Priming with DNMT inhibitors potentiates ICB in relapsed/refractory NK/T-cell lymphoma

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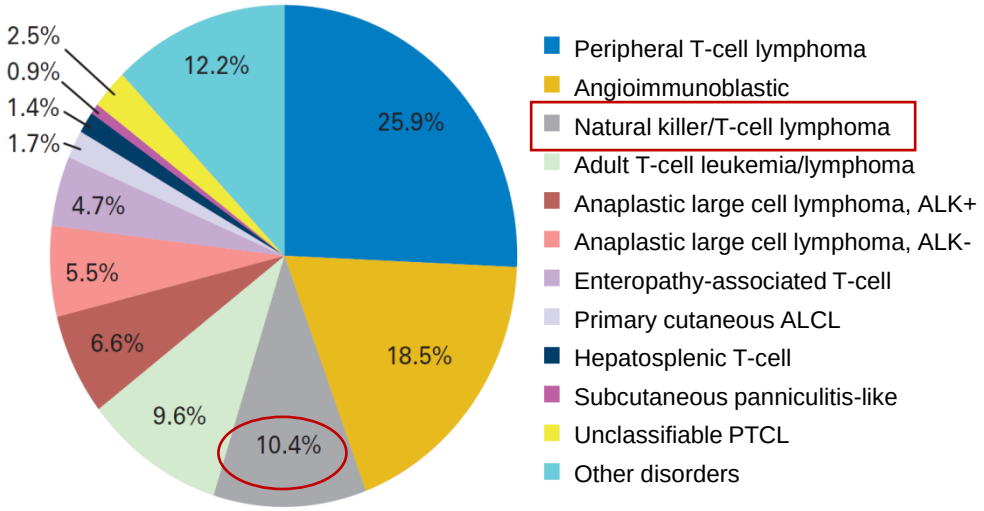
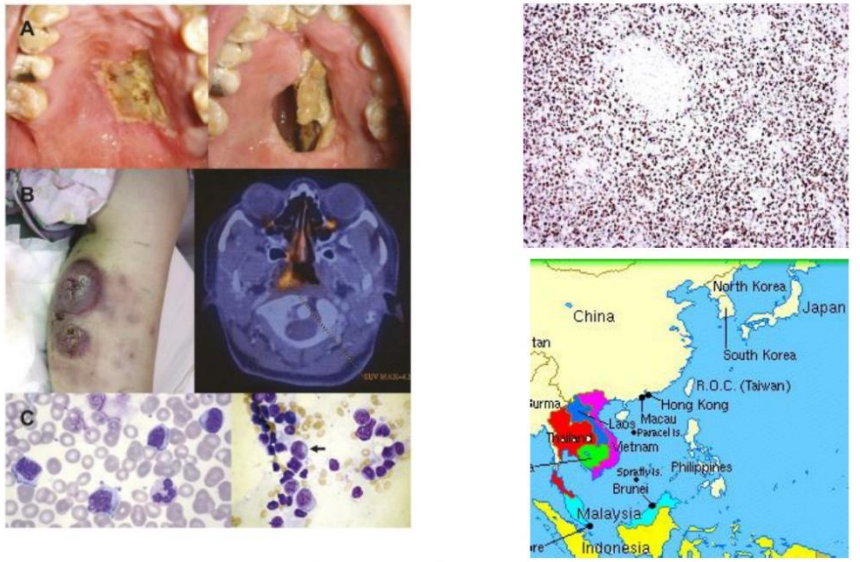
State Key Laboratory of Oncology in South China

2025.08.30@Singapore

Natural Killer/ T-cell lymphoma (NKTL)





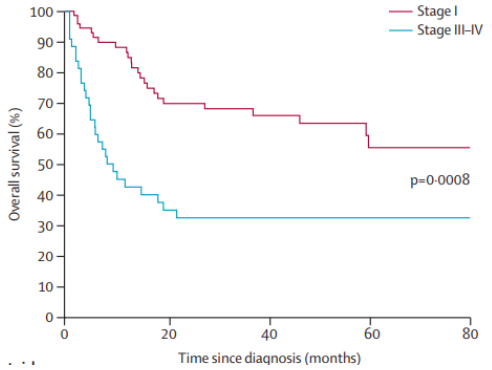
Tse E , and Kwong Y Blood 2013;121:4997-5005

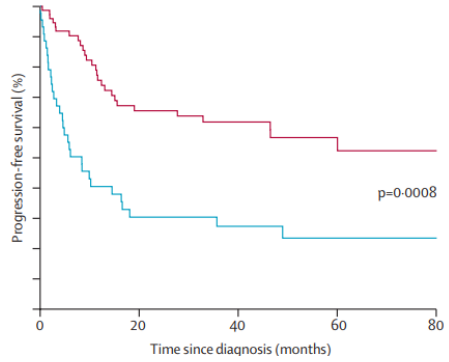
- More prevalent in Asians, and the native American population
- Very strong association with Epstein-Barr virus (EBV)
- Standard therapy including radiation+ chemotherapy (five year overall survival rate is 42%)

International T-cell Lymphoma Project; Delabie *et al.*, Blood 2010

Treatment (clinical challenge)

- Chemotherapeutic regimens
  - GDP (gemcitabine, dexamethasone, cisplatin)/L-asparaginase
  - GELOX (gemcitabine, L-asparaginase, and oxaliplatin)
  - P-Gemox (gemcitabine, oxaliplatin, pegaspargase)
  - SMILE (dexamethasone, methotrexate, ifosphamide, L-asparaginase, etoposide)
    - After 2 cycles: ORR and CR, 80% and 45%, respectively.
    - 1 year OS is about 50% (6 cycles)
- Early stage curable with chemo-radiotherapy
- Advance stage has 5 years OS less than 20%
- **No targeted therapy is currently available for R/R NKTL**.
- **No standard salvageable therapy for most R/R NKTL patients**





Vose, J., et al. J Clin Oncol, 2008. 26(25): p. 4124-30.
Huang, Huiqiang et al. . J Clin Oncol, 2023. 41(16):3032-3041.
Fox, Christopher P et al. The Lancet. Haematology, 2020. 7(4):e284-e294

1. Translating Lymphoma Genomics to New Therapeutics in NKTL

2. Deciphering Resistance Mechanisms of New Treatment in NKTL

Constitutive Activation of JAK-STAT Signaling Pathway in Natural Killer/T-Cell Lymphoma

Pathology International 2014; **64**: 263–266 doi:10.1111/pin.12166

Original Article

Activated Janus Kinase 3 expression not by activating mutations identified in Natural Killer/T-cell lymphoma

VOLUME 46 | NUMBER 2 | FEBRUARY 2014

Ying Guo,[1,2] Fumiko Arakawa,[1] Hiroaki Miyoshi,[1] Daisuke Niino,[1] Riko Kawano[1] and Koichi Ohshima[1]

[1]*Department of Pathology, School of Medicine, Kurume University, Kurume, Fukuoka, Japan and* [2]*Department of Pathology, State Key Laboratory of Cancer Biology, Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, China*

JAK3 hotspot Sanger seq in 36 NK/TCL

- WES of 1 NK/TCL
- WTS of 15 NK/TCL
- JAK and STAT hotspot Sanger in 40 NK/TCL

ARTICLE

Received 12 Jun 2014 | Accepted 2 Dec 2014 | Published 14 Jan 2015

nature COMMUNICATIONS

Activating mutations of *STAT5B* and *STAT3* in lymphomas derived from γδ-T or NK cells

Can Küç[1,*] Can Alka Lou Stau Francesc & Wing

- WES of 25 NK/TCL
- Targeted sequencing in 80 NK/TCL

nature genetics

VOLUME 47 | NUMBER 9 | SEPTEMBER 2015

Exome sequencing identifies somatic mutations of *DDX3X* in natural killer/T-cell lymphoma

Lu Jiang[1,20] Zhao-Hui Gu[1,20] Zi-Xun Yan[1,20] Xia Zhao[1,20] Yin-Yin Xie[1] Zi-Guan Zhang[1] Chun-Ming Pan[1] Yuan Hu[2] Jian-Da H Zhi-Gang Jing-Yi Sh Sai-Juan C

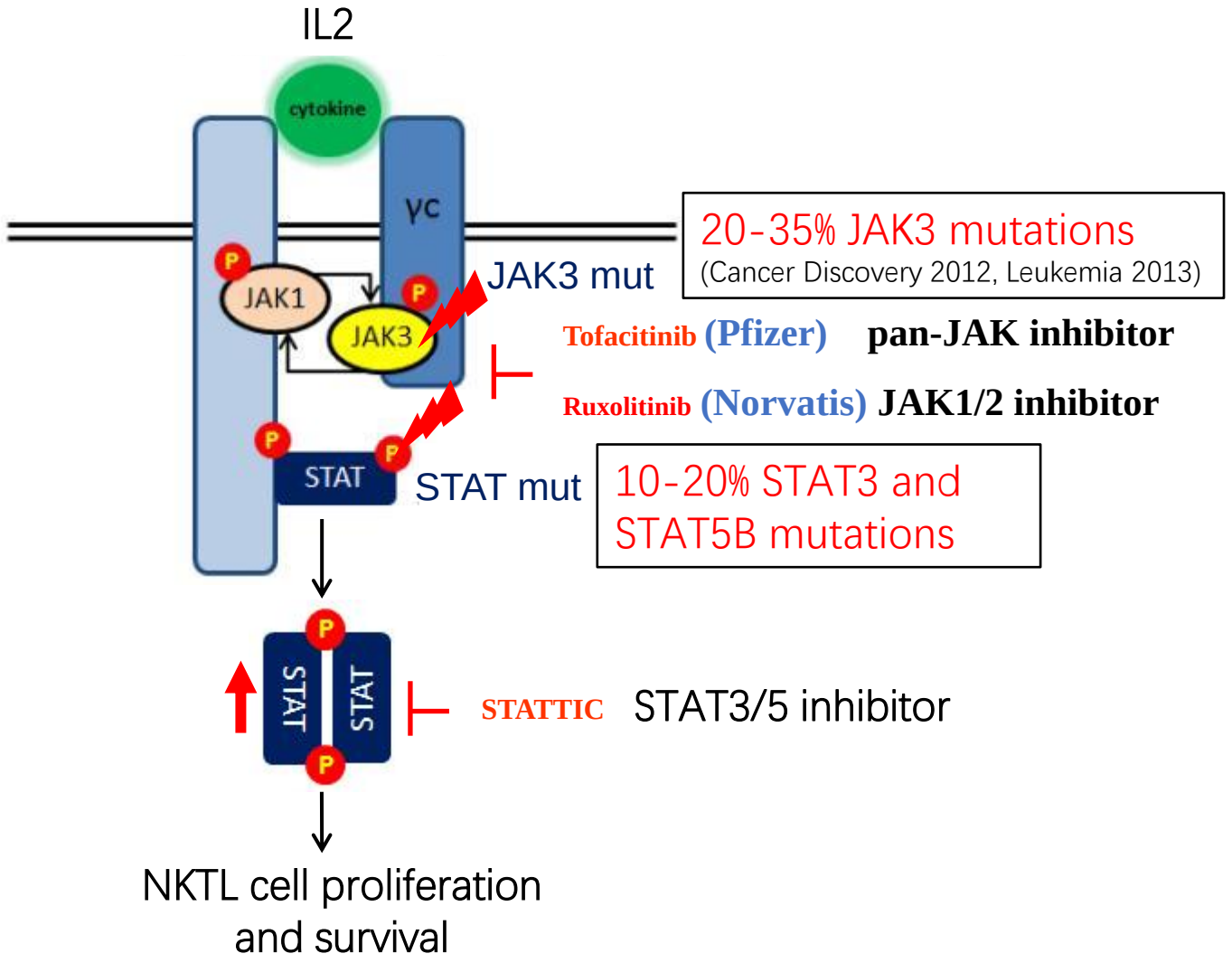
- WES of 9 NK/TCL
- Targeted sequencing in 21 NK/TCL
- *JAK3* hotspot Sanger in 17 NK/TCL

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2015

Genetic alterations of JAK/STAT cascade and histone modification in extranodal NK/T-cell lymphoma nasal type

Seungbok Lee[1,*], Ha Young Park[2,*], So Young Kang[3], Seok Jin Kim[4], Jinha Hwang[2], Seungho Lee[7], Soo Heon Kwak[5], Kyong Soo Park[5,6], Hae Yong Yoo[7], Won Seog Kim[4,*], Jong-Il Kim[1,2,8,*], Young Hyeh Ko[3,*]

JAK/STAT Pathway in NKTL: From Bench to Bedside



Targeting JAK3 activating mutants in NKTCL

Leukemia
https://doi.org/10.1038/s41375-017-0004-x

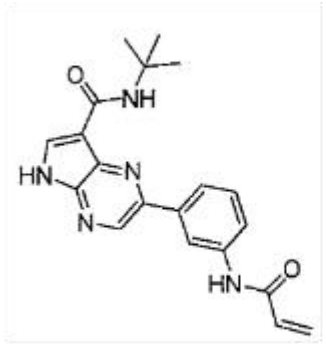
ARTICLE

Oncogenic activation of JAK3-STAT signaling confers clinical sensitivity to PRN371, a novel selective and potent JAK3 inhibitor, in natural killer/T-cell lymphoma

M.-L. Nairismägi[1] · M.E. Gerritsen[2] · Z.M. Li[3,4] · G.C. Wijaya[3,4] · B.K.H. Chia[1] · Y. Laurensia[1] · J.Q. Lim[1] · K.W. Yeoh[5] · X.S. Yao[3,4] · W.L. Pang[1] · A. Bisconte[2] · R.J. Hill[2] · J.M. Bradshaw[2] · D. Huang[1] · T.L.L. Song[1] · C.C.Y. Ng[3,4] · V. Rajasegaran[3,4] · T. Tang[6] · Q.Q. Tang[3,4] · X.J. Xia[7] · T.B. Kang[7] · B.T. Teh[3,4,8] · S.T. Lim[1,6,9] · C.K. Ong[1,10] · J. Tan[3,7]

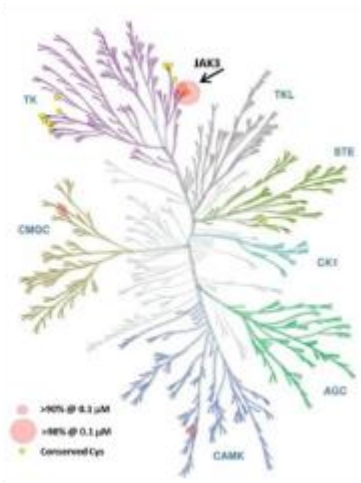
Received: 14 July 2017 / Revised: 17 November 2017 / Accepted: 4 December 2017

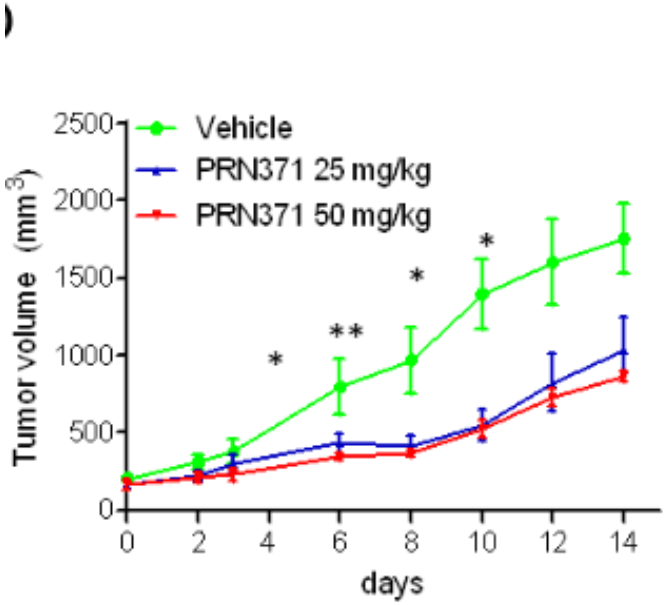
A



PRN371

B





PRINCIPIA BIOPHARMA

Oncogenic Activation of STAT3 in Natural Killer/T-Cell Lymphoma

> Blood. 2018 Sep 13;132(11):1146-1158. doi: 10.1182/blood-2018-01-829424. Epub 2018 Jul 27.

Oncogenic activation of the STAT3 pathway drives PD-

***STAT3* (22.0%)**

Multicenter Study > Cancer Cell. 2020 Mar 16;37(3):403-419.e6. doi: 10.1016/j.ccell.2020.02.005.

Genomic and Transcriptomic Characterization of Natural Killer T Cell Lymphoma

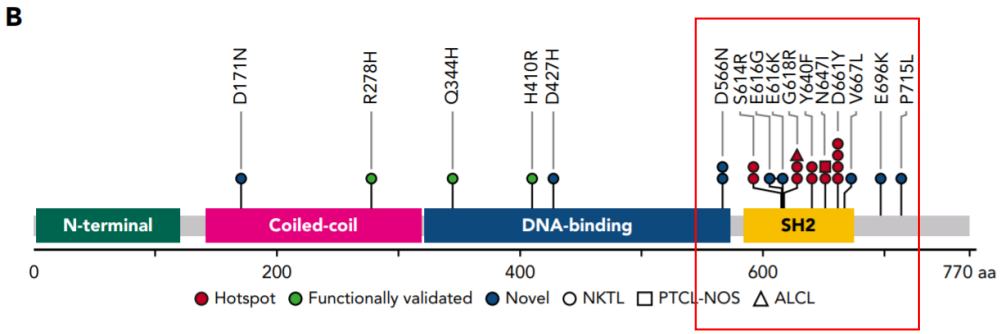
***STAT3* (21.1%)**

Multicenter Study > Nat Genet. 2015 Sep;47(9):1061-6. doi: 10.1038/ng.3358. Epub 2015 Jul 20.

