T CELL THERAPY FOR THE CONTROL OF EBV-RELATED NASOPHARYNGEAL CARCINOMA

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EBV-associated cancers

- Burkitt lymphoma (1964)
- **Nasopharingeal carcinoma (1970)**
- Lymphoproliferative diseases in hosts with impaired T-cell immunity (1982 $\rightarrow$)
- T-cell Lymphoma (1988)
- Hodgkin disease (1989)

Cellular immunotherapy - EBV-related LD

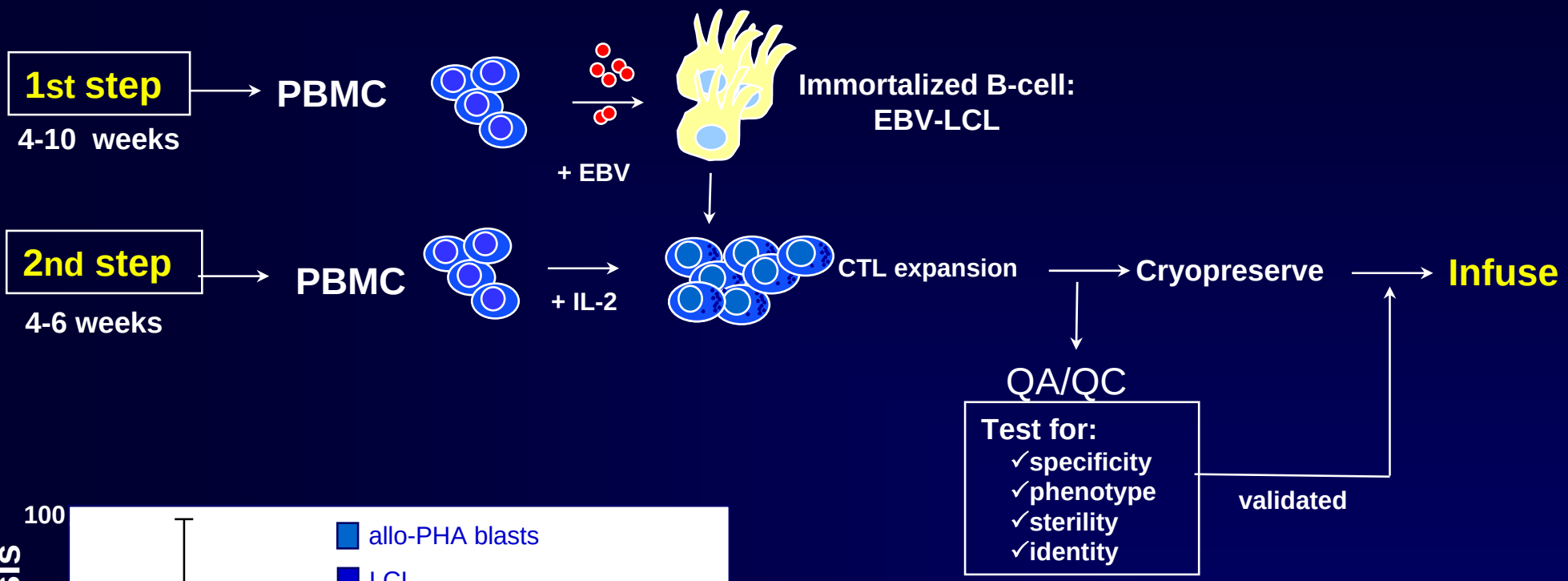
- Infusion of EBV-specific CTL produced resolution of EBV-related high-grade non-Hodgkin lymphoma (Rooney *et al.*, Lancet 1995 and Blood 1998)
- Treatment with EBV-specific CTL induced regression of relapsed EBV positive Hodgkin disease (Roskrow *et al.*, Blood 1998)
- Infusion of EBV-specific CTL prevented development of EBV-related post-transplant lymphoproliferative diseases (Comoli *et al.*, Blood 2002)

