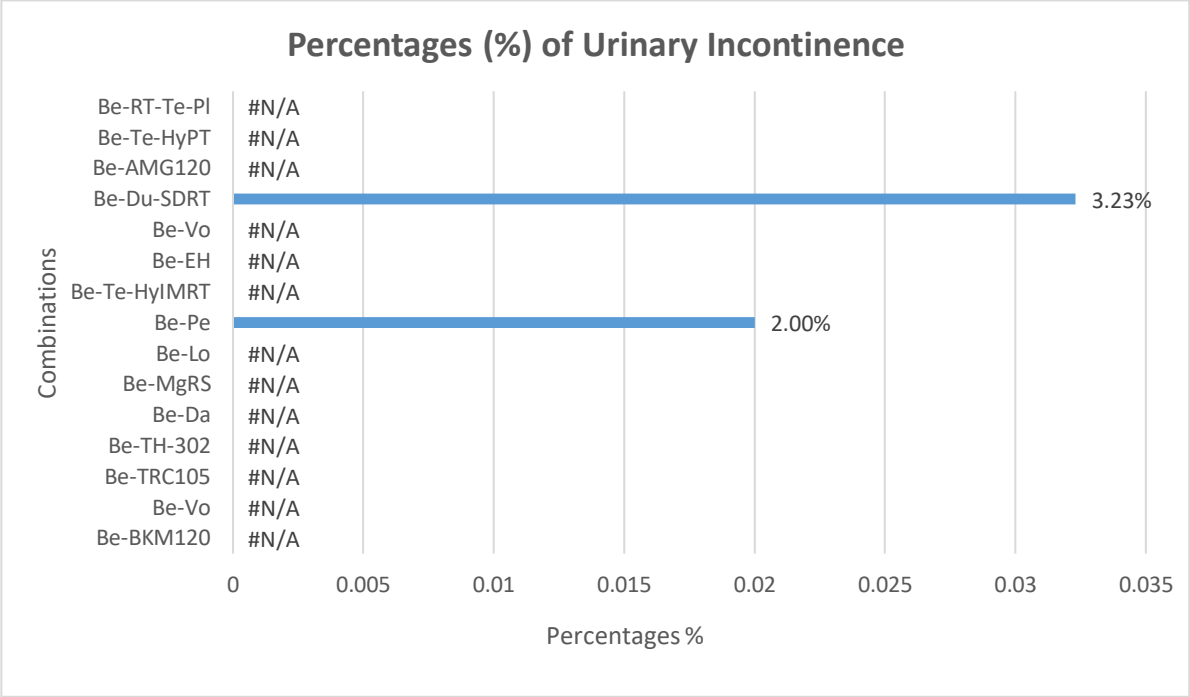
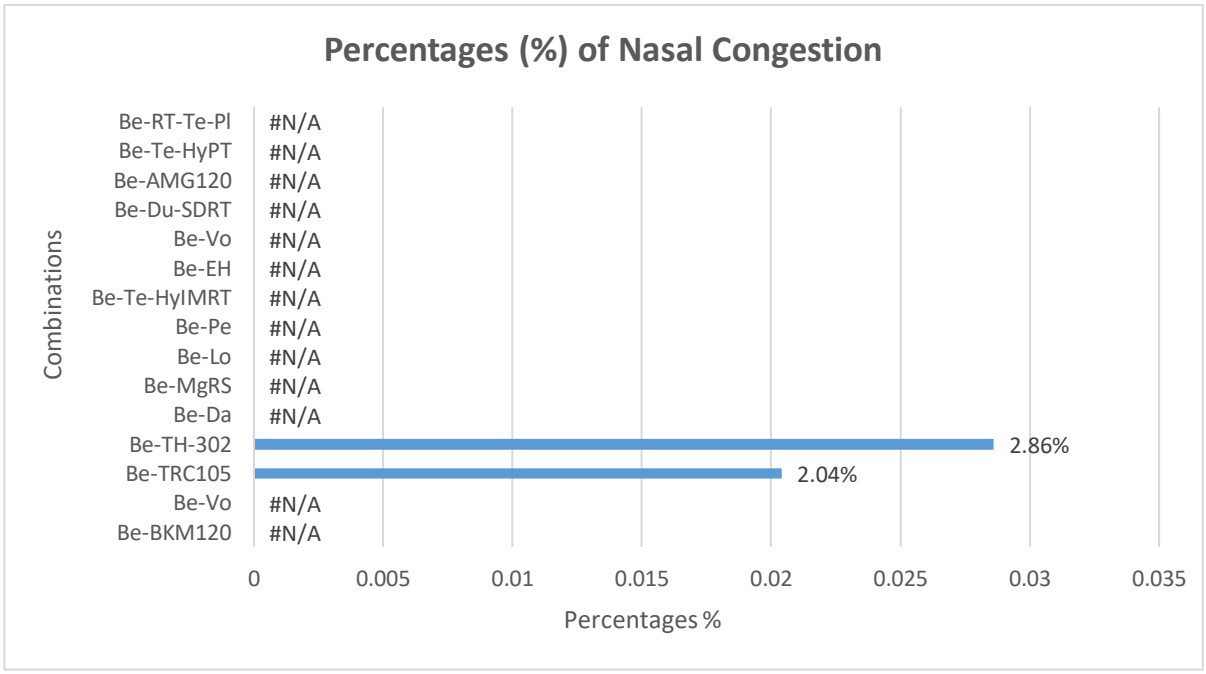


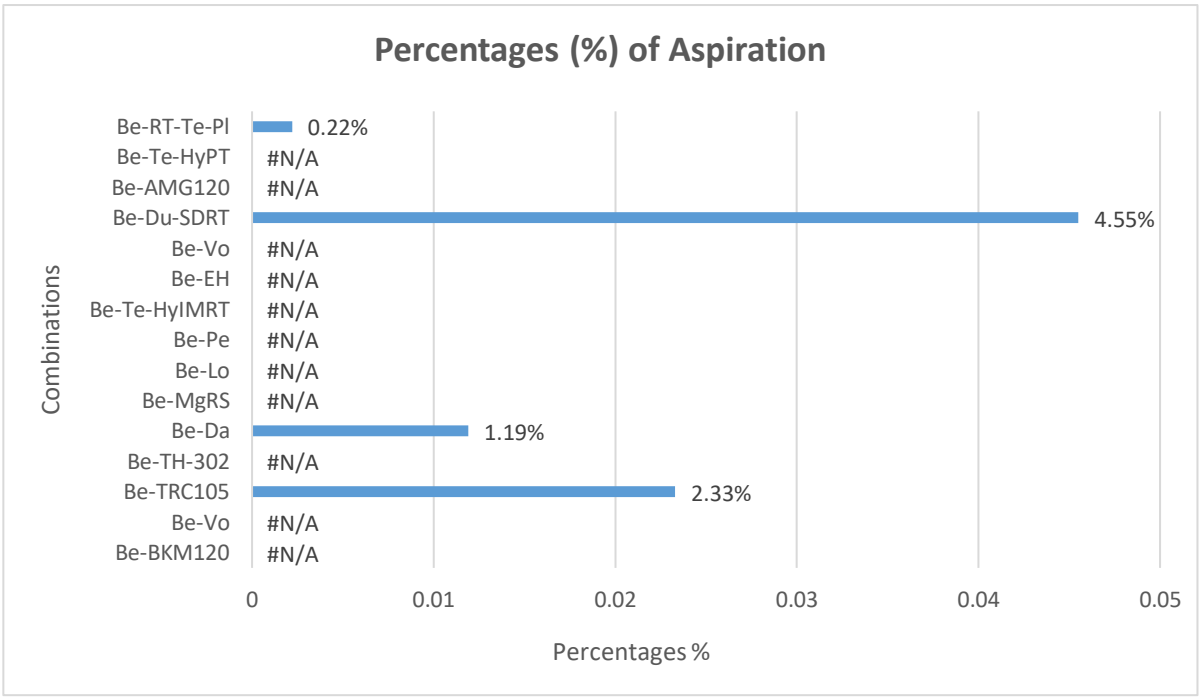
Figure 19: Percentage of infections and infestations in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizmumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Proteinuria; (B) Urinary Retention; (C) Urinary Incontinence. The values are presented as percentages in the graphs.

Respiratory, thoracic and mediastinal disorders are depicted by the following graphs:

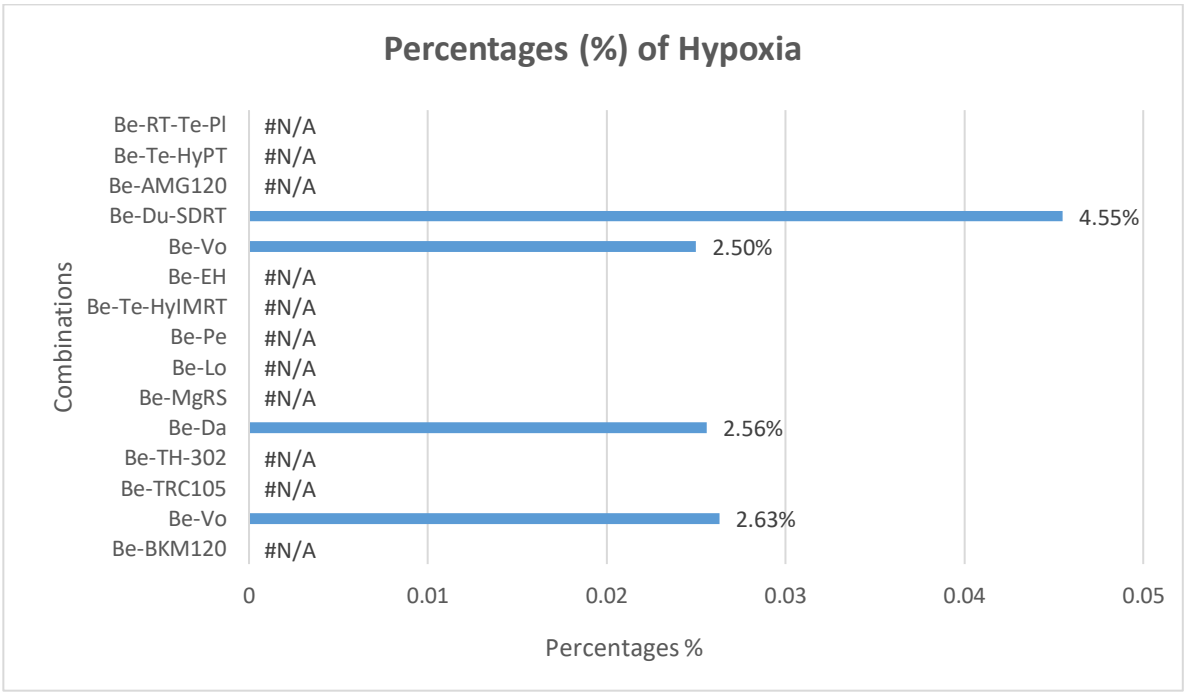
20(A)



