

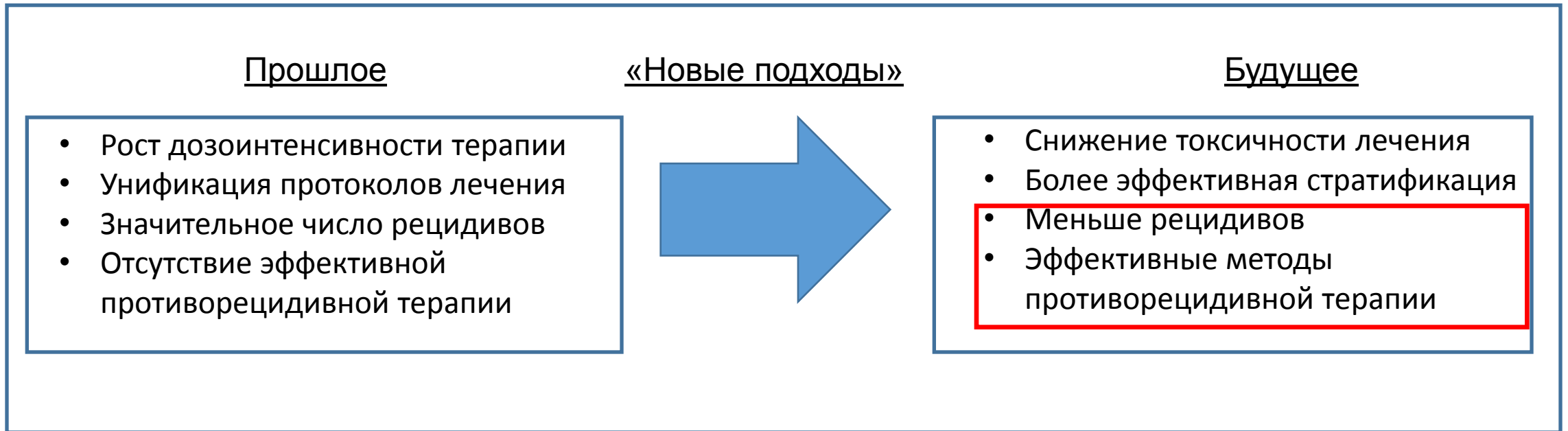


Тенденции в лечении пациентов с нейробластомой в России и в мире

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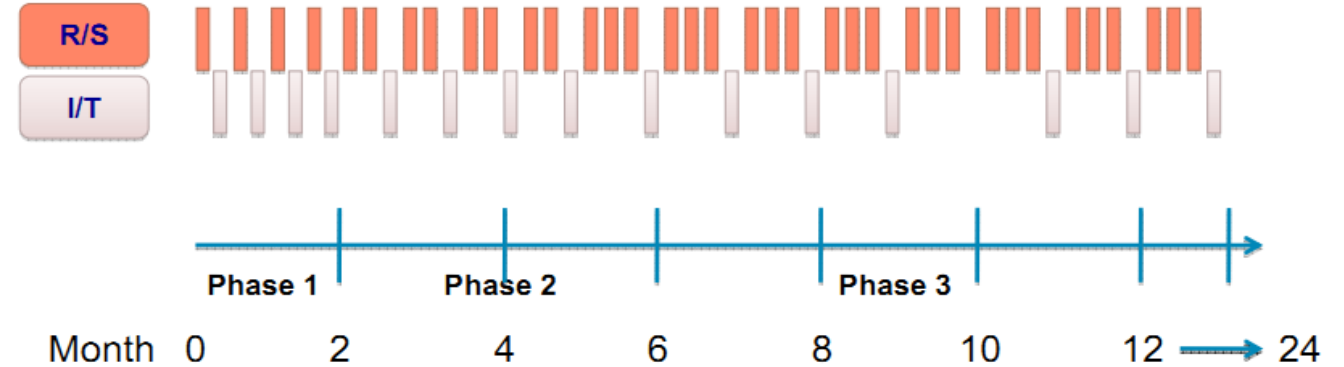
Будущее терапии



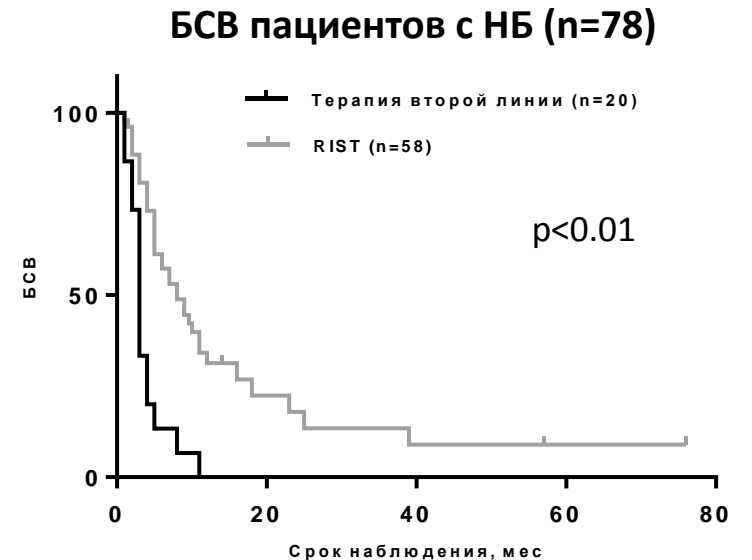
- **Первичная резистентность**
- **Резистентные рецидивы**
- **Рецидивы после ранее проведенной иммунотерапии**

ПХТ vs. RIST

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- RIST-rNB-2011, исследование II фазы (NCT01467986): сравнение RIST с I/T у пациентов с первично-резистентными формами и рецидивами НБ группы высокого риска.
- Всего 124 пациента с рецидивом (80%) или первичной резистентностью, MYCN+ в 39% случаев.
- Медиана БСВ 11 мес в группе RIST vs 5 мес в группе IT ($p = 0.019$), медиана ОВ 16 мес vs 4 мес ($p = 0.018$). Наиболее выраженный эффект при раннем рецидиве в группе MYCN+.
- Сравнимая токсичность



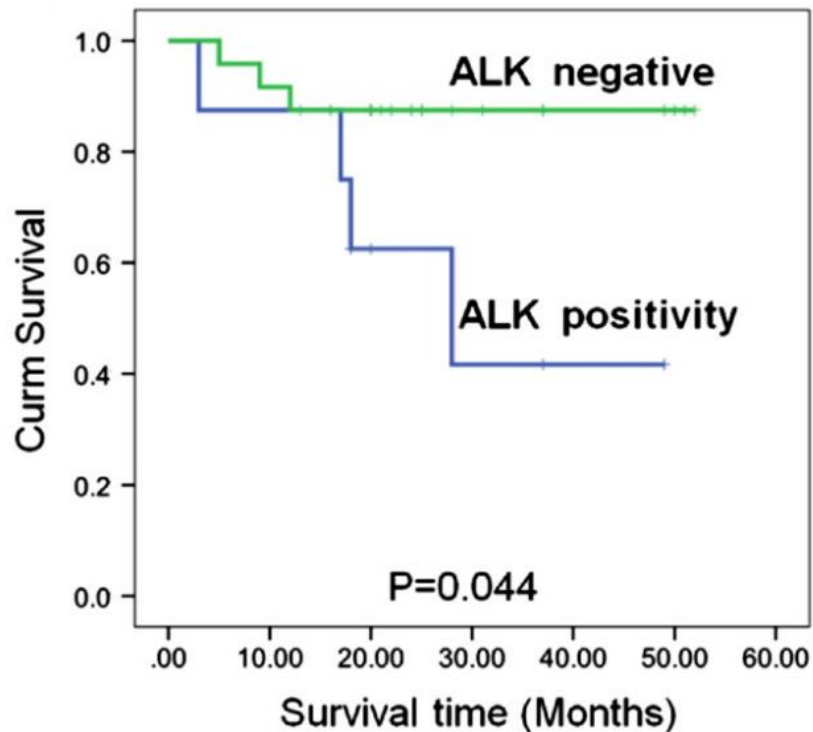
Частота вовлечения ALK

Когорта	N исследований	Частота выявления мутаций / амплификации
COG ANBL0532	242 пациента, HRG	53 (22%) мутация ALK 8 (3,3%) амплификация ALK
SIOPEN-HR-NBL1	721 пациент, HRG	61 (8,5%) активирующая мутация ALK
INFORM	124 пациента	28 (22,5%) активирующая мутация или амплификация ALK
GPOH	717 пациентов, HRG 198 случаев рецидива	75 (10,5%) активирующая мутация ALK 35 (17,7%) активирующая мутация ALK

- Мутация ALK в одном случае, длительная (14 мес) стабилизация на фоне терапии алектинибом

Ингибиторы ALK

Экспрессия ALK и прогноз заболевания¹



- Мутации и повышение экспрессии ALK ассоциированы с неблагоприятным прогнозом¹
- В исследовании 1-2 фазы ответы были зафиксированы у 3/11 пациентов с известными мутациями (Arg1275Gln), у 1/23 пациентов без известной мутации.
- Отдельные клинические случаи эффективности ингибиторов ALK^{2,3}

Опыт НИИДОГиТ

- Длительный ответ (10 мес) у пациента со вторым рецидивом;
- Ответ в течение 6 месяцев у пациента с прогрессированием на фоне терапии 2й и 3й линии;
- Высокая токсичность у реципиента алло-ТГСК

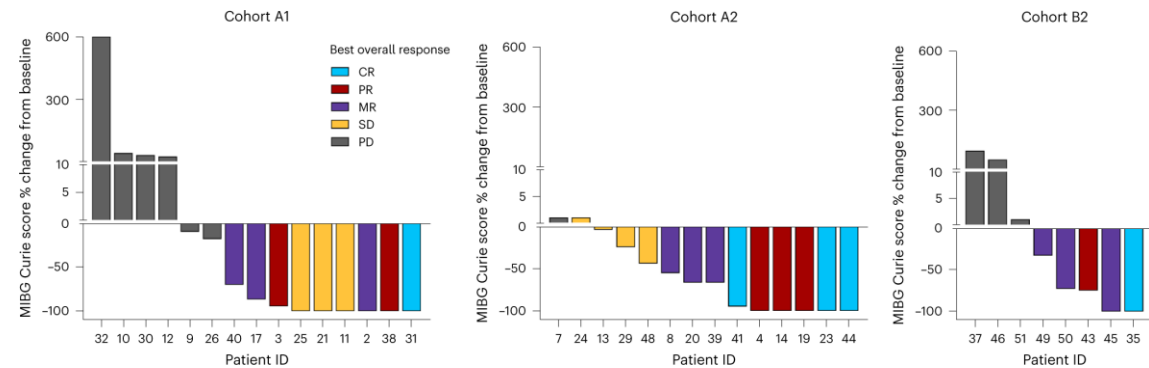
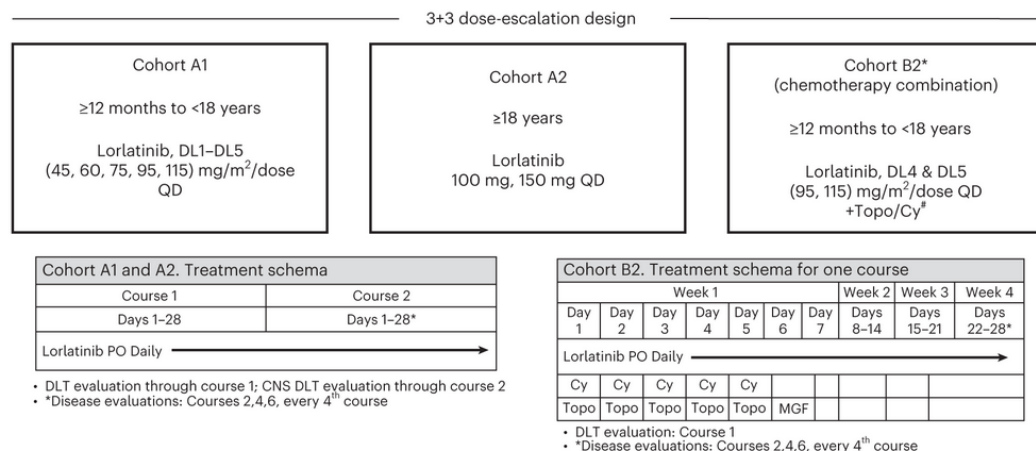
¹Wang M et al. Exp Mol Pathol 2013 Oct;95(2):124-30.

²Mossé YP et al. Lancet Oncol 2013 May;14(6):472-80.

³Verma P et al. South Asian J Cancer 2017 Apr-Jun;6(2):89-90.

⁴Heath JA et al. Pediatr Blood Cancer 2018 Jul;65(7):e27055. doi: 10.1002/pbc.27055.

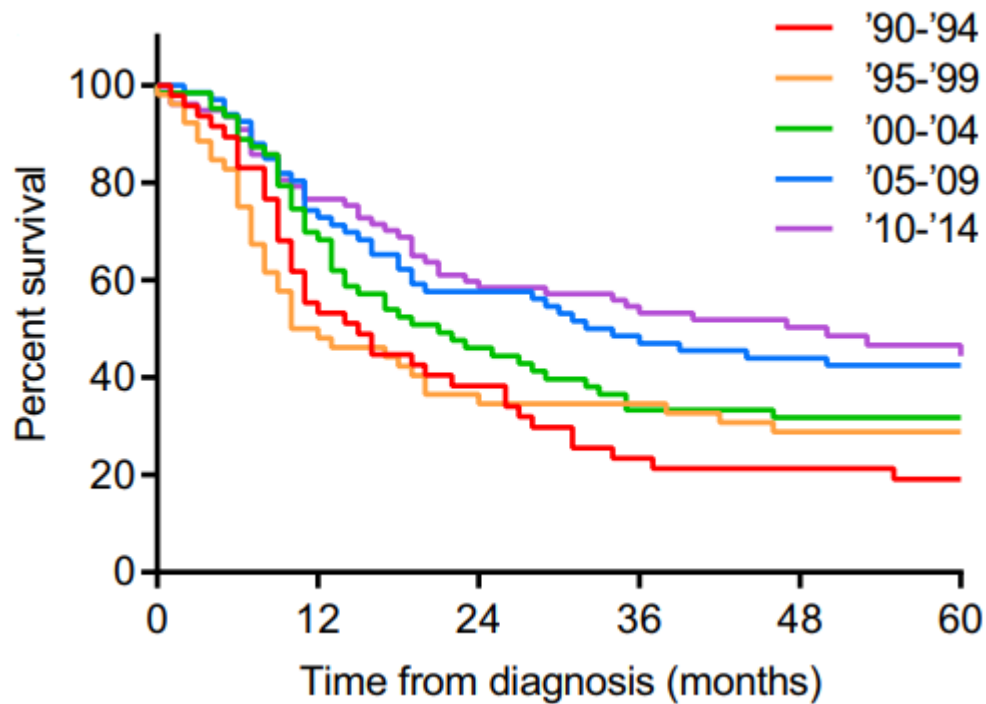
Результаты терапии лорлатинибом



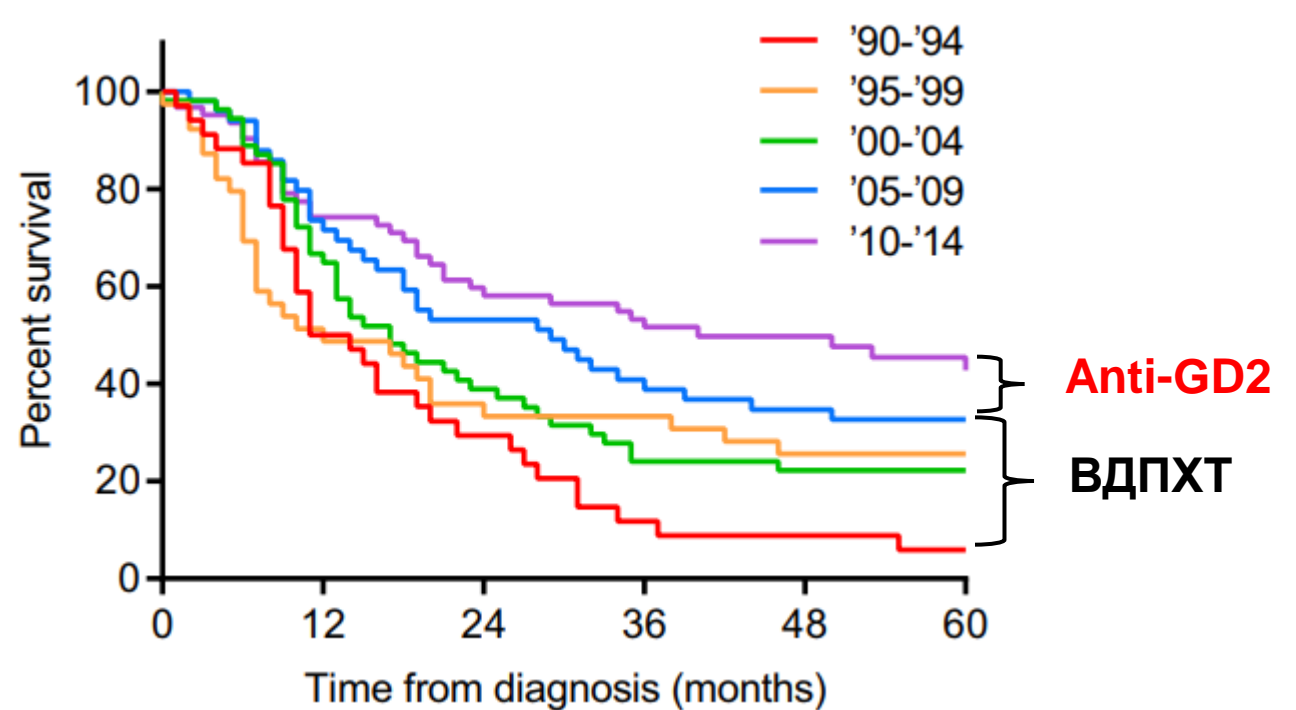
- Ответ на монотерапию (ПО/ЧО/стабилизация) в когорте <18 лет в 30% случаев; ≥18 лет в 67% случаев
- При комбинации с ПХТ у детей 63% ответов, в 13 из 27 (48%) случаев полный ответ по данным сцинтиграфии с MIBG
- Выявлен механизм резистентности у 11 (27%) пациентов, потерявших ответ: дополнительные мутации в сигнальном пути RAS-MAPK, дополнительные мутации ALK

