Future perspectives ?!?

T. Svoboda

Možné směry

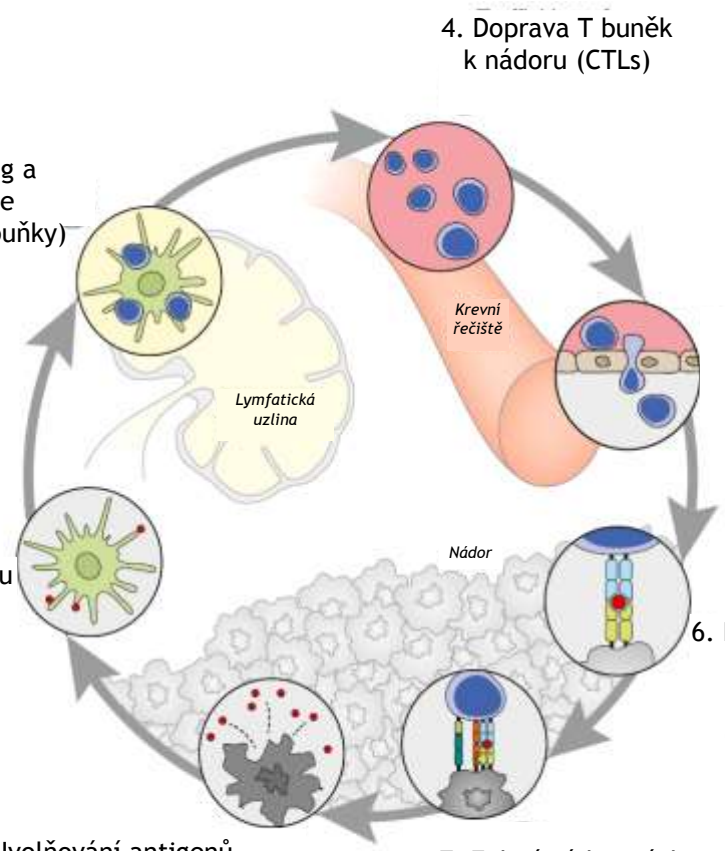
- 1. kombinace I.O a další cílené léčby, vč. antiVEGF
- 2. kombinace I.O a RT
- 3. budoucnost RT samostatné
- 3. směry nemožné

Role VEGF v imunitním prostředí nádoru

VEGF ovlivňuje několik kroků v cyklu imunity nádoru, což může vést k imunitnímu úniku

Krok 2

VEGF zhoršuje DC zrání, což vede ke sníženému primingu T-buněk



Krok 5

VEGF podporuje tvorbu dysregulované nádorové neovaskulatury, která brání infiltraci nádoru T-buněk a vyvolává smrt T-buněk

