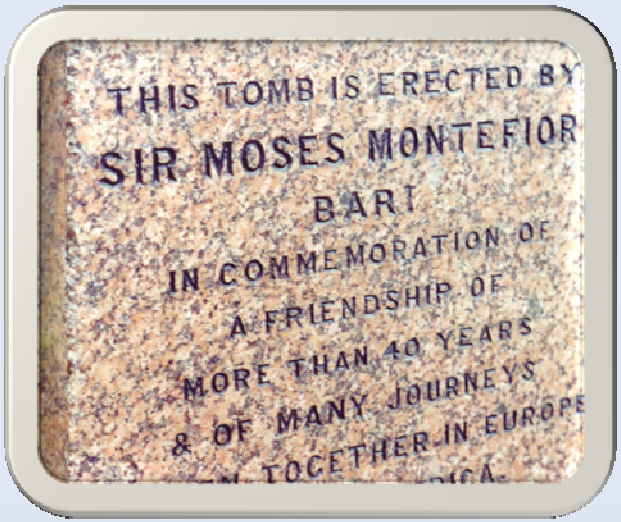
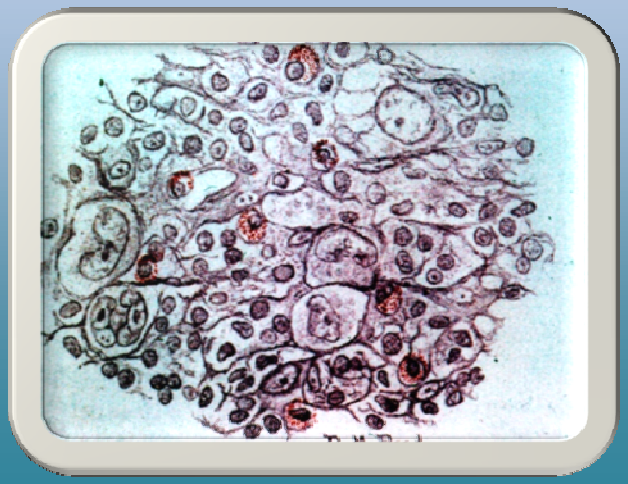
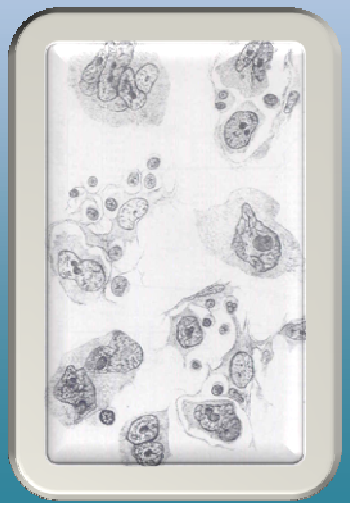


Tailored therapy for Hodgkin lymphoma based on predefined risk factors and early interim PET for response assessment and further therapy decisions. H2 ISR protocol





Study Purpose:

- To tailor therapy for HL based on risk factors and response to therapy so that patients at high risk of relapse receive intensified treatment and those at low risk of relapse receive the minimally safe dose which will maximize response and remission rates and minimize long-term toxicity.

- The protocol results will be compared to the GHSG results as well as previous results from Israel H1 study.

- A non-randomized 4-arm study / a non-inferiority study

The protocol is based on interim PET /CT scanning. Decision-making regarding initial chemotherapy will be based on stage and initial prognostic factors, while decisions concerning continued chemotherapy will be based **on results of interim PET scans.**

Patients with early stage disease and negative scans will be given a minimal accepted amount of chemotherapy according to the literature, while patients with positive scans will receive intensified chemotherapy.

Patients with advanced stage HL will also be treated with the aim to reduce chemotherapy intensity.

Thus, only those with three or more adverse prognostic signs according to the IPS will begin treatment with escalated BEACOPP and after two courses their response will be evaluated using a PET (PET-CT).

