# GENOMICS AND TARGETED THERAPY FOR MENINGIOMAS

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## Table 1

| WHO | Grade Description |
|---|---|
| Grade I (Benign) | • Any histologic pattern other than clear cell, chordoid, papillary, or rhabdoid.<br>• Lacks criteria of atypical or an aplasticmeningioma |
| Grade II (Atypical) | • Mitoses: 4–19 (10 hpf)<br>• Macronuclei, spontaneous necrosis, hypercellularity, small cell formation, sheeting architecture (Any 3 of these 5 parameters or possibly more)<br>• Meningioma protrudes into the parenchyma of the brain<br>• Clear cell or chordoid cell types |
| Grade III (Anaplastic) | • Mitoses: 20+ (10 hpf)<br>• Apparent anaplasia (carcinoma/sarcoma-like histology)<br>• Rhabdoid or papillary cell type |

**TABLE 2. Literature review of reported outcomes after GTR and STR of Grade II meningiomas**

| Authors & Year | No. of Cases | Simpson Grade(s) Corresponding to GTR | GTR Cases (%) | Outcomes After GTR | Outcomes After STR | Benefit of GTR |
|---|---|---|---|---|---|---|
| Yang et al., 2008 | 40 | I–II | 24 (60) | NA | NA | OR 0.416; p = 0.012 (PFS) |
| Mair et al., 2011 | 114 | I–II | 66 (73) | 59% 5-yr PFS | 32% 5-yr PFS | HR 0.396; p = 0.018 |
| Lee et al., 2013 | 90 | I–III | 71 (79) | 85% 5-yr PFS | 70% 5-yr PFS | HR 0.188; p = 0.007 |
| Park et al., 2013 | 83 | I–II | 55 (66) | 59% 5-yr PFS | 30% 5-yr PFS | p = 0.002 |
| Hardesty et al., 2013 | 258 | I–II | 149 (58) | 85% 5-yr PFS | 54% 5-yr PFS | RR 0.255; p <0.0001 |
| Choi et al., 2014 | 72 | I–II | 53 (74) | 92% 5-yr OS* | 61% 5-yr OS* | HR 0.108; p <0.001* |
| Hammouche et al., 2014 | 79 | I | 34 (43) | 74% 5-yr PFS | 32% 5-yr PFS | HR 0.45;† p = 0.005 |
| Zhao et al., 2015 | 89 | I–II | 72 (81) | NA | NA | HR 0.165; p = 0.021 (OS) |
| Sun et al., 2014[77,78] | 210 | I–III | 151 (72) | 89% 5-yr PFS | 48% 5-yr PFS | HR 0.169; p <0.001 |
| Wang et al., 2015 | 28 | NA | 14 (50) | 90% 3-yr PFS | 38% 3-yr PFS | p = 0.005 |

HR = hazard ratio; NA = not available; OR = odds ratio; RR = relative risk.

* Combined WHO Grade II and III meningiomas.

† Per Simpson grade.

# TREATMENT OF RECURRENT MENINGIOMAS

- The typical approach includes reoperation and radiotherapy (reirradiation more commonly performed with stereotactic radiosurgery).
- These interventions delay a subsequent recurrence but rarely prevent it entirely.
- When surgery and radiation therapy are no longer available, patients have very few medical treatment options with limited efficacy.