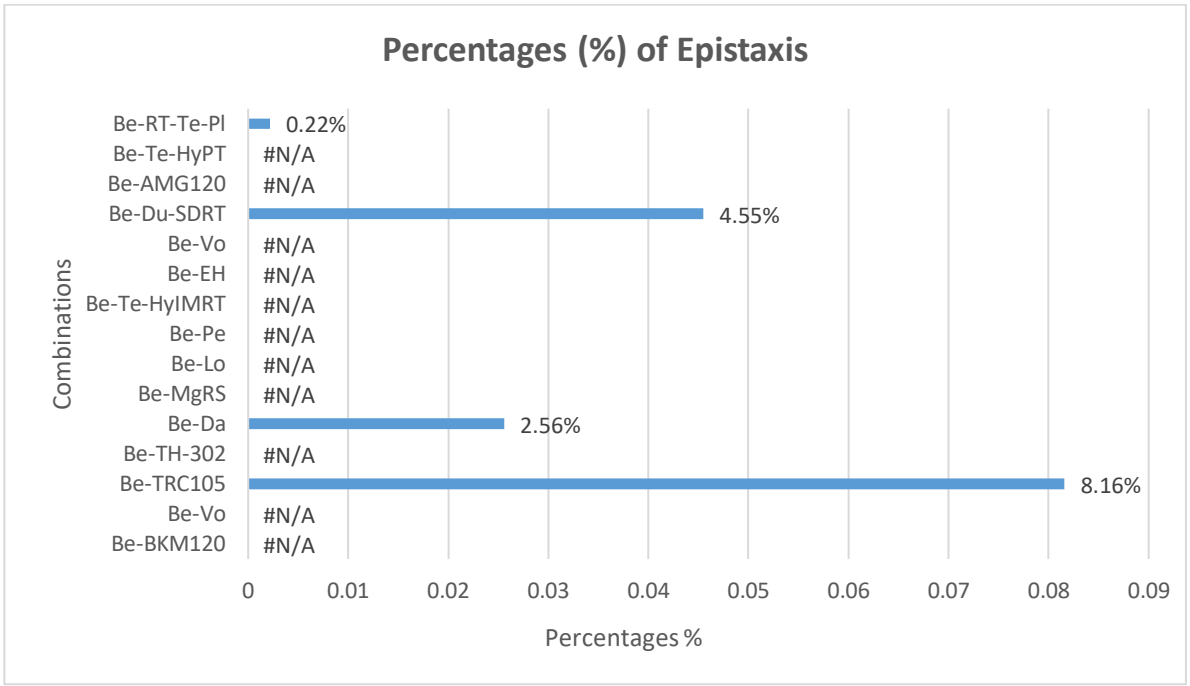
20(B)



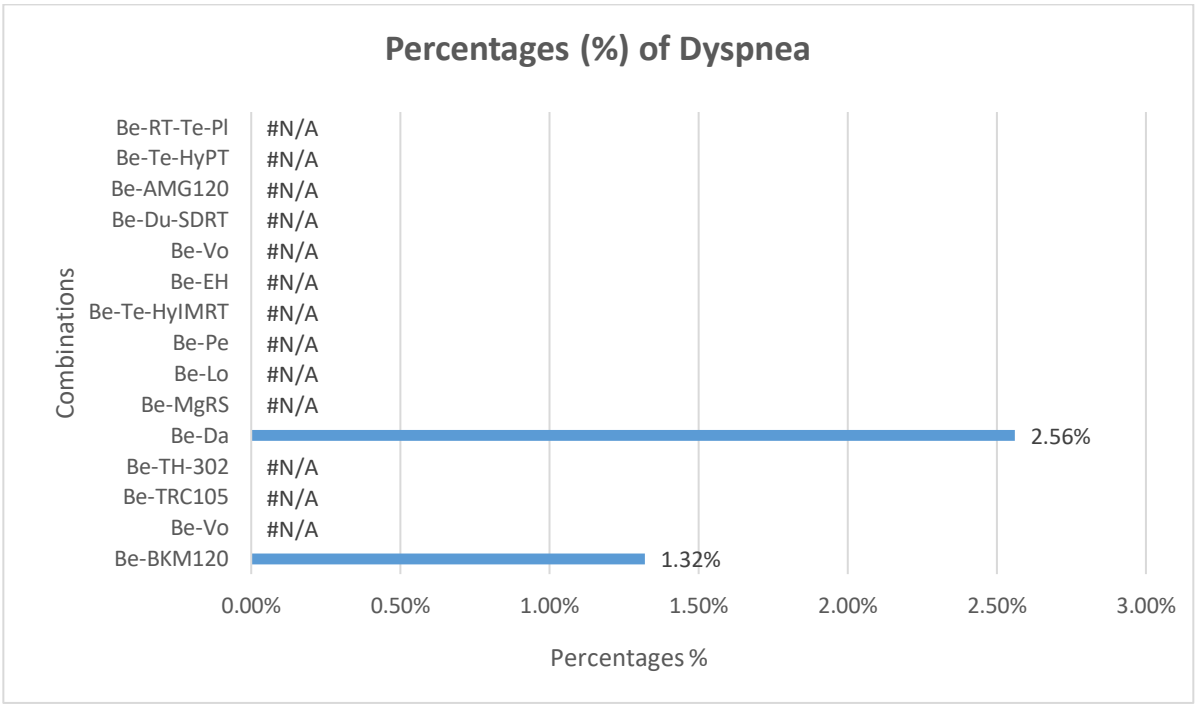
20(C)


Percentages (%) of Hypoxia
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
#N/A
#N/A
#N/A
4.55%
2.50%
#N/A
#N/A
#N/A
#N/A
#N/A
2.56%
#N/A
#N/A
2.63%
#N/A
0
0.01
0.02
0.03
0.04
0.05
Percentages %

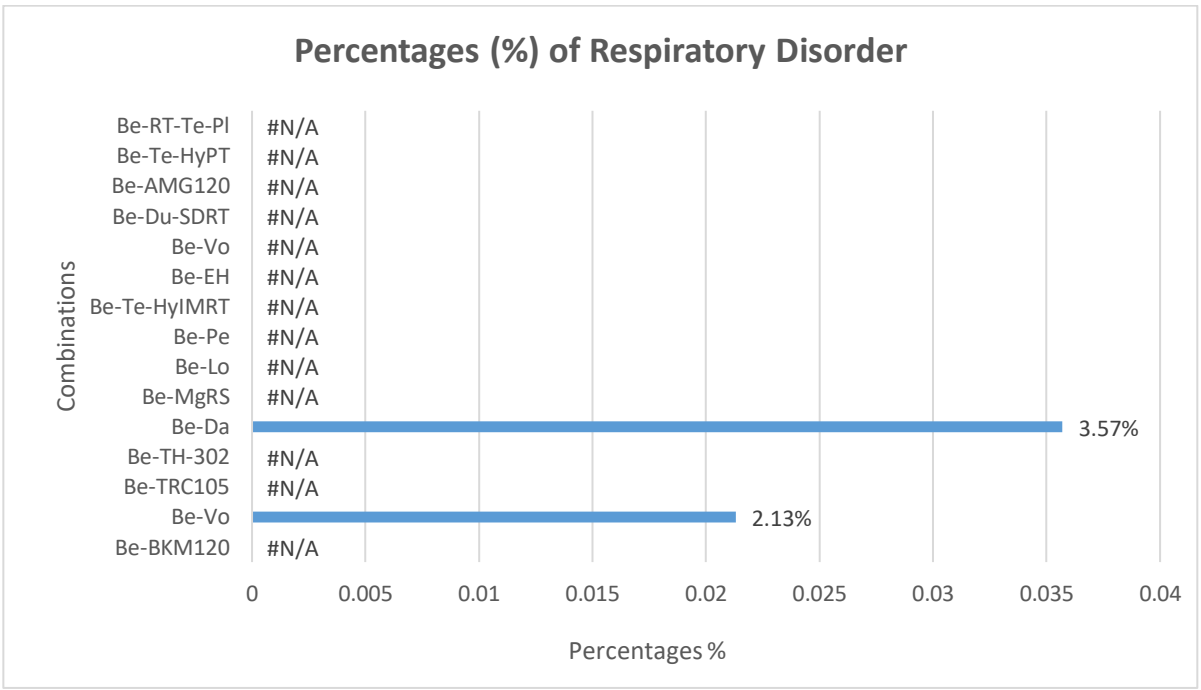
20(D)


Percentages (%) of Epistaxis
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
0.22%
#N/A
#N/A
4.55%
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
2.56%
#N/A
8.16%
#N/A
#N/A
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09
Percentages %

20(E)


Percentages (%) of Dyspnea
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
#N/A
2.56%
1.32%
0.00%
0.50%
1.00%
1.50%
2.00%
2.50%
3.00%
Percentages %

20(F)


Percentages (%) of Respiratory Disorder
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
#N/A
3.57%
2.13%
0
0.005
0.01
0.015
0.02
0.025
0.03
0.035
0.04
Percentages %

20(G)

