

inhibition was ameliorated by silencing of *RB1* and therefore could conceivably underlie an immune predatory selection pressure toward selection of *Rb1* altered populations whilst undergoing treatment with CDK4/6 inhibitors. The fact that CDK4/6 inhibition has recently been shown to increase PD-L1 expression in mouse models of breast cancer provides a clear rationale for anti-PD1 treatment as a combination therapy with CDK4/6 inhibition before the emergence of *Rb1* loss of function [18].

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Uncovering the links between systemic hormones and oncogenic signaling in the pathogenesis of meningioma

A number of risk factors have been associated with meningioma development including radiation exposure (radiation-induced meningioma), female gender, germline mutations, high body mass index and hormone exposure (Figure 1). The relationship

between meningioma risk and sex hormones has been of keen interest for decades, sparked by several observations. The most important of these has been the finding of estrogen receptor and progesterone receptor (PR) expression in a substantial portion of meningiomas [1, 2]. In addition, a link between meningiomas and hormones has been supported by the skewed gender distribution of meningiomas [3]. Low-grade meningiomas develop two times more often in women than in men, and three times more

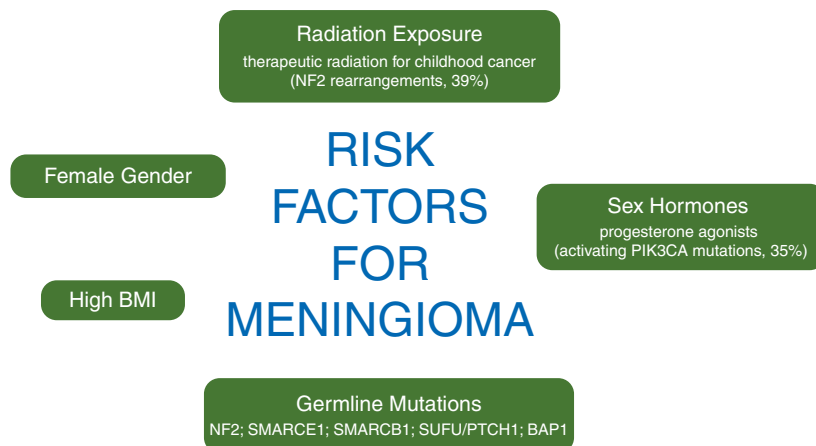


Figure 1. Risk factors associated with meningioma. Radiation-induced meningiomas can result from radiation exposure from nuclear weapons and from therapy for acute lymphoblastic leukemia and other childhood malignancies. Meningioma risk is also increased in women, in individuals with a high body mass index (obesity-associated meningiomas), in people taking sex hormones such as progesterone agonists (progesterone-associated meningiomas) and in people with tumor predisposition syndromes with mutations in *NF2*, *SMARCB1*, *SMARCE1*, *SUFU/PTCH1*, or *BAP1*. The mutational landscape can be influenced by these exposures. For instance, *NF2* rearrangements are enriched in radiation-induced meningiomas and activating mutations in *PIK3CA* are enriched in progesterone-associated meningiomas.

often in women during peak reproductive years [3]. Pregnancy has also been linked with the growth of extant unresected low-grade meningiomas and tumor size can decrease postpartum [3, 4]. Moreover, exogenous hormone use has also been associated with meningioma risk [3].

These observations suggested that hormone receptor antagonists might be useful therapeutics for meningioma. However, despite the expression of PR in 30%–80% of meningiomas [1, 2], PR antagonists have largely been unsuccessful in controlling meningioma growth. Encouraging results were observed in pre-clinical studies, yet, results have been mixed in clinical trials [5]. While studies enrolling limited numbers of patients (3–28 patients) have shown mostly favorable results, albeit with low response rates, a recently reported large, multicenter prospective, phase III clinical trial of the steroidal antiprogestone mifepristone (RU-486), failed to demonstrate improvement in disease progression [6].

Over the last 5 years, much of the focus in the meningioma field has shifted away from exploring the role of hormone receptors in meningioma pathogenesis toward genomic studies. These efforts have been very fruitful. As such, genomic analyses of meningioma have garnered increasing attention.

These genomics studies of meningioma have provided several fundamental observations. First, while somatic or germline mutations in the *NF2* tumor suppressor gene underlie the development of many meningiomas, numerous cases have somatic alterations in a wide range of other genes including *SMO*, *AKT1*, *PIK3CA*, *TRAF7*, *KLF4*, and *POLR2A* [7–11]. In addition, a subset of meningiomas arise in the setting of germline mutations in *SMARCB1*, *SMARCE1* [12] and *BAP1* [13, 14]. While recurrent copy number alterations have long been associated with higher grade meningiomas, *TERT* promoter mutations [15, 16] and distinct methylation patterns [15, 17] have recently been linked to aggressive meningiomas. The aberrations underlying meningioma pathogenesis are, therefore, varied and many.

