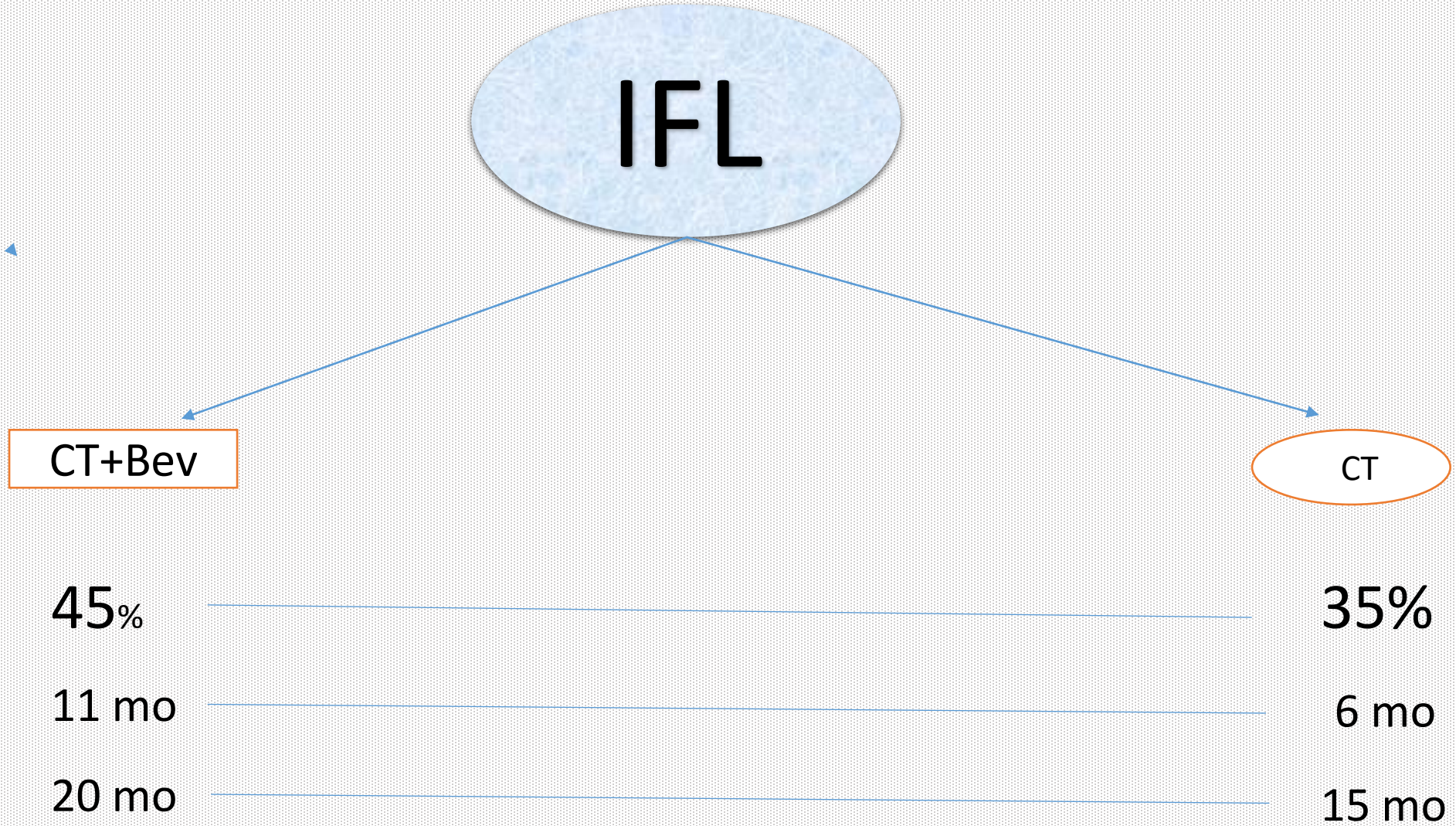
Dr Radheshyam Naik

HCG

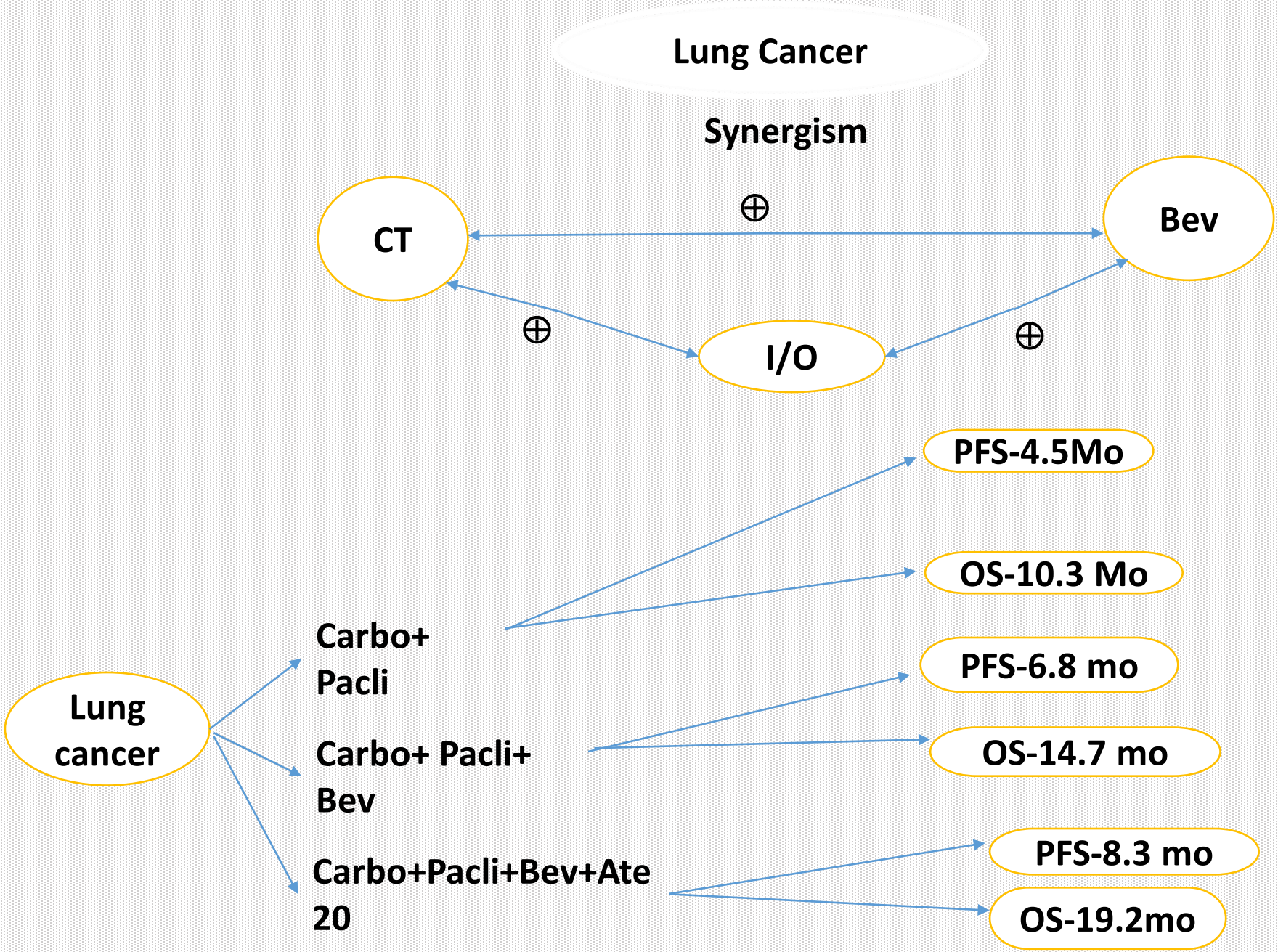

IFL
CT+Bev
CT
RR
PFS