**TABLE 1: List of potential medications for treatment of meningiomas***

| Medication | Mechanism of Action | Stage of Investigation† |
|---|---|---|
| cytotoxic agents | | |
| temozolomide (Temodar) | alkylating agent | Phase II trial: no clinical efficacy shown |
| irinotecan (Camptosar) | topoisomerase 1 inhibitor | Phase II trial: no clinical efficacy shown |
| hydroxyurea | ribonucleotide reductase inhibitor | Phase II trial: mixed results |
| trabectedin (Yondelis) | mechanism unclear; believed to make conformational changes to DNA strand, causing inhibition of transcription factor binding | preclinical: cell culture/in vitro |
| plant-derived agents | | |
| curcumin | interaction w/ multiple cell signaling proteins | preclinical: cell culture/in vitro |
| AKBA | induction of apoptosis, antiinflammatory | preclinical: cell culture/in vitro |
| hormonal agents | | |
| progesterone receptor binding agents | | |
| megestrol (Megace) | progesterone receptor partial agonist | SSCT: no survival benefit shown |
| mifepristone (RU-486) | progesterone receptor competitive antagonist | Phase III: no survival benefit shown |
| estrogen antagonists | | |
| tamoxifen | estrogen receptor competitive antagonist | SSCT: no survival benefit shown |
| somatostatins | | |
| octreotide (Sandostatin) | somatostatin mimetic | Phase II: some stabilization of disease |
| pasireotide (Signifor) | somatostatin mimetic, long-acting | Phase II trial: ongoing |
| GH receptor antagonists | | |
| pegvisomant (Somavert) | pegylated GH receptor antagonist | preclinical: animal models |
| IGF-I & -II antagonists | | |
| fenretinide | synthetic retinoid derivative | preclinical: cell culture/in vitro |

**Table 1: Most relevant genes involved in the pathogenesis of meningiomas and coded by those chromosomes more frequently altered in these tumors: chromosomal localization, type of genetic alteration and function.**

| *Gene* | *Locus* | *Product* | *Genetic alteration* | *Physiologic function* | *Role and/or impact on meningiomas* |
|---|---|---|---|---|---|
| ***Chromosome 22*** | | | | | |
| *NF2* | 22q12.2 | Merlin | Downregulation Several mutations# | Linkage of cell membrane proteins to the cytoskeleton | Early event in tumorigenesis [1, 2] [3] |
| *BAM22* | 22q12.2 | Beta-adaptin | Downregulation | Endocytosis | Potential early event in tumorigenesis [4] |
| *BCR* | 22q11 | Bcr | Downregulation | Serine/threonine kinase, GTPase activator | Potentially involved in tumorigenesis [5] |
| *TIMP3* | 22q12 | Metalloproteinase inhibitor3 | Hypermethylation | Inhibits MMP-2 and MMP9activity | Associated with high grade tumors [6] |
| ***Chromosome 1*** | | | | | |
| *ALPL* | 1p36.1-p34 | Alkaline phosphatase | Downregulation | Cell cycle control | Associated with high grade tumors and recurrence [7, 8] |
| ***Chromosome 6*** | | | | | |
| *HIST1H1C* | 6p21.1 | Histone H1.2 | Upregulation | Cell cycle | Associated with recurrence [9] |
| *CTGF* | 6q23.2 | Connective tissue growth factor | Downregulation | Growth factor | Associated with recurrence [9] |
| ***Chromosome 9*** | | | | | |
| *CDKN2A/p16INKα* | 9p21.3 | P16 | Downregulation; Hypermethylation | Cell cycle control | Associated with high grade tumors[10-13] |
| *CDKN2B/p15ARF* | 9p21.3 | P15 | Downregulation; Hypermethylation | Cell cycle control | Associated with high grade tumors [10, 11, 13] |
| *CDKN2A/p14ARF* | 9p21.3 | P14 | Downregulation; Hypermethylation | Cell cycle control | Associated with high grade tumors [10, 12-14] |
| *KLF4* | 9q31 | Kruppel-like factor 4 | Upregulation K409Q mutation | Transcription factor which induces pluripotency | Associated with tumorigenesis of non-NF2 and secretory meningiomas [3, 15] |
| ***Chromosome 14*** | | | | | |
| *NDRG2* | 14q11.2 | NDRG2 | Downregulation; Hypermethylation | Potentially involved in cell growth & apoptosis | Associated with high grade tumors and recurrence [16, 17] |
| *MEG3* | 14q32 | Noncoding RNA | Downregulation; Hypermethylation | Cell cycle | Linked to tumorigenesis & high grade tumors [18] |

