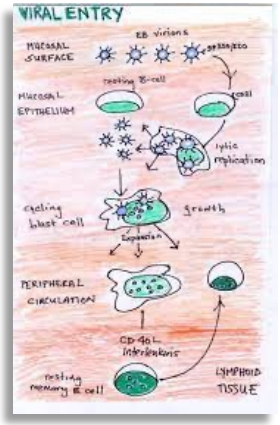
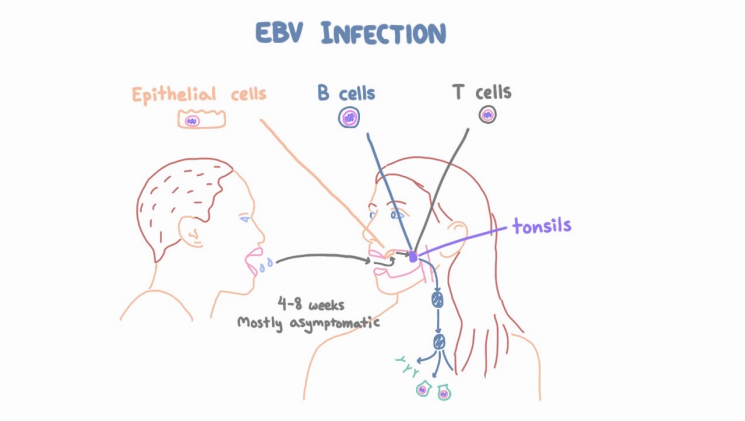
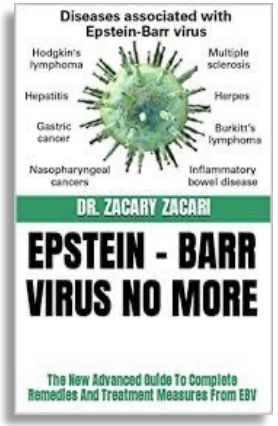






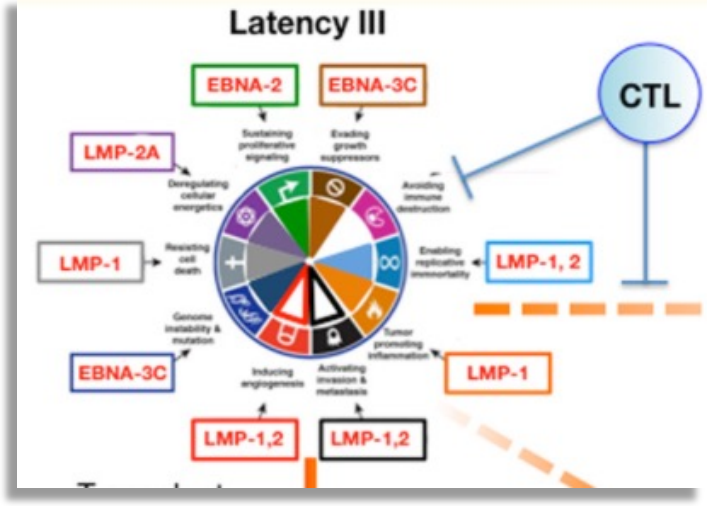
EBV DNA Takipleri ve EBV'yi Hedefleyen Tedaviler:

Ne Kadar Yararlı?

Dr. R.Aytaç ÇETİNKAYA

- Dünya nüfusu %90, EBV enfeksiyon geçirdiği
- Aseptomatik - Latent
- B lenfosit içinde immortal
- Viral kodlanmış transkripsiyon
- EBV nuclear antijen EBNA1, EBNA2, EBNA3A, EBNA3B, EBNA3C
- Latent Memran Protein LMP1, LMP2A, LMP2B

VIRUS	CANCER	V-ONC	PATHWAYS	CANCER HALLMARK
EBV	BL	EBNA		
	NHL, NPC	LMP-1	NFkB	
		LMP-2A	PI3K, ERK1/2	
HPV	CxCa, HNCC	E6	p53, mTOR, hTERT	
		E7	Rb	
		E5		
HBV	HCC	HBx	p53. Rb, Wnt, src, DNMTs, ras, PI3K JNK, NF-κB, ERK1/2. TGFβ, HDACs	
HCV	HCC	Core, NS3, Ns5A	p53, PARP, hTERT, TGFβ, HDACs,	
HTLV-1	ATLL	Tax	NFkB, CREB, PI3K, DDR	
		HZB	c-jun, E2F	
KSHV	KS	vFLIP	NFkB	
		LANA	p53, Rb, HIF, Notch, Wnt	
		vGPCR	PI3K-AKT-mTOR, ERK, p38, JNK, NFkB,	
		vIRF-1	αIFN, p53, ATM, Bim	



De Martel. Global burden of cancer attributable to infections in 2018: A worldwide incidence analysis. **Lancet Glob. Health 2020**, 8, e180–e190

Human Oncovirus Replication and Persistence Strategies

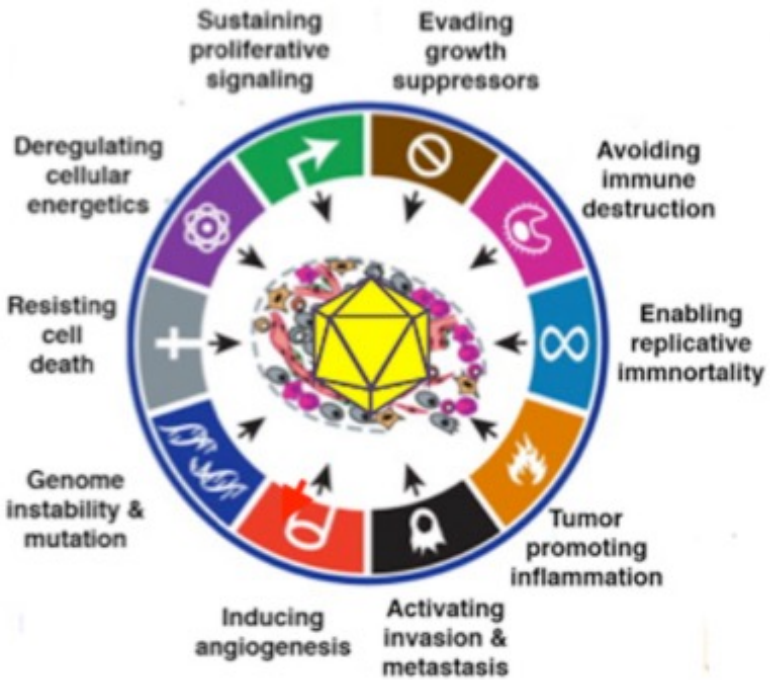
Find/ Create conditions for replication
- Induce the Cell cycle
- Metabolic reprogramming
- Inducing angiogenesis

Ensure correct replication
- Recruit or inhibit DDR

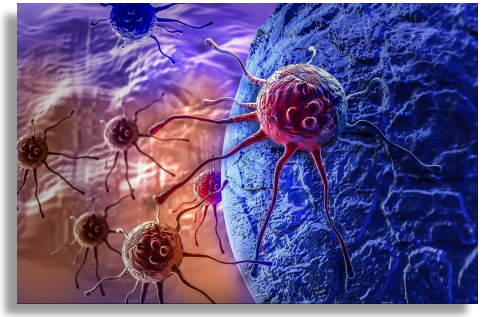
Maximize virus production
- prevent apoptosis until virion matures
- Immune evasion

Multiply latent episomes or provirus
- Cell survival
- Cell immortalization
- Cell proliferation

Hallmarks of Cancer



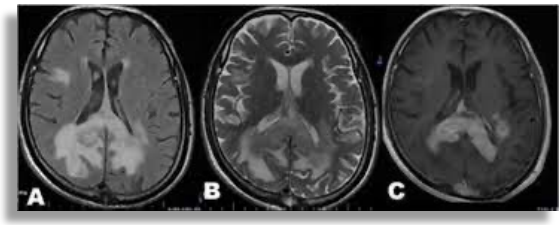
EBV malignite



Lenfoma

Hodgkin lenfoma (HL)

Hodgkin dışı lenfoma (NHL)



Yavaş ilerleyen lenfoma

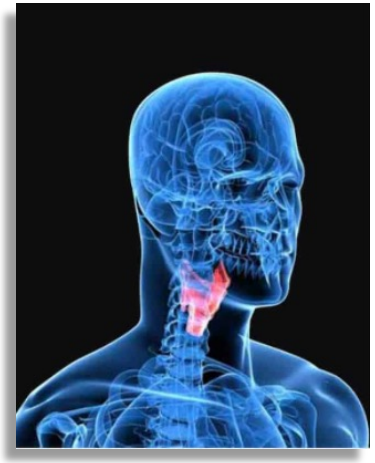
Folliküler lenfoma
Kronik lenfositik lösemi
İmmunositoma

Hızlı ilerleyen lenfoma

Diffuz büyük B hücreli lenfoma
T lenfomaların çoğunluğu
Mantle hücreli lenfoma

Çok hızlı ilerleyen lenfoma

Burkitt lenfoma
Lenfoblastik B lenfoma
Lenfoblastik T lenfoma



Hodgkin lenfoma & EBV DNA

- Gözlemsel klinik

- Tümör hücreleri içinde
- Viral nucleic acid (EBER)
- in situ hybridization (ISH)

- Plazma EBV DNA

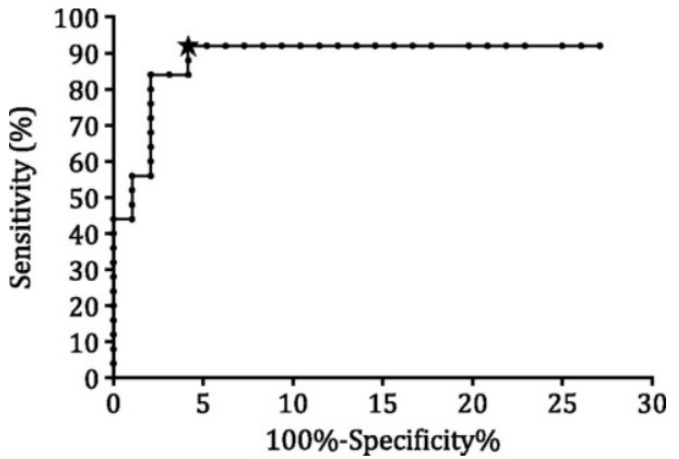
- 54 vaka & 274 kontrol
- cutoff of >60 viral copies/100 mL
- %96 uyumlu

- 6 ay tedavi 7 vaka & 125 kontrol
- doxorubicin, bleomycin, vinblastine, dacarbazine vs Stanford V

CLINICAL TRIALS AND OBSERVATIONS

Plasma Epstein-Barr virus DNA predicts outcome in advanced Hodgkin lymphoma: correlative analysis from a large North American cooperative group trial

Jennifer A. Kanakry,[1] Hailun Li,[2] Lan L. Gellert,[3] M. Victor Lemas,[1] Wen-son Hsieh,[4] Fangxin Hong,[2] King L. Tan,[5] Randy D. Gascoyne,[5] Leo I. Gordon,[6] Richard I. Fisher,[7] Nancy L. Bartlett,[8] Patrick Stiff,[9] Bruce D. Cheson,[10] Ranjana Advani,[11] Thomas P. Miller,[12] Brad S. Kahl,[13] Sandra J. Horning,[14] and Richard F. Ambinder[1]



Download : Download high-res image (70KB) Download : Download full-size image

Figure 2. **Trade-off of sensitivity vs specificity of plasma EBV copy number as a discriminator of EBER-ISH status, plotted as a receiver operating characteristic (ROC) curve.** Area under the ROC curve is 0.94 (95% confidence interval 0.86-1.01). Sensitivity and specificity are optimized at plasma EBV cutoff of >60 viral copies/100 μL plasma (★ on curve).