OS
45%
11 mo
20 mo
35%
6 mo
15 mo

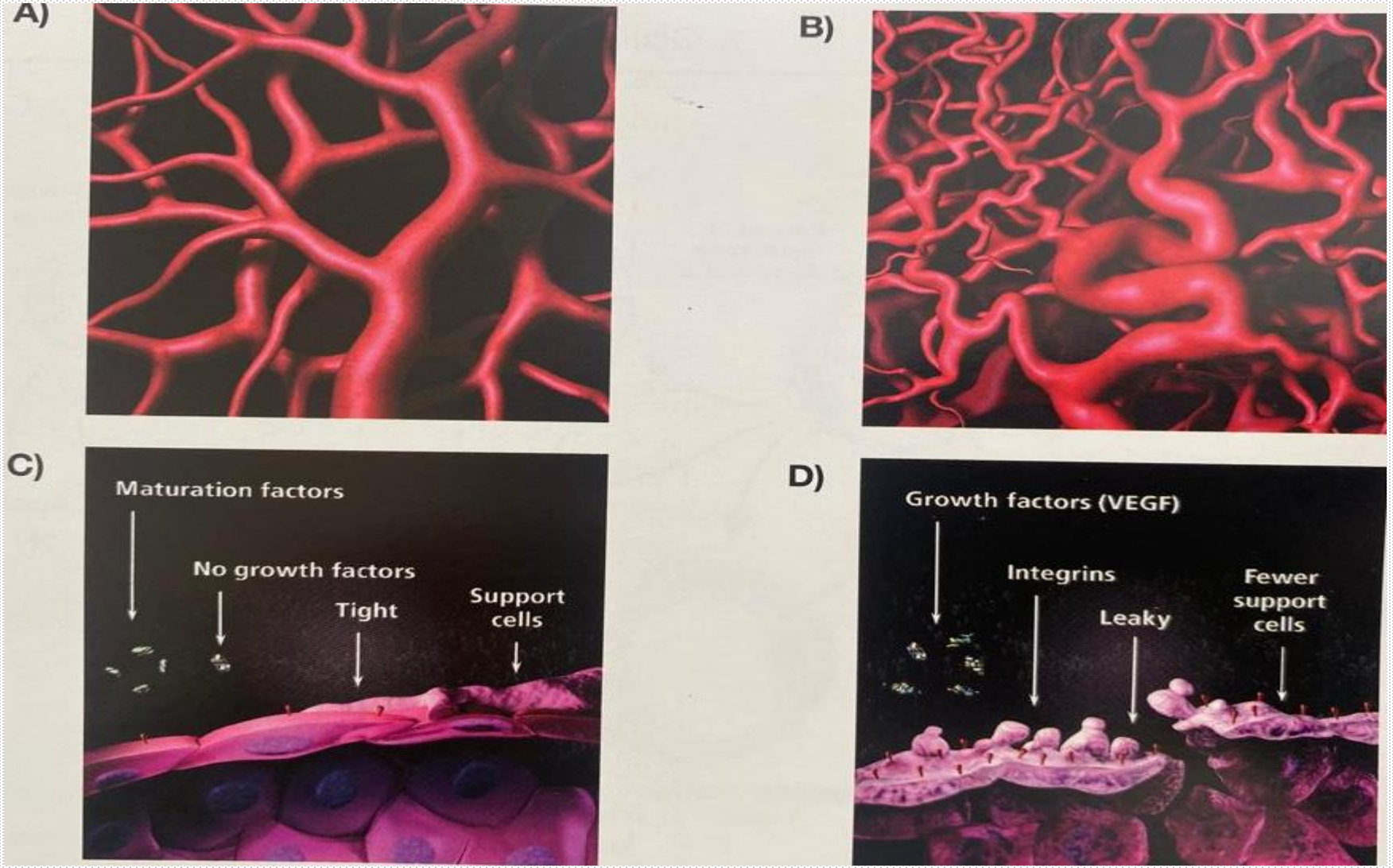
METANALYSIS

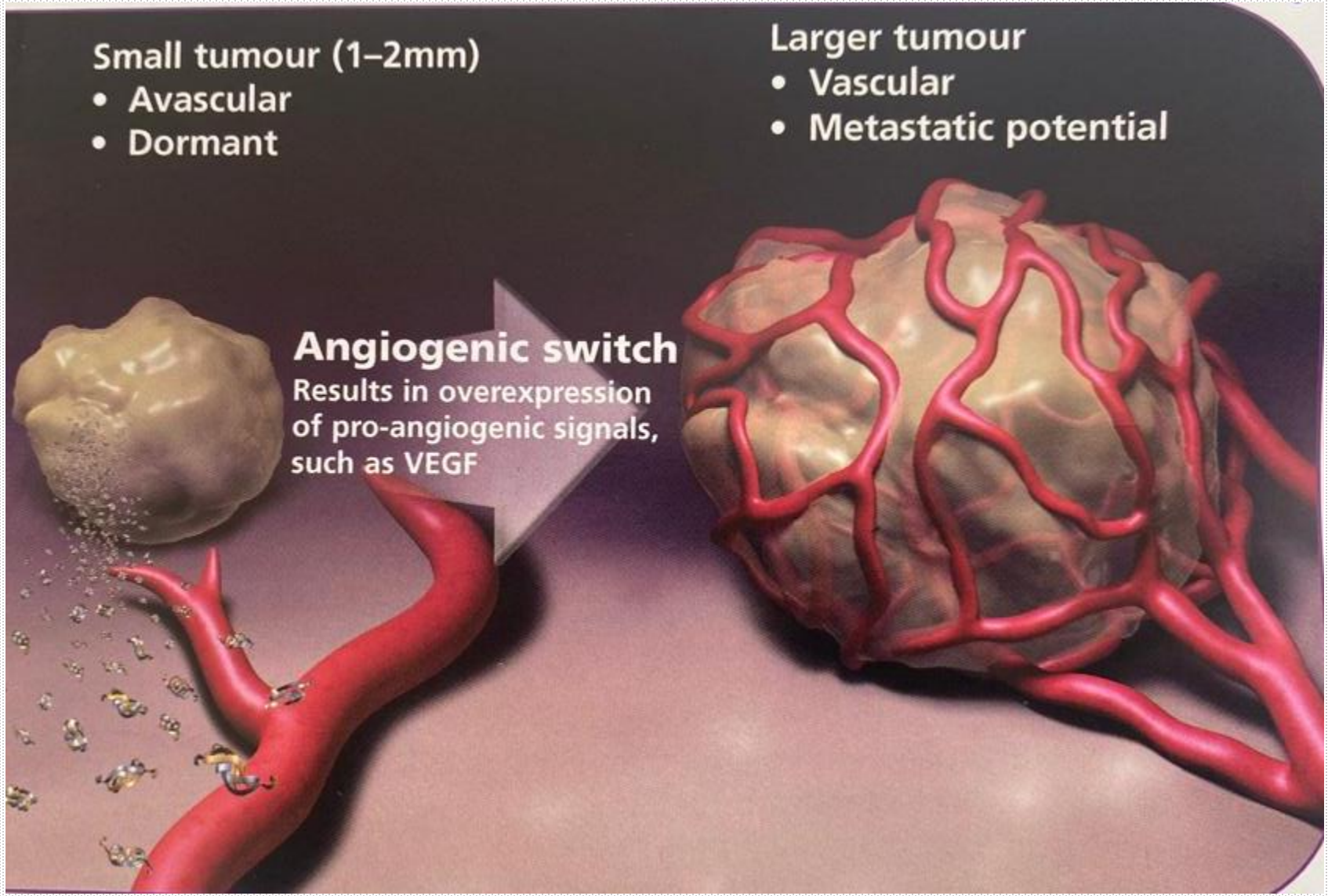
m.CRC

	CT+ Bev	CT
RR	HR- 0.89	1
PFS	HR-0.69	1
OS	HR-0.85	1

5FU> Irinotecan> Oxaliplat


Lung Cancer
Synergism
CT
Bev
I/O
Lung cancer
Carbo+ Pacli
Carbo+ Pacli+ Bev
Carbo+Pacli+Bev+Ate 20
PFS-4.5Mo
OS-10.3 Mo
PFS-6.8 mo
OS-14.7 mo
PFS-8.3 mo
OS-19.2mo