*Domingues et al, 2015*

| | | | | | |
|---|---|---|---|---|---|
| *AKT1* | 14q32 | Serine/threonine-protein kinase | Upregulation E17K mutation | Cell growth, Proliferation (activation PI3K pathway) | Associated with tumorigenesis of non-NF2 meningiomas [3, 19] |
| *TMEM30B* | 14q | Transmembrane protein 30B | Downregulation | Cell cycle | Associated with tumor recurrence [9] |
| ***Chromosome 17*** | | | | | |
| *STAT3* | 17q21.2 | Signal transducer and activator of transcription 3 | Upregulation | Transcription factor | Associated with high grade tumors [20, 21] |
| *RPS6K* | 17q23 | Ribosomal protein S6 kinase ($p70^{S6K}$) | Upregulation | Cell growth, Proliferation | Potentially involved in tumorigenesis [22] |
| ***Chromosome 18*** | | | | | |
| *DAL-1* | 18p11.32 | 4.1B | Downregulation | Links cell membrane proteins to cytoskeleton | Early event in tumorigenesis [23] / associated with progression [24] |
| *bcl-2* | 18q21.33 | Bcl-2 | Upregulation | Regulator of apoptosis | Associated with high grade tumors and recurrence [25] |
| ***Other chromosomes*** | | | | | |
| *SMO* | 7q32.3 | Smoothened, G protein-coupled receptor | Upregulation Several mutations[$] | Cell growth, proliferation (activation Hh pathway) | Associated with tumorigenesis of non-NF2 meningiomas [3, 19] |
| *TSLC1* | 11q23.2 | CADM1 | Downregulation | Cell adhesion | Associated with high grade tumors [26] |
| *TRAF7* | 16p13.3 | TNF receptor-associated factor 7 | Several mutations* | Proapoptotic E3 ubiquitin ligase | Associated with tumorigenesis of non-NF2 meningiomas [3, 15] |
| *CDH1* | 16q22.1 | E-cadherin | Downregulation | Cell adhesion | Associated with high grade tumors, recurrence and invasion [27, 28] |
| *TIMP1* | Xp11.3-p11.23 | Metalloproteinase inhibitor 1 | Downregulation | Inhibits MMP-9 activity | Tumor invasion [29] |

[#]Several NF2 mutations have been reported[30]. Only NF2 mutations reported by Clark et al[3] are listed here, underlined mutations were found in more than one tumor: K44X, W60X, Q115X, Y144X, Y153X, G161X, Y177X, Q178X,W191X, R198X, Y207X, L208P, Y217X, R262X, Q319X, Q324X, Q337X, R341X, E350X, Q362X, E366X, E427X, Q453X, Q459X, E460X.

[$]SMO mutations[3, 19]: R113Q, L412F, L522V, W535L, P647S. The mutations in common in both studies were: L412F and W535L; underlined mutations were found in more than one tumor.

*TRAF 7 mutations reported by Clark et al[3] included T145M, F337S, C388Y, **G390R**, G390E, **T391I**, P398T, **N520S**, **G536S**, S561N, **K615E**, Y621C, Q637H, R641C, H642Q, H642P, R653P, **R653Q**, V665A; mutations reported by Reuss et al[15] were: Q384E, G390E, G390R, T391I, P398S, K498E, N520S, N520H, N520T, H521N, G536S, G559V, S561N, Y563C, Y577D, K615E, Y621N, R641L, R641H, R653Q. Mutations found in both studies included: G390R, T391I, N520S, G536S, K615E, R653Q and they are highlighted in bold; underlined mutations were found in more than one tumor.

Domingues et al, 2015

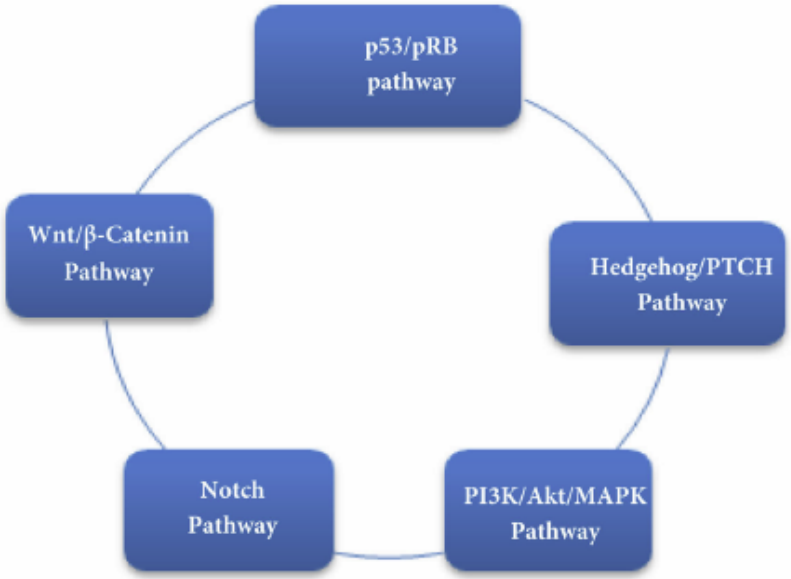


**Figure 2.**

Signaling pathways involving meningiomas.

