

## Immunotherapy and Meningioma

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### Abstract

*Meningioma is the most typical form of intracranial tumour. Meningioma represents the primary brain tumor that originates from the arachnoids cap cells, which are present in the membrane that covers the brain and spinal cord. Females are more prone to develop this malignancy as compared to males. According to the report of the Central Brain Tumor Registry of the United States, in 2010, more than 170,000 cases were reported to be diagnosed in the years 2004-2006. Meningioma is caused mainly due to the genetic mutations in neurofibromatosis and the 2 genes at chromosomal location 22q. The risk factors that play a major role may include ionizing radiations, neurofibromatosis type-2 and hormones. Immunotherapy has shown a promising development in the past few years. Recent activities have increased the understanding of the tumour microenvironment, various immunotherapeutic modalities or combination therapy. Additionally, the effects of such modalities in combination with immunotherapy in cancer patients are still exploratory phase.*

**Keywords:** *Meningioma, neurofibromatosis, Central Brain Tumor Registry, Arachnoid cap cells, Alteration in Chromosome 22, chromosomal region, Protein 4.1B alteration,, retinoblastoma protein, Neurofibromatosis Type-2, Monoclonal Antibodies, epidermal growth factor receptor, Vascular Endothelial Growth Factor A, Retinoblastoma protein, Chromosomal deletions and mutations, murine double minute 2 protein, hedgehog, Hairy/Enhancer of Split, Phosphatidylinositol 3-kinase (PI3K), platelet-derived growth factor BB, hypoxia inducible factor-1*

### INTRODUCTION

The most typical form of intracranial tumour is meningioma. Both the brain and spinal cord are covered by a very fine membrane. Meningioma originates from the arachnoids cap cells, which are present in this membrane.<sup>[1]</sup>

According to the report of the Central Brain Tumor Registry of the United States, in 2010, more than 170,000 cases were reported to be diagnosed in the years 2004-2006. Additionally, in the same year, approximately 155 death cases were recorded out of a population of 7,767 in the age group of 0-14 and 24 death cases out of a population of 3,009 in the age group of 15-19.<sup>[2]</sup> In the US, reported rates were marginally higher for black non-Hispanics (7.11 per 100,000 person-years) than for white non-Hispanics and Hispanics (6.14 and 6.30 per 100,000 years),

respectively.<sup>[2]</sup> Western countries like North America and Europe were found to have higher incidence compared to African and Asian countries.<sup>[3,4]</sup>

It represents more than 33.8% of all the primary tumors related to the central nervous system.<sup>[3]</sup> The incidence rates range from 0.3 per 100,000 in children<sup>[4]</sup> to 40 per 100,000 in individuals above 85 years of age.<sup>[5]</sup> According to the National Cancer Database, the survival rate for meningioma was found to be 69% over a period of five years.<sup>[6]</sup> There is an annual increase of about 7.8 cases per 100,000, out of which only 25% are found to be symptomatic.<sup>[7]</sup>

It includes different histopathologic and genetic characteristics. Females show predominance with a male-to female ratio of 1:1.4 to 2.6<sup>[8]</sup> and the incidence of 41.67% was observed at the age of 85 or above, which was the highest rate among all the age groups.<sup>[9]</sup>

**ETIOLOGY/PREDISPOSING FACTORS**

Meningioma represents the primary brain tumor and arises from the arachnoid cap cells. Meningioma is caused mainly due to the genetic mutations in neurofibromatosis and the 2 genes at chromosomal location 22q.

The risk factors involved with meningioma's are as mentioned below and represented in Fig.1:

**Hormones**

[10] Higher incidence in women as compared to men, together with the highest ratio in reproductive age, change in size of meningioma's during luteal phase and pregnancy, regression of multiple meningioma's following cessation of hormone therapy, presence of progesterone, estrogens and androgen receptors have been reported.

**Neurofibromatosis Type-2 (Nf2) Disorder**

[10] NF2 gene mutations on 22q12 site might lead to meningioma.

