Immunotherapy and vaccines Colon Cancer

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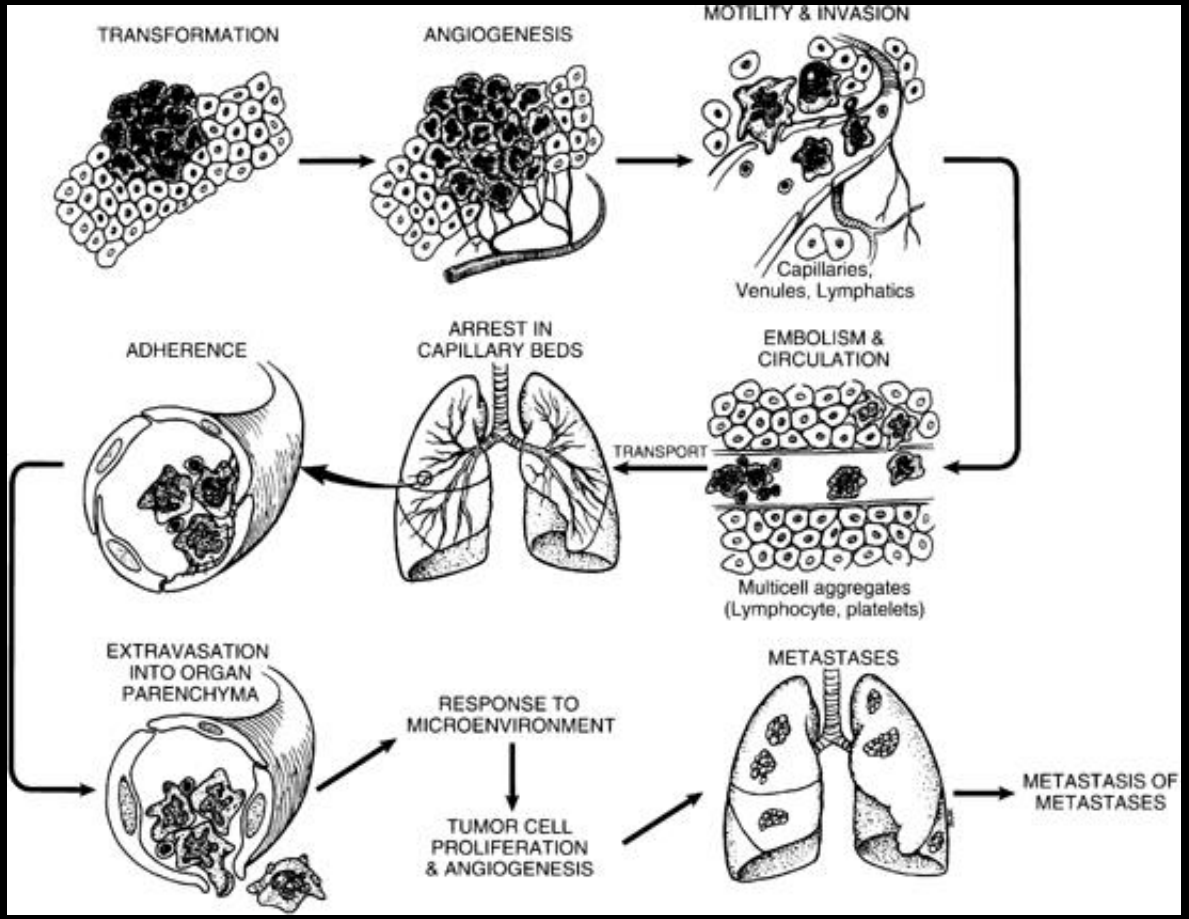
Immune system and Cancer



Immune system and Cancer

Differentiation antigens:	PSA, PSMA, MAGE, BAGE, etc
Foetal antigens:	CEA, αFP, βHCG, etc
Mutated functional structures :	p53, K-ras, etc
Over-expressed functional structures:	Growth factor receptors (ERB-B family), hormones (PTH-rP) adhesion molecules (EP-CAM-17.A), enzymes (proteases, thymidylate synthases) and/or the proteins responsible for drug resistance (PgP, MRPs and LRP),

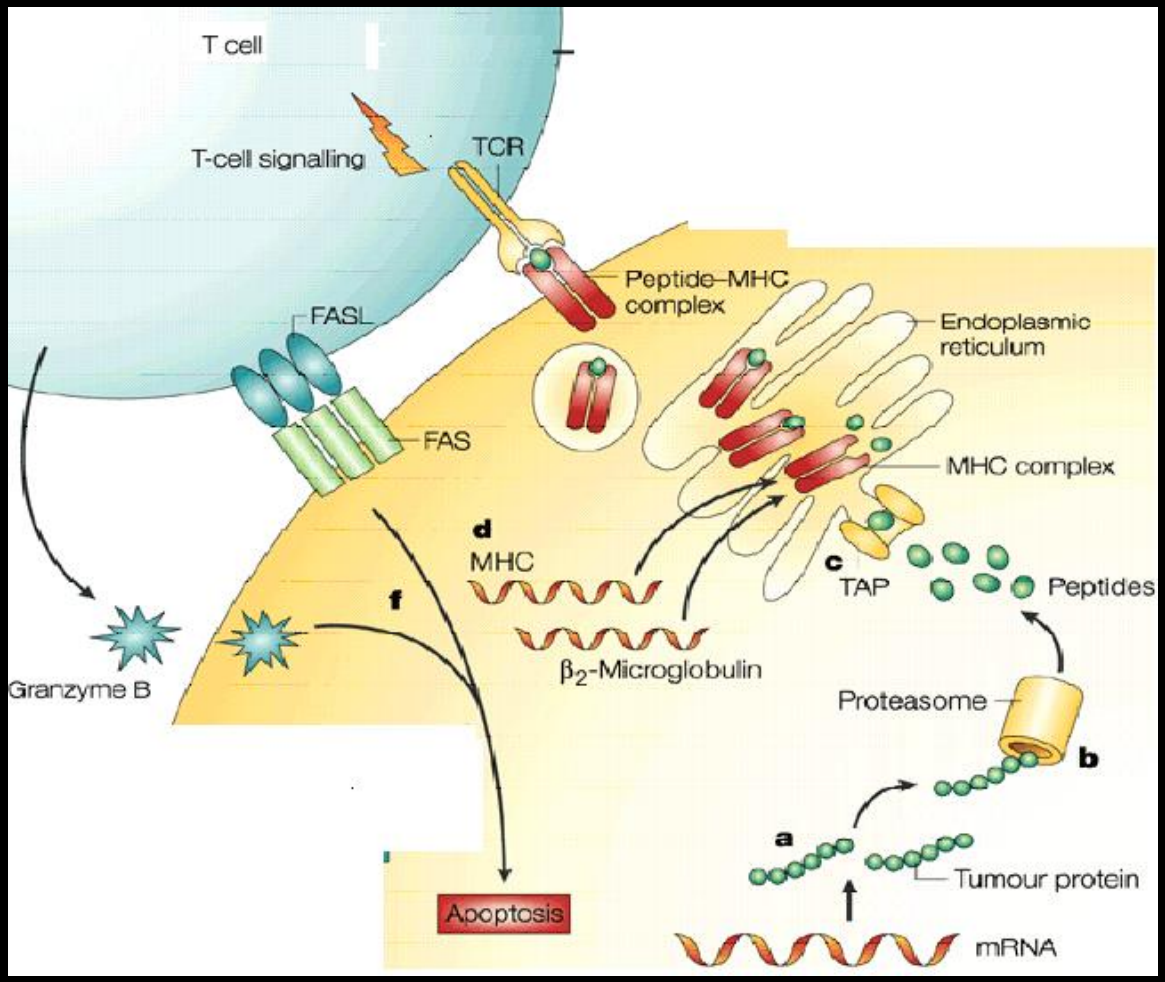
Immune system and Cancer

T cells are indispensable for an efficient immune response against cancer

Tumor rejection is dependent on CD8+ cytolytic T cells (CTLs).

CD4 + T cells are considered as immune-modulators (enhancers and regulators).

TCR recognition of antigen peptides



Immune system and Cancer

Tumor Immunology Paradigm:

Tumor cells may be recognised and killed by effector lymphocytes but cannot initiate by themselves an efficient immune-response

"…the generation of an efficient immune-response mostly depends on the ability of the immunizing agents or constructs
to deliver the target antigen(s) to professional antigen presenting cells"

Ongoing clinical trials

NON SPECIFIC IMMUNOSTIMULATION	**IMMUNOSTIMULATORY agents :** **- Recombinant vaccinia virus** **- IFNγ+celecoxib+combination of chemockines** **- IL7** **- Heat killed whom cell mycobacyerium** **- PGGbeta-Glucan binding to neutrophilis** **- GOLFIG chemo-immunoburst**
WHOLE CELL CANCER VACCINE	**Allogenic cancer cells**
DC BASED THERAPY	**-**Autologous DC intratumor injection loaded with frame shift antigens (MSI) -CEA pulsed DC+IL2 -Autologous DC
CELL THERAPY	**Autologous T cell therapy,** **genetically engineered T cells** **autologous DC therapy,**
PEPTIDE VACCINE	**Targeted peptide(s)** **- TSPP** **Mutated k-ras** **-Muc-1** **-HER2/neu** **-CEA (Cap-1)**
INHIBITION OF IMMUNOREGULATION	-Treg depletion -anti-CTLA4+ local radiation therapy

Improvement of Active Specific Immunotherapy

Combined strategies of treatment

- **Radio-immunotherapy**
- **Multicytokine combination**
- **Immunomodulating Antibodies** (Anti-CTLA-4; Anti PD1)
- **Immunomodulating Agents** (Tri-com, Anti-CD40)

- **Chemo-immunotherapy**

Chemo-immunotherapy

Chemotherapy often determines a fast shrinking of the immune-suppressive tumor mass.

