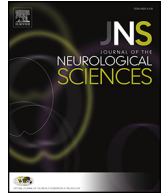




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## Review Article

## Management of glioblastoma in elderly patients



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## ABSTRACT

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults over 55 years of age. The median age of diagnosis for patients with GBM is 64 years old, with the incidence of patients between 75 and 85 increasing. The optimal treatment paradigm for elderly GBM patients continues to evolve due to the higher frequency of age-related and/or medical co-morbidities. Geriatric GBM patients have historically been excluded from larger, controlled clinical trials due to their presumed decreased likelihood of a sustained treatment response and/or a prolonged good outcome. Here, we highlight current treatment considerations of elderly GBM patients with respect to surgical, radiotherapeutic and systemic modalities, with considerations for improving future clinical outcomes for this patient population.

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## Contents

1. Introduction . . . . .	1
1.1. Glioblastoma biology and treatment in the elderly. . . . .	1
2. Role of surgical intervention . . . . .	2
2.1. Newly diagnosed GBM . . . . .	2
3. Radiotherapy. . . . .	3
4. Systemic therapy alone or in combination with radiotherapy for elderly patients with GBM . . . . .	4
4.1. Newly diagnosed GBM . . . . .	4
5. Other therapeutic modalities. . . . .	4
5.1. Immunotherapy . . . . .	4
5.2. Tumor-treating fields. . . . .	4
5.3. Recurrent GBM . . . . .	4
6. Conclusions . . . . .	5
Disclosures . . . . .	5
References . . . . .	5

## 1. Introduction

## 1.1. Glioblastoma biology and treatment in the elderly

Glioblastoma (GBM) is the most common malignant primary brain tumor in adults, and over half of GBM patients are 65 years of age or

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older at the time of diagnosis. Additionally, the proportion of elderly patients with GBM is projected to increase as the collective world population survives longer, highlighting the growing importance of managing elderly GBM patients [1]. While the current standard of care for younger patients includes surgical resection, followed by concurrent chemoradiation [2,3], the maximally-effective treatment of older patients had not been clearly defined since the clinical trials establishing standard of care for this patient population traditionally excluded individuals >70 years of age. Highlighting the need to tailor therapy in elderly patients when considering chemoradiation, median survival in large retrospective studies is six months for newly diagnosed GBM patients older than 65 when compared to 14.6 months for patients (median age 56 years old) in Stupp et al.'s randomized controlled trial [4–7]. However, it is often difficult to control for intensity of treatment when making cohort comparisons from retrospective data and many have suggested that despite the level 1 evidence, elderly patients receive less intensive therapy [8–10]. In addition to differences in treatment, other factors that may lead to worse outcomes in the elderly include KPS, differences in the GBM biology, and alterations in the central nervous system (CNS) that change with and/or contribute to gliomagenesis and proliferation.

The increased use of prognostic and predictive genetic and molecular tumor markers to guide therapy may also differ in incidence and utility in the elderly GBM patients. For example, GBM is now classified as two distinct entities based on the mutational status of the isocitrate dehydrogenase (*IDH*) gene [11]. *IDH* mutation correlates with a better patient survival outcome when compared to *IDH* wild-type tumors. *IDH1* mutations are a driving factor for the epigenetic, glioma CpG island phenotype (G-CIMP) [12], which is also associated with the proneural molecular subgroup [13]. Notably, while four distinct gene expression signatures (classical, mesenchymal, neural, proneural) and numerous gene mutations influence patient prognosis and treatment response, the relative frequency and prognostic value of these molecular criteria are not constant across patient age [1,14,15]. For instance, p53 mutations and EGFR amplification possess opposite prognostic value in young when compared to old GBM patients [16,17]. O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, results in a GBM that has greater sensitivity to temozolomide and radiotherapy and is an important prognostic and predictive molecular glioma phenotype that does not change with age [18]. Equally interesting are the potential factors inherent to the CNS that change with age and prior to GBM onset. Indoleamine 2,3 dioxygenase 1 (IDO1), an immunosuppressive molecule associated with pathogenic effects in glioma models and patients [19], is upregulated 400-fold in the CNS of 'old' animal subjects, when compared to young counterparts [20]; suggesting that, age-related factors contribute to the likelihood for gliomagenesis, survival, and/or progression.