OVERALL TREATMENT SCHEMA BASED ON RISK CATEGORIZATION

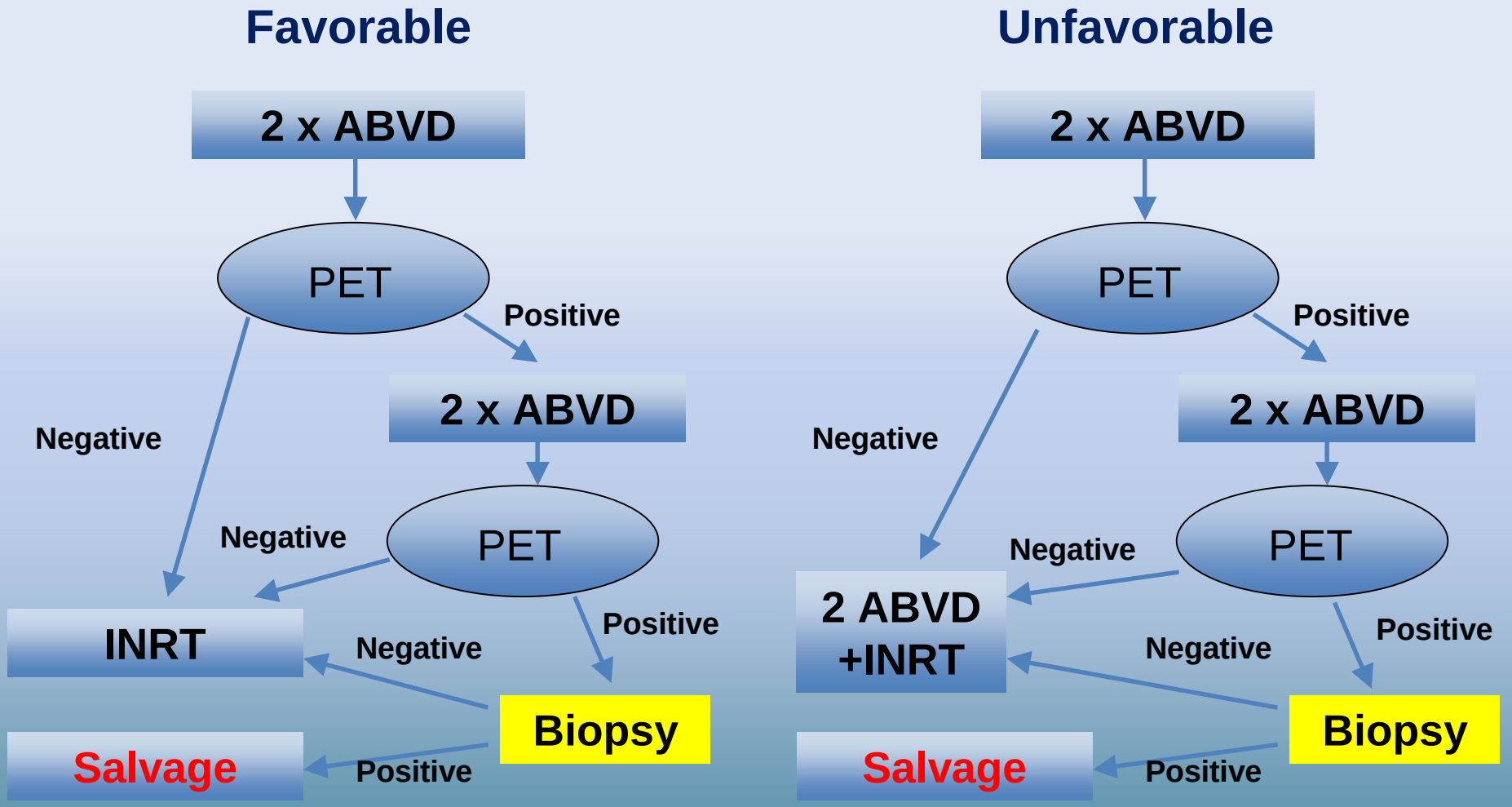
1.Early favorable: Planned treatment – 2 ABVD + 25.2 Gy INRT, if PET is negative after 2 courses (2 months after starting treatment)

2. Early unfavorable: Planned treatment – 4 ABVD + INRT, if PET is negative after 2 courses (2 months after starting treatment)

3. Advanced stage (B symptoms or Stage III, IV, score 0-2):
Planned treatment – 6 ABVD, if PET is negative after 2 courses (2 months after starting treatment).
If PET +, 4 additional courses of escalated BEACOPP.