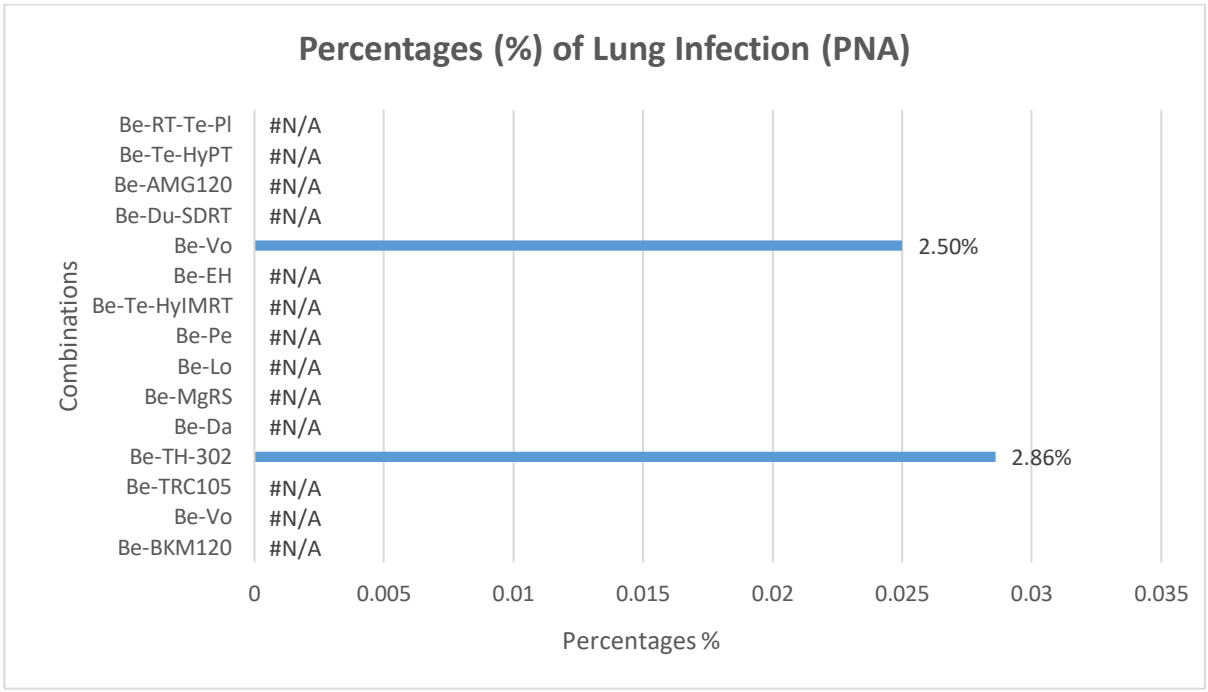
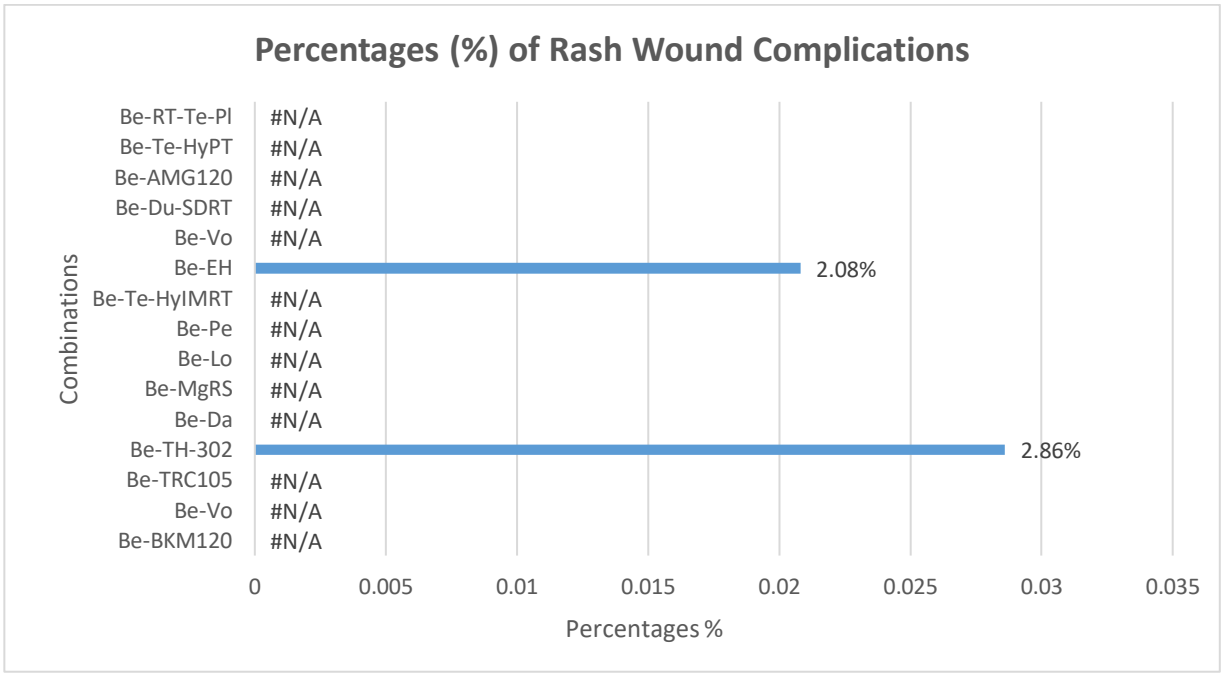


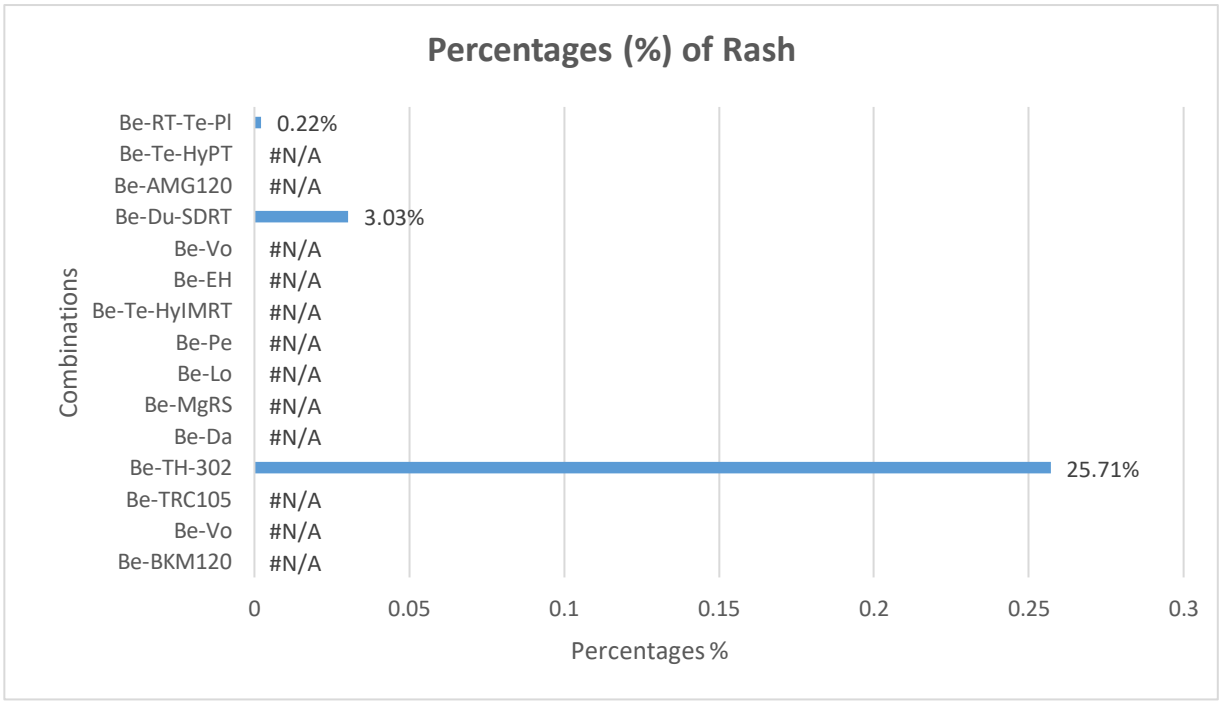
Figure 20: Percentage of respiratory, thoracic and mediastinal disorders in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH-302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Nasal Congestion; (B) Aspiration; (C) Hypoxia; (D) Epistaxis; (E) Dyspnea; (F) Respiratory Disorders; (G) Lung Infection (PNA). The values are presented as percentages in the graphs.

Skin and subcutaneous tissue disorders are depicted by the following graphs:

21(A)



21(B)



21(C)

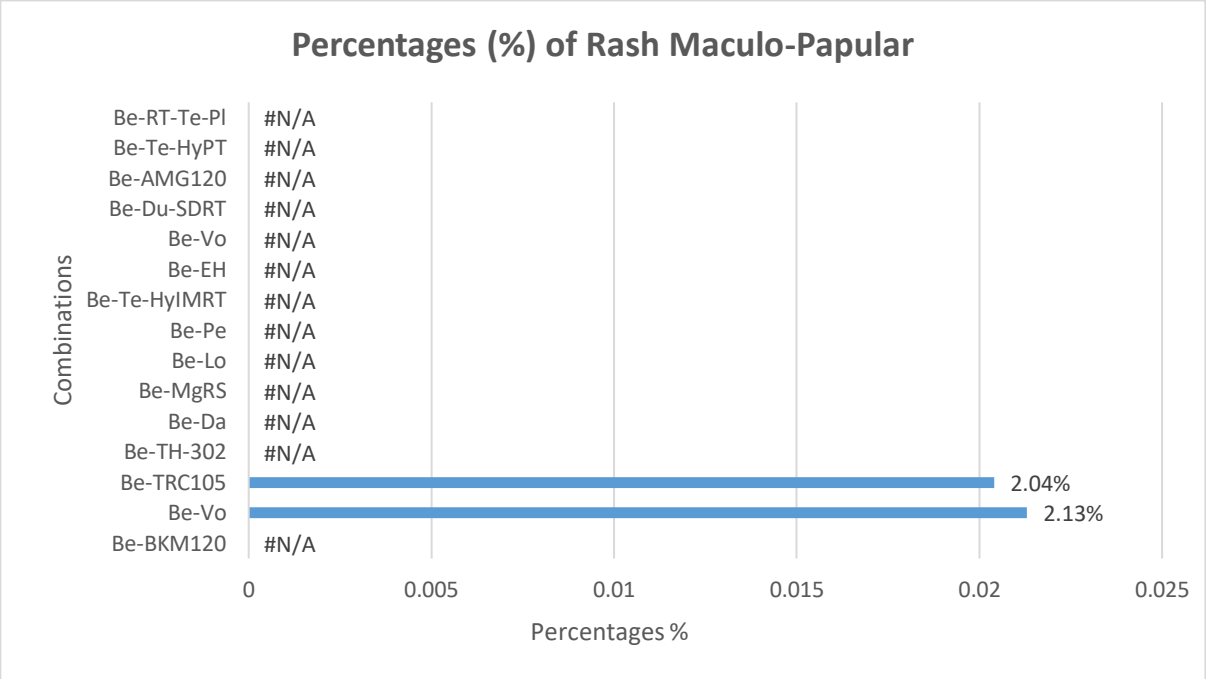
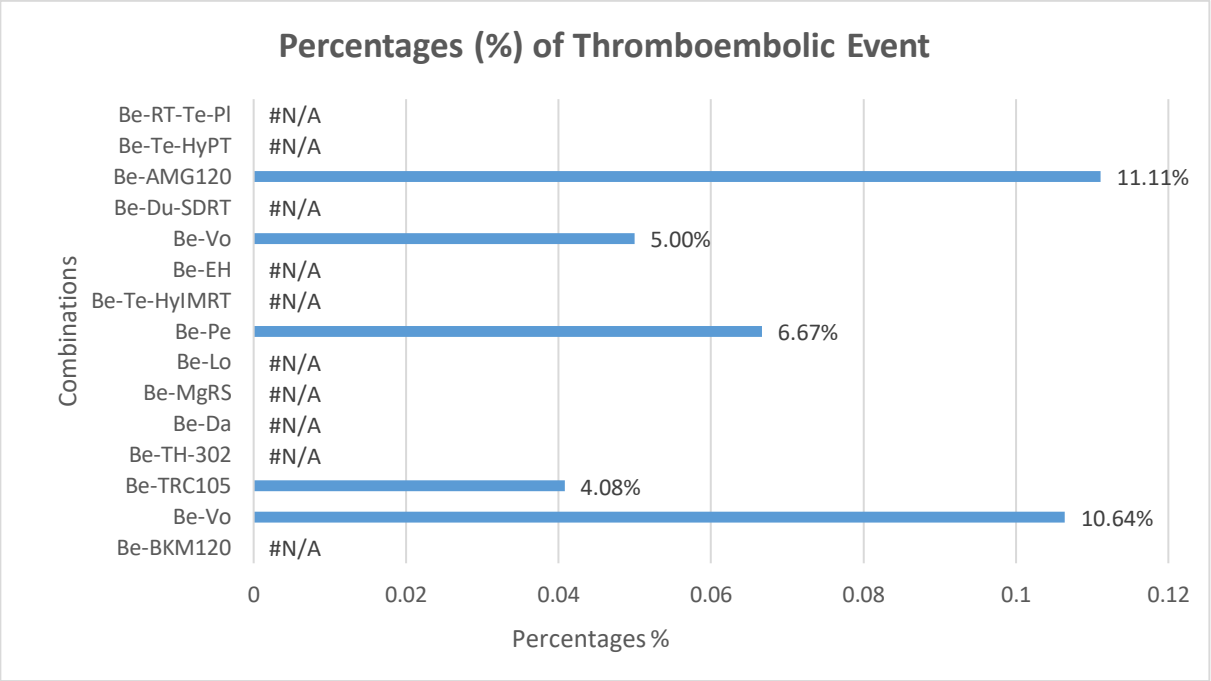