These are the main pathways that have been linked to meningioma proliferation, malignancy progression, and tumorgenesis. The p53/pRB pathway plays a major role in the cell cycle by controlling the transition from G1 to S phase through the tumor suppressor gene pRB. The hedgehog/PTCH pathway has genes that are responsible for cell growth activation and suppression regulated by the SMO gene but when activated GLI transcription factors can also be activated. The Notch pathway is mediated by a number of transmembrane and serves as an intracellular communication system relaying messages throughout the cell. The PI3K/AKT/MAPK are two pathways that have been linked to malignant menigiomas with high levels of phosphorylatedAkt found in Grade II/III menigiomas (PI3K/Akt) and recurrence rate of meningiomas increase with reduced levels of MAPK. The Wnt/$\beta$ catenin pathway deals more with benign (Grade I) menigiomas than with higher-grade menigiomas because many benign menigiomas have shown deletions in the APC gene whichis a major gene of this pathway. (Choy, Kim, Nagasawa, et al. 2011).

**TABLE 1: List of potential medications for treatment of meningiomas***

| Medication | Mechanism of Action | Stage of Investigation† |
|---|---|---|
| PDGFR antagonists | | |
| imatinib (Gleevec) | PDGFR antagonist | Phase II: some stabilization of disease |
| nilotinib/dasatinib | 2nd-generation PDGFR inhibitors | no studies |
| EGFR antagonists | | |
| gefitinib (Iressa) | EGFR antagonist | Phase II: no survival benefit shown |
| erlotinib (Tarceva) | EGFR antagonist | Phase II: no survival benefit shown |
| monoclonal antibodies | humanized monoclonal antibodies to EGFR | no studies |
| VEGFR antagonists | | |
| bevacizumab (Avastin) | humanized monoclonal antibody to VEGFR | SSCTs: mixed results |
| cediranib (Recentin) | VEGFR antagonist | no studies |
| combination antagonists | | |
| sorafenib (Nexavar) | dual VEGFR & PDGFR antagonist | no studies |
| sunitinib (Sutent) | dual VEGFR & PDGFR antagonist | Phase II: some stabilization of disease |
| vatalanib (PTK787) | dual VEGFR & PDGFR antagonist | Phase II: some stabilization of disease |
| farnesyl transferase inhibitors | | |
| tipifarnib (Zarnestra) | farnesyl transferase inhibitor | no studies |
| mTOR inhibitors | | |
| temsirolimus (Torisel) | mTOR inhibitor | no studies |
| everolimus (Afinitor) | mTOR inhibitor | no studies |
| immunomodulators | | |
| IFNα 2B | antiproliferative & antiangiogenic properties | Phase II: mixed results |
| PD-1/PD-L1 inhibitors | PD-1 receptor & ligand inhibitors | no studies |
| TL4 inhibitors | binding to TL4, preventing escape of immune surveillance mechanisms | preclinical: cell cultures/in vitro |
| possible adjunctive agents | | |
| calcium channel blockers | reduction of intracellular calcium concentrations | preclinical: animal models |
| statins | inhibition of MAPK pathway | preclinical: cell culture/in vitro |

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# Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: a RANO review

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# RESULTS OF STUDIES ON ANTI-ANGIOGENIC AGENTS IN MENINGIOMA

| Drug | n patients | PFS-6 | Citation |
|---|---|---|---|
| Bevacizumab | 14 | 85.7% | Lou et al, 2012 |
| Bevacizumab | 15 | 43.8% | Nayak et al, 2012 |
| Bevacizumab | 15 | 93% | Nunes et al, 2013 |