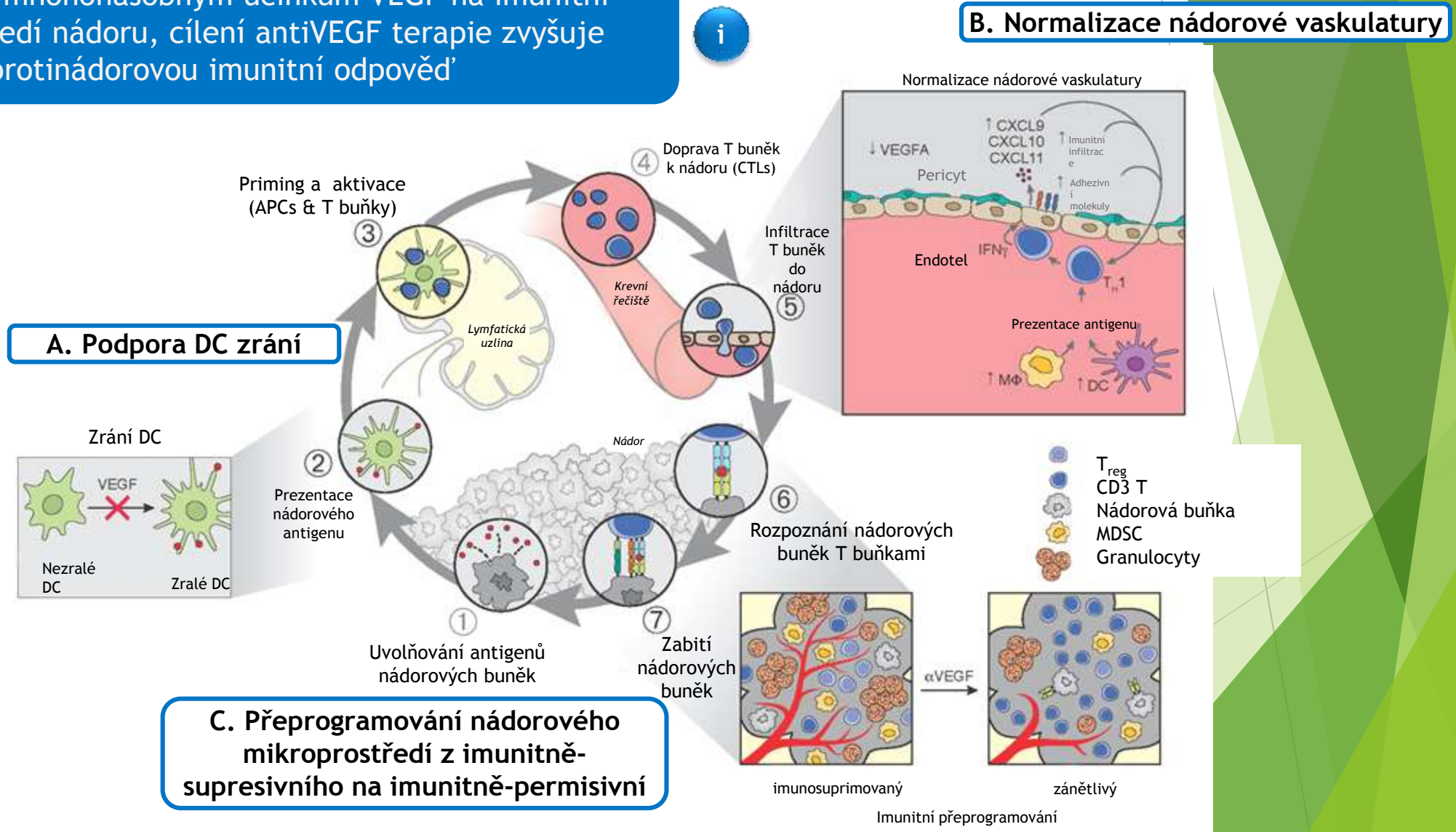
Kroky 6-7

VEGF stimuluje expanzi supresorových buněk odvozených od myeloidů (MDSC), což vede k imunosupresivnímu mikroprostředí nádoru a tlumené imunitní odpovědi proti nádoru

Chen DS, Mellman I. *Immunity*. 2013;39:1-10; , Hegde PS, et al. *Semin Cancer Biol*. 2017. doi: 10.1016/j.semcancer.2017.12.002.

Cílení VEGF v imunitním prostředí nádoru

Vzhledem k mnohonásobným účinkům VEGF na imunitní mikroprostředí nádoru, cílení antiVEGF terapie zvyšuje protinádorovou imunitní odpověď

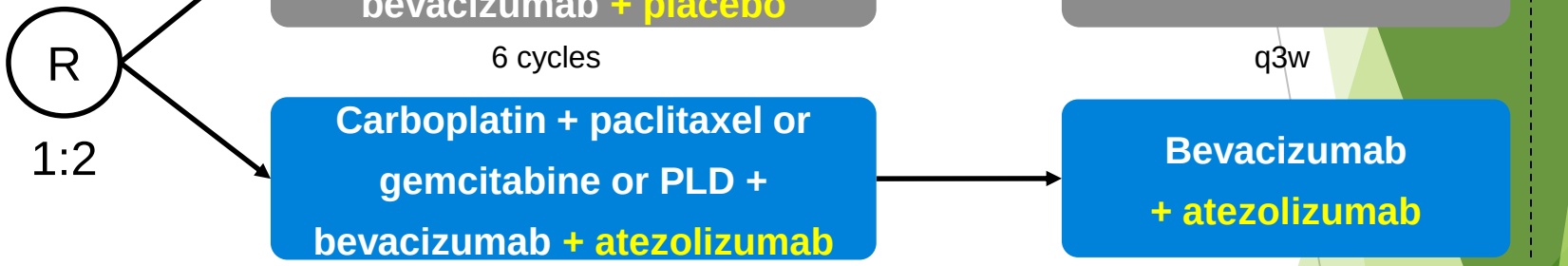


Hegde PS, et al. *Semin Cancer Biol*. 2017. doi: 10.1016/j.semcancer.2017.12.002.

