SOLİD TÜMÖRLERDE METRONOMİK TEDAVİ KLİNİK UYGULAMALAR

DR.BETÜL SEVİNİR

ULUDAĞ ÜNİVERSİTESİ TIP FAKÜLTESİ

Metronomik Kemoterapi

Anti-tümöral ilaçların

- Küçük dozlarda
- Uzun süreli
- Yakın aralıklarla
- İlaçsız ara vermeden kullanılmasıdır
- Kanserle savaşta önemli bir stratejidir
- Daha az toksik ve direnç sorununun üstesinden gelen tedavi yaklaşımıdır

- Kerbel, Folkman, Hanahan 2000
- Tek merkez deneyimi , birkaç olgu
- Çelişkili sonuçlar
- Klinik araştırmalar artıyor
- Çoğunluk küçük faz II çalışmaları (n:20-40)
- Faz III ve randomize çalışmalar var
- Rekürens olmamış hastalar için protokoller geliştiriliyor
- En iyi zamanlama ve optimum dozlar araştırılıyor

Metronomics Global Health Initiative

- Pediatrik araştırmalar %10-15
- Çalışma grupları ve konuya özel toplantılar var
- Fourth Metronomic and Anti-angiogenic Therapy Meeting 2014
- Second International Workshop on Metronomic and Anti-Angiogenic Chemotherapy in Paediatric Oncology 2010
- Metronomics Global Health Initiative
- Metronomik tedavi yeni bir onkolojik kavram olarak önem kazanmaktadır

KEMOTERAPÖTİK İLAÇLAR	DİĞER İLAÇLAR
Alkilleyici ajanlar Siklofosfamit Temozolomid İfosfamit	Anti-VEGF ajanlar Bevacizumab
Antimetabolitler Metotreksat, 5-FU	Cox inhibitörleri Celecoxib
Antimikrotübül ajanlar Vinblastin Vinorelbin Vinkristin	mTor inhibitörleri Sirolimus Everolimus
Antrasiklinler Idarubisin	Tirozin kinaz inhibitörleri Sunitinib Sorafenib Imatinib Dasatinib Nilotinib
Topoizomeraz inhibitörleri Etoposid Topotekan	Diğer Fenofibrat Fluvastatin Retinoik asit Talidomit Zoledronik asit Valproik asit

Journal of Pediatric Hematology/Oncology:
November 2006 - Volume 28 - Issue 11 - pp 720-728
doi: 10.1097/01.mph.0000243657.64056.c3
Original Articles

A Pilot Pharmacokinetic and Antiangiogenic Biomarker Study of Celecoxib and Low-dose Metronomic Vinblastine or Cyclophosphamide in Pediatric Recurrent Solid Tumors

Stempak, Diana PhD[*†]; Gammon, Janet BSc, RN[*]; Halton, Jacqueline MD[‡]; Moghrabi, Albert MD[§]; Koren, Gideon MD[†‖]; Baruchel, Sylvain MD[*†‖]

- **n:13 hasta**
- **Celecoxib 250 mg/m2 PO**
- **Vinblastin 1mg/m2 İV haftada 3 kez**
- **4 hastada stabil hastalık**

BEYİN TÜMÖRLERİNDE METRONOMİK TEDAVİ

YÜKSEK RİSKLİ PEDİATRİK BEYİN TÜMÖRLERİNDE EŞZAMANLI RADYOTERAPİ VE METRONOMİK TEMOZOLOMİD

Sterba J,et al. Neoplasma 2002;49(2):117-20.

- **Temozolomid ve radyoterapi ile pilot çalışma**
- **Kötü prognozlu 8 çocuk hasta**
- **170 cGy fr. Toplam 55/56 Gy radyoterapi**
- **Birlikte temozolomid 90 mg/m2/gün 42 gün**
- **Kemik iliği baskılanması 21.gün gözlendi**
- **Sonuç:**
- **Yüksek riskli medulloblastoma: 2 hastada erken, 1 hastada tedavi sonunda tam yanıt**
- **3 hastada tam olmayan yanıt**

PEDİATRİK ONKOLOJİDE METRONOMİK TEDAVİNİN GELİŞİMİ

- 4 ilaçlı metronomik kemoterapi rejimi
- Devamlı PO talidomit ve celecoxib, alterne metronomik etoposid ve siklofosfamid
- Relaps olmuş, kür şansı düşük 20 çocuk (Median tanı yaşı 8.5 y)
- Tedavinin uygulanabilirliği ve etkinliği araştırıldı

Tanı

- Ependimom :5
- HG gliom/pons gliomu: 6
- Meulloblastom:1
- Osteosarkom: 4
- RMS:2
- Desmoplastik KYH tümör:1
- Ewing sarkomu:1

Sonuç: 8/20 Hızlı ilerleme, 3/20 parsiyel cevap ve 7/20 stabil hastalık
10 hastanın remisyonda kalma süreleri uzadı
%50 klinik yarar
Minimal hastalıkta daha etkili

Kiaran. A feasibility trial of antiangiogenic (metronomic) chemotherapy in pediatric patients with recurrent or progressive cancer. J Pediatr Hematol/Oncol 2005 ; 27:573-81.

Clinical Therapeutics/Volume 30, Number 7, 2008

Research Letter

Metronomic Etoposide/Cyclophosphamide/Celecoxib Regimen Given to Children and Adolescents with Refractory Cancer: A Preliminary Monocentric Study

Nicolas André, MD, PhD[1,2]; Angelique Rome, MD[1]; Carole Coze, MD, PhD[1]; Laetitia Padovani, MD[3]; Eddy Pasquier, MD[2,4]; Laurence Camoin, MD, PhD[5]; and Jean Claude Gentet, MD[1]

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ABSTRACT

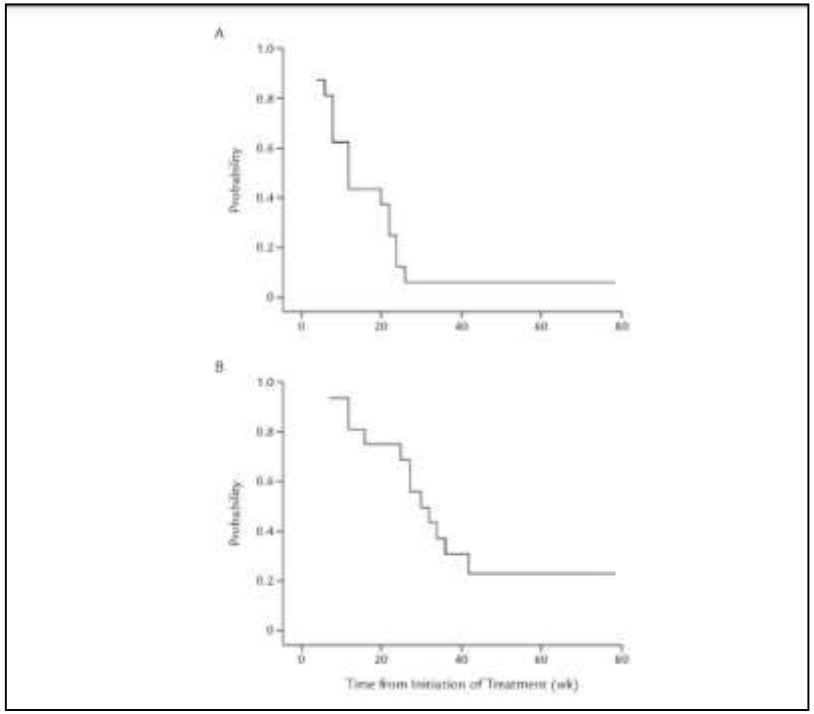
Background: Metronomic chemotherapy (MC) is the administration of chemotherapy at doses below the maximal tolerated dose on a frequent schedule of administration, with no prolonged drug-free breaks.

Objective: The aim of this research was to assess the effectiveness and tolerance of a metronomic etoposide/cyclophosphamide/celecoxib regimen in children and adolescents with refractory cancer.

Methods: This retrospective, single-center study evaluated the use of MC with etoposide 25 $mg/m^2 \cdot d^{-1}$ (days 1–14), cyclophosphamide 25 $mg/m^2 \cdot d^{-1}$ (days 15–28), and celecoxib 100 to 400 mg/d (days 1–28), in children with refractory, or high-risk relapsing, 2 patients. One patient with meningeal carcinomatosis developed bilateral subdural hematoma for which the role of MC could not be ruled out. Circulating endothelial cells were elevated in 3 out of 3 patients in whom they were quantified and who were progressing while under MC.

Conclusion: The MC regimen we report here was associated with disease stabilization without major toxicities. This assessment of MC in children and adolescents warrants further studies. (*Clin Ther*. 2008; 30:1336–1340) © 2008 Excerpta Medica Inc.

Key words: metronomic chemotherapy, angiogenesis, children, oncology, circulating endothelial cells.



En iyi yanıt 20 hafta süreyle stabil hastalık gözlenmesidir 7/17 olgu %41

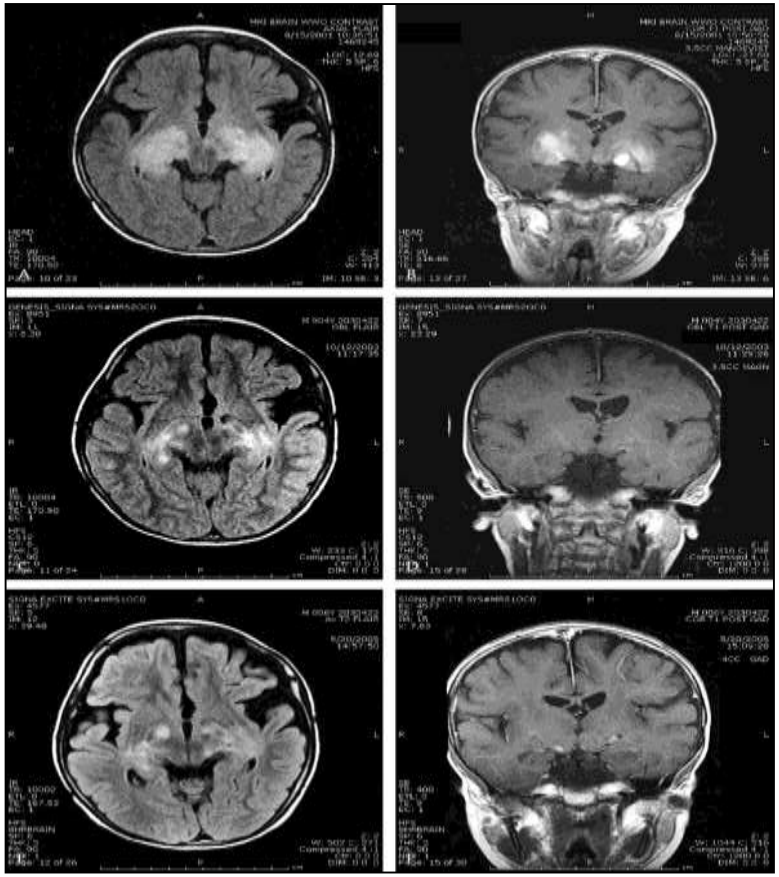
Metronomik tedavi alan refrakter kanserli çocuk ve ergenlerde (A) EFS, (B) OS (N = 17) . André N. 2008

PEDİATRİK ONKOLOJİDE METRONOMİK TEDAVİNİN GELİŞİMİ

TABLE 1. Patient Characteristics and Duration of Therapy on the Four-Drug Antiangiogenic Chemotherapy Protocol