Hodgkin lenfoma & EBV DNA

- 5 yıllık vaka kontrol
- 30 HL & 70 kontrol
- Plazma EBV DNA 19 (%63) (aralık 500 ila 430.000 kopya/mL)
- İmünohistokimyasal kıyasla %87.5 doğrulukla pozitif
- duyarlılığı ve özgüllük sırasıyla %87.5 ve %81.8
- İlk kür tedavi %100 Plazma EBV DNA PCR negatifleşme
- Adriamycin, Bleomycin, Vinblastine, Dacarbazine (ABVD)

› Indian Pediatr. 2015 Aug;52(8):681-5. doi: 10.1007/s13312-015-0696-9.

Plasma Epstein Barr virus (EBV) DNA as a biomarker for EBV associated Hodgkin lymphoma

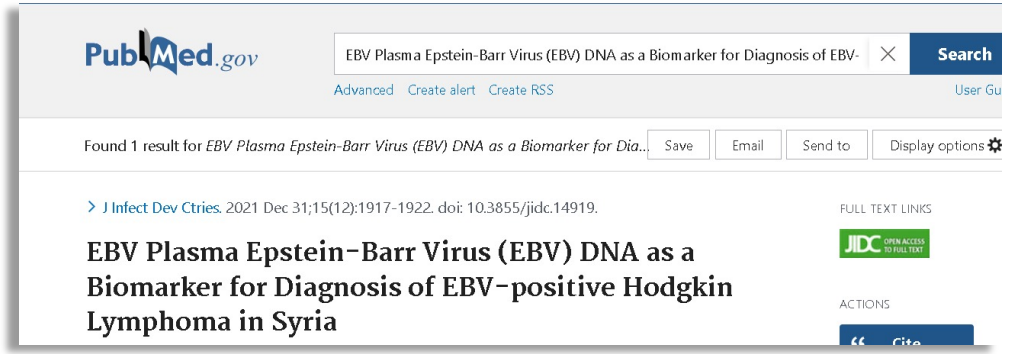
Veronique Dinand [1], Anupam Sachdeva, Sanghamitra Datta, Sunita Bhalla, Vinod Kalra, Chand Wattal, Nita Radhakrishnan

PET: Metastaz Relaps ??

		Total (n=30)	EBV positive (n=19)	EBV negative (n=11)	P value
Sex		24:6	19: 0	5: 6	0.001[a]
Median (IQR) age, y		8.7 (3.5-18)	8 (5.5-12)	12 (8-15)	0.10[b]
Stage I		4	4 (21.1%)	0	0.37[c]
II		9	6 (31.6)	3 (27.3	
III		4	2 (10.5)	2 (18.2)	
IV		13	7 (36.8)	6 (54.5)	
B symptoms		17	10 (52.6)	7 (63.6)	0.70[c]
Bulky disease		7	5 (26.3)	2 (18.2)	1.0[c]
Involved LN areas	1-2	12	8 (42.1)	4 (36.4)	0.90[c]
	3-4	12	7 (36.8)	5 (45.5)	
	≥5	6	4 (21.1)	2 (18.2)	
Anemia (Hb <10.5 g/dL)		12	8 (42.1)	4 (36.4)	1.00[c]
Immunophenotype	Mixed cellularity	19	15 (78.9)	4 (36.4)	0.05[c]
	Nodular sclerosis	6	2 (10.5)	4 (36.4)	
	Lymphocyte predominant	2	0	2 (18.2)	
	Unclassified	3	2 (10.5)	1 (9.1)	
EBV IHC (n=27)	Positive	16	14/16 (87.5)	2 (12.5)	

qPCR: real-time quantitative polymerase chain reaction; [a]Fisher's exact test, [b]Mann Whitney U-test, [c]Pearson's Chi square test. LN: lymph node. IHC: immunohistochemistry.

Hodgkin lenfoma & EBV DNA



- 60 HL & 60 kontrol (yaş ve cinsiyet)
- Tümör hücresi LMP1 immünohistokimyasal boyama
- 25/60 hasta LMP1 (+)
- 25/25 Plazma EBV DNA (+) %100

	EBV positive Hodgkin lymphoma (n = 25)		EBV negative hodgkin lymphoma(n = 35)	
	LMP1-IHC* positive	Median plasma EBV DNA†	LMP1-IHC * negative	Median plasma EBV DNA†
	(n)	Copies/ml	(n)	Copies/ml
Clinical stage				
Advanced stage	25/25 (100%)	1.1×10^4	17/35(48.6%)	undetectable
Limited stage	0/25 (0%)		18/35(51.4%)	undetectable
Treatment responses evaluation (over 20 months)				
patients had relapsed lymphoma	8/25(32%)	1.3×10^4	0/35(0%)	
patients had Refractory lymphoma	5/25(20%)	1.1×10^4	0/35(0%)	
patients had responded to treatment	12/25 (48%)	1.9×10^3	35/35 (100%)	undetectable

LMP1-IHC *: latent membrane protein-1 (LMP1) immunohistochemistry stains; plasma EBV DNA†: plasma Epstein-Barr Virus DNA.

Burkitt lenfoma & EBV DNA

- EMBLEM çalışma grubu retrospektif
- (Epidemiology of Burkitt lymphoma in East African children and minors)

- 25 BL & 25 kontrol

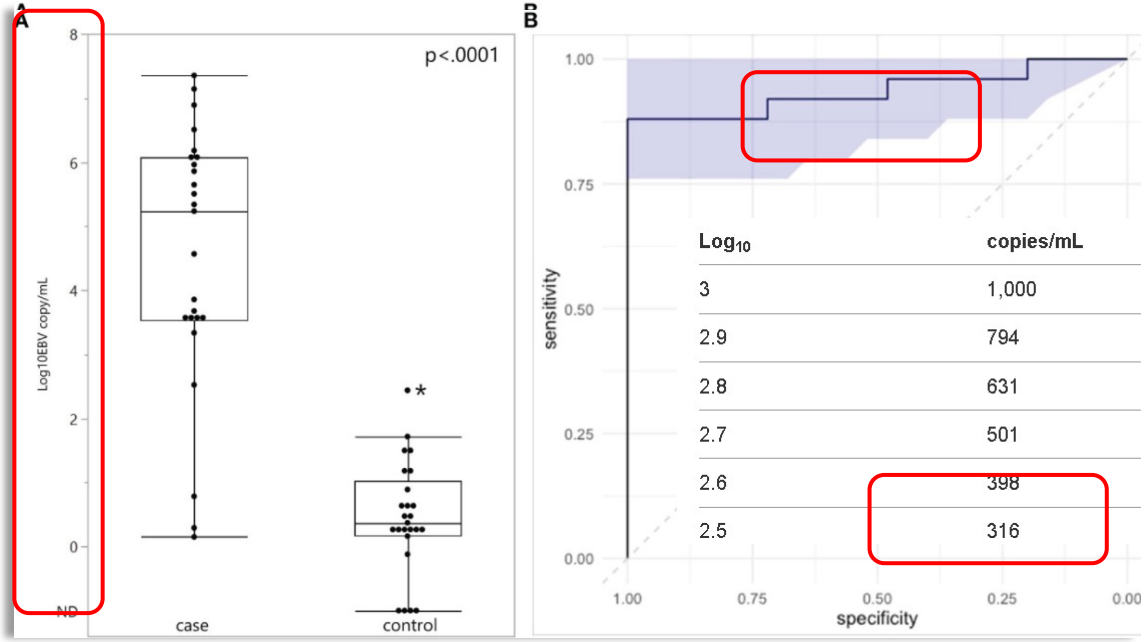
- Plazma EBV DNA 5.23 log10 kopya/mL BL
- Kontrol grubu 0.37 log10 kopya/mL

- Treshol EBV DNA seviyesi 2.52 log10 kopya/mL
- duyarlılığı ve özgüllük %88

Front. Oncol., 14 December 2021 | https://doi.org/10.3389/fonc.2021.804083

Plasma EBV DNA: A Promising Diagnostic Marker for Endemic Burkitt Lymphoma

Rena R. Xian[1,2], Tobias Kinyera[3,4], Isaac Otim[3,4], Joshua N. Sampson[5], Hadijah Nabalende[3,4], Ismail D. Legason[3,4], Jennifer Stone[2], Martin D. Ogwang[3,4], Steven J. Reynolds[6], Patrick Kerchan[3,7], Kishor Bhatia[5], James J. Goedert[5], Sam M. Mbulaiteye[5†] and Richard F. Ambinder[1,2*†]

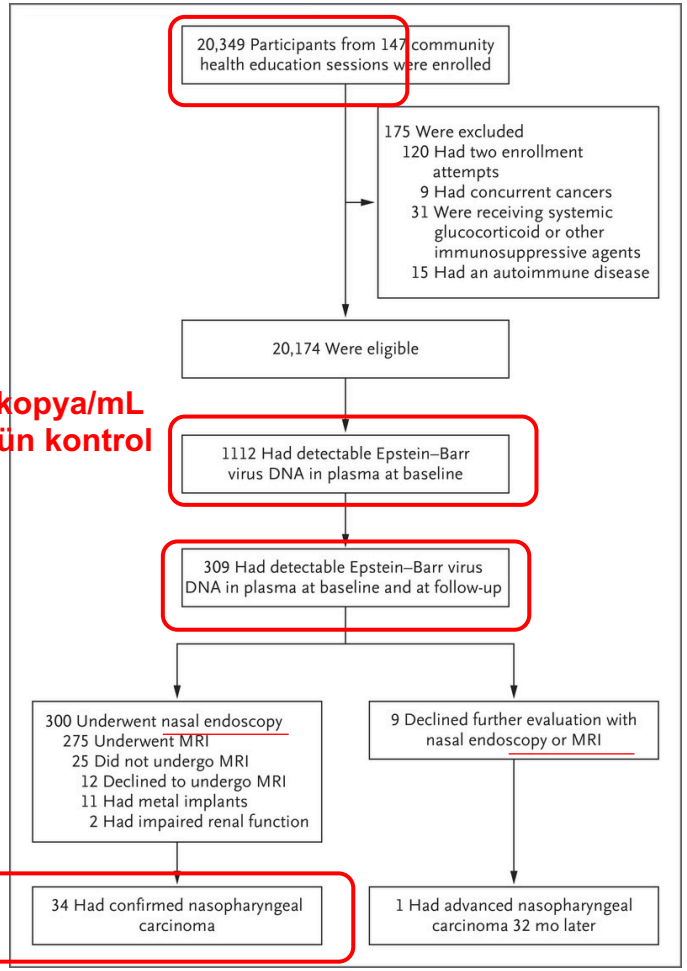


The NEW ENGLAND JOURNAL of MEDICINE

Analysis of Plasma Epstein–Barr Virus DNA to Screen for Nasopharyngeal Cancer

K.C. Allen Chan, F.R.C.P.A., John K.S. Woo, F.R.C.S., Ann King, F.R.C.R., Benny C.Y. Zee, Ph.D., W.K. Jacky Lam, F.R.C.S., Stephen L. Chan, F.R.C.P., Sam W.I. Chu, B.Sc., Constance Mak, B.S.N., Irene O.L. Tse, B.N., Samantha Y.M. Leung, B.N., Gloria Chan, R.N., Edwin P. Hui, F.R.C.P., et al.