**Ionizing Radiations**

[10] Exposure to ionizing radiations increases the risk of meningioma between six to ten folds. Patients, who have been exposed to ionizing radiation, either from atomic bomb or as a part of diagnostic or treatment modalities, are at high risk of developing meningioma.

**WHO CLASSIFICATION**

According to the WHO Classification, meningioma can be categorized into 3 classes that have been mentioned in Table 1:

**Table 1.** Classification of meningioma according to WHO<sup>[11]</sup>

WHO Grades	Types of Meningioma
WHO Grade I (Benign)	Meningothelial meningioma Fibrous (fibroblastic) meningioma Transitional (mixed) meningioma Psammomatous meningioma Angiomatous meningioma Microcystic meningioma Secretory meningioma Lymphoplasmacyte-rich meningioma Metaplastic meningioma
WHO Grade II (Atypical)	Atypical meningioma Clear-cell meningioma Chordoid meningioma
WHO Grade III (Malignant)	Anaplastic (malignant) meningioma Rhabdoid meningioma Papillary meningioma

Usually, meningiomas are benign in nature and hence, asymptomatic at earlier stages and in some cases, for a lifetime. The symptoms may include headache, seizures, behavioural changes, confusion, tinnitus, progressive focal neurologic deficit, weakness and nausea.<sup>[12]</sup>

**PATHOPHYSIOLOGY AND MOLECULAR BASIS**

The pathophysiology of meningiomas include different pathways and are explained below:

**Alteration in Chromosome 22**

Neurofibromatosis type 2 patients usually exhibit meningiomas due to the alteration at 22q12.2

chromosomal region, which encodes for the NF2-gene. This NF2 gene, in turn, encodes for a tumor suppressor cytoskeleton protein, merlin.<sup>[13]</sup>

**Alteration in Protein 4.1b/Dal-1**

Protein 4.1B alteration has been reported to be involved in the development of meningioma. This protein is encoded by DAL-1 or EPB41L3 gene. The protein regulates cell proliferation and cell death. A small portion of this protein, DAL-1, regulates tumor suppression via U2 domain, which exists in between the functional regions of the protein.<sup>[14]</sup>

**PROGRESSION OF MENINGIOMA**

**Chromosomal Deletions**

**Chromosome 1**

According to the studies, when chromosome 1p is deleted, it encourages the progression of meningiomas. The high-grade tumors are usually caused due to this abnormality. The deletion of this chromosome can only lead to the progression and cannot initiate the tumor. Rate of recurrence is quite high, in case of absence of chromosome 1p.<sup>[15]</sup>

**Chromosome 14**

The deletion of this chromosome is the third major reason for the progression of meningiomas.<sup>[16]</sup> The association of NDRG2, presents on the 14q chromosomal region, with tumor suppression, has been reported.<sup>[17]</sup>

**Chromosome 9**

The deletion of this chromosome occurs at 9p21 site, in case of anaplastic meningiomas. Alteration may occur due to the loss of genes, encoding p14, p15 and p16.<sup>[18, 19]</sup> P14 acts on the p53 pathway and hence, regulates the apoptosis of the cell.<sup>[13]</sup>