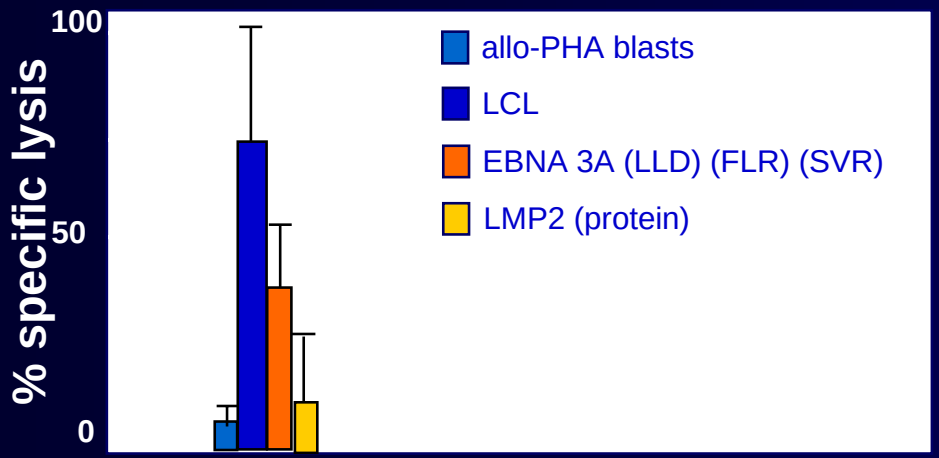
Cellular therapy for EBV-related NPC: *RATIONALE*

- NPC tumor cells express a restricted number of viral proteins, namely EBNA1, LMP1 and LMP2 - **Cohen: N Engl J Med 2000**
  - NPC cells show high levels of HLA class I alleles on the cell surface and have normal expression of the MHC-encoded putative peptide transporters TAP-1 and TAP-2, as well as of other components of the class I processing pathway - **Khanna, Cancer Res 1998**
  - EBV-specific CTLs are present in patients with newly diagnosed NPC, with a specificity for EBV latent protein LMP2 - **Lee, J Immunol 2000**

NPC cells are capable of immunological processing and CTL recognition

Generation of EBV polyspecific CTLs (Rooney 1995)





CTL phenotype	%	CD3+CD8+	%
CD3+	90 (68-99)	CCR7+CD45RA+	4±4
CD4+	30 (4-90)	CCR7+CD45RA-	7±7
CD8+	**60** (8-96)	**CCR7-CD45RA-**	**79±18**
CD8+/56+	10 (0-33)	CCR7-CD45RA+	10±7

Published Ahead of Print on October 3, 2005 as 10.1200/JCO.2005.02.6195

VOLUME 23 · NUMBER 35 · DECEMBER 10 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cell Therapy of Stage IV Nasopharyngeal Carcinoma With Autologous Epstein-Barr Virus–Targeted Cytotoxic T Lymphocytes

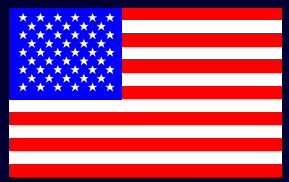
Patrizia Comoli, Paolo Pedrazzoli, Rita Maccario, Sabrina Basso, Ornella Carminati, Massimo Labirio, Roberta Schiavo, Simona Secondino, Chiara Frasson, Cesare Perotti, Mauro Moroni, Franco Locatelli, and Salvatore Siena

Therapy with EBV-specific CTLs in NPC: OUR PREVIOUS EXPERIENCE

- 10 patients with **refractory** and poor prognosis NPC
- QW or Q2W **infusions of "*low-dose*"** poly-specific CTLs (20-80 x 10^6)
  - are **feasible and safe**
  - provide **clinical benefit** in some patients

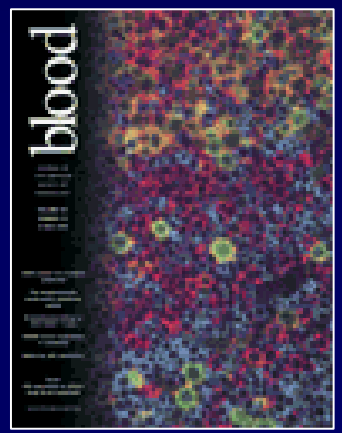
P Comoli *et al*. J Clin Oncol 2005

Therapy with EBV-specific CTLs in NPC
HUSTON EXPERIENCE



- 10 patients treated with poly-specific CTLs (4 receiving CTLs in remission)