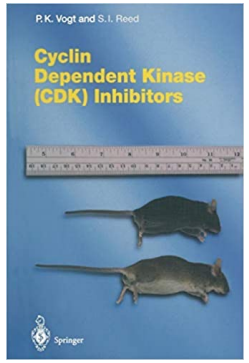
August 10, 2017
N Engl J Med 2017; 377:513-522
DOI: 10.1056/NEJMoa1701717

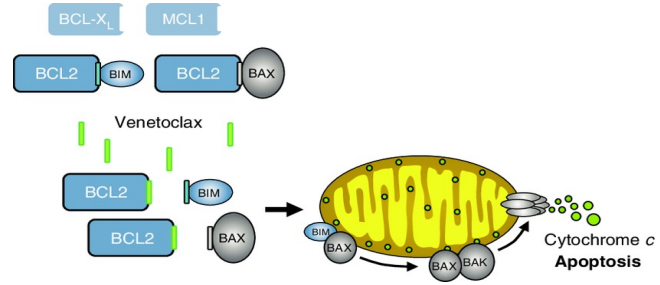


>20 kopya/mL
34 gün kontrol

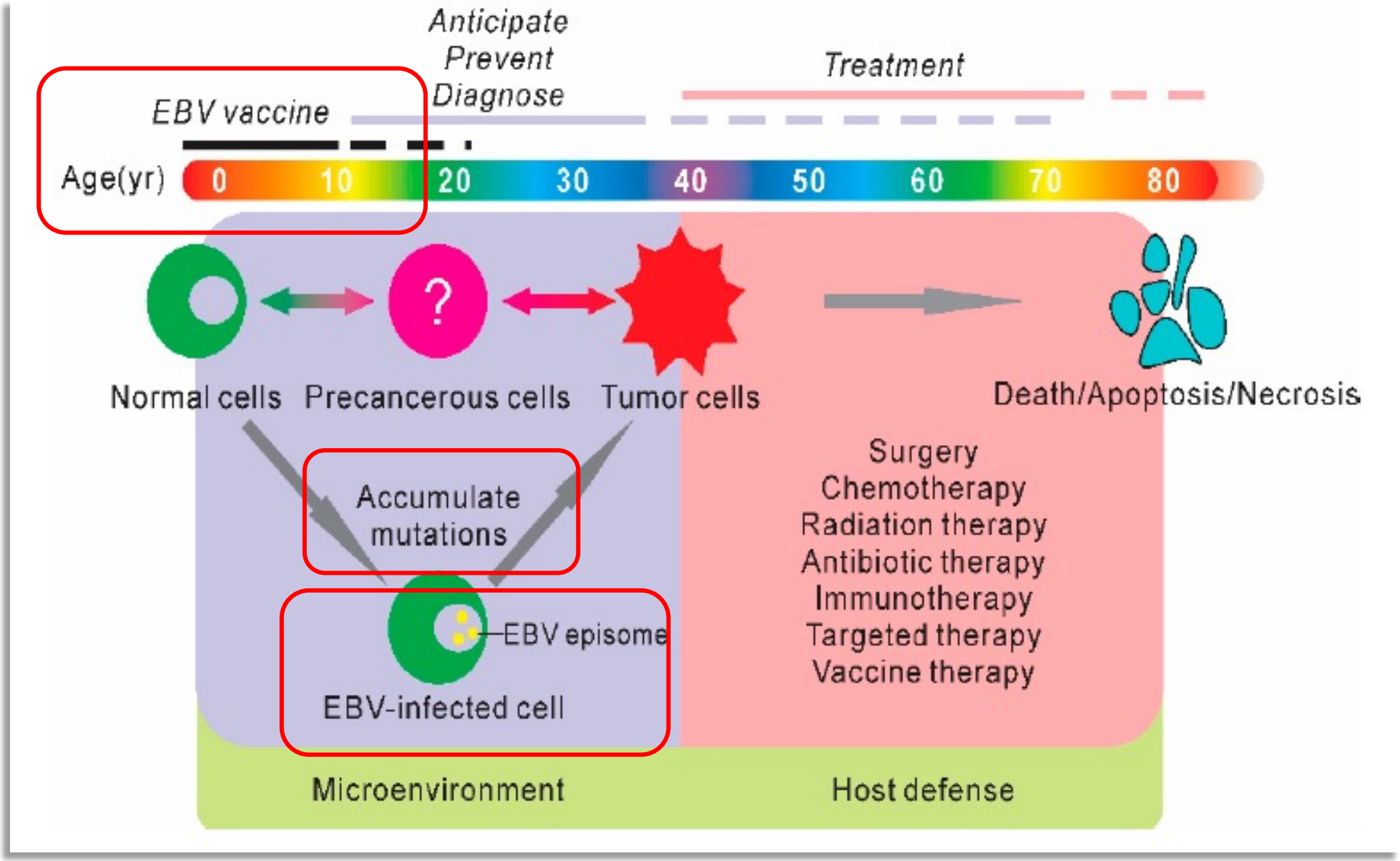
Table 2. Sensitivity and Specificity of the Two-Stage Screening Protocol for the Detection of Nasopharyngeal Carcinoma.*

Finding	Screen-Positive (N=308)†	Screen-Negative (N=19,865)
Confirmed nasopharyngeal carcinoma by the screening protocol or nasopharyngeal carcinoma reported to have developed within 1 yr — no.	34	1
No nasopharyngeal carcinoma within 1 yr after screening — no.	274	19,864
Sensitivity — % (95% CI)	97.1 (95.5–98.7)	
Specificity — % (95% CI)	98.6 (98.6–98.7)	
Positive predictive value — % (95% CI)	11.0 (10.7–11.3)	
Negative predictive value — % (95% CI)	99.995 (99.99–100.00)	
Proportion of stage I/II disease in the 34 cases of nasopharyngeal carcinoma identified by screening — % (95% CI)	70.6 (69.6–72.5)	



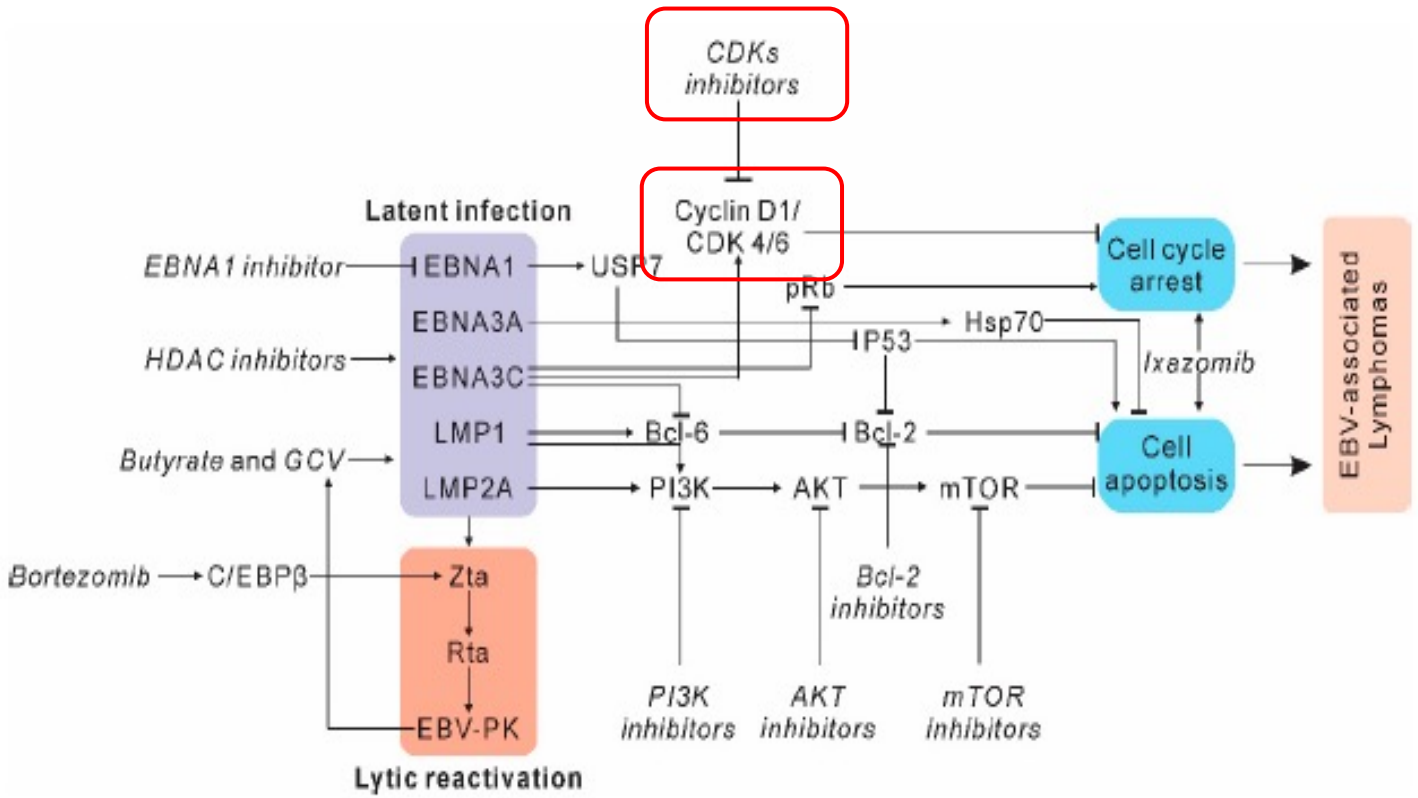


EBV Lenfoma & Tedavi


Anticipate
Prevent
Diagnose
Treatment
EBV vaccine
Age(yr)
0
10
20
30
40
50
60
70
80
?
Normal cells
Precancerous cells
Tumor cells
Death/Apoptosis/Necrosis
Accumulate mutations
EBV episome
EBV-infected cell
Surgery
Chemotherapy
Radiation therapy
Antibiotic therapy
Immunotherapy
Targeted therapy
Vaccine therapy
Microenvironment
Host defense