**Chromosome 17**

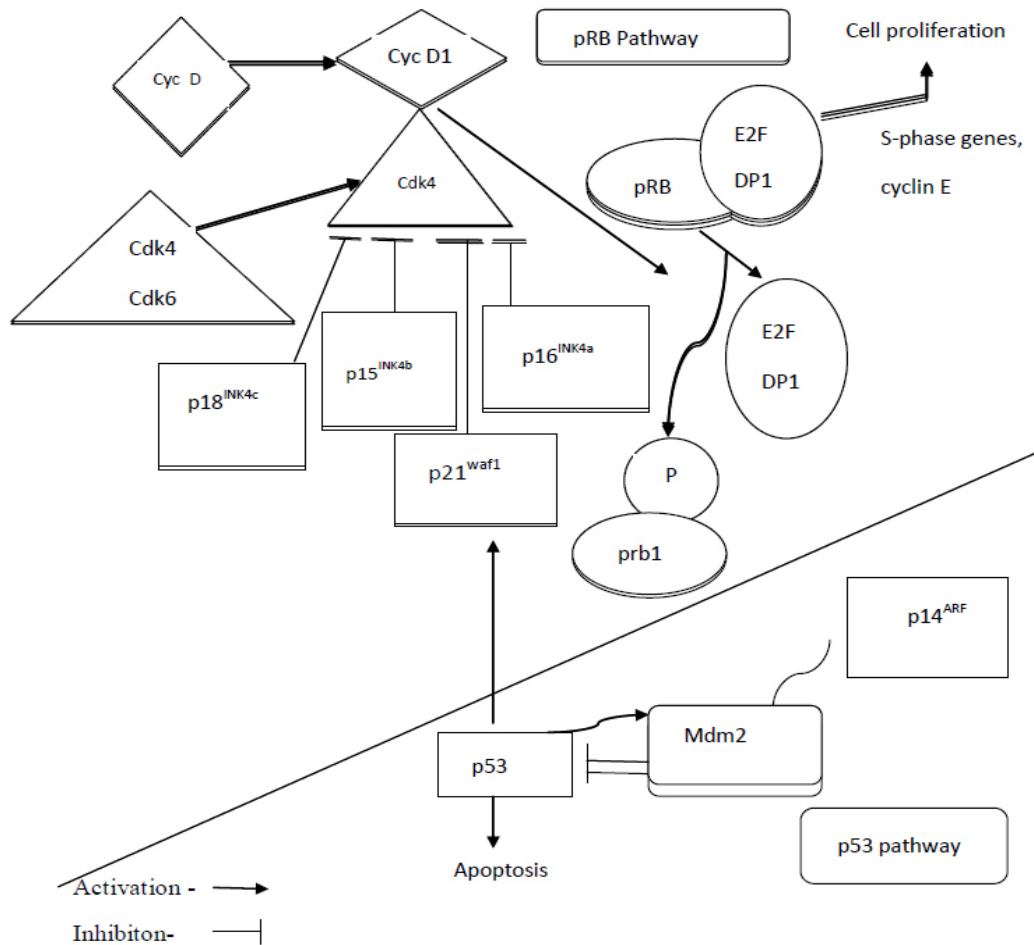
Modification in ribosomal protein S6 kinase (RPS6K) at 17q23 chromosomal site might be responsible for the progression of malignant meningiomas.<sup>[20, 21]</sup>

**Chromosome 18**

When missense mutation occurs in APM-1 gene at 18q21 chromosomal region, it can lead to the progression of meningiomas.

**Activation of telomerase/hTERT**

Activation of telomerase is found to be responsible for anaplastic meningiomas and most of the atypical meningiomas.<sup>[22]</sup>



**Fig. 1.** Modification of Cell Cycle via pRB/p53 pathways.

### Modification of retinoblastoma protein (pRB) pathway and p53 pathway

Chromosomal deletions and mutations of the genes that regulate the pRB dependent pathway, namely: p<sup>16INK4 $\alpha$</sup> , p<sup>15INK4B</sup> and p14ARF result in the progression of anaplastic meningiomas. The G1/S-phase is inhibited by pRB with the help of E2F-DP protein. Cyclin D is responsible for the cell cycle progression, but when the mitogenic signals are triggered, the level of cyclin D increases and leads to the adherence of cyclin D to Cdk4 or Cdk6. This results in the phosphorylation of pRB and release of E2F-DP and leads to S-phase regulating gene transcription.<sup>[23]</sup>

The p53 pathway, with the help of p14<sup>ARF</sup>, acts as a feedback inhibitor of the pRB pathway.<sup>[24,23]</sup> When pRB is phosphorylated, it augments p14<sup>ARF</sup> transcription. P53 is normally degraded, when murine double minute 2 protein (MDM2) proto-oncogene binds to it. p14<sup>ARF</sup> inhibits MDM2, resulting in an increased p53 activity. Meningiomas result from the loss of p14<sup>ARF</sup>. Fig.1 gives a brief overview of both these pathways.