ATALANTE/MO29996 (GINECO, ENGOT): Phase III atezolizumab + chemotherapy + BEV in platinum-sensitive ROC

- Platinum-sensitive ROC
- 1 or 2 prior lines of carboplatin-based therapy
- EOC, non-mucinous
- ECOG ≤1
- Prior PARPi and/or BEV allowed
- Prior CIT excluded
- Entry biopsy mandatory

n=614



Stratification factors:

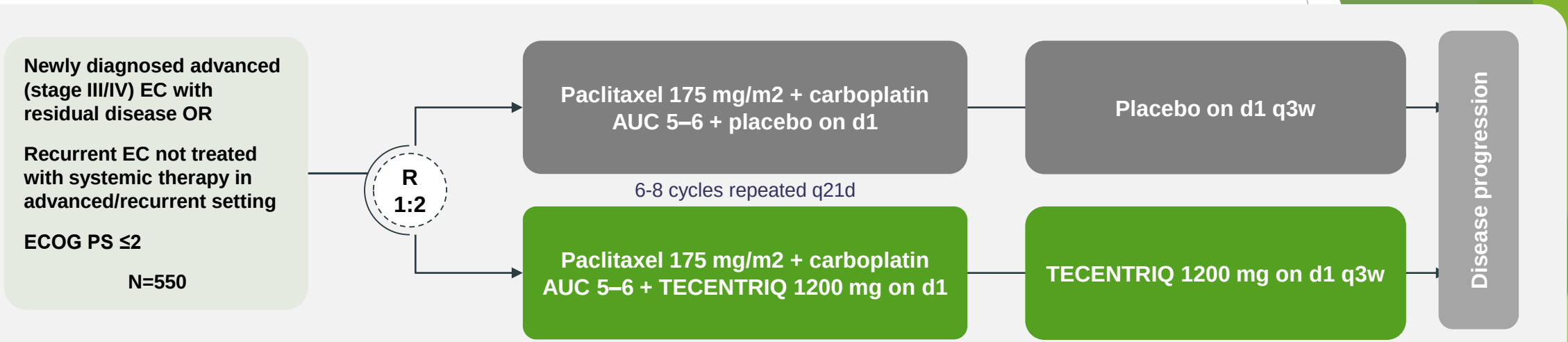
- TFIp (6–12 vs >12 months)
- Chemotherapy backbone (paclitaxel vs gemcitabine vs PLD)
- PD-L1 expression (IC0 vs IC1+ with SP142)

Primary endpoint: **PFS in ITT and PD-L1+**

Secondary endpoints: OS, TFST, TSST, ORR, PROs, HRQoL, PFS2, PFS and ORR per irRECIST

MDD = minimally detectable difference

AtTEnd/MO39872 (Mango, ENGOT)
Phase III 1L atezolizumab + standard of care in EC



Stratification Factors

- Country
- Histological type (endometrioid vs other)
- Disease (recurrent vs advanced at primary diagnosis)
- MSI status (MSS vs MSI vs non-evaluable) evaluated by IHC