Exome sequencing identifies somatic mutations of DDX3X in natural killer/T-cell lymphoma

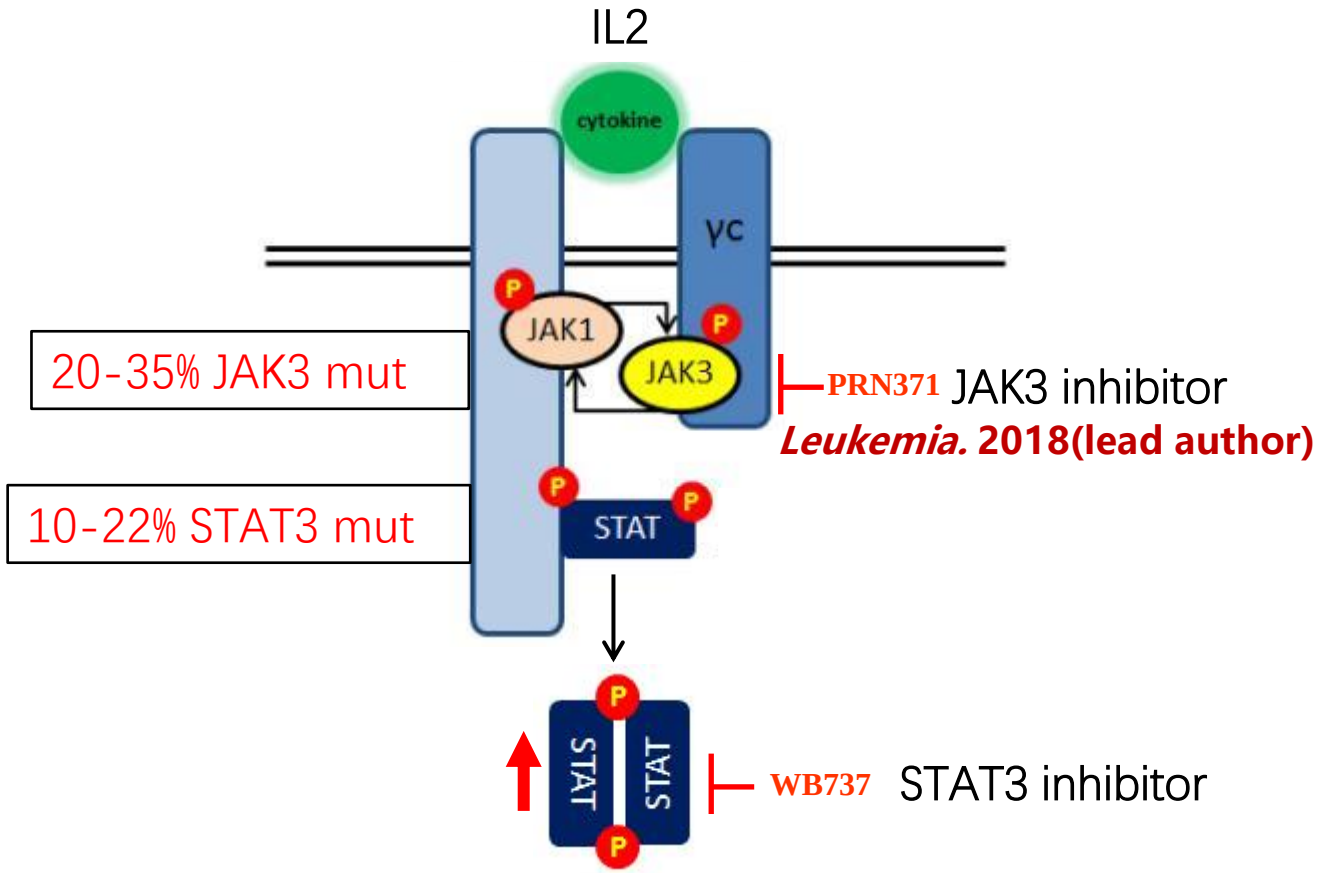
***STAT3* (10.5%)**

Gain of function mutations



Küçük, Can et al. Nature communications.2015

Targeting JAK3/STAT Signaling in R/R NKTL



***Medcomm.* 2023 (lead author)**

NMPA approved for clinical trial

1. Translating Lymphoma Genomics to New Therapeutics in NKTL

2. **Deciphering Resistance Mechanisms of New Treatment in NKTL**

Background： New Therapeutics in R/R NKTL

SUGGESTED TREATMENT REGIMENS[a]

RELAPSED/REFRACTORY THERAPY

- Clinical trial

Preferred regimens[g,h]
- Pembrolizumab
- Nivolumab

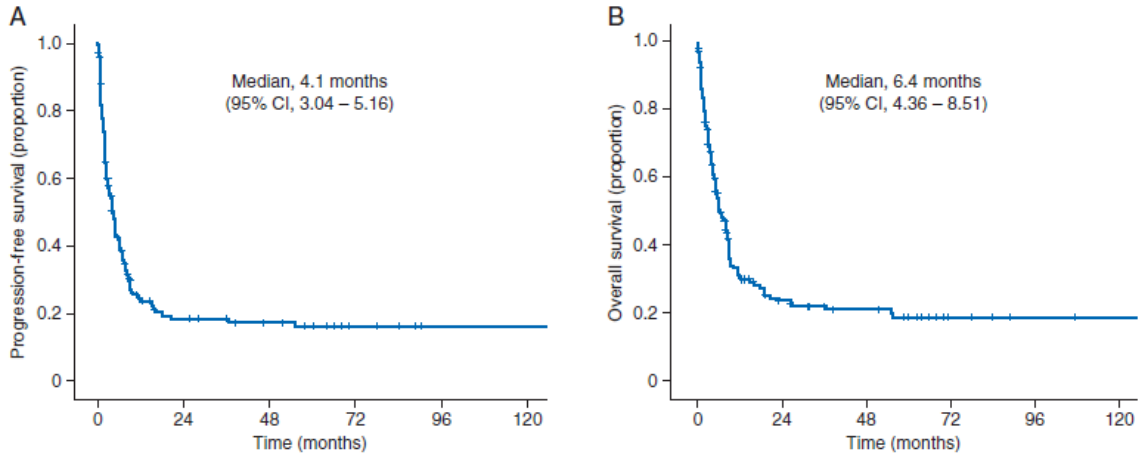
Other recommended regimens (alphabetical order)
- Single agents
  - Brentuximab vedotin for CD30+ disease
  - Pralatrexate
- Combination regimens (alphabetical order)
  - Asparaginase-based combination chemotherapy regimen (ENKL-B 1 of 3) not used in first-line therapy
  - DHA (dexamethasone and cytarabine) + platinum (cisplatin or oxaliplatin)
  - DHA (dexamethasone and cytarabine) + carboplatin (category 2B)
  - ESHAP (etoposide, methylprednisolone, and cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, and cisplatin)
  - GemOx (gemcitabine and oxaliplatin)
  - ICE (ifosfamide, carboplatin, and etoposide)

Useful in certain circumstances
- RT[f]
- Belinostat[i]
- Romidepsin[i]

NCCN guideline：

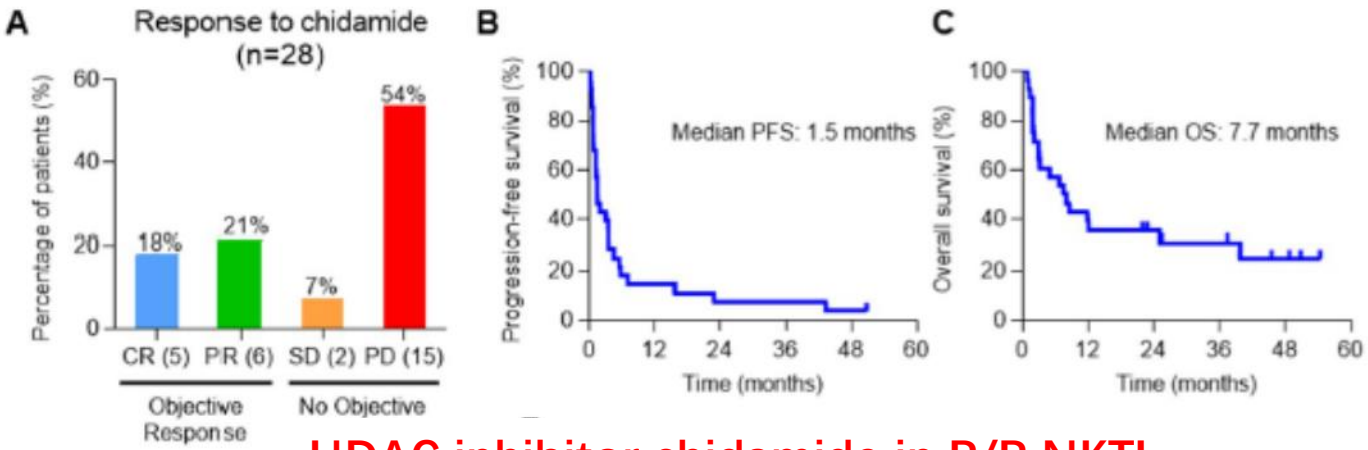
Second line treatment for R/R NKTL:

Chemotherapy/Epigenetic drug/ICB



Second line chemotherapy in R/R NKTL

Ann Oncol 2017; **28**(9): 2199-205.



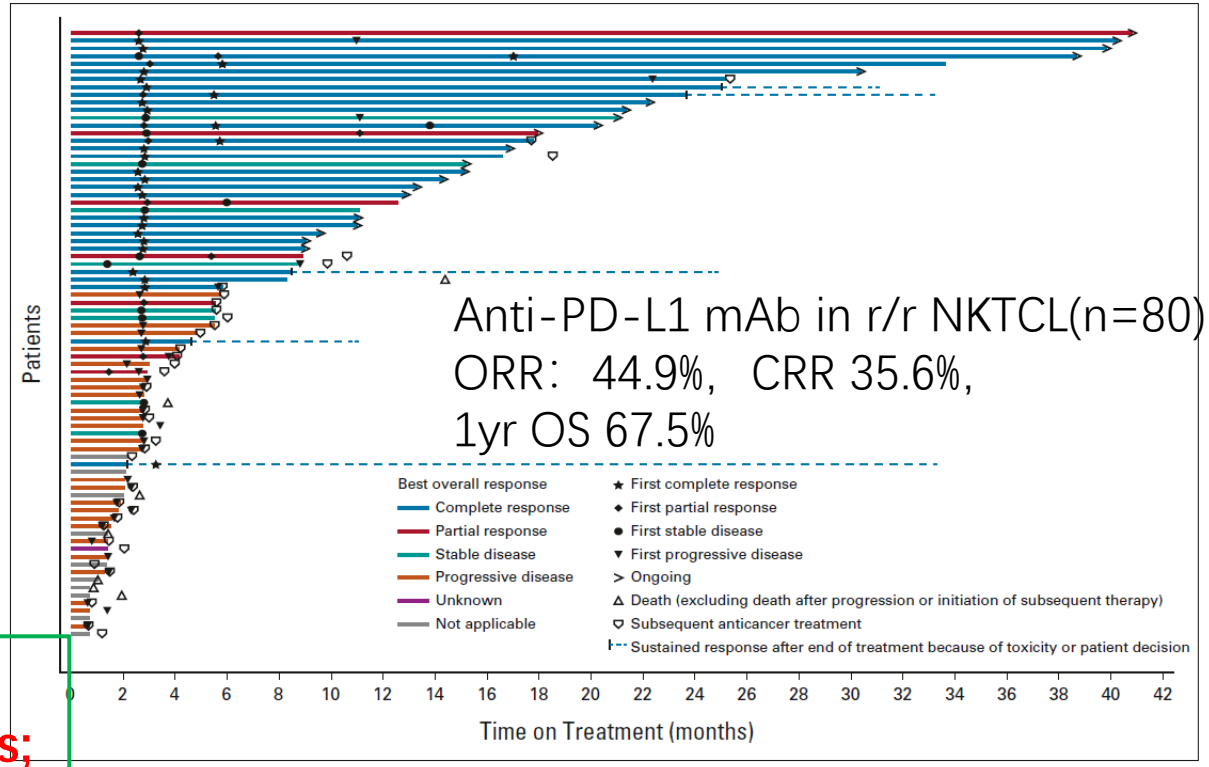
HDAC inhibitor chidamide in R/R NKTL

Chen *et al. Clinical Epigenetics* (2023) *15:19*

Background： ICB in R/R NKTL

Immunotherapy represented by anti-PD-1 monoclonal antibody(PD-1 mAb) has shown unique efficacy in R/R NKTCL：

时间	作者	药物	例数	ORR(%)	CRR（%）	PFS	OS
2020	Shi YK[68]	Geptanolimab	22	40.9	NA	NA	NA
2020	Kim SJ[69]	Avelumab	21	38.0	24.0	2.7 月(中位 PFS)	NA
2021	Tao R[70]	Sintilimab	28	75	21.4	4.1 月(中位 DOR)	78.6%(2 年)
2023	Huang H[71]	Sugelimab	80	44.9	35.9	82.5%(1 年 DOR)	67.5%(1 年)
2023	Bachy E[73]	Tislelizumab	22	31.8	18.2	2.7 月(中位 PFS)	中位 8.8 月
2023	Lee JY*[72]	Pembrolizumab	59	40.7	28.8	21.5%（2 年）	28.5%（2 年）



J Clin Oncol 41:3032-3041.

Challenges in ICB：

- **Response to anti-PD-1/L1 varies in different trials;**
- **Intrinsic and acquired resistance**
- **Combined ICB therapy?**

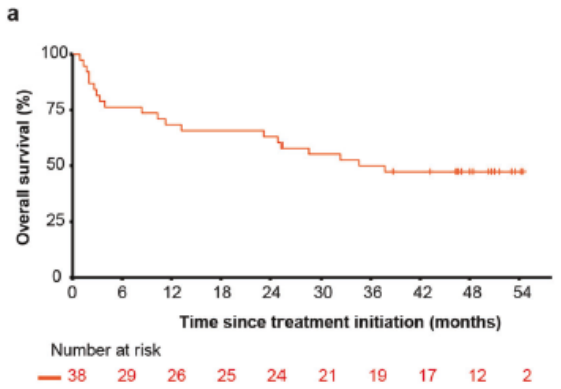
Background：Epigenetic drug + PD-1 in NKTL

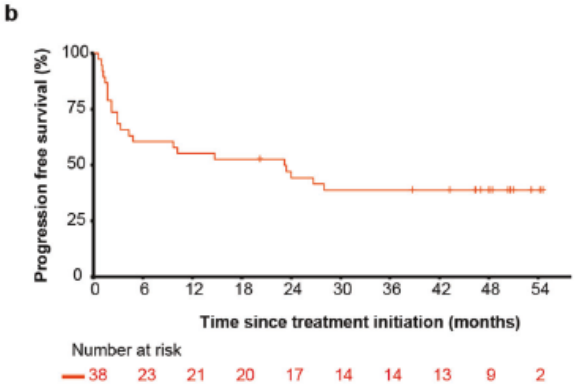
Signal Transduction and Targeted Therapy www.nature.com/sigtrans

ARTICLE OPEN

Sintilimab (anti-PD-1 antibody) plus chidamide (histone deacetylase inhibitor) in relapsed or refractory extranodal natural killer T-cell lymphoma (SCENT): a phase Ib/II study

Yan Gao[1,2], Haixia He[3], Xueping Li[4], Liling Zhang[5], Wei Xu[6], Ru Feng[7], Wenyu Li[8], Yin Xiao[5], Xinxiu Liu[5], Yu Chen[9], Xiaoxiao Wang[1,2], Bing Bai[1,2], Huijing Wu[10], Qingqing Cai[1,2], Zhiming Li[1,2], Jibin Li[11], Suxia Lin[12], Yanxia He[1,2], Liqin Ping[1,2], Cheng Huang[1,2], Jiaying Mao[1,2], Xiujin Chen[1,2], Baitian Zhao[11] and Huiqiang Huang[1,2]





Sintilimab plus chidamide show encouraging CR rate and DOR in PD-1 treatment naïve RR-NKTCL. However, there are still **50% patients were refractory/recurrence.**

Urgent need to explore new combination therapy to overcome the immunotherapy-R/R NKTL

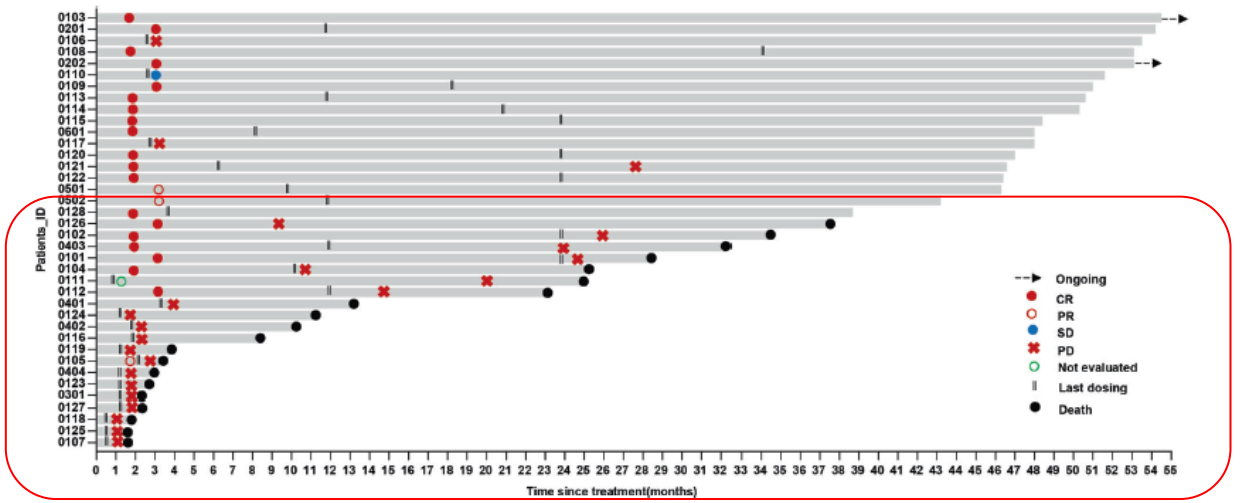
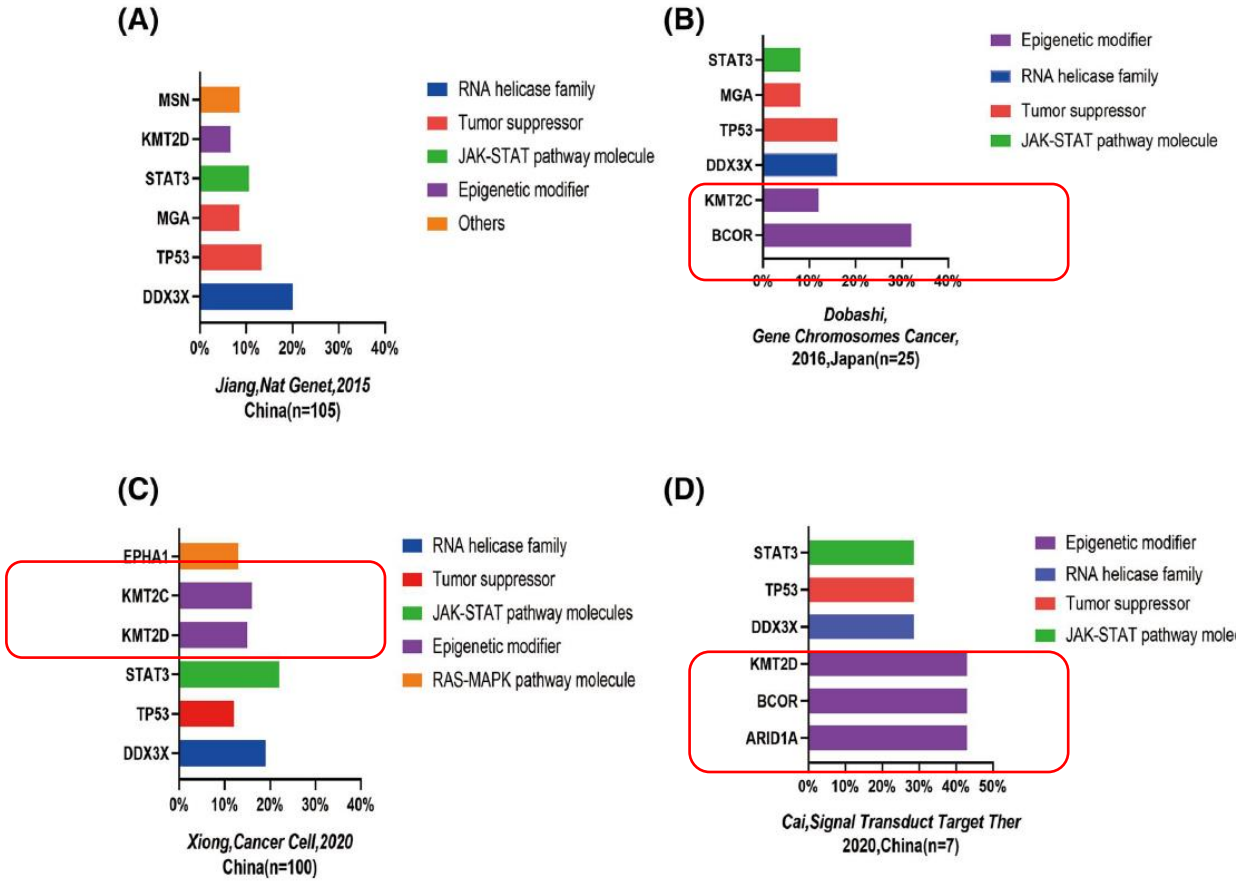
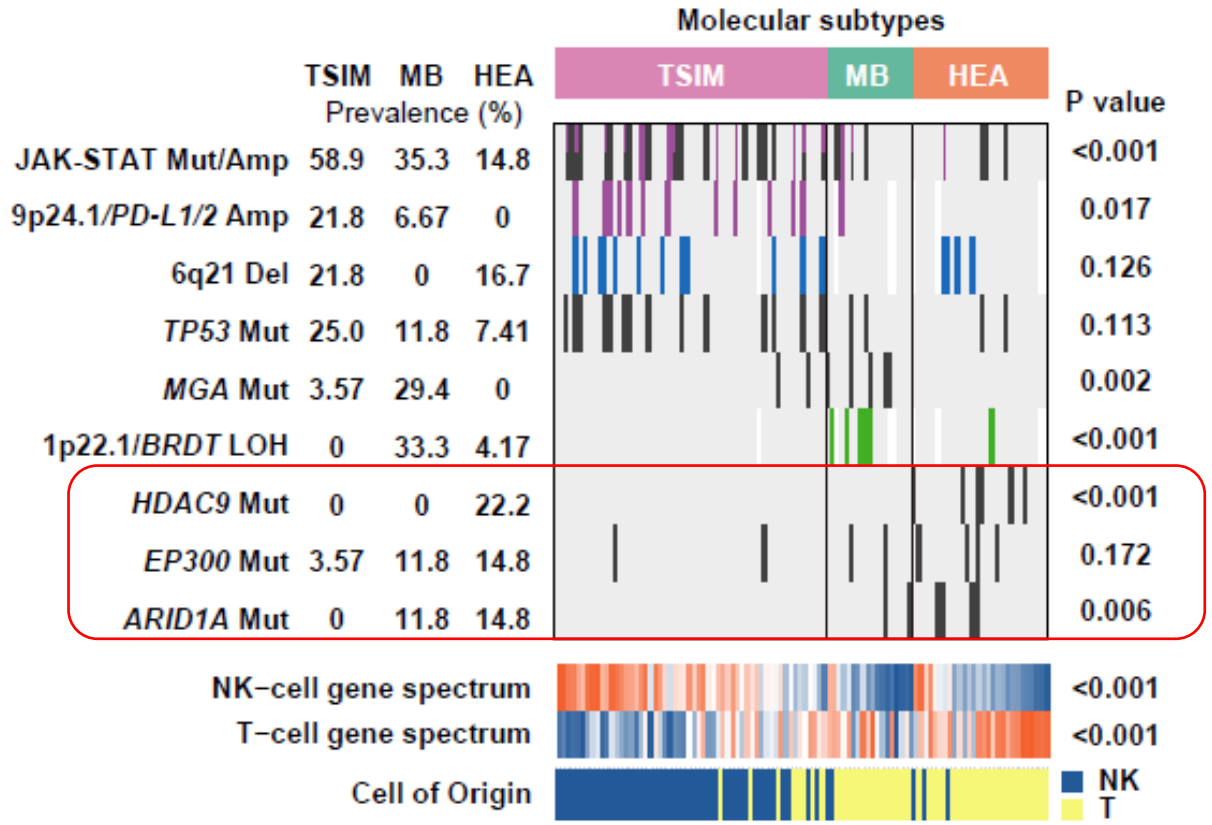