# RESULTS OF STUDIES ON ANTI-ANGIOGENIC AGENTS IN MENINGIOMA

| Drug | n. patients | PFS-6 | Citation |
|---|---|---|---|
| **Vatalanib** | 21 | 37.5% | Raizer et al, 2014 |
| **Sunitinib** | 36 | 42% | Kaley et al, 2015 |

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# Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma

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See the editorial by Marosi, on pages 7–8.

nature genetics

# Genomic sequencing of meningiomas identifies oncogenic *SMO* and *AKT1* mutations

Priscilla K Brastianos[1–4,11], Peleg M Horowitz[3–6,11], Sandro Santagata[3,7], Robert T Jones[1,8], Aaron McKenna[4], Gad Getz[4], Keith L Ligon[3,7], Emanuele Palescandolo[8], Paul Van Hummelen[1,8], Matthew D Ducar[1,8], Alina Raza[1,8], Ashwini Sunkavalli[1,8], Laura E MacConaill[1,8], Anat O Stemmer-Rachamimov[3,9], David N Louis[3,9,10], William C Hahn[1,3,4,8], Ian F Dunn[3,4,6] & Rameen Beroukhim[1,3–5,8]

# CONCLUSIONS 1

- Important advances have been achieved in the last decades in our understanding of the genetic/chromosomal alterations in meningiomas.

- Current knowledge points out to the existence of several different pathways of tumorigenesis and clonal evolution which may target different genes in low vs high-grade tumors as well as among low-grade meningiomas.

- Although NF2 mutation is the most frequently observed alteration of a single gene, early mutations involving genes other than NF2 have emerged as alternative oncogenic pathways in NF2 non-mutated tumors.

# CONCLUSIONS 2

- The establishment of an effective therapy for recurrent or progressive meningioma refractory to standard treatments is so far hampered by several factors:
  - Lack of critical molecular alterations to be targeted
  - Lack of preclinical animals models
  - Lack of data regarding the natural history of untreated meningiomas → need to measure the growth rate in clinical trials

# Trabectedin for recurrent grade II or III meningioma: a randomized phase II study of the EORTC Brain Tumor Group

**EORTC protocol 1320-BTG**

# Introduzione

| | |
|---|---|
| *Obiettivo(i)* | **Fase II – Attività, Sicurezza e QoL della Trabectedina**<br>• End point primario: PFS.<br>• End point secondari: PFS-6, mPFS, BOR, OS, OS-6, OS-12, mOS, sicurezza, QoL |
| *Studio randomizzato* | 2:1 Korn design |
| *N° pazienti totale* | 86<br>• 57 nel braccio sperimentale<br>• 29 nel braccio di controllo |
| *N° pazienti al centro* | 6 |
| *Arruolamento* | *18 mesi* |

# Criteri di inclusione

- ✓ ≥ 18 anni
- ✓ Meningioma grado II (chordoid meningioma, clear cell meningioma, atypical meningioma, emangiopericitoma) o grado III (papillary meningioma, rhabdoid meningioma, anaplastic/malignant meningioma, emangiopericitoma anaplastico)
- ✓ Progressione radiologica (crescita ≥ 25% nell'ultimo anno) o nuova lesione (sia intra che extra cerebrale)
- ✓ Non disponibilità di altre terapie locali (resezione o radioterapia)
- ✓ Non precedenti terapie sistemiche antineoplastiche per il meningioma
- ✓ Lesione misurabile (10 x 10 mm) durante lo screening
- ✓ ECOG 0-2
- ✓ Aspettativa di vita > 9 settimane
- ✓ Non precedenti di neoplasie invasive negli ultimi 5 anni (eccetto cancro cutaneo non melanoma adeguatamente trattato, cancro prostatico di basso rischio e clinicamente localizzato e neoplasia cervicale intraepiteliale adeguatamente trattata)
- ✓ Non processi infettivi attivi; malattie epatiche croniche attive, incluse epatiti B, C o cirrosi
- ✓ Non utilizzo concomitante di:
  - ✓ farmaci sperimentali
  - ✓ fenitoina, claritromicina, vaccini, fenobarbital, ciclosporina, verapamil, per interazione farmacocinetica con trabectedina.
- ✓ AE CTCAE ≤ grado1