Pt. No.	Diagnosis	Age At First Dx (yrs)	# of Surgeries	# XRT	# of Previous Chemos	# of Previous Therapies With VP16/Cyclo	Duration of Remission Prior to 4-Drug Therapy (wks)	6 Months on Study?	Time on 4-Drug Therapy (wks)	Progression-Free Survival (wks)
1	Glioblastoma	7	1	1	1	0	14	No	4	4
2	Ependymoma	2	1	0*	2	1	11	No	3	3
3	Optic glioma	0.5	2	0*	2	0	25	Yes	112	>167
4	Ependymoma	0.8	1	1	2	0	48	Yes	58	58
5	Osteosarcoma/retinoblastoma	1	2	1	3	1	372	No	5	5
6	Primitive neuroectomdermal tumor, then osteosarcoma	2	3	1	2	1	6	No	15	15
7	Osteosarcoma	14	3	0	1	1	61	Yes	28	28
8	Diffuse pontine glioma	14	0	1	1	0	3	No	23	23
9	Ependymoma	0.5	2	0*	0†	0	5	Yes	78	>152
10	Desmoplastic small round cell tumor	18	1	0	1	1	6	No	13	13
11	Rhabdomyosarcoma	7	1	2	2	2	30	No	12	12
12	Neurofibromatosis type 1; glioblastoma multiforme	5	2	1	1	0	31	No	3	3
13	Ewing sarcoma	8	1	2	2	2	248	No	15	15 (withdrew consent)
14	Osteosarcoma	6	1	1	2	0	29	No	2	2 (dose-limiting toxicity)
15	Spindle cell	2	2	1	2	1	36	Yes	83	83
16	Ependymoma	5	3	1	0†	0	9	Yes	96	>123
17	Rhabdomyosarcoma	14	1	3	6	2	18	No	9	9
18	Ependymoma	5	3‡	1	0	0	41	Yes	87	>124
19	High-grade glioma	16	1	1	1	0	46	No	9	9
20	Medulloblastoma	3	1	1	1	1	160	Yes	85	>126

Kiaran. J Pediatr Hematol/Oncol 2005 ; 27:573-81



A-B Bilateral supratentoriyal gliom
C–D Tedavi bitimindeki değerlendirme
E-F Tedavi kesiminden 2 yıl sonraki görüntü

Kiaran. J Pediatr Hematol/Oncol 2005 ; 27:573-81

- **Daha güçlü anti-anjiogenik özellik gösteren fenofibrat eklendi**
- **Bu 5 ilaçlı metronomik tedavi relaps olmuş ve kür beklenmeyen 101 hastada uygulandı**
- **Farklı tanıları olan 8 katman oluşturuldu**

COMBAT I

(Combined Oral Maintenance Biodifferentiating and Antiangiogenic Therapy)

Protokolde

-Celecoxib

-Retinoik asit

-Etoposid

-Temozolomid var

22 Hasta alındı

Bu çalışmada cevap hızı %32, klinik yarar %77

- **Tam yanıt :3 Kısmi yanıt:4 Stabil hastalık:10 (6 aydan uzun)**
- **2 yıl EFS <%10, 2 yıl OS %30**
- **Uzun süreli klinik sonuçlar kötü**
- **Sterba et al 2004**

COMBAT I PROTOKOLÜ

Agent	Dose	Route	Schedule	Cycle length
Celecoxib (Celebrex®)	200 mg/m^2/day	p.o. divided b.i.d.	days 1–77	
Etoposide (VePesid®, Lastet®)	25 mg/m^2/day	p.o. in the a.m.	days 1–21	11 weeks
Temozolomide (Temodal®)	60 mg/m^2/day	p.o. in the a.m.	days 36–77	(77 days)
Isotretinoin (Roaccutane®)	100 mg/m^2/day	p.o. divided b.i.d.	days 1–14, 29–42, 57–70	

Fig. 1. Protocol COMBAT I.

COMBAT II ve III PROTOKOLLERİ

- COMBAT II ve III : Çok merkezli klinik çalışma
- Protokole yeni ilaçlar katıldı
- COMBAT II

-Fenofibrat (peroksizom proliferatör reseptör α- agonisti) ve vitamin D

- COMBAT III

-Anti-VEGF antikoru bevacizumab

- Relaps olmuş yüksek riskli hastalar:

Beyin tümörleri,nöroblastoma, sarkomlar

- Toplam 81 hasta (Çek Cumhuriyeti, Fransa ve Slovakya)

COMBAT PROTOKOLLERİ

Agent	Dose	Route	Schedule	Cycle length
Celecoxib (Celebrex®)	200 mg/m²/day	p.o. divided b.i.d.	days 1–77	
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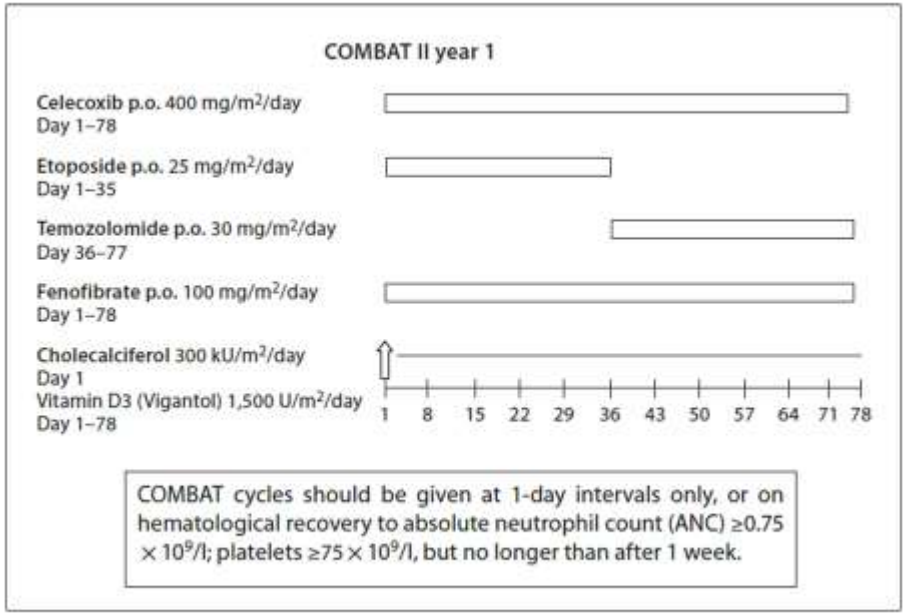
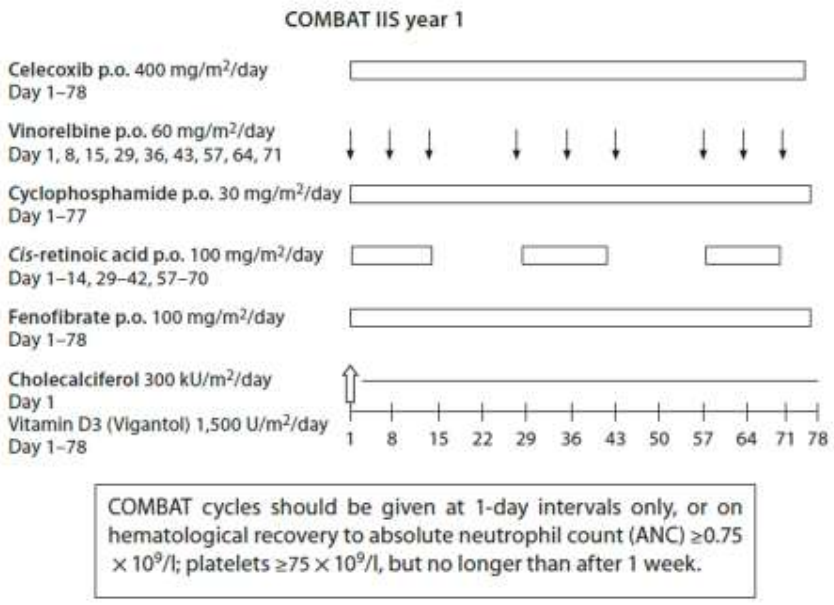
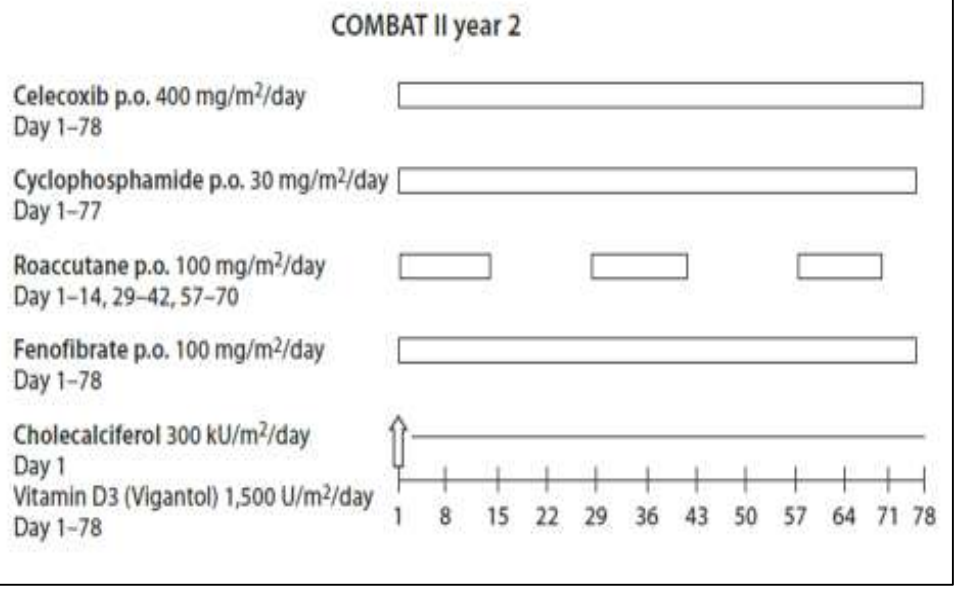
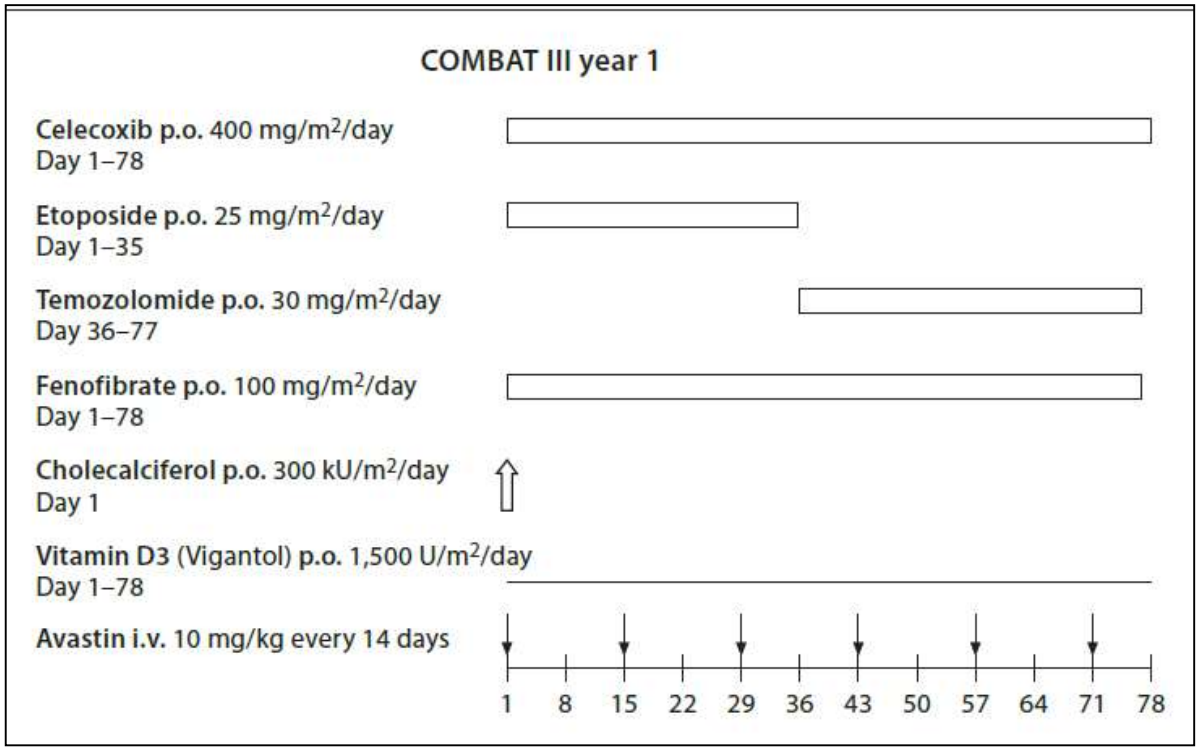
ig. 1. Protocol COMBAT I.