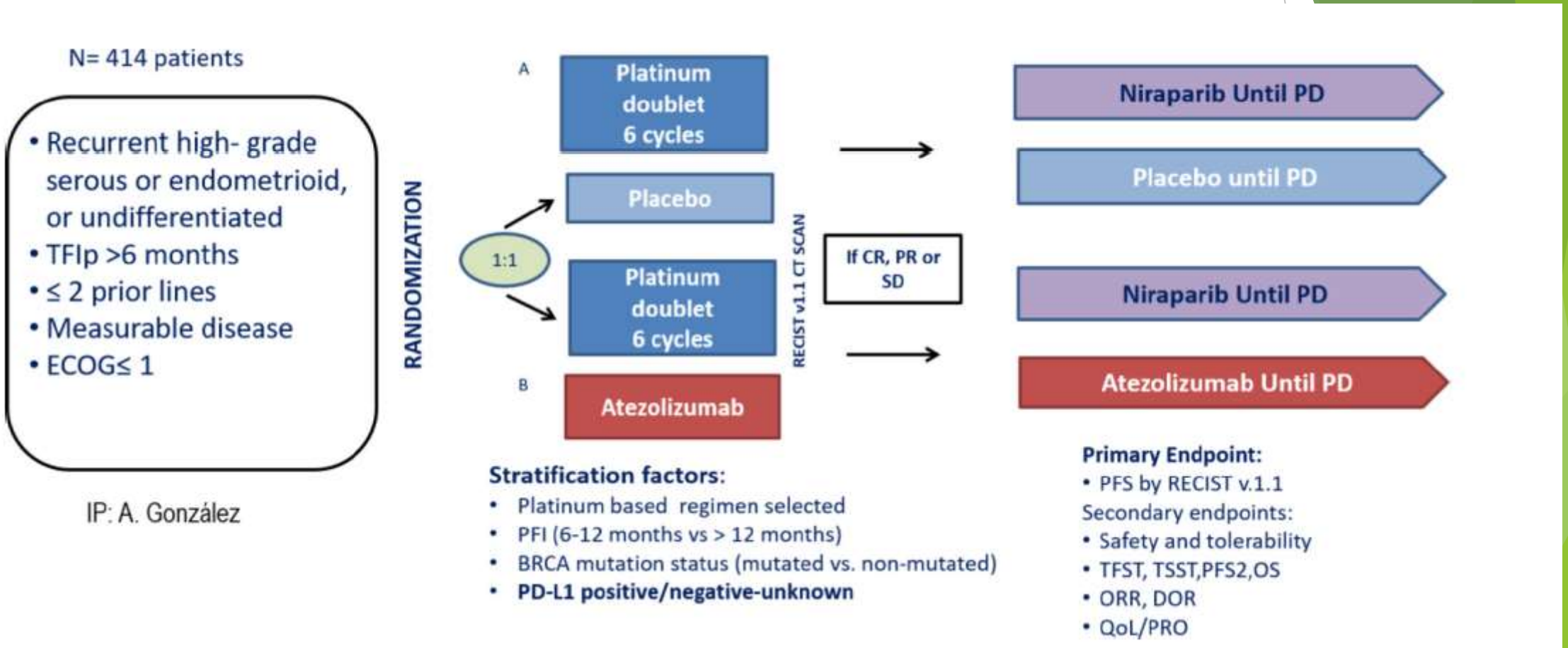
Co-primary endpoints:

- OS HR 0.70 (median OS 18 → 25.7 months)
- PFS HR 0.70 (median PFS 10 →14.3 months)
- Overall 2-sided alpha 5%, ≥80% power

Key secondary / other endpoints:

- ORR, DoR
- Safety
- QoL

ANITA trial


N= 414 patients
• Recurrent high- grade serous or endometrioid, or undifferentiated
• TFIp >6 months
• ≤ 2 prior lines
• Measurable disease
• ECOG≤ 1
IP: A. González
RANDOMIZATION
1:1
A
Platinum doublet 6 cycles
Placebo
B
Platinum doublet 6 cycles
Atezolizumab
RECIST v1.1 CT SCAN
If CR, PR or SD
Niraparib Until PD
Placebo until PD
Niraparib Until PD
Atezolizumab Until PD
Stratification factors:
• Platinum based regimen selected
• PFI (6-12 months vs > 12 months)
• BRCA mutation status (mutated vs. non-mutated)
• PD-L1 positive/negative-unknown
Primary Endpoint:
• PFS by RECIST v.1.1
Secondary endpoints:
• Safety and tolerability
• TFST, TSST,PFS2,OS
• ORR, DOR
• QoL/PRO