Several drugs including 5-FU as well as radiotherapy are able to change tumor cell phenotype, to induce apoptosis, to activate intracellular danger signals and eat me molecules.

Many drugs induce up-regulation of antigenic molecular structures
(such as EGFR, CEA, and thymidylate synthase)

Chemo-immunotherapy

Effects of chemotherapy on human immune-system

Chemotherapy can suppress the granulocyte mediated response to bacterial and mycotic infections.

No clear effect has been demonstrated on antigen specific CTL response or DTH which seems to be augmented by many cytotoxic drugs .

Several drugs have been used in combination with immunological treatments in therapeutic mouse models.

Chemo-immunotherapy

5-Fluorouracil–Based Chemotherapy Enhances the Antitumor Activity of a Thymidylate Synthase–Directed Polyepitopic Peptide Vaccine

Pierpaolo Correale, Maria Teresa Del Vecchio, Giuseppa Di Genova, Gianni Gori Savellini, Marco La Placa, Chiara Terrosi, Marzio Vestri, Renato Urso, Francois Lemonnier, Angelo Aquino, Enzo Bonmassar, Giorgio Giorgi, Guido Francini, Maria Grazia Cusi

Journal of the National Cancer Institute, Vol. 97, No. 19, October 5, 2005

TS/PP poly-epitope peptide vaccine

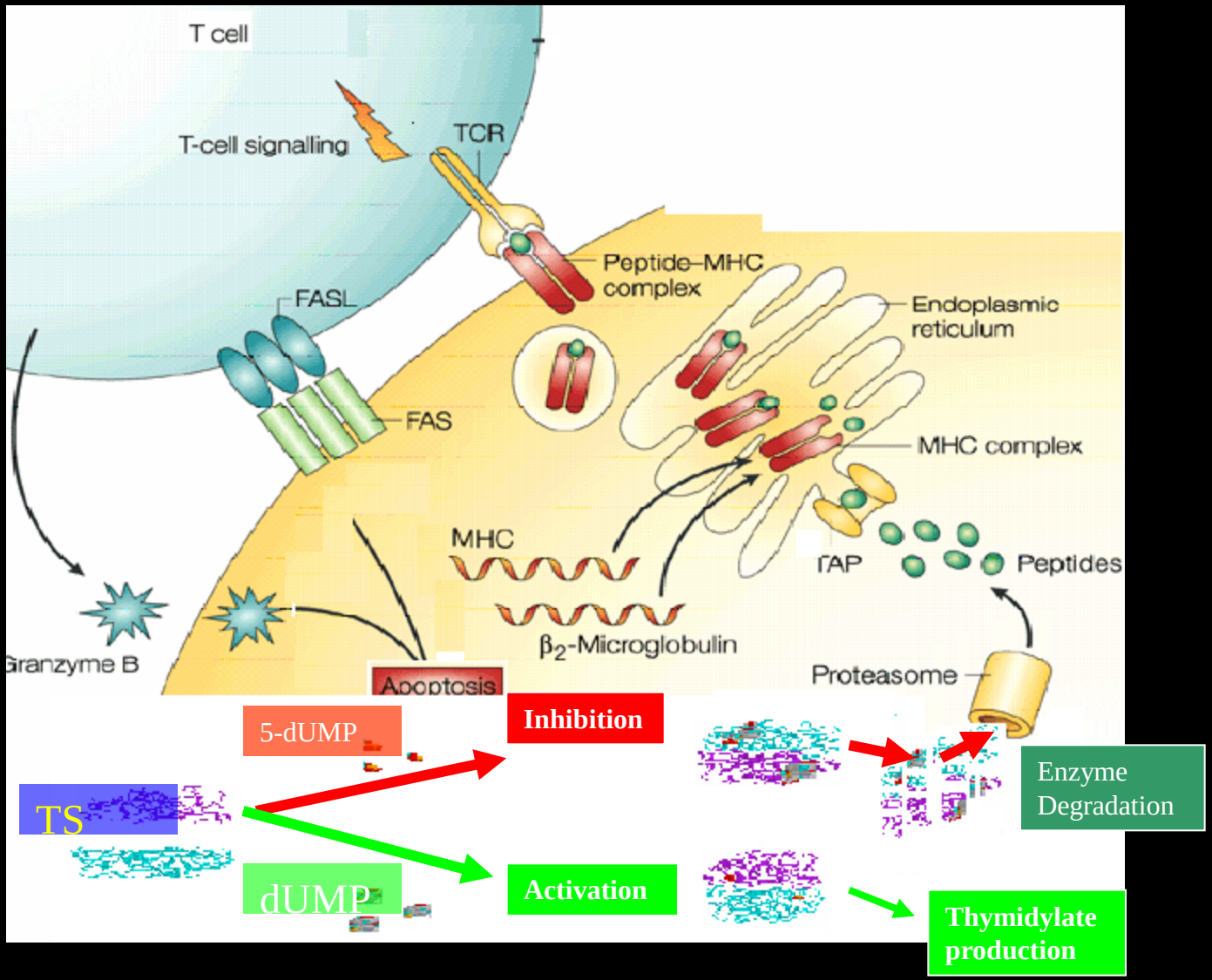
Thymidylate Synthase (TS)

TS is the main source of thymidine for DNA duplication and is the pharmacological target inhibited by 5-FU and other common antimetabolites.

TS expression in normal cells is under the cell cycle control system being expressed only during the S phase.

TS is capable of auto-regulation, thus a rapid and transient up-regulation of this enzyme is commonly observed few hours after 5-FU exposure in colon cancer cells *in vitro*

Thymidylate Synthase degradation



TS/PP poly-epitope peptide vaccine

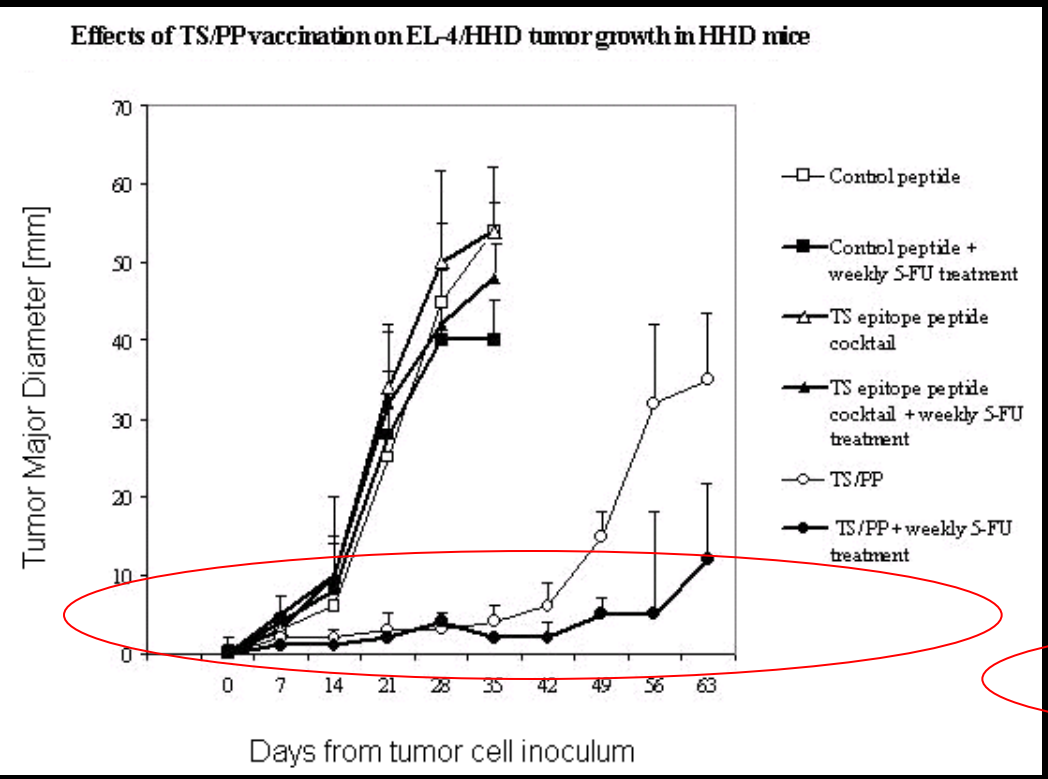
Peptide description

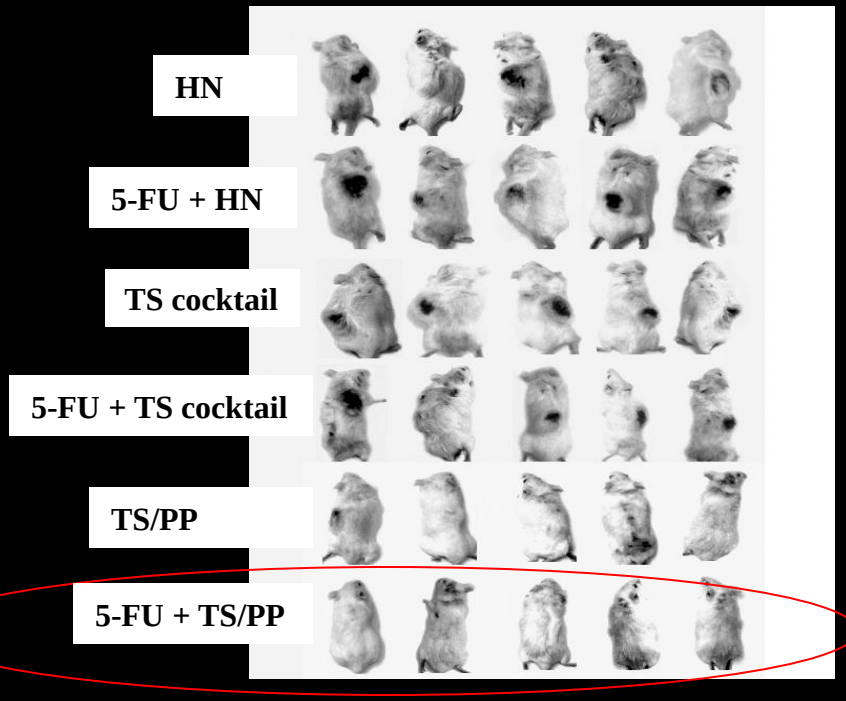
Nome peptide	Sequenza Amino-acidica	Posizione aa. rispetto alla sequenza della TS nativa	Saggio di legame a sHLA-A(*)02.01 (T2 test)	[a]Epitopi predetti con capacità potenziali di legame a aplotipi di HLA Classe I
TS-1	**TLGDAHIYL**	**245-253**	**+++**	**1,A2**
TS-2	**YMIAHITGL**	**229-237**	**+++**	**1,A2;1,A1**
TS-3	**FLDSLGFST**	**111-119**	**+++**	**1,A2**
TS/PP	**YMIAHITGLFLDSLGFSTTLGDAHIYL**		**-**	**5,A2; 1,A3, 1,A1; 5,A24, 1, B44, (and 8, [b]HLA-Dr),**
Pos CTR (CEA) peptide CAP-1	**YLSGANLNL**		**+++**	**1,A2**