Fig. 3 Swimmer plots showing timing of response, as assessed by investigators (as-treated population, N = 38). Bars represent individual patients

Gao Y, STTT 2024

Background：Epigenetics & NKTL



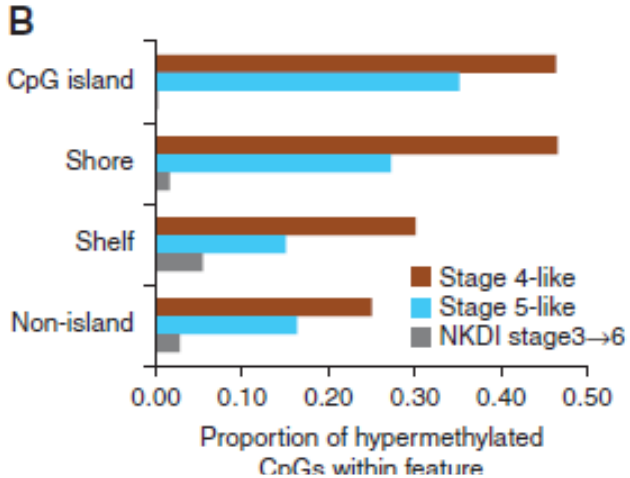


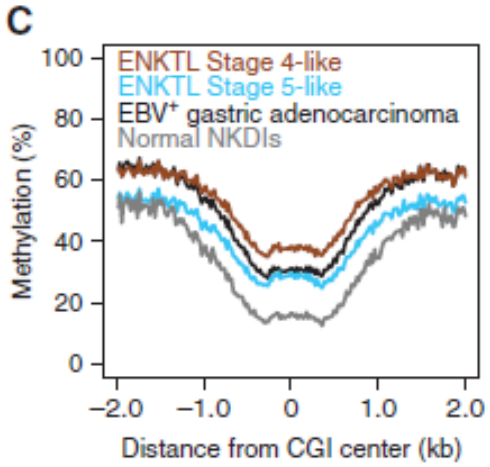
Epigenetic aberrations are critical as genetic abnormalities in NKTCL.

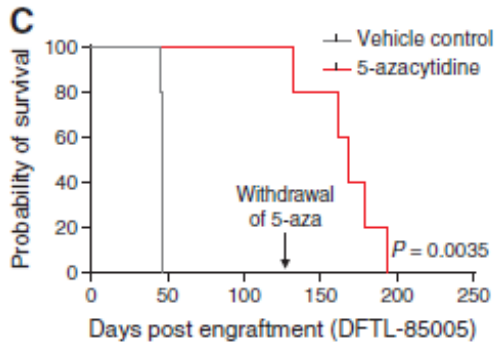
Hematological Oncology. 2023;41:221–229.

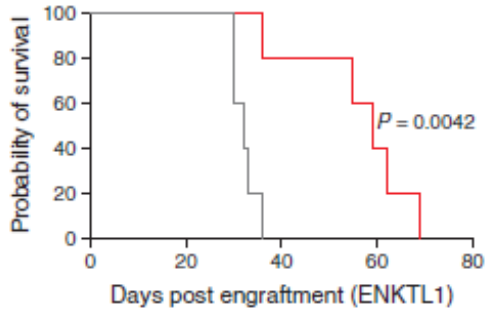
Xiong et al.,Cancer Cell （2020）

Background： DNA hypermethylation in NKTL



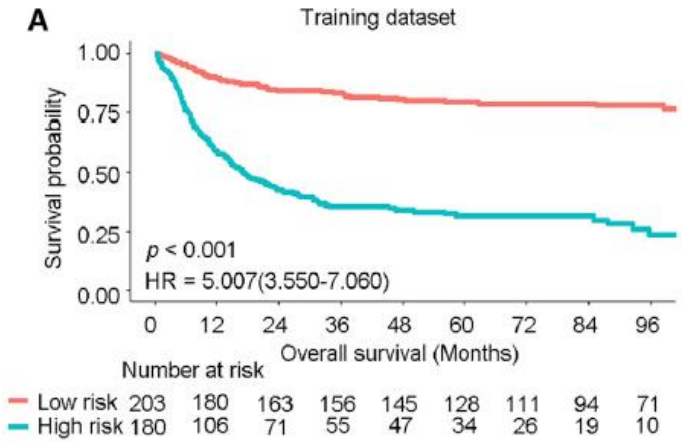


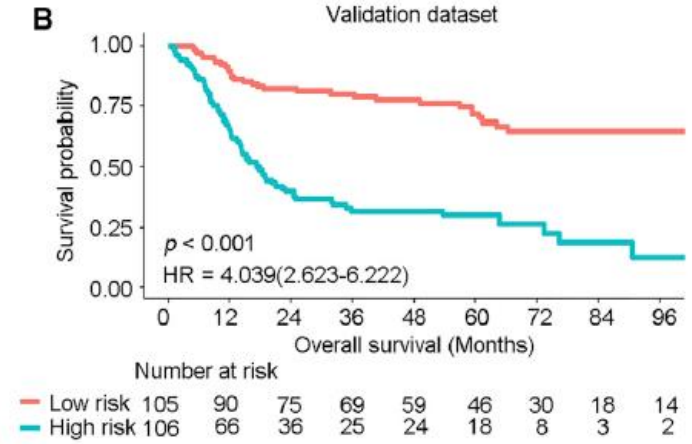




DNA hypermethylation in NKTL;
5-aza(DNMTi) significantly prolongs survival rate in PDX models。

Blood Cancer Discov 2022; 3(2): 154–69.

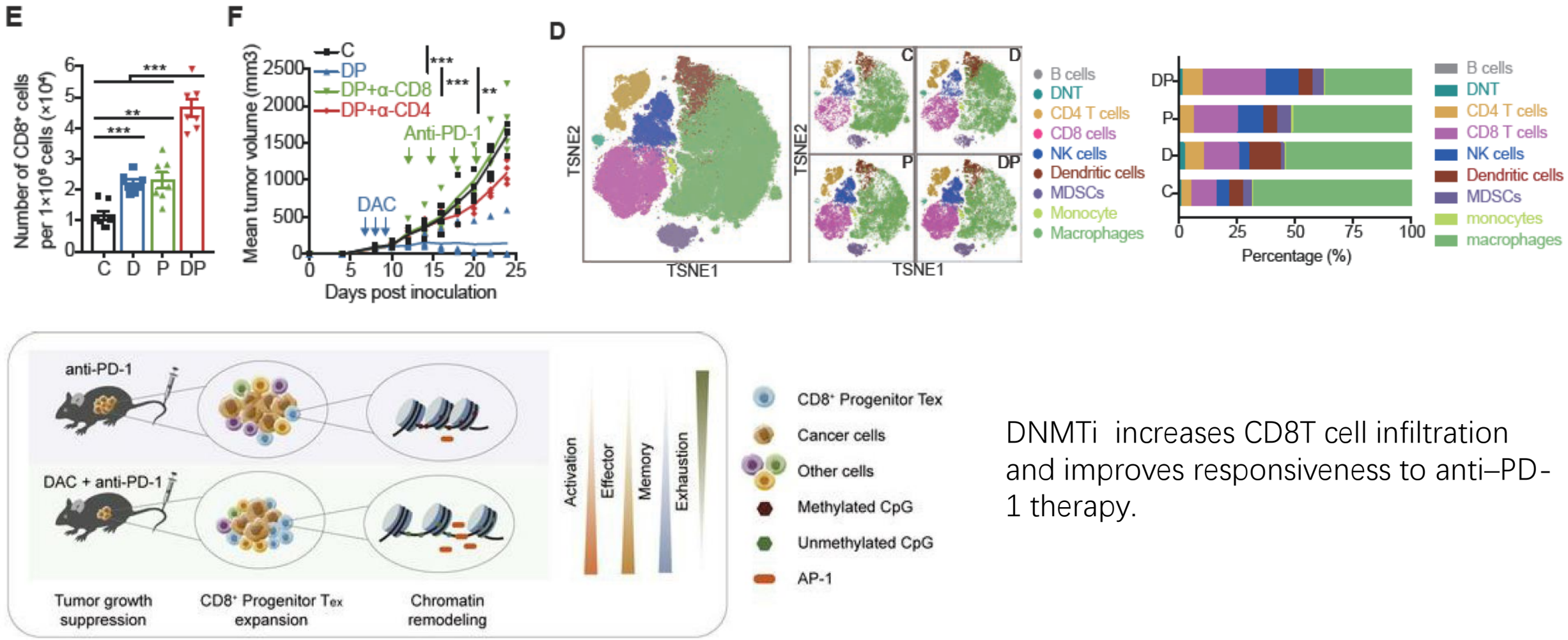




Methylation of ctDNA is correlated with poor prognosis in patients with NKTCL

Cell Reports Medicine 4, 100859, February 21, 2023

Background：DNMTi + PD-1



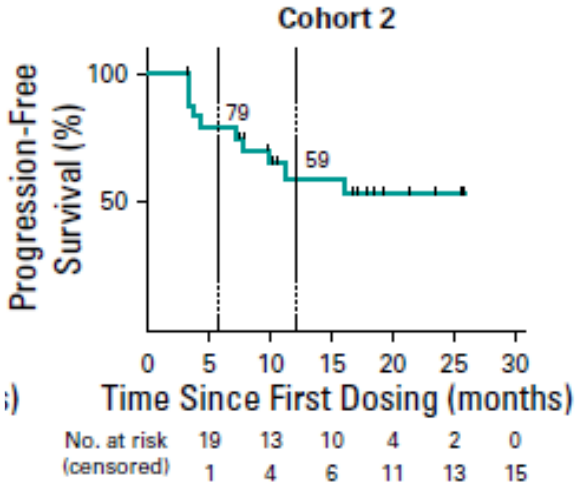
DNMTi increases CD8T cell infiltration and improves responsiveness to anti–PD-1 therapy.

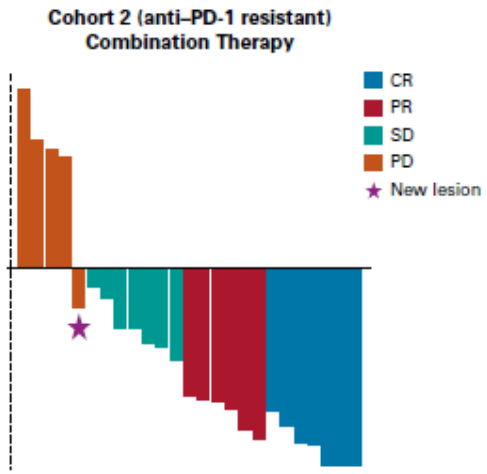
J Clin Invest. 2023 Apr 3;133(7):e165673.

Background：Epigenetic + PD-1 in HL

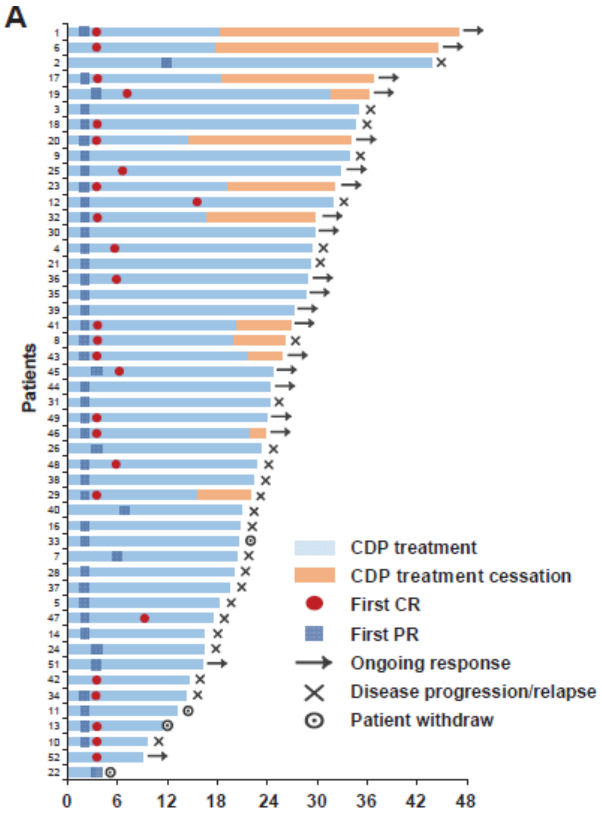
TABLE 2. Rates of Objective Response and Complete Remission

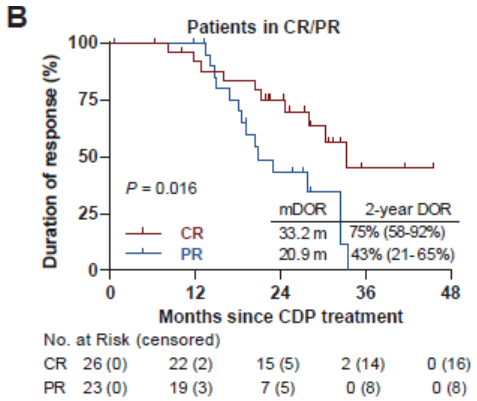
Variable	Cohort 1 (anti–PD-1 naïve) Camrelizumab Monotherapy	Cohort 1 (anti–PD-1 naïve) Decitabine + Camrelizumab Combination	Cohort 2 (anti–PD-1 resistant) Decitabine + Camrelizumab Combination
All patients			
Patient No.	19	42	25
ORR (95% CI)	90 (67 to 99)	95 (95 to 99)	52 (31 to 72)
CR rate (95% CI)	32 (13 to 57)	71 (55 to 84)	28 (12 to 49)

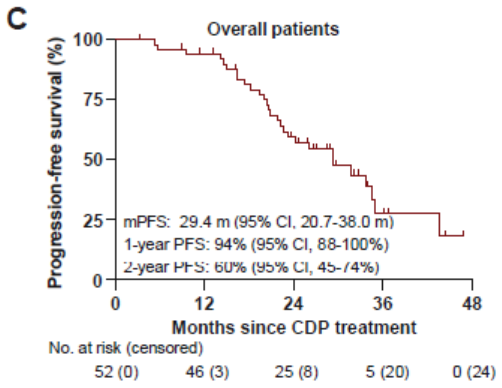




PD-1-R/R HL patients, DAC+PD1 achieves ORR 52%。(DP therapy)
（J Clin Oncol. 2019 Jun 10;37(17):1479-1489. ）







DP therapy-R/R HL patients（**Chidamide+DAC**+PD1）achieves ORR to 94%。
（ Blood. 2024 Oct 31;144(18):1936-1950.）

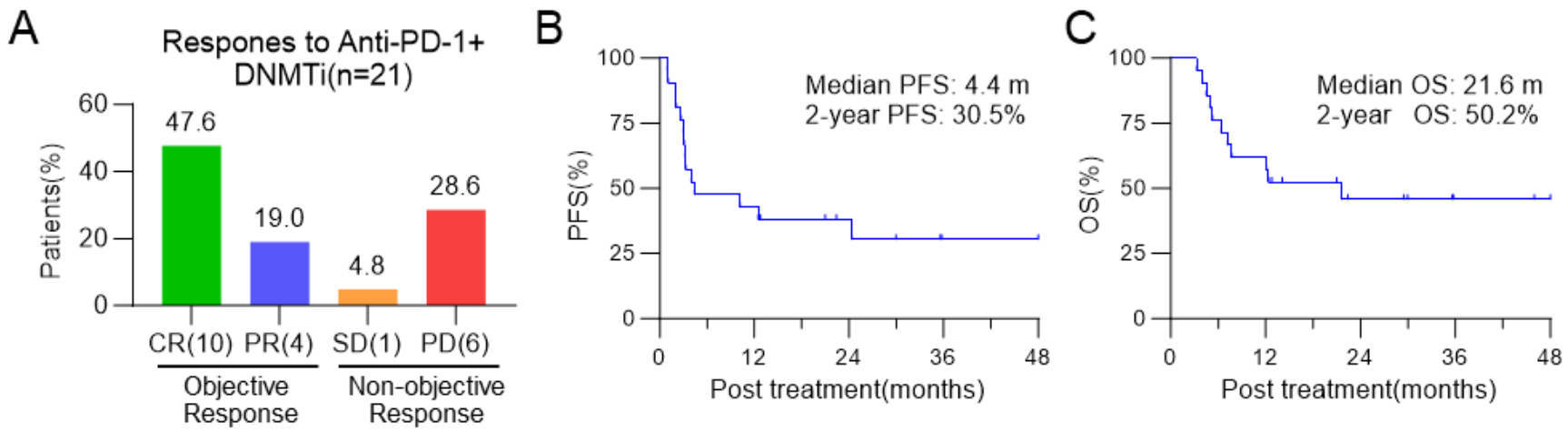
Clinical Challenges in Salvage therapy for R/R NKTL

Q: Whether DNMT inhibitors could enhance the anti-tumor efficacy of anti-PD-1 therapy in R/R NKTL and underlying mechanism?

Anti-PD-1 Combined with DNMT Inhibitors were effective for R/R NKTL Patients Resistant to Prior Immune Checkpoint Blockade (ICB) Therapy

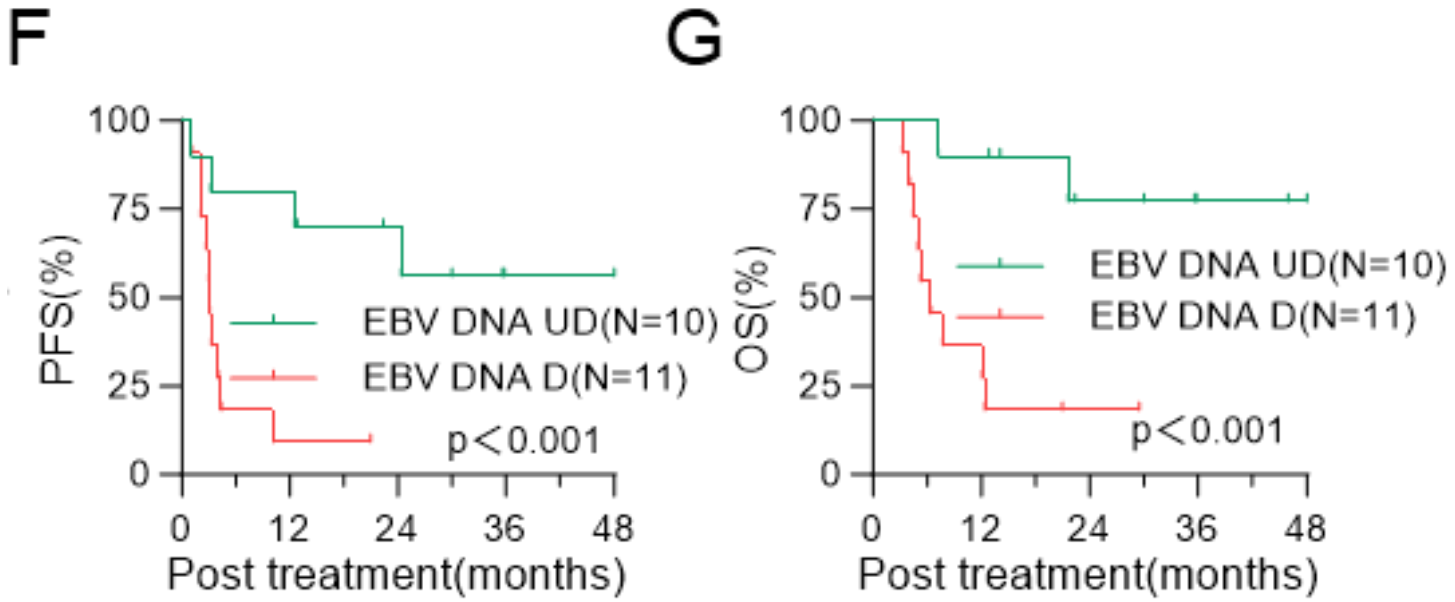
Preliminary clinical data: 21 patients with R/R NKTL who had relapsed or were refractory to ICB-based therapy:

Sintilimab 200mg Q3W in combination with DNMT inhibitor decitabine (DAC) 10mg D1-5 or azacytidine (AZA) 100mg D1-5.