COMBAT III year 1
Celecoxib p.o. 400 mg/m2/day
Day 1–78
Etoposide p.o. 25 mg/m2/day
Day 1–35
Temozolomide p.o. 30 mg/m2/day
Day 36–77
Fenofibrate p.o. 100 mg/m2/day
Day 1–78
Cholecalciferol p.o. 300 kU/m2/day
Day 1
Vitamin D3 (Vigantol) p.o. 1,500 U/m2/day
Day 1–78
Avastin i.v. 10 mg/kg every 14 days
1 8 15 22 29 36 43 50 57 64 71 78

Zapletalova D. Oncology 2012;82:249-60

Oncology

Clinical Study

Oncology 2012;82:249–260
DOI: 10.1159/000336483

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Metronomic Chemotherapy with the COMBAT Regimen in Advanced Pediatric Malignancies: A Multicenter Experience

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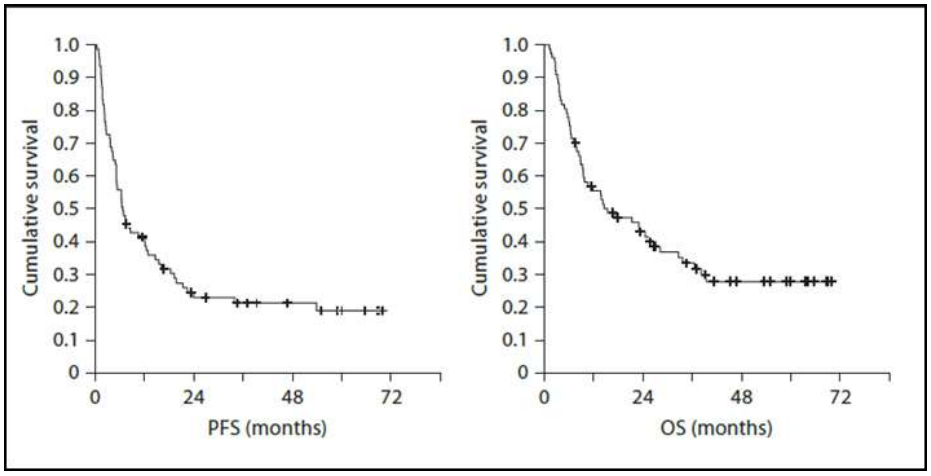
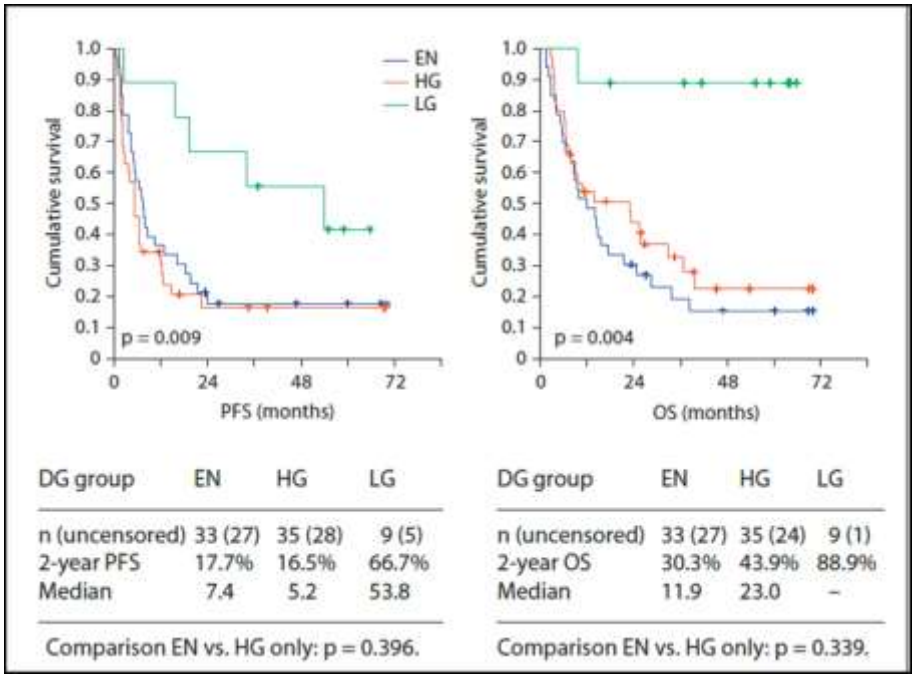
Table 4. Patient response to metronomic chemotherapy

Diagnostic group		n	Median survival months	Events deaths n (%)
EN	MBL	13	40.8	9 (69)
	Neuroblastoma	11	21.7	10 (91)
	Other embryonal, non-sarcomatous	9	30.7	8 (88)
HG	Sarcoma	17	35.2	13 (76)
	Other	18	60.9	11 (61)
LG		9	–	1 (11)

76 hasta katıldı



2 yıl PFS%23 Median:6.7 ay
2 Yıl OS %43 Median:15.4 ay
Sınırlar:1.3-69.9 ay



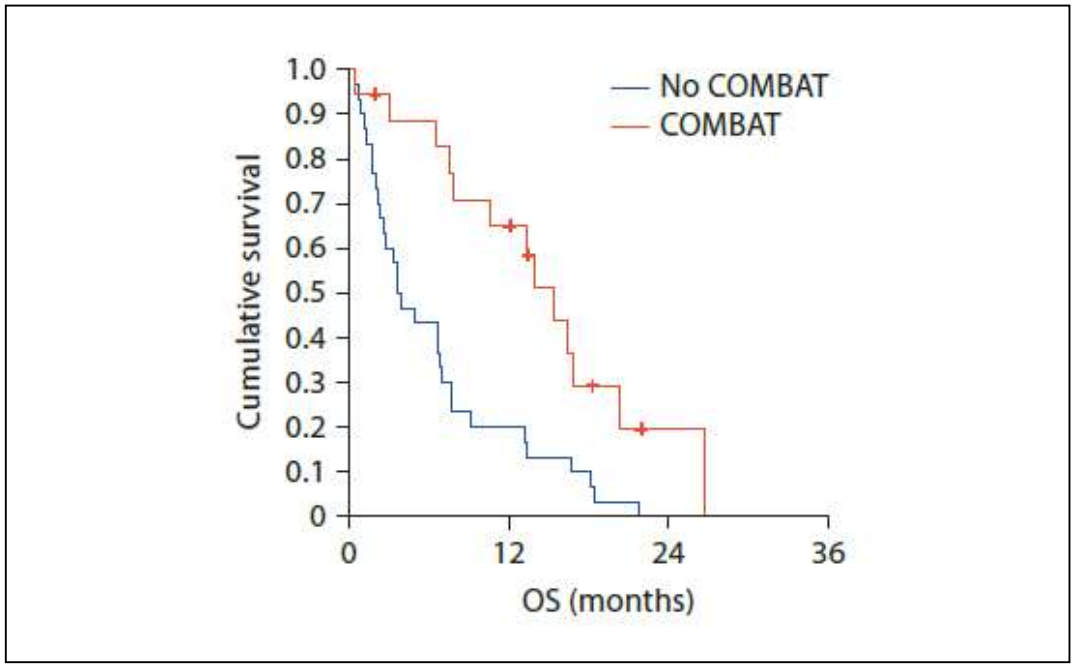
DG group	EN	HG	LG
n (uncensored)	33 (27)	35 (28)	9 (5)
2-year PFS	17.7%	16.5%	66.7%
Median	7.4	5.2	53.8

Comparison EN vs. HG only: p = 0.396.

DG group	EN	HG	LG
n (uncensored)	33 (27)	35 (24)	9 (1)
2-year OS	30.3%	43.9%	88.9%
Median	11.9	23.0	–

Comparison EN vs. HG only: p = 0.339.

n:74 hasta
Eksitus %68 (n:50)
Tam remisyon:%15(n:11)
SD/PR: % 9 (n:7)
PD: % 8 (n:6)



	COMBAT(n:18)	DİĞER (MTD)(n:30)	p
Progresyon zamanı (Ortanca)	18.1 ay	11.7 ay	0.015
Genel yaşam (Ortanca)	15.4ay	3.9 ay	0.001

- **COMBAT II ve III daha üstün**
- **Metronomik tedavinin MTD'a göre daha fazla sağkalım gözlendi**

Pediatr Blood Cancer 2014;61:636–642

A Phase II Trial of a Multi-Agent Oral Antiangiogenic (Metronomic) Regimen in Children With Recurrent or Progressive Cancer

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Background. Preclinical models show that an antiangiogenic regimen at low-dose daily (metronomic) dosing may be effective against chemotherapy-resistant tumors. We undertook a prospective, open-label, single-arm, multi-institutional phase II study to evaluate the efficacy of a "5-drug" oral regimen in children with recurrent or progressive cancer. ***Procedure.*** Patients ≤21 years old with recurrent or progressive tumors were eligible. Treatment consisted of continuous oral celecoxib, thalidomide, and fenofibrate, with alternating 21-day cycles of low-dose cyclophosphamide and etoposide. Primary endpoint was to assess, within eight disease strata, activity of the 5-drug regimen over 27 weeks. Blood and urine angiogenesis markers were assessed. ***Results.*** One hundred one patients were enrolled; 97 began treatment. Median age was 10 years (range: 191 days–21 years); 47 (49%) were female. Disease strata: primitive neuroectodermal tumor (PNET, 8), leukemia (4), neuroblastoma (3), and miscellaneous tumors (18). Treatment was generally well tolerated; most common toxicities were hematologic. Twenty-four (25%) patients completed 27 weeks therapy without progression, including HGG: 1 (5%), ependymoma: 7 (37%), LGG: 7 (58%), medulloblastoma/PNET: 1, neuroblastoma: 1, and miscellaneous tumors: 7 (39%). Best response was complete response (one patient with medulloblastoma), partial response (12), stable disease (36), progressive disease (47), and inevaluable (1). Baseline serum thrombospondin levels were significantly higher in patients successfully completing therapy than in those who progressed ($P = 0.009$). ***Conclusion.*** The 5-drug regimen was well tolerated. Clinical activity was demonstrated in some but not all tumor strata. Pediatric Blood Cancer 2014;61:636–642

Geniş bir seri, n:97

- Median 10 y (191 gün–21 y)
- E/K:50/47

Hastalık grupları

- Lösemi 4
- Kemik tümörü 12
- Nöroblastoma3
- Yüksek glioma21
- Düşük dereceli glioma12
- Ependimom19
- Medulloblastom/PNET8
- Çeşitli tumors18

CNS 9/ Non-CNS9

- Olguların %25'i 27 hf.lık tedaviyi tümörde ilerleme olmadan tamamladı
- HGG: 1 (%5),
- Ependimom: 7 (%37)
- LGG: 7 (%58)
- Medulloblastom/PNET: 1
- NBL: 1
- Çeşitli tümörler: 7 (%37)
- CR:1 (Medulloblastom)
- PR:12
- SD:36
- PD:47

Faz II Tedavi protokolü

5-Drug Oral Regimen: Dosing Schedule

Medication	Dosing schedule
Continuous	
Thalidomide	Start at 3 mg/kg (rounded to nearest 50 mg) daily
	Increase dose weekly by 50 mg as tolerated to 24 mg/kg (max 1,000 mg) daily
Celecoxib	<20 kg: 100 mg twice daily
	20–50 kg: 200 mg twice daily
	>50 kg: 400 mg twice daily
Fenofibrate	90 mg/m^2 (max 200 mg) daily
Alternating 21 day cycles	
Etoposide	50 mg/m^2 daily for 21 days
Cyclophosphamide	2.5 mg/kg (max 100 mg) daily for 21 days

Patients with history of significant myelosuppression with prior therapy initiated etoposide at 35 mg/m^2 day and escalated to 50 mg/m^2 as tolerated.

Beş İlaçlı Metronomik Tedavi ve Yanıt

Clinical Outcomes by Disease Strata

		Best response					
Stratum	**N**	**CR**	**PR**	**SD**	**PD**	**NE**	**Completed 27 weeks therapy**
High grade glioma	21	—	1	7	13	—	1 (5%)
Ependymoma	19	—	2	10	7	—	7 (37%)
Low grade glioma	12	—	4	5	3	—	7 (58%)
Bone tumors	12	—	—	1	10	1	—
Medulloblastoma/PNET	8	1	1	1	5	—	1 (13%)
Leukemia	4	—	—	1	3	—	—
Neuroblastoma	3	—	—	2	1	—	1 (33%)
Miscellaneous	18	—	4	9	5	—	7 (39%)
Miscellaneous CNS Tumors	9	—	3	5	1	—	5(56%)
Miscellaneous non-CNS tumors	9	—	1	4	4	—	2(22%)

CNS, central nervous system; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable. One patient with anaplastic glioneuronal tumor (miscellaneous CNS tumors strata) and best response SD sustained a CR during continuation therapy.