- Clinical results:
  - decrease of viral load
  - 2 documented CR, 1 PR, 1 SD



Straathof *et al*. Blood 2005

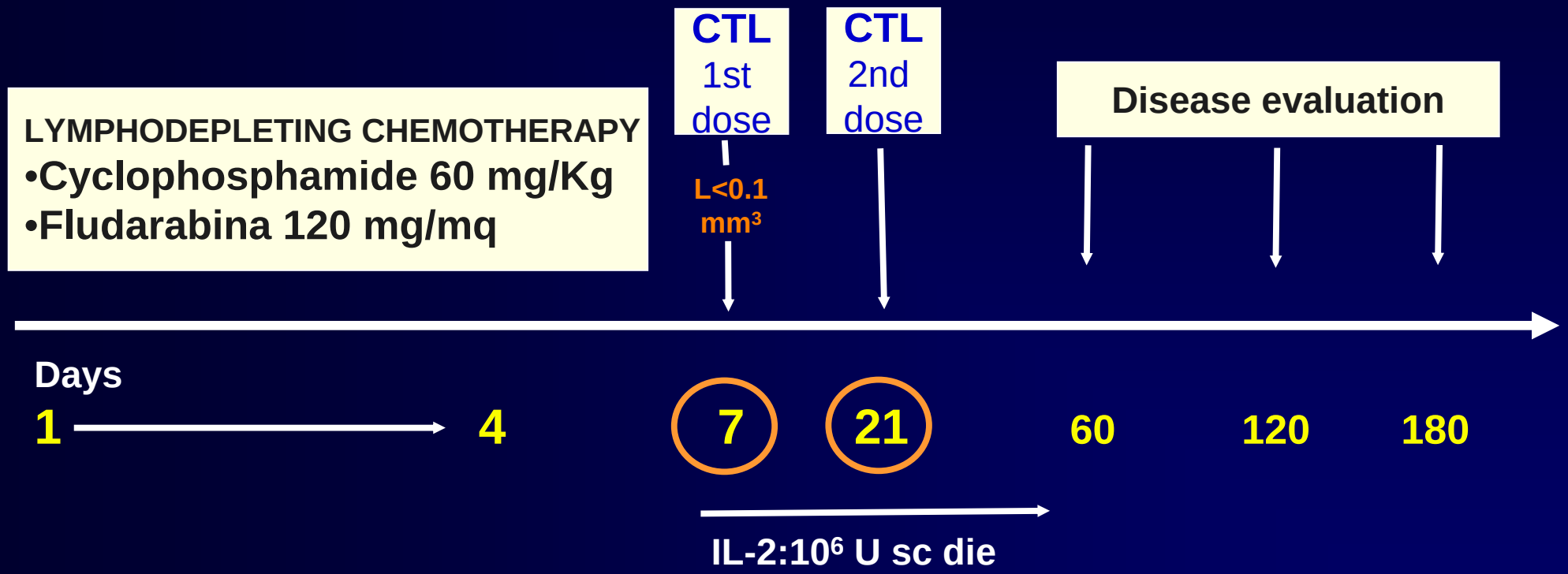
PRESENT STUDY

- infusion of **higher CTL doses**
- following **lymphodepleting chemotherapy**
  - **Yee, PNAS 2002**
  - **Rosenberg, PNAS 2004**
  - **Dudley, JCO 2005**

PATIENTS – INCLUSION CRITERIA

- Less than 70 years with istologically-confirmed EBV-related NPC
- Disease in progression after two lines of chemotherapy and not amenable to complete surgical resection or local conventional treatments
- Measurable disease (RECIST criteria)
- Normal organ function
- Informed consent