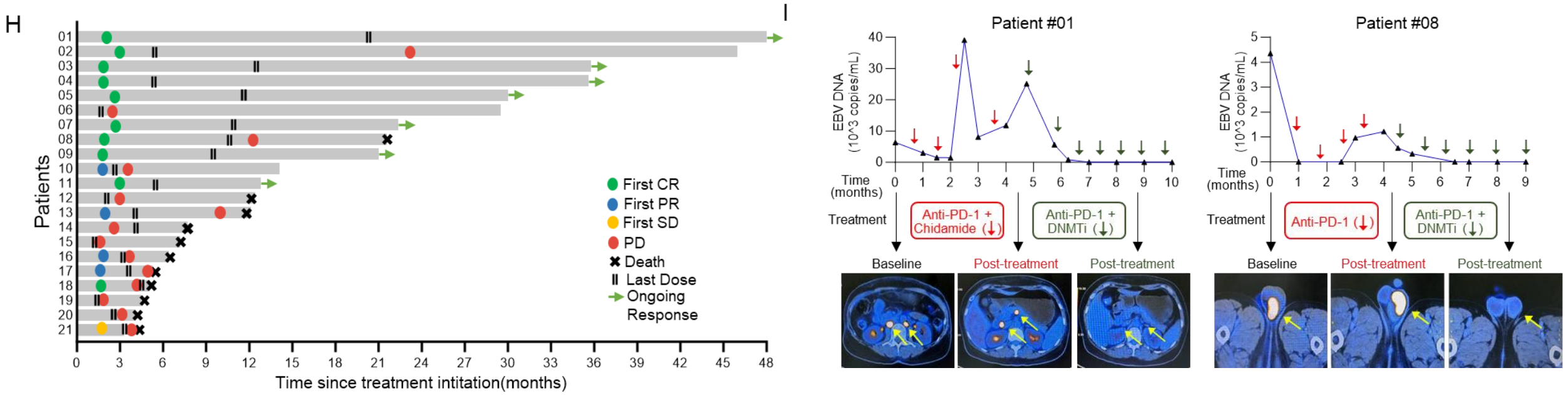
The combination of anti-PD-1 mAb with DNMT inhibitors resulted in favorable clinical responses and survival benefit.

Anti-PD-1 Combined with DNMT Inhibitors were effective for R/R NKTL Patients Resistant to Prior Immune Checkpoint Blockade (ICB) Therapy



Persistent plasma EBV-DNA positivity was identified as an independent adverse prognostic factor.

Anti-PD-1 Combined with DNMT Inhibitors were effective for R/R NKTL Patients Resistant to Prior Immune Checkpoint Blockade (ICB) Therapy



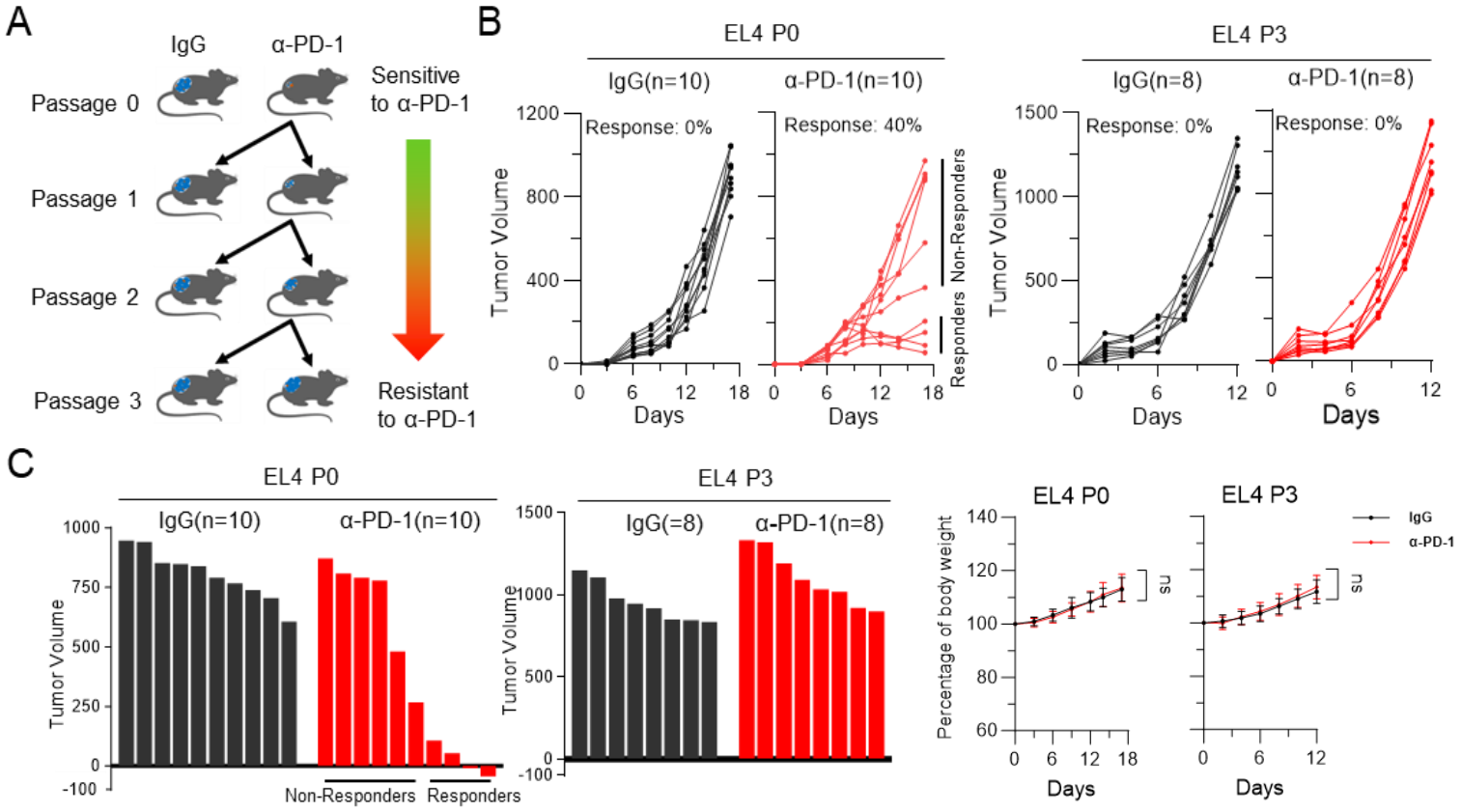
(H) Swimmer plot; (I) PET/CT images and dynamic changes in EBV-DNA copy number for two patients who achieved CR

Clinical Limitations of DNMTi+PD1 in NKTL

- Clinical response is unpredictable
- Biomarkers are highly needed for patient stratification
- Resistant mechanism remains unclear

Q: The underlying mechanisms responsible for DNMT inhibitors in R/R NKTL?

Establishing Anti-PD-1 Treatment–Resistant Preclinical Mouse Model

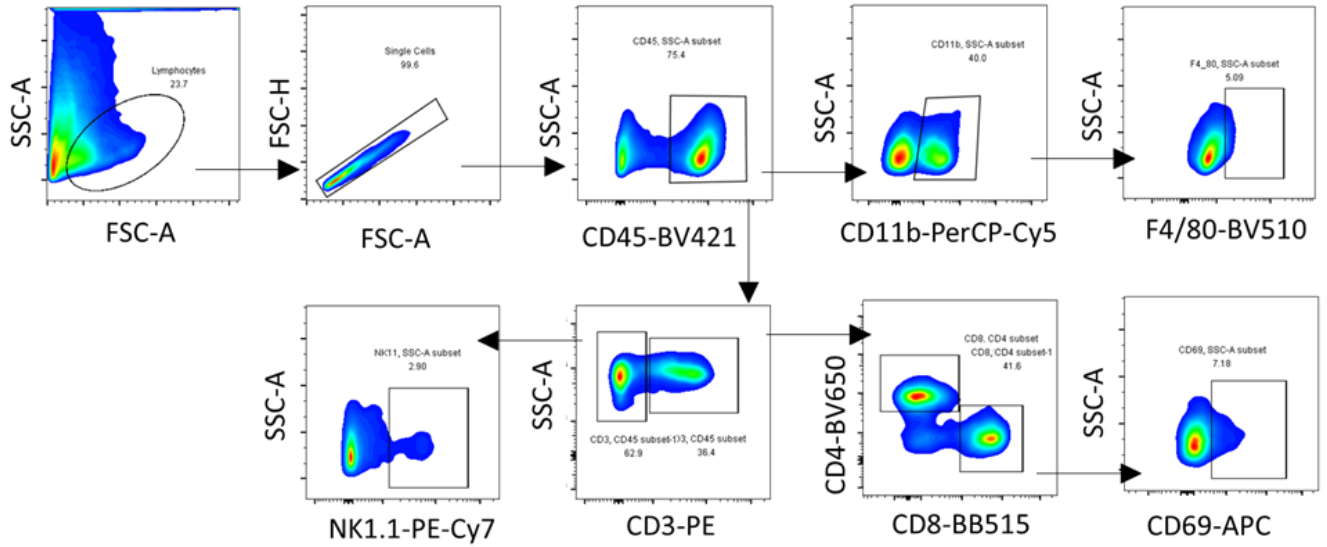


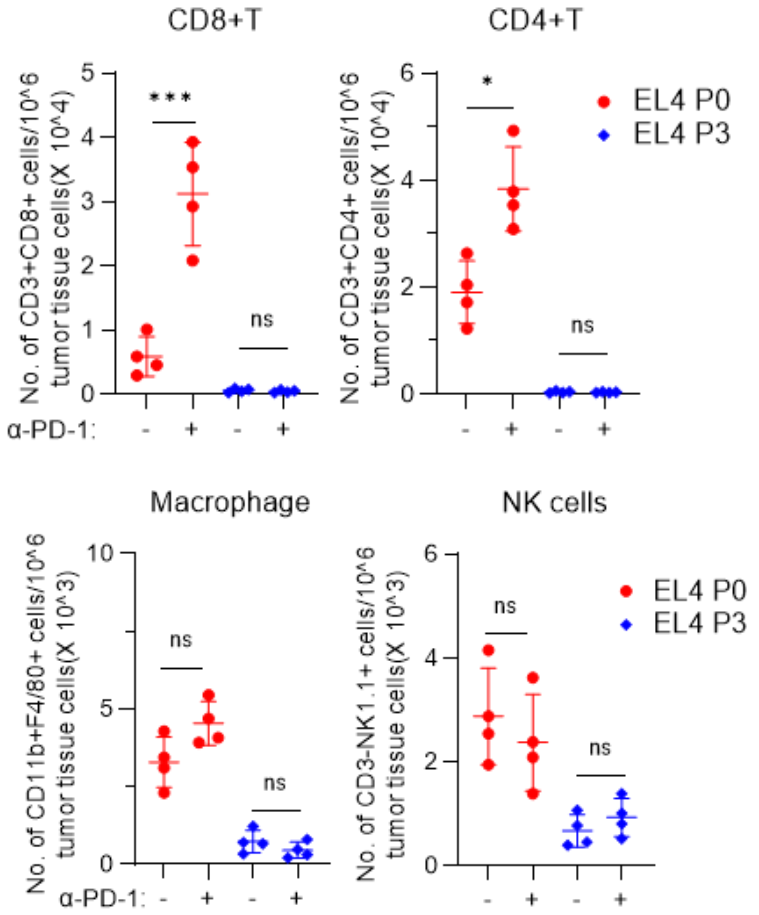
Established a novel anti-PD-1-resistant xenograft model by administering three rounds of anti-PD-1 mAb treatment in EL4-tumor bearing mice:

The resistance to anti–PD-1 treatment observed in patients is recapitulated in the EL4-P3 mouse model.

Anti-PD-1 Treatment–Resistant Preclinical Mouse Model Exhibits Immune-Exclusion Features

A



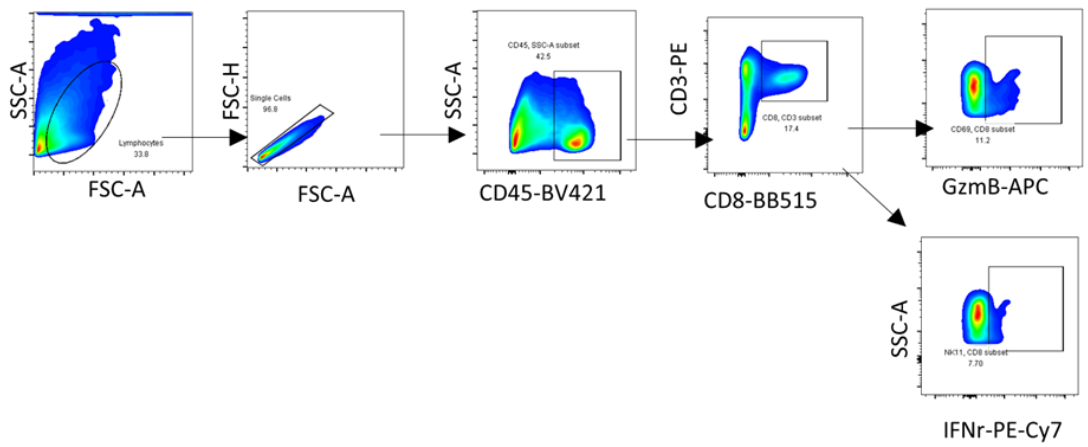


Tumor-infiltrating immune cells assess(FACS):

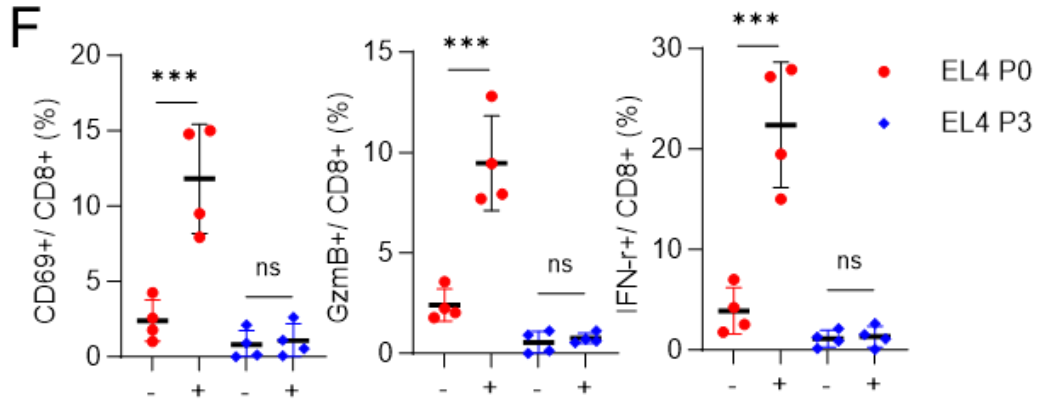
Anti-PD-1 treatment significantly increased the CD8+ T cells infiltrating in EL4 P0 tumor but not in EL4 P3 tumor

Anti-PD-1 Treatment–Resistant Preclinical Mouse Model Exhibits Immune-Exclusion Features

B

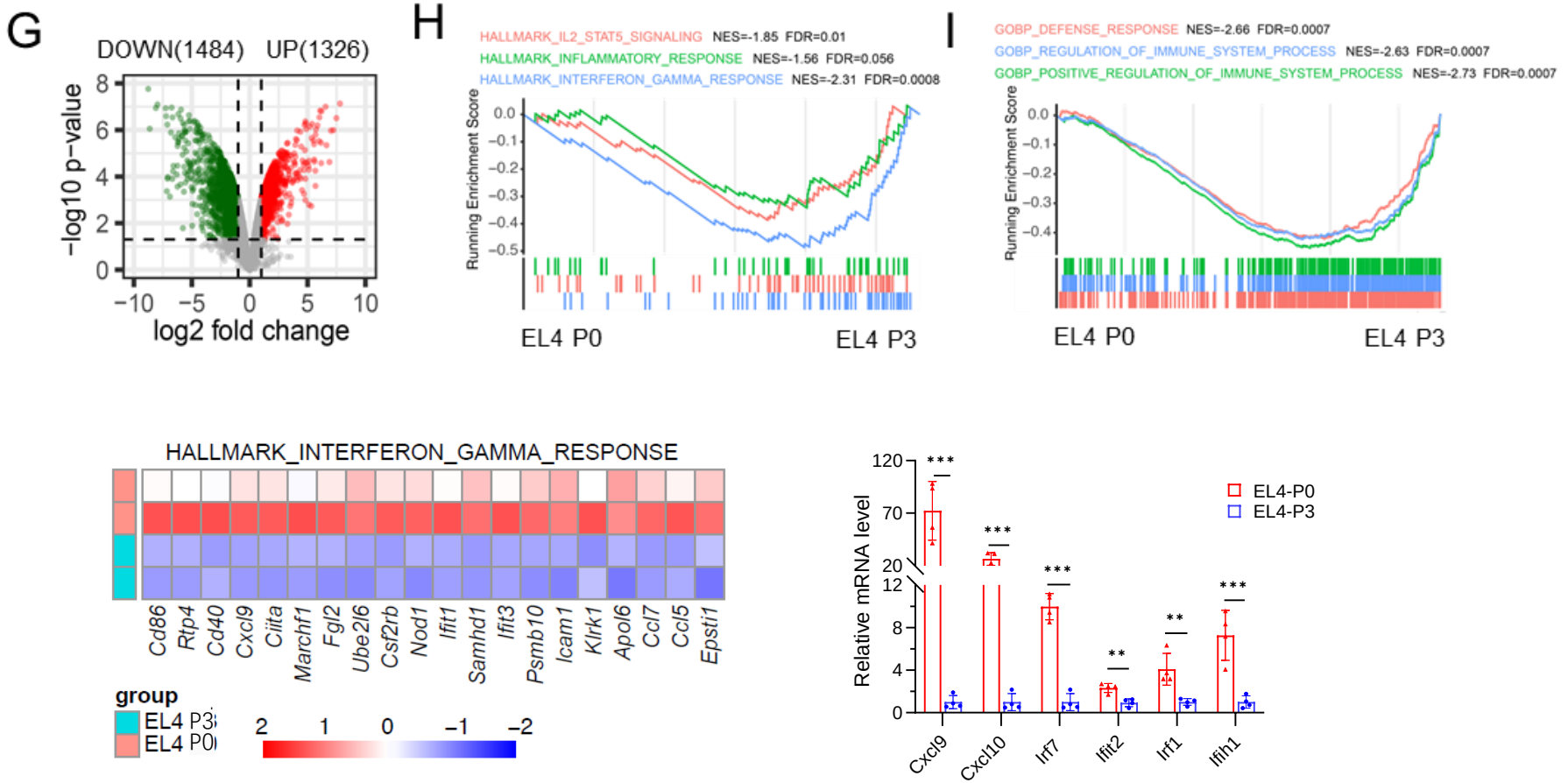


F



Tumor-infiltrating immune cells assess(FACS):
A higher proportion of CD8+ T cells expressed the activation markers in EL4 P0 tumor with anti–PD-1 treatment.