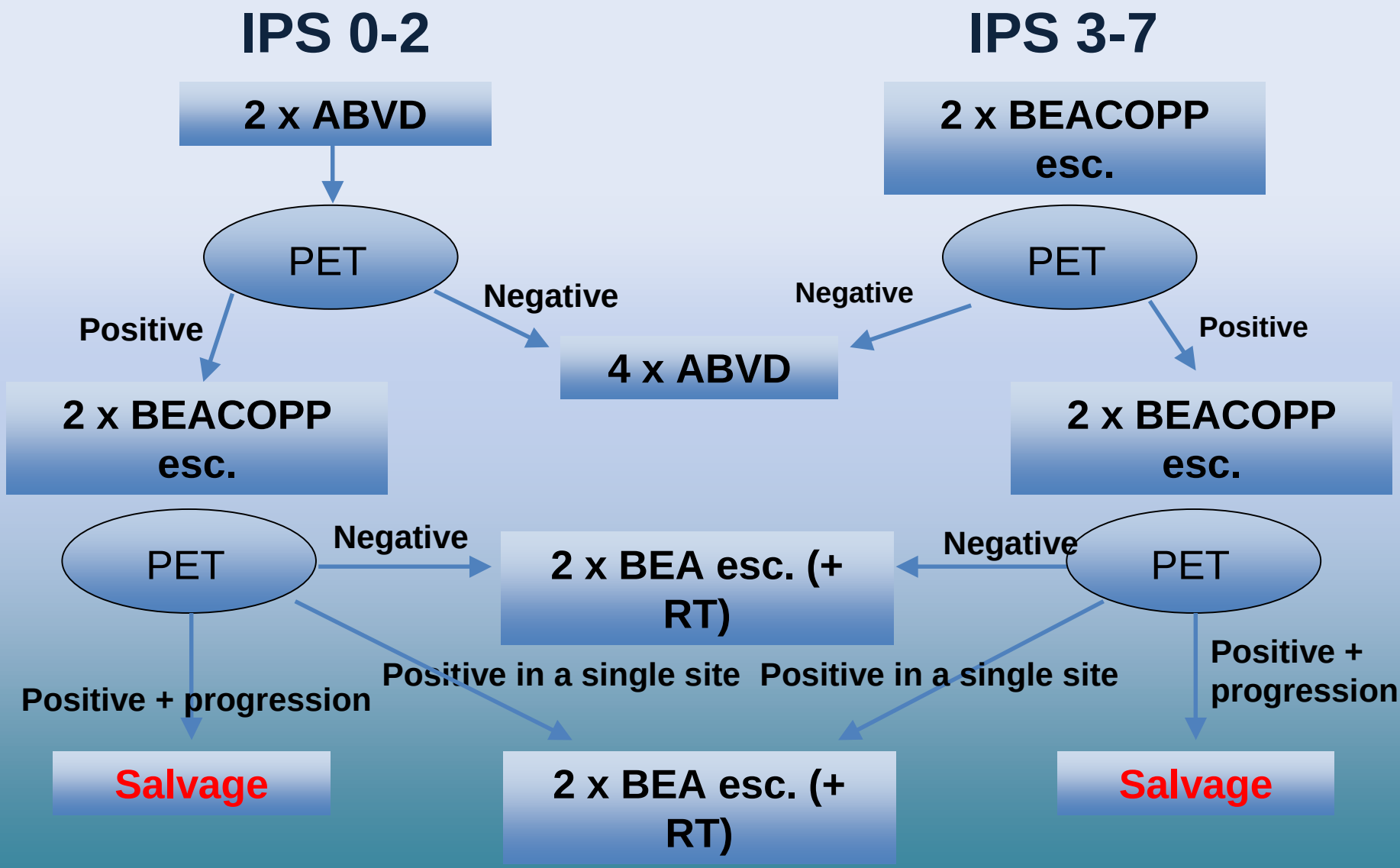
4. Patients with advanced disease (IPS score 3-7) start with escalated BEACOPP. Interim PET is performed after 2 courses. If negative, continue treatment with ABVD x 4. If positive, continue escalated BEACOPP.

Israel H2 trial – stages IA and IIA



Risk factors: Extra-nodal disease, MM>10cm, ESR > 50, ≥3 regions, Age > 50, LD histology

Israel H2 trial for advanced stages



Interim PET/CT dynamic visual score for HD patients

0- No evidence of residual uptake.

1- Single site uptake.

2- More than one residual site with markedly decreased intensity compared to baseline in those sites.

3- No change in number of sites with pathologic uptake; however, reduced intensity of uptake in those sites compared to baseline.

4- No change in number of sites or intensity or appearance of new sites of uptake.