Robison NJ. Pediatr Blood Cancer 2014;61(4):636-42.

Pediatr Blood Cancer 2012;59:511–517

Antiangiogenic Metronomic Therapy for Children With Recurrent Embryonal Brain Tumors

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Background. Median survival time of recurrent embryonal brain tumors is short regardless of salvage chemotherapy used. An evolving alternative approach to conventional chemotherapy is to target neovascularization by interfering with tumor angiogenesis at various levels. ***Procedure.*** From November 2006 to December 2010, 16 patients (median age: 9 years) with recurrent (9 first, 7 multiple) embryonal brain tumors were treated with an antiangiogenic multidrug combination regimen (bevacizumab, thalidomide, celecoxib, fenofibrate, etoposide, and cyclophophamide) and additional intraventricular therapy (etoposide and liposomal cytarabine). ***Results.*** At a median of 33 months, 10/16 patients are alive. 4/4 patients with CNS primitive neuroectodermal tumors (CNS PNET) and 1/7 pat[illegible]stoma (MB) died of tumor progression dur-

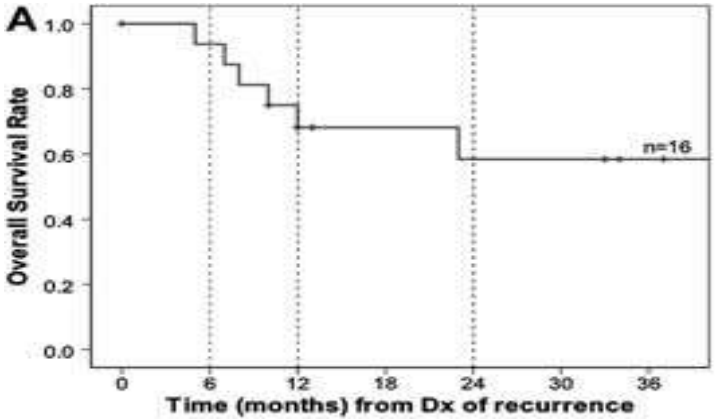
Windows Live Photo Gallery

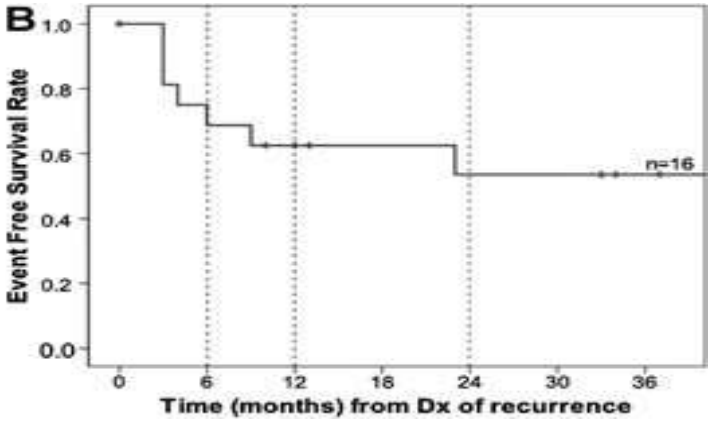
23 months, the remaining five patients with MB are alive for 12, 33, 33, 37, and 58 months. For the seven patients with MB, both overall survival (OS) and event free survival (EFS) after 6 months was 100%, after 12 months 85.7 ± 13%, and after 24 months 68.6 ± 19%. In contrast, for patients with CNS PNET, both OS and EFS after 6 months was 75.0 ± 22% and 0.0% and all patients had died by 12 months. Low-dose oral etoposide and cyclophosphamide was reduced after a median of 2 months and discontinued after a median of 11 months. Toxicities were manageable and therapy was generally well tolerated. ***Conclusion.*** Our results suggest that the chosen antiangiogenic drug combination is particularly beneficial for patients with MB and warrants further investigation. Pediatr Blood Cancer 2012;59:511–517.

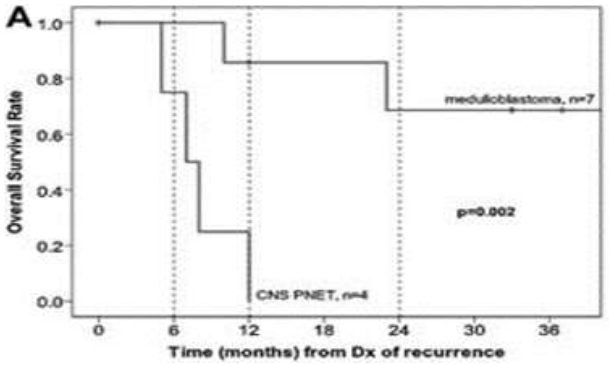
Nüks medulloblastom ve PNET tanılı 16 hasta (1.relaps:9, 2-3.relaps:7 hasta)
Bevacizumab, talidomit,celecoxib,fenofibrat, metronomik etoposid, siklofosfamid ve 2 haftada bir intraventriküler etoposid ve liposomal sitarabin
Sonuçlar 33.ayda 10/16 hayatta
Bu kötü prognozlu grupta 2 yıl EFS, 3 yıl OS gözlendi

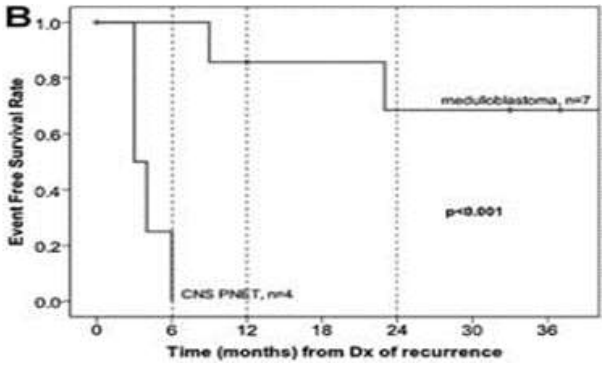
Nüks embriyonal beyin tümörlerinde antianjiogenik metronomik tedavi sonuçları

A: **OS 6 ay %93, 12 ay % 68 ve 24 ay % 58**
B: **EFS 6 ay %68, 12 ay % 62 ve 24 ay % 53**









Peyrl et al.Pediatric Blood & Cancer 2012;59:511-7.

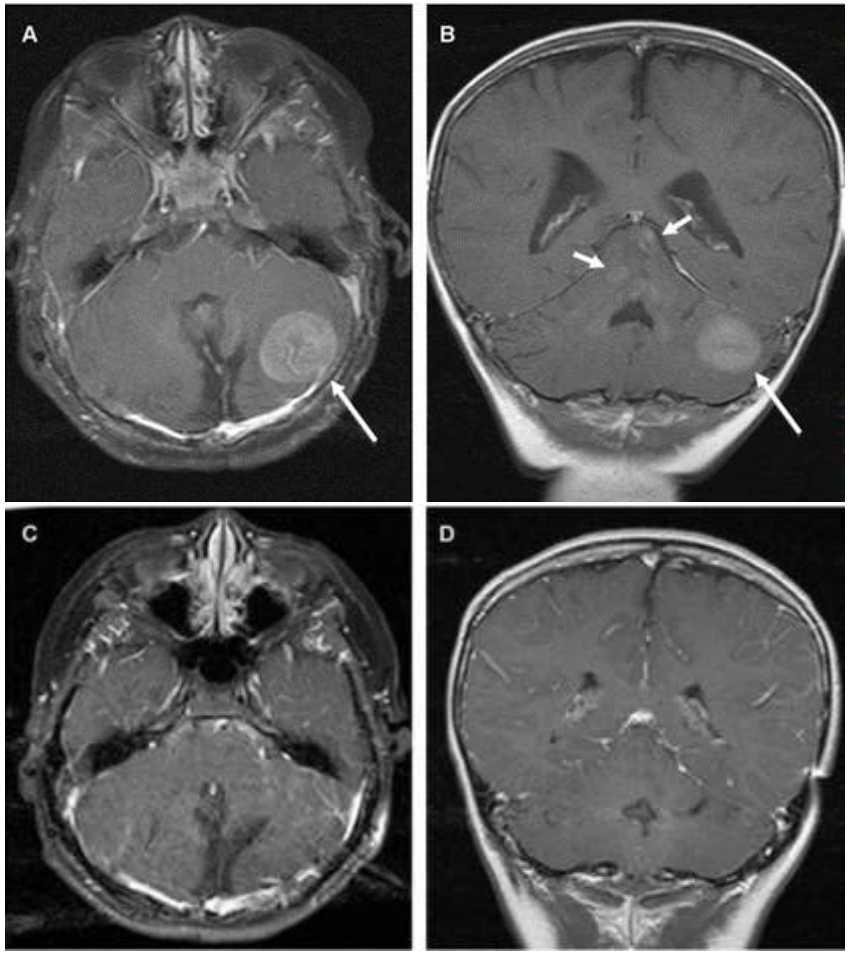
BEYİN TÜMÖRLERİNDE METRONOMİK TEDAVİ

ÇOCUKLUK ÇAĞINDA NÜKS BEYİN TÜMÖRLERİNDE METRONOMİK ORAL TOPOTECAN – FAZ II ÇALIŞMA

Minturn JE,et al. Pediatr Blood Cancer 2011;56(1):39-44. doi: 10.1002/pbc.22690.

- **Dirençli, nüks,ilerleyici hastalık olan primer SSS tümörleri**
- **≤ 21 y (Median 9 y) , n:31 hasta**
- **Hastalar:**
- **Ependimom (n = 4),**
- **Yüksek dereceli glioma (n = 6)**
- **Beyin sapı gliomu (n= 13)**
- **PNET (n = 8)**
- **Oral topotekan 0.8 mg/m2/gün Her 28 günde bir 21 gün devamlı**
- **Sonuç ve yorum**
- **Değerlendirilen hasta sayısı :26**
- **PNET tanılı 2 hastada objektif cevap (+) 7 ve 9.5 yılda remisyonda yaşıyorlar**
- **Dört hastada stabil hastalık (median 4.6 ay)**
- **Oral topotekan güvenli ve PNET'li 2 hastada sağkalıma katkısı gözlendi**