[a]Predicted according to the Ken Parker's Algorythm
[b]Predicted according to the H.G. Rammensee's algorithm
(H.G. Rammensee, J. Bachmann, and S.Stevanovic on the book "MHC Ligands and peptide Motifs".

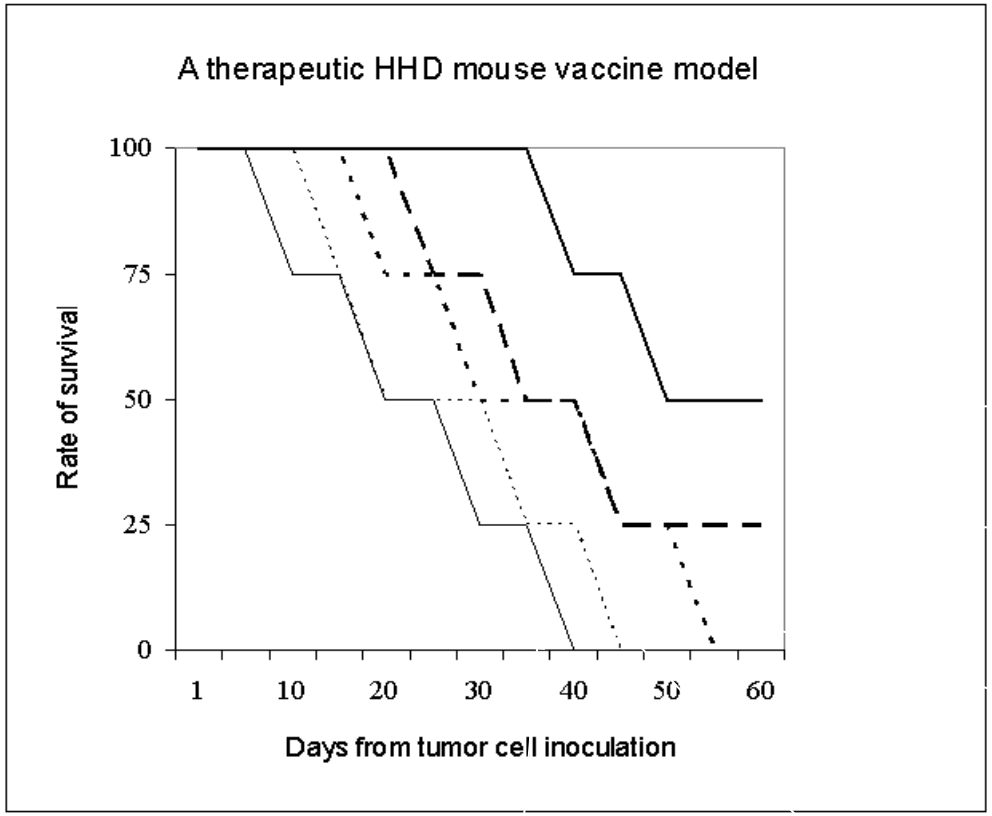
Chemo-immunotherapy

TS/PP Vaccination, a preventive HHD mouse model





Chemo-immunotherapy



TS/PP + GOLF (Late)

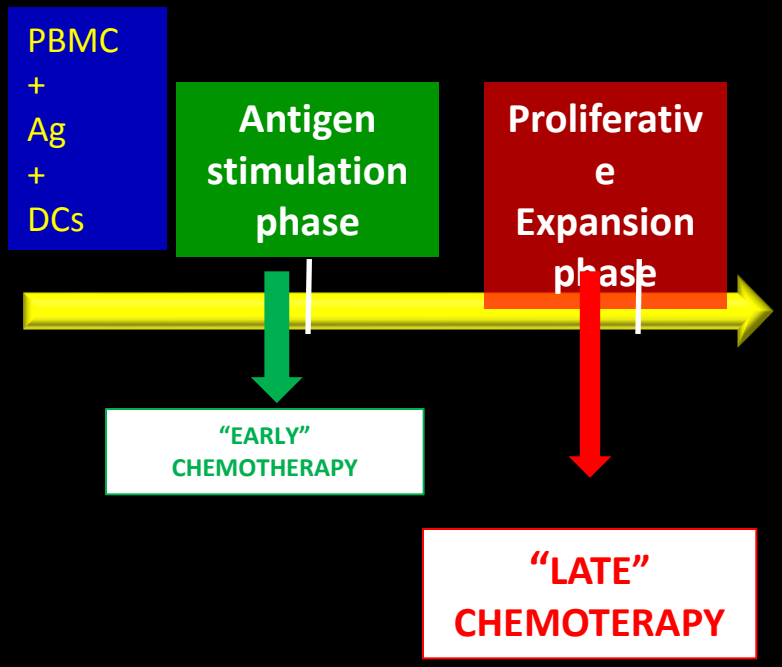
TS/PP + GOLF (Early)