Влияние на результаты лечения

Общая выживаемость (n=306)

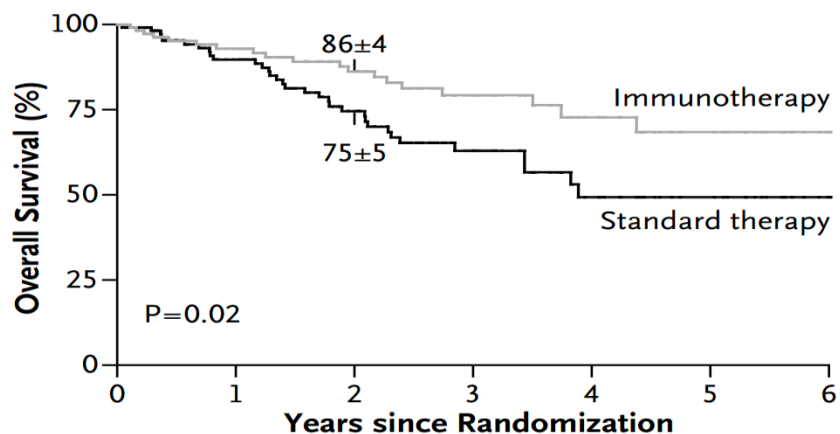


Бессобытийная выживаемость (n=306)

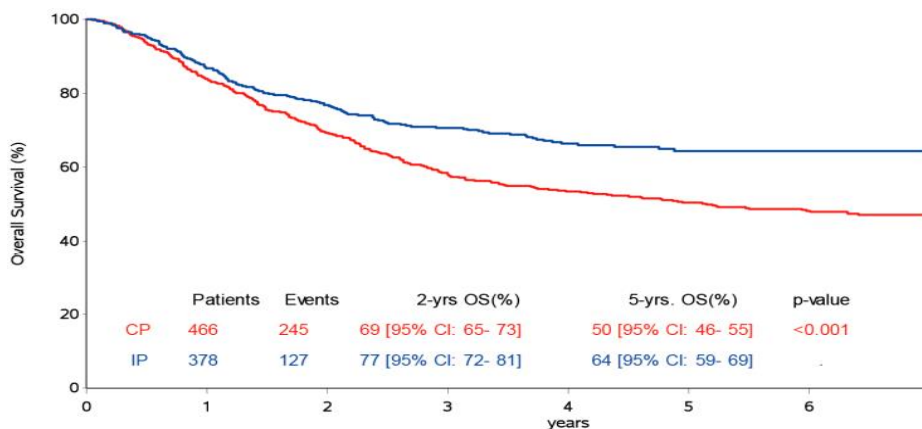


«Эра иммунотерапии»

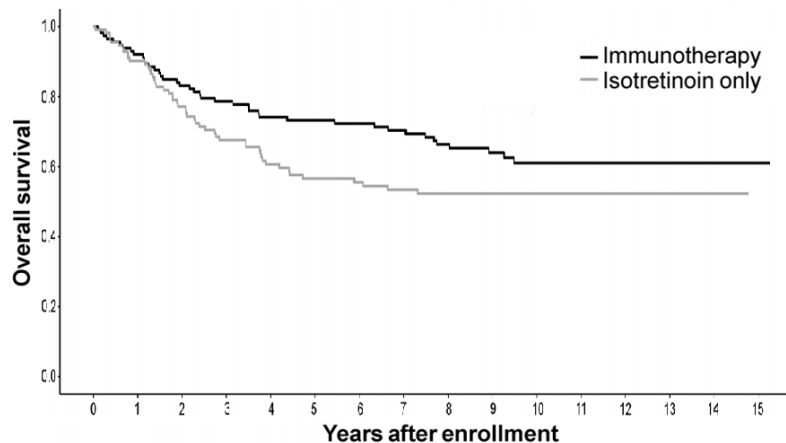
Когорта COG ANBL0032 (n=226)



Когорта SIOPEN HR-NBL1 (n=844)



Отдаленные результаты



Применение поддерживающей анти-GD2 терапии у пациентов с НБ группы высокого риска приводит к достоверному увеличению долгосрочной БСВ и ОВ

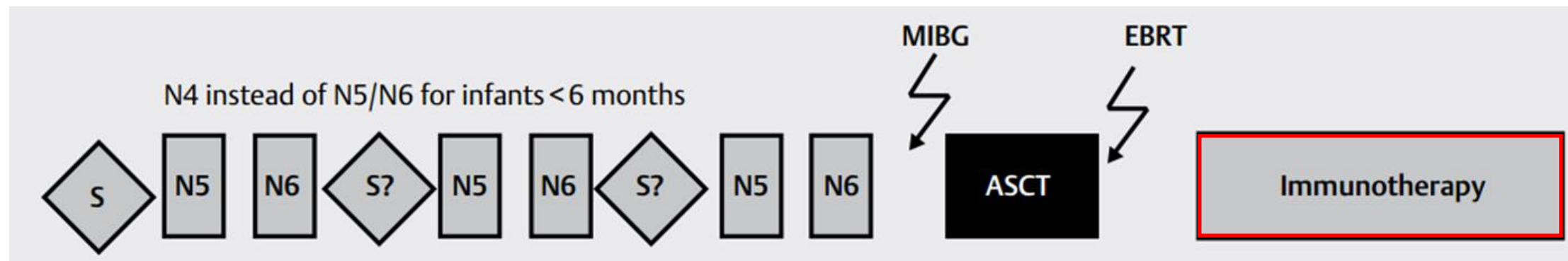
¹ Yu A et al. NEJM 2010;363:1324-1334

² Yu AL et al. Clin Cancer Res 2021;27(8):2179-2189.

³ Ladenstein R et al. Cancers (Basel) 2020 12(2): 309.

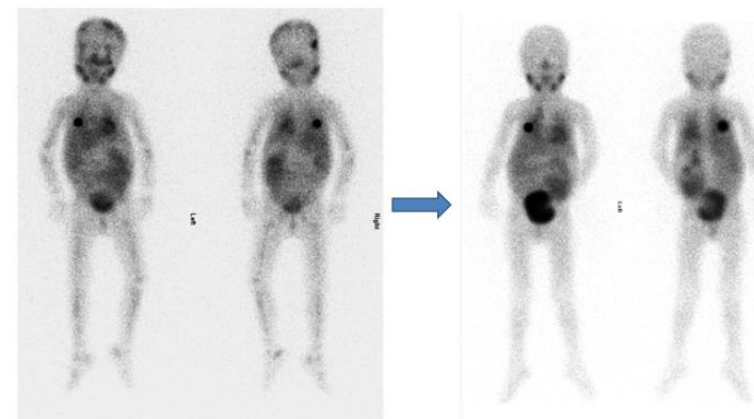
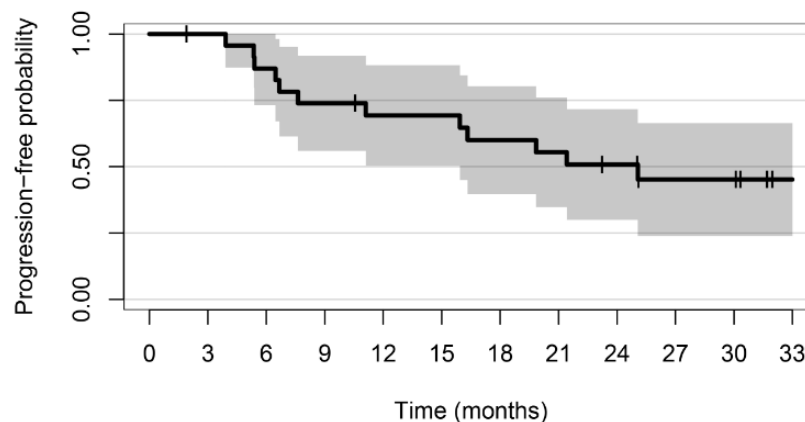
Терапия в группе высокого риска

Концепция лечения группы высокого риска GPOH ¹



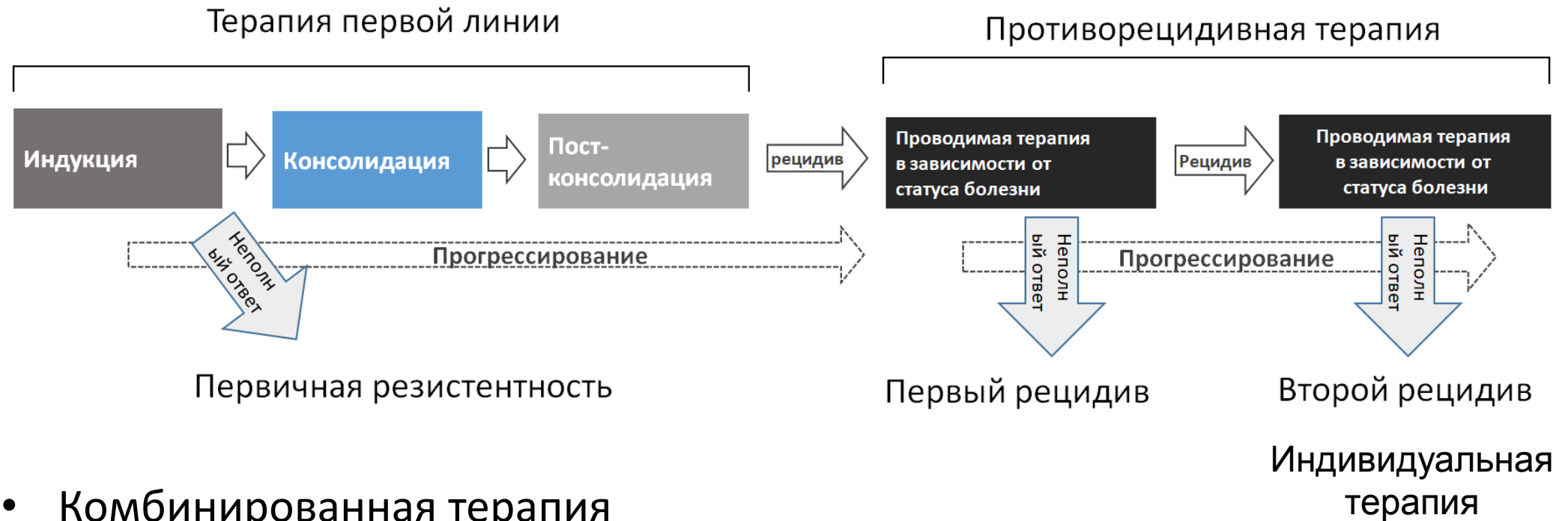
- Значительная часть пациентов получает терапию в соответствии с текущими рекомендациями GPOH

Тактика снижения ИНТЕНСИВНОСТИ



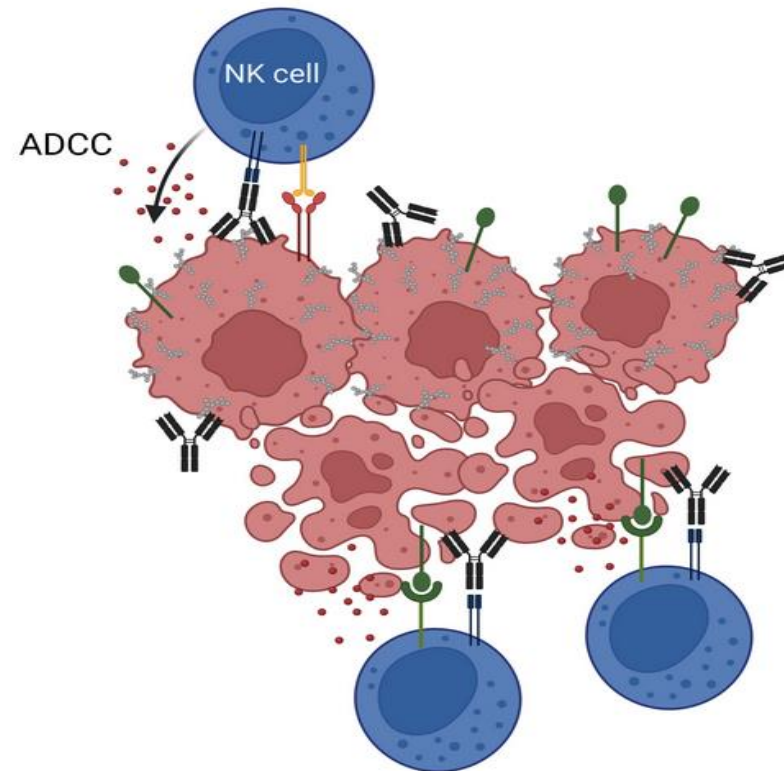
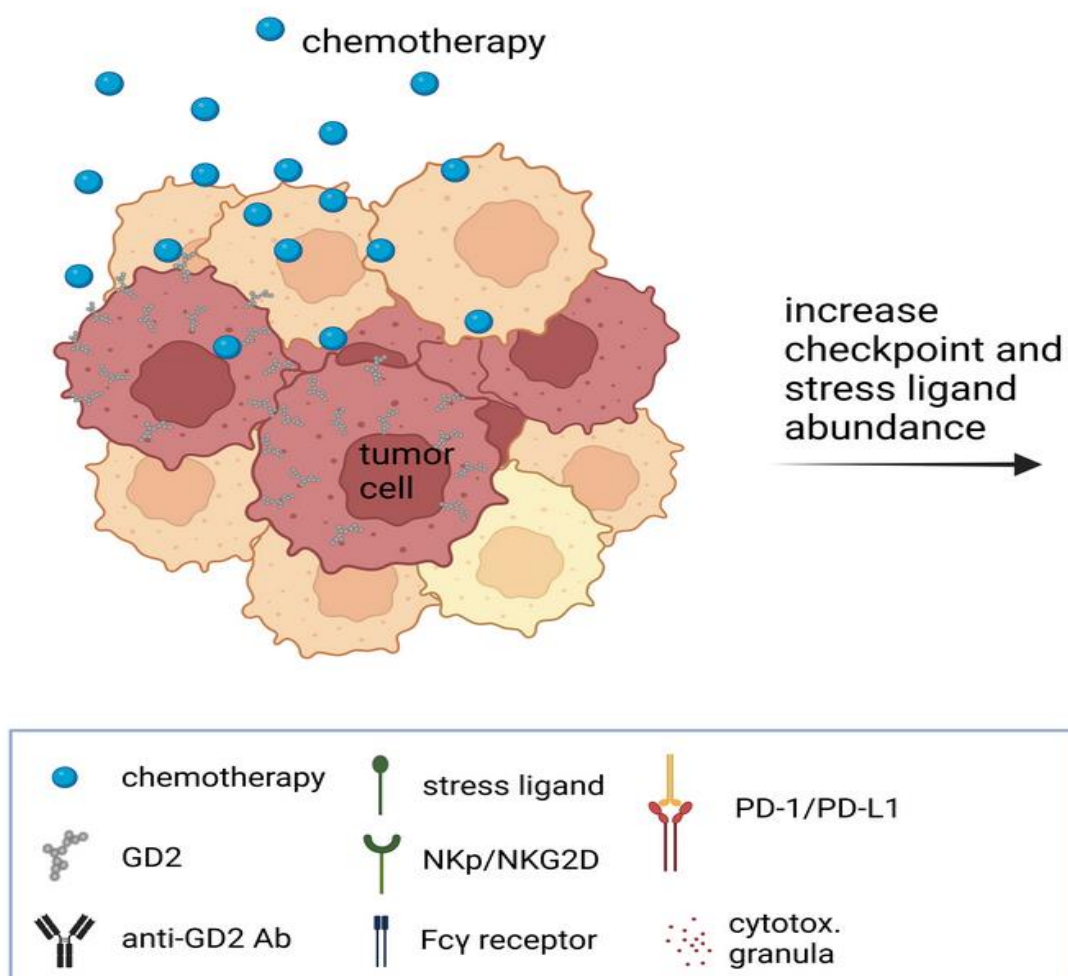
- Исследование II фазы Memorial Sloan Kettering 16-1643 (Clinicaltrials.gov NCT03033303): оценка БСВ у пациентов с НБ группы высокого риска в первой ПР, получивших накситамаб + ГМ-КСФ + роаккутан (5 циклов терапии).
- Всего 59 пациентов (2017-2020), медиана возраста 3,5 года.
- 2-летняя БСВ 73%, ОВ 97%.
- 5/16 рецидивов в ЦНС. А
- Отсутствие преимущества в группе с предшествующей ауто-ТГСК.