However, the *IDH* mutation is far more frequent among younger adults when compared to older individuals [21–23]. In turn, when addressing issues surrounding GBM in the elderly we are predominantly addressing *IDH* wild-type GBM. Acknowledgment of the impact of these markers on overall survival leads to stratification in current clinical trials while further complicating retrospective comparisons.

Aside from biomarkers, medical co-morbidities and patient frailty are more challenging to directly quantify, but likely play roles in survival and quality of life outcomes. Treatment response is often complicated by other medical considerations including co-morbid disease, polypharmacy and an increased susceptibility to adverse treatment effects [2,24,25]. Finally, caregivers of elderly cancer patients who take on the significant time commitment and physical, financial, and emotional toll associated with scheduling, managing, and supporting a loved one with a terminal disease are often elderly themselves [26,27]. This burden places both the patient and the caregiver at risk for health, economic, and psychosocial strain during the treatment process, and highlights the continued need for nursing and physician assistance and support during the entire treatment journey.

Here, we re-evaluate the evidence for therapeutic management via surgical intervention, radiotherapy, systemic modalities and tumor treating fields (TTF) (Table 1).

## 2. Role of surgical intervention

### 2.1. Newly diagnosed GBM

The operative treatment of newly diagnosed GBM in elderly patients has traditionally been more conservative, often limited to a biopsy, rather than an aggressive surgical resection. The rationale for this approach is based on the worse prognosis. However, this paradigm is currently being challenged by a growing body of literature demonstrating a survival benefit in elderly patients undergoing a more aggressive tumor resection.

Similar to young adults, observational-, retrospective- and large population-based analyses suggest that both gross total and subtotal resection is associated with improved survival when compared to biopsy alone, or to the lack of surgical intervention in older GBM patients – with gross total resection demonstrating the greatest benefit to patient survival [28–34]. Interestingly, a single-center retrospective analysis (N = 361) confirmed that there was no statistically significant difference in PFS or OS between young and elderly patients undergoing tumor resection, though old age was associated with a worse prognosis in the GBM patient subset that was treated with biopsy, alone, further arguing that the option for surgical resection should not be withheld from GBM patients [35]. Attempts at case-control studies to reduce the confounding bias implicit to retrospective studies also find benefits for surgical resection when compared to brain biopsy in patients over 65 years old [33].

These findings do not imply that all elderly patients are appropriate candidates for an aggressive surgical resection, as selection bias cannot be excluded when evaluating retrospective analyses. Chaichana et al. reported that a < 80 KPS, COPD, motor/language/cognitive-deficit and tumor size >4.0 cm were preoperative factors associated with worse survival among GBM patients >65 years old who underwent aggressive resection [30]. Independently KPS was found to be the most important prognostic factor in GBM patients >70 years prior to surgery and after treatment with corticosteroids [36–38]. These results highlight the importance of identifying preoperative factors that prognosticate the benefit of surgical resection. Additional work is necessary to define patients with superior potential for responding to surgical resection while co-discriminating against those with the highest likelihood of pre-/post-operative risk due to open surgery.

Surgical complications tend to happen more frequently in elderly GBM patients. A retrospective analysis at the Mayo clinic concluded that patients were more likely to receive a biopsy, rather than resection, if the tumor was deep-seated or presented as multifocal lesions (n = 105) [39]. Seven patients (6.7%) developed new persistent neurological deficits post-operatively and 6 patients (5.7%) suffered post-operative hemorrhage although it should be noted that all patients with post-operative hemorrhage came from the biopsy-only cohort. The risk of permanent complications and deficits following surgery for elderly GBM patients is important because these impairments are often associated with decreased survival and a worse quality of life.