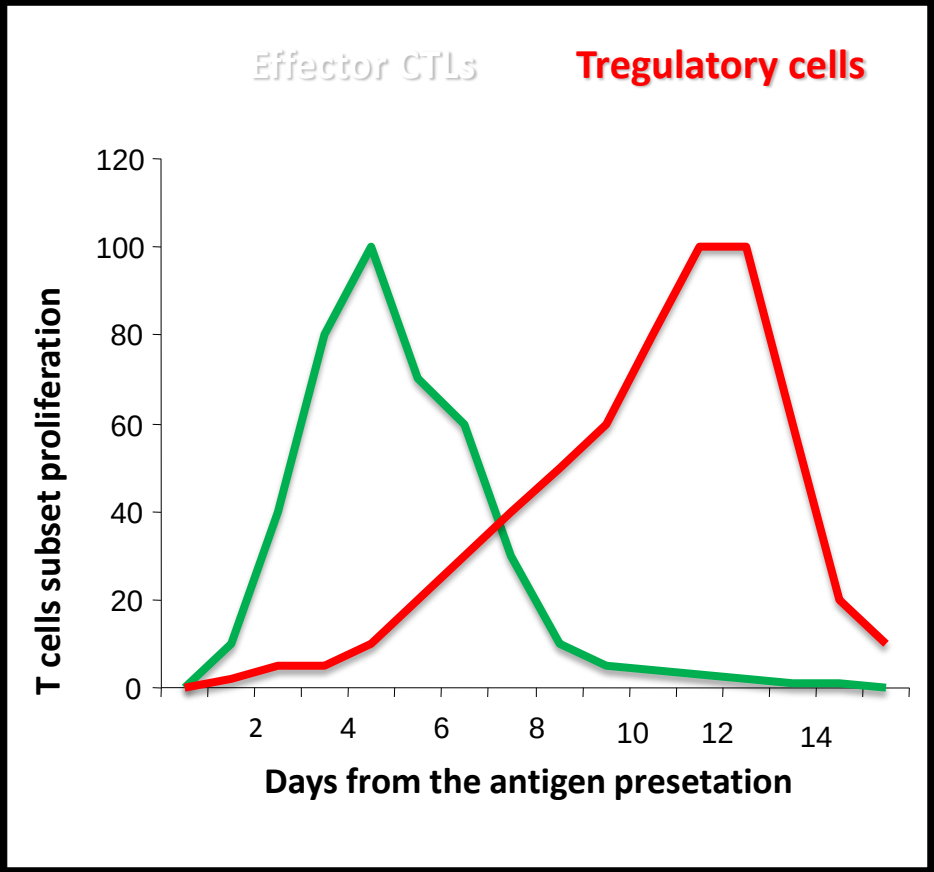
GOLF

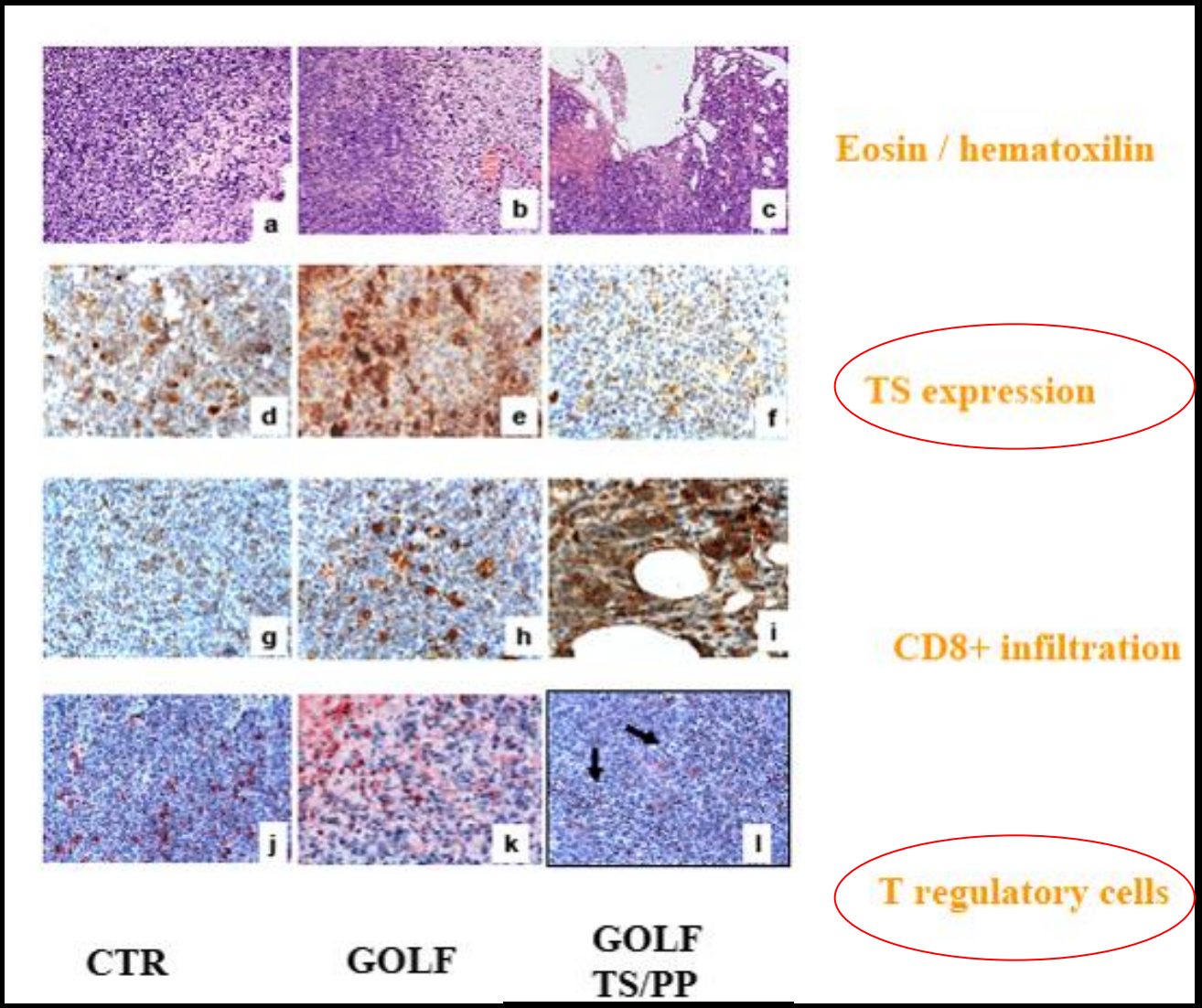
HN

TS/PP

Proliferation of CTL and T reg subsets in T cell cultures







Late chemotherapy

In conclusion…

TS/PP vaccination exerts therapeutic efficacy when used in sequential combination with 5-FU based poly-chemotherapy in HHD mice inoculated with autologous lymphoma cells.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Chemo-Immunotherapy of Metastatic Colorectal Carcinoma With Gemcitabine Plus FOLFOX 4 Followed by Subcutaneous Granulocyte Macrophage Colony-Stimulating Factor and Interleukin-2 Induces Strong Immunologic and Antitumor Activity in Metastatic Colon Cancer Patients

Pierpaolo Correale, Maria Grazia Cusi, Kwong Yok Tsang, Maria Teresa Del Vecchio, Stefania Marsili, Marco La Placa, Chiara Intrivici, Angelo Aquino, Lucia Micheli, Cristina Nencini, Francesco Ferrari, Giorgio Giorgi, Enzo Bonmassar, and Guido Francini

Clinical Rationale for the GOLFIG I Trial

- **GOLF**
  - gemcitabine
  - oxaliplatin
  - folinic acid
  - 5-FU

The GOLF regimen is a safe treatment with significant anti-tumor activity in patients with advanced colo-rectal, pancreatic, and gasric cancer

P.Correale, S.Messinese, M.Caraglia, S.Marsili, R. Petrioli, F. Ceciarini, L.Micheli, C.Nencini, A.Neri, G.Vuolo, A.Guarnieri, A Abruzzese, S.D Prete, G.Giorgi, and G.Francini. A novel biweekly multi-drug regimen of gemcitabine, oxaliplatin, 5-fluorouracil (5-FU), and folinic acid (FA) in pre-treated patients with advanced colorectal carcinoma. Br J Cancer. 2004, May 4;90(9):1710-4.

- **IG-1**

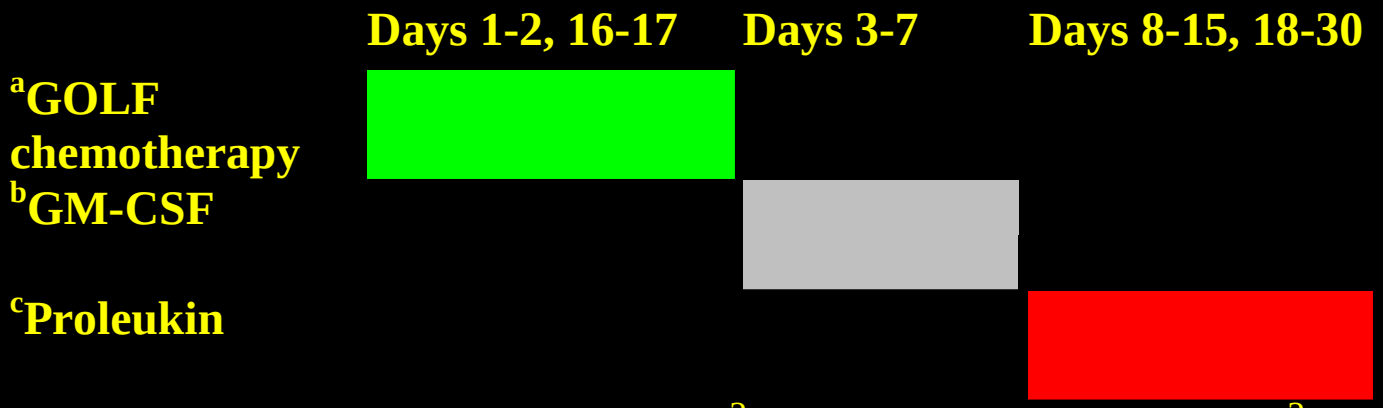
  GM-CSF

  Low dose IL-2

The IG-1 regimen is a safe multicytokine treatment with anti-tumor activity and ability of inducing DC and antigen specific lymphocyte amplification and activation in cancer patients

P. Correale, G. Campoccia, K. Y. Tsang, L. Micheli, G. Cusi, M. Sabatino, G. Bruni, S. Sestini, R. Petrioli, D. Pozzessere, S. Marsili, G. Fanetti, G. Giorgi, and G. Francini. Recruitment of dendritic cells and enhanced antigen specific immune-reactivity in cancer patients treated with hrGM-CSF (molgramostim) and hr IL-2: results from a Phase Ib Clinical Trial. **Eur J Cancer 37 (7):892-902, 2001.**

Schedule treatment

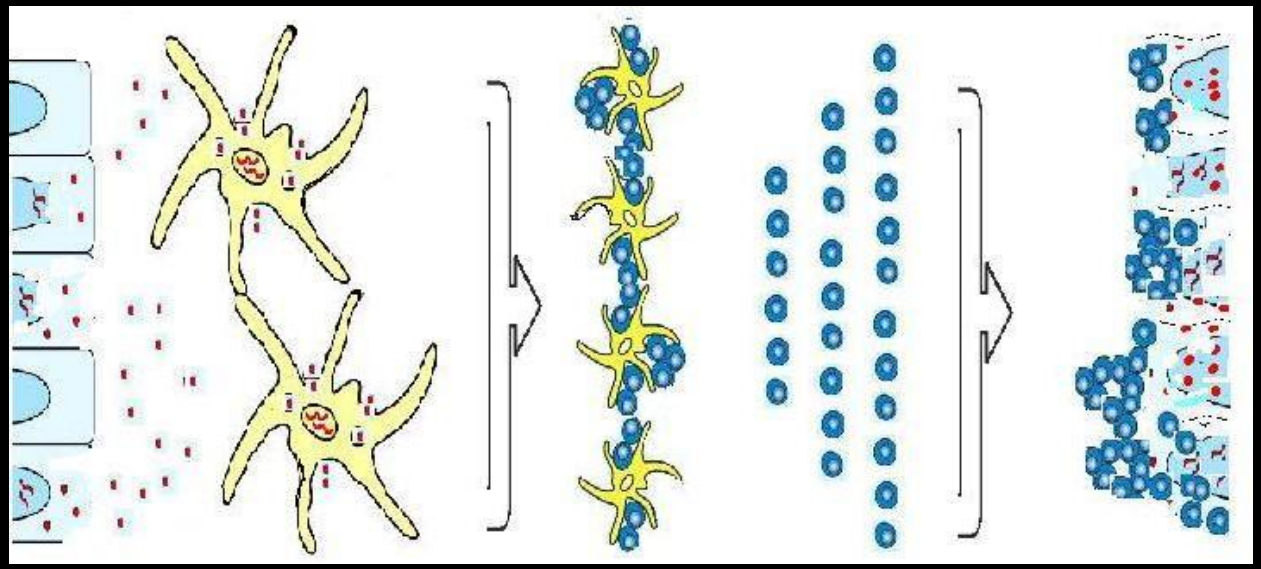


[a]GOLF = gemcitabine, 1g /m^2; oxaliplatin, 85 mg/m^2; levofolinic acid, 100mg/m^2; bolus 5-fluorouracil, 400 mg/m^2; 24 h infusion 5-fluorouracil 800 mg/m^2

[b]GM-CSF = Molgramostim, 150 μg/day /Salgramostim 100 μg/day

[c]Proleukin = Aldesleukin, 500,000 IU x 2 day

Rationale



Chemotherapy

GM-CSF

IL-2

CTL

Aim of the study:

to investigate the anti-tumor and immunological activity and toxicity of the novel chemo-immunotherapy GOLFIG regimen in advanced colo-rectal cancer patients.