Metronomik oral topotekan ile tam yanıt

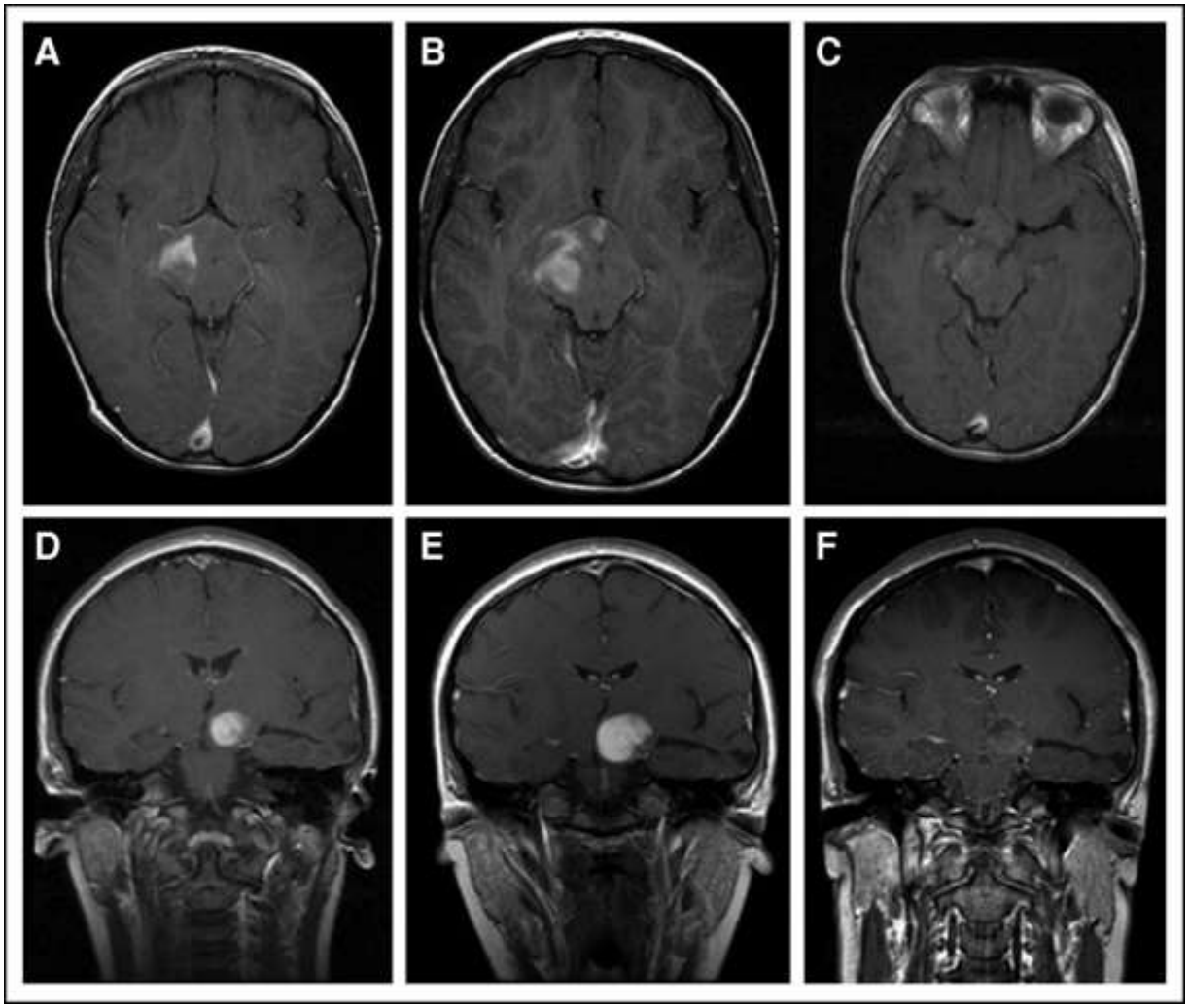


T1 ağırlıklı MR

A-B: Tedavi öncesinde sol serebellar kitle ve leptomeningeal yayılım

C-D: 15 kür topotekan alan hastada 6 yıl sonraki görüntüleme

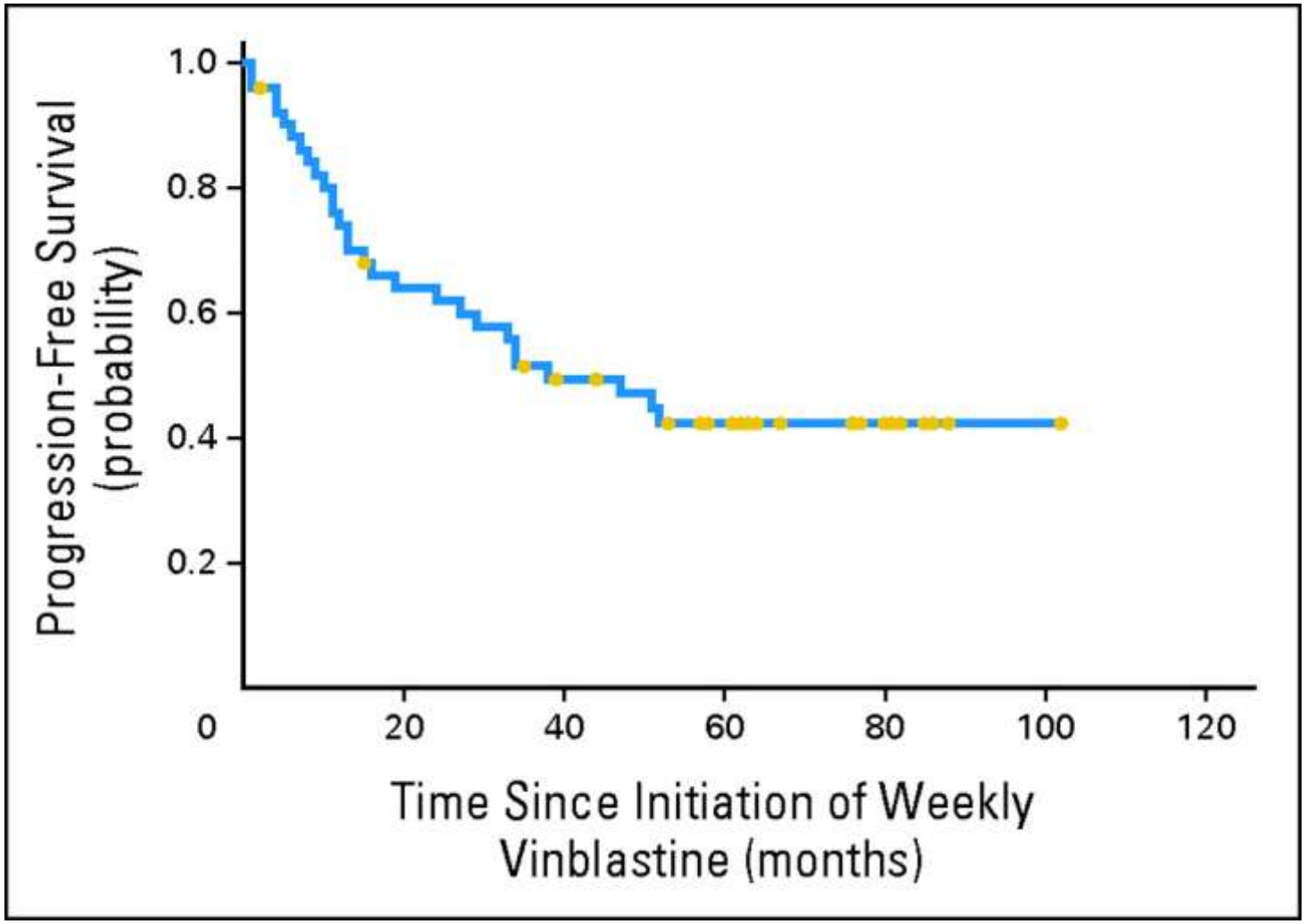
Haftalık Vinblastin ile Tedavi Yanıtı



Eric Bouffet et al. JCO 2012;30:1358-1363

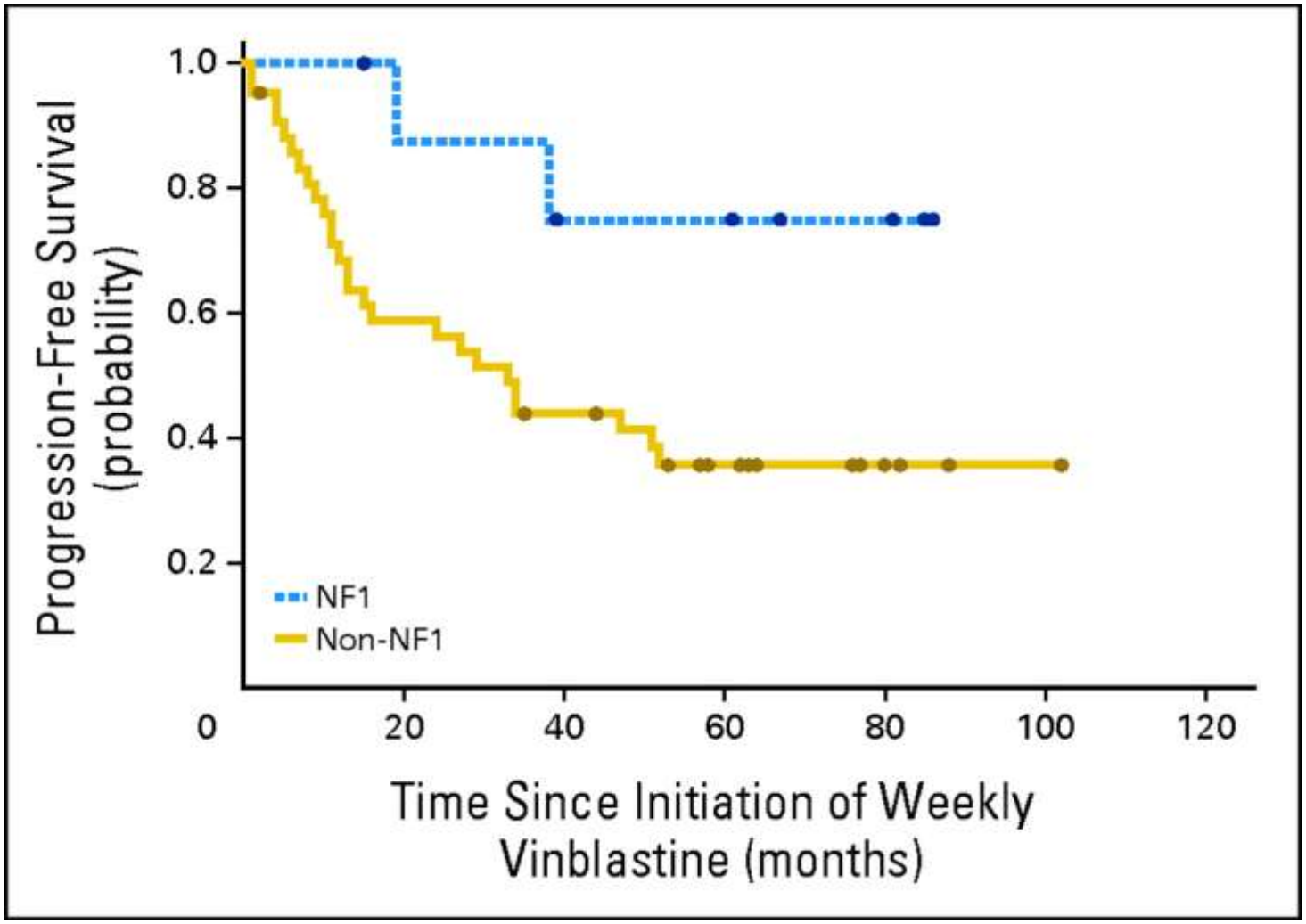
(A-C) Kısmi yanıt (D-F) Stabil hastalık ve gerileme ve gerileme

PFS (n: 51 olgu)



Eric Bouffet et al. JCO 2012;30:1358-1363

NF1 OLAN VE OLMAYAN HASTALARDA PFS (NF1; P = .04).



Eric Bouffet et al. JCO 2012;30:1358-1363

Cancer Medicine

Open Access

SHORT REPORT

Can metronomic maintenance with weekly vinblastine prevent early relapse/progression after bevacizumab–irinotecan in children with low-grade glioma?