Возможная тактика преодоления резистентности

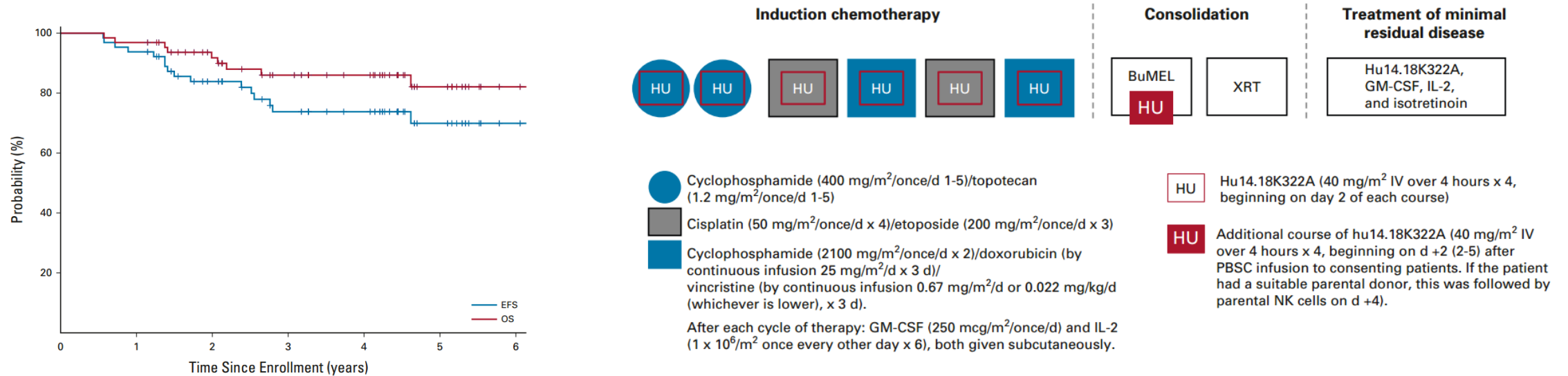


- Комбинированная терапия
- Изменение стратегии терапии (перенос иммунотерапии из постконсолидации в индукцию)
- Повторная иммунотерапия

Механизм действия комбинированной терапии



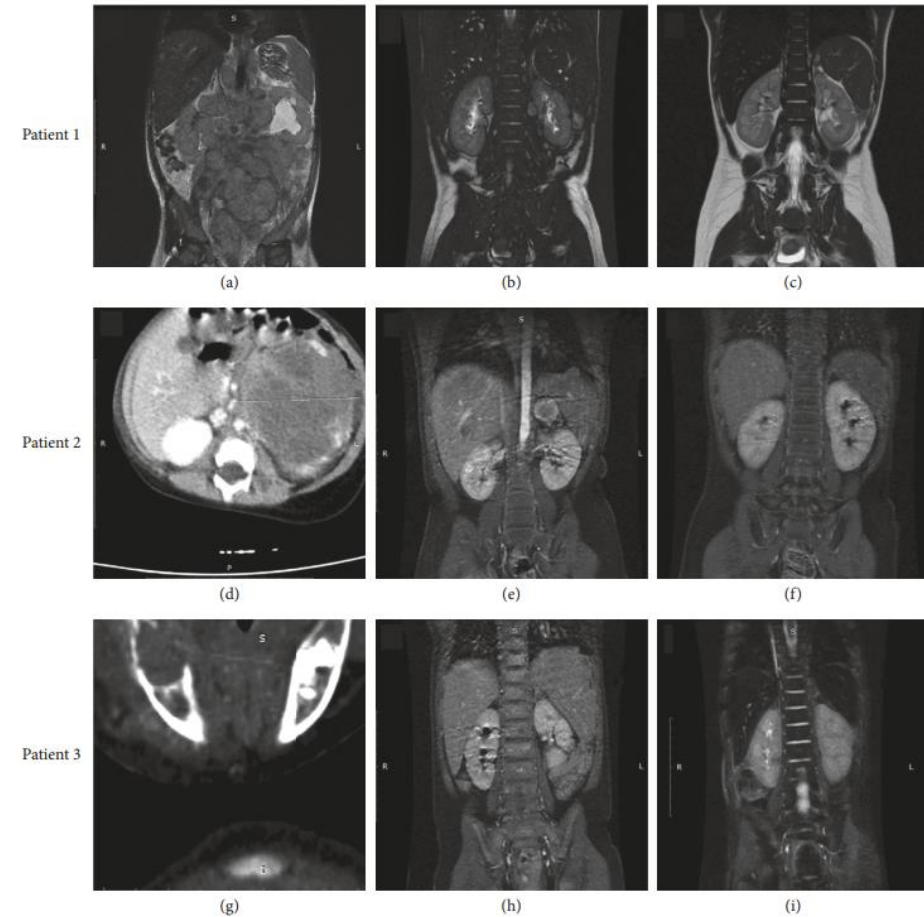
Повышение числа ответов на индукционную терапию



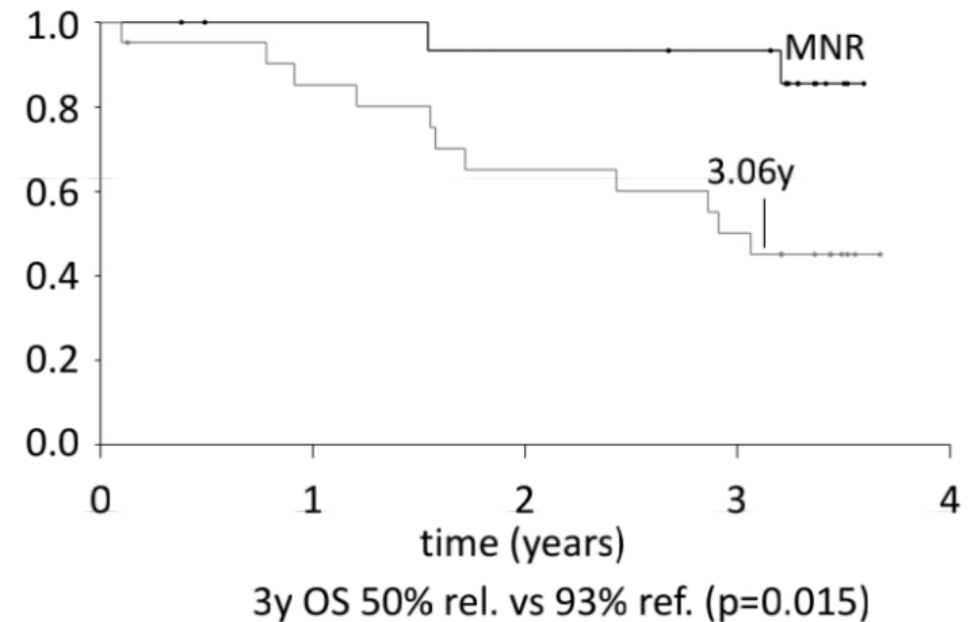
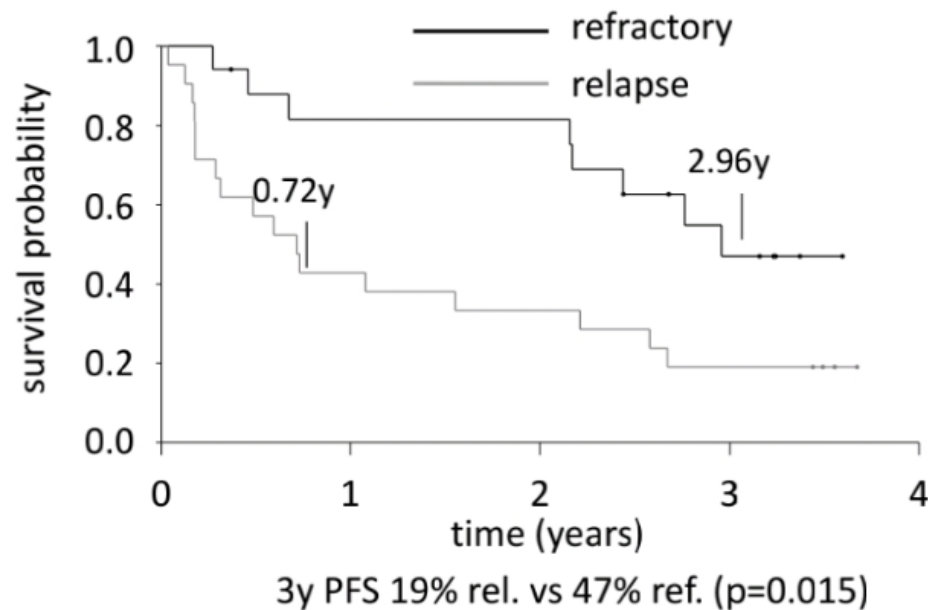
- 64 пациента, получивших hu14.18K322A в индукционной терапии.
- ЧО/ПО после 2 циклов у 42/63 пациентов (66.7%; 95% CI, 55.0 to 78.3), степень ответа коррелировала с медианой пиковой сывороточной концентрации hu14.18K322A
- ЧО/ПО после завершения индукционной терапии у 62/63 (97%) пациентов 3-летняя БСВ 73.7%, ОВ 86.0%

Повышение числа ответов на индукционную терапию

	At diagnosis	After COJEC	After DB
Patient 1	<ul style="list-style-type: none"> (i) Primary tumor in left adrenal gland with metastases in multiple abdominal and pelvic lymph nodes (ii) Intra- and retroperitoneal masses ≤ 5 cm on MRI (iii) CNS and BM involvement (iv) Very high tumor marker levels (NSE, HVA, VMA) 	<ul style="list-style-type: none"> (i) Shrinkage of tumors to ≤ 2 cm on MRI (ii) Total response according to BM involvement (iii) PR according to CNS involvement 	<p>After 1 cycle of DB and 2 cycles of TVD:</p> <ul style="list-style-type: none"> (i) Further shrinkage of tumors on MRI (ii) NSE, HVA, and VMA levels normalized (iii) No evidence of leptomeningeal thickening and solid CNS metastases on CNS MRI (iv) No BM involvement <p>After surgery:</p> <ul style="list-style-type: none"> (i) 100% tumor necrosis <p>After 1 cycle of TVD, 1 cycle of DB, BuMel + ASCT, and 4 cycles of DB:</p> <ul style="list-style-type: none"> (i) No residual tumors in the abdomen and no signs of leptomeningeal thickening on MRI (ii) No BM involvement (iii) Patient in full remission
Patient 2	<ul style="list-style-type: none"> (i) Primary tumor in left adrenal gland with enlarged para-aortic and paracaval lymph nodes (ii) Total BM involvement (iii) High tumor marker levels (NSE, HVA, VMA) 	<ul style="list-style-type: none"> (i) PR in primary tumor and local lymph nodes on MRI (ii) No BM involvement 	<p>After 1 cycle of DB and surgery:</p> <ul style="list-style-type: none"> (i) 98% tumor necrosis <p>After another cycle of DB:</p> <ul style="list-style-type: none"> (i) NSE, HVA, and VMA levels normalized <p>After BuMel + ASCT and 3 cycles of DB:</p> <ul style="list-style-type: none"> (i) No residual tumors on MRI (ii) No BM involvement (iii) Patient in full remission
Patient 3	<ul style="list-style-type: none"> (i) Primary tumor in left adrenal gland with bone metastasis on mandibula and local cervical lymphadenitis (ii) Total BM involvement (iii) High tumor marker levels (NSE, HVA, VMA) 	<ul style="list-style-type: none"> (i) Patient developed severe pancytopenia due to BM progression accompanied by secondary paraneoplastic membranous glomerulopathy (ii) Higher HVA and VMA than those at diagnosis (iii) Shrinkage of primary tumor and metastasis on mandibula and full regression in cervical lymph nodes on MRI (iv) Both kidneys were 2 cm larger than on the initial MRI, without focal lesions and with a normal ratio (v) Nearly total BM involvement 	<p>After 3 cycles of DB and I/T:</p> <ul style="list-style-type: none"> (i) Size of kidneys and renal function normalized (ii) No BM involvement (iii) Tumor markers normalized <p>After surgery and radiotherapy:</p> <ul style="list-style-type: none"> (i) No residual tumors on MRI <p>After BuMel + ASCT and another 3 cycles of DB:</p> <ul style="list-style-type: none"> (i) Patient in full remission according to tumor markers, trephine biopsy, CNS and abdominal MRI, and DOTA



Моно-иммуноterapia при резистентности или рецидиве

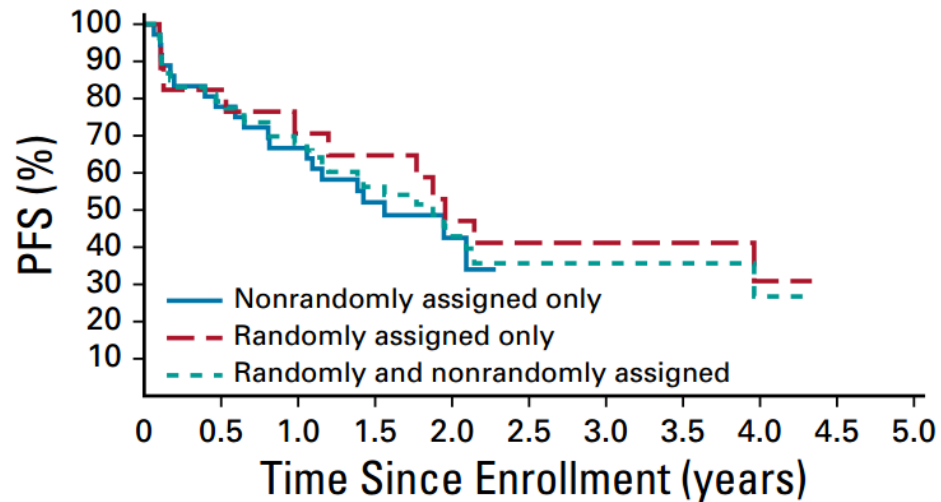


- 38 пациентов с первичной резистентностью/рецидивом
- 5 циклов монотерапии диутуксимабом бета (10 мг/м² x 10) без IL-2
- 26% ЧО/ПО (50%) в группе первичной резистентности, медиана длительности ответа 238 дней



Химио-иммуноterapia

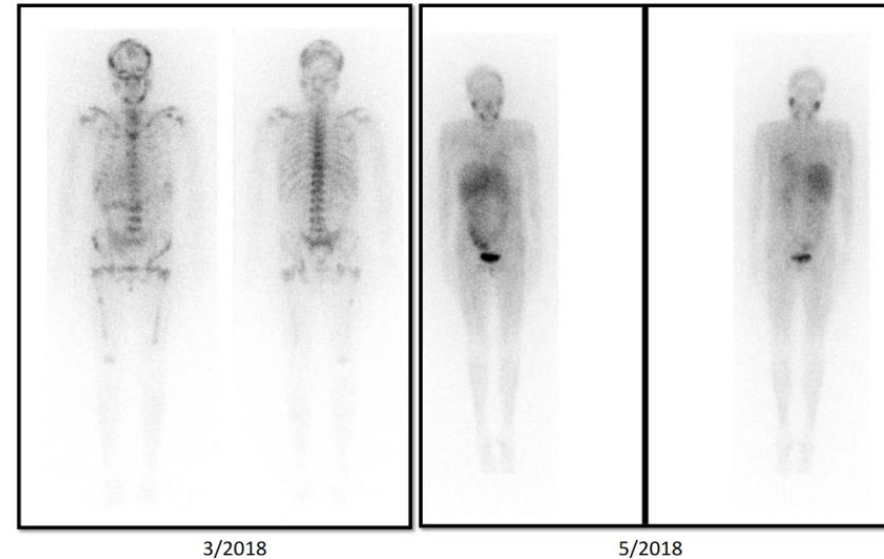
Эффективность динутуксимаба ¹



- ПО/ЧО у 22/53 пациентов (41,5%), стабилизация у 22/53 (41,5%)
- 1-летняя БСВ и ОВ 67.9% ± 6.4% (95% CI, 55.4% to 80.5%) и 84.9% ± 4.9% (95% CI, 75.3% to 94.6%), соответственно

¹ Mody R et al. J Clin Oncol 2020 Apr 28;JCO2000203.