### Modification of Hedgehog (Hh) Pathway

On adherence of hedgehog (Hh) with its receptor, patched (PTCH), the inhibition of a protein called smoothened (SMO) by PTCH does not occur anymore.<sup>[25-28]</sup> This activates transcription factors like GLI, which include different growth activators and suppressors.<sup>[29-31]</sup> Launreseau et al. observed that in some cases of meningiomas, out of 32 genes related to Hh pathway, 16 genes responsible for cell growth were enhanced and 7 genes responsible for the inhibition of Hh pathway were suppressed. IGF2 and SPP1 were also found to be overexpressed in patients with high-grade meningioma.<sup>[26]</sup>

### Modification of Notch Pathway

Notch Pathway is responsible for the communication between the cells via Notch 1-4 proteins.<sup>[32]</sup> Hairy/Enhancer of Split (HES) transcriptional regulators act as effectors for Notch Pathway.<sup>[32,33]</sup> The progression of meningioma highly depends on Notch pathway deregulation. Groucho/Transducer family co-repressors, TLE2 and TLE3 are highly regulated in meningiomas. They are known to enhance HES1 activity.

### Modification Of Pi3k/Akt Pathway

The Phosphatidylinositol-3-kinase (PI3K)/Akt Pathway is responsible for cellular functions like differentiation, cellular growth and apoptosis. In meningiomas, this

pathway gets activated abnormally due to mutations in the AKT1 gene, which encodes for the key effector of this pathway.<sup>[34]</sup> When PDGF and/or EGF adhere to their receptors, it leads to the auto-phosphorylation. This happens, when a catalytic unit gets allosterically activated. The auto-phosphorylation activates the adaptor proteins in the vicinity, which then activates PI3K protein through its PI10 subunit. When PI3K is activated, it leads to the phosphorylation of Akt and furthermore, via rapamycin (mTOR), it activates p70<sup>S6K</sup>.<sup>[35]</sup> In anaplastic and atypical meningiomas, Mawrin et al.,<sup>[36]</sup> observed that Akt was present in very high amount in the phosphorylated form.

### Modification of Mapk Pathway

It has been observed that a number of genes related to MAPK pathway are over expressed in meningiomas, which include MPK1, MINK, FOS and IRF-1.<sup>[37]</sup> When PDGF and/or EGF adhere to their receptors, they lead to the activation of tyrosine kinase and the tyrosine residues are auto-phosphorylated. These residues, then get attached to the Grb2 and Sos proteins that take them to the vicinity of the cell membrane.<sup>[38]</sup> When the MAPK pathway is activated, it activates and phosphorylates Raf and MAPK.<sup>[36,39,40]</sup> The use of MAPK inhibitor, PD98059, has been correlated with the slow cell growth and activation of apoptosis.<sup>[36]</sup>

### Modification of Growth Factors

Several signaling pathways like Ras/Raf, P13K/Akt and MAPK regulate the growth factors. It has been observed that the growth factors like platelet-derived growth factor BB (PDGF-BB), along with its receptor PDGFR- $\beta$ , are highly expressed in patients with meningioma.<sup>[41-43]</sup>

The activation of epidermal growth factor receptor (EGFR) might result in meningioma,<sup>[42,44]</sup> which might be due to:<sup>[42,45,46]</sup>

1. Expression of ligands of EGFR.
2. Expression of Transforming growth factor alpha (TGF- $\alpha$ ).
3. Presence of EGF in meningiomas.

### Modification of Angiogenic Pathways

The association of Vascular Endothelial Growth Factor A (VEGF-A) and meningiomas have been conflicting. However, recurrent cases of meningioma have shown to be associated with VEGF-A expression, which is regulated by EGF and PDGF. Over-expression of VEGF

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and its regulator hypoxia inducible factor-1 (HIF-1) have been observed in meningiomas.<sup>[47]</sup>