Marie Amélie Heng[1], Laetitia Padovani[2], Philippe Dory-Lautrec[3], Jean Claude Gentet[1], Arnaud Verschuur[1,4], Eddy Pasquier[4,5], Dominique Figarella-Branger[5,6], Didier Scavarda[7] & Nicolas André[1,4,5]

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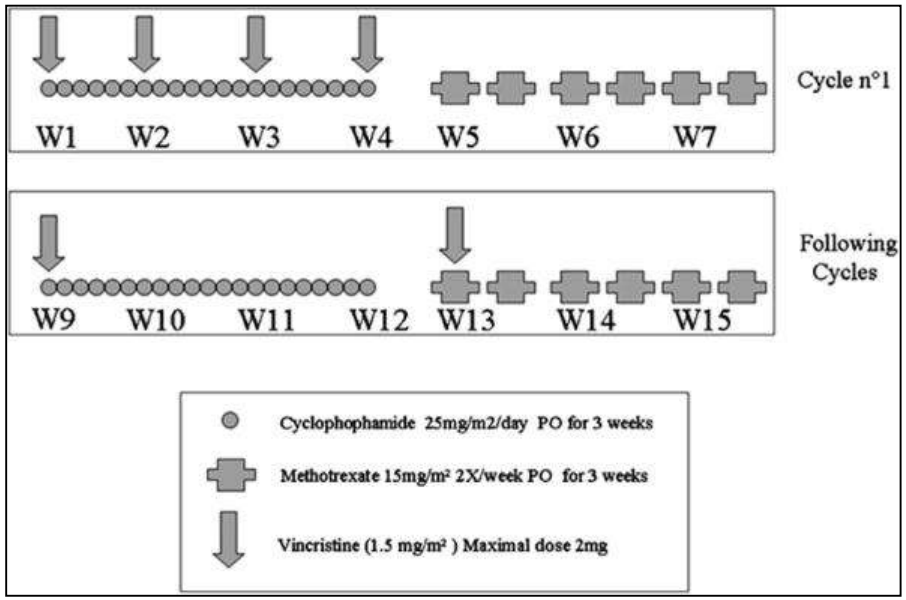
- Afrika’da yapılan ilk pilot çalışmada metronomik kemoterapi sorgulandı
- Düşük gelir düzeyindeki ülkelerde kanser tedavisi yetersiz
- Sağkalım ve prognoz çok kötüdür
- Tahminen yıllık yeni tanılı hasta sayısı 200,000 çocuk olup %25’i sağ kalmaktadır

METRO-MALI-01 METRONOMİK REJİMİ



Nefroblastom 5 Retinoblastom 6 Nörolastom 1
En iyi yanıt SD: 3/12

Children Treated With Metronomic Chemotherapy in a Low-income Country: METRO-MALI-01.
Fousseyni, J Pediatr Hematol/Oncol 2011;33:31-4

Metro-Mali-02

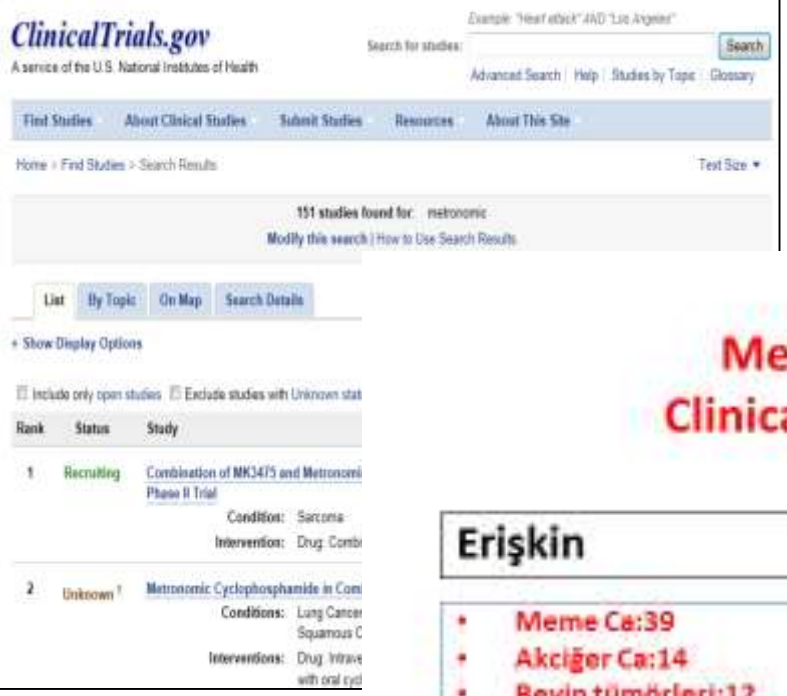
-Metro-Mali-02

(French-African Group of Paediatric Oncology)

Faz 2 çalışma

Günlük düşük doz siklofosfamit , valproik asid, haftalık vinkristin, ve haftada iki kez metotreksat kombinasyonu

Nüks veya dirençli pediatrik solid tümörler



Metronomik Tedavi Klinik Araştırmaları
Clinical Trials.gov (ABD)—03.05.2016 (n:152)

Erişkin

- Meme Ca:39
- Akciğer Ca:14
- Beyin tümörleri:12
- Kanser:10
- Kolorektal Ca:8
- Over Ca:7
- Pankreas Ca:7
- İleri evre karma:6
- NET:5
- Yumuşak doku sarkomları:4
- Multiple miyelom:4
- Baş-boyun:4
- Prostat:4
- Jinekolojik:3
- Melanom:3
- Adrenokortikal Ca, Anjiosarkom, RCC,HCC, Penil, Gastrik Ca,Lösemi/MDS,Lenfoma: Birer çalışma

Çocuk ve ergen

- Nüks/dirençli solid tümörler, SSS tm: 7
- Nöroblastom:5
- Osteosarkom:2

KEMOTERAPÖTİK İLAÇLAR	DİĞER İLAÇLAR
Alkilleyici ajanlar Siklofosfamit Temozolomid İfosfamit	**Anti-VEGF ajanlar** Bevacizumab
Antimetabolitler Metotreksat, 5-FU	**Cox inhibitörleri** Celecoxib
Antimikrotübül ajanlar Vinblastin Vinorelbin Vinkristin	**mTor inhibitörleri** Sirolimus Everolimus
Antrasiklinler Idarubisin	**Tirozin kinaz inhibitörleri** Sunitinib Sorafenib Imatinib Dasatinib Nilotinib
Topoizomeraz inhibitörleri Etoposid Topotekan	**Diğer** Fenofibrat Fluvastatin Retinoik asit Talidomit Zoledronik asit

- Vinorelbin, siklofosfamid, capecitabin, metotreksat ve bevacizumab meme karsinomunda ümit verici
- Vinorelbin, siklofosfamid, etoposid and metotreksat prostat karsinomunda ve küçük hücreli dışı akciğer karsinomlarında etkili
- Capecitabine ±bevacizumab gastrik, kolorektal and hepatoselüler karsinomda etkili
- Siklofosfamit ve bevacizumab over kanserinde önerildi
- Gemcitabine, capecitabine, sorafenib,everolimus RCC
- Temozolomid ve bevacizumab GBM
- Pazopanib
- PROPRANOLOL

- **Yeni yaklaşımlar:**

-Standart protokollerdeki yüksek doz kemoterapi ile başlayıp ilaçları düşük dozda idame etmek

-Metronomik yaklaşımı hedeflenmiş tedavilerle uygulamak

- **Bireyselleştirilmiş düşük doz**

PEDİATRİK ARAŞTIRMA

11 studies found for: metronomic,pediatric

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☐ Include only open studies ☐ Exclude studies with Unknown status

Rank	Status	Study
1	Recruiting	Metronomic Therapy for Pediatric Patients With Solid Tumors at High Risk of Recurrence **Condition:** Solid Tumor **Interventions:** Drug: Bevacizumab; Drug: Cyclophosphamide; Drug: Valproic Acid; Drug: Temsirolimus
2	Active, not recruiting	Low Dose Chemotherapy Versus Best Supportive Care in Progressive Pediatric Malignancies **Condition:** Malignant Childhood Neoplasm **Intervention:** Drug: Low dose chemotherapy
3	Recruiting	Phase I Dose Escalation Study of Topotecan and Pazopanib in Children With Recurrent/Refractory Solid and CNS Tumours **Conditions:** Solid Tumors; Central Nervous System Tumors **Intervention:** Drug: Topotecan and Pazopanib
4	Recruiting	Anti-Angiogenic Therapy Post Transplant (ASCR) for Pediatric Solid Tumors **Conditions:** Glioma; Neuroectodermal Tumors, Primitive; Wilms Tumor; Rhabdomyosarcoma; Sarcoma, Ewing; Osteosarcoma; Retinoblastoma **Interventions:** Drug: Metronomic Cyclophosphamide; Drug: Thalidomide
5	Completed Has Results	Etoposide, Cyclophosphamide, Thalidomide, Celecoxib, and Fenofibrate in Relapsed or Progressive Cancer **Conditions:** Central Nervous System Tumor, Pediatric; Leukemia; Lymphoma; Neuroblastoma; Sarcoma; Unspecified Childhood Solid Tumor, Protocol Specific **Interventions:** Drug: celecoxib; Drug: cyclophosphamide; Drug: etoposide; Drug: fenofibrate; Drug: thalidomide
6	Recruiting	Sirolimus in Combination With Metronomic Chemotherapy in Children With Recurrent and/or Refractory Solid and CNS Tumors **Condition:** Cancer **Interventions:** Drug: Sirolimus; Drug: Celecoxib; Drug: Etoposide; Drug: Cyclophosphamide
7	Completed Has Results	A Phase II Study of Pegylated Interferon Alfa 2b (PEG-Intron(Trademark)) in Children With Diffuse Pontine Gliomas **Condition:** Diffuse Intrinsic Pontine Glioma **Interventions:** Procedure: adjuvant therapy; Biological: pegylated interferon alfa
8	Not yet recruiting	Dose-Finding of Propranolol in Combination With Metronomic Fixed Oral Cyclophosphamide Based on Bivariate Efficacy-tolerability Outcome in Patients With Locally Advanced or Metastatic Angiosarcoma: A Collaborative and Innovative Phase I-II Sequential Trial by the French Sarcoma Group (GSF/GETO) **Condition:** Angiosarcoma **Intervention:** Drug: PROPRANOLOL
9	Active, not recruiting	Aflac ST0901 CHOANOME - Sirolimus in Solid Tumors **Conditions:** Ewing's Sarcoma; Osteosarcoma; Astrocytoma; Atypical Teratoid/Rhabdoid Tumor; Ependymoma; Germ Cell Tumor; Glioma; Medulloblastoma; Rhabdoid Tumor; Retinoblastoma; Clear Cell Sarcoma; Renal Cell Carcinoma; Wilms Tumor; Hepatoblastoma; Neuroblastoma; Rhabdomyosarcoma **Intervention:** Drug: sirolimus
10	Recruiting	Prospective Clinical Trial Evaluating Metronomic Chemotherapy in Patients With High-grade, Operable, Non-metastatic Osteosarcoma of the Extremity **Condition:** High Grade Osteosarcoma
11	Recruiting	Multimodal Molecular Targeted Therapy to Treat Relapsed or Refractory High-risk Neuroblastoma **Condition:** Neuroblastoma Recurrent **Interventions:** Drug: Dasatinib; Drug: Rapamycin; Drug: Irinotecan; Drug: Temozolomide

Nüks riski yüksek solid tümörlerde metronomik tedavi

NCT02446431

- Başlangıç: 28 Nisan 2015
- Hasta alımı sürüyor
- **Amacı:Nüksü önlemek**
- **12 ay-31 yaş**
- **Tanı: RMS, osteosarkom, Ewing sarkomu, diğer yumuşak doku sarkomları**
- **Tek kol**
- **Metronomic Therapy for Pediatric Patients With Solid Tumors at High Risk of Recurrence : A multi-Institutional study**

42 günlük döngü x 10 kür (420 gün)

1-Bevacizumab:IV, 10mg/kg 1. ve 8.günler

2-Siklofosfamit:PO, 25mg/m2 1-14. günler (Maksimum 50mg/doz)

3-Valproik asit:PO,5mg/kg (TID)22-35.gün

4-Temsirolimus:IV,25mg/m2, 22. ve 29.günler

Condition	Intervention	Phase
Solid Tumor	Drug: Bevacizumab Drug: Cyclophosphamide Drug: Valproic Acid Drug: Temsirolimus	Phase 0

Pediatrik ilerleyici kanserlerde düşük doz KT ile iyi destek bakımın karşılaştırılması

NCT01858571 Hindistan

- Destek bakım ile metronomik KT karşılaştırılması
- Faz 3
- Çift kör plasebo kontrollü
- 5-18 yaş
- En az iki kez yinelemişekstra kraniyal solid tümörler

- Progresyon olana kadar kullanılır

- **Low Dose Chemotherapy Versus Best Supportive Care in Progressive Pediatric Malignancies**

Condition	Intervention	Phase
Malignant Childhood Neoplasm	Drug: Low dose chemotherapy	Phase 3