TREATMENT PLAN

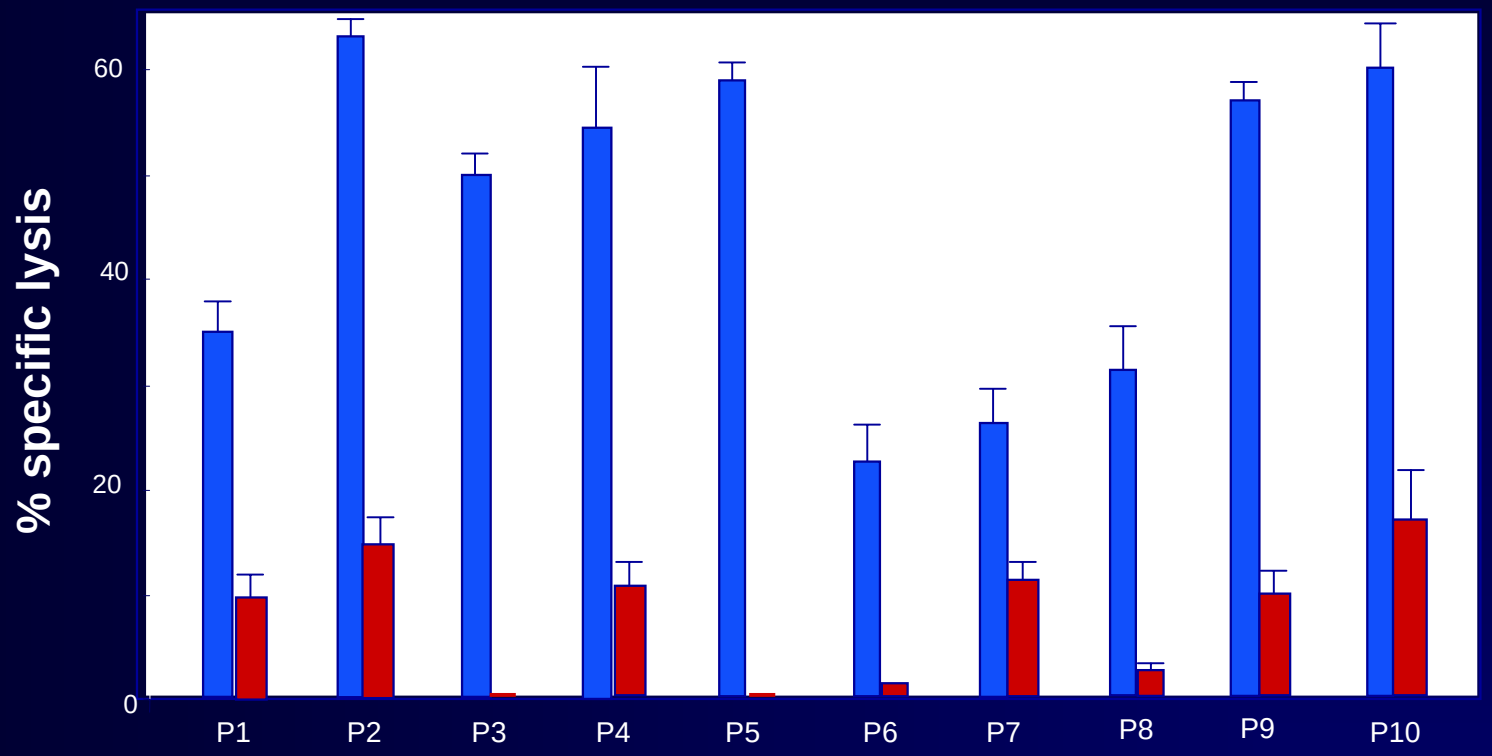


Maintenance "low-dose" CTLs in pts with response

Main characteristics of treated patients

Patient	Age (yr)	Sex	Stage at diagnosis	Site(s) of tumor involvement at the time of cell therapy	Prior therapies	ECOG PS
1.RZ	19	F	IV (T4N2M0)	Liver, spleen	RT 3 lines of CT	0
2.AM	65	M	III (T3N1M0)	Primary tumor, skull base	2 lines of CT, RT, surgery	0
3.JW	21	M	III (T3N1M0)	Primary tumor, skull base	2 lines of CT, RT	0
4.ST	40	F	III (T2N2M0)	Skull base, neck	3 lines of CT, RT	1
5.GG	48	M	IV (T2N2M1)	Primary tumor, skull base	2 lines of CT, RT, surgery	1
6.PC	64	M	III (T3N0M0)	Primary tumor	2 lines of CT, RT	0
7.VL	49	M	Unknown	Skull base, lung, lymph nodes, orbital cavity	3 lines of CT, RT surgery	1
8.MC	40	M	Unknown	Primary tumor, skull base	3 lines of CT, RT	0
9.GFMB	66	M	IV (TXN2M1)	Primary tumor, limph nodes	3 lines of CT	0
10.MM	46	M	II (T2N1M0)	Lung, lymph nodes, liver	2 lines of CT, RT, surgery	1