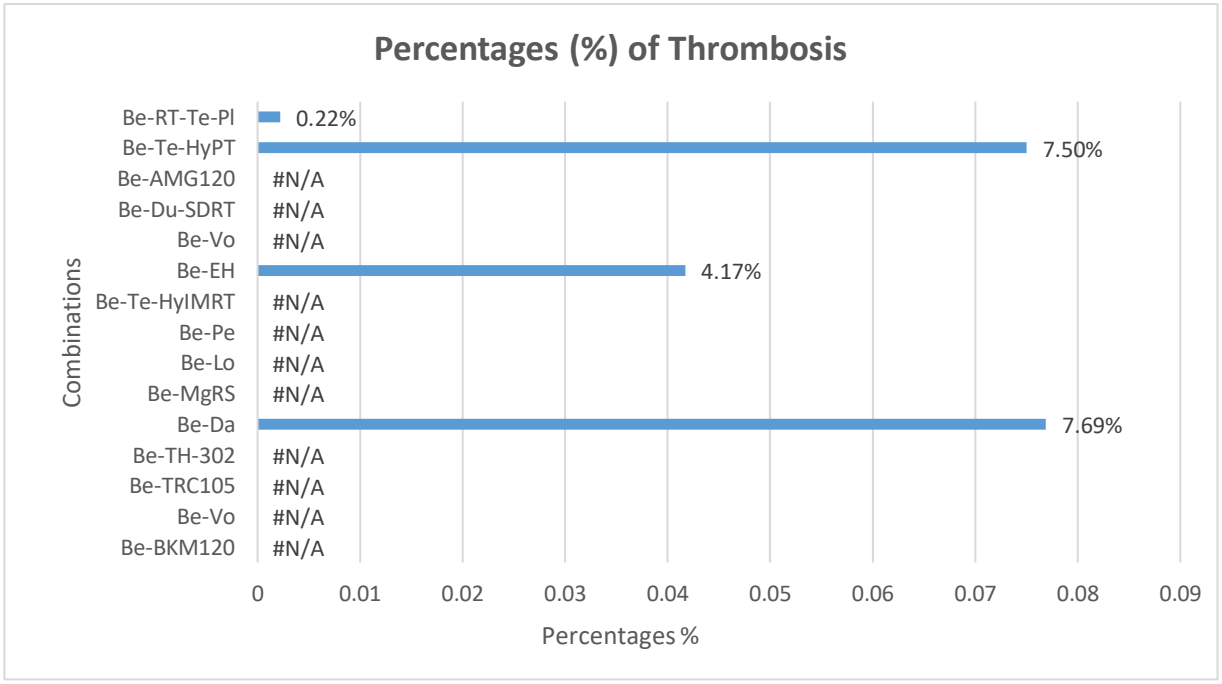
Figure 21: Percentage of infections and infestations in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Wound Complications; (B) Rash; (C) Rash Maculo-Papular. The values are presented as percentages in the graphs.

Vascular disorders are depicted by the following graphs:

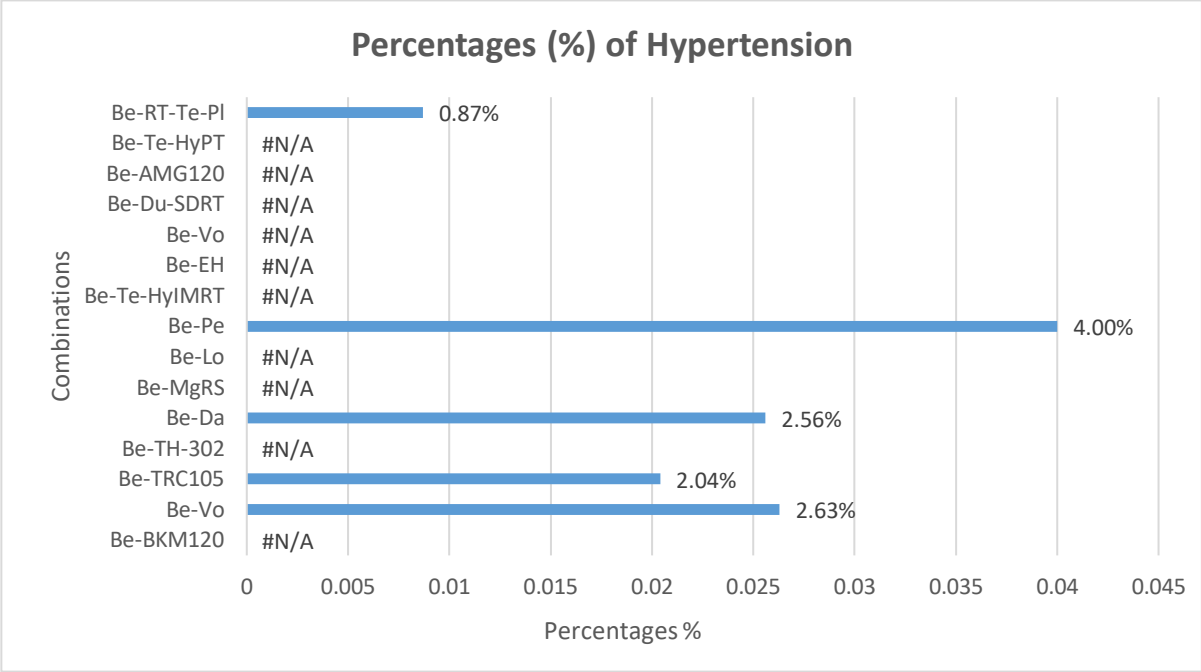
22(A)



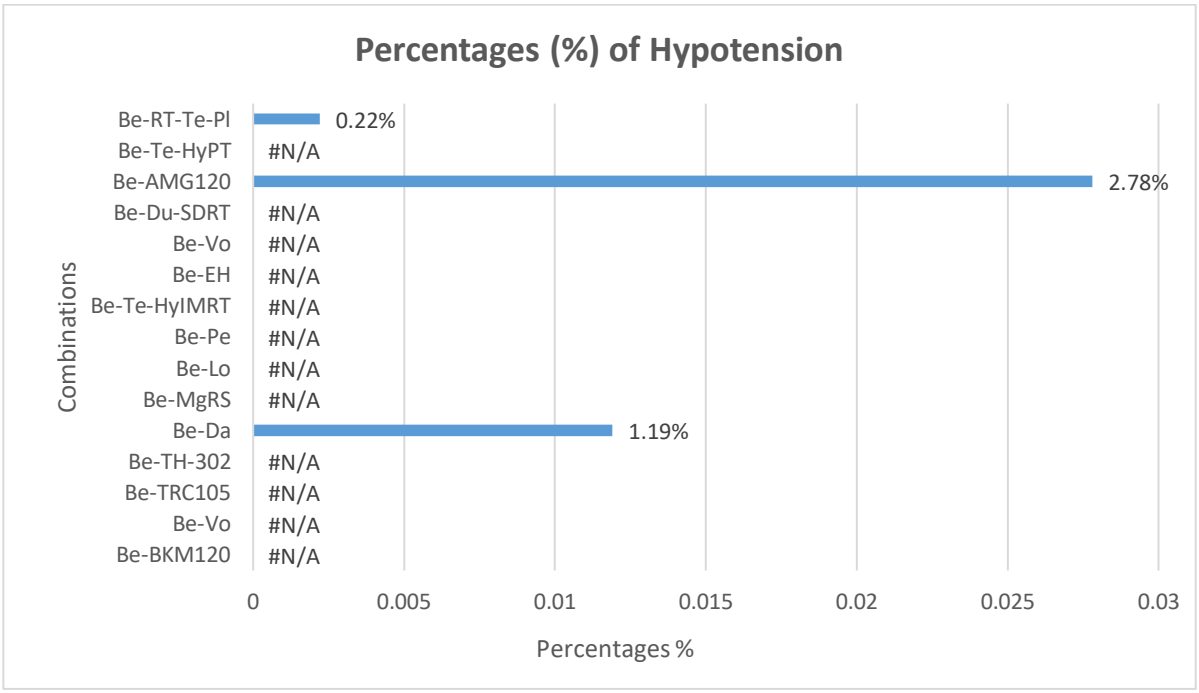
22(B)