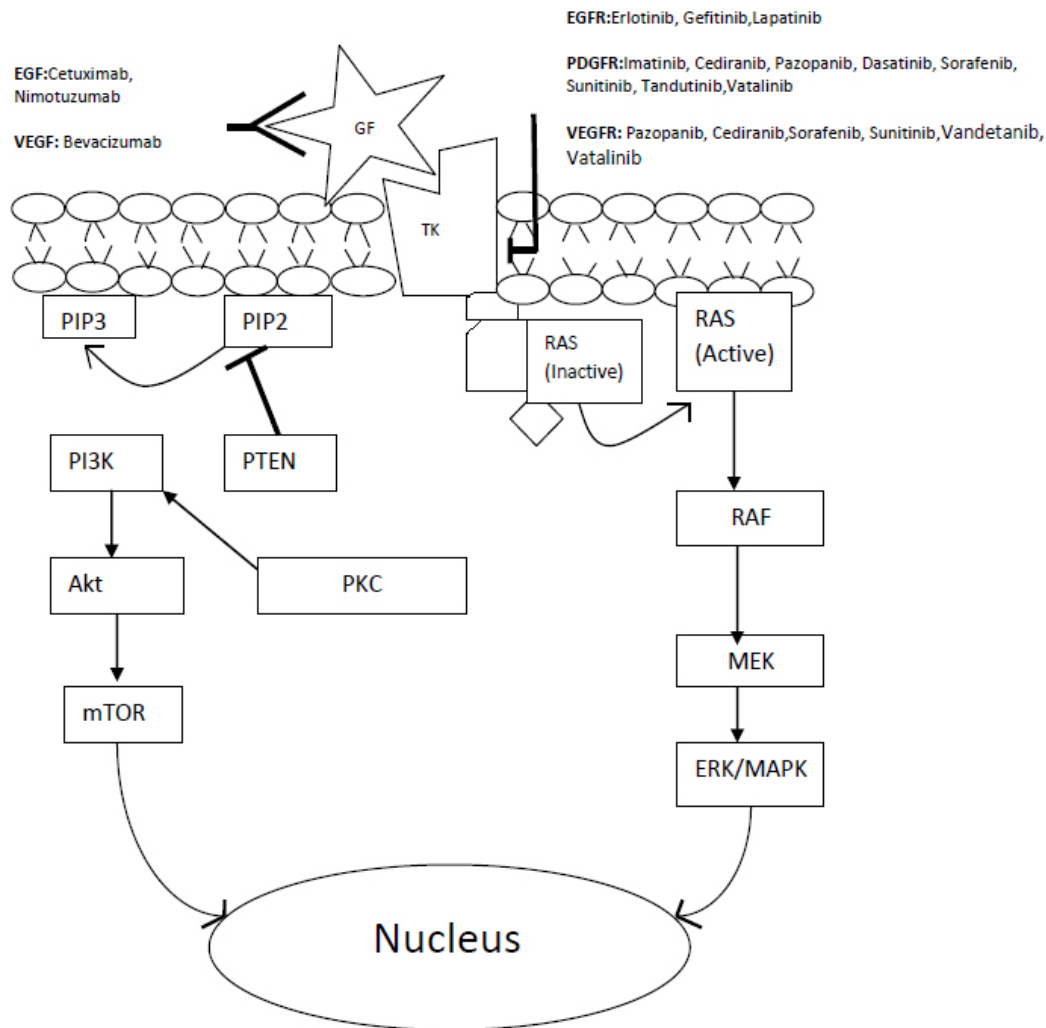
### Cyclooxygenase-2

Cyclooxygenase-2 is an enzyme responsible for inflammatory responses. As observed by Ragel

et al.,<sup>[48]</sup> Cox-2 was overexpressed in patients with meningioma.

### IMMUNOTHERAPY

Figure 2 represents various molecular agents, along with the pathway on which they act.