Эффективность накситамаба ²



- Ответы: ПО (26%), ЧО (11%), в том числе у 64% пациентов, ранее получавших ПХТ и 42%, получавших иммунотерапию
- Меньше ответов (25%) при амплификации MYCN

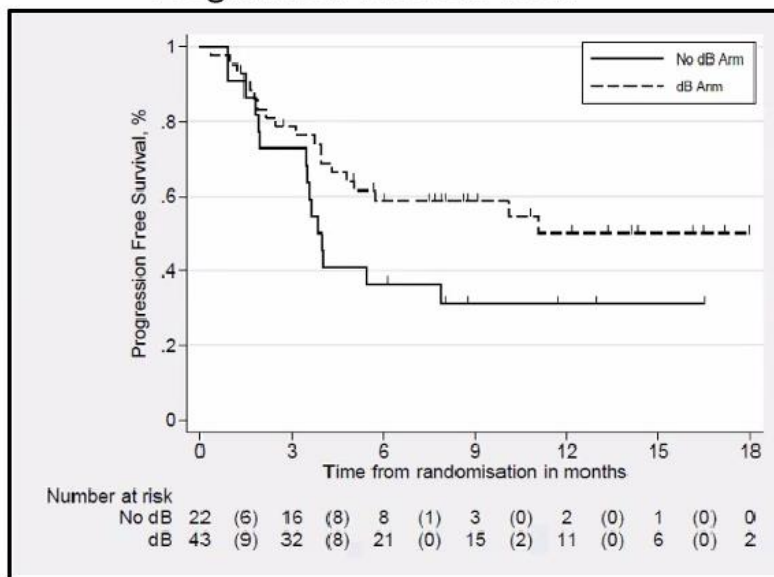
² Modak S et al. © 2022 by American Society of Clinical Oncology.

Результаты BEACON Immuno (n=43)

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Progression Free Survival

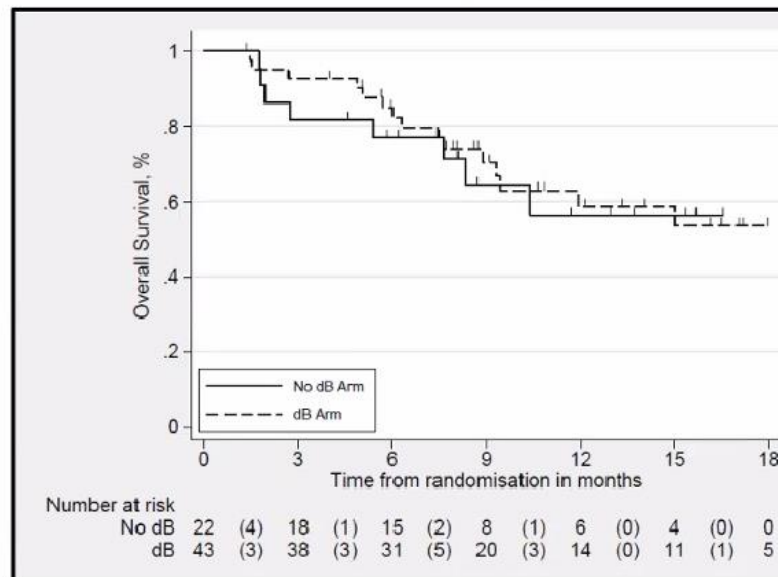


1 year PFS 27% (no dB) and 57% (+dB)

Unadjusted HR 0.56 (p=0.09)

Adjusted HR (topo admin) 0.63 p=0.19

Overall survival



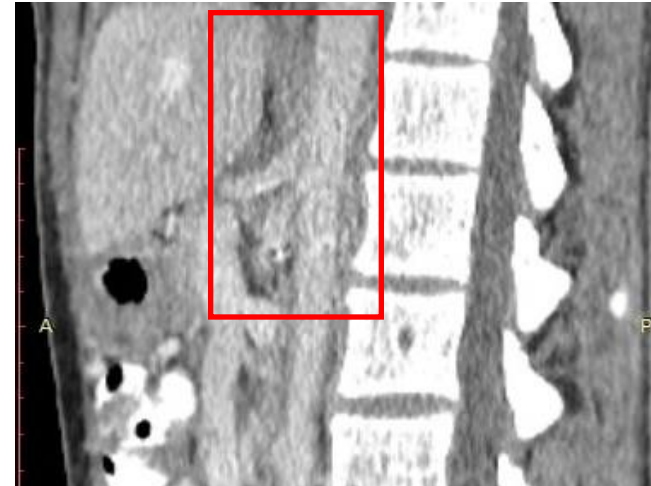
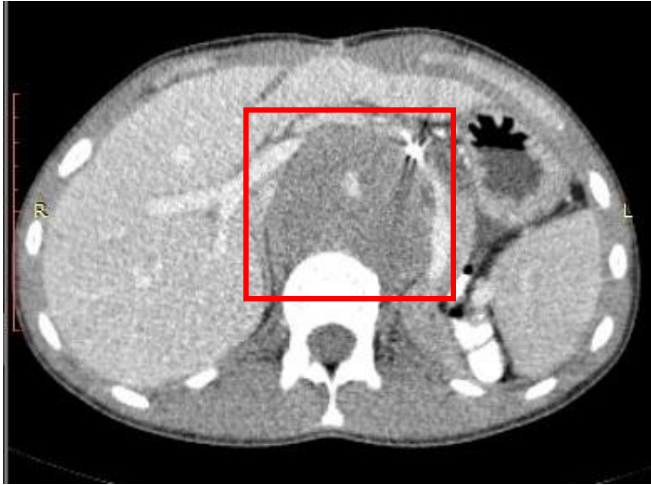
Unadjusted HR 0.89 (p=0.79)

Adjusted HR (topo admin.) 0.99 p=0.99

12 patients in 'no dB' arm received cross over treatment

	No dB (22)	+ dB (43)
Complete response	2 (9.1%)	5 (11.6%)
Partial response	2 (9.1%)	10 (23.3%)
Stable disease	12 (54.5%)	16 (37.2%)
Progressive disease	6 (27.3%)	10 (23.2%)
Withdrawn early because of toxicity	0	2 (4.6%)
Overall response rate (PR + CR)	4 (18.2%)	15 (34.8%)

Клинический случай



- Низкодифференцированная нейробластома левого надпочечника IV стадия INSS, M стадия INRGSS, MYCNamp-, del1p36+, группа высокого риска (2011).
- Терапия по протоколу GPOH NB2004
- Первый поздний локальный рецидив (2017).
- Хирургическое лечение
- Второй ранний локальный рецидив (2018).
- Хирургическое лечение
- Третий локальный рецидив (2021)
- ПХТ второй линии (стабилизация)
- 5 циклов HITS

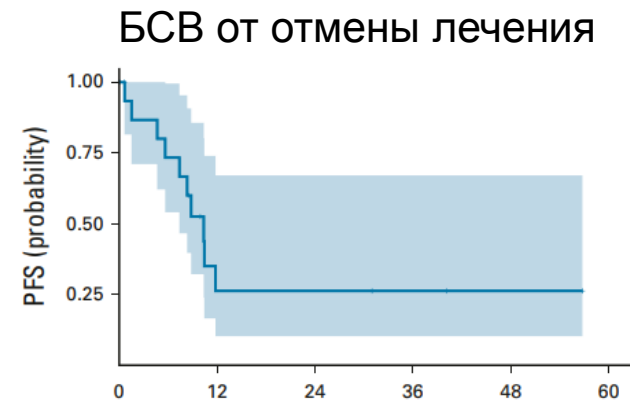
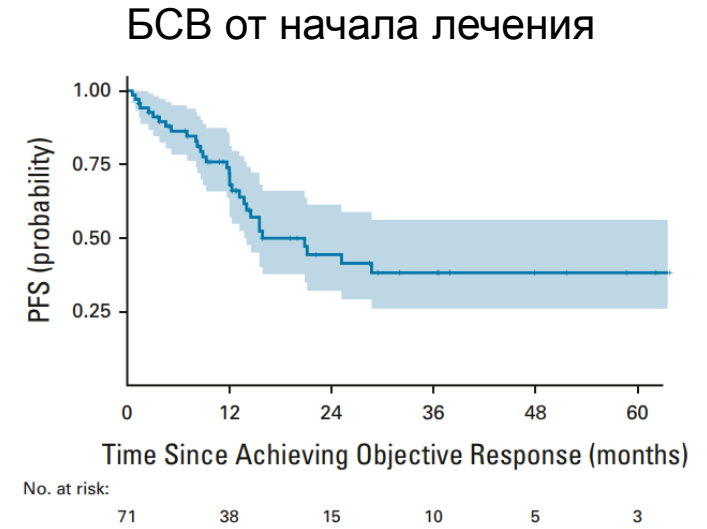
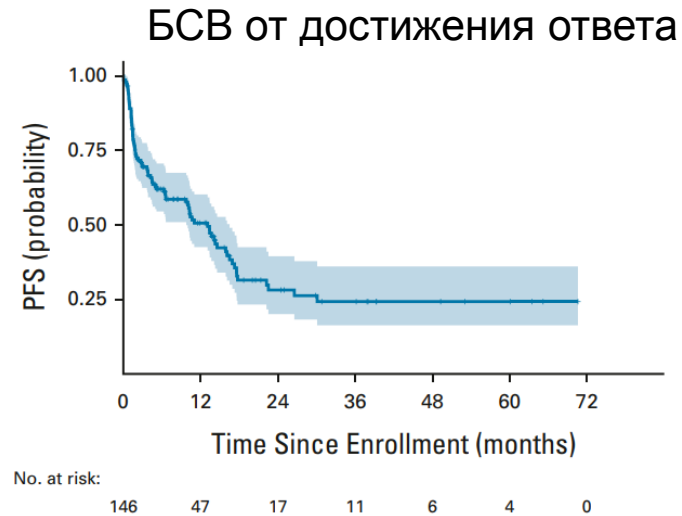
Применение для преодоления резистентности

Response	Best Response					No. Improved (%)	
	PD	SD	MR	PR	CR		
First response	PD	44	0	0	0	0 (0.0)	
	SD	—	31	1	1	3	5 (13.0)
	MR	—	—	6	0	3	3 (33.3)
	PR	—	—	—	20	14	14 (41.2)
	CR	—	—	—	—	23	0 (0)

NOTE. Response classification determined by International Neuroblastoma Response Criteria.

Abbreviations: CR, complete response; I/T/DIN, irinotecan/temozolomide/dinutuximab; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease.

- Медиана в 4,5 (1-31) циклов терапии
- 2-летняя БСВ 28%
- Медиана длительности ответа 15,9 мес



Повторное проведение химио-иммунотерапии



Characterizing Response to Repeated Episodes of Chemoimmunotherapy in Patients with Relapsed and Refractory Neuroblastoma

Oneyama S¹, Prorok R¹, Frazer B¹, Marachelian A^{1,2}

¹Children's Hospital Los Angeles, Pediatric Hematology Oncology, Los Angeles, California, United States, ²University of Southern California, Department of Pediatrics, Los Angeles, California, United States

Background:

Temozolomide, Irinotecan and Dinutuximab (T/I/D) is a mainstay in treatment of relapsed and refractory neuroblastoma (RR-NB). Alternative chemoimmunotherapy (CI): Cyclophosphamide, Topotecan and Dinutuximab (C/T/D) is utilized with limited data describing response. Understanding how RR-NB responds to repeated CI could guide therapeutic decision-making.

Aim:

Describe response to repeated administration of CI in patients with RR disease

Methods:

Retrospective study at Children's Hospital Los Angeles to evaluate patients who received 2 or more treatment episodes (TEs) of CI for RR-NB.

Results:

Nineteen patients were identified. Fourteen patients received T/I/D for at least 2 TEs (Group 1) and 10 patients received C/T/D following T/I/D for a subsequent TE (Group 2); Five patients fell into both Groups 1 and 2. For all TEs, median number of cycles was 4.5 (range 1-18).

For the first TE in Group 1, best overall response (BOR) was: 5 complete response (CR), 1 partial response (PR), 3 minor response (MR), 2 stable disease (SD), 1 progressive disease (PD) and 2 not evaluable. For the second TE with T/I/D, BOR rate of PR/CR was 57% and of PR/CR/MR was 71%. For patients who had PR/CR in first TE, BOR of PR/CR was 100% for subsequent TEs with T/I/D.

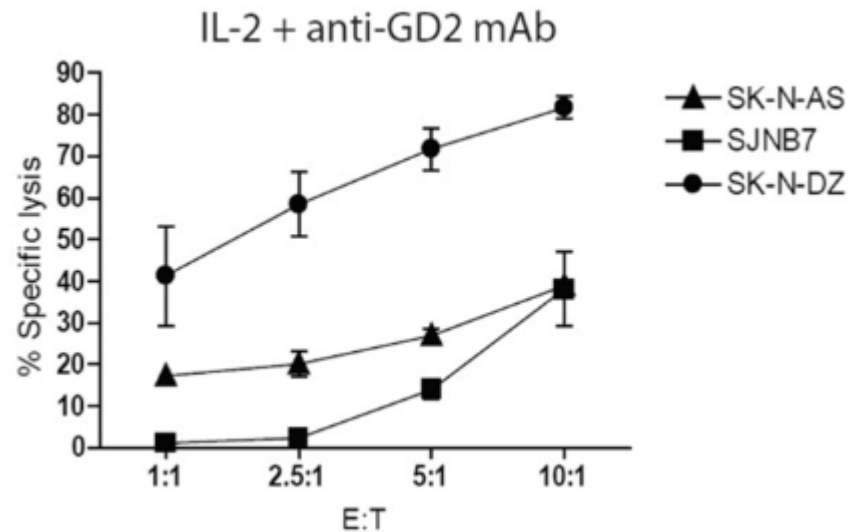
For the first TE in Group 2, BOR was: 3 CR, 1 PR, 2 MR and 4 SD. Three patients with initial response to T/I/D had PD in later cycles. BOR rate of CR/PR for C/T/D following T/I/D was 50%. For patients who had BOR of PR/CR in prior episodes of T/I/D, subsequent BOR of PR/CR when treated with C/T/D was 75%. For patients with prior BOR of MR or SD with T/I/D, 33% had BOR of PR/CR and 50% had BOR of SD when given C/T/D.

Conclusion:

Treatment with repeat CI results in BOR of CR/PR/MR for most patients with SD or better in first TE. For both T/I/D and C/T/D, having a BOR of CR/PR may be predictive of response in subsequent TEs. The use of C/T/D may result in response despite PD on T/I/D. Future studies to investigate the predictive potential of prior response to CI are needed.

- 19 пациентов, ранее получавших химио-иммунотерапию
- Клинический эффект в 71% случаев
- Ответ у 100% пациентов, ранее демонстрировавших ответ на химио-иммунотерапию

Роль экспрессии GD2



- 152 пациента с НБ группы высокого риска
- Экспрессия GD2 в 94% случаев
- 20 пациентов получили anti-GD2
- Рецидив в 5 случаях, снижение экспрессии GD2 при рецидиве

Low GD2 expression as a mechanism of resistance to chemoimmunotherapy with dinutuximab

Keyel M¹, Davidson H¹, Estrada A¹, Irwin M², Hogarty M³, Reynolds C¹
¹Cancer Center and Departments of Pediatrics, Internal Medicine, and Cell Biology and Biochemistry, School of Medicine, Texas Tech University Health Sciences Center Lubbock, TX, , United States, ²University of Toronto; Department of Pediatrics, Hospital for Sick Children, Toronto, ON, , Canada, ³University of Pennsylvania; Pediatrics, Children's Hospital of Philadelphia and Perelman School of Medicine, Philadelphia, PA, , United States

Plenary Session 4: Precision therapy, May 16, 2023, 2:30 PM - 3:30 PM

Introduction: Chemoimmunotherapy with anti-GD2 antibodies is used for treating progressive disease (PD) neuroblastoma and is being evaluated with induction chemotherapy. While most neuroblastomas express GD2, low or negative GD2-expressing neuroblastomas occur and may not benefit from anti-GD2 therapy. We sought to determine the relationship between GD2 expression and response to chemoimmunotherapy in patient-derived xenografts (PDXs) and to determine the frequency of low GD2 expression in neuroblastoma patients.

Methods: We quantified dinutuximab binding to neuroblastoma cells in marrow by multi-color flow cytometry, gating out CD45+ cells and gating on cells positive for the non-GD2 neuroblastoma antibody HSN (binds to 100% of neuroblastomas) to define % positive and median fluorescence intensity (MFI). We assessed 104 bone marrow, 9 tumor, and 15 blood samples (88 pretherapy, 40 at PD) from neuroblastoma patients on Children's Oncology Group protocol ANBL00B1. Event-free survival (EFS) was assessed for subcutaneous PDXs in nu/nu mice treated with 15 mg/kg temozolomide (TMZ) + irinotecan 7.5 mg/kg (IRN) (days 1-5 and 21-25) +/- 15 mg/kg dinutuximab (days 2, 4, 22, 24).