(GOLFIG= GOLF poly-chemotherapy + sc Interleukin -2, and GM-CSF)

Patient Characteristics (N= 46)			
Characteristic		**No. of Pts**	%
Age, years Median Range	62 28-83		
Sex Male Female		27 19	58.6 41.3
ECOG performance status 0 1 2 3		23 13 6 4	50 28.2 13 8.6
Tumor type Colon cancer Rectal cancer		39 7	84.7 15.2
Metastatic site Hepatic Non hepatic (bone, lung, peritoneum, pelvis, ovary, nodes)	32 36		
First line chemotherapy		12	26

Occurrence of adverse events (46 patients*)

Type of toxicity	% of events	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Hematological	44.8%				
Anemia	17.2%	6.9 %	6.9%	3.45%	
Neutropenia	10.3%	10.3%			
Thrombocytopenia	20.7%		10.3%	10.3%	
Gastroenteric toxicity	27.6%				
Nausea/vomiting	6.9%	3.45%	3.45%		
Diarrhea	17.2%	6.98%		6.9%	3.45%
Mucositis	20.7%	10.3%		6.9%	3.44%
Transaminase elevation	None				
Fever	69%	27.6%	27.6%	3.45%	3.45%
Asthenia	6.9%			3.45%	3.45%
Anorexia	None				
Neurological toxicity	24.1%		24.1%		
Arrhythmia	3.45 %	3.45%			
Hypersensitivity	13.8%	3.45%	3.4%	3.45%	3.45%
Bleeding	2.2% (1 case)				2.2 % (1 case)
Bone pain	25.3%				
Brain transitory ischemia				2.2% (1 case)	

*A median of 10 cycles of chemo-immunotherapy per patients could be administered

Clinical response (N= 46)

Best response	Number of patients	%
CR PR SD PD	10 16 16 4	21.7 34.7 34.7 8.6
Overall response (CR + PR) (95% CI)	26	56.5 (42.1 – 69.8)
Disease control (CR + PR + SD) (95% CI)	42	91.3 (79.6 – 96.4)

CR **complete response,** ***PR*** **partial response,** ***SD*** **stable disease,** ***PD*** **progressive disease.**

Immunological effects induced by the GOLFIG Chemo-immunotherapy in colon cancer patients

A) Risk of disease progression

Prognostic variable	P	Risk Ratio (95% CI)
Autoimmunity	0.0046*	0.1646 (0.0472-0.5738)
Age	0.1059	0.9764 (0.9485-1.0051)
Liver metastases	0.3401	0.7044 (0.3429-1.4470)
Previous chemotherapy	0.7919	0.8986 (0.4060-1.9886)
Performance status	0.0877	1.2872 (0.9634-1.7200)
Sex	0.6697	1.1621 (0.5827-2.3176)

B) Risk of death

Prognostic variable	P	Risk Ratio (95% CI)
Autoimmunity	0.0256*	0.0884 (0.0105-0.7440)
Age	0.6415	0.9916 (0.9570-1.0274)
Liver metastases	0.8232	0.8970 (0.3457-2.3275)
Previous chemotherapy	0.7046	0.8201 (0.2941-2.2867)
Performance status	0.0042*	1.7248 (1.1881-2.5040)
Sex	0.7519	0.8776 (0.3905-1.9721)

Autoimmunity and *performance status* resulted as the most predictive variables of prolonged time to progression and survival (*) Statistically significant values.

Chemo-immunotherapy

The results of this study show that the GOLFIG regimen is well tolerated and exerts a high objective response / disease control rate and a *prolonged time to progression* in colorectal carcinoma patients as a second/third line of treatment

A phase III Trial in advanced colorectal carcinoma in first line of therapy:
GOLF poly-chemotherapy followed by sc GM-CSF and low dose IL-2 versus the best standard chemotherapy, FOLFOX-4.
(GOLFIG-2 Trial)

Prot. 457/05

Chemo-immunotherapy

A Randomized phase III (GOLFIG2) Trial
GOLFIG vs FOLFOX

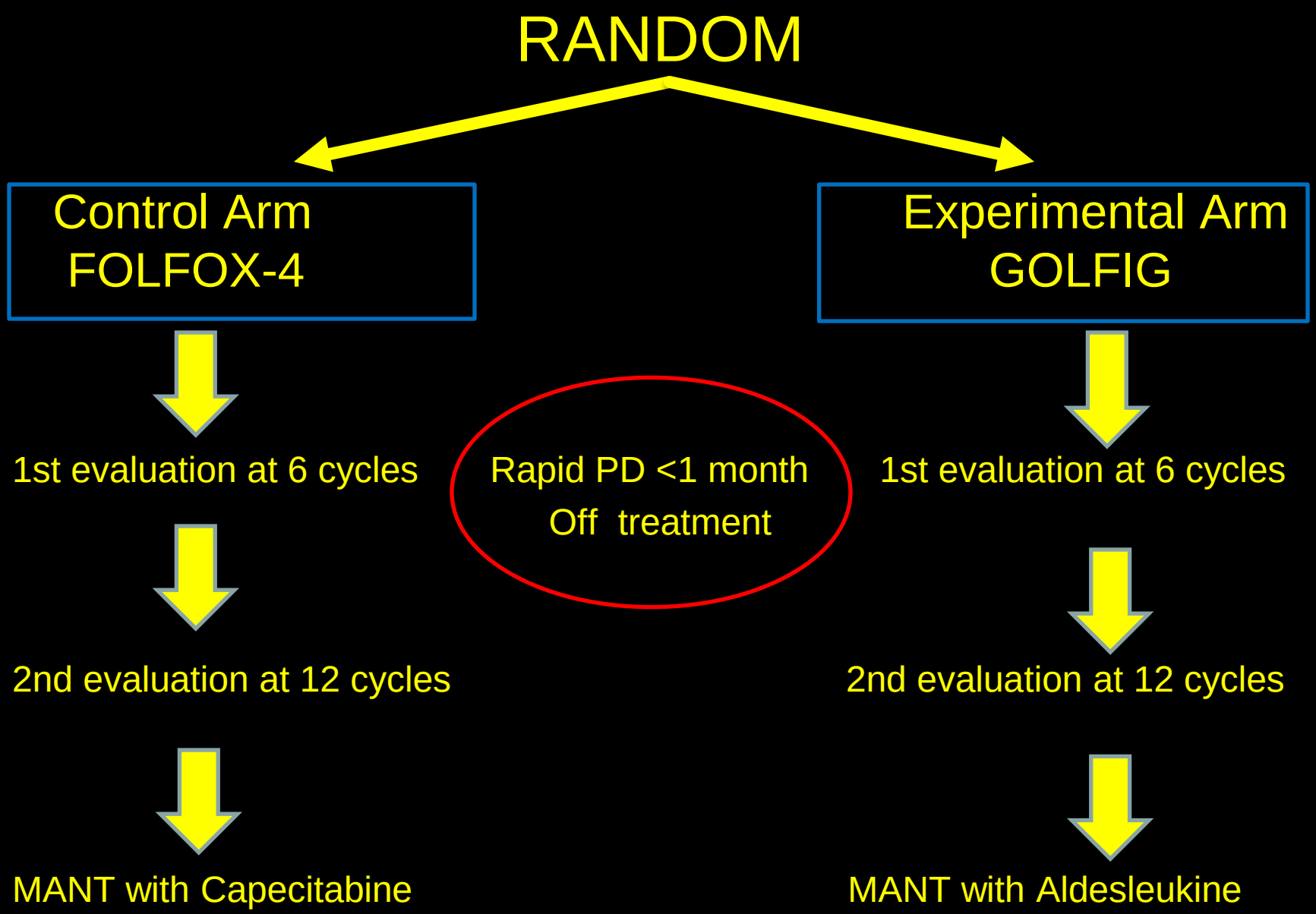
Primary endpoints: **Progression Free Survival**

Secondary endpoints: **Objective Response**
Overall Survival
Immune-biological Activity

Statistical Sample = 180 patients; First update = 90 events

Operative Centers = Siena, Catanzaro, Forlì, Firenze, Roma "Tor Vergata", Cagliari

Study Design



Chemo-immunotherapy

	GOLFIG	FOLFOX-4
Randomized Patients	**63**	**61**
Age	**66**	**68**
Median ECOG	**1**	**1**
Males	**42**	**41**
Females	**21**	**21**
Liver Metastases	**65 (%)**	**64 (%)**
Surgery	**88 (%)**	**88 (%)**