Genomic studies of meningioma have also revealed links between these newly identified oncogenic drivers and tumor morphology, location within the cranium and level of

chromosomal instability (CIN). For instance, meningiomas that harbor *NF2* mutations generally are strongly associated with fibrous histology [8, 9], those with chromosomal polysomies with angiomatous histology [18], those with *KLF4/TRAF7* mutations with secretory features [11], and those with mutations in *SMO*, *AKT1*, *PIK3CA*, and *POLR2A* with meningothelial features [7–9]. *NF2*-mutant meningiomas typically arise from the meninges covering the cerebral convexities or the posterior fossa of the skull base, and harbor increased CIN whereas many non-*NF2* mutant meningiomas generally arise in the anterior or middle fossa of the skull base and lack CIN [7–9]. The distinct pattern of mutations underlying meningioma arising in the anterior/middle cranial fossa versus those arising over the cerebral convexities may be explained by the embryological origin of the meninges from two sources—the meninges that cover the cerebral hemispheres derive from the neural crest, while those that cover portions of the skull base derive from the cephalic mesoderm [19].

In addition to expanding our understanding of the pathogenesis of meningioma, these genomic analyses have also highlighted the promise of targeted therapies for meningioma patients. Meningiomas with mutations in genes such as *SMO*, *AKT1* and *PIK3CA* may be vulnerable to pathway-specific inhibitors [8, 10]. A recent report of a partial response and durable control of a metastatic *AKT1* (E17K)-mutant meningothelial meningioma to a pan-AKT inhibitor underscores the role of PI3K/AKT oncogenic signaling in fostering meningioma growth [20].

Amidst this intense focus on meningioma genomics, Peyre et al. have made a remarkable observation that redirects our attention back to earlier work on hormone receptors in meningioma, linking the hitherto disparate influences of sex hormones and oncogenic signaling in meningioma development [21]. In a cohort of 40 women who had meningiomas resected following long-term exposure to progesterone agonists (38 cyproterone acetate; 1 megestrol acetate; 1 chlormadinone acetate), the investigators found that over one-third of these patients (14 patients) had tumors with activating *PIK3CA* mutations compared with only 3% in a comparable population of women. All cases with

PIK3CA mutations expressed PR in 50%–100% of the tumor cells. These progestin-associated meningiomas were frequently multiple suggesting synchronous primaries or seeding from a related clone and frequently occurred in the skull base. The progestin-associated meningiomas had neither *PTEN* loss nor *PIK3R1* mutations, nor an increased frequency of AKT1-E17K mutations, suggesting a specific role for *PIK3CA* mutations in the pathogenesis of meningiomas in the setting of progesterone agonists. Interestingly, a shift in the spectrum of mutations has also been observed recently in radiation-induced meningiomas that are highly enriched for rearrangements in *NF2* [22].

The work of Peyre et al. raises many important areas for further investigation. While the evidence to date suggests that *PIK3CA*-mutant meningiomas arise predominantly in women [8, 9, 21], it remains unclear the fraction of these meningiomas that arise due to chronic exposure to progesterone agonists. The current study clearly suggests that continued exposure to progesterone agonists may drive the growth of *PIK3CA*-mutant meningiomas, yet *PIK3CA*-mutant meningioma cell lines or animal models are not yet available to test this hypothesis. In addition, using progesterone antagonists to treat a patient population stratified by *PIK3CA* mutation status has not yet attempted. Hence, while the current data suggest that *PIK3CA*-mutant meningiomas may be hormone-dependent cancers, further work is required. Interestingly, in a different study, patients who developed meningiomas—often multiple and in the skull base—during long-term use of cyproterone acetate, had stabilization of tumor growth and tumor regression after hormone withdrawal [23]. Presumably, based on insights from the current study, some but not all of the responsive patients in that cohort may have had *PIK3CA*-mutant meningiomas.

Most importantly, why and how would progesterone foster the growth of *PIK3CA*-mutant meningiomas? One possibility is through the elevated levels of PR that have been associated with *PIK3CA* mutation in a study of nearly 20 000 tumor samples (>40 cancer types) [24] or the alterations in hormone receptor binding that can result from PI3K-pathway activation [25]. A myriad of possibilities exists for the interplay and cross-talk between the PI3K-pathway and PR activity. Valuable lessons may be learned from hormone-dependent cancers such as breast, endometrial and prostate cancers [26] in which genomic alterations in steroid hormone receptors including amplifications, splice variants and point mutations as well as alterations in hormone receptor cofactors have been identified.