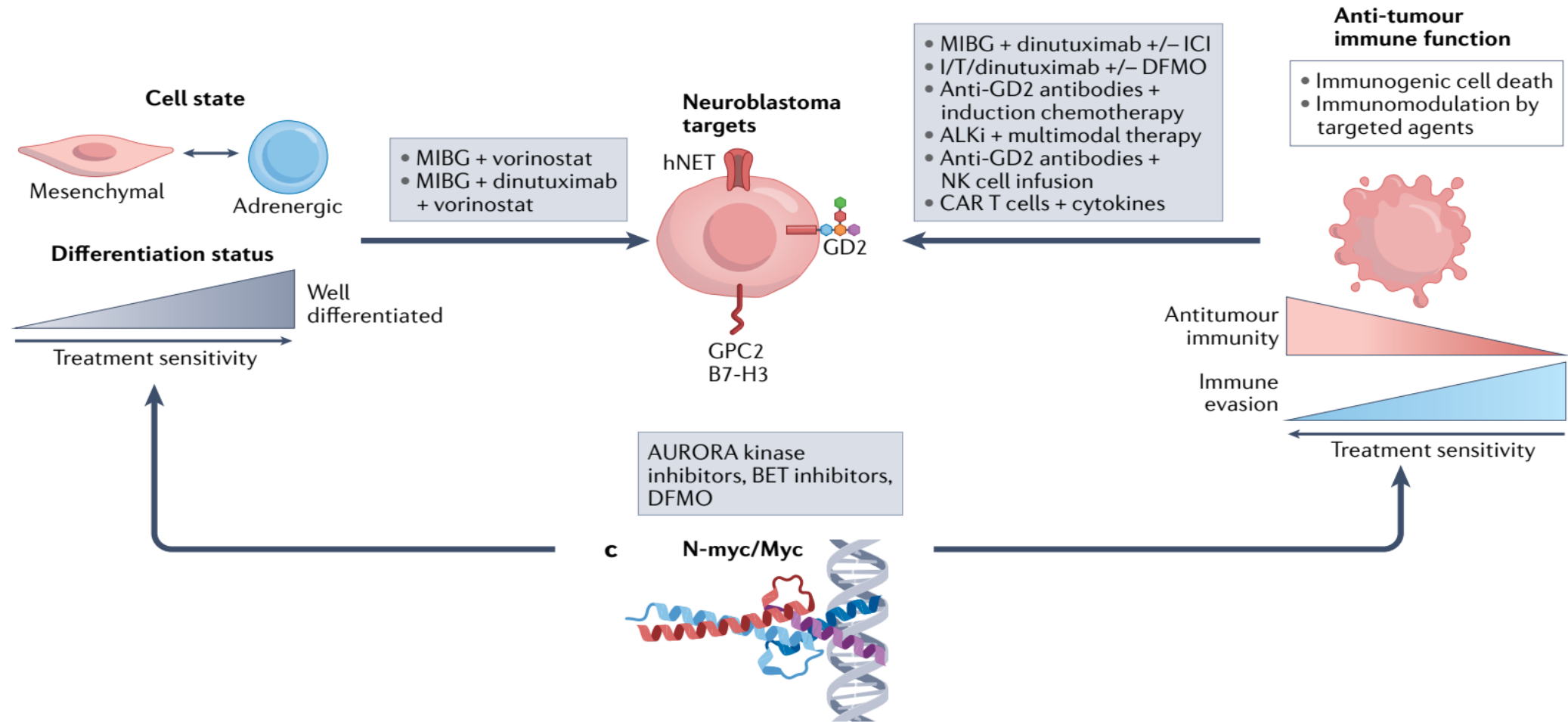
Results: Based on % positive and intensity of dinutuximab binding we defined 4 groups of patient samples: high, intermediate, low, and very low dinutuximab binding. GD2 expression was very low in 13% pretherapy and 15% PD patient samples, and low in 29% pretherapy and 40% PD samples. We assessed activity of TMZ/IRN +/- dinutuximab in neuroblastoma PDXs (3 PD, 1 established pretherapy). In COG-N-480x (pre-therapy PDX, high GD2 expression) dinutuximab increased 300-day EFS to 100% vs 20% with TMZ/IRN (p=0.04). In COG-N-452x (intermediate GD2 expression) dinutuximab increased 300-day EFS to 50% vs 0% for TMZ/IRN (p=0.01). Dinutuximab did not enhance TMZ/IRN activity in COG-N-519x (very low GD2) or Felix PDX (low GD2).

Conclusions: Low GD2 expression occurs in neuroblastoma. Neuroblastoma PDXs in nu/nu mice provide a preclinical model to assess antibody activity when combined with chemotherapy. In > 10% of patient marrow samples analyzed, dinutuximab binding was comparable to levels seen in PDX's that did not benefit from dinutuximab. Quantifying GD2 expression by flow cytometry is a potential biomarker of activity for dinutuximab in patients treated with anti-GD2 based chemoimmunotherapy.

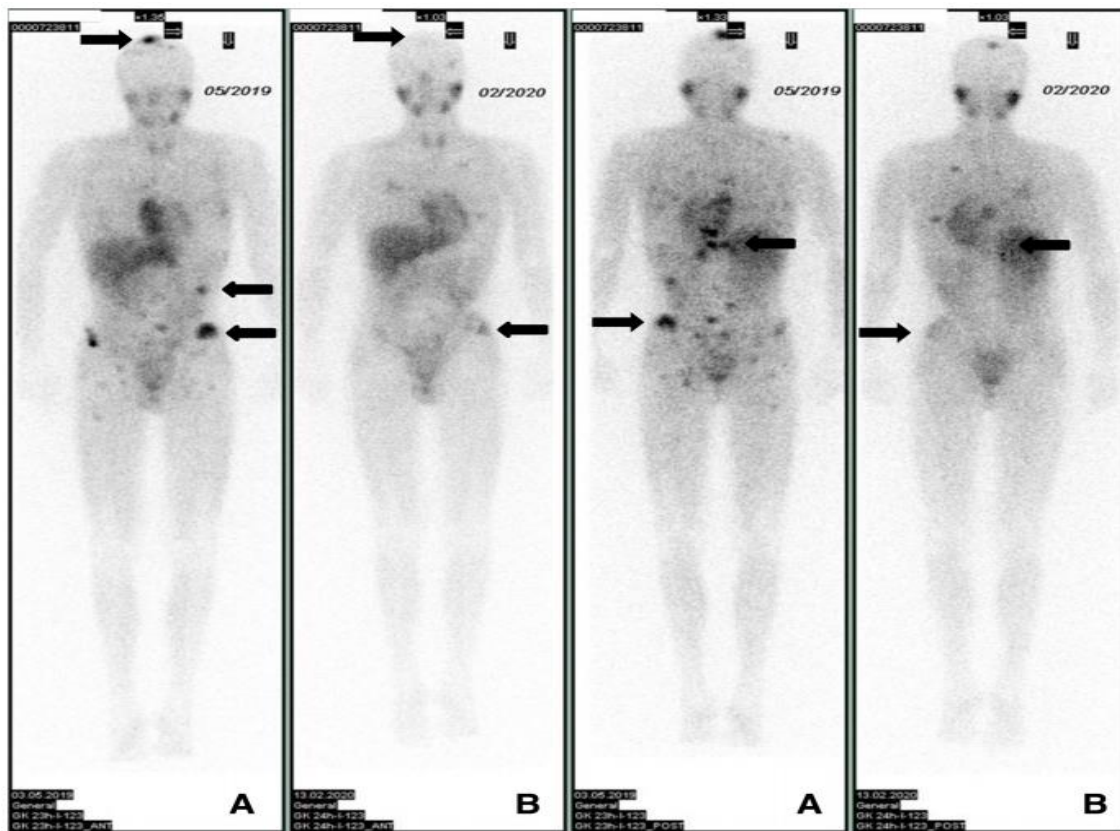
¹ Terzik T et al. *Pediatr Dev Pathol* 2018 Jul-Aug;21(4):355-362.

² Keyel M et al. ANR 2023 Oral Session

Возможные стратегии комбинированной иммунотерапии



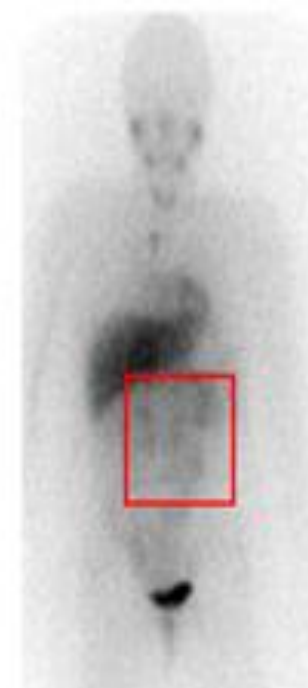
Комбинация с ИИКТ



Перед ТГСК

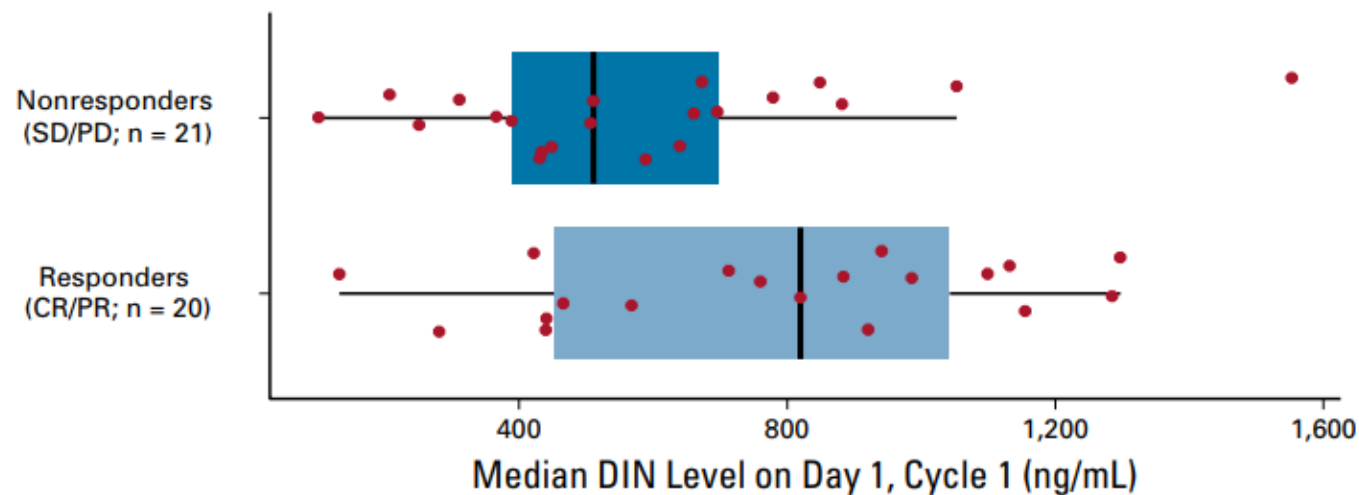
Д+120

Д+500

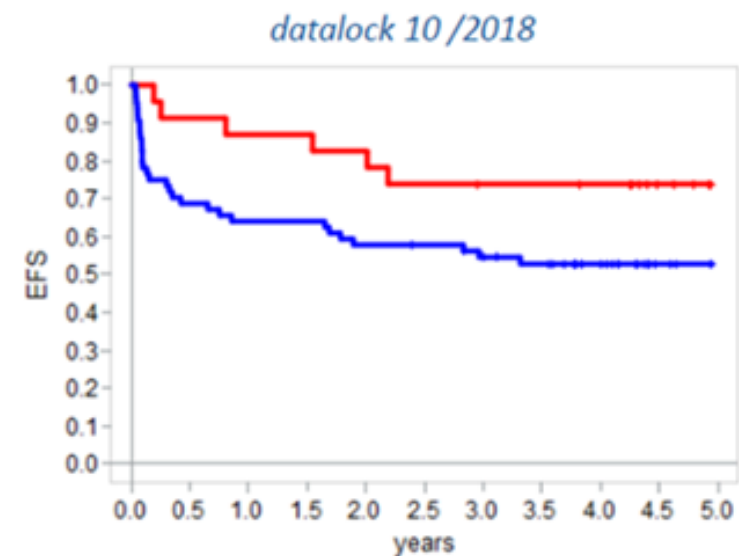


Иммуногенность антител к GD2

Сывороточный уровень антител и вероятность ответа



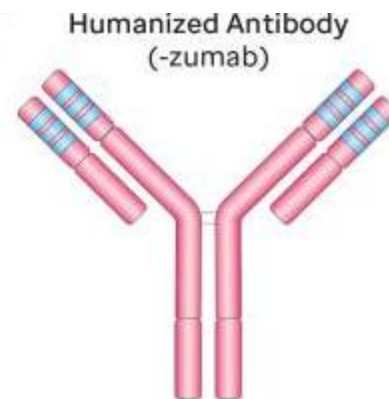
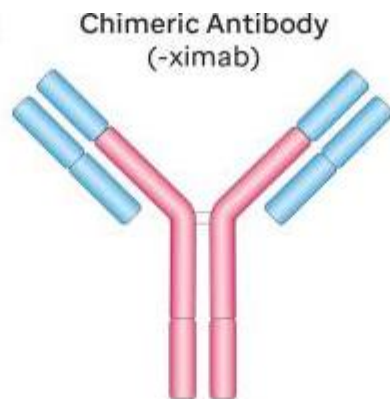
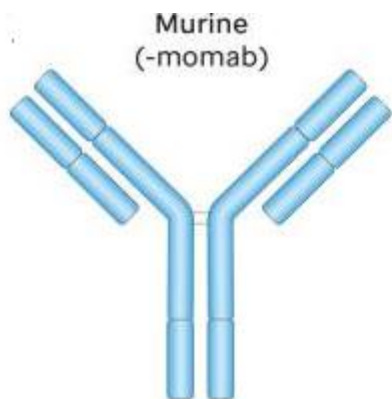
Уровень НАСА и БСВ



¹ Mody R et al. J Clin Oncol 2020 Apr 28;JCO2000203.

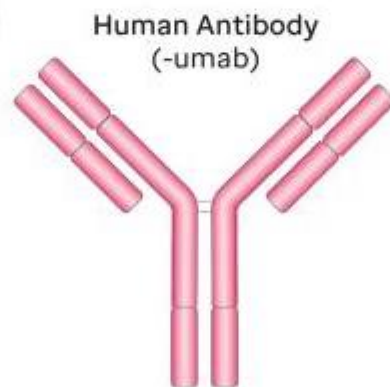
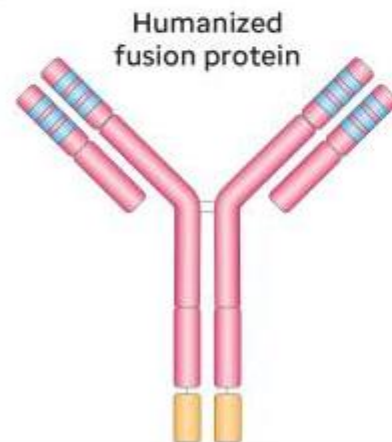
Siebert N, Lode H et al. (2018)

Модификация моноклональных антител



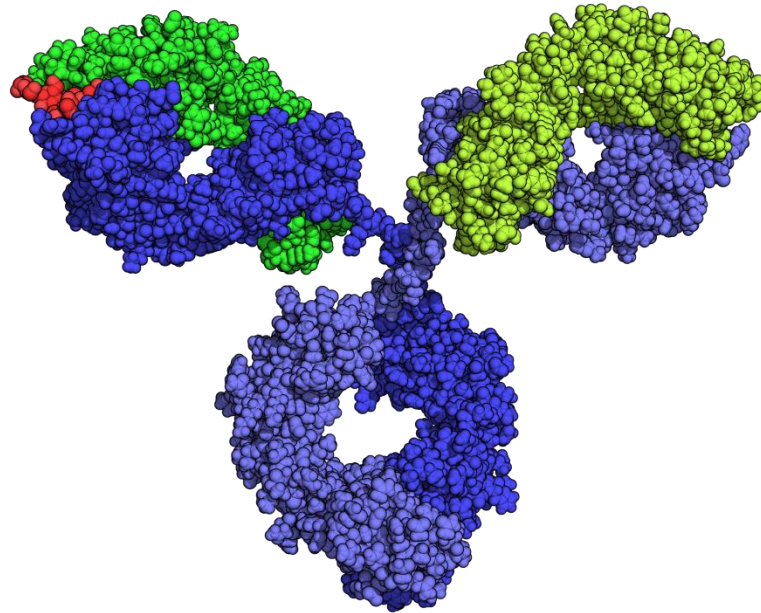
Dinutuximab (Ch14.18)
Dinutuximab beta

Hu14.18K322A
Naxitamab



- Снижение степени активации комплемента
- Менее выраженная нейропатическая боль
- Меньшая иммуногенность