**Fig.2.** Various molecular agents, along with the pathway on which they act. The immunotherapeutics on the left act on EGF and VEGF, while those on the right act on EGFR, VEGFR and PDGFR.<sup>[49]</sup>

**Table-2.** Non-FDA Approved Monoclonal Antibody Drugs<sup>[50,51]</sup>

#### A. Monoclonal Antibodies (mAbs)

##### a. Non-FDA Approved mAbs

mAbs	Clinical trial identifier number	Phase	Study design	Target
Bevacizumab	NCT01125046	Phase II	Efficacy Study, Open Label	VEGF/VEGFR
Everolimus + Bevacizumab	NCT00972335	Phase II	Safety/Efficacy Study, Open Label	mTOR and VEGFR

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**Table-3. Non-FDA Approved Adoptive Cell Therapy<sup>[52,53]</sup>**

### B. Adoptive Cell Therapy

#### a. Non-FDA Approved Adoptive Therapy

T-cells	Clinical trial identifier number	Phase	Study design	Target
Alloreactive CTL (alloCTL)	NCT01144247	Phase I	Safety/Efficacy Study, Open Label	Leucocyte antigens
Allogenic lymphocytes + Aldesleukin	NCT01082926	Phase I	Safety Study, Open Label	White Blood cells

**Table-4. Non-FDA Approved mTOR Inhibitors<sup>[54]</sup>**

### C. mTOR Inhibitors

#### a. Non-FDA Approved Inhibitors

mTOR inhibitors	Clinical trial identifier number	Phase	Study design	Target
Everolimus	NCT01880749	Phase 0	Pharmacokinetics/ Dynamics Study	mTOR

**Table-5. Non-FDA Approved Tyrosine Kinase Inhibitors<sup>[55-60]</sup>**

### D. Tyrosine Kinase Inhibitors

#### a. Non-FDA Approved Kinase Inhibitors

Tyrosine kinase inhibitors	Clinical trial identifier number	Phase	Study design	Target
Imatinib	NCT00904735	Phase II	Open Label	Ribonucleotide reductase and PDGF
Sunitinib	NCT00589784	Phase II	Safety/Efficacy Study, Open Label	PDGFR & VEGFR
Vatalanib	NCT00348790	Phase II	Safety/Efficacy Study, Open Label	VEGFR
Erlotinib	NCT00045110	Phase I & Phase-II	Safety/Efficacy Study, Open Label	EGFR
Gefitinib	NCT00025675	Phase II	Efficacy Study	EGFR
Cediranib	NCT00326664	Phase I	Safety Study/Open Label	VEGFR

**Table-6. Non-FDA Approved Vaccine Therapy<sup>[61]</sup>**

### E. Interferon Therapy

#### a. Non-FDA Approved Interferon Therapy

Interferon therapy	Clinical trial identifier number	Phase	Study design	Target
Recombinant Interferon Alfa (INF alpha)	NCT00002965	Phase II	Efficacy Study	CD8+T cells

**Table-7. Non-FDA Approved Proteasome Inhibitor<sup>[62]</sup>**

### F. Proteasome Inhibitor

#### a. Non-FDA Approved Proteasome Inhibitors

Biological	Clinical trial identifier number	Phase	Study design	Target
Bortezomib	NCT00994500	Phase I	Safety Study/Open Label	26 S proteasome



### CONCLUSION

Meningioma represents more than one-third of CNS tumors. Females are more prone to develop this malignancy as compared to males. The risk factors that play a major role may include ionizing radiations, neurofibromatosis type-2 and hormones. Chromosomal deletions and several signaling and angiogenic pathways may be involved in the progression of meningioma. No FDA approved immunotherapies are available as of now. Immunotherapy has shown a promising development in the past few years. Recent activities have increased our understanding of the tumour micro environment, various immunotherapeutic modalities or combination therapy (like chemotherapy and immunotherapy). Additionally, the effects of such modalities in combination with immunotherapy in cancer patients are still exploratory phase.

### ABBREVIATIONS

**EGFR:** Epidermal Growth Factor Receptor, **HIF-1:** Hypoxia Inducible Factor-1, **Hh:** hedgehog, **HES:** Hairy/Enhancer of Split, **HIF-1:** hypoxia inducible factor-1, **mAbs:** Monoclonal Antibodies (mAbs), **MDM2:** Murine Double Minute 2 protein, **NF2:** Neurofibromatosis Type-2, **pRB:** Retinoblastoma protein, **PI3K:** Phosphatidylinositol 3-kinase, **PDGF-BB:** Platelet-Derived Growth Factor BB, **VEGF-A:** Vascular Endothelial Growth Factor A

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