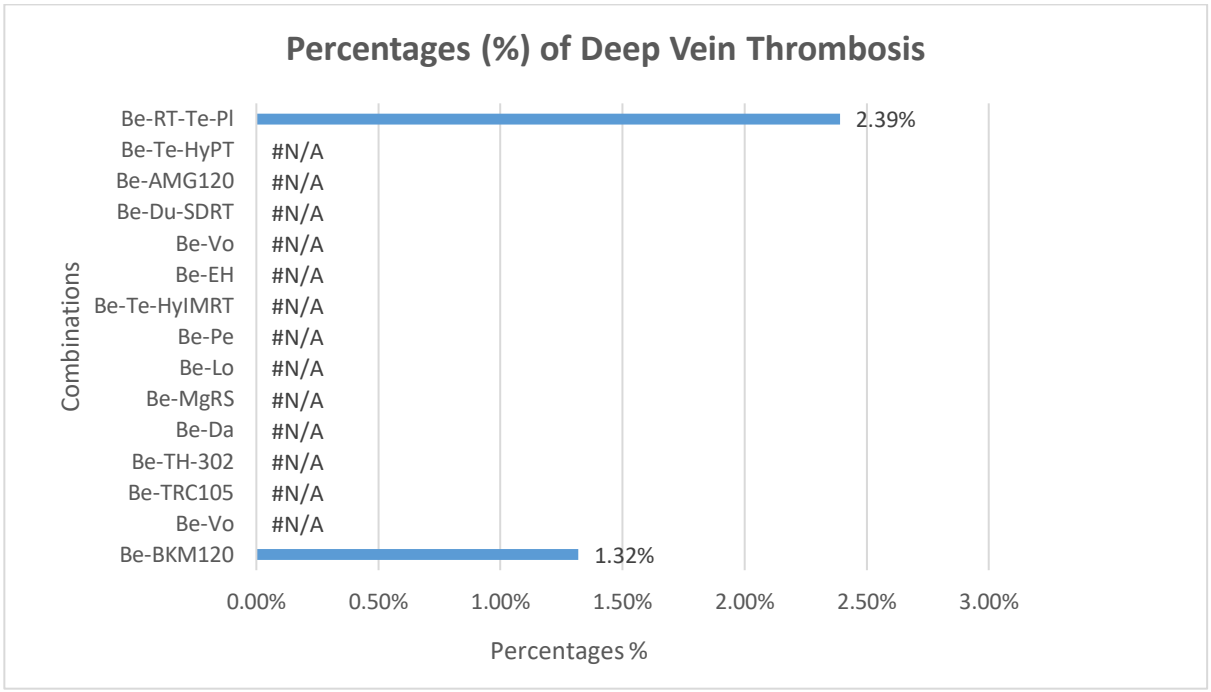
22(C)


Percentages (%) of Hypertension
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
0.87%
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
4.00%
#N/A
#N/A
2.56%
#N/A
2.04%
2.63%
#N/A
0
0.005
0.01
0.015
0.02
0.025
0.03
0.035
0.04
0.045
Percentages %

22(D)


Percentages (%) of Hypotension
Combinations
Be-RT-Te-Pl
Be-Te-HyPT
Be-AMG120
Be-Du-SDRT
Be-Vo
Be-EH
Be-Te-HyIMRT
Be-Pe
Be-Lo
Be-MgRS
Be-Da
Be-TH-302
Be-TRC105
Be-Vo
Be-BKM120
0.22%
#N/A
2.78%
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
1.19%
#N/A
#N/A
#N/A
#N/A
0
0.005
0.01
0.015
0.02
0.025
0.03
Percentages %

22(E)



22(F)

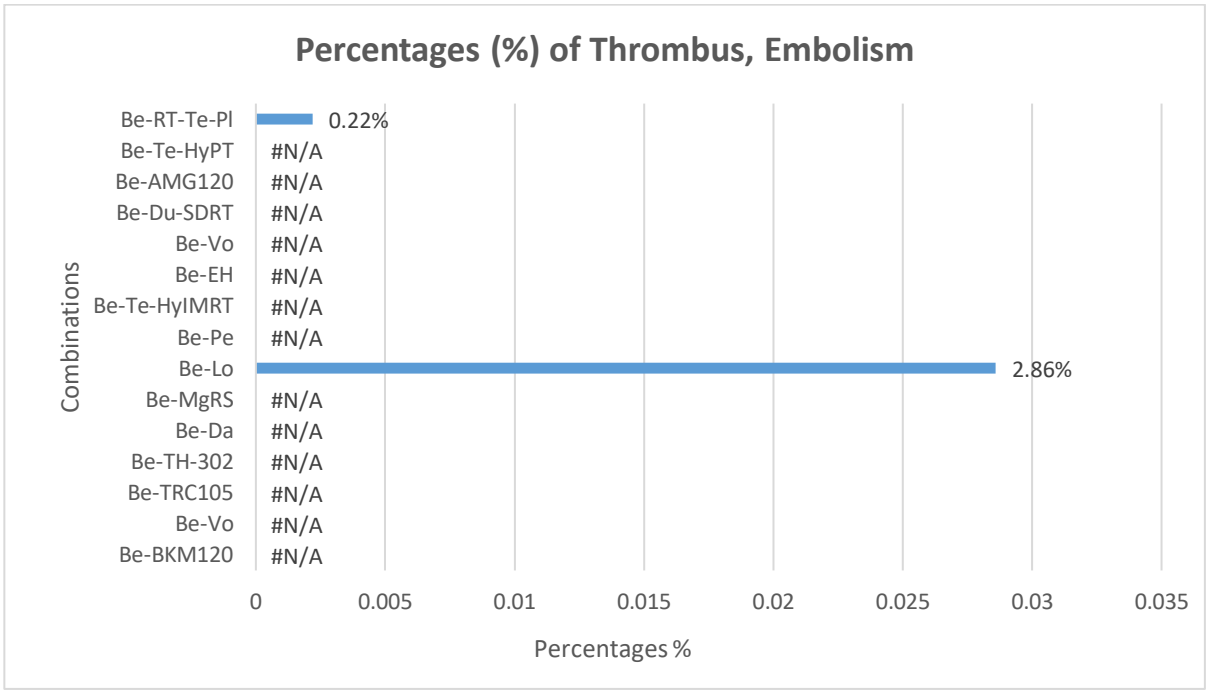


Figure 22: Percentage of infections and infestations in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-

TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab + Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). (A) Thromboembolic Event; (B) Thrombosis; (C) Hypertension; (D) Hypotension; (E) Deep Vein Thrombosis; (F) Thrombus, Embolism. The values are presented as percentages in the graphs.

3.3.3 Mortality Rate:

In terms of mortality or death rate, patients receiving the combination of Bevacizumab + Temozolomide + Hypofractionated RT had the greatest mortality rate of 100% (according to NCT00782756) and patients who received the treatment of the combination of Bevacizumab + TH- 302 (Evofosfomide) had no mortality of 0.00% (according to NCT02342379) and Bevacizumab + Vorionstat had the lowest mortality rate of 2.13% (according to NCT01266031). The mortality rate of 5 out 15 studies were not found yet.

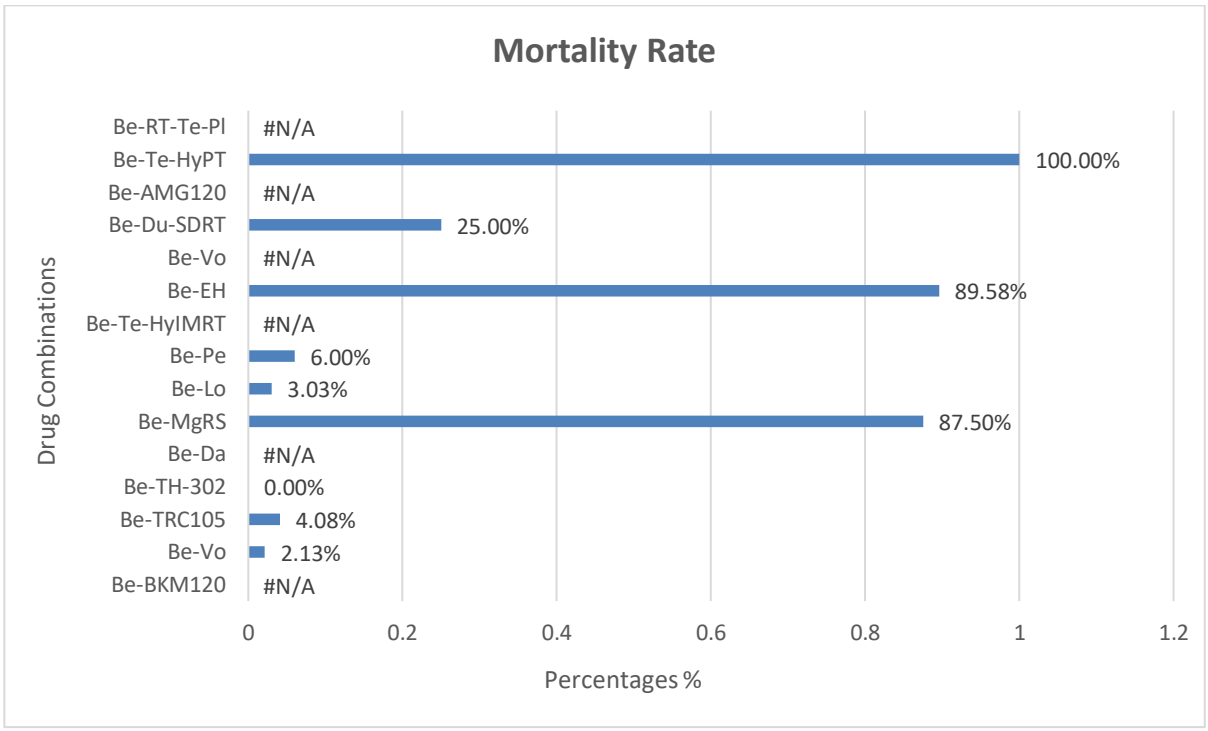


Figure 23: Mortality rate in patients receiving Bevacizumab and drug and therapy combination treatment. The different combinations that were observed are: Bevacizumab+BKM120 or oral inhibitor of PI3 kinase (Be-BKM120), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + TRC 105 (Be-TRC105), Bevacizumab + TH- 302 or Evofosfomide (Be-TH 302), Bevacizumab + Dasatinib or Placebo (Be-Da), Bevacizumab + Magnetic Radiosurgery (Be-MgRS), Bevacizumab + Lomustine (Be-Lo), Bevacizumab +/- Pembrolizumab (Be-Pe), Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy (Be-Te-HyIMRT), Bevacizumab +

Erlotinib Hydrochloride (Be-EH), Bevacizumab + Vorionstat (Be-Vo), Bevacizumab + Durvalumab + Standard Radiotherapy (Be-Du-SDRT), Bevacizumab + AMG 102 (Be-AMG120), Bevacizumab + Temozolomide + Hypofractionated Radiotherapy (Be-Te-HyRT), Bevacizumab + RT + Temozolomide + Placebo (Be-RT-Te-Pl). The values are presented as percentages in the graphs.