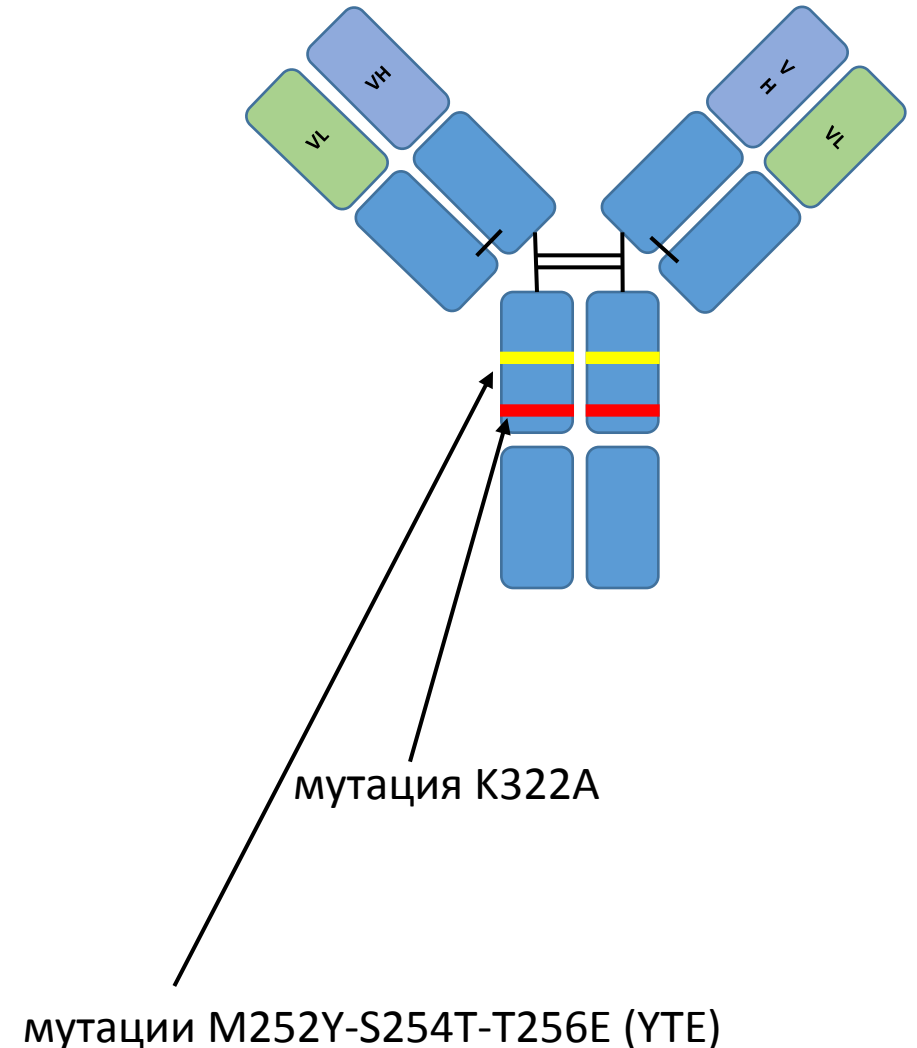
BCD-245 – оригинальная молекула BIOCAD, разрабатываемая для anti-GD2 терапии



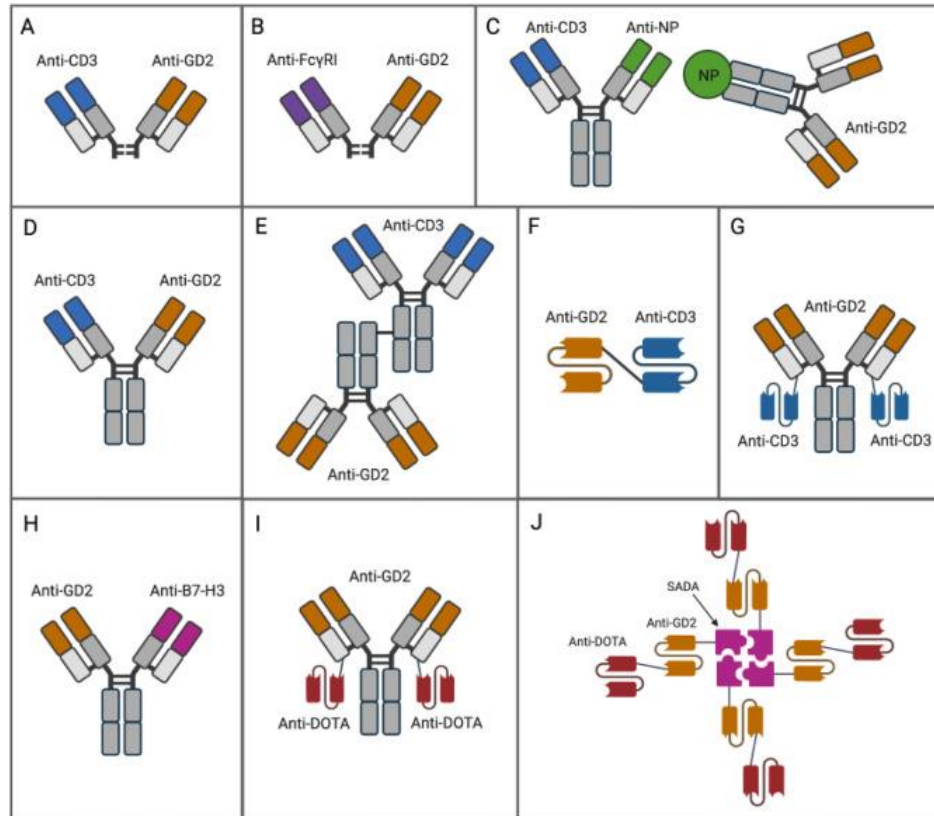
- моноклональное антитело, разрабатываемое для лечения нейробластомы
- специфически связывается с GD2, расположенным в большом количестве на поверхности клеток нейробластомы
- связывание BCD-245 с GD2 позволяет организму обнаруживать и уничтожать клетки опухоли

BСD-245 vs динутуксимаб бета

- Гуманизация VH/VL 80-81% - позволяет снизить вероятность образования аутоантител и токсичность
- Модификация «YTE» – позволяет увеличить период полужизни антитела в организме пациента, за счет чего можно снизить дозу и кратность введения препарата
- Модификация K322A - влияет на степень выраженности CDC эффекта, что отражается в снижении токсического и проявления off target эффектов
- Афукозилированный вариант антитела – достигается усиление связывания антитела с FcγR, что усиливает ADCC эффект – основной рабочий механизм действия антител

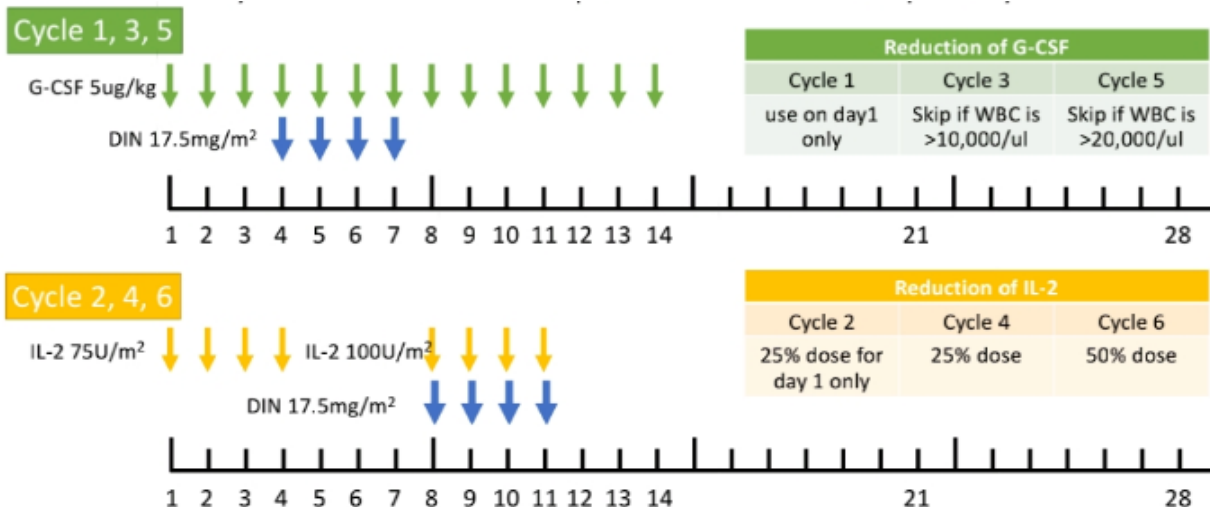


Биспецифические антитела



- Биспецифическое (GD2 и B7H3) антитело SNIPER
- B7H3 в основном экспрессируется опухолевыми клетками, в минимальной степени экспрессируется нормальными клетками, в т.ч. Клетками нервной системы
- Подтверждена методом проточной цитометрии специфичность к B7H3+/GD2+ опухолевым клеткам
- Связанное с радиоактивной меткой антитело специфически связывается в модели с B7H3+/GD2+ опухолями
- Цитотоксичность соответствует таковой для anti-GD2 аратов и превышает цитотоксичность anti-B7H3

Алло-ТГСК от KIR-несовместимого донора пуповинной крови



UPN	Age at first DIN	Primary refractory or Relapse	Source	Conditioning	Reason for discontinue DIN	Total courses of DIN
1	8	Primary	CB	MEL + TBI 12Gy	TMA, VOD/SOS Renal dysfunction	1
2	5	Relapse	CB	MEL + TBI 12Gy	Renal dysfunction	3
3	5	Relapse	CB	FLU + MEL + TBI 2 Gy	-	6
4	8	Relapse	CB	FLU + MEL + TBI 2 Gy	Disease progression	1
5	7	Relapse	CB	FLU + MEL + TBI 2 Gy	Disease progression	2
6	6	Primary	CB	FLU + MEL + TBI 2 Gy	Disease progression	3
7	6	Primary	CB	FLU + MEL + TBI 2 Gy	-	3
8	4	Primary	CB	FLU + MEL + TBI 2 Gy	-	2

KIR ligand-incompatible allogeneic cord blood transplantation for relapsed stage 4 neuroblastoma in a multicenter trial

Kataoka S¹, Nishio N², Arakawa Y², Kakuda H³, Tamura S⁴, Terui K⁵, Hamada S⁶, Karakawa S⁷, Takahashi Y²
¹Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan, ²Department of Hematology/Oncology, Saitama Children's Medical Center, Saitama, Japan, ³Department of Hematology/Oncology, Chiba Children's Hospital, Chiba, Japan, ⁴Department of Pediatrics, Kyoto City Hospital, Kyoto, Japan, ⁵Department of Pediatrics, Hirosaki University Graduate School of Medicine, Hirosaki, Japan, ⁶Department of Pediatrics, University of the Ryukyus Hospital, Okinawa, Japan, ⁷Department of Pediatrics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan

Background: There is only a 3% 5-year overall survival rate after recurrence of stage 4 neuroblastoma, and there are few cases of long-term survival. In the setting of autologous transplantation for patients with high-risk neuroblastoma, it has been reported that the survival rate was significantly higher in patients with natural killer (NK) cells missing any killer immunoglobulin-like receptor (KIR) ligands than in patients with matching all KIR ligands.

Aims: We conducted a multicenter clinical study of KIR ligand-incompatible allogeneic cord blood transplantation (CBT) to test the antitumor effect of NK cells.

Methods: From 2010 to 2020, 22 patients with recurrent stage 4 neuroblastoma who received KIR ligand-incompatible allogeneic CBT were included. They were 16 boys and 6 girls, with a median age of 6.7 years (range: 3.4–10.8 years) at the time of transplantation. Before CBT, 14 patients achieved the second or third complete response; the remaining 8 had residual diseases. For CBT, a conditioning regimen consisting of fludarabine, melphalan, and low-dose total body irradiation was mainly used.

Results: The median follow-up period after CBT was 3.7 years, and the 5-year overall survival rate was 57.3% ± 21.6%, with a 5-year progression-free survival rate of 45.5% ± 20.8%. Moreover, 9 patients were alive with no disease progression, 2 were alive with disease, and the remaining 11 died. Seven deaths were caused by neuroblastoma progression, three by transplant-related mortality, and one by second malignancy. In order to determine the disease status during CBT, we compared the second response group (n = 13) who achieved the second complete response at CBT and the residual disease group (n = 9) who had residual disease or second recurrence at CBT. The 3-year cumulative relapse rate in the second response group was significantly lower than in the residual disease group (23.1% vs. 66.7%, p = 0.04). Six long-term survivors without disease progression were found more than 5 years after CBT.

Conclusions: KIR ligand-incompatible allogeneic CBT as immunotherapy could be a salvage treatment option for relapsed neuroblastoma. However, this treatment should only be considered after the patient has achieved complete response prior to CBT.

3-летняя ОВ 57%, БСВ 45%

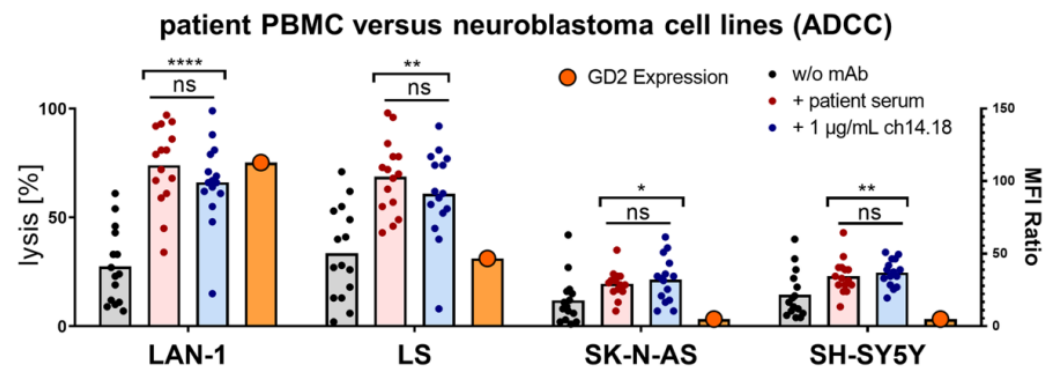
¹ Nishio N et al. ANR 2023 Poster Session.

¹ Kataoka S et al. ANR 2023 Abstracts.

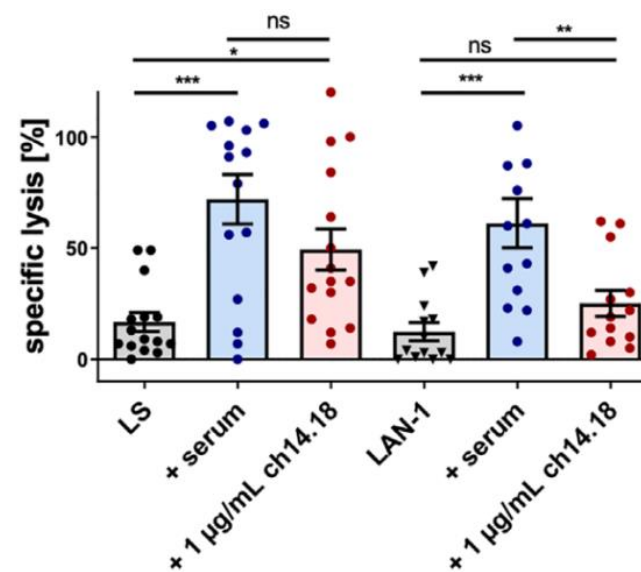


Механизм действия иммунотерапии после гапло-ТГСК

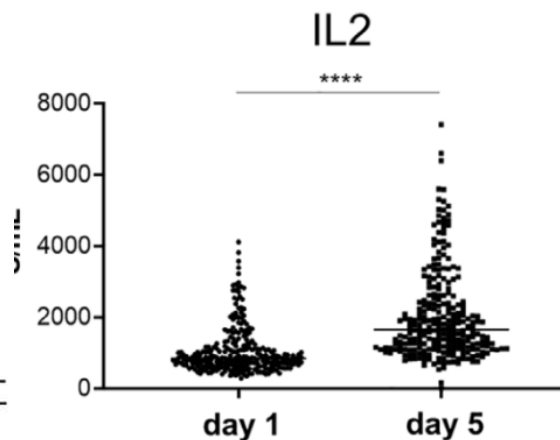
Комплемент-зависимая цитотоксичность



Активность НК-клеток



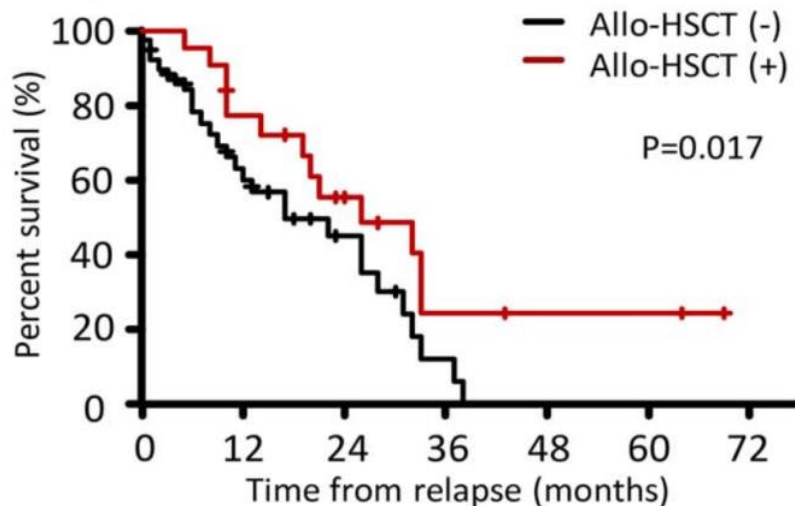
Уровень IL-2



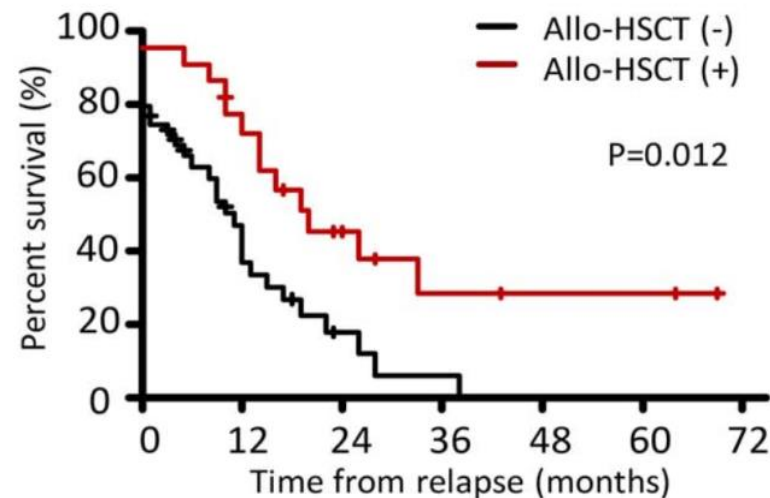
36 пациентов с рецидивом нейблстомы IV стадии группы высокого риска, получивших гапло-ТГСК в рамках исследования I/II фазы (NCT02258815)