Significant Downregulation of Interferon Pathways in Anti-PD-1 Treatment–Resistant Mouse Model

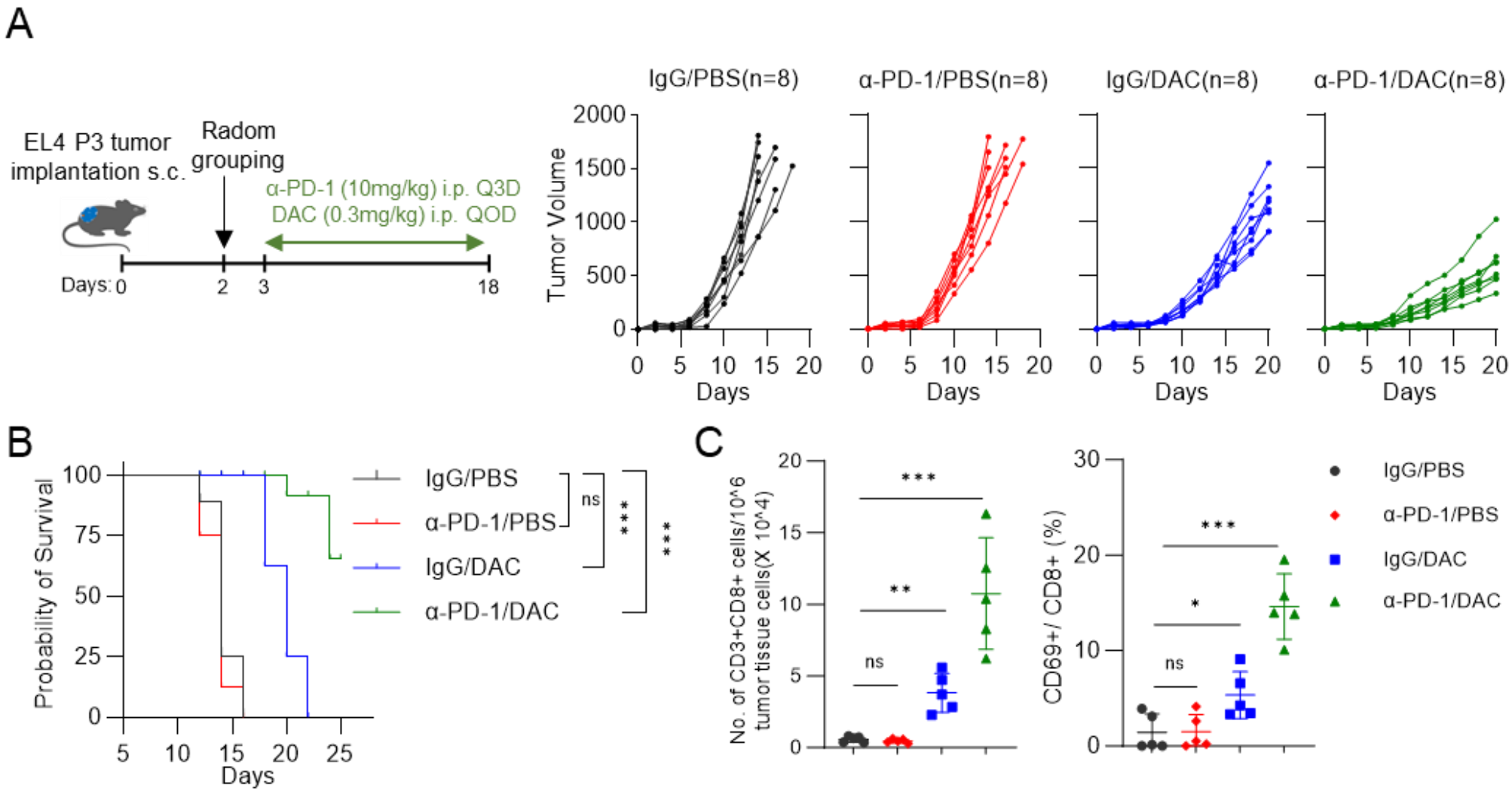


Bulk tumor RNA-seq comparing EL4 P0 an d EL4 P3 tumor:
Significant downregulation of immune-related pathways in EL4 P3 tumors

An Anti-PD-1 Treatment–Resistant Preclinical Mouse Model Exhibits Immune-Exclusion Features

Q: Whether combined with DMT inhibitors could restore the anti-PD-1 sensitivity in EL4-P3 tumor?

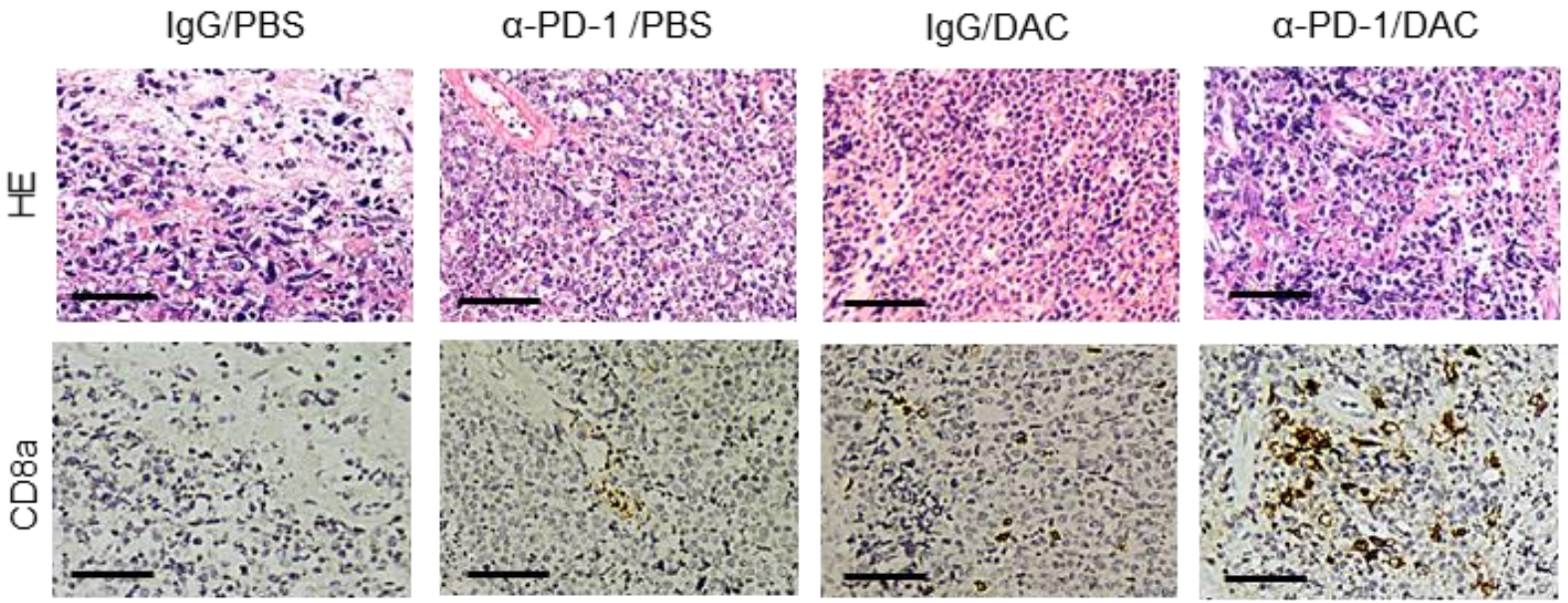
DNMT Inhibitor Treatment Restores Sensitivity to Anti-PD-1 Therapy In Vivo

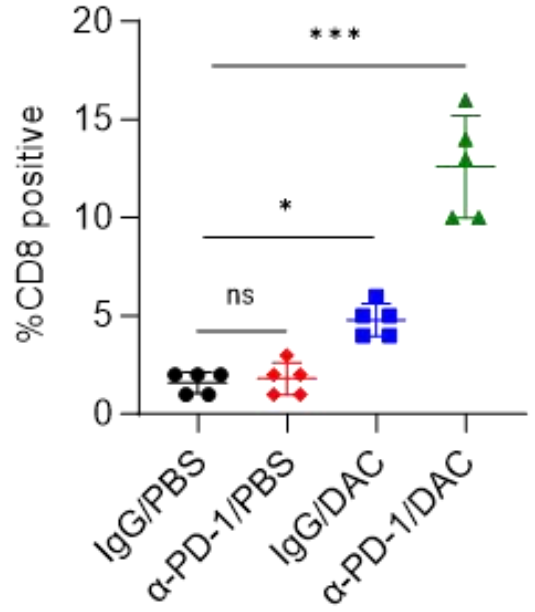


The combination therapy markedly

DNMT Inhibitor Treatment Restores CD8+ T cells Infiltration

D

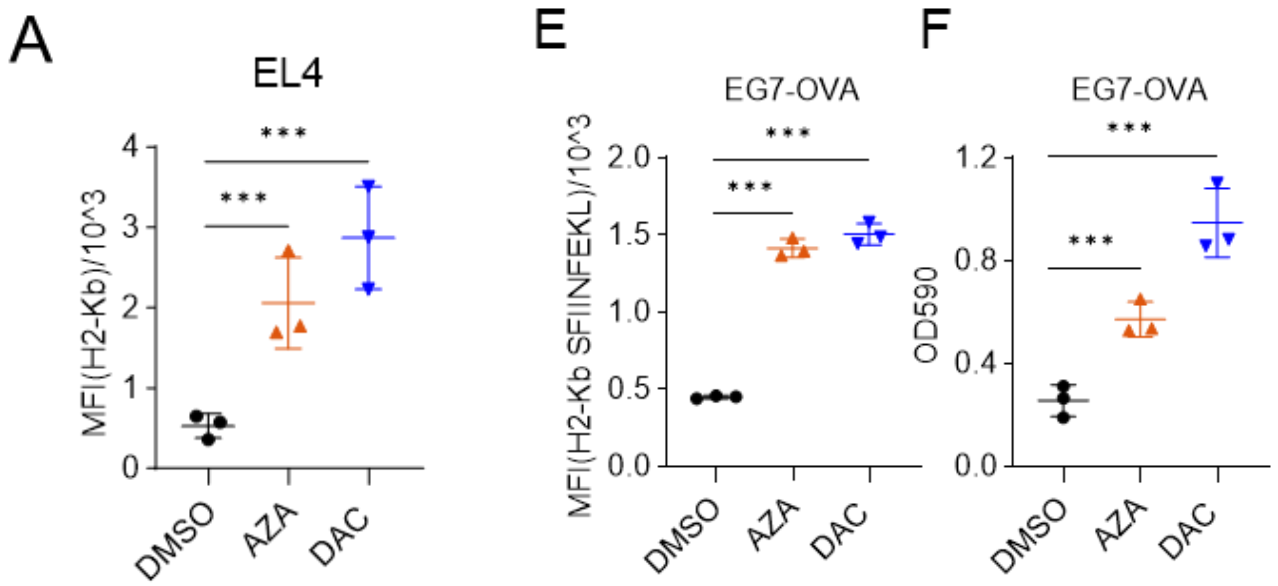




IHC analysis that showed a significant increase of tumor infiltration of CD8+ T cells in combination treatment group.

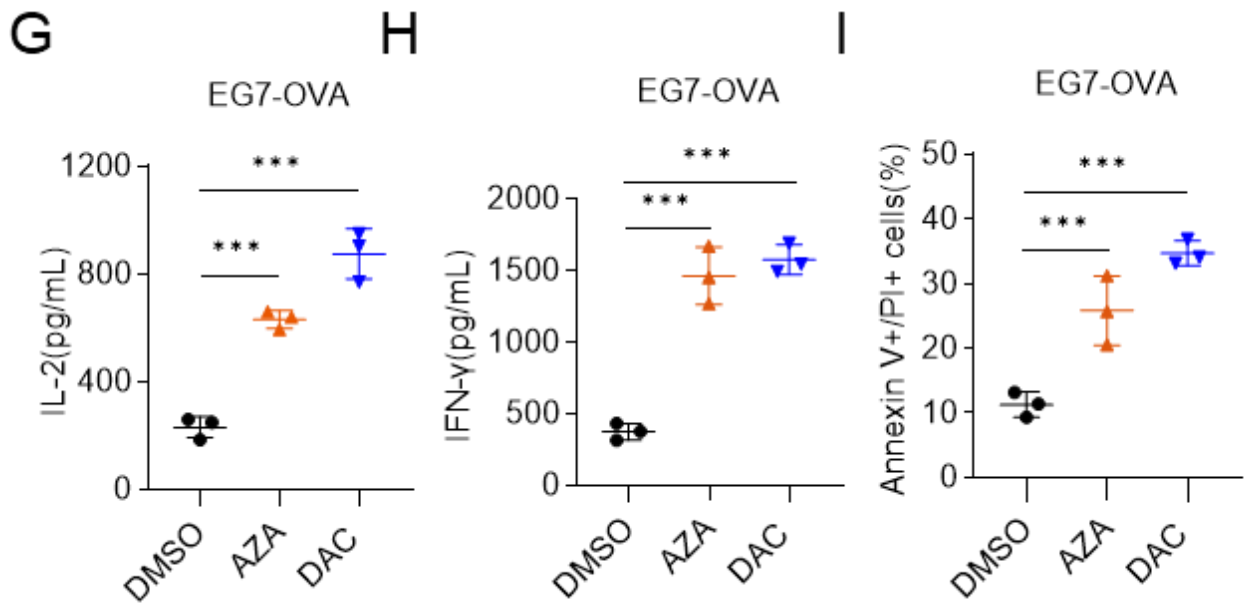
In vitro studies to assess the impact of DNMT inhibitor treatment on T cell activation.

DNMT Inhibitors Enhanced CD8+ T cell Cytotoxicity In Vitro



DNMT inhibitors pretreated EL4/EG7-OVA cells showed increased expression level of MHC-I complex and enhanced IL-2 promoter activity of B3Z cells.

DNMT Inhibitors Enhanced CD8+ T cell Cytotoxicity In Vitro.

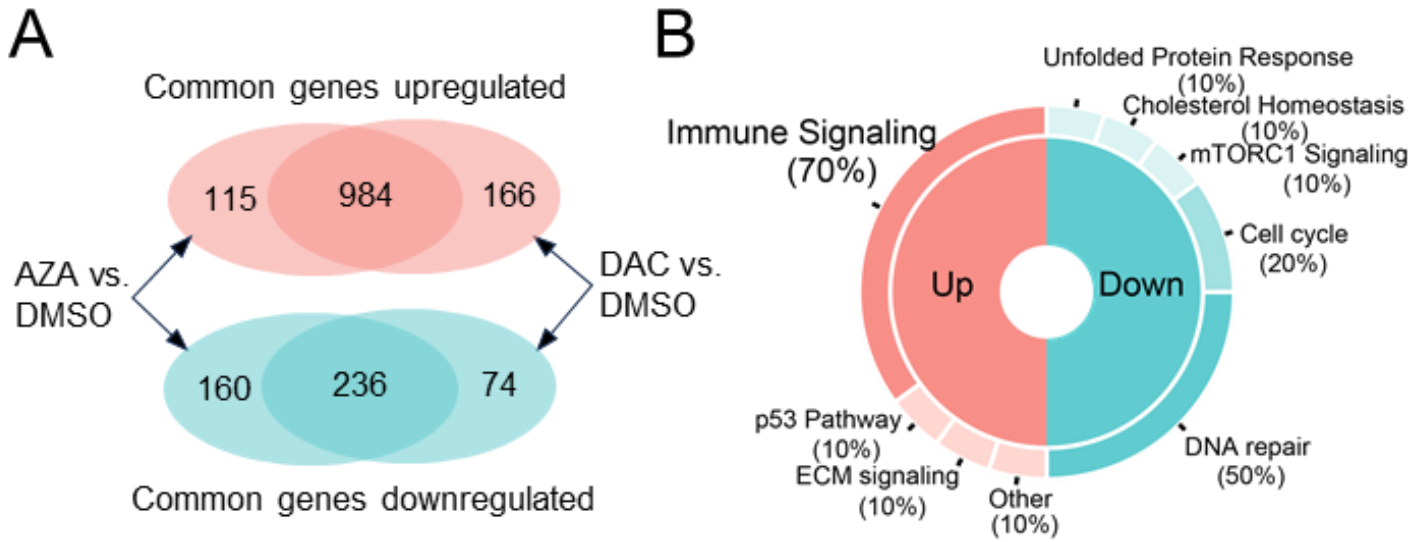


In vitro co-culture： DNMT inhibitors enhance OT-I cells activation and cytotoxicity.

DNMT Inhibitor Treatment Restores Sensitivity to Anti-PD-1 Therapy and Enhances CD8+ T-Cell Cytotoxicity

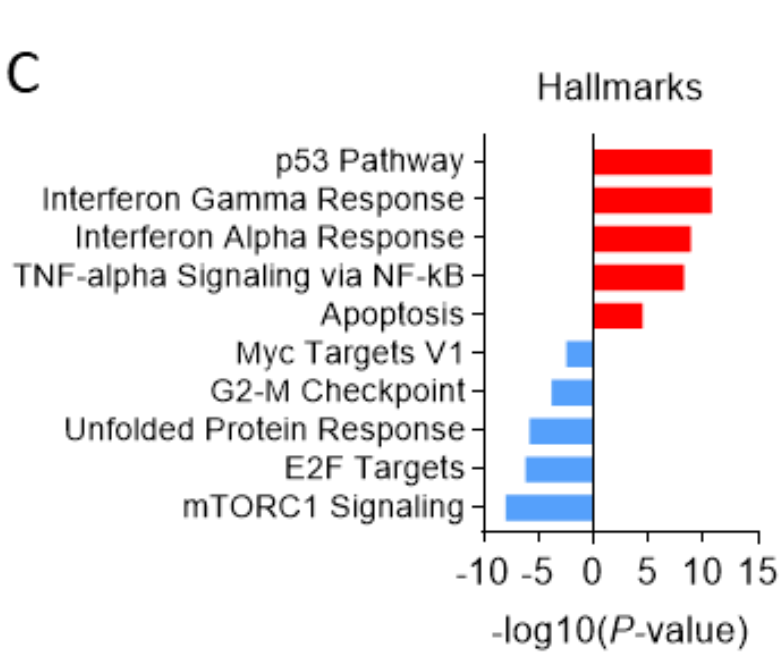
Q: How DNMT inhibitor treatment contributes to the immune-stimulatory phenotype in EG7-OVA cells?

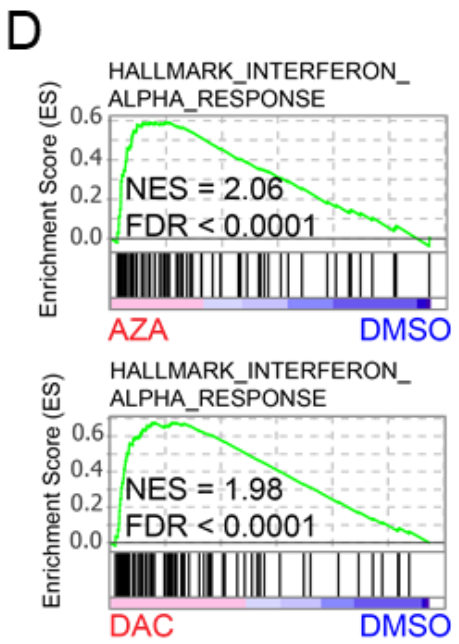
DNMT inhibitors Upregulated Interferon Signaling Pathway.