Importantly, these studies described above often fail to include functional or quality of life (QOL) outcome measures making it more difficult to gauge the risks and benefits. Accordingly, although one study found longer survival times for patients who underwent open surgical resection, the time to deterioration did not differ between the patients who only underwent a stereotactic biopsy and those who received an open resection [32]. Conversely, other reports suggest that functional recovery or post-operative KPS score is improved following a resection of any extent compared to a biopsy and, furthermore, the patients who underwent the more aggressive surgery did not have higher rates of mortality or morbidity [28]. Certainly, any life-prolonging surgery that

**Table 1**  
Therapeutic clinical trials for elderly patients with glioblastoma.

Author	Year	n	Age	KPS	Surgery	Radiation	Chemo-therapy	OS	PFS
Vuorinen [32]	2003	30	≥65	≥60	Resection Biopsy	NA <sup>a</sup>	NA	171 days 85 days	NA
Hernandez [41]	1990	14	No age mandated. Range 47–75.	≤60	NA	WBRT 43–45 Gy in 1 Gy fractions 3 times a day, plus 9–12 Gy boost in 1.5–2 Gy daily fractions	NA	30.4 weeks	
Keime-Guibert [40]	2007	85	≥70	≥70	NA	50.4 Gy in 1.8 Gy fractions Supportive care	NA	29.1 weeks 16.9 weeks	14.9 weeks 5.4 weeks
Roa [42]	2004	100	≥60	≥50	NA	60 Gy in 30 fractions 40 Gy in 15 fractions	NA	5.1 months 5.6 months	NA
Roa [43]	2015	98	≥50 ≥65 ≥65	50–70 50–70 80–100	NA	25 Gy in 5 fractions 40 Gy in 15 fractions	NA	7.9 mo 6.4 mo	4.2 mo 4.2 mo
Wick [45]	2012	412	>65	≥60	NA	60 Gy in 30 fractions	TMZ (100 mg/m <sup>2</sup> ) 7 days on/7 days off	8.6 mo 9.6 mo	NA
Malmstrom [46]	2012	342	≥60	NA <sup>b</sup>	NA	30.4 Gy in 3.5 Gy fractions 60 Gy in 2 Gy fractions	TMZ (200 mg/m <sup>2</sup> ) D1–5	8.3 mo 7.5 mo 6.0 mo	NA
Minniti [67]	2009	43	≥70	≥60	NA	30 Gy in 5 Gy fractions	TMZ (150–200 mg/m <sup>2</sup> ) × 12	9.3 mo	6.3 mo
Brandes [65]	2003	79	>65	≥60	NA	59.4 Gy in 1.8–2 Gy fractions 59.4 Gy in 1.8–2 Gy fractions	NA PCV TMZ	11.2 mo 12.7 mo 13.9 mo	NA
Perry [47]	2017	562	≥65	<sup>c</sup>	NA	40 Gy in 15 fractions	RT (40 Gy)/TMZ (75 mg/m <sup>2</sup> daily)+ TMZ (150–200 mg/m <sup>2</sup> ) D1–5 × 12	7.6 mo 9.3 mo	5.3 mo 3.9 mo

KPS, Karnofsky performance score; OS, overall survival; PFS, progression free survival; PFS6, 6 month progression free survival; RT, radiation therapy; NA, not available; TMZ, temozolomide; PCV, procarbazine, CCNU, vincristine.

<sup>a</sup> Non-randomized RT regimen. Some patients received no RT. Those who did received 16–60 Gy.

<sup>b</sup> Did not utilize KPS. Utilized WHO score.

<sup>c</sup> Did not utilize KPS. Utilized ECOG score (ECOG 0–2).

results in a significant impairment in patient's QOL must be considered in the context of the patient's wishes and may ultimately not be deemed beneficial.

Turning toward large prospective cohorts and randomized trials helps to minimize the above mentioned bias. The Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA) provided early evidence supporting surgical resection in older patients, based on the elderly group >50 years of age that received a surgical resection, surviving longer than individuals within the same age group undergoing biopsy alone [7]. Supporting this approach, a small randomized trial (n = 30) investigating the role of debulking surgery versus biopsy in GBM patients aged ≥65 and with a KPS >60, determined that, craniotomy and surgical resection yielded a greater survival advantage when compared to stereotactic biopsy (171 days vs. 85 days, p = 0.035), although the two groups clinically deteriorated at similar rates [32]. Accordingly, an independent analysis using RPA confirmed that the extent of resection, performance status and patient age influenced patient prognosis, and that age was an independent predictor of survival for patients who received either a gross total resection or a partial resection compared to those who only received a biopsy [37]. Also, in a Phase III randomized clinical trial examining the use of 5-aminolevulinic acid to improve a neurosurgeon's ability to detect and resect invasive glioma cells the >55 years of age cohort performed better compared to traditional white light surgical resection. Clinically important there was no difference in severe adverse events or adverse events between the groups. These data suggest that aggressive surgical resection is a therapeutic option to be considered for prolonging survival in carefully selected elderly patients with glioblastoma.