Chapter 4: Discussion

In this study, based on the outcome or efficacy of the treatment including response to the treatment such as OS, PFS, time on treatment, treatment related adverse effects and death rate, 15 various types of drug and therapy combinations with the drug "Bevacizumab" are evaluated. Bevacizumab is known as a recombinant humanized monoclonal immunoglobulin G1 (IgG1) antibody. With the great affinity and by attaching to the all human VEGF isoforms, it neutralizes the biologic actions of VEGF and this neutralization occurs by inhibiting the attachment of VEGF to the endothelial cell receptors which are VEGFR-1 and VEGFR-2. Bevacizumab has six framework sections of a VEGF-binding murine monoclonal antibody. Angiogenesis and the modulation of vascular permeability of the blood-brain barrier are both important functions of VEGF. Bevacizumab binds to VEGF and blocks it from interacting with the endothelial cell surface receptors VEGFR-1 and VEFGR-2. Neutralizing VEGF's biological action inhibits tumor growth and vasogenic cerebral edema via reducing tumor angiogenesis (Gil-Gil et al., 2013). Though a few clinical trials of phase II and phase III was not succeed to a meaningful overall survival benefit but secured documentation of extended progression free survival was detected by the usage of newly diagnosed bevacizumab (AVAglioB021990 and RTOG-0825) in GBM patients (García-Romero et al., 2020). In addition, Bevacizumab alone does not improve health-related quality of life (HRQoL) of recently investigated GBM participants, the key question is whether it improves HRQoL throughout the period of progression free survival. End long documentation from the two studies of AVAglio and RTOG 0825 shows that there is no effect on HRQoL in the period of progression free survival when the addition of bevacizumab to standard-of-care treatment has occured, but the NRG study, which may include patients with tumor progression, greater symptom burden, worse quality of life, and decline in neurocognition has been detected (Kim et al., 2018). Although BEV is a tempting therapy option for GBM, it has well-known side effect. Bevacizumab as single therapy for individuals with repetitive GBM has been linked to a variety of serious side effects of various severity including 20 to 36.9% of headache, overall 27.4% of hemorrhage, 12.5

to 29.8% of hypertension, thromboembolic event of 8 to 12.5%, fatigue of 32 to 63%, and proteinuria of 2.1 to 10% (Yu et al., 2016). In patients with glioblastoma. Bevacizumab may boost cell sensitivity to other cytotoxic drugs, making it a useful therapeutic agent to use in conjunction with chemotherapy or radiation. For recurrent glioblastoma, bevacizumab has been used both alone and in conjunction with radiation and chemotherapy or other different combination of drug (Li et al., 2017).

In this review, a comparison of the efficacy and outcomes in the treatment of glioblastoma is illustrated by analyzing the findings of a good number of clinical trials where different combination of medications were used with Bevacizumab. This comparison provides not only an idea of the treatment with bevacizumab but also demonstrates the idea of the treatment of different drug and therapy combination in conjunction with bevacizumab to assess the treatment effectiveness.

In the treatment of glioblastoma multiforme, the combined regimen of BKM120 (oral inhibitor of PI3 kinase) and bevacizumab contained phase I and phase II trials. Participants administrating 3+3 distinctive dose intensification outline in the trial of phase I and also monitored by a single-arm trial of phase II. In the trial of phase I, participants were treated for a median of 11 weeks (1–48 weeks). BKM120/bevacizumab was found to be tolerable in a phase I investigation, despite the fact that the single-agent MTD of 100 mg regularly was higher than BKM120 MTD of 60 mg regularly in the combined regimen. Disease progression (50%) was the most common reason of the discontinuation of treatment. Toxicity in 2 participants that showed 17%; participant decision of 2 that also showed 17%; and death on study in 2 participants and the percentage of 17 were the other reason of treatment discontinuation. Pneumonia was the cause of death in two patients in the trial. In phase I, no objective feedbacks were detected. In phase II, the treatment median of 18 weeks of that ranged from <1 to 161 weeks was obtained in participants. Trouble sanction of the regimen even with a decreased BKM120 dose was also detected in the participants of phase II trial. In this period, the most prevalent cause for 58% of treatment discontinuation was disease

continuation. Toxicity found in 9 participants with 16%; intercurrent illness found in 2 participants with 4%; decline in performance status found in 1 participant with 2%; administration of other therapy found in 2 participants with 4%; and non-compliance found in 1 participant with 2%. Due to toxicity, 20 patients (26%) had one or both medicines terminated, and the disruption of the dose of BKM120 were prevalent. This combination produced no unanticipated effects. Because these symptoms are frequently linked to glioblastoma, the prevalence of numerous CNS related side effects such as mood swings, disorientation, and cognitive disturbance may be extremely reported. In this treatment 32% of responsive rate with a median PFS of 5.3 months and a PFS-6 of 44% detected in bevacizumab-naive patients. None of these findings suggest an improvement compared to early recorded scheme of bevacizumab only. Participants who administrated bevacizumab as a front-line treatment demonstrated minimal activity with the regimen. BKM120/bevacizumab proved tough to administer; there were a lot of medicine discontinuations and dosage disruptions. This combination treatment did not be evident to have any more action than bevacizumab alone (Hainsworth et al., 2019).

Incorporation of vorionstat and bevacizumab, there were two phase of trial which were phase 1 and phase 2. For the first 20 patients in phase 1, 3+3 outline along with DLT estimation occurring enclosed by the period of 1st 4 weeks. Phase 2 study used Bayesian adaptive design (BAR) and Bayesian continuous monitoring (BCM) where at the beginning of the trial (10 per group) participants were shuffled equitably between in two groups. Since the experiment continued and more statistics became available, the shuffled segment started to favor the treatment with a longer median PFS on average. As a result, the more successful therapy was more expected to be given to each subsequent participant. Hypertension, anorexia, anemia, drowsiness, motion sickness, headache, hyperglycemia, cognitive disturbance and seizure were the most common adverse effects in this treatment. Most of them were classified as category 2 in terms of extremity. In the middle of two groups, there was no notable difference in case of category 3 toxicities associated with the treatment. There were about 3 participants who faced major side effects including cat

gory 4 or 5 perhaps associated with the treatment included 1 in the only bevacizumab group with category 4 lowering ejection fraction and 2 in the bevacizumab with vorinostat group with category 4 colonic perforation and category 5 thromboembolic event. This study looked at whether inhibiting HDAC with vorinostat could improve outcomes in participants along with repetitive GBM by targeting putative refusal procedure to bevacizumab therapy. The poor tolerance of irinotecan was documented in phase 1 investigation of the combined regimen of bevacizumab, vorinostat, and irinotecan, and researchers advocated trying bevacizumab with vorinostat solely for improved tolerance. Therefore, the combination was well tolerable. A research phase 2 with the combined regimen of panobinostat and bevacizumab in participants who had regular GBM that was terminated too early due to intermediate data that was not be encountered the continued enrollment criteria. There was no improvement in PFS6 or OS. Finally, a PFS6 of 53.8% was recorded for the combined regimen of bevacizumab, vorinostat, with temozolomide, and it did not outperform archival controls by a considerable margin. The ability to assess the genuine efficacy of the combination was hindered by these non-shuffled trials with archival controls and extensively pre-treated participants (Beer et al., 2019).

In the treatment of TRC 105 (anti-endoglin monoclonal antibody) with bevacizumab, TRC105 with a dose of 10 mg per kg per week was given to 22 repetitive GBM participants with or without bevacizumab. TRC105 was started after one week of bevacizumab lead-in monotherapy in individuals receiving dual treatment. A median PFS of 1.38 months was recorded in five participants who received only TRC105, a median PFS of 1.81 months (95%CI: 1.25 to 2.07) was recorded in 14 participants who received both TRC105 and bevacizumab (Liu et al., 2021). This combination showed the lowest PFS in comparison to the other combined regimens in this study. According to the Clinical Trial Identifier (NCT01648348), the serious adverse effect rate for this combination was 30.61% including fatigue (25%), confusion (25%), epistaxis (8.16%), anemia (4.08%), thromboembolic event (4.08%).

Incorporation of TH-302 or Evofosfamide with bevacizumab, Evo is known as the nitroimidazole

prodrug of bromo-isophosphoramide mustard (Br-IPM) that is a cytotoxin. Intracellular reductases decrease Evo at the nitroimadazole site of the prodrug when exposed to hypoxic conditions, resulting in the secretion of Br-IPM. Motion sickness, skin reckless, drowsiness and vomiting were most common adverse event when TH-302 was used as a monotherapy (Briskin et al., 2015). In this combination therapy, until disease progression, every two weeks' patient received bevacizumab at a dose of 10 mg per kg at intravenous route and TH-302 at a dose of 670 mg following in 6 week cycles. The foremost endpoint was PFS4. The trial medication was given to 36 individuals. The treatment was well tolerated, with the most ordinary poisonous reckless along of the lower abdomen as predicted. The primary goal was reached, and the PFS4 rate was 25%, which compares favorably to historical controls (10%). In bevacizumab-refractory glioblastoma, evofosfamide had limited efficacy, with continuation and stability correlated with radiographic characteristics at guideline. ("Монте-Карло Моделирование Структурных Окт Изображений Кожи Человека in Vivo С Использованием Экспериментальных B-Сканов И Распределения Оптических Свойств," 2018). Apart from second category of epidermal toxic effects, which indicated a 25% dose decrease after reduction to category 1, no dose adjustments were recommended for toxic effects categories 1 through 3. Non-hematologic sensitivity of 3rd grade (apart from ALT/AST elevations, sickness, or vomiting) indicated a 25% dosage modification. Overall, Evo was well absorbed, and without any drug related side effects of 4th grade or higher (AEs). Despite the high morbidity associated with GBM, toxicity was easily controlled when patients were taught to apply phenylephrine/glycerin/petrolatum cream as a preventative measure. The pattern of toxic effects of evofosfamide with Bev is superior to that of commonly used glioblastoma combination regimens like bevacizumab with irinotecan or lomustine. Evo plus Bev AEs did not cause any of our patients to stop taking the medication, and just three of them had grade 3 adverse events. The reaction ratio as a whole of 17% in this trial is wider than that of any earlier recorded for Bev refractory illness in the research, indicating that more research on Evo in this scenario is needed (Briskin et al., 2015).