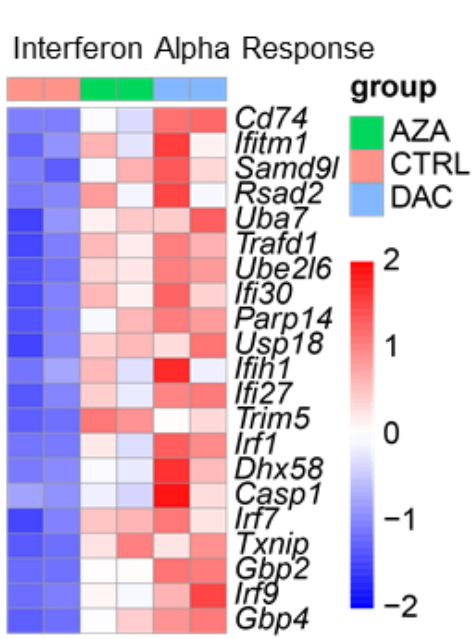


The transcriptomic changes observed were highly similar between the AZA and DAC treatment groups and 70% of the upregulated genes were enriched in immune signaling pathways

DNMT inhibitors Upregulated Interferon Signaling Pathway

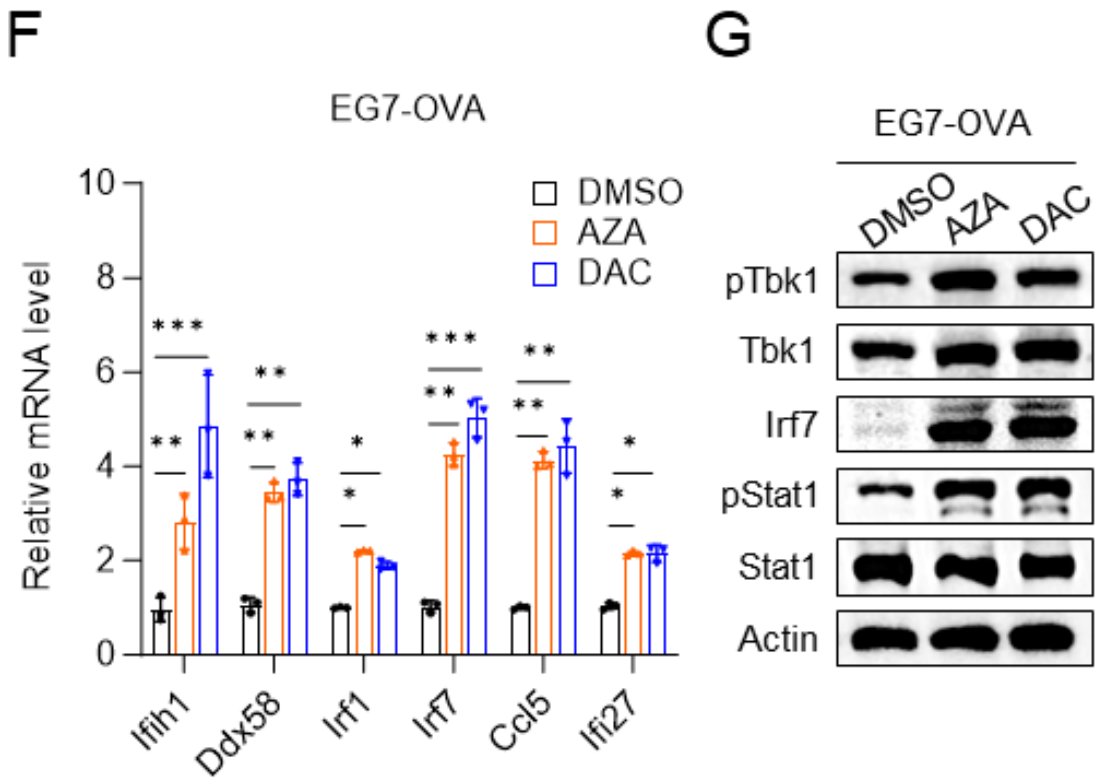




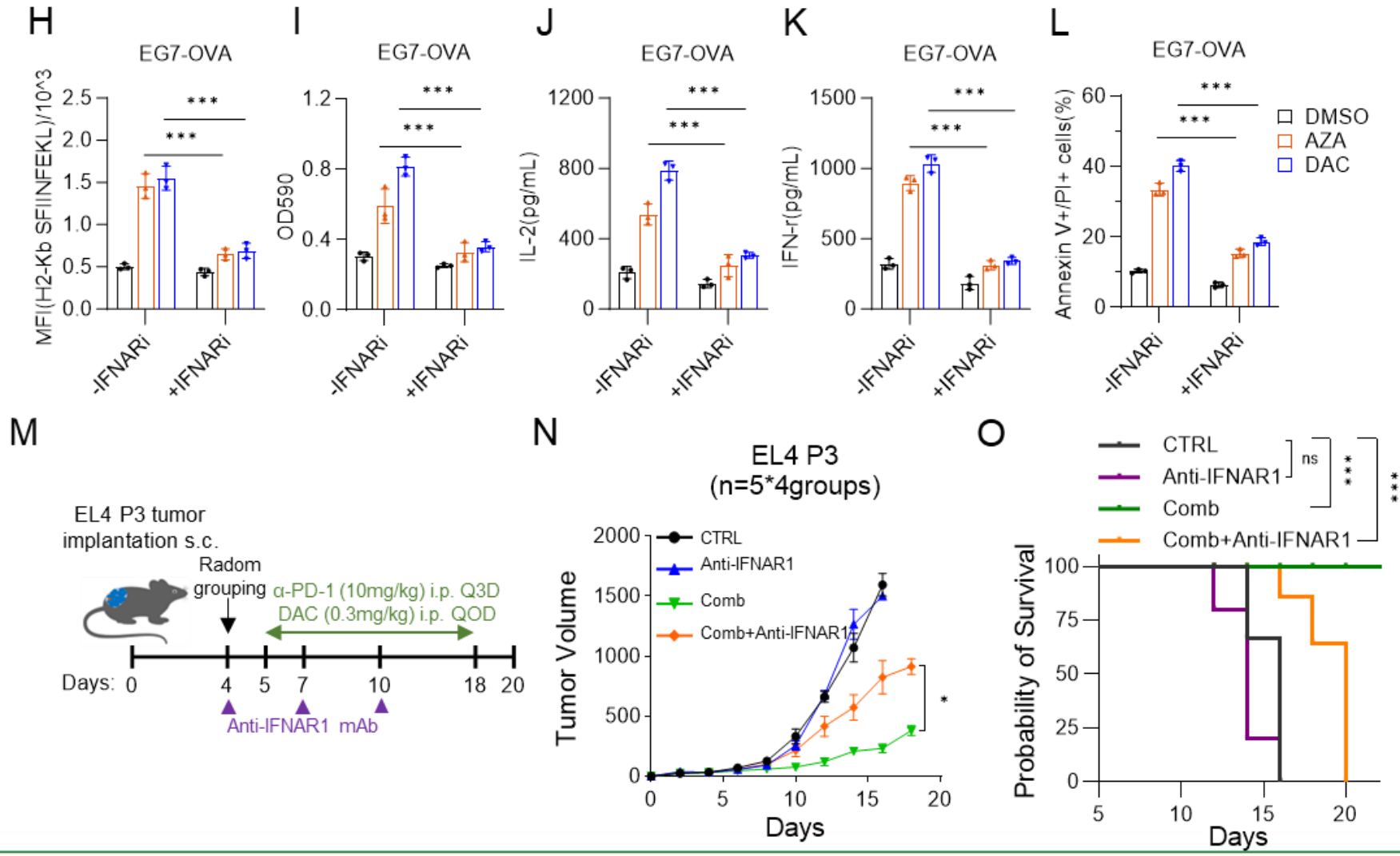


The top five enriched pathways among the upregulated genes were showed:
Including the "Interferon Gamma Response" pathways, which were downregulated in anti-PD-1 treatment-resistant EL4 P3 tumors.

DNMT Inhibitors Upregulated Interferon Signaling Pathway



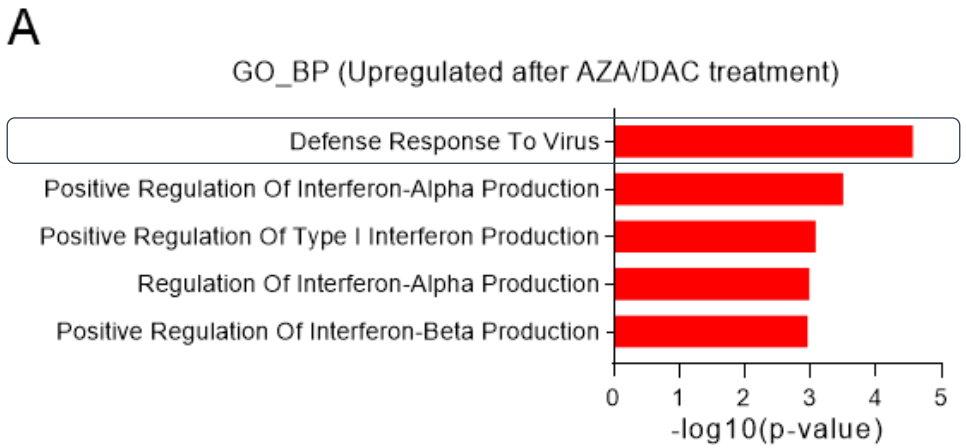
Anti-tumor immune response induced by DNMT inhibitors is dependent on tumor-derived type I interferon signaling in NKTL



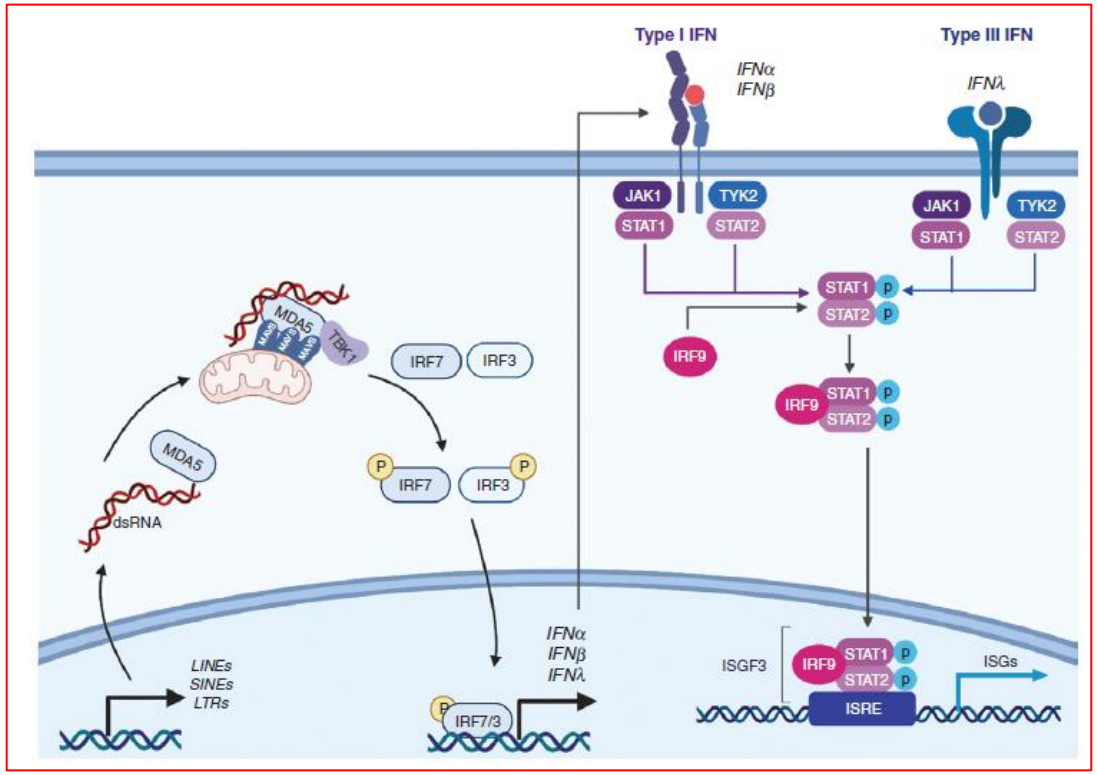
DNMT Inhibitors Trigger Interferon Signaling to Enhance T-Cell Activation

Q: The underlying mechanisms by which DNMT inhibitor treatment activates the interferon pathway?

DNMT Inhibitor-induced Immune Responses Mediated by RNA Sensing Pathway.



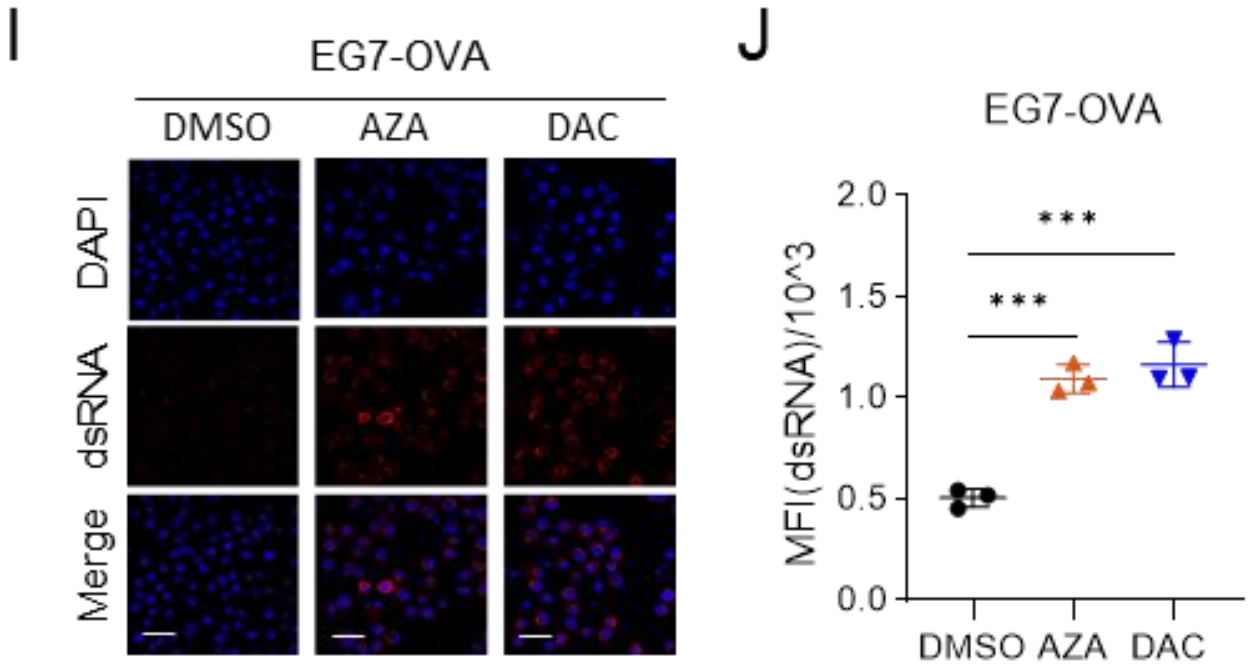
Further GO enrichment analysis revealed that terms associated with antiviral responses and type I interferon signaling were significantly upregulated



Type I interferon signaling mediated by viral mimicry. (Cancer Discov 2021;11:2707–25)

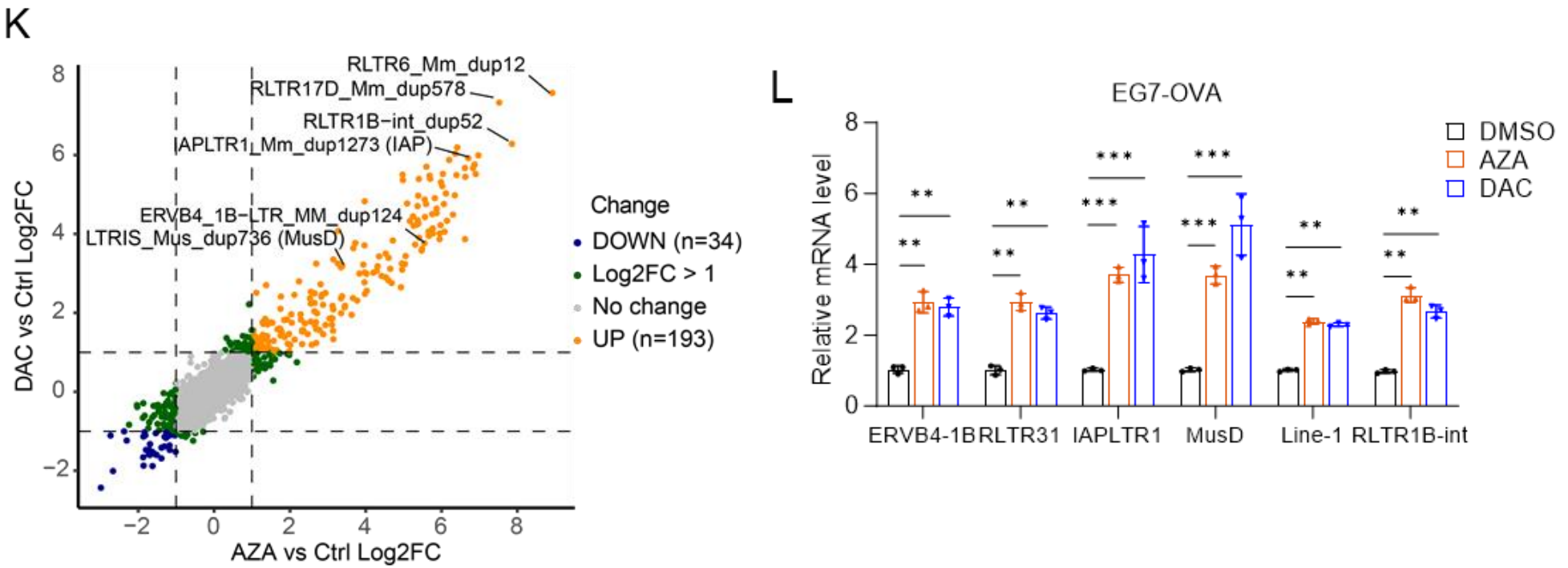
Q: Whether DNMT inhibitors can induce ERV expression and activate viral mimicry, thereby triggering type I interferon responses?

DNMT Inhibitors Induce Viral Mimicry in EG7-OVA cells.



Fluorescence microscopy and flow cytometry analysis revealed a significant increase in dsRNA formation following DNMT inhibitor treatment.

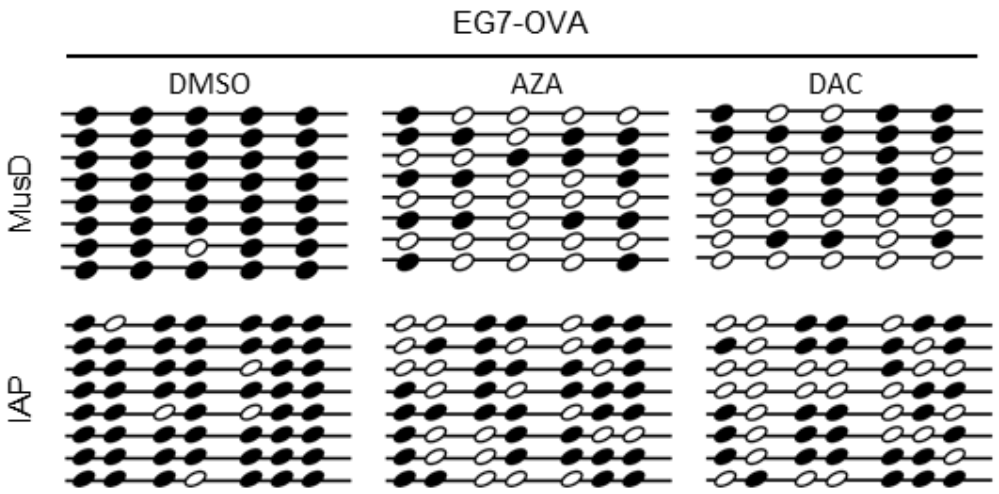
DNMT Inhibitors Induce Viral Mimicry in EG7-OVA cells.

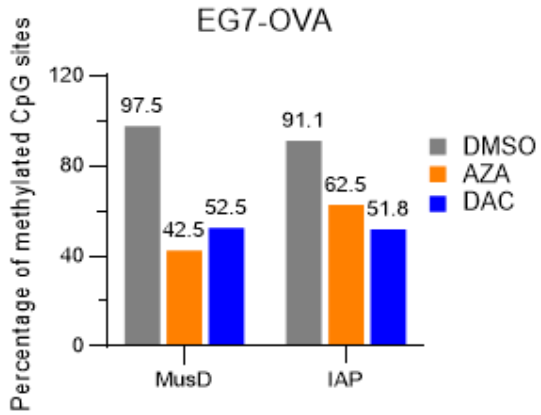


Strand-specific RNA sequencing data showed that **a cluster of retrotransposons was upregulated** by DNMT inhibitor and RT-qPCR validation.