Although further randomized trials would be needed to more clearly establish the role of surgical resection in older GBM patients, the current evidence supports the use of aggressive surgical resection in elderly patients who are reasonable surgical candidates.

### 3. Radiotherapy

As already discussed, advanced age is associated with a lower likelihood of undergoing a surgical resection for GBM patients. Older patients may also be less likely to receive radiation, chemotherapy, or combinatorial treatment. There are concerns about tolerability with regards to radiation in particular in the elderly population. Fatigue is a frequent toxicity seen in the majority of patients receiving cranial radiation and this may be more pronounced in the elderly. Cognitive decline is also a concern, particularly on the background of possible suboptimal cognitive baseline function or cognitive reserve. Finally, the social logistical issues involved in daily transport to radiation treatments are often more cumbersome in the elderly population. The effects of these factors on outcomes such as quality of life and survival have not been studied extensively in an age-dependent manner. This is in part secondary to the short OS and inability for longitudinal follow up for quality of life (QOL) studies in this patient population.

A number of clinical trials have addressed the role of radiation therapy in the treatment of elderly GBM patients. Level 1 evidence demonstrates that radiation alone (50.4 Gy in 28 fractions) appears superior to supportive care with respect to OS (7 months vs. 4.25 months) in patients of advanced age (>70 years old) [40]. A number of shorter-course radiation regimens have been evaluated in this patient population. For instance, an early trial utilizing a 3 week course of whole-brain radiation to 43–45 Gy with a 9–12 Gy boost was shown to be both safe and feasible in hospitalized patients with poor performance status [41]. This cumbersome approach in a frail patient population is not utilized in the contemporary setting. More recent studies of once daily short-course radiation in the outpatient setting have helped define our current approach. A 3 week course (15 fractions) of focal radiation to 40 Gy was found to be equivalent to radiation alone to 60 Gy in patients ≥60 years old [42]. An even more truncated course of radiotherapy alone (25 Gy in 5 fractions) was equivalent to the short course regimen

(40 Gy in 15 fractions) described above when utilized in frail and elderly patients [43]. These studies provide a template on which radiation therapy in the elderly can be tailored in a patient-specific manner. They also provide the groundwork upon which combinatorial regimens should be explored in this patient population.

#### 4. Systemic therapy alone or in combination with radiotherapy for elderly patients with GBM

##### 4.1. Newly diagnosed GBM

Although the value of chemotherapy has been well characterized in younger patients with GBM, its role in the management of older patients is less certain. Stupp et al.'s seminal trial suggested that the benefit of chemotherapy combined with radiation therapy may be less pronounced when compared to radiotherapy alone in the older subset of patients included in the trial [2]. Furthermore, the presence of MGMT (O<sup>6</sup>-methylguanine-DNA-methyltransferase) promoter methylation acts as a prognostic marker and a predictor of benefit from temozolomide (TMZ) treatment [44].

A recent landmark Phase III international (CCTG CE.6/EORTC 26062-26,061/TROG 08.02) randomized control trial confirms previous retrospective work. The trial compared radiation therapy alone (40 Gy, 15 fractions) vs. radiation therapy (40 Gy, 15 fractions) with concomitant daily TMZ (75 mg/m<sup>2</sup>), followed by adjuvant TMZ (5 days every 28 days) for 12 cycles in newly diagnosed GBM patients at least 65 years old (median age = 73 years old) [45]. This trial mimics the pivotal EORTC/NCIC trial with 3 notable changes: 1) shorter course (i.e. more convenient dosing) radiation therapy with higher doses per fraction, 2) a shorter course of concomitant TMZ, and 3) a greater number (12 vs. 6) of cycles of adjuvant TMZ. A significant improvement in overall survival (OS) (9.3 vs. 7.6 months) and progression free survival (PFS) (5.3 vs. 3.9 months) was seen in the combinational chemoradiotherapy arm. Strikingly, there is even a trend toward a survival benefit in patients who had an unmethylated MGMT promoter. Importantly, the improvement in OS and PFS were achieved in the context of reasonable tolerability – with the expected hematologic toxicities well within an acceptable range for patient safety. While toxicity was slightly higher in the combined therapy arm QOL also did not appear to be substantially affected with the addition of chemotherapy to radiation alone. It is important to note that there has been no direct comparison of the above described regimens to standard course (6 week) radiation with concomitant TMZ followed by adjuvant TMZ in the elderly population.