Konak Faktörlerini ve Sinyal Yollarını Hedefleyen Tedavi

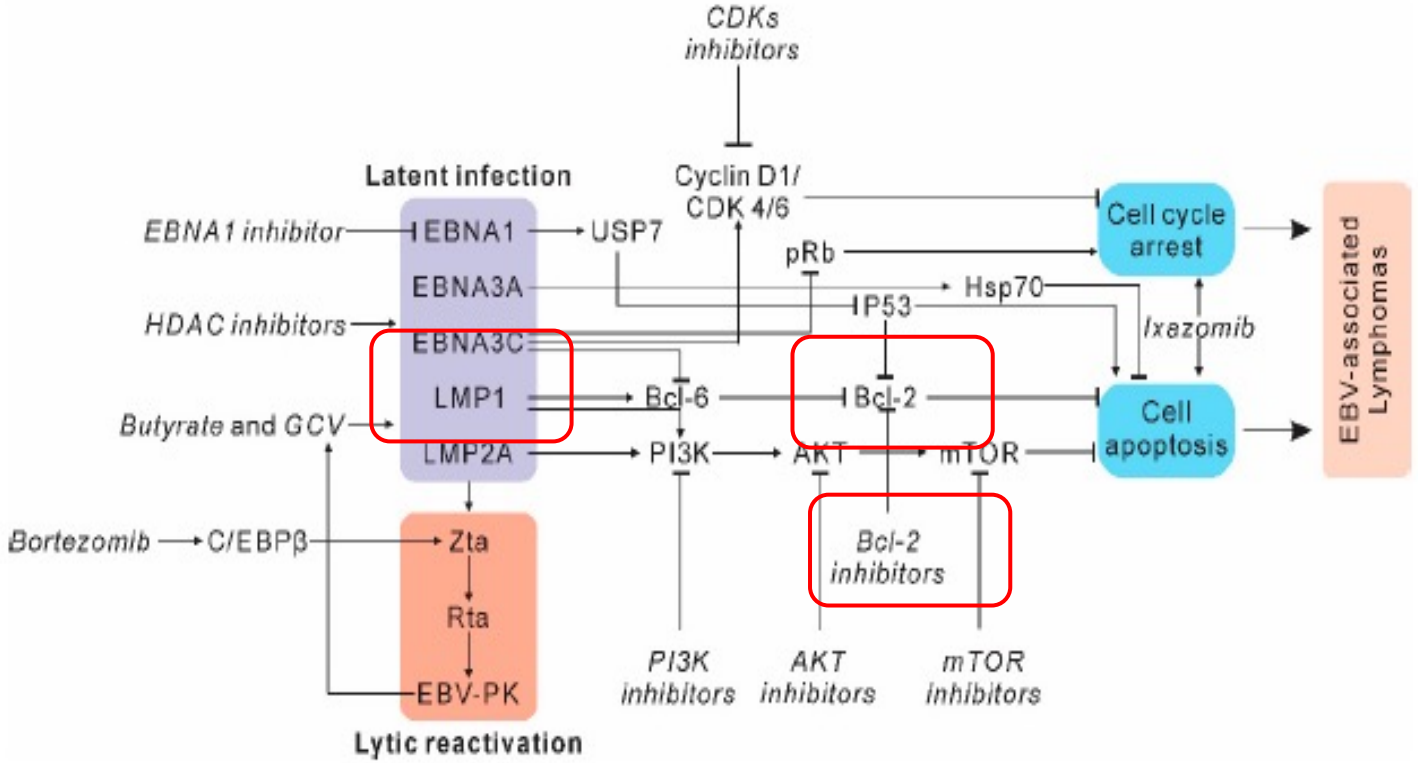
- Siklin D
- Sikline bağımlı kinaz (CDK)
- Latent enfeksiyon
- Litik enfeksiyon geçiş



Tsang, C.M;Cyclin D1 overexpression supports stable EBV infection in nasopharyngeal epithelial cells. **Proc. Natl.Acad. Sci. USA 2012**, 109, E3473–E3482

Konak Faktörlerini ve Sinyal Yollarını Hedefleyen Tedavi

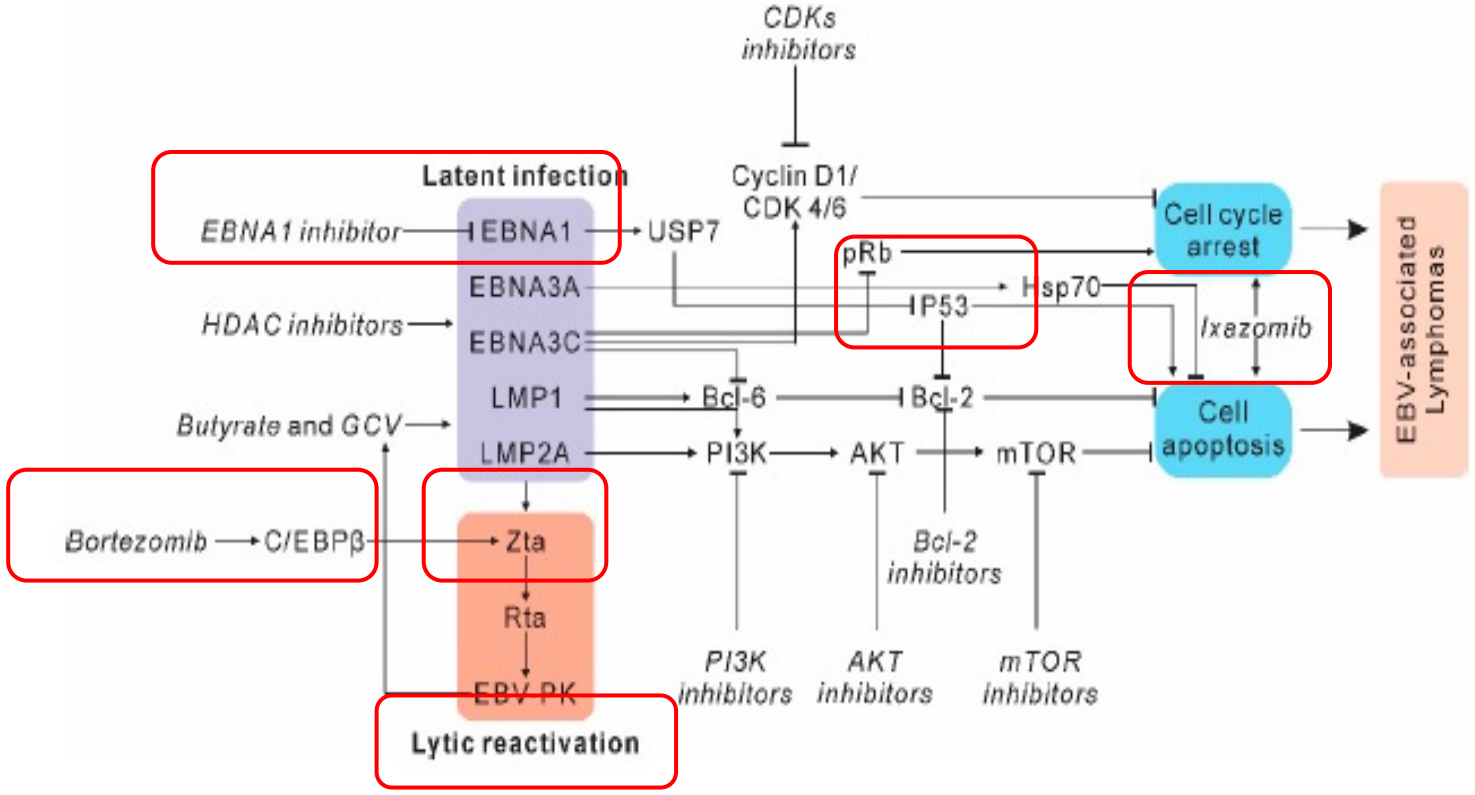
- antiapoptotic protein Bcl-2
- Bcl-6 ana düzenleyici
- viral latent antijen EBNA3C
- ABT-199 (venetoclax)
- Souers ve ark. (2013) Etkili
- Price ve ark. (2017) EBV ile ölümsüzleşmiş B lenfosit için etkisiz
- Erken EBV ile enfekte etkili



TPei, Y.; An essential EBV latent antigen 3C binds Bcl6 for targeted degradation and cell proliferation. **PLoS Pathog**. **2017**, 13, e1006500
Souers, A.J.;ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat. Med. **2013**, 19, 202–208.
Price, A.M.; Epstein-Barr virus ensures B cell survival by uniquely modulating apoptosis at early and late times after infection. eLife **2017**, 6, e22509.

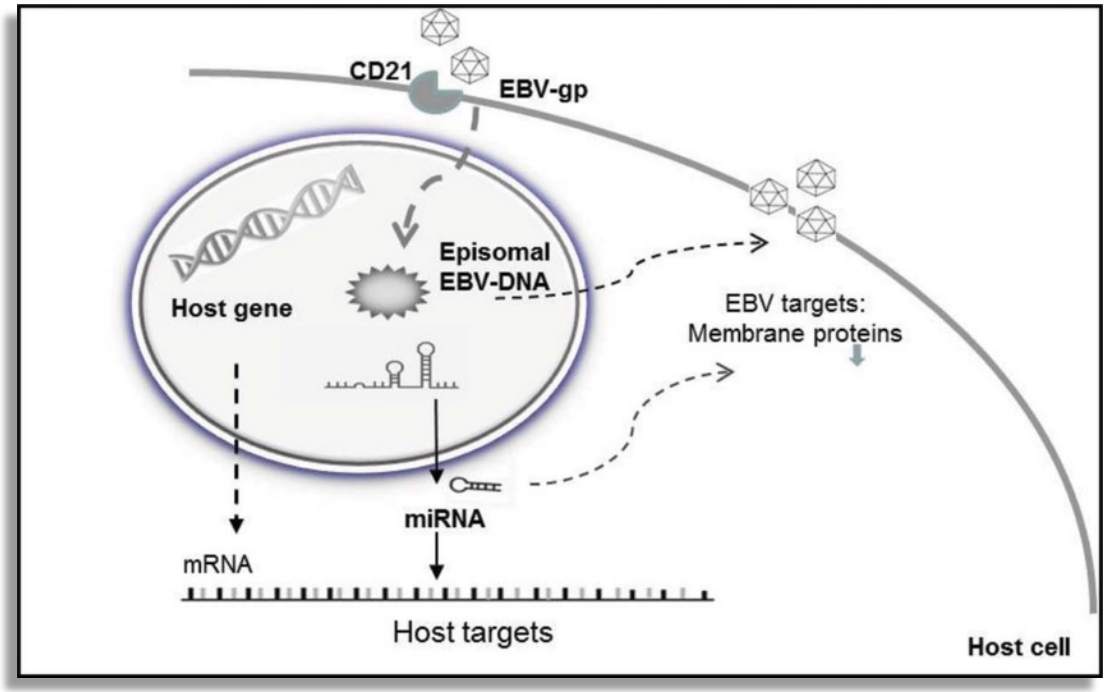
Konak Faktörlerini ve Sinyal Yollarını Hedefleyen Tedavi