DNMT Inhibitors Induce de-methylation of ERV Promoters

N



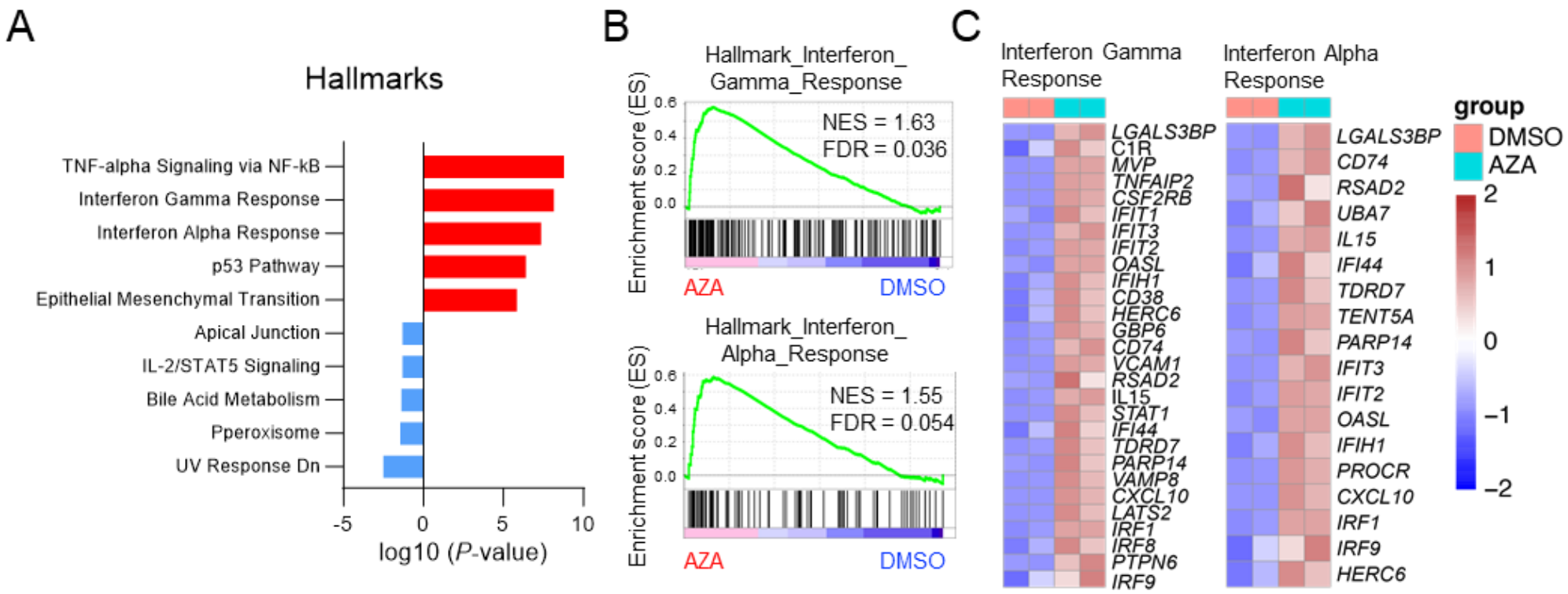


Bisulfite sequencing analysis revealed that **DNMT inhibitor treatment led to a significant decrease in the percentage of methylated CpG sites** in the promoters of MusD and IAP

DNMT Inhibitors Induce Viral Mimicry via Demethylation of ERV promotor.

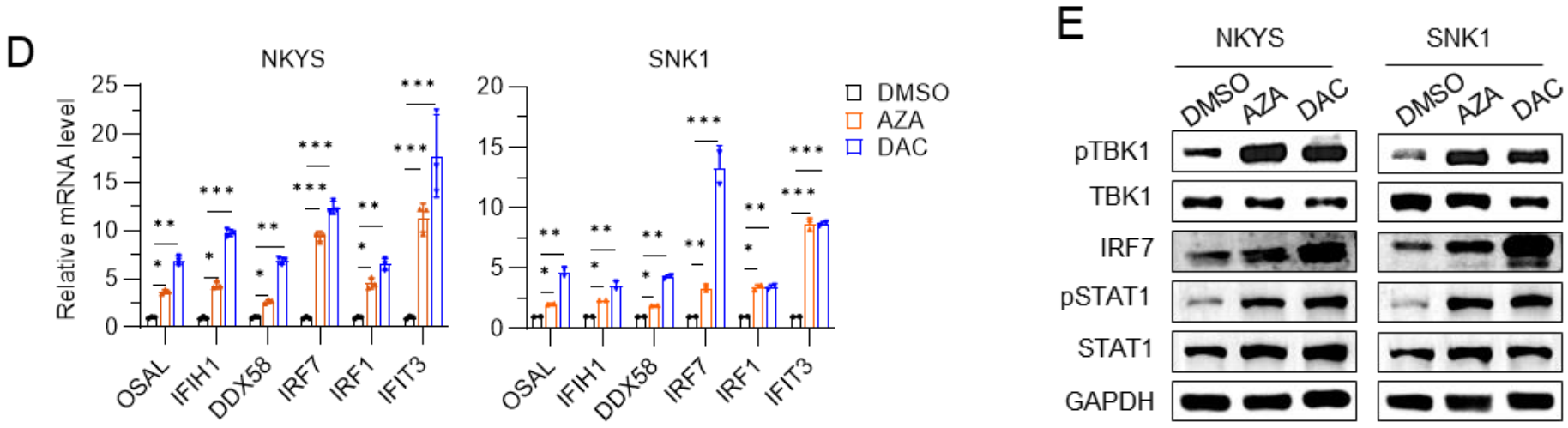
Q: Whether the findings observed in mouse cells could be recapitulated in human NKTL cell lines?

DNMT Inhibitors Activate Interferon Pathway in Human NKT cell lines.



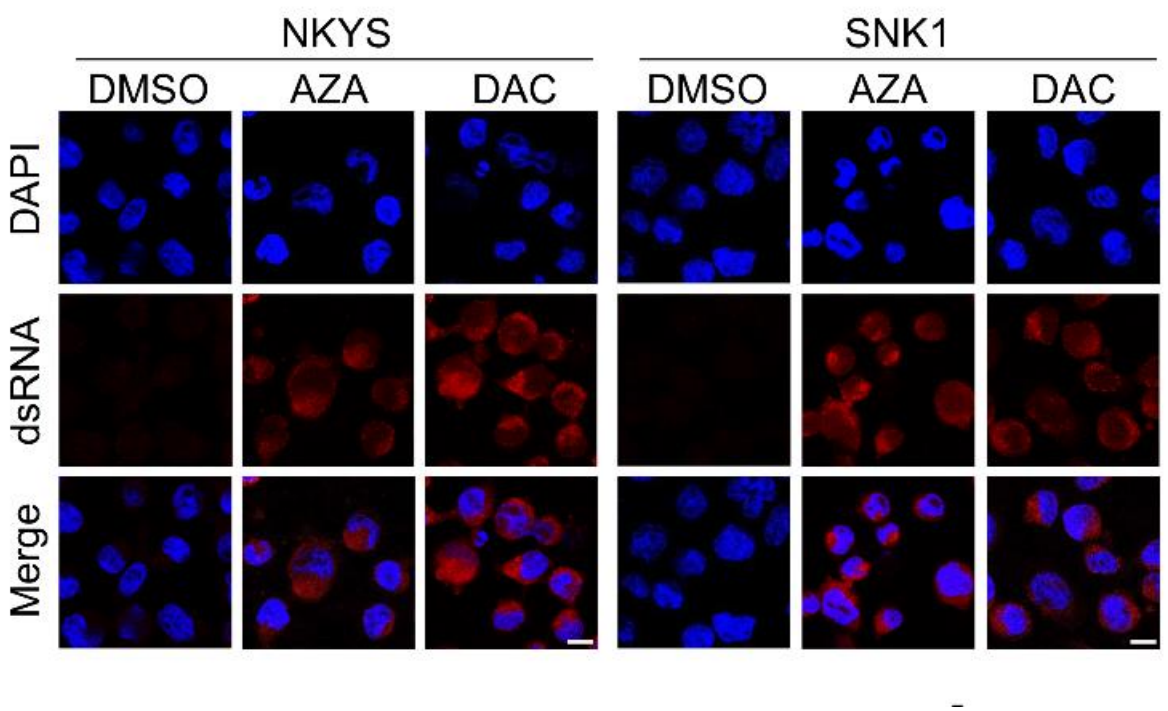
RNA sequencing on NKYS cells treated with AZA or DMSO:
“Interferon Gamma Response” and “Interferon Alpha Response” were among the most significantly upregulated pathways

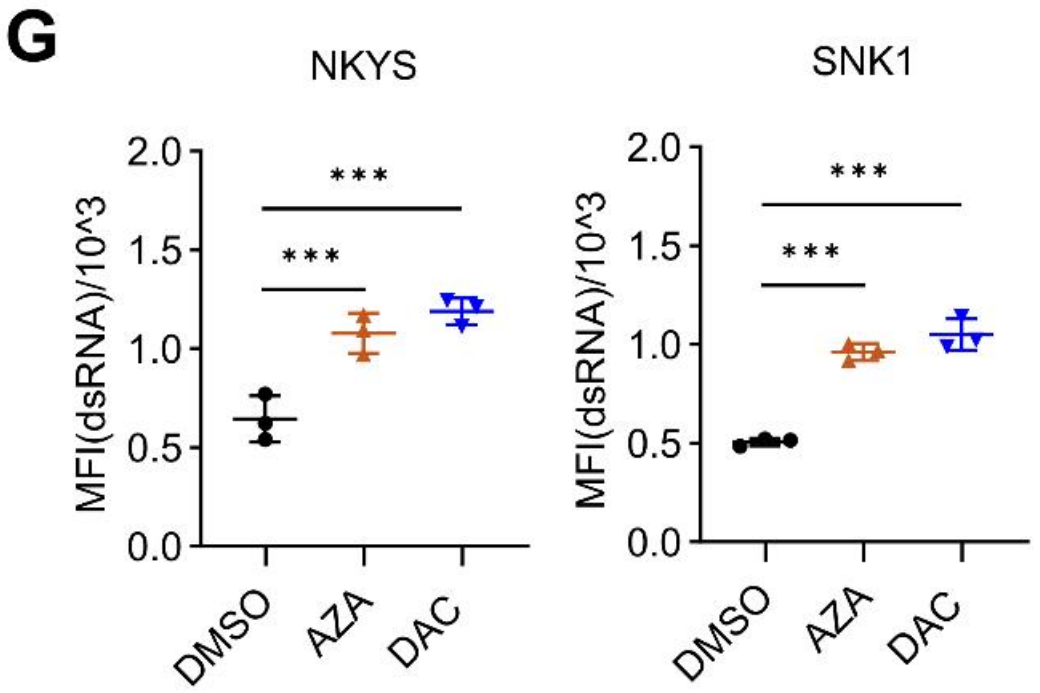
DNMT Inhibitors Activate Interferon Pathway in Human NKTL cell lines



RT-qPCR and Western blot analysis further confirmed that DNMT inhibitors induced ISGs expression and activation of the TBK1-STAT1 signaling axis in both NKYS cells and SNK1 cells, another human NKTL cell line

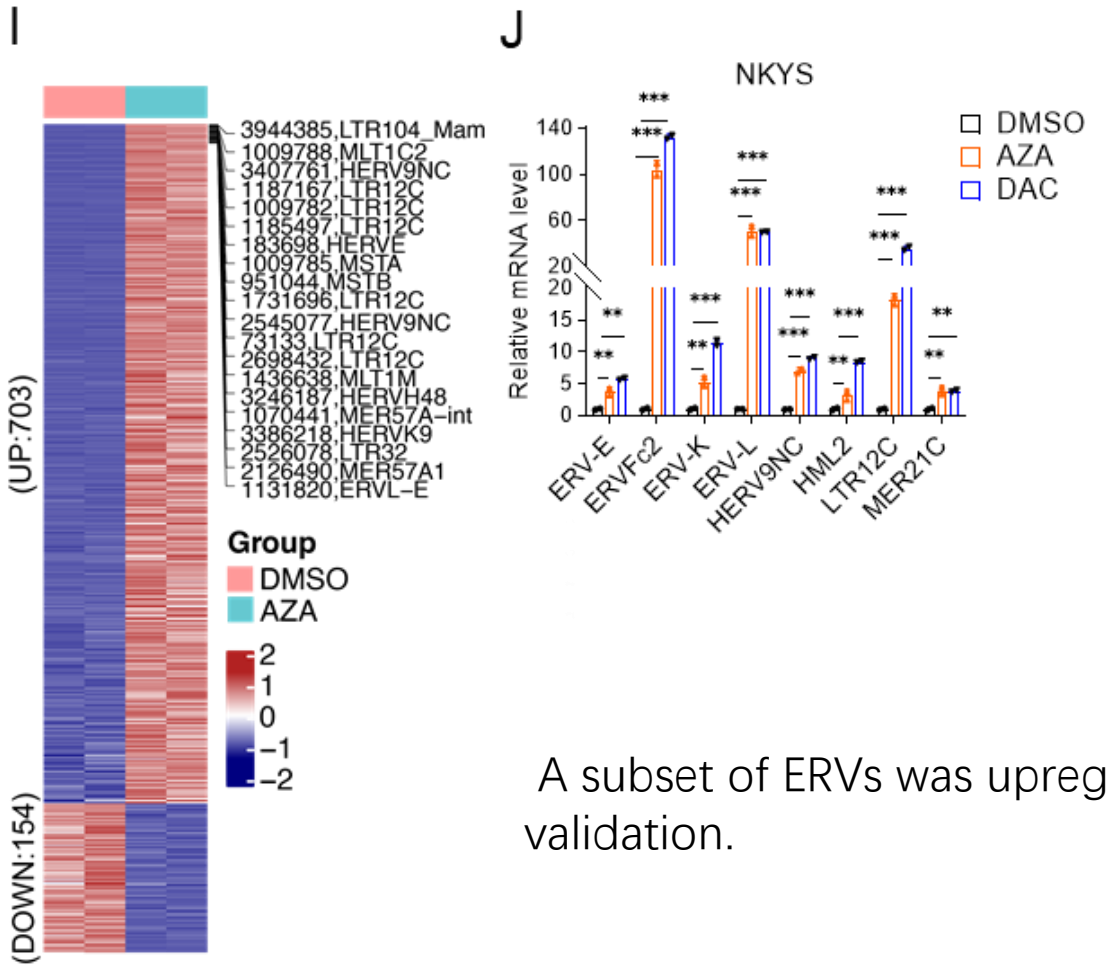
DNMT Inhibitors Induce Viral Mimicry in Human NKTL cell lines

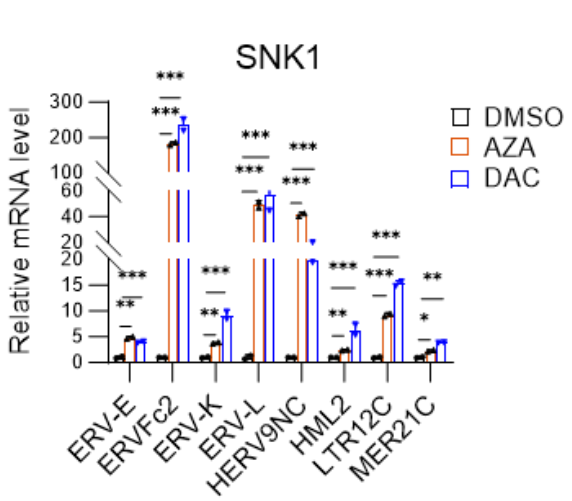




DNMT inhibitors resulted in a significant increase in dsRNA formation in both NKYS and SNK1 cells.

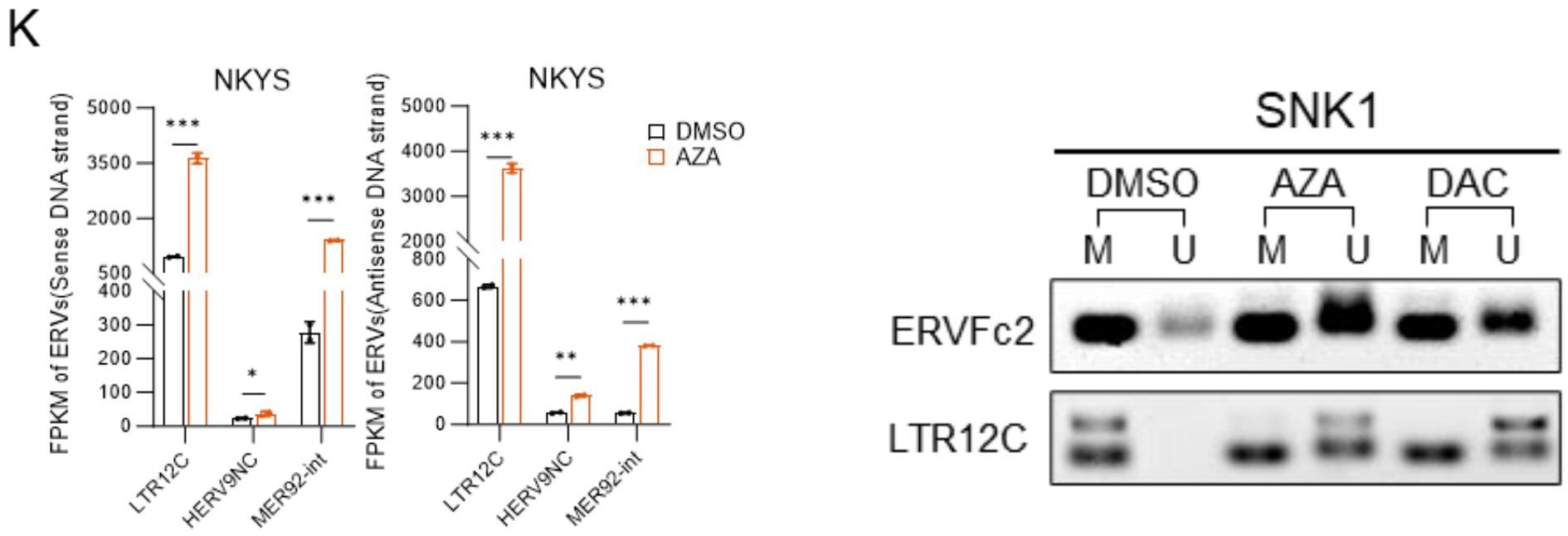
DNMT Inhibitors Induce Viral Mimicry in Human NKTL cell lines





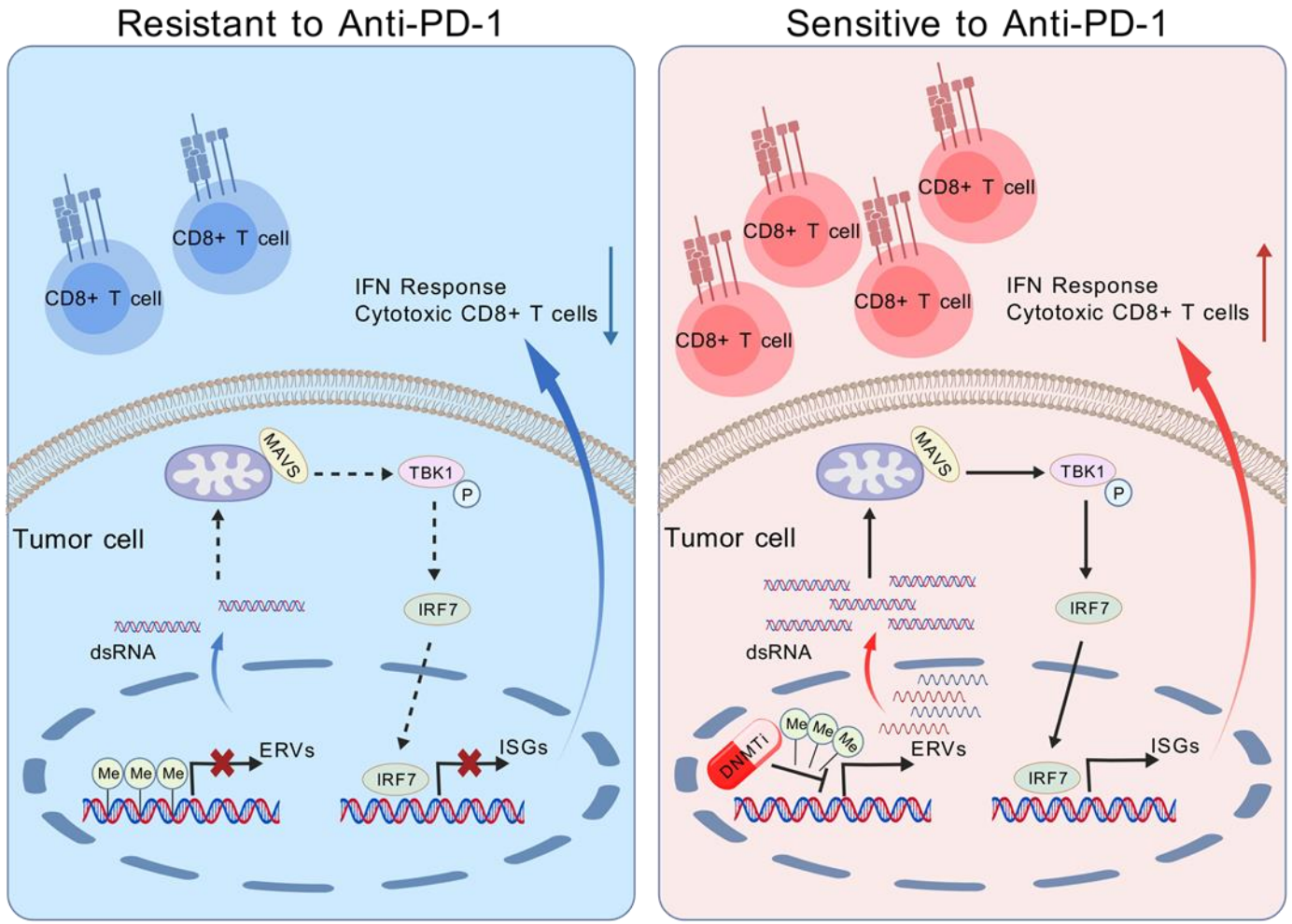
A subset of ERVs was upregulated by AZA in NKYS cells and RT-qPCR validation.