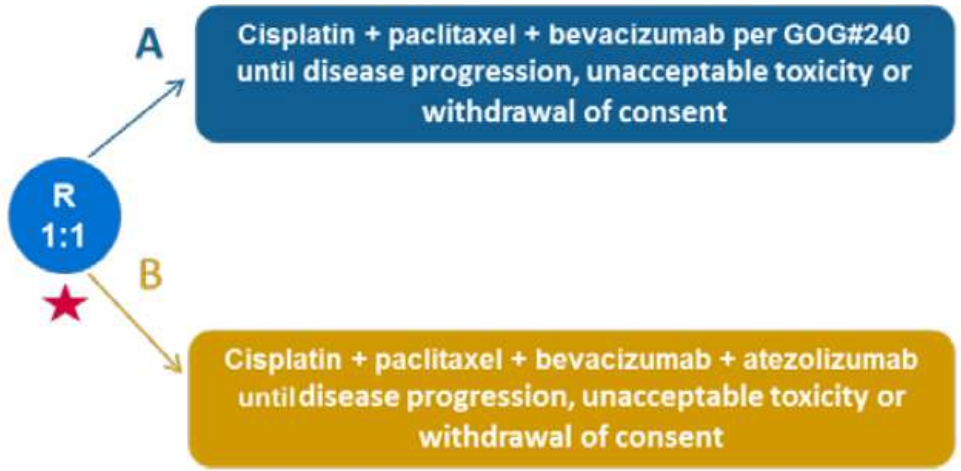
BEATcc trial

Eligibility criteria:

- Persistent/Recurrent/ metastatic cervical cancer
- ECOG PS 0/1
- No prior systemic anti-cancer therapy for metastatic or recurrent disease.
- Available archival or fresh tumour for PD-L1 expression

Stratification factors:

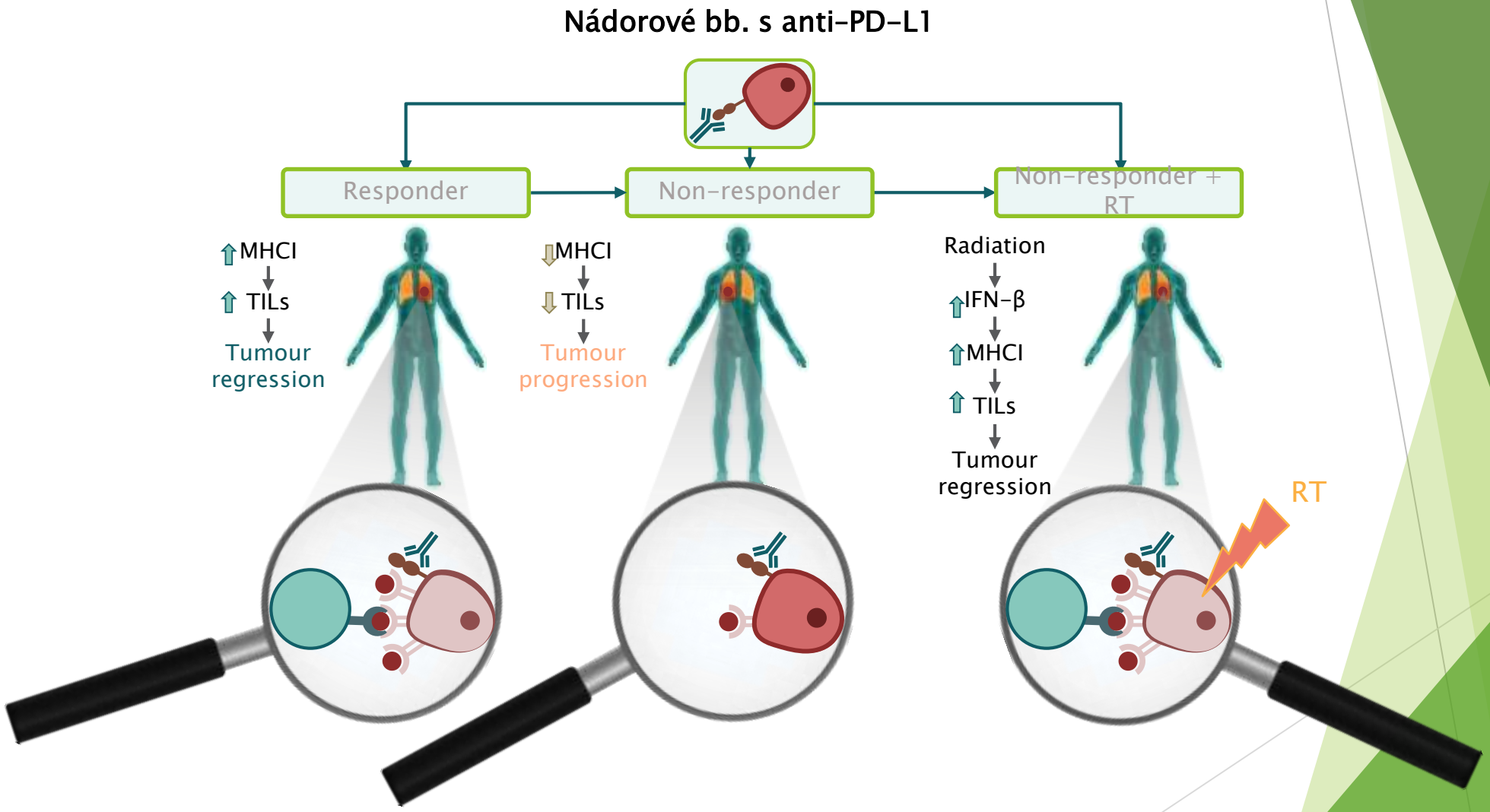
- Prior concurrent Cisplatin-RT
- Histology: SCC vs. ADK (including adenoSquamous)
- Chemotherapy backbone (cisplatin vs carboplatin)