Arms	Assigned Interventions
Experimental: Low dose chemotherapy Alternating cycles of Cycle A and B (Each cycle includes 3 weeks of drug administration) with each drug rounded off to the nearest tablet/capsule size. Cycle A • Daily oral Thalidomide (at 3mg/kg) • Daily oral Celecoxib (100 mg BID for patients < 20 kg, 200 mg BID for patients 20-50 kg, and 400 mg BID for patients > 50 kg) • Daily oral Etoposide (50 mg/m2/d) Cycle B • Daily oral Thalidomide (at 3mg/kg) • Daily oral Celecoxib (100 mg BID for patients < 20 kg, 200 mg BID for patients 20-50 kg, and 400 mg BID for patients > 50 kg) • Daily oral Cyclophosphamide (2.5 mg/kg/d to a maximum of 100 mg/d) every 21 days	Drug: Low dose chemotherapy **Metronomic** chemotherapy schedule : Alternating cycles of Cycle A and B (Each cycle includes 3 weeks of drug administration) with each drug rounded off to the nearest tablet/capsule size. Cycle A • Daily oral Thalidomide (at 3mg/kg) • Daily oral Celecoxib (100 mg BID for patients < 20 kg, 200 mg BID for patients 20-50 kg, and 400 mg BID for patients > 50 kg) • Daily oral Etoposide (50 mg/m2/d) Cycle B • Daily oral Thalidomide (at 3mg/kg) • Daily oral Celecoxib (100 mg BID for patients < 20 kg, 200 mg BID for patients 20-50 kg, and 400 mg BID for patients > 50 kg) • Daily oral Cyclophosphamide (2.5 mg/kg/d to a maximum of 100 mg/d) every 21 days Other Name: •Thalidomide •Celecoxib •Etoposide •Cyclophosphamide
Placebo Comparator: Best supportive care Placebo: Alternating cycles of Cycle A and B (Each cycle includes 3 weeks of drug administration) • Capsules of same size and color as used in **metronomic** therapy Best supportive care • Management of pain as per WHO standard for pain management	Drug: Low dose chemotherapy **Metronomic** chemotherapy schedule : Alternating cycles of Cycle A and B (Each cycle includes 3 weeks of drug administration) with each drug rounded off to the nearest tablet/capsule size. Cycle A • Daily oral Thalidomide (at 3mg/kg) • Daily oral Celecoxib (100 mg BID for patients < 20 kg, 200 mg BID for patients 20-50 kg, and 400 mg BID for patients > 50 kg) • Daily oral Etoposide (50 mg/m2/d) Cycle B • Daily oral Thalidomide (at 3mg/kg) • Daily oral Celecoxib (100 mg BID for patients < 20 kg, 200 mg BID for patients 20-50 kg, and 400 mg BID for patients > 50 kg) • Daily oral Cyclophosphamide (2.5 mg/kg/d to a maximum of 100 mg/d) every 21 days Other Name: •Thalidomide •Celecoxib •Etoposide •Cyclophosphamide

Nüks ve dirençli solid tümörlerde Topotekan ve Pazopanib doz çalışması (TOPAZ)

NCT02303028

- **Başlangıç: 25 Kasım 2014** **42 hasta alınması planlanıyor**
- **Hasta alımı sürüyor**
- **Faz 1**
- **Solid tümörler**
- **2-21 yaş**
- **Phase I Dose Escalation Study of Topotecan and Pazopanib in Children With Recurrent/Refractory Solid and CNS Tumours (TOPAZ)**

Condition	Intervention	Phase
Solid Tumors Central Nervous System Tumors	Drug: Topotecan and Pazopanib	Phase 1 Phase 2

Arms	Assigned Interventions
Experimental: Topotecan and Pazopanib Low dose Topotecan will be given metronomically at the dose level assigned at study entry, in combination with a fixed dose of Pazopanib	Drug: Topotecan and Pazopanib Dose escalation of low-dose metronomic Topotecan with a fixed dose of Pazopanib Other Names: - Hycamtin - Votrient

Pediatrik solid tümörlerde transplantasyon sonrasında anti-anjiogenik tedavi

NCT 01661400

- Başlangıç: 30 Haziran 2012 ABD
- **6 ay-21 yaş**
- **SSS tm, Wilms tümörü, sarkomlar**
- **Anti-Angiogenic Therapy Post Transplant (ASCR) for Pediatric Solid Tumors**

- **Siklofosfamit PO, 2.5mg/kg/gün <40 kg**

  >40kg 100mg/gün
- **Talidomit 3mg/kg/gün**
- **Transplantasyon sonrası 30.günde başlanır, en az 86 gün devam edilir**

Nüks veya ilerleyici kanserde etoposid, siklofosfamit, talidomid, celecoxib ve fenofibrat

NCT00357500

- **Başlangıç: 26 Haziran 2006**
- **Çalışma bitti**
- **Faz II**
- **<21 yaş**
- **27 Hafta tedavi**

- **Robison et al Pediatr Blood Cancer 2014**
- **Etoposide, Cyclophosphamide, Thalidomide, Celecoxib, and Fenofibrate in Relapsed or Progressive Cancer**

Condition	Intervention	Phase
Central Nervous System Tumor, **Pediatric** Leukemia Lymphoma Neuroblastoma Sarcoma Unspecified Childhood Solid Tumor, Protocol Specific	Drug: celecoxib Drug: cyclophosphamide Drug: etoposide Drug: fenofibrate Drug: thalidomide	Phase 2

- Talidomit PO, 3mg/kg/gün haftalık doz artımı ile 1000mg'a ulaş 1-9.haftalar
- Celecoxib PO, 2xgün, <20kg 100mg, 20-50 kg 200mg,>50 kg 400mg

  1-9.haftalar
- Fenofibrat PO, 90 mg/m2 (Maksimum 200mg) 1-9.haftalar
- Etoposid PO, 50mg/m2/gün 1-3. ve , 7-9.haftalar
- Siklofosfamit PO, 2.5 mg/kg/gün 4-6.haftalar (maksimum 100mg)
- Her 9 haftada bir , en az 3 kez tekrarlanır

Çocuklarda nüks ve refrakter solid tümörlerde sirolimus ile metronomik kemoterapinin kombinasyonu NCT02574728

- **Başlangıç: 2 Ekim 2015**
- **Faz II**
- **Dirençli veya nüks tümörler (SSS, NBL,sarkomlar,Wilms tümörü)**
- **12 ay-30 yaş**
- **Sirolimus in Combination With Metronomic Chemotherapy in Children With Recurrent and/or Refractory Solid and CNS Tumors**

- **Sirolimus PO, 2mg/kg/gün (serum konsantrasyonu 10-15 ng/ml)**
- **Celecoxib PO,100mg 2xgün**

  Her 6 hh 1 kür

  (16 kür, 2 yıla kadar)
- **Etoposid PO, 50mg/m2 (Maksimum 100 mg)**
- **Siklofosfamit 2.5 mg/kg(Maksimum 100 mg**

  Her kürün ilk 3 haftası

  (16 kür, 2 yıla kadar)

Diffüz pons gliomlu çocuklarda peg. İnterferon alfa 2b ile faz II çalışması

NCT00036569

- **Başlangıç: 10 Mayıs 2002**
- **Faz II**
- **Hasta sayısı 32**
- **<21 yaş**
- **Pons gliomları**

- **A Phase II Study of Pegylated Interferon Alfa 2b (PEG-Intron^{R}) in Children With Diffuse Pontine Gliomas**

- **İnterferon-alfa SC,**
  0.3 mg/kg haftada 1
  4 hf
- **(Radyoterapi bitiminden**
  2-10 hafta sonra başlanır
  başlanıp devam edilir)
- **İlerleyici hastalık olana kadar**

Condition	Intervention	Phase
Diffuse Intrinsic Pontine Glioma	Procedure: adjuvant therapy Biological: pegylated interferon alfa	Phase 2

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: A Phase II Study of Pegylated Interferon Alfa-2b (Peg-Intron (TM)) in Children With Diffuse Pontine Gliomas

İleri evreli veya metastatik anjiosarkomda metronomik kemoterapi ve propranolol kombinasyonu (GSF/GETO) (PROPAN)

NCT02732678

- **Başlangıç: 29 Mart 2016**
- **Hasta alımı başlamadı**
- **>15 yaş**
- **Anjiosarkom**
- **Faz I, Faz II**
- **Dose-Finding of Propranolol in Combination With Metronomic Fixed Oral Cyclophosphamide Based on Bivariate Efficacy-tolerability Outcome in Patients With Locally Advanced or Metastatic Angiosarcoma: A Collaborative and Innovative Phase I-II Sequential Trial by the French Sarcoma Group (GSF/GETO) (PROPAN)**

- **Propranolol 80 mg/gün**
  120 mg/gün
- **160 mg/gün**

Solid tümörlerde sirolimus Aflac ST0901 CHOANOME

NCT01331135

Başlangıç: 6 Nisan 2011

Tanı

- Ewing sarkomu, Osteosarkom
- Astrositom, ATRT, Ependimom
- Glioma, Medulloblastom
- Germ hücreli tm
- Rabdomiyosarkom, Rabdoid tümör
- Retinoblastom
- CCSK, Renal hücreli karsinom, Wilms tümörü
- Hepatoblastom, Nöroblastom

Faz 1

- **Hasta sayısı 24**
- **<30 y**
- **Oral sirolimus 1mg/m^2 dozundan başlayarak 3 mg/m^2'ye çıkılır**
- **42 gün kullanılır**

- **Aflac ST0901 CHOANOME - Sirolimus in Solid Tumors (Aflac ST0901)**

Arms	Assigned Interventions
Experimental: sirolimus treatment Dose escalation of sirolimus with starting dose at 1 mg/m2 and increasing to a possible 3 mg/m2.	Drug: sirolimus daily administration of sirolimus in oral form starting at a dose of 1 mg/m2 and increasing to a possible 3 mg/m2.

Non-metastatik ekstremite osteosarkomlarında metronomik tedavi

NCT02273583

- Başlangıç: 7 Temmuz 2014
- **<30 yaş**
- **Hasta sayısı:738**
- **Faz 2**
- **Beklenen sonuç 5 yıl EFS**

- **Preop kemoterapi MAP 10 hf**
  MAP:(Yüksek doz Mtx-ADR-Cisplatin)
- **Cerrahi**
- **Randomizasyon**
- **Deneysel kol:**
  MAP 31 hf
  İdame düşük doz oral CYC ve MTX 73 hf. devamlı
- **Kontrol grubu:**
  MAP 31 hf

- **Prospective Clinical Trial Evaluating Metronomic Chemotherapy in Patients With High-grade, Operable, Non-metastatic Osteosarcoma of the Extremity**

Multimodal Molecular Targeted Therapy to Treat Yüksek riskli nöroblastomada multimodal moleküler hedeflenmiş tedavi (RIST-rNB-2011)

NCT01467986

- **Başlangıç: 27 Ekim 2011**
- **Hasta alınıyor**
- **<25 y**
- **Multimodal Molecular Targeted Therapy to Treat Relapsed or Refractory High-risk Neuroblastoma (RIST-rNB-2011)**

Condition	Intervention	Phase
Neuroblastoma Recurrent	Drug: Dasatinib Drug: Rapamycin Drug: Irinotecan Drug: Temozolomide	Phase 2

Study Type: Interventional

Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Factorial Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Prospective, Open Label, Randomized Phase II Trial to Assess a Multimodal Molecular Targeted Therapy in Children, Adolescent and Young Adults With Relapsed or Refractory High-risk Neuroblastoma