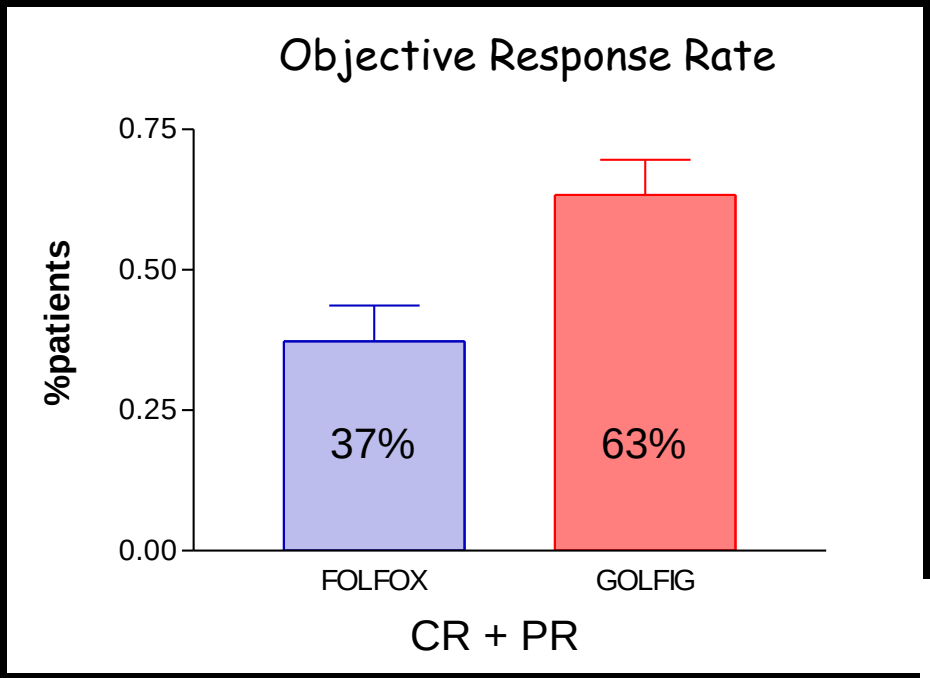
TOXICITY	% of cases FOLFOX (61 Pz)	% of cases GOLFIG (63 Pz)
Hematologic toxicity G2-3	34%	46%
TVP	8%	0%
Diarrea	8%	17,4%
Nausea/Vomit	4.9%	14.2%
Asthenia	4.9%	4.7%
Fever	4.9%	19%
Neurotoxicity	4.9%	11.1%
Oxaliplatin reaction	1.6%	4.7%
Flushing	0%	3.1%
Autoimmunity	0%	12.6%
Sudden Death	4.9%	0%

Clinical response

	FOLFOX (N= 61)		GOLFIG (N= 63)	
	Number of patients	%	Number of patients	%
Best response				
CR	3	4.9%	5	7.9%
PR	19	31%	33	52.3%
SD	16	26.2%	16	25.3%
PD	21	34.4%	6	9.5%
Overall response (CR + PR)		37%		63%
Disease control (CR + PR +SD)		64%		90%

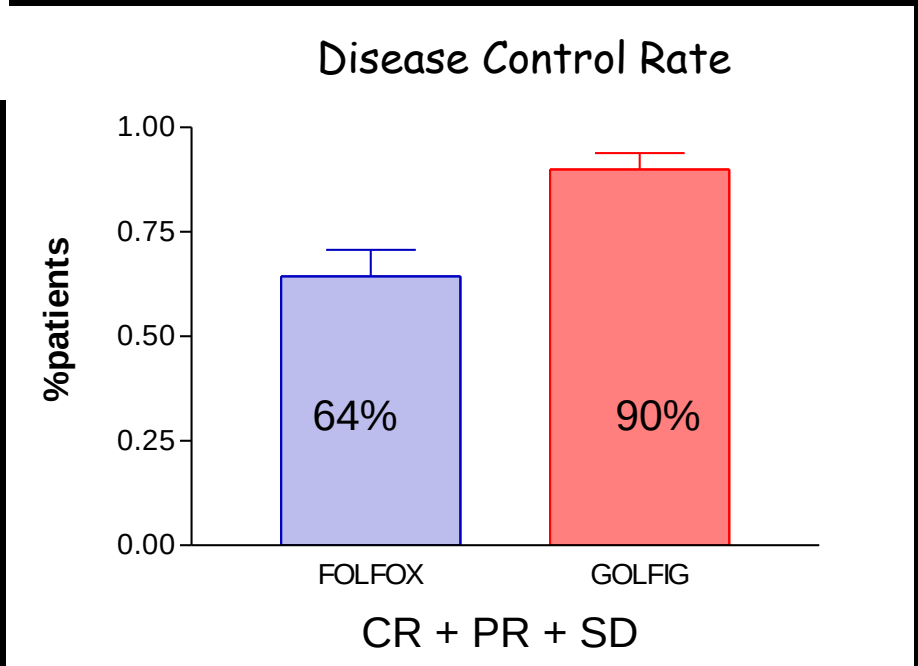
Median follow-up 18 months

Anti-tumor activity

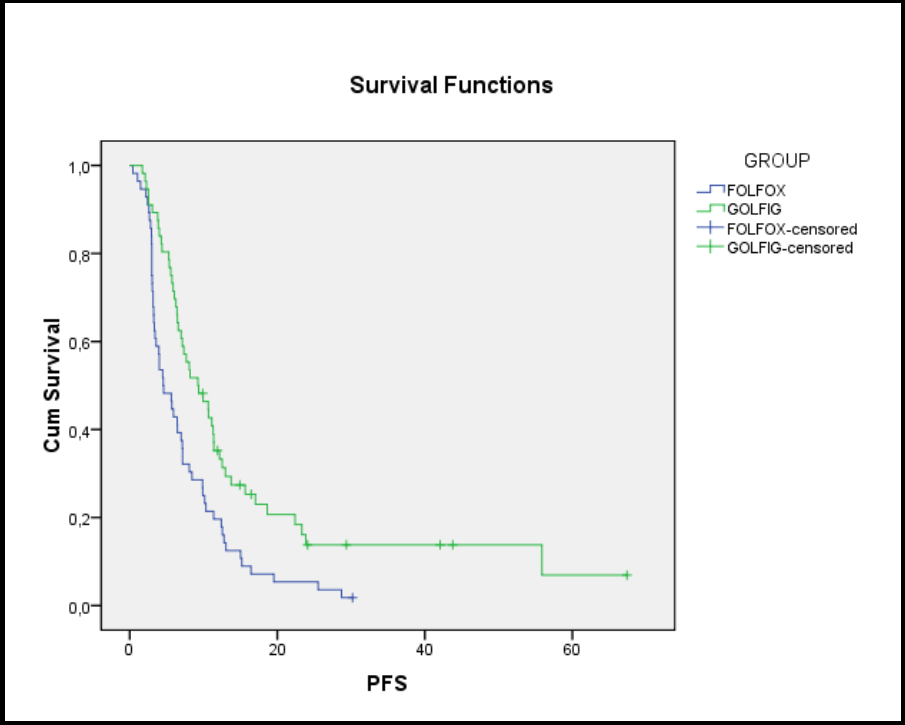


p=0.00423

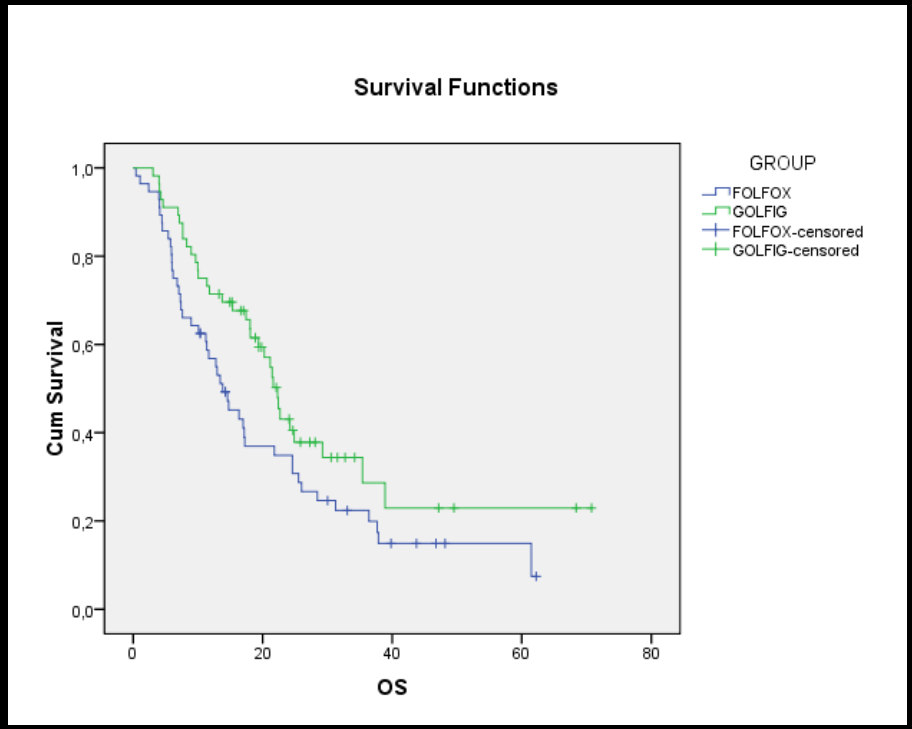
p= 0,00073



First Interim Analysis

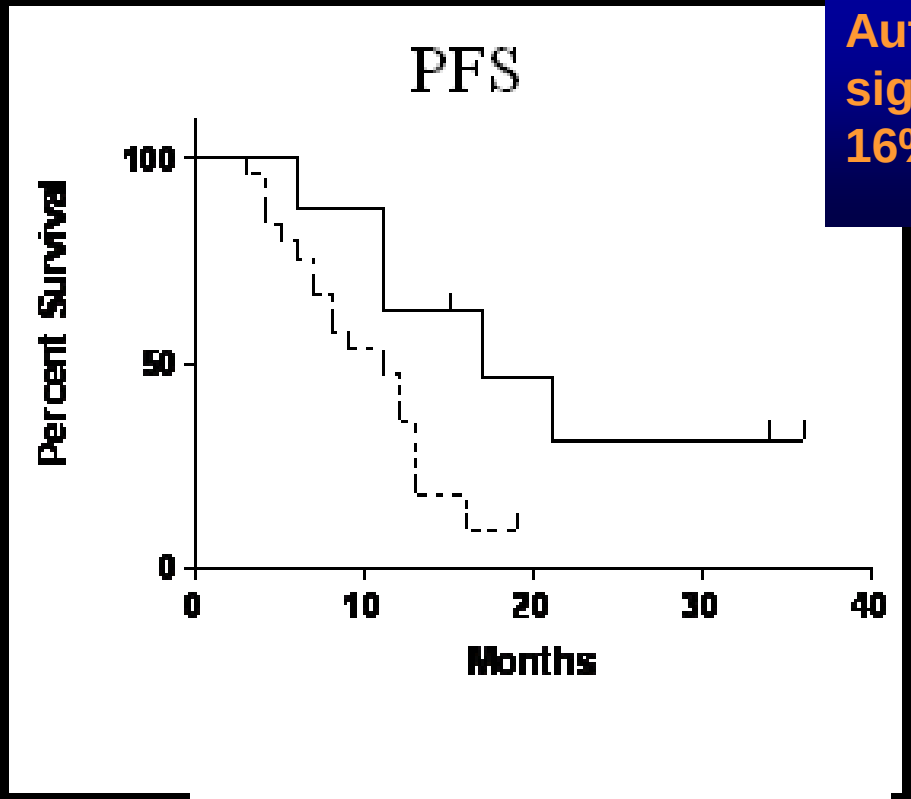


FOLFOX: 7.4 months (IC 95% 5.7-9.1)
GOLFIG: 16.5 months (IC 95% 11.2-21.8)
(p=0.0015; HR 0.6433- IC 95% 0.4049-0.8870)