Primary endpoint:
OS
Secondary endpoints:
PFS
ORR
Safety
PRO/HRQoL

★ A tumour tissue biopsy collected within 3 months prior to study enrolment will be mandatory in the absence of an archival biopsy. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, more than one core (if clinically feasible) should be submitted for evaluation. Retrieval of already available, recent (within 3 months prior to study enrolment) tumour sample can occur outside the 28 day screening period. Paired recent biopsies at baseline (lesion not previously irradiated; within 3 months of randomization) and at progression disease will not be mandatory, nevertheless they are encouraged as long as these are feasible.

Kombinovaný efekt RT a imuno-onkologické léčby



IFN-β: interferon beta; MHCI: major histocompatibility complex I; PD-1: programmed cell death protein 1; RT: radiotherapy; TIL: tumor-infiltrating lymphocyte.
Schoenhals JE et al, Cancer J 22:130, 2016.

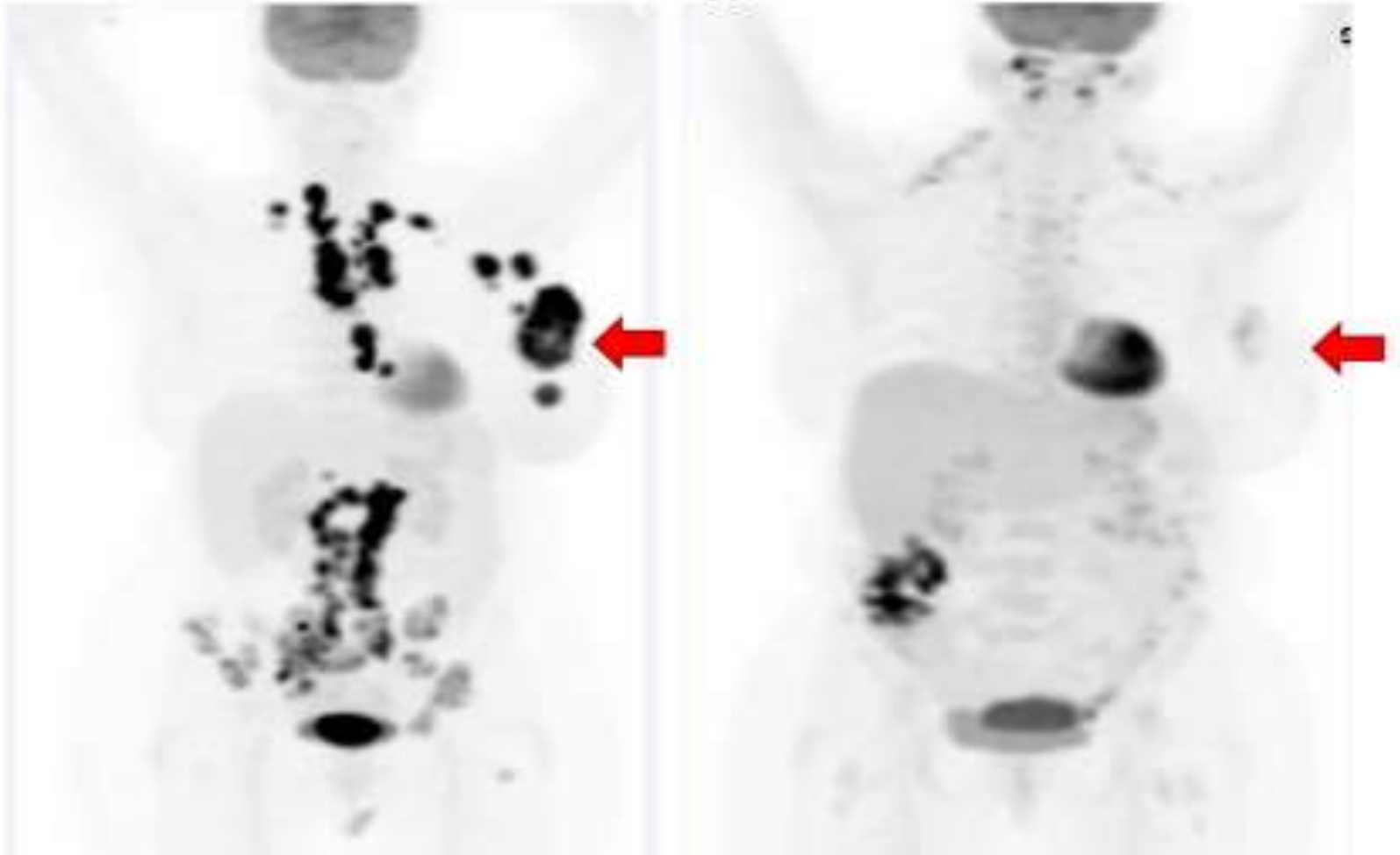
Kombinace pokroků = ISABR

- I.O + SBRT
- Konkomit. nebo sekvenčně
- LD 15-25 Gy jednorázově (účinnější v indukci imun.odpovědi než 3x5 Gy, což je D min)
- Vyšší LD naopak koreluje se supresí nádorově specifické imunity prostřednictvím splenických Treg a produkcí efektorových CD8+

Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach?
Michael B. Bernstein, Sunil Krishnan, James W. Hodge and Joe Y. Chang Nature 2016