When dasatinib used together with bevacizumab, dasatinib is a Src transcription factors blocker that has been shown to successfully reduce bevacizumab-induced glioma expansion, yielding towards the hypothesis that pairing bevacizumab with dasatinib might increase bevacizumab effectiveness in patients with relapsed GBM. After the phase 1 trial was completed, individuals with relapsed GBM were randomly assigned to administer 100 mg of oral dasatinib for two times in a day (group A) or placebo (group B) on days 1 to 14 of each 14-day cycle, with 10 mg per kg of intravenous bevacizumab on day 1 of each 14-day cycle. The foremost outcome was PFS6. However**,** even though the PFS6 value was quantitatively greater in people medicated with bevacizumab plus dasatinib and the value for group A was 28.9% [95 percent CI, 19.5 percent - 40.0 percent]) than in people medicated with single-agent bevacizumab and the value for group B: 18.4% [95 percent CI, 7.7% -34.4 percent]), the discrepancy was not statistically significant (P =.22), therefore, the foremost target was not achieved. The most common treatment-related AEs (all grades pertaining to therapy) were 62.0% of fatigue, 52.9% of anemia, 44.6% of thrombocytopenia, and 41.3% of diarrhea. Lymphopenia was the most prevalent hematological damage exceeding level 3 recorded with 9.6% in group A and 2.6% in group B, while hypophosphatemia with 14.5% was recorded in group A and 2.6% was recorded in group B, moreover, fatigue was the greatest similar other than hematological damaged with the rate of 12% in group A and 0% in group B. During the research, 4 of the participants passed away where 2 were in group A and 2 were in group B. One participant who passed away was thought to be linked to the therapy. This participant when he was only given bevacizumab, had grade 5 pneumonias and had an unknown absolute neutrophil level. Although the current study's findings suggested that the usage of dasatinib and bevacizumab is not able enough to improve the therapeutic findings in individuals. There was a tendency toward an enhancement in PFS6 with dasatinib usage that did not achieve statistical validity, as well as a statistical significant enhancement in the length of reaction with dasatinib therapy in participants with recurrent GBM. (Galanis et al., 2019).

In the treatment of Border Zone Stereotactic Radiosurgery (BZ-SRS) with bevacizumab, in phase

II trial, participants received BZ-SRS with bevacizumab with the dose of 10 mg per kg one day earlier and one day after day 14, then 10 mg per kg daily for every 14 days unless progress was made. There were no dosage decreases for bevacizumab. If bevacizumab might be stopped due to side effects, the dose would not change when therapy resumes. Any side effects caused by or possibly caused by bevacizumab had be treated in accordance to standard health systems. Because The ultimate half-life of bevacizumab was about 2 to 3 weeks, stopping it causes gradual clearance for a period of months. There is no antidote available for bevacizumab. Adverse effects such as hypertension, hemorrhage, venous thrombosis, arterial thromboembolic event, congestive heart failure, proteinuria were responsible for permanent discontinuation of bevacizumab, however, the findings suggested that this combination showed significant outcome for overall survival rate (Ml, 2016).

In the treatment with the combined regimen of lomustine with bevacizumab, individuals received bevacizumab as a single drug intravenously per two weeks at a dosage of 10 mg/kg unless clinical recurrence as well as worsening of the symptoms. After that the dosage of bevacizumab was reduced for per three weeks to the combo group and lomustine was first given at a dosage of 90 mg per m2 per 6 weeks, however, this dose was also reduced to 75 mg per m2 after 12 participants and 27 cycles of the medication had 17 of stage 3 and 7 of stage 4 hematological toxic effects. Total of 7 participants had stage 4 effects where 1 participant had leukopenia, 1 participant had neutropenia, 2 participants had thrombocytopenia, and 3 participants had lymphopenia, moreover, total of 17 participants had stage 3 hematological toxic events where 4 participants had leukopenia, 3 participants had neutropenia, 4 participants had thrombocytopenia, 6 participants had lymphopenia were reported for overall of 12 participants who medicated with lomustine of pervious greater dose in pairing with low dose bevacizumab, therefore, dose reduction at 75mg/m2 was required. During the trial perid, no unanticipated side events or medication-related deaths were identified in any of the arms. In this treatment, it was observed that at the arm of low dose bevacizumab and lomustine, median PFS was no broader significantly in comparison to the

bevacizumab group alone. In case of median OS, low dose bevacizumab and lomustine arm did not show significant outcome in comparison to the bevacizumab arm alone. At first recurrence, the negligible dosage bevacizumab with lomustine group had a statistically significant trend toward prolonged median PFS contrasted to the bevacizumab group alone, however, median OS of participants medicated with negligible-dosage of bevacizumab with lomustine was not substantially broader than those who medicated with only bevacizumab. The experiment was halted midway due to the foremost endpoint of PFS being futile. The combined treatment group had a wider median PFS and OS, especially in glioblastoma participants along with a first recurrence, suggesting therapeutic efficacy in this cohort. However, these findings did not contact statistical validity due to the limited number of participants undergoing in this study, therefore, in individuals with recurrent glioblastoma, the pairing of negligible-dosage of bevacizumab and lomustine was not proved to be more accurate versus conventional-dosage of bevacizumab. More research is essential for a better understanding of which segments would be benefited the greatest from this combined treatment (Weathers et al., 2016).

Incorporation of pembrolizumab with or without bevacizumab, if more than one dose limiting toxicity (DLT) was reported among the first six patients, Cohort A included a safety lead-in with a planned de-escalation of pembrolizumab doses. Patients were randomized 5:3 to a combination of pembrolizumab plus bevacizumab of group A or single agent pembrolizumab of group B once the MTD/RP2D was determined in the safety lead-in (cohort B). During the safety lead-in, which established the RP2D of 200 mg pembrolizumab IV every three weeks plus 10 mg/kg bevacizumab biweekly, no DLTs were seen. The majority of TRAEs, including immune-related AEs, were low-grade. There were no TRAEs in grade 5. No grade 4 TRAEs occurred in cohort A, and hypertension was the most common grade 3 occurrence (20%). A single grade 4 TRAE occurred in cohort B, and it was cerebral edema that developed during the dexamethasone taper as the tumor progressed. The most prevalent grade 3 occurrence was a headache (10%). Due to a

treatment-related adverse event, one patient in cohort B terminated study treatment (grade 2 arthralgia). For glioblastoma, the clinical outcome of bevacizumab is to inhibit the activity of VEGF and it is limited to an enhancement in PFS but not OS. This research looked at whether concurrent VEGF blocking could improve pembrolizumab's anti-tumor activity in recurrent glioblastoma patients. In comparison to bevacizumab monotherapy, conventional dose of bevacizumab and pembrolizumab in combination failed to enhance PFS or OS. Therefore, Pembrolizumab was found to be ineffective for recurrent glioblastoma either used alone or in combination with bevacizumab (Nayak et al., 2021).

In the combined treatment of temozolomide and hypofractionated intensity-modulated radiation therapy with bevacizumab, there were no hypo-IMRT interruptions or delays observed. During hypo-IMRT, no acute hematological toxicities were reported. Following hypo-IMRT, 33% of individuals developed neutropenia or thrombocytopenia, necessitating rotation pauses and the limitations to complete whole dosage of interlaced temozolomide. Moreover, 2 patrticipants reported stage 3 wound dehiscence, 2 patients reported pulmonary embolism and 1 patient reported stroke. In addition, 20 participants passed away resulting in the growth of tumors (67%). Consequences of a cerebral cellulitis in 2 participants, infection in 1 participant, and unexpected death from a supposed seizure in 1 participant were among the other causes of death. However, phase II trial of this combined regimen indicated that hypo-IMRT in conjunction with temozolomide and bevacizumab provides equivalent survival to standard treatment for newly diagnosed glioblastoma, though the rate of assumed radio necrosis was substantially greater than expected. No clinical radiation necrosis was observed in a previous research using the same kind of radioactivity treatment with temozolomide yet without bevacizumab. BEV was thought to protect against necrosis, however, with this precise hypofractionated radiation protocol, this would not necessarily be the scenario. BEV's "radio protective" effects may be due to reduced edema and vascular permeability, which makes radio necrosis less visible and dysfunctional, but it has no impact on tissue damage. Furthermore, it's probable that the inclusion of BEV aided in the

development of necrosis. Lastly, it appears that BEV does not improve efficacy in GBM patients when combined with RT and TMZ (Ney et al., 2015).

In the treatment of erlotinib hydrochloride with bevacizumab, around 115 patients were enrolled where about 48 patients who had MGMT unmethylated tumors. All the patients completed the treatment of RT with TMZ. With a probable link to the bevacizumab plus erlotinib combination, a total of 928 adverse effects were recorded. The majority, around 885 were stages 1 or 2. Approximately 40 participants in stages 3 and 3 are in stages 4 and 5 incidents occurred, indicating that the treatment went over well. 1 patient experienced a stage 4 stroke and bowel perforation, both of them are known side effects of the post-radiation therapy. The recorded 13.2 months of median OS was only few more months greater than the earlier results of 12.7 months, indicating that the trial did not show an increase in OS for this patient cohort. Patients with GBM who received this combination of treatment had made some progress, however, MGMT amplifiers that are not methylated have had a harder time. For this group of patients with a worse prognosis, new therapeutic techniques are required in the future. Indeed, because of this necessity, it has been proposed that temozolomide be avoided in this cohort in order to broaden the variety of novel medicines that might be evaluated in newly diagnosed patients. When TMZ was used in several trials, but this one was the most successful when it was administered in unmethylated participants, omitting TMZ did not result in a lower survival rate (Raizer et al., 2016).

In phase 2 trial of the combined regimens of vorionstat with bevacizumab, vorionstat is a hydroxamic acid derivative with anticancer effects, acting directly as an HDAC inhibitor and indirectly as an antiangiogenic. In this trial, 55% of lymphopenia, 45% of leukopenia, 35% of neutropenia, and 33% of hypertension were reported as the most frequent grade 2 and upper treat related toxicities. 5 participants with 12.5% reported toxicities that were excessively severe as a result of the medication, which were known as significant non hematological toxic effects of grade 4 or 5 or a grade 2 or higher central nervous system (CNS) hemorrhage, according to the protocol. In addition, during this trial period, 2 patients died due to tumor progression and death that isn't

otherwise indicated. No one had a finished feedback, but a partial incomplete feedback was established in 9 participants. As a result, the incidence of radiological sensitivity was 22.5% and 95% CI was 12.1% to 37.7%. Although the partial responses described are intriguing, measuring response can be problematic because bevacizumab might cause a "pseudoresponse" in glioblastoma due to improved membrane permeability. Though the medication with the combination bevacizumab and vorinostat was gently tolerated, this regimen still had no advantage on progression-free survival following 6 months., with a 30% of PFS6 vs prior records of 40% as well as in case of median OS in comparison with BEV alone. As a result, the paring of bevacizumab and vorinostat might not be explored as a treatment alternative for individuals with relapsed glioblastoma, according to the findings of this study (Ghiaseddin et al., 2018).