Characteristics of CTL lines



E/T ratio 5:1

EBV-LCL

EBV-LMP2

CD8	70%	HLA-DR	98%
CD4	16%	CD8/ CD56	8%
CD56	14%		

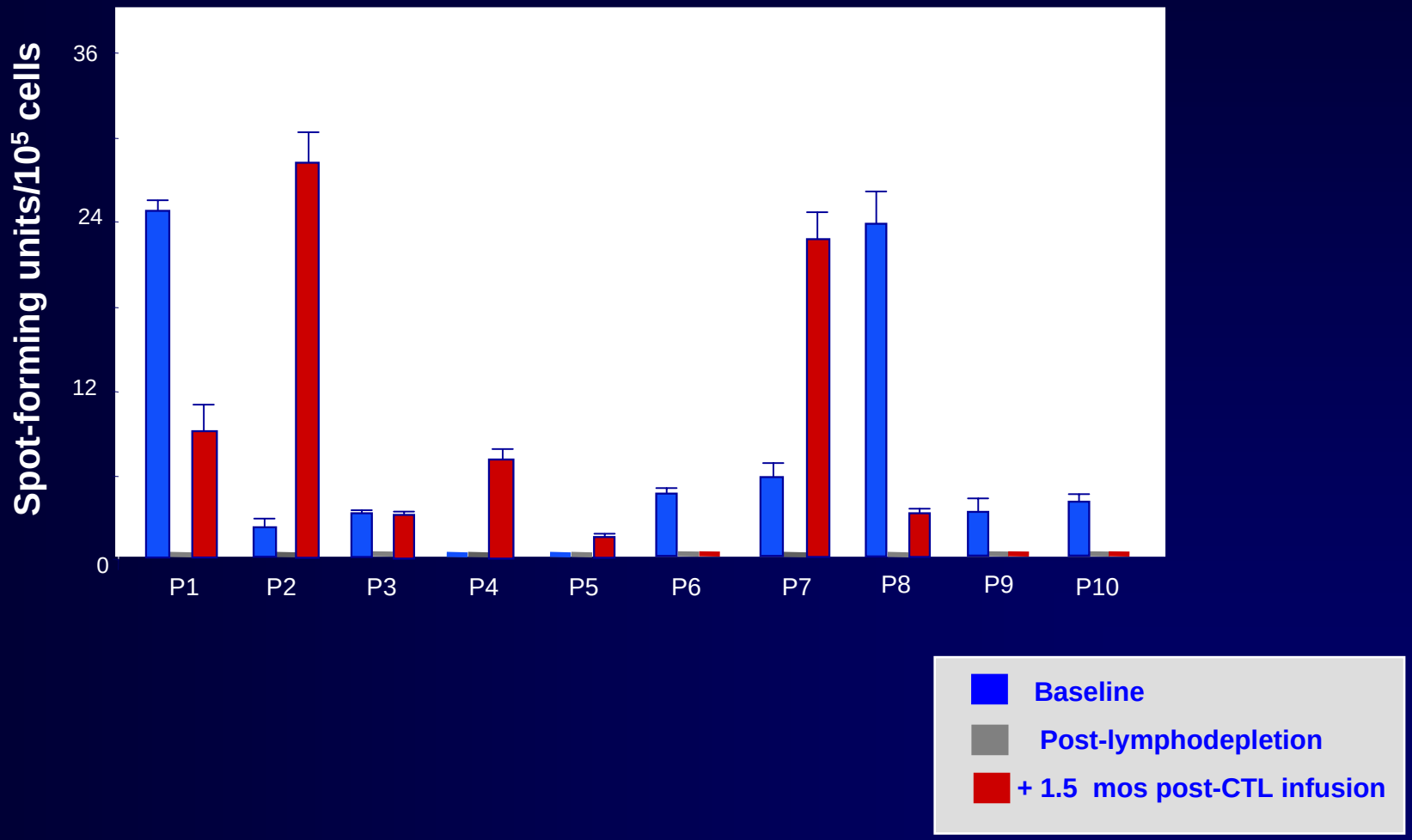
RESULTS (1)

- Median time to CTL production: 3.5 months
- Chemotherapy well tolerated
  - No grade III-IV non-hematological toxicity
  - Grade IV uncomplicated neutropenia in 3
  - Manageable in the outpatient setting
- Dose of CTL *per* infusion:
  - median 370 x 10^6
  - range: 160-500x10^6

RESULTS (2): CTL therapy and Outcome

Patient	Total CTL dose	Adverse Events	Outcome
1.RZ	5.6×10^8	None	SD (4 months)
2.AM	13.8×10^8	Inflammatory reaction at the disease site; Fever and tremors at the 2^{nd} infusion	PR (8 months)
3.JW	5.2×10^8	None	PD
4.ST	14×10^8	None	SD (8 months)
5.GG	5.6×10^8	None	PD
6.PC	7.2×10^8	None	SD (11+ months)
7.VL	9.6×10^8	Orbital oedema and visual field defects	PR (5 months)
8.MC	8×10^8	None	MR (10+ months)
9.GFMB	6.4×10^8	None	PD
10.MM	7.2×10^8	None	PD