Dann EJ, Bar-Shalom R et al. Haematologica, in press, 2010

PET scoring criteria for a single site of HL at diagnosis

In case of a single focus of FDG uptake on the baseline PET/CT study, the response on the interim study will be defined as follows:

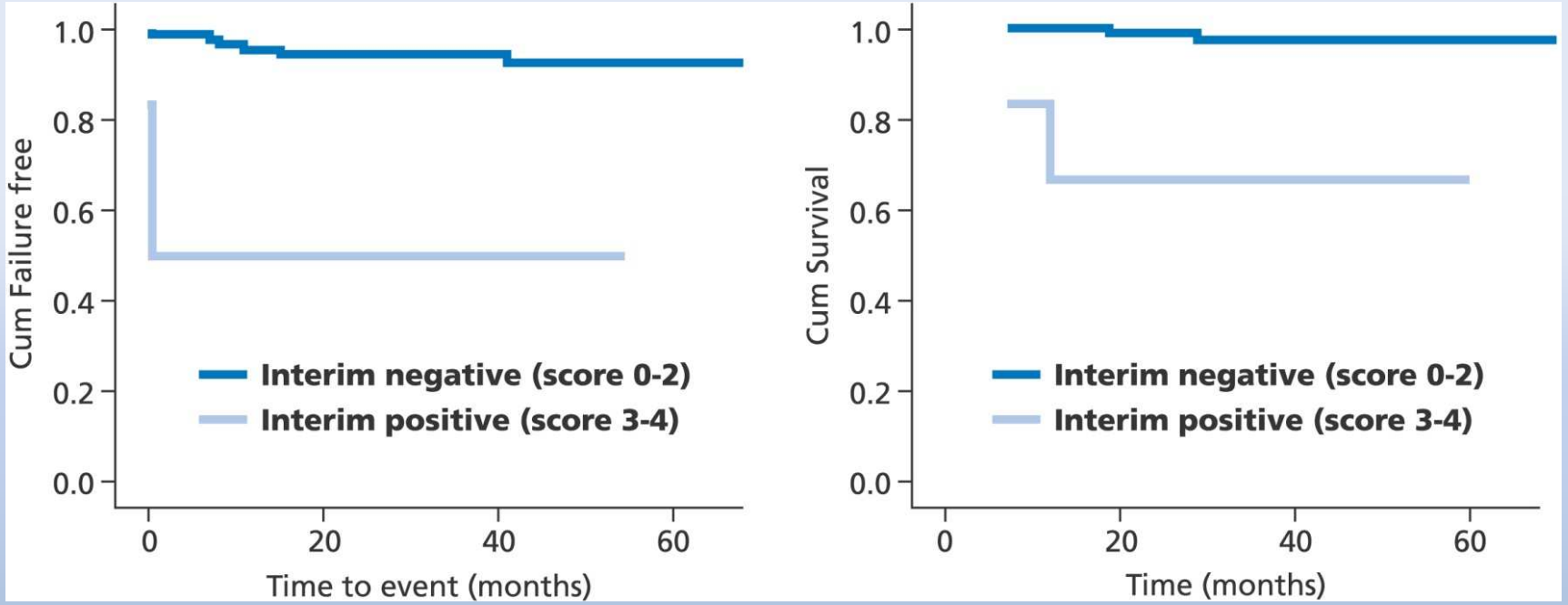
Score 0 – Negative PET (disappearance of uptake in the single site)

Score 1a – Residual uptake in a single site, reduced in area and intensity, compared to normal mediastinal or liver blood pool uptake)

Score 3a – Residual uptake in a single site, equal to or higher than uptake in normal mediastinal or liver blood pool uptake (the reference organ will be the hottest of these two), with or without change in uptake area.

Score 4a – No change in intensity or increase in intensity and area of FDG uptake in a single site, or the appearance of new foci of abnormal FDG uptake consistent with disease progression.

Overall survival and event free survival according to interim PET/CT dynamic visual score (DVS)



OS and EFS for patients with the interim DVS of 0-2 versus the DVS of 3-4. For these groups of patients the 4-year OS is 0.97 versus 0.67 (p<0.0001) and FFS is 0.92 versus 0.50 (p=0.0001)

Dann EJ, Bar-Shalom R et al Prepublished DATA

4.1 Eligibility Criteria

Histologically or cytologically confirmed classic HL
Nodular Sclerosis
Mixed cellularity
Lymphocyte depletion
Lymphocyte rich classical HL
FDG avid HL
A mass demonstrated on CT scan in site of abnormal uptake
No previous malignant disease except non-melanoma skin cancer
No prior therapy for HL
Age 18-60 years. In view of unacceptable toxicity of escalated BEACOPP for patients above age 60, they are not eligible for the protocol.

To date 118 patients have been recruited

Treatment group	Number of patients	Interim PET/CT Positive/Negative	Progression
Early favorable	15	3/12	1
Early unfavorable	55	1/	1
Advanced standard risk	26	0/26	2
Advanced high risk	22	4/18	1

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