Arms	Assigned Interventions
Active Comparator: Irinotecan, Temozolomide Patients randomized to the control arm receive irinotecan (I) and temozolomide (T) alone.	Drug: Temozolomide Pharmacotherapeutic Group: Antineoplastic agents - Other alkylating agents, ATC-Code: L01A X03 Excipients: Capsule content: Anhydrous lactose, Sodium starch glycolate Type A, Colloida anhydrous silica, Tartaric acid, Stearic acid. Capsule shell: Gelatine, Titanium dioxide (E171). Printing ink: Shellac Propylene glycol, Titanium dioxide (E171), Sunset yellow FCF Aluminium Lake (E110) Formulation: capsule, hard Route of Administration: orally, Temomedac hard capsules should be administered in the fasting state. The capsules must be swallowed whole with a glass of water and must not be opened or chewed Other Name: Temomedac® Drug: Irinotecan Pharmacotherapeutic Group: cytostatic topoisomerase-I-inhibitor ATC-Code: L01XX19 Excipients: Sorbitol (E420), lactic acid, sodium hydroxid (to adjust the pH to 3.5), water for injection Formulation: concentrate for solution for infusion Route of Administration: intravenously Other Name: Irinomedac®
Experimental: Rapamycin, Dasatinib, Temozolomide, Irinotecan Patients with rNB receive on the study arm the experimental combination of rapamycin (R)- mTOR Inhibitor, dasatinib (D)- protein kinase inhibitor irinotecan (I)- cytostatic topoisomerase-I-inhibitor and temozolomide (T)- Antineoplastic agent	Drug: Dasatinib Pharmacotherapeutic Group: protein kinase inhibitor ATC-Code: L01XE06 Excipients: Tablet core: Lactose monohydrate, Cellulose, microcrystalline, Croscarmellose sodium, Hydroxypropyl cellulose, Magnesium stearate. Film-coating: Hypromellose, Titanium dioxide, Macrogol 400 Formulation: film coated tablet Route of Administration: orally. Patients should be instructed to swallow the tablets as a whole and not to split, chew, or crush them. Other Name: Sprycel® Drug: Rapamycin Pharmacotherapeutic Group: Immunosuppressive agents - mTOR Inhibitors ATC-Code: L04A A10 Excipients: Polysorbat 80, Phosal 50 PG ((3-sn-Phosphatidyl)choln from Soy beans, Propylenglycol, lipid acid mono- and -diglyceride from Soy oil, Ethanol (1.5% bis 2.5%), Soy lid acid and Palmityl ascorbic acid) Formulation: Oral solution Route of Administration orally sodium hydroxid (to adjust the pH to 3.5), water for injection Formulation: concentrate for solution for infusion Route of Administration: intravenously Other Name: Irinomedac®
Experimental: Rapamycin, Dasatinib, Temozolomide, Irinotecan Patients with rNB receive on the study arm the experimental combination of rapamycin (R)- mTOR Inhibitor, dasatinib (D)- protein kinase inhibitor irinotecan (I)- cytostatic topoisomerase-I-inhibitor and temozolomide (T)- Antineoplastic agent	Drug: Dasatinib Pharmacotherapeutic Group: protein kinase inhibitor ATC-Code: L01XE06 Excipients: Tablet core: Lactose monohydrate, Cellulose, microcrystalline, Croscarmellose sodium, Hydroxypropyl cellulose, Magnesium stearate. Film-coating: Hypromellose, Titanium dioxide, Macrogol 400 Formulation: film coated tablet Route of Administration: orally. Patients should be instructed to swallow the tablets as a whole and not to split, chew, or crush them. Other Name: Sprycel® Drug: Rapamycin Pharmacotherapeutic Group: Immunosuppressive agents - mTOR Inhibitors ATC-Code: L04A A10 Excipients: Polysorbat 80, Phosal 50 PG ((3-sn-Phosphatidyl)choln from Soy beans, Propylenglycol, lipid acid mono- and -diglyceride from Soy oil, Ethanol (1.5% bis 2.5%), Soy lid acid and Palmityl ascorbic acid) Formulation: Oral solution Route of Administration orally Other Name: Rapamune® Drug: Irinotecan Pharmacotherapeutic Group: cytostatic topoisomerase-I-inhibitor ATC-Code: L01XX19 Excipients: Sorbitol (E420), lactic acid, sodium hydroxid (to adjust the pH to 3.5), water for injection Formulation: concentrate for solution for infusion Route of Administration: intravenously Other Name: Irinomedac® Drug: Temozolomide Pharmacotherapeutic Group: Antineoplastic agents - Other alkylating agents, ATC-Code: L01A X03 Excipients: Capsule content: Anhydrous lactose, Sodium starch glycolate Type A, Colloida anhydrous silica, Tartaric acid, Stearic acid. Capsule shell: Gelatine, Titanium dioxide (E171). Printing ink: Shellac Propylene glycol, Titanium dioxide (E171), Sunset yellow FCF Aluminium Lake (E110) Formulation: capsule, hard Route of Administration: orally, Temomedac hard capsules should be administered in the fasting state. The capsules must be swallowed whole with a glass of water and must not be opened or chewed Other Name: Temomedac®

Metronomic Treatment in Children and Adolescents With Recurrent or Progressive High Risk Neuroblastoma (METRO-NB2012)

NCT02641314

- Başlangıç: 15 Aralık 2015
- **F.Berthold-Cologne**
- **≥2 y, <21 y**
- **Nüks veya dirençli nöroblastom**
- **3 ay yaşam beklentisi olan hastalar**
- **Faz 2**

Condition	Intervention	Phase
Neuroblastoma Recurrent	Drug: metronomic therapy	Phase 2

Study Type: Interventional
Study Design: Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Phase 2 Trial of Metronomic Treatment in Children and Adolescents With Recurrent or Progressive Neuroblastoma (NB)

NCT02641314

- **28 günlük döngüler halinde dönüşümlü 8 kür**

  PCCVE

  (Propranolol,celecoxib,siklofosfamid,vinblastin,etoposid)

  PCCV

  (Propranolol, celecoxib,siklofosfamid,vinblastin)

- **Takiben 5 kür PCCV (Toplam 13 kür, 364 gün)**

- **Propranolol 0.5 mg/kg/gün PO 1.gün**

  a mg/kg/gün PO 2.gün

  b mg/kg/gün PO 3-365 gün 2 doza bölerek

  (Maksimum doz 120 mg)
- **Celecoxib 400 mg/m^2 PO 1-365 gün (Maksimum doz 800 mg) 2 doza bölerek**
- **Siklofosfamid 1.gün 500 mg/m^2 İV 1 s infüzyon**

  2-365 gün 25 mg/m2/gün tek doz

  (Maksimum doz 50 mg)
- **Vinblastin 3mg/m^2/gün İV 1 ve 15. gün (Her iki haftada bir)**

  (Maksimum doz 6 mg)
- **Etoposid 25mg/m^2gün PO 1-21.gün 1-3,9-11,17-19, 25-27.hf Tek doz**

  (Maksimum doz 50 mg)

Reküren yüksek dereceli Gliomalarda
Temozolomid ve Askorbik Asit Tedavisi
NCT02168270

- **Başlangıç: 29 Mayıs 2014**
- **Faz I**
- **Metronomik Temozolomid ve İV Askorbik Asid**
- **Reküren yüksek dereceli Gliom**
- **Anaplastik tümörler GBM**

- **Askorbik asid İV 90-120 dk, hf 3 kez**
- **Temozolomid PO 1-28 günler**
- **Her 4 haftada bir tekrarlanan 12 kür**
- **Çalışma kapatıldı (Katılım 3)**

- **Pediatrik solid tümörlerde**

-Vinkristin 15 mg/m2

-Cyc 25 mg/m2,

-MTX 15 mg/m2

n:7/12 Stabil hastalık

- **Topotekan 0.8 mg/m2 3 hf 28 günde bir**

n:6/26 Progresyon yok

Taylor & Francis

Cancer Investigation

ISSN: 0735-7907 (Print) 1532-4192 (Online) Journal homepage: http://www.tandfonline.com/loi/icnv20

Metronomic Dosing of Chemotherapy: Applications in Pediatric Oncology

Diana Stempak Ph.D., Dugald Seely N.D. & Sylvain Baruchel Director M.D.

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- Children’s Oncology Group (COG), faz 1 çalışma
- Ewing sarkomlu çocuklarda standart tedaviye ek olarak metronomik vinblastin ve celecoxib eklenmesi olumlu sonuç verdi
- Yalnız 3 doz sınırlayıcı toksisite görüldü

NANT 2007-02

Dirençli veya nüks yüksek riskli nöroblastomlu çocuklarda siklofosfamid ve zoledronik asit ± bevacizumab

Siklofosfamid 28 günlük siklusun 1.gününde yüksek doz, ardından devamlı düşük doz olarak verilir

Fizibilite ve toksisiteyi soruşturan bir araştırma

Allogeneic Tumor Cell Vaccination With Oral Metronomic Cytoxan in Patients With High-Risk Neuroblastoma (ATOMIC)

NCT01192555

Purpose

Neuroblastoma is the second most common solid tumor seen in children, but causes approximately 15% of childhood cancer deaths each year. Patients with high-risk disease require treatment with a combination of chemotherapy, surgery, radiation, and stem cell transplant; however, many will have their disease come back within 3 years. Due to this high rate of relapse, this study is being done to investigate an experimental treatment option for children whose disease has returned.

This clinical trial is for patients with neuroblastoma that has either come back after treatment or never went away in the first place. A series of immunizations will be administered using a tumor vaccine and add low-dose chemotherapy to be taken by mouth on a daily basis. The hope is that the vaccine will cause the immune system to recognize and kill more types of neuroblastoma tumors. Additionally, the immunizations will be combined with daily low dose chemotherapy. Daily low-dose chemotherapy, also know as **metronomic** chemotherapy, works by attacking the blood vessels that allow tumors to grow. Using **metronomic** doses of a drug called cytoxan can also decrease T regulatory cells, a specific type of cell that tumors use to hide from the immune system.

The purpose of this study is to test the safety and anti-tumor effect of the tumor cell vaccination plus low dose, **metronomic** chemotherapy in treating patients with relapsed/refractory neuroblastoma.

Condition	Intervention	Phase
Neuroblastoma	Biological: Neuroblastoma Vaccine Drug: Cytoxan	Phase 1 Phase 2

Study Type: Interventional

Study Design: Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: A Phase I/II Study Using Allogeneic Tumor Cell Vaccination With Oral **Metronomic** Cytoxan in Patients With High-Risk Neuroblastoma (ATOMIC)

GLATO 2006

- **GLATO 2006**

(Latin-American Group for the Treatment of Osteosarcoma)

- **Randomize faz 3 etkinlik araştırması**
- **Metastatik osteosarkom**
- **Geleneksel kemoterapi ve cerrahi ile kombine olarak metronomik siklofosfamid ve metotreksat**

- Randomize faz 2 araştırma (NCT00643565)
- Metastatik RMS ve diğer yumuşak doku sarkomlu çocuk ve ergenler
- Standart kemoterapi ile kombine olarak bevacizumab

- Yeni tanı yüksek dereceli gliom ve diffüz intrensek pons gliomu tanılı çocuklar ve genç erişkinlerde (NCT00890786)
- Radyoterapi ve temozolamid ile kombine bevacizumab içeren pilot çalışma

- St Jude Children’s Research Hospital (Memphis, TN).
- Refrakter solid tümör ve lösemi tanılı çocuklar ve genç yetişkinler
- Faz 1 çalışma düşük doz siklofosfamid ile birlikte bevacizumab ve sorafenib

A significant risk lies in using metronomic therapy in children where angiogenesis plays an important role in physiological growth. The effect of exposure to long-term chemotherapy on normal endothelial and vascular tissues is unknown.

Symposium For Metronomics and Economics: Review Article

Metronomic Therapy: Chemotherapy revisited

Noronha V, **Krishna MV**, **Patil V**, **Joshi A**, **Banavali SD**, **Prabhash K**
Department of Medical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India

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Abstract

Cytotoxic antiproliferative chemotherapeutic agents are the mainstay of treatment in cancers. Chemotherapy is usually administered every 2–3 weeks. Along with acute toxicity and long-term effects of cumulative doses, this strategy potentially allows regrowth of the tumor in the interval period and leads to the emergence of resistant populations of tumor cells. Moreover, even with intense chemotherapy, the outcome is stagnating for most of the tumors. There has been recent interest in the use of chemotherapy in fractionated doses which is far below the maximum tolerated dose. This is called metronomic scheduling of chemotherapy. Here, we review the biology and evidence for metronomic chemotherapy.

Key words: Chemotherapy, metronomics, economics

J Pediatr Hematol Oncol. 2013 Nov;35(8):632-3. doi: 10.1097/MPH.0b013e3182707c00.

Metronomic scheduling of anticancer agents for a refractory orbital pseudotumor in a child.

Elhoudzi J[1], Rome A, Padovani L, Gentet JC, André N.

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Publication Types, MeSH Terms, Substances

Metronomik tedaviden ne bekliyoruz?

- Metronomik tedaviler hastalık kontrolünün yetersiz olduğu durumlarda uygulanmıştır
- Daha az toksik etki
- Daha uzun süreli tümör kontrolü
- Yaşam kalitesi yüksek doz kemoterapi şemalarına göre daha iyidir
- Poliklinik ve ev koşullarında sürdürülebilir
- Düşük ve orta gelirli ülkelerde tedavi şansı (Metronomik-Ekonomik)