Prior to the phase III trial described above, there were key studies which helped lay the groundwork for that pivotal trial. While prior randomized trials compared various radiation schedules alone versus chemotherapy alone, comparisons to more aggressive chemo radiotherapy were limited. A meta-analysis of 16 non-randomized studies found that combined radiation and TMZ provided a survival benefit for elderly GBM patients who had a favorable KPS and had undergone an extensive surgical resection [46]. There was also an increase in toxicities in these patients, although these toxicities were considered tolerable. These data suggested, as does the surgical data, that applying the aggressive standard of care used in younger patients is safe and appropriate in the elderly population. The randomized NOA-08 clinical trial demonstrated non-inferiority of a 7-day-on/7-day-off schedule of TMZ (100 mg/m<sup>2</sup>) compared to radiation therapy alone (60 Gy in 30 fractions of high-dose radiation) for patients older than 65 years of age with a KPS > 60. No differences between the regimens in health related QOL were detected [47]. The subgroup analyses showed improved OS for patients with MGMT promoter methylation treated with TMZ compared with radiation therapy. The NORDIC trial randomized patients to either TMZ alone (200 mg/m<sup>2</sup> D1–5) vs short-course radiation (30.4 Gy in 3.5 Gy fractions) vs standard RT (60 Gy in 30 fractions) and found superior OS with either TMZ alone or short-course RT alone compared to the longer course RT. Toxicity was comparable between the two groups.

Grade 3/4 fatigue was 24% in the chemotherapy arm and 20% in the radiation arm [48]. These results argue for consideration of chemotherapy alone for elderly patients with a methylated MGMT promoter for which radiation therapy is contraindicated or would be impractical; whereas in the group of elderly patients with unmethylated MGMT promoters, radiation treatment alone versus radiation plus TMZ should be given strong consideration. Many argue that chemotherapy alone has the advantage of requiring less frequent and fewer total trips to a medical provider compared to radiation alone.

#### 5. Other therapeutic modalities

##### 5.1. Immunotherapy

Immunotherapeutic agents have demonstrated significant efficacy in the treatment of multiple solid malignancies, leading to a rise in their exploration for malignant gliomas. High grade gliomas such as GBM lead to more blood brain barrier breakdown and are associated with an increased number of tumor infiltrating lymphocytes; however, multiple immunosuppressive factors found in the tumor microenvironment severely limit any immune response mounted against the tumor [49]. Together, these findings suggest that there is potential for the use of immunotherapy in patients with GBM. Immunotherapeutic approaches are being explored for GBM include peptide vaccines, dendritic cell vaccines, engineered oncolytic viruses, engineered CAR T-cell therapy, and checkpoint inhibitors and other small molecule inhibitors, and combinations of the aforementioned therapies. Importantly, older individuals have a reduced ability of the adaptive immune system to respond to challenges, which might contribute to their poorer prognosis with GBM and may limit the effectiveness of immunotherapy in this patient population [50,51]. The benefit of immunotherapeutic agents for patients with GBM is currently being explored in a series of clinical trials. These trials typically do not have older age as exclusion criteria.