Despite the exciting progress in our understanding of meningioma pathogenesis, many questions remain. The fascinating link between sex hormones and the development of *PIK3CA*-mutant meningiomas that Peyre et al. have uncovered is assured to stimulate further efforts to integrate epidemiological, genomic and functional information. Such multifaceted approaches should reveal further insights into the complicated relationship between systemic hormonal and metabolic cues and the development of meningioma.

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Phase I–II trial designs: how early should efficacy guide the dose recommendation process?

Oncology has the highest number of drug development failures, which calls for improvement in drug development methodology [1]. Following the two therapeutic revolutions of targeted agents and immune therapies, several drug development paradigms have been challenged, including the systematic recommendation of the maximum tolerable dose as recommended phase II dose (RP2D) [2]. More and more trials seek to determine the ‘optimal biological dose’ (dose associated with the most desirable effect on a pre-specified biomarker). Furthermore, although determination of safety profile of a new agent remains the primary end point of phase I trials, efficacy is more and more often brought forward as a co-primary end point. This has resulted in significant transformations over the last few years, with phase I sample sizes and number of expansion cohorts being multiplied [3]. Such expansion cohorts are sometimes disguised single arm phase II studies, resulting in a two-step design made of a dose-escalation phase, based on toxicity only, followed by a ‘signal-searching’ expansion phase with stopping rules for futility [4].

In this context, should we take into account efficacy to guide dose-escalation and dose-recommendation? In this issue of *Annals of Oncology*, Yan et al. [5] illustrate, using clear examples, that responses at doses other than the RP2D are not integrated in the overall efficacy evaluation, and propose the phase I–II EffTox model-based design, which utilizes both toxicity and efficacy data to guide dose-recommendation. Doses are escalated if the agent is safe and if more activity is expected; doses are de-escalated if lower doses appear almost equally active but less toxic; agents without sufficient activity at any safe dose are halted early. Dose that allows reaching the optimal efficacy-toxicity trade-off is further selected.

Agents such as nivolumab or pembrolizumab might have benefited from such design, as similar efficacy was observed at several dose levels in initial dose-escalation trials, and optimal dose had to be secondarily refined in later-stage randomized trials [6]. However, EffTox has been reported in four trials only since its introduction in 2004 [7–11]. It is therefore important to identify settings in which this method brings significant added value, as well as to acknowledge potential limitations in its implementation.

EffTox requires a homogeneous patient population selected for drug sensitivity. The four trials discussed by Yuan and colleagues were all carried out in very well-defined populations.

Strict selection of patients in phase I has pros and cons. For a highly-specific drug whose mechanism of action is precisely characterized, strict selection should be recommended, whatever the frequency of the molecular profile of interest. Successful examples include the ALK-ROS inhibitor lorlatinib [12] and the NTRK/ROS1/ALK inhibitor entrectinib [13]. In other situations, no selection should be applied as efficacy signals might otherwise be missed—as illustrated by the famous case of the multikinase inhibitor sorafenib, which turned out to be a poor Raf inhibitor but a potent antiangiogenic. The identification of the target population is a delicate process; for example, crizotinib appeared ineffective after the inclusion of the first unselected dose escalation cohort [14]; the unique observed response could luckily be associated with ALK translocation, leading to a subsequent molecular enrichment during the expansion cohort. It would have been erroneously abandoned, had an early stopping rule for activity been applied. Therefore, it may be wise to only apply enrichment in the dose-expansion phase, unless preclinical data justify it. In this respect, EffTox might be best-suited for trials with accurately defined populations.

Even if the population of interest is somehow determined, can we characterize the dose–activity relationship in phase I–II trials that enroll often limited sample sizes of refractory patients? Gupta et al. (*JNCI* 2012) found that 95% of the phase I trials ($n = 1908$ patients) reported less than two objective responses, making it impossible to assess statistically any dose trends. In the absence of randomization, detecting moderate differences in activity is challenging [15].

Phase I trials should also be designed with a view to expediting drug development, which mandates rapid dose-escalation in the absence of safety concerns. Three trials using EffTox evaluated efficacy 42–90 days after treatment initiation [8, 9, 11]; waiting such delay for deciding on dose-escalation raises practical concerns. Conversely, the efficacy end point of the last trial [10] was defined at 48 h after treatment initiation, making EffTox very efficient. However, late toxicities [16, 17] might not be well-captured by EffTox. To address this, the Late-Onset EffTox method has been proposed [18], which incorporates time-to-event data of ‘treated yet-non-assessed patients’; clinical evaluation of this method is warranted. Overall, EffTox might be most relevant when unique, homogeneous and validated early surrogate biomarkers of efficacy are available, e.g. a decrease of 2-hydroxygluturate under isocitrate-dehydrogenase (IDH) inhibitors in IDH-mutant acute myeloid leukemia [19].