FOLFOX: 21.5 months (IC 95%: 16.1-26.0)
GOLFIG: 30.5 months (IC 95% 22.8-38.2)
(p=0.0496; HR 0.9192- IC 95% 0.6028-1.387)

Chemo-immunotherapy and autoimmunity



Autoimmunity signs observed in 16% of the patients

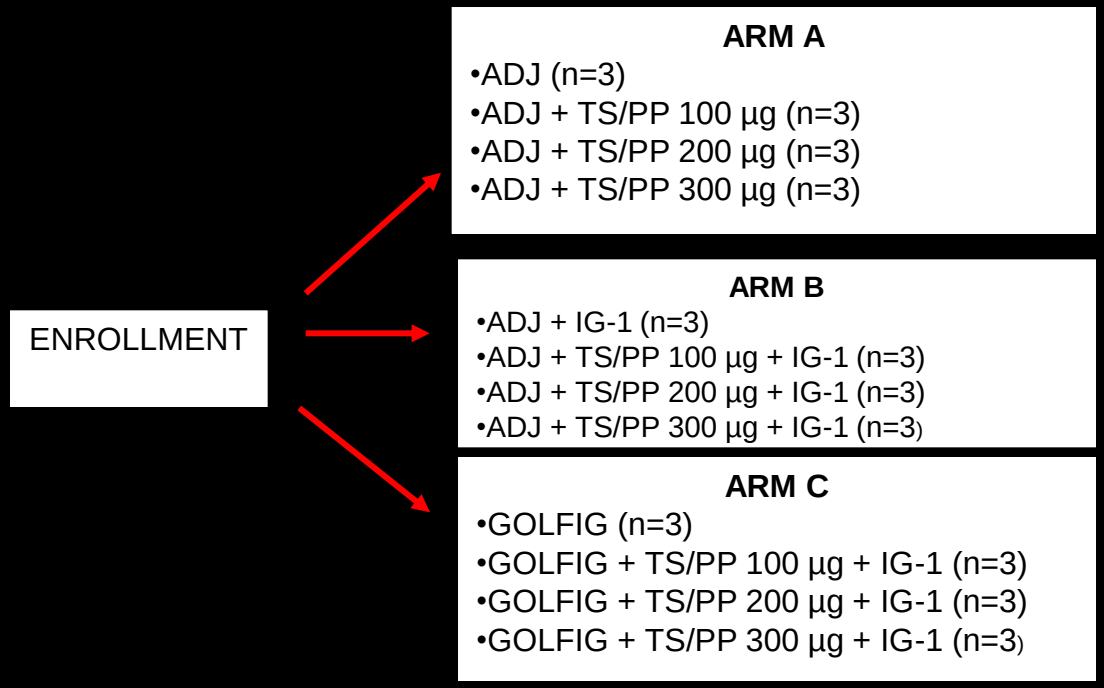
CONCLUSIONS

At the first interim analysis our results demonstrated the efficacy of GOLFIG regimen in the treatment of advanced colon cancer.

This is the first randomized study which suggests the efficacy of a bio-chemotherapy regimen designed to generate an active immune-response in colon cancer.

TSPP/VAC 1 - Phase IB trial

Clinical evaluation of TSPP vaccine alone or in combination with immunoadjuvant cytokines (IG-1 regimen / aldesleukine e GM-CSF) or Chemo-immunotherapy (GOLFIG regimen / gemcitabine, oxaliplatin , levofolinic acid and 5-FU + IG-1) in cancer patients.



Study name: **TSPP/VAC-1**
EUDRACT number: **2009-016897-33**

24/ 3/ 2011

TSPP/VAC1 Trial

Based on the results of preclinical studies, we designed a Phase Ib trial (TSPP/VAC1), to investigate in a dose-escalation setting, the safety and the biological activity of TSPP vaccination alone (arm A) or in combination with GM-CSF and IL-2 (arm B) in cancer patients.

Patient population

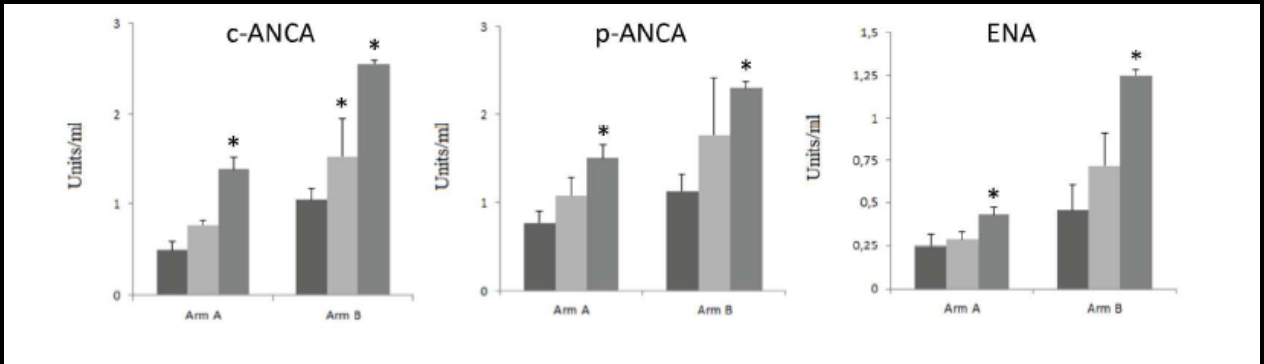
Twenty one pretreated metastatic cancer patients, with a good performance status (ECOG ≤ 1) and no severe organ failure or immunological disease, were enrolled in the study (12 in arm A, 9 in arm B) between April 2011 and January 2012 with a median follow-up of 28 months.

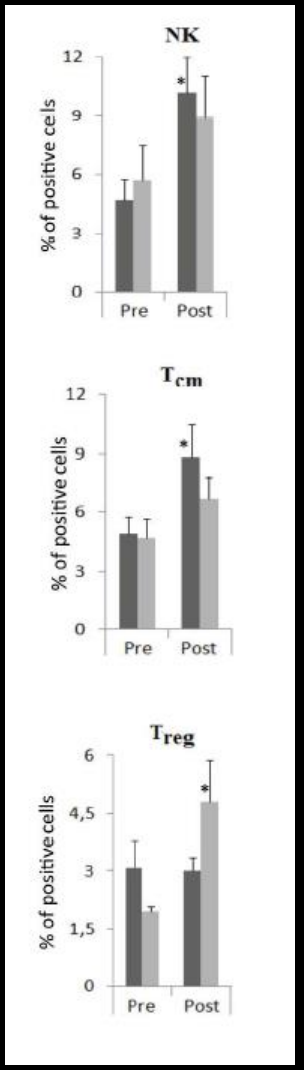
Toxicity

TSPP resulted safe and its maximal tolerated dose (MTD) was not achieved. There was no grade 4 toxicity. The most common adverse events were grade 2 dermatological reactions to the vaccine injection, cough, rhinitis, fever, poly-arthralgia, gastro-enteric symptoms and to a lesser extent, moderate hypertension and hypothyroidism.

Table 1. Patients characteristics, toxicity, adverse events and response.
he enrolment code was composed by patient's initials/ arm of enrolment (A or B) / dose level (DL).