Алло-ТГСК у пациентов с рецидивом

Влияние алло-ТГСК на ОБ

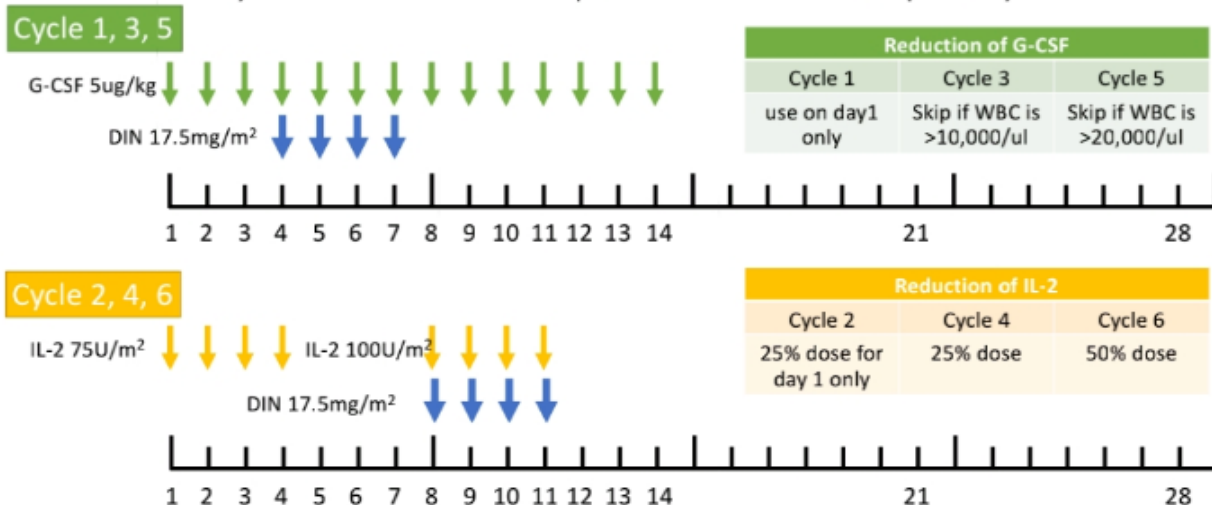


Влияние алло-ТГСК на БСВ



Factor	N	Univariate analysis			Multivariate analysis		Univariate analysis			Multivariate analysis	
		HR (95% CI)	3-year OS ± SE (%)	P	HR (95% CI)	P	HR (95% CI)	3-year PFS ± SE (%)	P	HR (95% CI)	P
Local alone	10	0.4	51.4 ± 18.7	0.042	0.4	0.108	0.3	51.4 ± 18.7	0.01	0.4	0.098
Distant meta.	51	(0.1–1.0)	8.8 ± 5.7		(0.2–1.2)		(0.1–0.8)	7.9 ± 5.1		(0.1–1.2)	
Allo-HSCT	39	0.5	12.0 ± 7.6	0.053	0.4	0.017	0.4	6.0 ± 5.5	0.004	0.4	0.012
	22	(0.3–1.0)	24.3 ± 11.5		(0.2–0.8)		(0.2–0.8)	28.3 ± 12.0		(0.2–0.8)	

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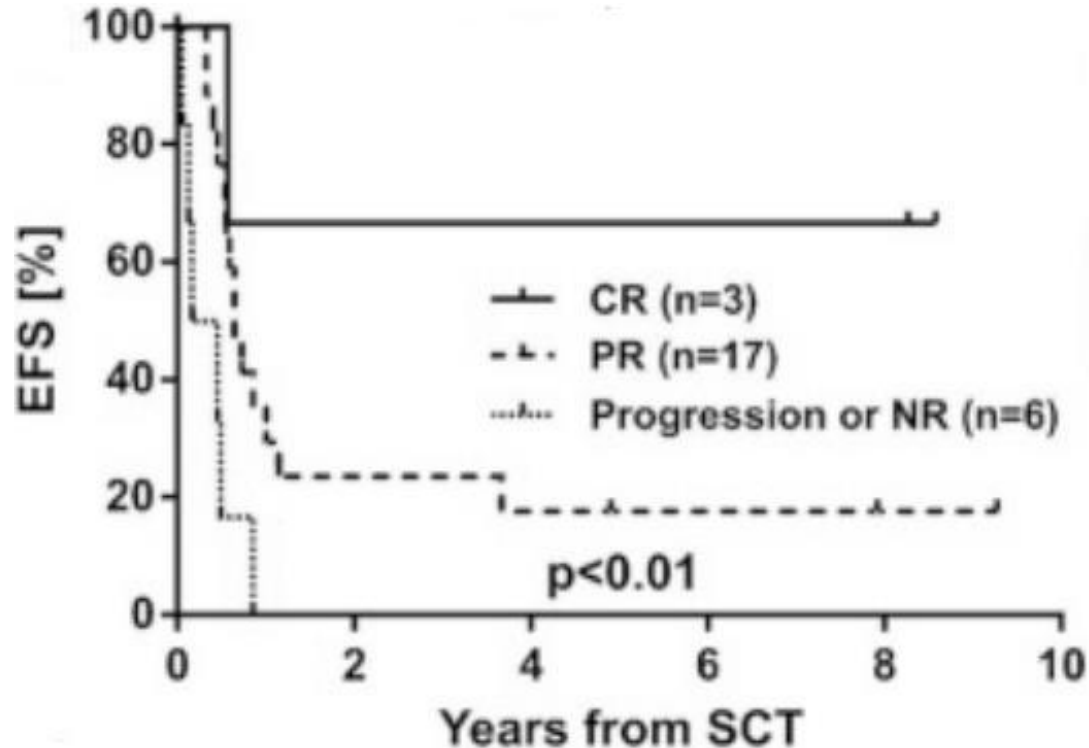
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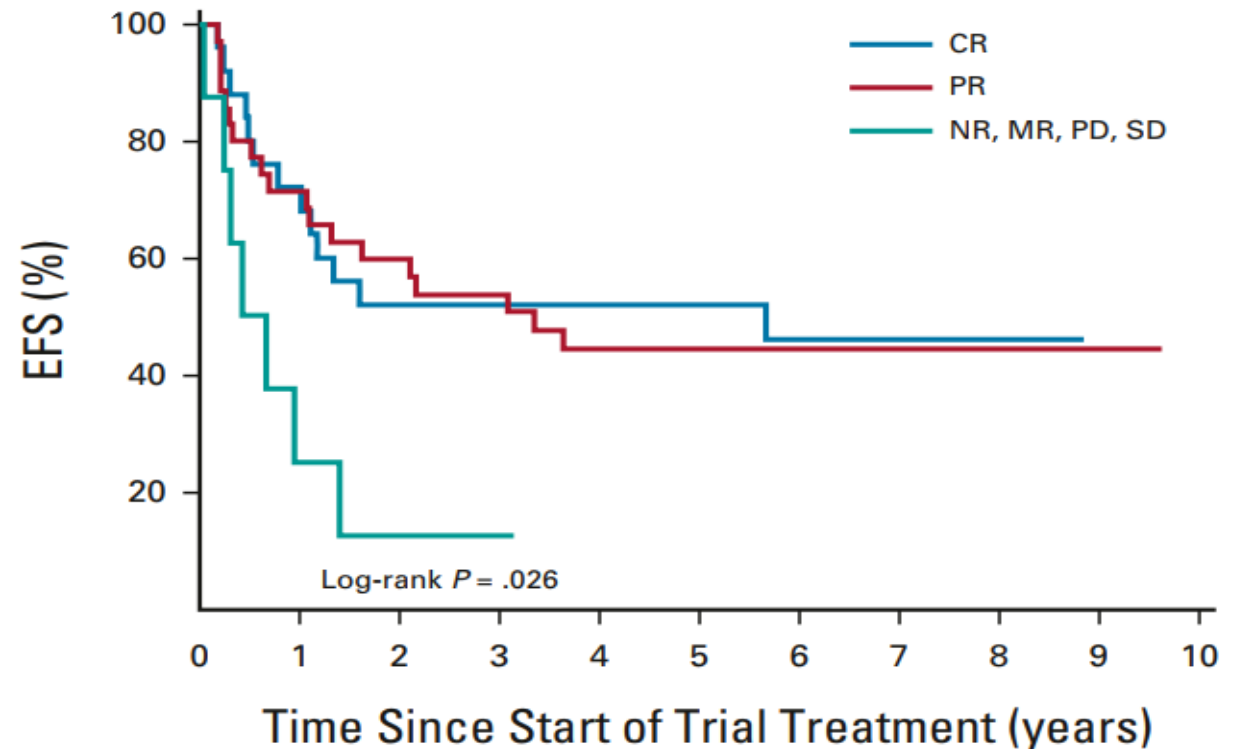


Алло-ТГСК от гаплоидентичного донора

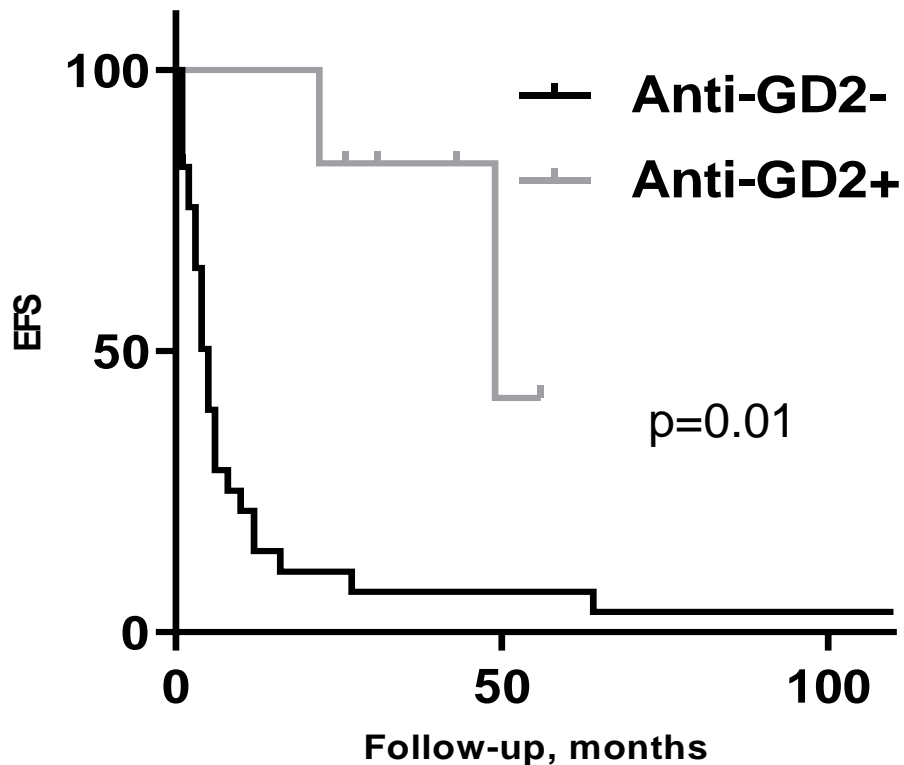
БСВ в зависимости от ответа,
Пилотное исследование



БСВ в зависимости от ответа,
Комбинация с иммунотерапией



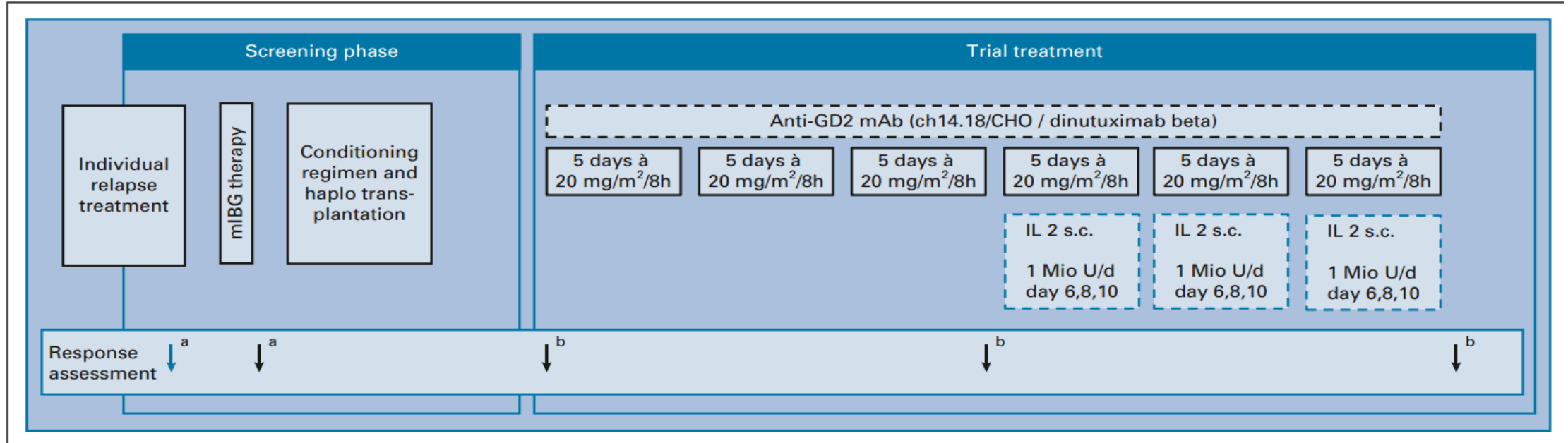
Иммунотерапия после гапλο-ТГСК



Возр.	Показания	Н курсов	Осложнения	Статус
10	IV ст., 1 ^й поздн.рец., 2 ^я ПР, гапло-ТГСК (ПО)	1	неврологич. (зрение)	ПО, 56 мес
6	IV ст., 1 ^й поздний системный рец., гапло-ТГСК (ПО)	5	лихорадка	Рец., 12 мес.
5	IV ст., 1 ^й поздн.рец., 2 ^я ПР, гапло-ТГСК	5	лихорадка, сыпь	ПО, 43 мес.
8	IV ст., 1 ^й поздн.рец., 2 ^я ПР, гапло-ТГСК	5	гипотония	ПО, 31 мес.
17	IV ст., 1 ^й поздн.сист.рец., ЧР, гапло-ТГСК	5	Гипотония	ЧО, 12 мес.
9	IV ст., 1 ^й поздн.сист.рец., ПО, гапло-ТГСК	5	Гипотония	Рец., 22 мес.