RESULTS (3): Immunological effects of CTL infusion - response to LMP2



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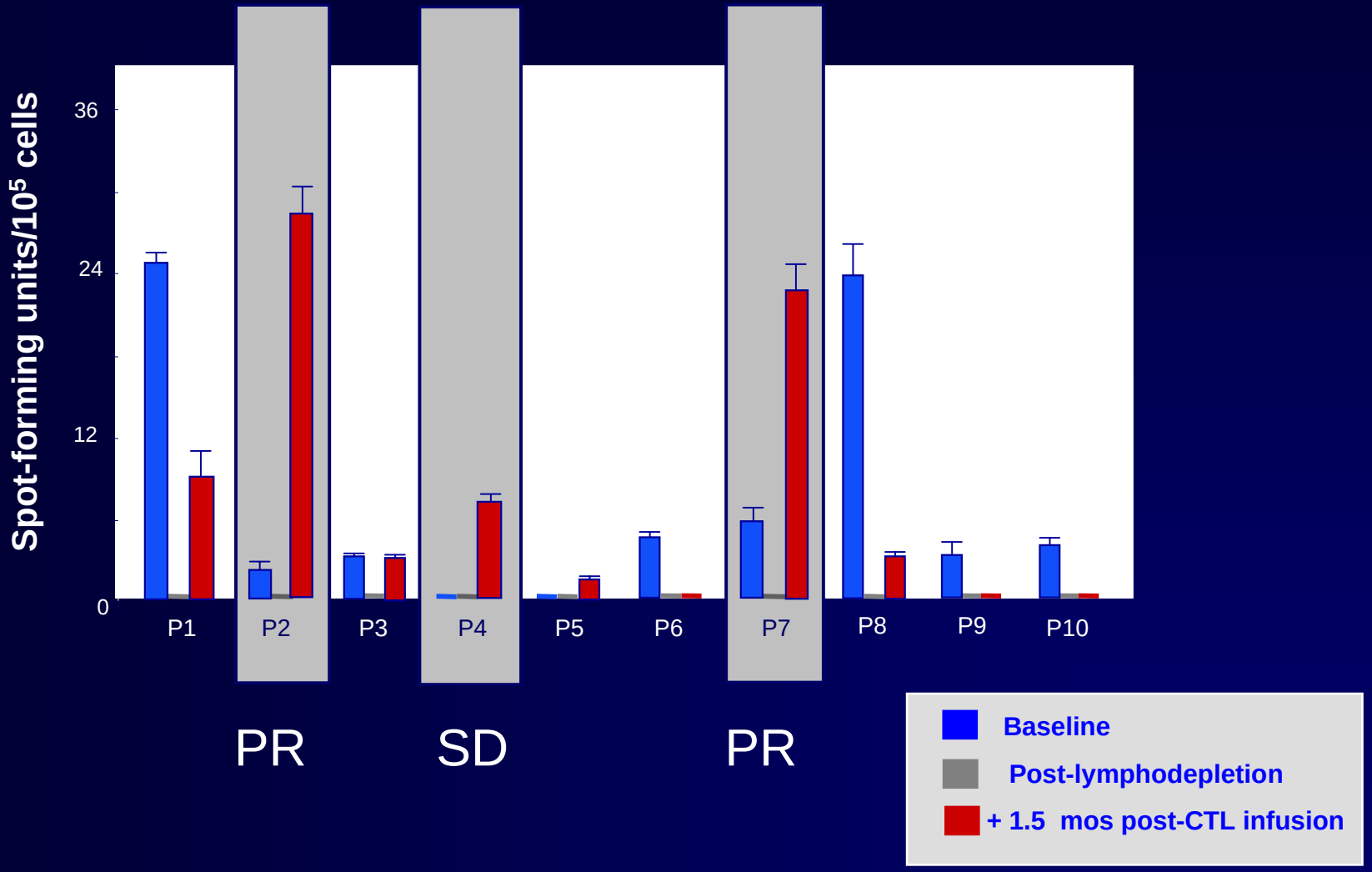

CONCLUSIONS

- **Feasible and well tolerated**
  - **No significant side effects from lymphodepleting chemotherapy and CTL infusion**
- **Clinical benefit observed in advanced-stage, chemo-refractory patients**
- **Response seems associated to an increase in the frequency of peripheral blood T-cells specific for EBV subdominant antigens expressed by the tumor**

FUTURE DIRECTIONS

- Cell therapy with EBV-specific CTL **earlier** in the course of NPC disease
- Increasing the number of **LMP2 and/or LMP1-specific T cells** in the infusion product

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FONDAZIONE IRCCS INT - MILANO

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