DNMT Inhibitors Induce ERV Expressed and Promoter de-methylation.



Both sense and antisense transcription of these DNMT inhibitor-induced ERVs were concurrently increased and methylation-specific PCR revealed the presence of unmethylated bands exclusively in DNMT inhibitor-treated cells.

Proposal model illustrating the role of DNMT inhibitors in enhancing anti-tumor immunity in the NKTL pre-clinical model.

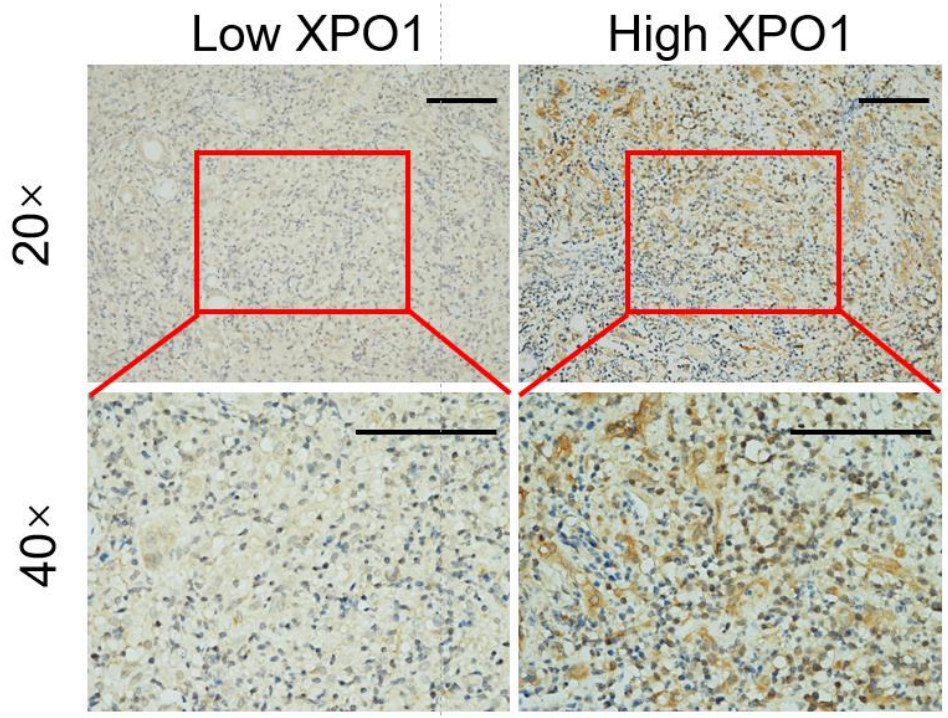


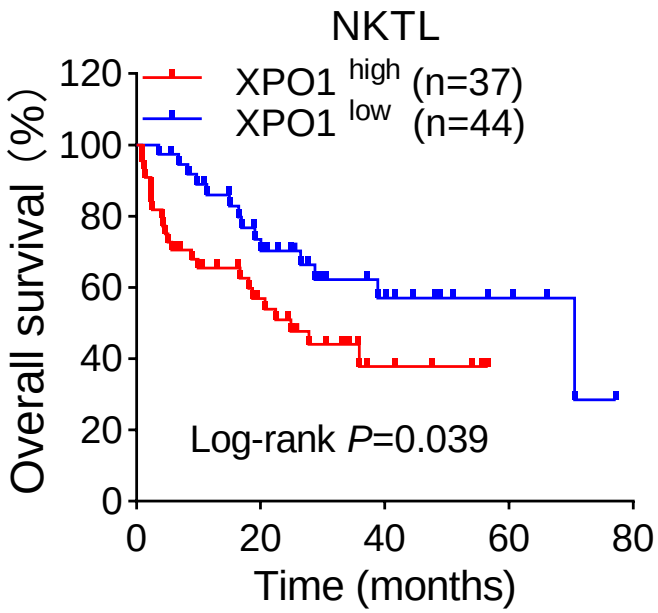
In mouse and human NKTL cell lines: DNMT inhibitors induce DNA demethylation in the promoter region of ERVs, resulting in the accumulation of dsRNA and triggering a viral mimicry response which activates the type I interferon pathway, thereby potentiating anti-tumor immunity.

Cancer Discovery 2025 accepted

XPO1 is highly expressed in NKTL

An NKTL cohort from SYSUCC (n=81)

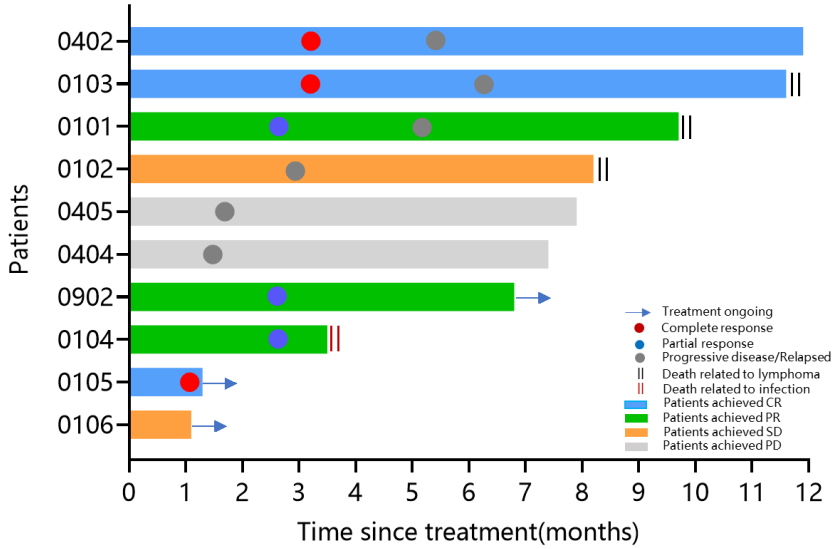




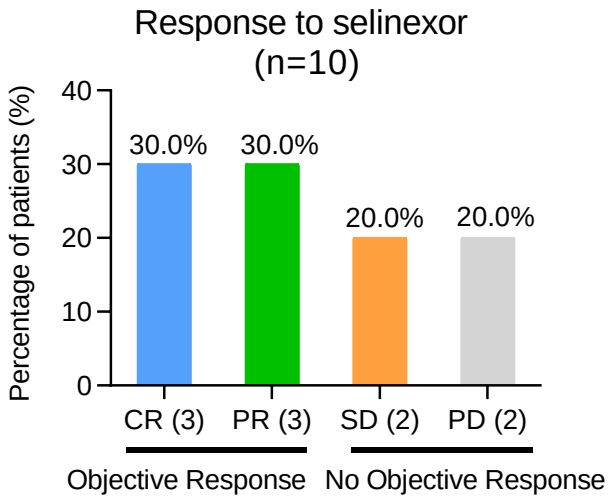
XPO1 may represent a potential therapeutic target for R/R NKTL patients

Summary of clinical implications of Selinexor in R/R NKTL

A A single-arm, phase Ib clinical trial (NCT04425070)



B



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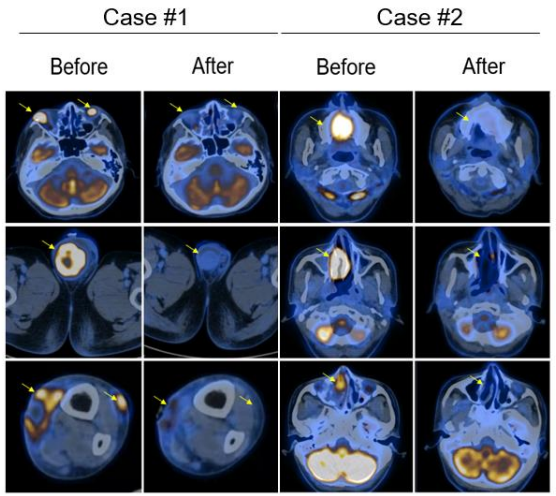

In summary , 3 out of 10 NKTL patients are complete response to selinexor.

Combined CDK4/6 and XPO1 inhibition enhances anti-tumor activity in natural killer/T-cell lymphoma

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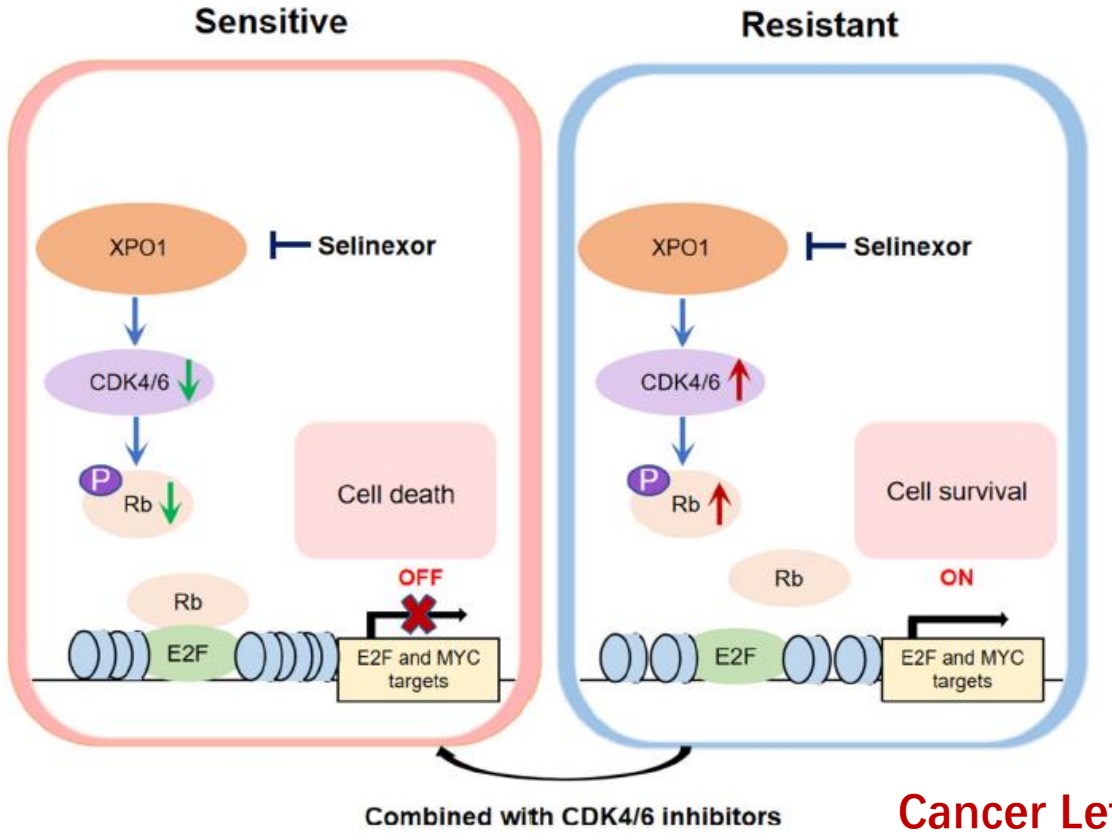
Original Articles

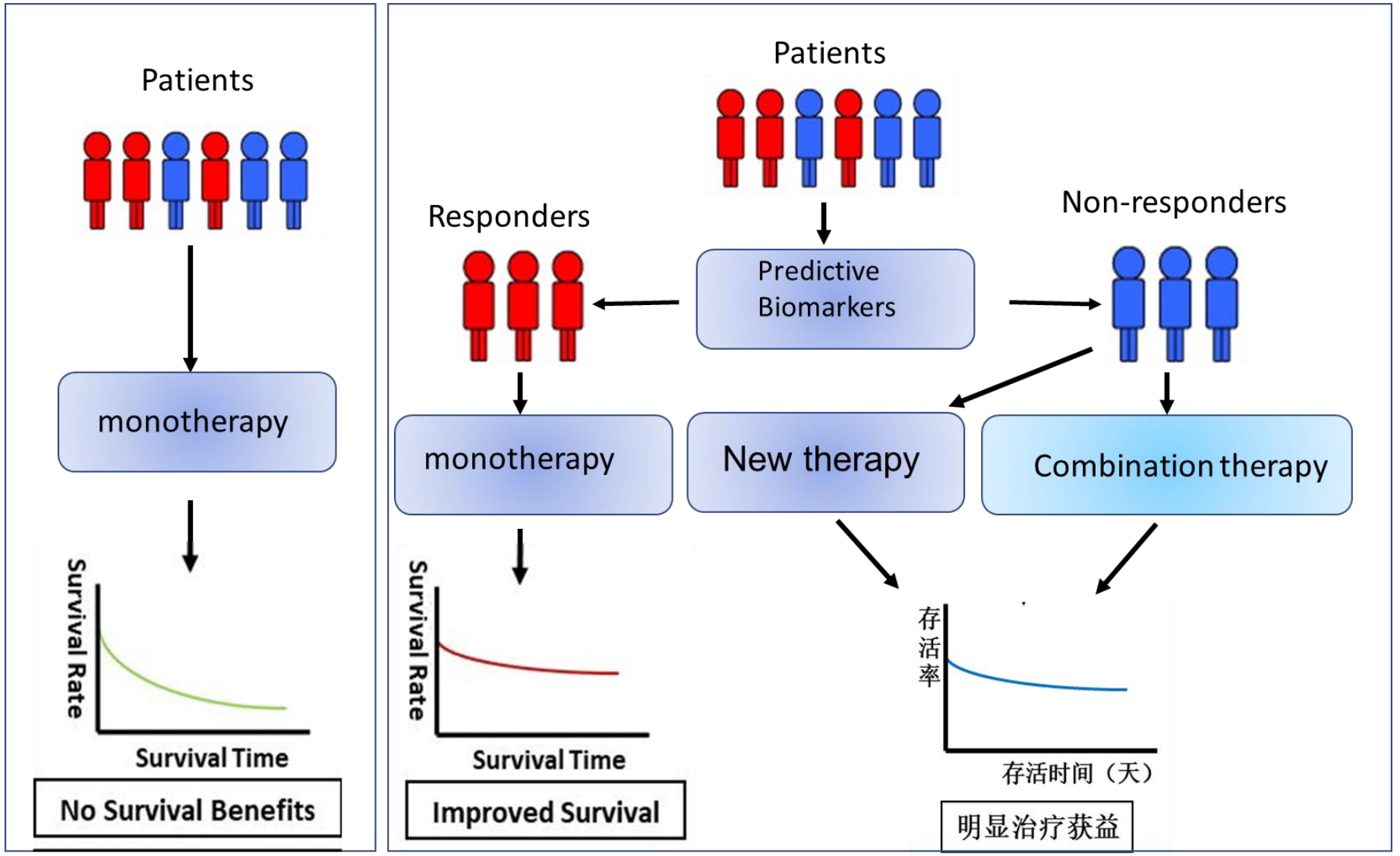
CDK4/6 inhibition augments anti-tumor efficacy of XPO1 inhibitor selinexor in natural killer/T-cell lymphoma

Yali Wang[a,b,1], Jianfeng Chen[a,1], Yan Gao[a,1], Kelila Xin Ye Chai[c], Jing Han Hong[d], Peili Wang[a], Jinghong Chen[e], Zhaoliang Yu[f], Lizhen Liu[g], Cheng Huang[a], Nur Ayuni Muhammad Taib[c], Kerry May Huifen Lim[c], Peiyong Guan[h], Jason Yongsheng Chan[i], Dachuan Huang[c], Bin Tean Teh[d,e,i], Wenyu Li[g], Soon Thye Lim[j], Qiang Yu[d,h], Choon Kiat Ong[c,d], Huiqiang Huang[a], Jing Tan[a,i,k,*]

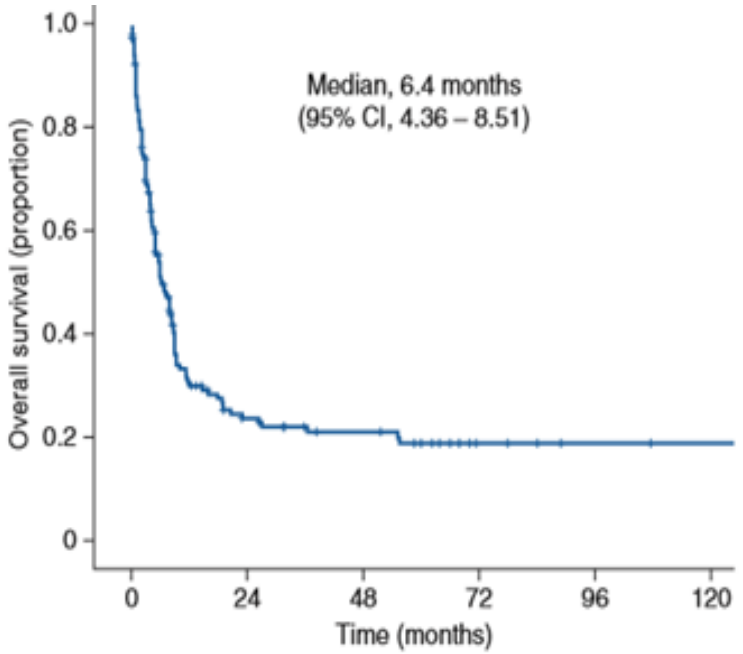


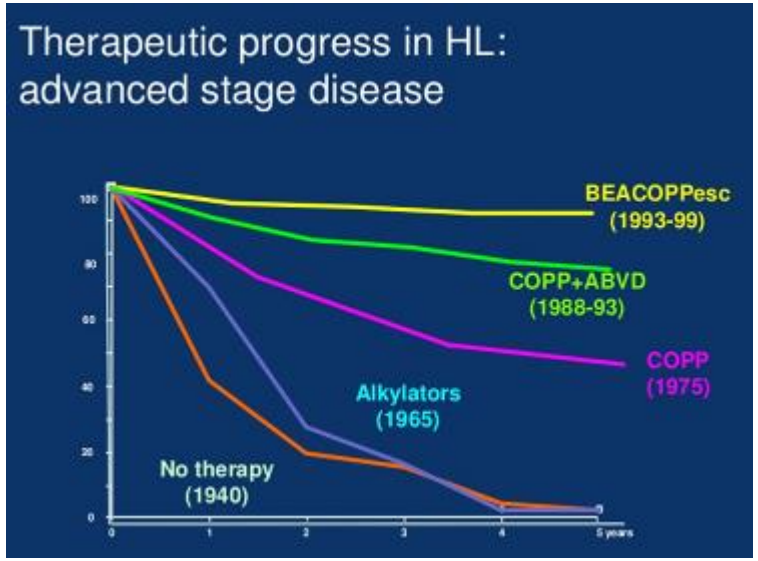
Cancer Letter 2024

Translating lymphoma genomics to new therapeutics



Perspectives in Lymphoma translational research





Through Collaboration We can Advance Science and Improve Treatment

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Bei Jingxin Lab
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