I.O + RT : abskopální efekt

Figure 3. Baseline (left) and week 13 (right) PET/CT for partial responder #1. A 54 yo woman with widespread mTNBC received RT to a left breast mass (red arrow) and pembro #1. Subsequent pembro doses were held due to hyperbilirubinemia. At 13 weeks, a PR in the RT field and a CR in the disease outside of the RT field were noted, representing a 68% total reduction in tumor burden that was durable for 33 weeks.



The Radiosurgery Society is Co-Sponsoring the Presidential Symposium at the 66th Annual Meeting of the Radiation Research Society

FLASH: An Exemplar of Multidisciplinary "Transgenerational" Radiation Research

Wednesday, October 21, 2020

2:30 pm ET/11:30 am PT

Virtual Event

Presentations by:

- Jolyon Hendry, BSc, MSc, PhD, DSc
- Douglas R. Spitz, PhD
- Marie Catherine Vozenin, PhD, HDR
- Charles B. Simone II, MD, FACRO

Registration Deadline is October 9, 2020.

Click to Register

View the RRS Meeting Schedule At-a-Glance

Transgender mania = naše etická povinnost !?

- 1,4 mil. v USA a 25 mil. celosvětově
- Lékař se má vzdělat v této problematice a potřebách těchto lidí, aby byl rovný v diskuzi
- Uzpůsobit převlíkárny, čekárny
- Vytvořit specif. guidelines a upravit decision-making
- Zavzít transgender komunitní lídry do tvorby standardů
- Zvýšit počet transgender lékařů (zlepšení přístupu pac. k léčbě a tím výsledků)
- Vytvářet vlastní studie a databáze