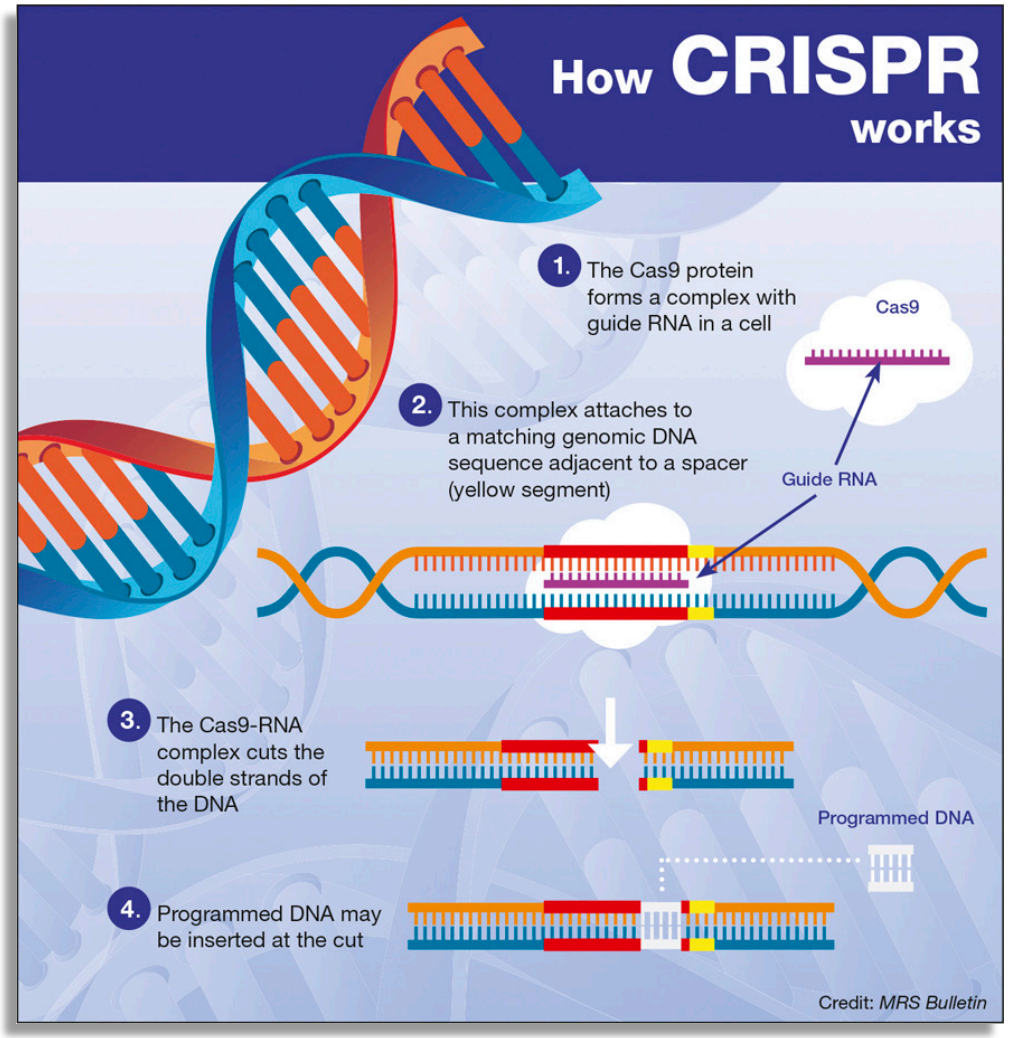
- ubiquitin/proteasome
- EBNA1 inh. P53
- FDA onaylı IXAZOMİB oral ilaç
- BORTEZOMIB 2011
- Bağlanma Zta proteini
- Burkitt lenfoma



T Ganguly; Targeted therapy for EBV-associated B-cell neoplasms. Mol. **Cancer Res. 2019**, 17, 839–844.
Shirley C.M.; Bortezomib induction of C/EBPbeta mediates Epstein-Barr virus lytic activation in Burkitt lymphoma. Blood 2011, 117,6297–6303

EBV ile İlişkili Lenfomalarda CRISPR-CAS9 Tedavi Uygulamaları





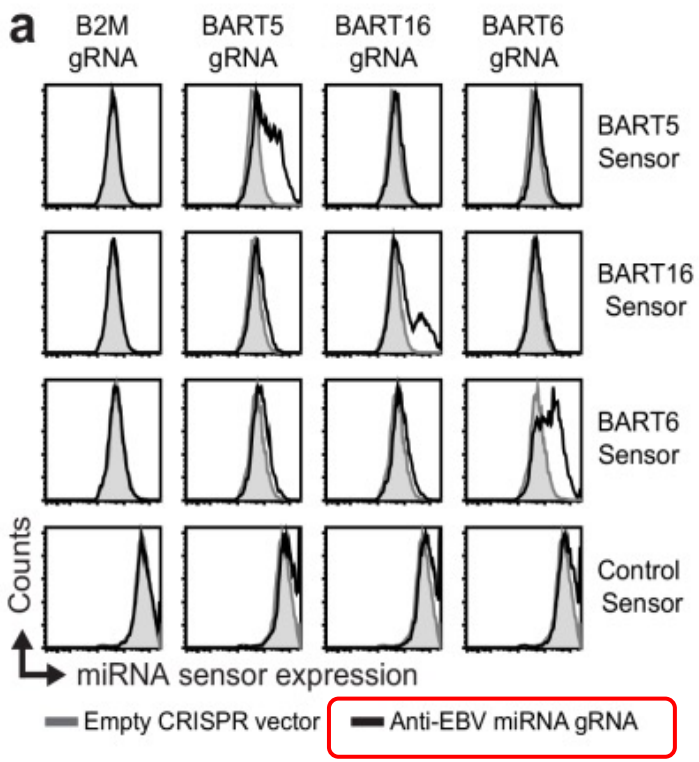
EBV ile İlişkili Lenfomalarda CRISPR-CAS9 Tedavi Uygulamaları

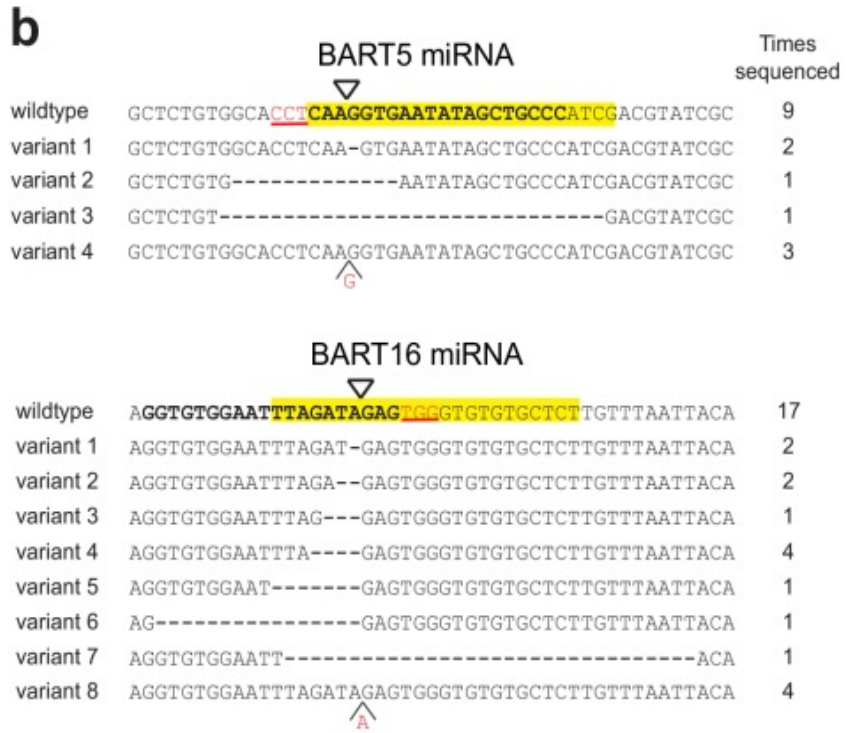
PLOS | PATHOGENS

RESEARCH ARTICLE

CRISPR/Cas9-Mediated Genome Editing of Herpesviruses Limits Productive and Latent Infections

Ferdy R. van Diemen[1], Elisabeth M. Kruse[1☯], Marjolein J. G. Hooykaas[1☯], Carlijn E. Bruggeling[1], Anita C. Schürch[1], Petra M. van Ham[1], Saskia M. Imhof[2], Monique Nijhuis[1] Emmanuel J. H. J. Wiertz[1‡], Robert Jan Lebbink[1‡*]