ID	Age/Sex	HLA	Site of primary tumor	Metastatic sites	Number of previous treatments	Number of vaccinations
Arm A						
MF/A/DL1	**/F**	**A2**	**Colorectal cancer**	Liver, lung	11	3
RA/A/DL1	**/F**	**A2**	**Colorectal cancer**	Abdomen, nodes	7	3
AS/A/DL1	**/M**	**A2**	**Colorectal cancer**	Liver, lung	3	3
LV/A/DL2	**/M**	**A11**	**Colorectal cancer**	Lung, nodes	7	6
OA/A/DL2	**/M**	**A1**	**NSCLC**	Brain, bone, liver,lung	3	6
SG/A/DL2	**/M**	**A25**	**Colorectal cancer**	Abdomen, nodes	4	6
ZS/A/DL3	**/F**	**A2**	**Colorectal cancer**	Nodes, adrenal	3	32
MA/A/DL3	**/F**	**A23**	**Gallbladder Carcinoma**	Peritoneum, nodes	1	28
CM/A/DL3	**/F**	**A2**	**Breast cancer**	Lung, skin, pleura	3	12
AR/A/DL3	**/M**	**A2**	**NSCLC**	Lung, nodes	1	3
PN/A/DL3	**/F**	**A1**	**Colorectal cancer**	Lung, bone	3	3
SN/A/DL3	**/M**	**A2**	**Colorectal cancer**	Liver, lung	3	3
Arm B						
PL/B/DL1	**/F**	**A1**	**NSCLC**	Lung, nodes	4	5
RV/B/DL1	**/M**	**A2**	**Gastric cancer**	Liver, peritoneum	1	3
PGB/B/DL1	**/M**	**A26**	**NSCLC**	Brain, lung, nodes	3	3
GL/B/DL2	**/F**	**A24**	**Colorectal cancer**	Liver, abdomen	3	3
PP/B/DL2	**/F**	**A2**	**Colorectal cancer**	Lung, liver, peritoneum	5	3
FG/B/DL2	**/M**	**A24**	**Colorectal cancer**	Peritoneum, nodes	3	3
SF/B/DL3	**/F**	**A24**	**NSCLC**	Liver, abdomen	3	15
M/B/DL3	**/M**	**A1**	**Colorectal cancer**	Lung, liver, peritoneum	4	3
BA/B/DL3	**/F**	**A30**	**NSCLC**	Peritoneum, nodes	2	3





Immunobiological acitivity

We detected a significant rise in auto-antibodies and TS-epitope-specific CTL precursors in both arms.

Patient in arm A showed rise in central memory CTLs and NK subsets

Patients in arm B showed a significant rise in systemic inflammatory markers and TH1 phenotype with appearance of immunosuppressive regulatory T cells

Antitumor activity

In this very advanced and multi-treated patients' set, TSPP showed evidence of antitumor activity;

Arm A (12 Pts) : one partial response and 6 disease stabilizations (SD) with a mean *progression free survival* (PFS) of 6.4 (95% CI= 3.66-9.2) months and a mean overall survival (OS) of 10.98 (95% CI= 7.56-14.4)
Six patients (50%) survived more than 12 months and 2 of them [ZS/A/DL3 with colorectal (CC) carcinoma and MA/A/DL3 with gallbladder adenocarcinoma (GBC)], survived free of progression for more than 20 months.

Arm B (9 Pts) : 2 SD with a PFS of 3.69 (95% CI= 1.55-5.82) months and an OS of 5.9 (95% CI= 4.11-7.69) months. Only one patient (SF/B/DL3 with a NSCLC) survived more than 15 months

Conclusions

Taken together, our findings provide the framework for the evaluation of the TSPP anti-tumor activity in further clinical trials.

Maximal Tolerated dose (MTD) was not achieved

The most effective biological dose of TSPP was 300 ug

The addition of GM-CSF and IL-2 does not give any immunological antitumor advantage to the treatment.

Poly-epitope peptide vaccination to thymidylate synthase (TSPP) and GOLFIG chemo-immunotherapy for treatment of metastatic colorectal cancer patients. TSPPVAC1/Arm C phase Ib trial

Arm-C is the third part of the multi-arm *TSPPVAC1* phase Ib trial

Twenty-seven patients, 14 males and 13 females, with a good performance status and pretreated metastatic colorectal cancer were enrolled.

Patients received biweekly poly-chemo-immunotherapy according to the GOLFIG regimen

TSPP/VAC1 Arm C

Concomitant treatment: Seventeen patients received concomitant TSPP sc. injections (Day 7 and 21) on biweekly bases, at different dosage [3 patients received 100µg (DL-1); 3, 200 µg (DL-2) and 11, 300 µg (DL-3)].

Sequential treatment: Thirteen patients received GOLFIG regimen alone [dose level(DL)-0] and then TSPP vaccination every 3 weeks. TSPP vaccination was only given to patients whose disease did not progress

Toxicity

Either concomitant or sequential GOLFIG / TSPP treatment was very active and relatively safe.

There was one case of grade 4 hematological toxicity and three cases of late oxaliplatin reaction.
Grade (g) 1-2 adverse events, consisting of hematological and gastro-enteric toxicity were very common.
Dermatological reactions to the vaccine injection (12 cases), fever (10 cases), rhinitis, conjunctivitis, and poly-arthralgia (10 cases) were similarly frequent.

Biological activity

Patients undergone the concomitant treatment showed:

- peripheral blood increase in lymphocyte, monocyte, and eosynophil counts; CPR, ESR, myeloperoxidase.

- induction of a Th2 phenotype and rise of IL-10

- induction of auto-antibodies (ENA, p-ANCA, c-ANCA)

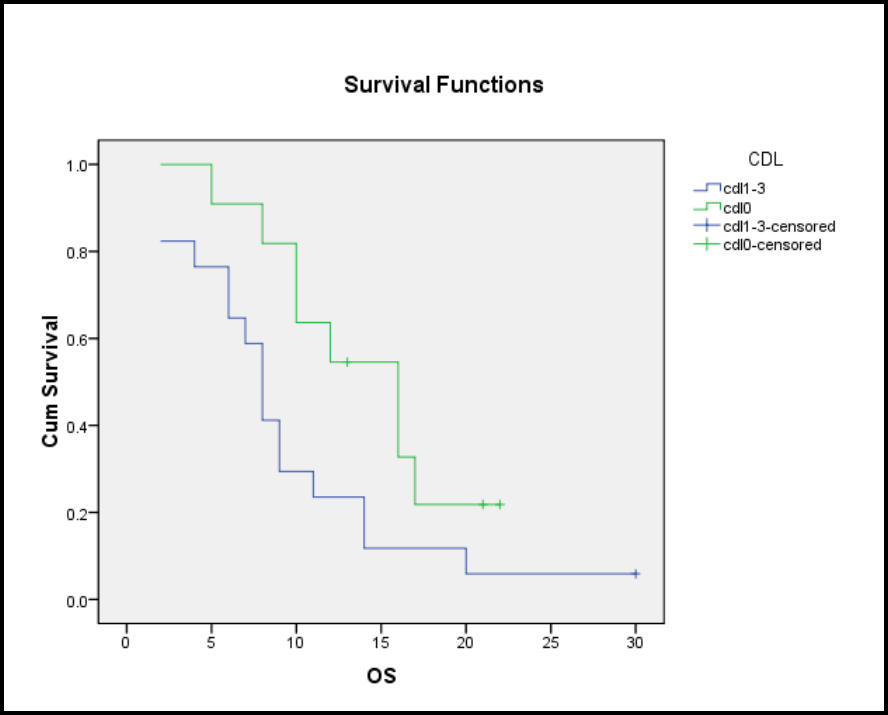
- augmented expression of central-memory-, effector memory-, regulatory-T cells, natural killers, and TSPP-specific CTL precursors.

Antitumor activity

TSPP vaccination does not modify anti-tumor activity of the GOLFIG regimen.

Concomitant treatment (DL1-3) (17 pts): 4 PR (23.5%), 8 SD (47.1%) and 5 progression of disease (PD) (29.4%) with a PFS and OS of 4 (+/- 0.738) and 9.4 (+/- 1,67) months, respectively.

Sequential treatment (DL0) (12 pts) : 6 PR (50%) and 4 SD (30%) with a median PFS and OS of 6.25 (+/- 0.038) and 14.24 (+/- 1,67) months, respectively.



Means and Medians for Survival Time

CDL	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
cdl1-3	9.412	1.674	6.130	12.693	8.000	.676	6.674	9.326
cdl0	14.236	1.666	10.971	17.501	16.000	2.905	10.306	21.694
Overall	11.956	1.546	8.926	14.987	9.000	1.323	6.407	11.593

a. Estimation is limited to the largest survival time if it is censored.

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	4.126	1	.042

Test of equality of survival distributions for the different levels of CDL.

Conclusions

- TSPP vaccination is safe and well tolerated and does not enhance GOLFIG toxicity.

- We were unable to identify a MTD for TSPP vaccination in combination with GOLFIG poly-chemo-immunotherapy.

- The most significant antitumor activity was recorded when TSPP vaccine was given after 10 course of GOLFIG chemo-immunotherapy

Conclusion

TSPP / GOLFIG treatment resulted active and safe in colon cancer patients and TSPP MTD was not achieved.

The most effective biological and antitumor activity of TSPP vaccination was achieved at the dosage of 300μg.

The anti-tumor activity recorded either in combined and sequential treatment was very promising and grants the rationale for further studies in colon cancer patients

TSPP/VAC1 trial

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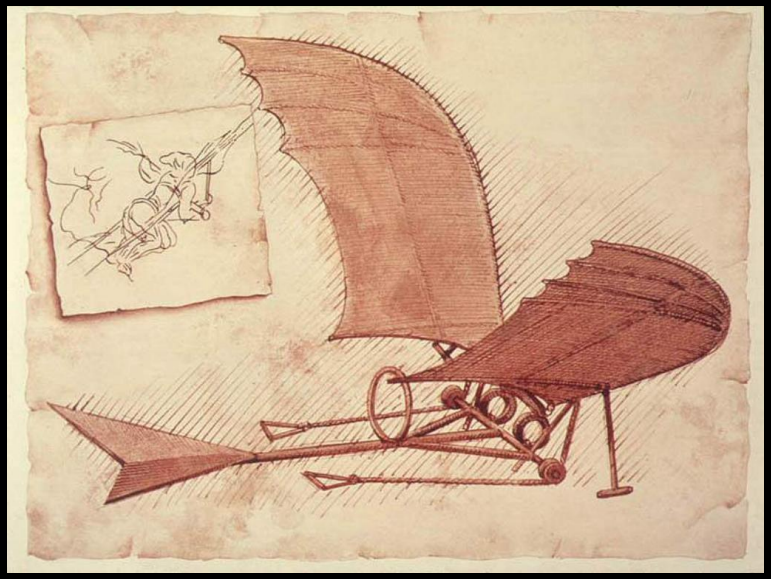

Only who dares can fly ..

Louis Sepulveda