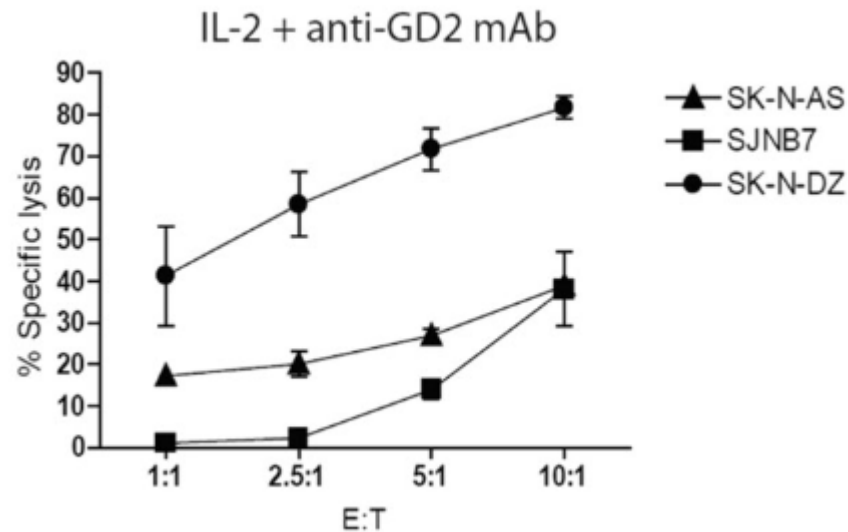
4 из 6 пациентов ранее получали иммунотерапию

Воспроизводимость результатов исследования



- Миелоаблативный РК
- TCRαβ деплеция
- 64% пациентов получили MIBG-терапию
- Более интенсивный режим иммунотерапии (20 мг/м²/сут 5 дней), больше (6-9 циклов иммунотерапии)

Роль экспрессии GD2



- 152 пациента с НБ группы высокого риска
- Экспрессия GD2 в 94% случаев
- 20 пациентов получили anti-GD2
- Рецидив в 5 случаях, снижение экспрессии GD2 при рецидиве

Low GD2 expression as a mechanism of resistance to chemoimmunotherapy with dinutuximab

Keyel M¹, Davidson H¹, Estrada A¹, Irwin M², Hogarty M³, Reynolds C¹
¹Cancer Center and Departments of Pediatrics, Internal Medicine, and Cell Biology and Biochemistry, School of Medicine, Texas Tech University Health Sciences Center Lubbock, TX, , United States, ²University of Toronto; Department of Pediatrics, Hospital for Sick Children, Toronto, ON, , Canada, ³University of Pennsylvania; Pediatrics, Children's Hospital of Philadelphia and Perelman School of Medicine, Philadelphia, PA, , United States

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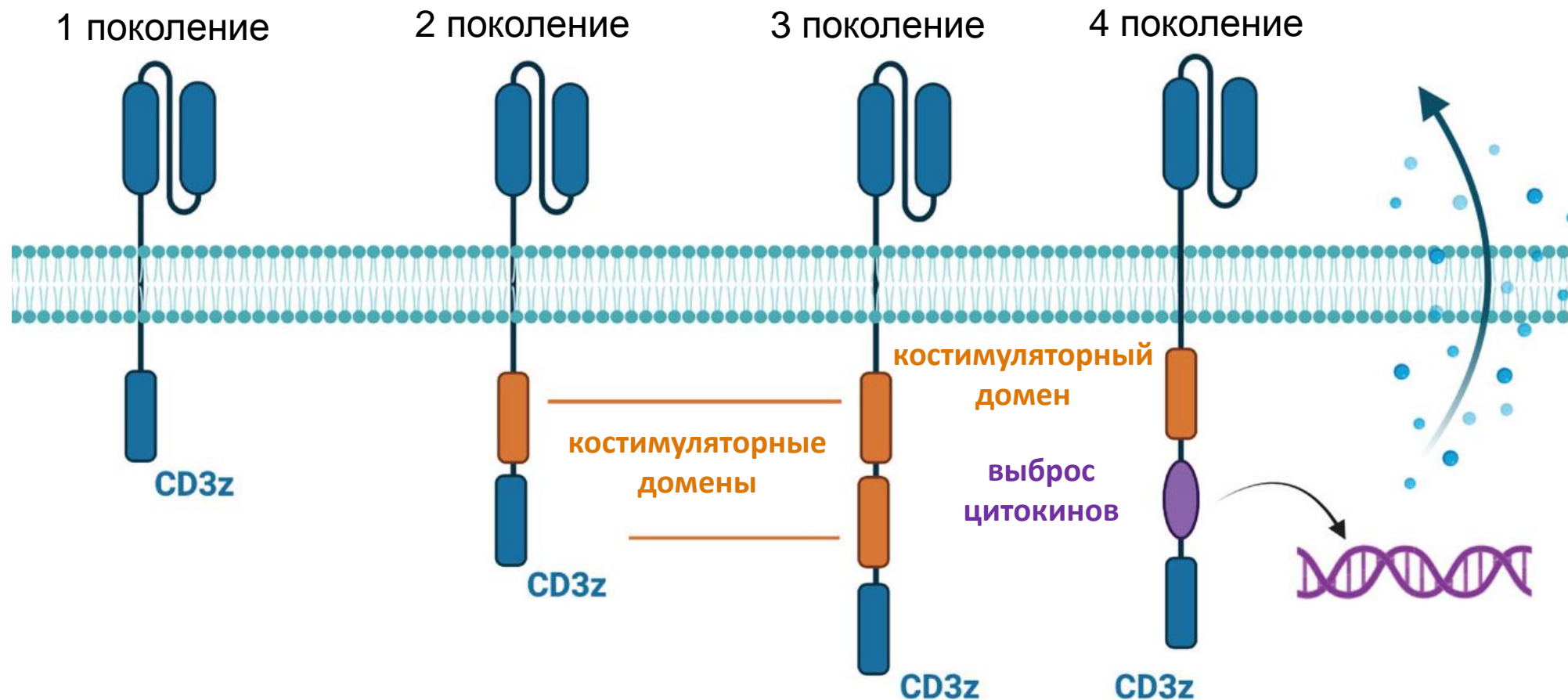
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Conclusions: Low GD2 expression occurs in neuroblastoma. Neuroblastoma PDXs in nu/nu mice provide a preclinical model to assess antibody activity when combined with chemotherapy. In > 10% of patient marrow samples analyzed, dinutuximab binding was comparable to levels seen in PDX's that did not benefit from dinutuximab. Quantifying GD2 expression by flow cytometry is a potential biomarker of activity for dinutuximab in patients treated with anti-GD2 based chemoimmunotherapy.

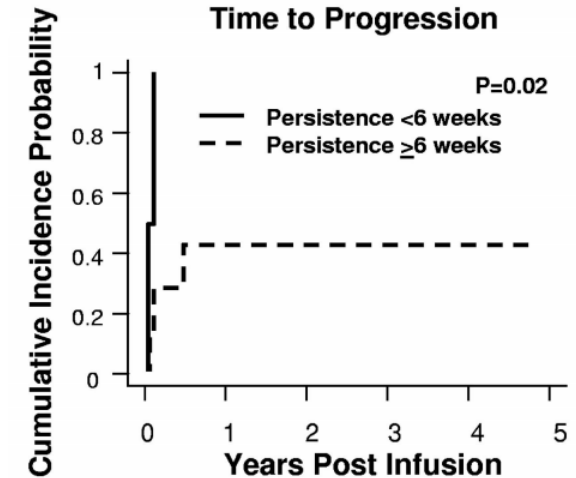
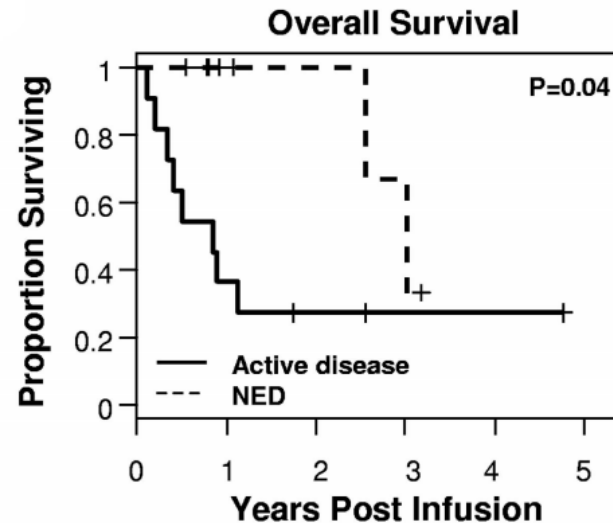
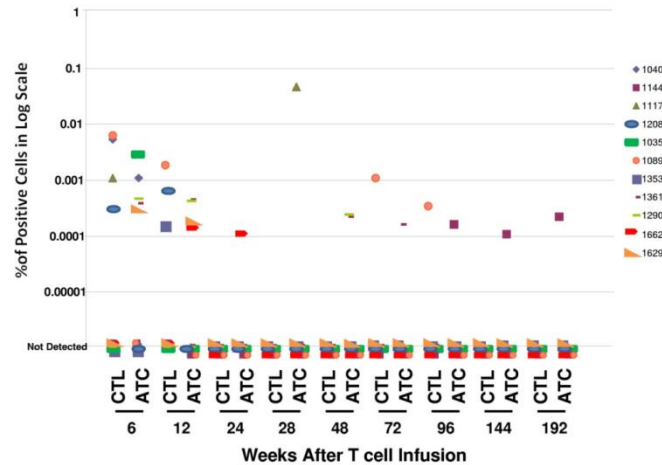
¹ Terzik T et al. *Pediatr Dev Pathol* 2018 Jul-Aug;21(4):355-362.

² Keyel M et al. ANR 2023 Oral Session

Поколения CAR-T

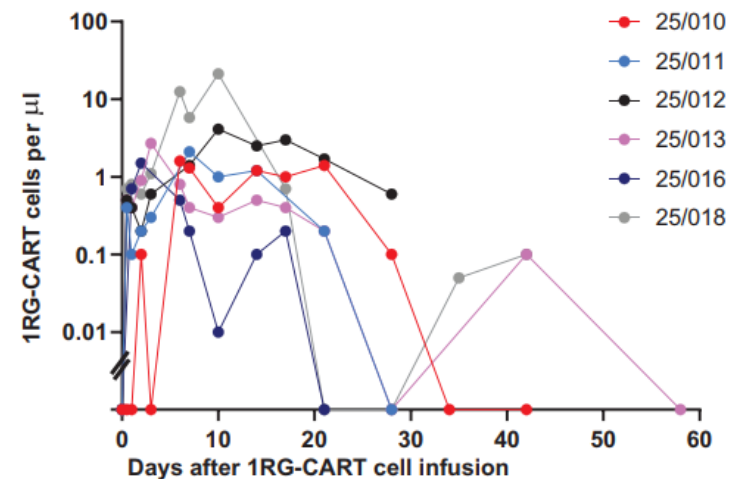
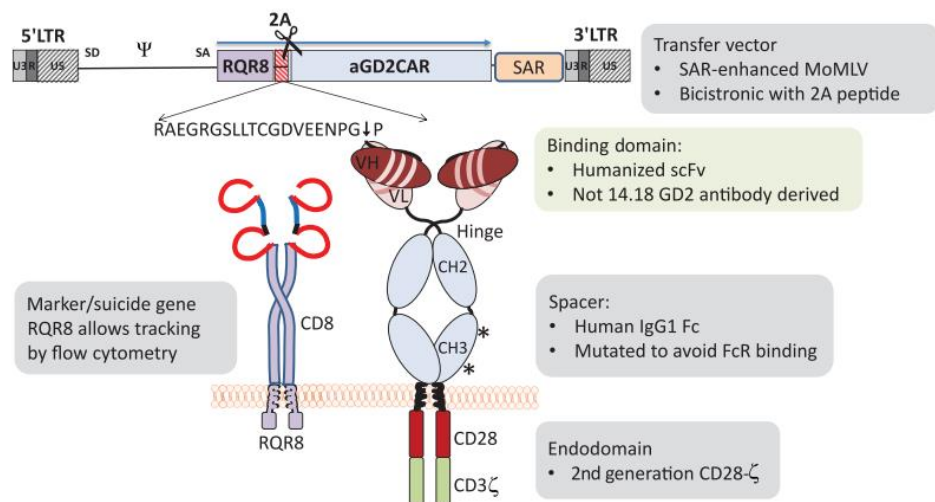


Анти-GD2 CAR-T первого поколения



- 19 пациентов с нейробластомой высокого риска (8 в ремиссии и 11 с активным заболеванием)
- Клетки сохранялись в крови в среднем в течение 6 недель
- В 3/11 случаев длительный полный ответ у пациентов с остаточными костными очагами
- Тенденция к лучшим результатам при длительном персистировании CAR-T клеток

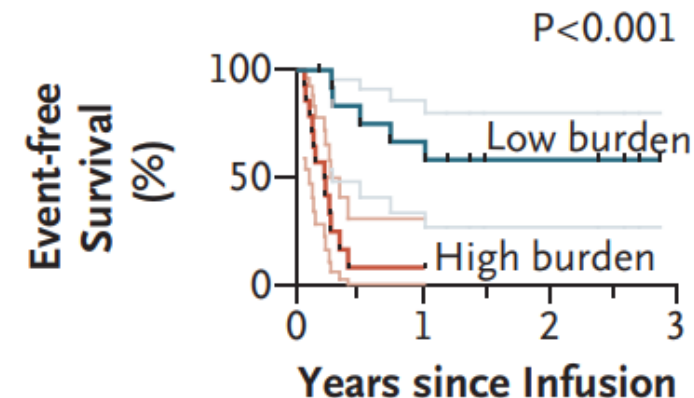
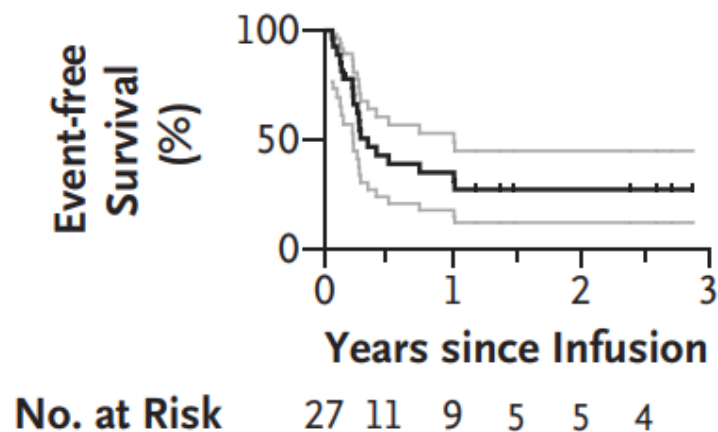
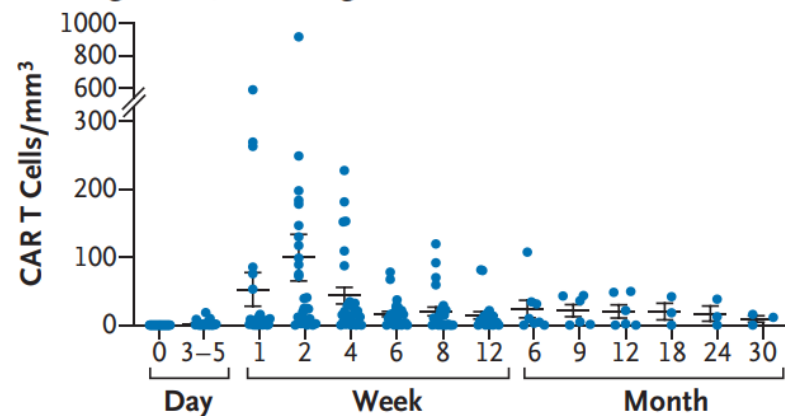
Анти-GD2 CAR-T второго поколения



- 12 детей с резистентным течением заболевания/рецидивом
- Лимфооплеция: флударабин-циклофосфан
- Отсутствие объективных ответов на Д+28 согласно стандартным радиологическим критериям
- В максимальной дозовой когорте 3 ответа на более поздних сроках, синдром выброса цитокинов у двух пациентов
- Отсутствие off-tumor токсичности

Анти-GD2 CAR-T третьего поколения

Circulating Levels, According to Time since Infusion



- 27 детей (12 с первичной резистентностью, 14 с рецидивом, 1 с высоким риском рецидива)
- Приемлемая токсичность, возможность активации «гена самоубийства»
- В 26 из 27 случаев длительное (от 1 до 30 месяцев) персистирование
- Ответ на лечение в 17 из 27 (63%) случаев: полный ответ у 9 пациентов, частичный у 8 пациентов
- В группе из 21 пациента, получивших рекомендованную дозу клеток, через три года после завершения терапии 60% были живы, а 36% сохраняли полный ответ

Выводы

- Достигнут предел эффективности иммунотерапии в постконсолидации
- Перспективные стратегии комбинированной иммунотерапии
- Место иммунотерапии в схеме лечения смещается на этап индукции ремиссии
- Возможность повторного применения иммунотерапии
- Наличие нескольких доступных коммерческих форм препаратов повышает доступность лечения

VIII КОНФЕРЕНЦИЯ

НЕЙРОБЛАСТОМА

Спасибо за внимание!



МОСКВА | 30/09 – 1/10