BamHI A rightward transcripts: BARTs

EBV ile İlişkili Lenfomalarda CRISPR-CAS9 Tedavi Uygulamaları

PLOS | PATHOGENS

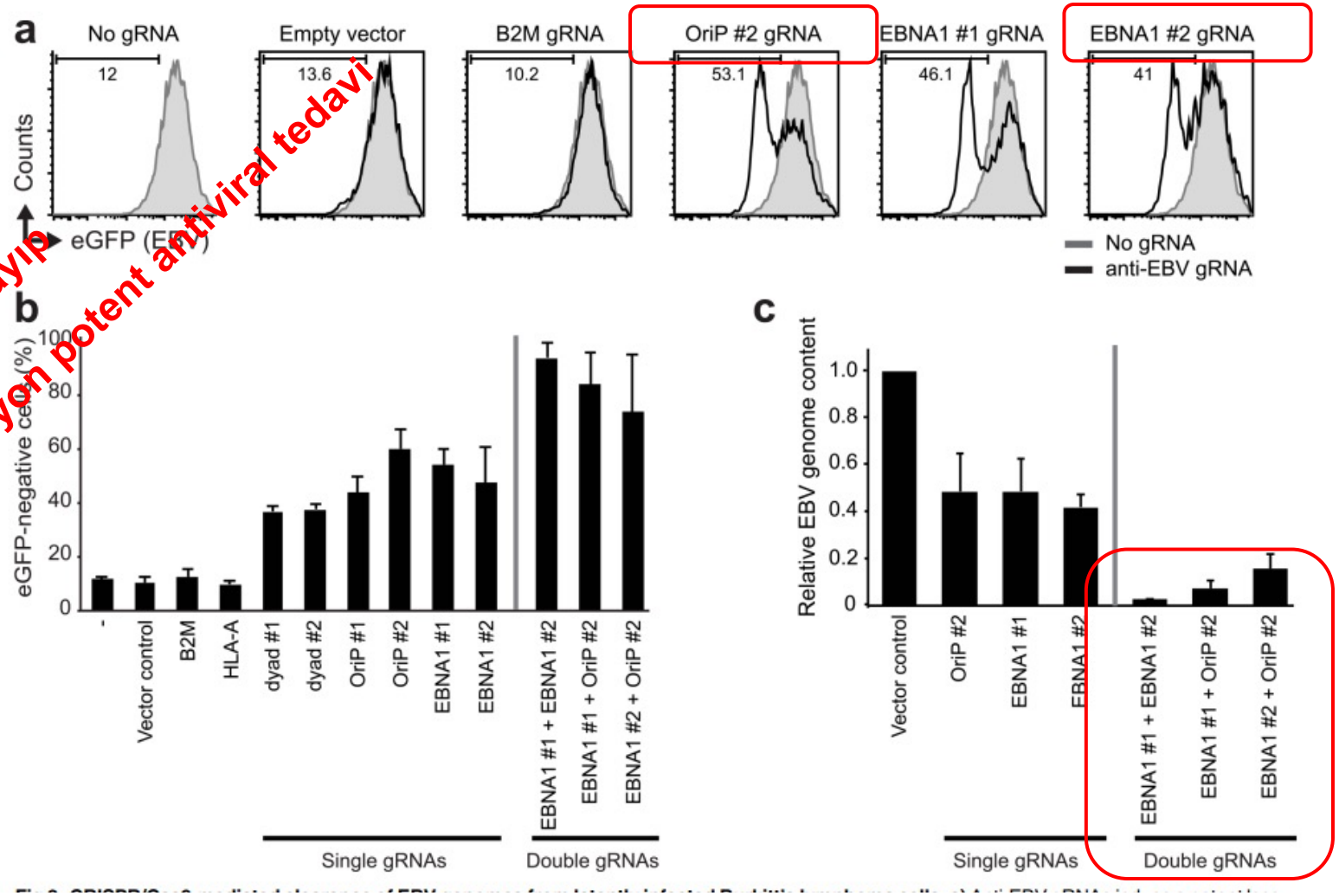
RESEARCH ARTICLE

CRISPR/Cas9-Mediated Genome Editing of Herpesviruses Limits Productive and Latent Infections

Ferdy R. van Diemen[1], Elisabeth M. Kruse[1☯], Marjolein J. G. Hooykaas[1☯], Carlijn E. Bruggeling[1], Anita C. Schürch[1], Petra M. van Ham[1], Saskia M. Imhof[2], Monique Nijhuis[1], Emmanuel J. H. J. Wiertz[1‡], Robert Jan Lebbink[1‡*]

EBV genom %95 kayıp

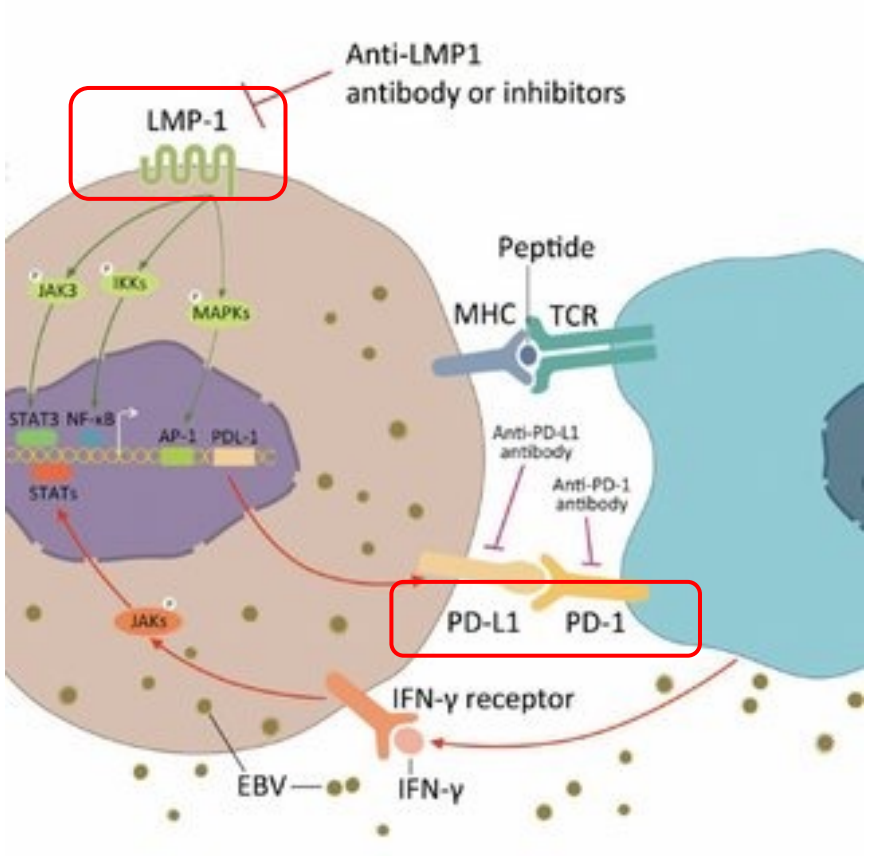
Latent enfeksiyon potent antiviral tedavi



Guide RNA:gRNA

EBV origin of replication: OriP

İmmünoterapi ve Hücre Tedavisi



EBV ile enfekte hücre yüzeyde LMP1 ve PD1/PDL1

Anti-PD1 Pembrolizumab

a. EBV pozitif tümör tedavisinde 7/15 (%47)

b. NKTCL (6/14, %44)

c. Primer mediastinal B-cell lenfoma (PBMCL) (25%)

Anti-CD20 Rituximab

a. Post-transplant lymphoproliferative disorders (PTLD) %32-79

Kim, S.J.; Comparison of ecacy of pembrolizumab between Epstein-Barr viruspositive and negative relapsed or refractory non-hodgkin lymphomas. Cancer Res. Treat.**2019**, 51, 611–622.
Kwong, Y.-L.; PD1 blockade with pembrolizumab is highly eective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. Blood **2017**, 129, 2437–2442.

EBV ile İlişkili Lenfomalar Tedavi Uygulamaları

Identifier	Year Started	Study Title	Phase
		PD-1/PD-L1	
NCT04058470	2019	Toripalimab in Combination with R-CHOP for Elderly Patients with Untreated Diffused B-Cell Lymphoma	I/II
NCT04181489	2019	Sintilimab in Combination with R-CHOP in Patients with Treatment-naive EBV-positive Diffuse Large B-cell Lymphoma (DLBCL), NOS	II
NCT04084626	2019	PD1 Antibody and Lenalidomide as a Treatment for EBV-associated Hemophagocytic Lymphohistiocytosis (HLH) or Chronic Active EBV Infection (CAEBV)	III
NCT03586024	2018	Pembrolizumab in Relapsed/Refractory Extranodal NK/T- Cell Lymphoma, Nasal Type and EBV-associated DLBCL	I/II
NCT03258567	2017	Nivolumab in EBV-Positive Lymphoproliferative Disorders and EBV-Positive Non-Hodgkin Lymphomas	II
NCT03038672	2017	Nivolumab with or without Varlilumab in Treating Patients with Relapsed/Refractory Aggressive B-cell Lymphomas	II
		T-cell Therapy	
NCT04156217	2019	EBV-TCR-T Cells for EBV Infection and EBV-Associated Post-Transplant Lymphoproliferative Disease After HSCT	I
NCT03789617	2018	Evaluate the Efficacy and Safety of EBV Induced Natural T Lymphocyte (EBViNT) Cell in Patients with Progressive EBV Positive Extranodal NK/T-cell Lymphoma Where Standard Treatments Have Failed	I/II
NCT03671850	2018	VT-EBV-N for Treatment of Severe in EBV Positive Extranodal NK/T Cell Lymphoma Patients	II
NCT03394365	2018	Tabelecleucel for Solid Organ or Allogeneic Hematopoietic Cell Transplant Participants with EBV-Associated Post-Transplant Lymphoproliferative Disease (EBV+ PTLD) After Failure of Rituximab or Rituximab and Chemotherapy	III
NCT03392142	2018	Tabelecleucel for Allogeneic Hematopoietic Cell Transplant Subjects with EBV-Associated Post-Transplant Lymphoproliferative Disease (EBV + PTLD) After Failure of Rituximab (MATCH)	III
NCT03044743	2017	PD-1 Knockout EBV CTLs for Advanced Stage EBV Associated Malignancies	I/II
		Modified-TCR	
NCT01956084	2013	Cytotoxic T Cells to Treat Relapsed EBV-positive Lymphoma (ALCI2)	I
		CAR-T Therapy	
NCT03233854	2017	CD19/CD22 Chimeric Antigen Receptor (CAR) T Cells in Adults with Recurrent/Refractory B-Cell Malignancies	I

EBV ile İlişkili Lenfomalar Tedavi Uygulamaları

Identifier	Year Started	Study Title	Phase
		PD-1/PD-L1	
		HDAC Inhibitors	
NCT03397706	2018	Dose Escalation & Expansion Study of Oral VRx-3996 & Valganciclovir in Subjects with Relapsed/Refractory EBV-Associated Lymphoid Malignancies	I/II
		Monoclonal Antibodies	
NCT02924402	2016	Study to Evaluate Safety and Tolerability of XmAb13676 in Patients with CD20-expressing Hematologic Malignancies	I
NCT02670616	2016	Study of Ibrutinib in Combination with Rituximab-CHOP in EBV-positive Diffuse Large B-cell Lymphoma	II

Yonggang Pei; Targeted Therapies for Epstein-Barr Virus-Associated Lymphomas. Cancers 2020, 12, 2565; doi:10.3390/cancers12092565

Antiviral Tedavi & Lenfoma

NEOPLASIA | NOVEMBER 21, 2006

A phase 1/2 trial of arginine butyrate and ganciclovir in patients with Epstein-Barr virus-associated lymphoid malignancies