# Criteri di inclusione

- ✓ Adeguate funzioni epatiche, renali ed ematologiche durante lo screening:

| | |
|---|---|
| Neutrofili | ≥ 1.5 x $10^9$/L |
| Emoglobina | ≥ 9 g/dL o ≥ 5.6 mmol/L |
| Piastrine | ≥ 100 x $10^9$/L |
| Bilirubina totale | ≤ 1 x ULN |
| ALT, AST, ALP*, Creatinina Fosfochinasi (CPK) | ≤ 2.5 x ULN |
| *Se ALP > 2.5 x ULN | isoenzimi epatici 5-nucleotidasi o GGT devono essere entro i limiti |
| Albumina | ≥ 30 g/L |
| Creatinina sierica | ≤ 1.5 x ULN (clearance > 30 mL/min, formula di Cockcroft e Gault) |

- ✓ Funzioni cardiache normali (LVEF valutato con MUGA/ECHO entro i limiti di norma), ECG a 12 derivazioni normale (NCS). Le seguenti condizioni instabili *non* sono permesse:
  - ✓ Insufficienza cardiaca congestizia
  - ✓ Angina pectoris
  - ✓ Infarto miocardico entro un anno dalla registrazione/randomizzazione
  - ✓ Ipertensione arteriosa incontrollata definita da Pressione arteriosa ≥ 150/100 mmHg nonostante terapia medica
  - ✓ Aritmie clinicamente significative
- ✓ Pazienti con valori scostati di:
  - ✓ +/- 5% (per valori ematici)
  - ✓ +/- 10% (per valori chimici)
  - ✓ dai normali limiti sono accettabili. Un massimo di +/- 2 giorni dalla visita è consentito

# Ricerca traslazionale e HRQoL

- ✓ Raccolta blocchetti o 30 slides di 5 µm per ogni surgery per la revisione centralizzata (Ki67, densità microvascolare, e densità dei macrofagi associata al tumore, con la risposta al trattamento)
- ✓ Raccolta RM per la revisione centralizzata (sebbene le decisioni di trattamento siano basate sulla valutazione oggettiva al Centro)

- ✓ QoL - Valutazione della Trabectedina:
  - ✓ Su funzione del ruolo, funzioni fisiche, funzioni cognitive, fatica, diarrea, nausea e vomito sia durante che dopo il trattamento.
  - ✓ Sui sintomi e sulle scale funzionali:
    - ✓ QLQ-C30 (v. 3)
    - ✓ BN-20

# Bracci di trattamento

- **Trabectedina**
  - *Ciclo di 3 settimane*: somministrata con **infusione di 24 ore ogni 3 settimane (giorno 1 ogni 21 giorni) con una dose iniziale di 1.5 mg/m$^2$ BSA**
  - **Pretrattamento con dexametasone 20 mg IV per 30 minuti prima dell'infusione di trabectedina**
  - Somministrata tramite catetere venoso centrale fortemente raccomandata
  - Fino a progressione o tossicità inaccettabile o ritiro del consenso da parte del paziente
- **Local standard of care**
  - Idrossiurea
  - *Ciclo di 3-4 settimane*
  - *In caso di interruzione per ragioni diverse dalla progressione, nessun altro trattamento è consentito prima della progressione*

# Braccio con trabectedina

**Ciclo di 3 settimane con una dose iniziale di 1.5 mg/m$^2$ BSA**

Al giorno 1 di ogni ciclo o entro le 72 ore prima:

- Esame clinico generale
- Valutazione degli AE
- Ematochimici:
  - esami dello screening
  - *per il braccio con la trabectedina: 3 volte per i primi 2 cicli, poi 2 volte per i successivi / esami settimanali durante i primi due cicli, dopo almeno una volta tra due cicli successivi (oltre a quelli del giorno 1)*
- Terapie concomitanti
- HRQoL a week 3, week 6, week 12, week 24 (inviare a 1320@eortc.be)
- Test di gravidanza ogni 2 cicli
- TC torace/addome solo se clinicamente indicata; se le lesioni non sono chiare rieffettuare dopo 9 settimane
- Somministrazione della terapia

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