##### 5.2. Tumor-treating fields

Tumor-treating fields (TTF) is an FDA-approved device for the treatment of newly diagnosed and recurrent GBM. The device (Optune, Novocure) consists of a set of arrays that must be worn over a shaved scalp nearly continuously. These arrays create electrical fields that are thought to interfere with mitoses and lead to cellular apoptosis. Currently, TTF is added to the treatment regimen after the completion of radiation therapy with concomitant TMZ (i.e. when adjuvant TMZ cycles are started). The EF14 trial that led to the device's approval for newly diagnosed GBM patients did not have an age cutoff, and patients were enrolled between 20 and 83 years of age (median age = 57 years), although details regarding the outcomes for patients in different age cohorts have not been published to date [52]. Analyses demonstrating benefit in the ≥50 year old population have recently been presented [53]. For patients with recurrent GBM, more modest benefits were observed with TTF [54]. The EF11 trial enrolled patients that ranged in age from 23 to 80 years old (median age = 54 years) and found no improvements in OS for the TTF group, but QOL analyses favored TTF therapy across most domains. In turn, TTF can be considered as a potential therapeutic option regardless of age.

##### 5.3. Recurrent GBM

As expected, evidence from clinical trials is lacking to help guide the management of older patients with recurrent GBM, and given the poor prognosis best supportive care measures are often the only treatment option considered. As such, more aggressive management decisions must be influenced by the results of trials that evaluate treatments in patients of all ages and inferred from clinical outcomes observed outside of clinical trials.

The role for reoperation and repeat resection is currently undefined for older patients. A recent large, retrospective study out of Germany found that re-resection is beneficial for GBM patients of all ages [55]. Multiple re-resections lead to the largest survival benefits, although each re-resection was associated with additional surgical complications. And while age is a prognostic factor for outcome, even within the older patients there is no evidence that multiple re-resections are an inappropriate treatment course. Certainly, the older patients considered for resection as a salvage therapy are likely to be at a higher preoperative performance status than patients for whom repeat resection is not offered, and, as expected, higher KPS score is a prognostic factor for re-operated recurrent GBM patients [56–58]. Nevertheless, re-operation seemed to be the most effective salvage strategy in selected elderly patients with a KPS  $\geq$  60% [59]. The reported 51 week post-progression survival in this study was comparable to the literature for recurrent GBM patients, which is largely comprised of younger patients with often more favorable prognostic factors [60].

One medical option that has re-emerged for older patients is the oral nitrosourea, lomustine. This chemotherapeutic is easily dosed, typically 110 mg/m<sup>2</sup> once every 6 weeks for a total of 6 cycles if efficacious and tolerated [61,62]. However, this chemotherapy has the potential for significant, prolonged cytopenia and this must be considered in the older, frailer population.

Another option is intravenous administration of the antiangiogenic anti-vascular endothelial growth factor (VEGF) antibody bevacizumab (Avastin, Genetech). This therapeutic agent is associated with improved PFS and radiographic response rates, which are secondary in part to its mechanism of action of decreasing cerebral edema and normalizing the tumor vasculature [63,64]. This agent may be most beneficial for patients with more robustly enhancing tumors that are associated with substantial cerebral edema. There is even some evidence that bevacizumab may offer some benefit to patients even if it is used is delayed until a later line of therapy [65].

The dearth of studies exploring second line chemotherapy treatment for recurrent or progressive GBM in the elderly creates a void of information that needs to be filled by additional randomized trials.

## 6. Conclusions

Older GBM patients have tended to receive more conservative treatment approaches than their younger counterparts with the rationale that these patients have a worse overall prognosis and are higher operative risks and are more likely to suffer adverse effects of aggressive chemo- and radiotherapy regimens. However, this patient population is an extremely heterogeneous group, with patient and tumor specific factors influencing prognosis and treatment response.

In summary, small studies, retrospective studies, and an evaluation of the older subgroups in randomized control trials supports surgical resection in elderly patients who are good surgical candidates. Furthermore, the available evidence including recent randomized data suggests that chemotherapy and radiation therapy are well tolerated and appropriate for older GBM patients. Various ongoing and completed clinical trials are currently exploring the optimal surgical, chemotherapeutic, and radiotherapy treatment regimens, as well as the effectiveness of combinatorial treatment paradigms for elderly GBM patients. Additionally, a trend of including elderly patients can be seen in recent randomized trials. As these older patients make up a majority of GBM patients this will facilitate trial accrual and provide for a clearer understanding regarding differences in outcomes between the elderly and non-elderly and the potential biological factors which can be influencing these differences.

## Disclosures

R.V.L serves on advisory boards for Abbvie, Asta Zeneca, and Ziopharm, given an internal lecture/presentation for Abbvie, and

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