In the combination of durvalumab and standard radiotherapy with bevacizumab, durvalumab is an anti-PD-L1 human IgG1 mAb. Blocking PD-1/PD-L1 signaling has been demonstrated to be beneficial in solid tumors; findings suggest that PD-1/PD-L1 signal is a major factor in contributing to immunosuppression in GBM (Autoridad Nacional del Servicio Civil, 2021). Moreover, radiation therapy promotes cell death that produces tumor antigens, which may help anti-PD-(L)1 therapy to work better. In this phase II trial, there were 5 cohorts of patient received durvalumab as a dosage of 10 mg per kg in each 2 weeks. Group A participants had new unmethylated GBM after maximum safe resection and they received durva + standard radiation that is followed by durva monotherapy (Reardon et al., 2019). Groups B2 and B3 patients received durva + BEV as a dosage of 10mg per kg Q2W and durva +BEV as a dosage of 3mg per kg Q2W respectively (Autoridad Nacional del Servicio Civil, 2021). The median OS and OS12 for participantts with newly unmethylated glioblastoma after ordinary medication was 12.7 months and 50%, approximately, in the past (Reardon et al., 2019). Fatigue, dysphonia, elevated ALT, AST, amylase, or lipase, diarrhea, hypertension, arthralgia, headache, and proteinuria were the greated prevalent treatment-related adverse events (TRAEs) for both groups. For groups B2/B3, the incidence of TRAEs by maximum CTCAE grade (Gr) 3 was 24.2/6.1%, Gr4: 0/6.1%, and Gr5:

0/0% (Autoridad Nacional del Servicio Civil, 2021). Patients are still alive in 20% of cases, with survival times ranging from 15.7 to 34.9 months. It would be worth to mention that systemic and tumor immunocorrelative studies are still pending. In conjunction with RT, durvalumab was well tolerable and it appeared to be effective in patients with newly unmethylated GBM, further research may be required (Reardon et al., 2019). Durvalumab in combination with bevacizumab had no effect on the outcome of durvalumab alone (Autoridad Nacional del Servicio Civil, 2021). In the combined regimen of bevacizumab with AMG 102 or rilotumumab which is an antibody that prevents HGF (hepatocyte growth factor) from malignant cells multiplication and mobility are suppressed by interaction to the c-Met receptor. The use of rilotumumab in combination with BEV is to prevent tumor expansion that may be aided by a simultaneous impact of vasculitis and tumor multiplication. An intent feedback of 27.8% included total feedback of 2.8% and partial response of 25% was reported. The research using rilotumumab alone to treat patients of recurrent malignant glioblastoma found a median OS of 6.5 months and a median PFS of 4.1 weeks. BEV alone had a median OS of 7.8 months (95% CI: 5.3–13.5) and a median PFS of 4 months (95% CI: 3–6) in a statistical comparative trial. Addition of rilotumumab with bevacizumab enhanced the median OS to 11.2 months (95% CI: 7.0–17.5) and the median PFS to 4.8 months (95% CI: 2.7–7.1). Even though bevacizumab plus rilotumumab improved median survival by 3–4 months that was evaluated by comparing to particular medications, it would not improve BEV's PFS on its own. The slight increase in median OS might be considered against the regimen's toxic events. Unacceptable treatment related toxicities such as stage 2 central nervous system (CNS) hemorrhage (none) or stage 4/5 non hematological events (6% patients) were reported. Rates of toxic effects of 5% were considered "acceptable," and rates of 20% were considered "unacceptable." Despite the fact that **gl**ioma patients frequently experienced venous thromboembolic events, and this mixture did not cause excessive toxic effects, a number of 4 participants (11%) developed stage 3 pulmonary embolism, and it was a clinically important condition. Fatigue of 58%, voice change of 37%, weight gain of 36%, hypoalbuminemia of 33%,

and allergic rhinitis were other prominent medication-related adverse events seen by 20% of participants (31%). Overall, the combination of BEV with rilotumumab increased the number of adverse events, both expected and unexpected. When compared to BEV alone, rilotumumab in pairing with BEV did not enhance intent feedback, OS, or PFS. Nevertheless, rilotumumab along with bevacizumab was an active therapy in glioblastoma participantts, according to the improvement in OS. Rilotumumab in conjunction with bevacizumab has a high toxicity profile, making it unsuitable for usage in the treatment of glioblastoma (Affronti et al., 2018).

Combination of bevacizumab, temozolomide and hypofractionated radiotherapy in phase II trial was typically well tolerated, and each drug's toxicity profile was followed. Because of thrombotic microangiopathy and renal failure of stage 4 that was irreparable, 1 participant stopped receiving bevacizumab. 1 patient had a grade 4 surgical wound infection that did not dehisce, but he was able to continue the treatment. 2 patients suffered pulmonary embolism of grade 4 and 1 patient had a late ischemic stroke. While on therapy, an individual having a tendency of uncontrollable seizures passed away abruptly at the time of sleeping; autopsy revealed no tumor hemorrhage or thromboembolic effect. In 2 asymptomatic patients, central nervous system bleeding was detected, a stage 1 intratumoral hemorrhage and a stage 1 hemorrhage in a pre-existing cavernoma in a patient taking concurrent complete dosage of anticoagulation. After one year, 37 patients were alive with the OS of 93%; 95% CI: 84 to 100, achieving the trial's foremost goal. 87% of complete response and 57% of partial response were reported. Within the first four months after radiation, none experienced symptoms that might be got worse or radiographic pseudoprogression. Participants found this schedule to be a relatively manageable therapeutic option than standard chemoradiotherapy because it used fewer corticosteroids and had a significantly abbreviated radiation plan consists of six therapies in two weeks that was contrary to the typical 30 therapies offered everyday throughout six to seven episodes. With little negative effects on quality of life and survival rates equivalent to those seen with other regimens, this regimen seemed to be safe (Omuro et al., 2014).

In this overall study, one phase III trial of the combined regimen of bevacizumab, placebo, temozolomide and radiotherapy in the treatment go glioblastoma was analyzed. There were 458 about participants in the bevacizumab group and about 463 participants in the placebo group. The bevacizumab group had a longer median progression-free survival of 10.6 months and the placebo group had a shorter median PFS of 6.2 months. At 1 year (P=0.049), the OS for bevacizumab and placebo were 72.4% and 66.3%, respectively, and at two years (P=0.24), 33.9% and 30.1%, respectively. After surgery or biopsy, patients received radiotherapy with the drugs (bevacizumab, placebo and temozolomide). There was also a maintenance phase. Pseudoprogression was identified in 10 participants with 2.2% who received bevacizumab and 43 participants with 9.3% who received placebo. There were no significant variations in ultimate survival between the subsets of participants with methylation versus unmethylated MGMT status. 98.5% of participants who were given bevacizumab and 96.0% of participants who were given placebo reported adverse events of any severity. Major adverse occurrences, as well as stage 3 or greater adverse occurrences (66.8% vs. 51.3%), were more likely in the bevacizumab group than in the placebo group (38.8% vs. 25.6%) and stage 3 or greater adverse occurrence that are frequently linked with bevacizumab (32.5% vs. 15.8%). The bevacizumab group had a greater rate of whole and stage 3 or greater arterial thromboembolic events than the placebo group. The incident resolved in 19 of 27 patients who had an arterial thromboembolic effect in the bevacizumab group (70.4%) and 3 out of 7 participants who had an arterial thromboembolic effect in the placebo group (42.9%). In each group, one devastating arterial thromboembolism was reported. Bleeding, wound healing difficulties, GI perforation, and congestive heart failure were among the major side events seen in far more often usual in the bevacizumab group. Grade 5 adverse events in 20 participants with 4.3% vs. 12 participants with 2.7% and adverse events resulting to treatment termination in 122 participants with 26.5% vs. 61 participants with 13.6% were far more often usual in the bevacizumab group than in the placebo group. In both groups, the greatest frequent reason for death was progressive disease. Disease development was the reason of death in 309 of the 339

participants who died (91.2%) in the bevacizumab group and 301 of the 333 patients who died in the placebo group (90.4%). This study found that combining bevacizumab along with the conventional radiotherapy–temozolomide, regarding the medication of freshly afflicted glioblastoma, it did not strengthen overall survival but did improvement in median progression-free survival of 4.4-month, with regard to the living standards and practical competence remaining unchanged (Chinot et al., 2014).

Chapter 6: Conclusion

The most familiar and foremost malignant brain tumor in elderly individuals is glioblastoma that is very confrontational and has a terrible prognosis. Numerous drugs, therapies or medications have been practiced in the treatment of glioblastoma, nevertheless, the drug "Bevacizumab" has been increasingly used in the treatment of recurrent glioblastoma. Besides, several drug and therapy combinations are available that take part in a consequential function in the treatment of glioblastoma as well. Each combination is incompatible with each other due to the mechanism of action, adverse effects, toxicities, efficiency, effectiveness, time on treatment or follow up time, rate of mortality and so forth. Bevacizumab, both as a single agent and in combination, improves PFS, but there were no analytical and remarkable improvements in OS for those with relapsed GBM. It would be a hope that improved outcomes might be achieved by combination therapy. In this study, the most recent 5years of clinical trials of different combinations of drug and therapy were taken to consideration for settling a remarkable outcome by assessing their efficacies. According to the all available data, it would be stated that patient receiving Bevacizmumab + Temozolomide + Hypofractionated Intensity Modulated RT combination is more efficient with less adverse effect and the combination of Bevacizumab + Temozolomide + Hypofractionated Radiotherapy is more effective with moderate adverse effects than other combinations. Moreover, Bevacizumab with other drugs such as Evofosfomide (TH-302), TRC105, BKM120, Vorionstat, Dasatinib, Lomustine, Pembrolizumab, Erlotinib Hydrochloride, Durvalumab and therapies such as Magnetic Radiosurgery, Standard Radiotherapy are still available and yield significant out in the treatment of glioblastoma However, this outcome is still an argumentative, hence, there is still lacking of relevant and sufficient information and data, therefore, further research on the combined medication regimens is required to evaluate more beneficial outcomes and to overcome the challenges of the treatments. Although these drug combinations are practiced widely in the treatment of glioblastoma. As a result, bevacizumab and temozolomide based treatments are

known as first line treatment for glioblastoma multiforme. This treatment works against VEGF activity, inhibits angiogenesis, and so limits tumor progression by limiting the proliferation of malignant cells and production of DNA.

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