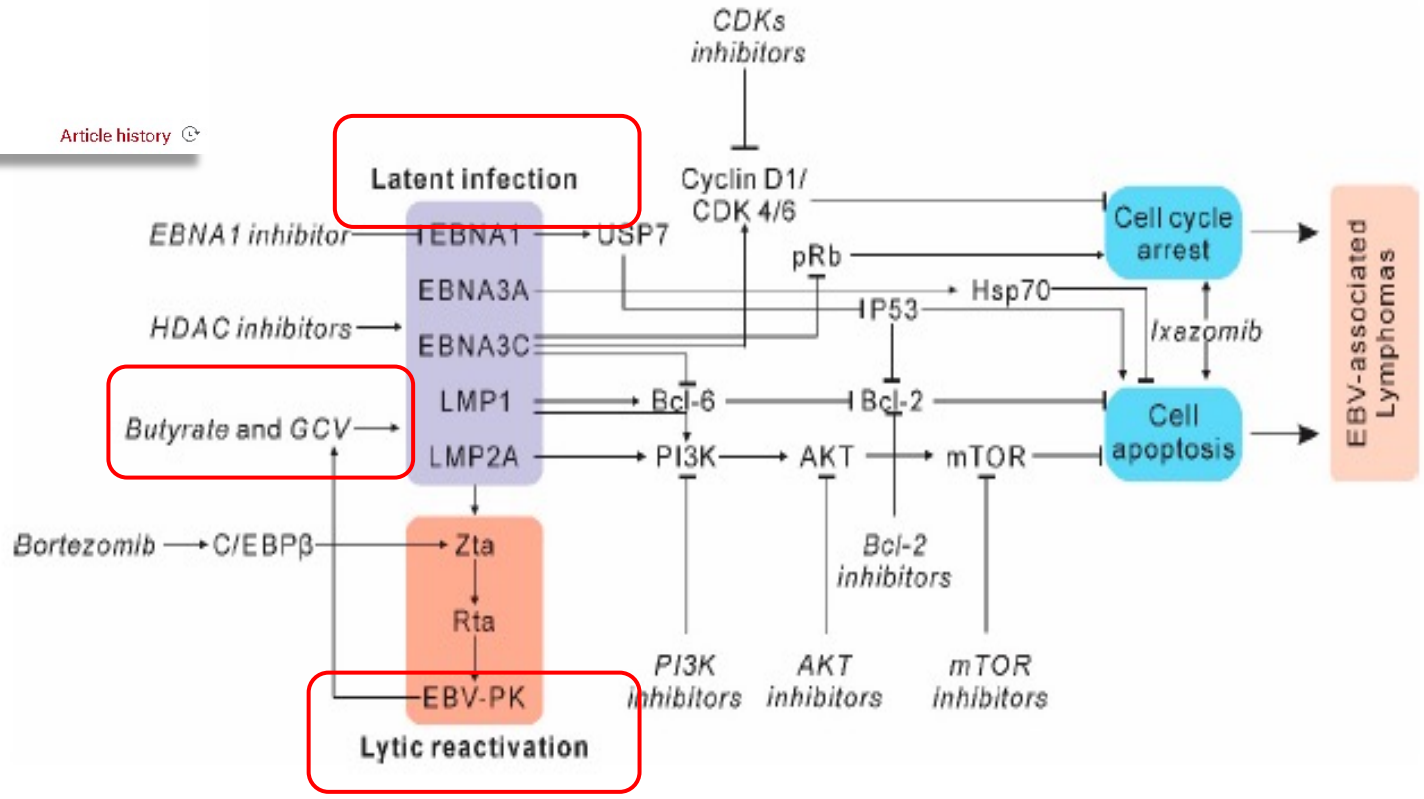
Clinical Trials & Observations

Susan P. Perrine, Olivier Hermine, Trudy Small, Felipe Suarez, Richard O'Reilly, Farid Boulad, Joyce Fingeroth, Melissa Askin, Arthur Levy, Steven J. Mentzer, Massimo Di Nicola, Alessandro M. Gianni, Christoph Klein, Steven Horwitz, Douglas V. Faller

Check for updates

Blood (2007) 109 (6): 2571-2578.

https://doi.org/10.1182/blood-2006-01-024703 Article history



Relaps ????

Refraktör ????

Antiviral Tedavi & Lenfoma

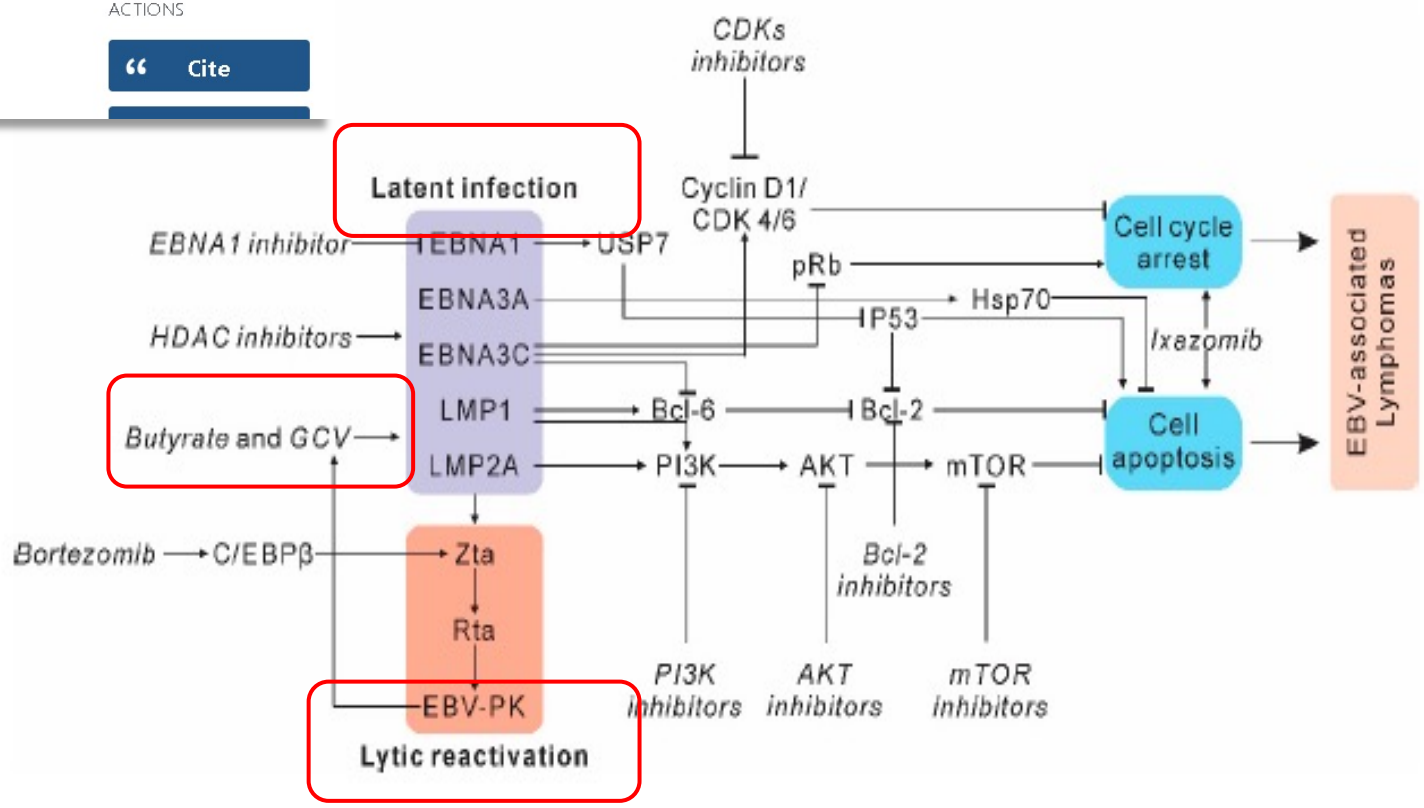
J Virol. 2010 May;84(9):4534-42. doi: 10.1128/JVI.02487-09. Epub 2010 Feb 24.

The Epstein-Barr virus (EBV)-encoded protein kinase, EBV-PK, but not the thymidine kinase (EBV-TK), is required for ganciclovir and acyclovir inhibition of lytic viral production

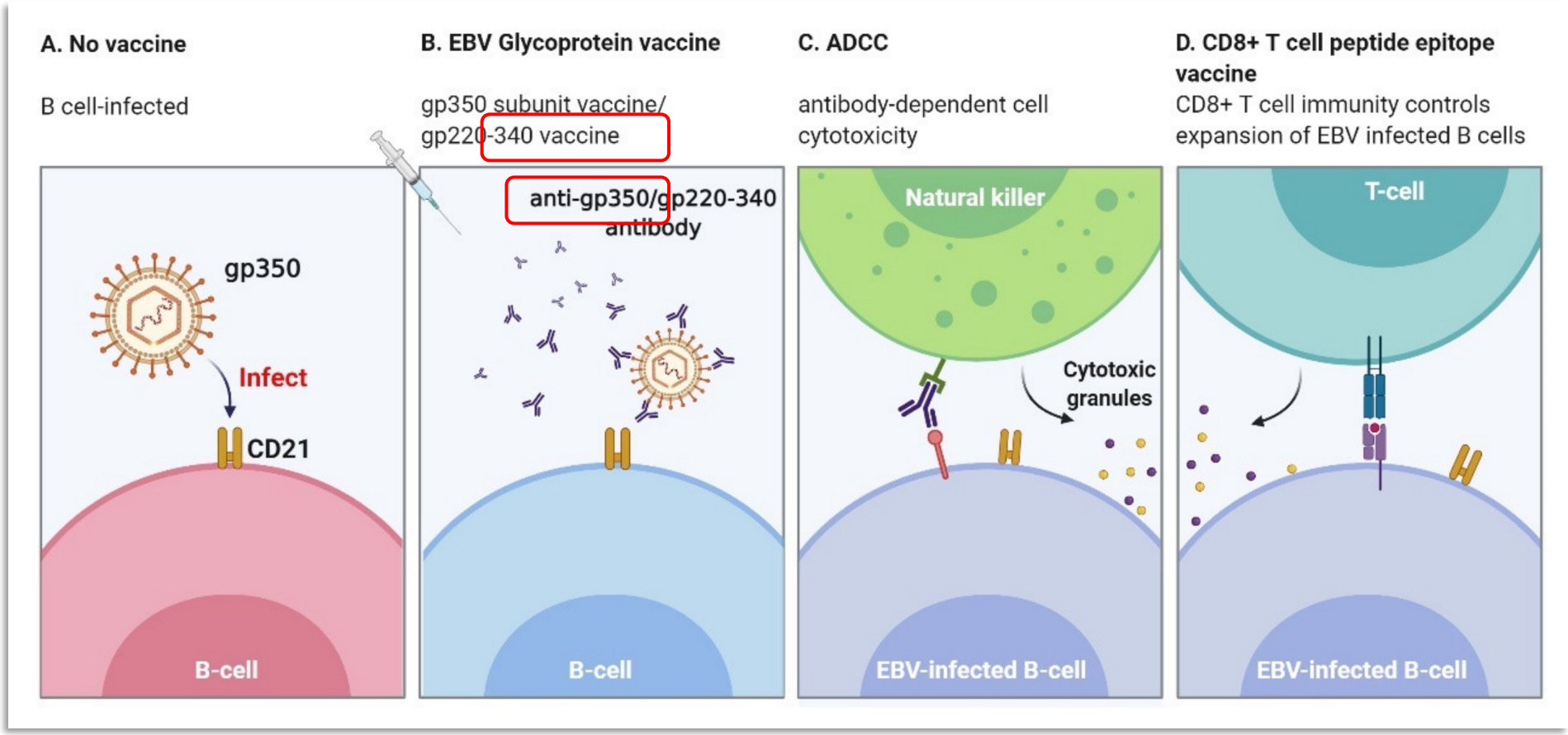
Qiao Meng [1], Stacy R Hagemeier, Joyce D Fingeroth, Edward Gershburg, Joseph S Pagano,

EBV thymidine kinase (EBV-TK)

EBV-protein kinase (EBV-PK) asiklovir ve gansiklovir direnç

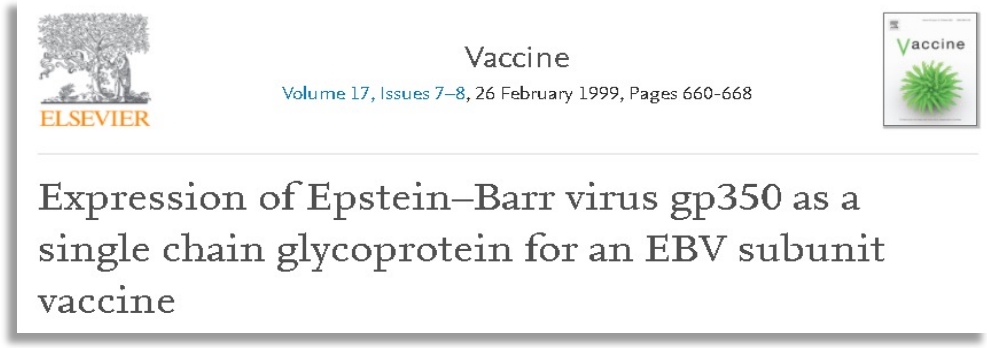


EBV & AŞI Uygulamaları

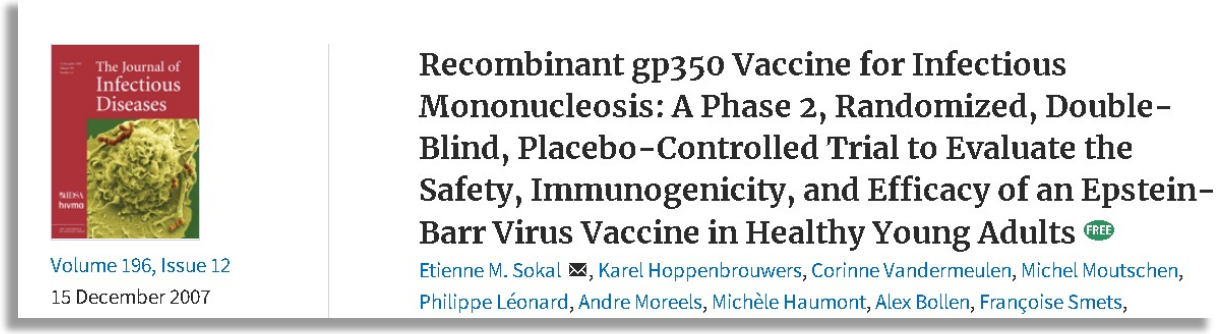


Epstein, M.A.; Protection of cottontop tamarins against Epstein-Barr virus-induced malignant lymphoma by a prototype subunit vaccine. **Nature 1985**, 318, 287–289
Cohen, J.I. Epstein-barr virus vaccines. **Clin. Transl. Immunol. 2015**, 4, e32.

EBV & AŞI Uygulamaları

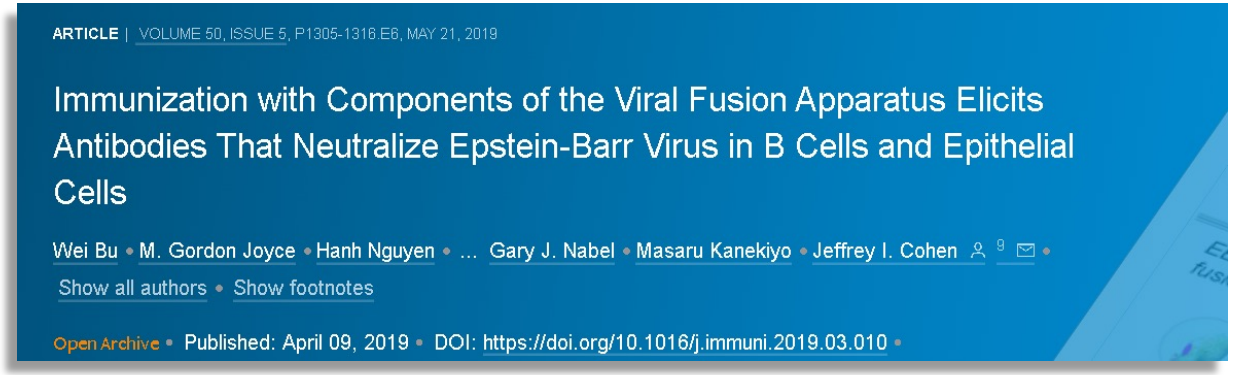


- ✓ Çin hamsteri yumurtalık hücre
- ✓ Rekombinant gp350 proteini aşısı
- ✓ Tavşanlarda yüksek nötralize edici EBV antikor titre



- ✓ Rekombinant EBV alt birim gp350
- ✓ Faz II klinik araştırma
- ✓ Asemptomatik EBV enfeksiyon başarısız

EBV & AŞI Uygulamaları



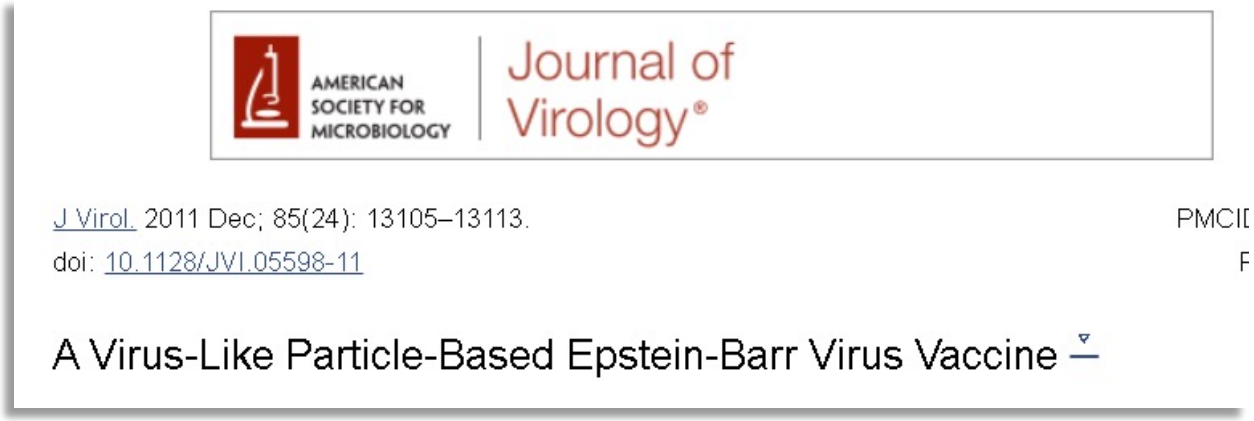
ARTICLE | VOLUME 50, ISSUE 5, P1305-1316.E6, MAY 21, 2019

Immunization with Components of the Viral Fusion Apparatus Elicits Antibodies That Neutralize Epstein-Barr Virus in B Cells and Epithelial Cells

Wei Bu • M. Gordon Joyce • Hanh Nguyen • ... Gary J. Nabel • Masaru Kanekiyo • Jeffrey I. Cohen • Show all authors • Show footnotes

Open Archive • Published: April 09, 2019 • DOI: https://doi.org/10.1016/j.immuni.2019.03.010 •

- ✓ EBV gp350 + gH/gL veya gH/gL/gp42 nanopartikülleri, güçlü nötralize edici antikor indüklediği
- ✓ B hücreleri ve epitel hücrelerinde EBV enfeksiyonunu nötralize ettiği
- ✓ Aşı antikorları, virüs aracılı hücre füzyonunu bloke



AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Virology®

J Virol. 2011 Dec; 85(24): 13105–13113. PMCI

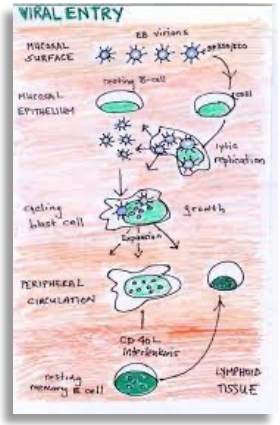
doi: 10.1128/JVI.05598-11 F

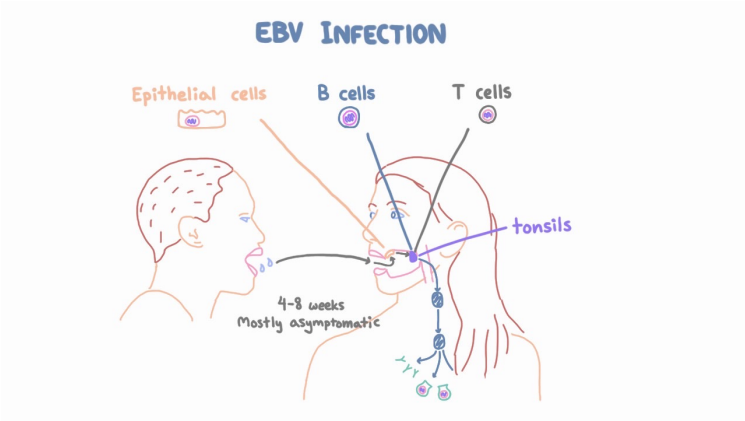
A Virus-Like Particle-Based Epstein-Barr Virus Vaccine

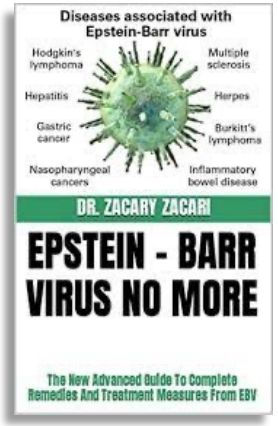
- ✓ Deney hayvan (murine) çalışması
- ✓ DNA free VLP aşısı
- ✓ Yüksek titre nötralize antikorlar

EBV & AŞI Uygulamaları

- ✓ Moderna Therapeutics
- ✓ Beş EBV glikoproteini kodlayan mRNA aşısı (gp350, gH/gL/gp42 ve gB)
- ✓ Enfeksiyöz mononükleoz oranını azaltabilir
- ✓ Klinik öncesi geliştirme aşamasında







EBV DNA Takipleri ve EBV'yi Hedefleyen Tedaviler:

Ne Kadar Yararlı?

Dr. R.Aytaç ÇETİNKAYA