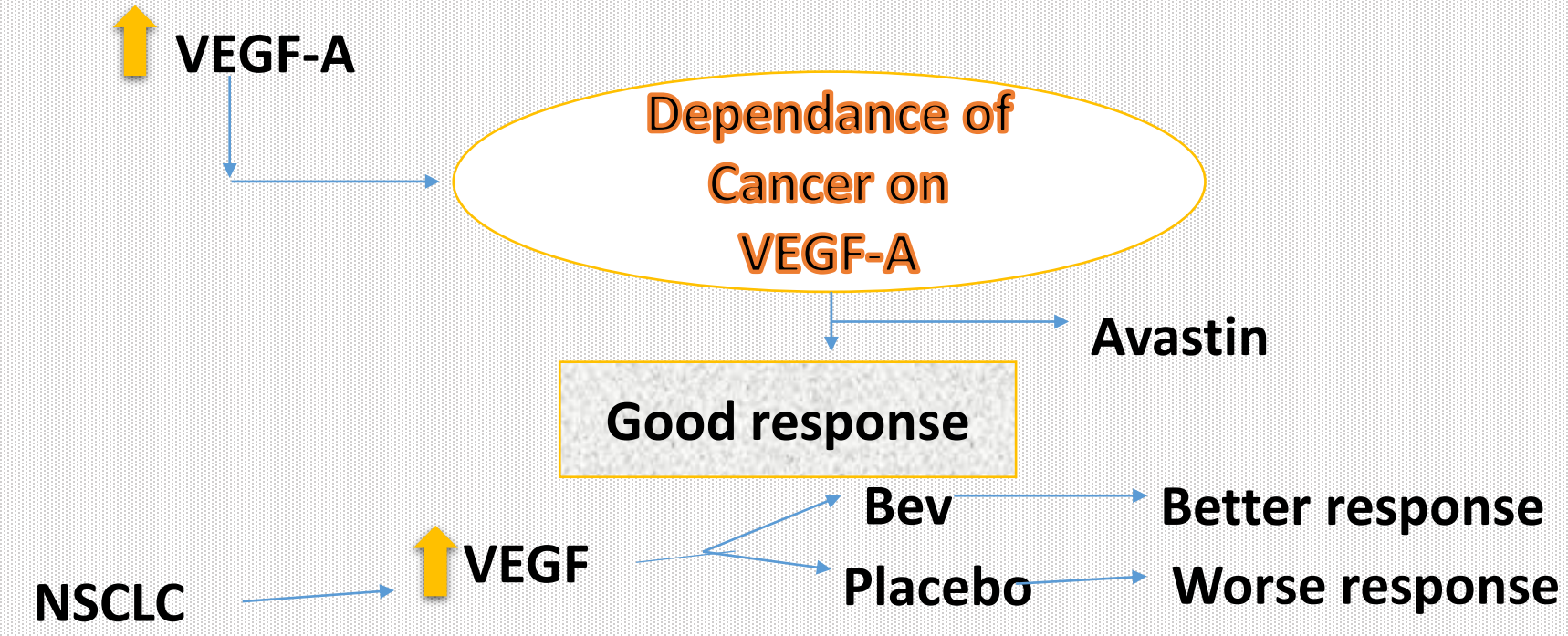

A)
B)
C)
Maturation factors
No growth factors
Tight
Support cells
D)
Growth factors (VEGF)
Integrins
Leaky
Fewer support cells


Small tumour (1–2mm)
• Avascular
• Dormant
Angiogenic switch
Results in overexpression of pro-angiogenic signals, such as VEGF
Larger tumour
• Vascular
• Metastatic potential

VEGF in tissues

- **Normal Cells - 280 (Densitometry units)**
- **Early adeno ca - 570 (Densitometry units)**
- **Locally adv ca - 710 (Densitometry units)**
- **Metastatic - > 1000 (Densitometry units)**

VEGF-A



Metanalysis → Phase 3 trials → Failed to predict efficacy of Avastin

But pre Rx – VEGF-A levels ≅ prognosis

Role of VEGF

- ↑ Neoangiogenesis
- ↑ BV Permeability
- ↑ Mets
- ↑ Lymphoangiogenesis
- Cancer cell protection
- Resistant to Chemo
- Resistant to RT
- ↓ Immunity

↑ VEGF levels in blood/Cancer

↓

Bad prognostic factor

Tissue - VEGF

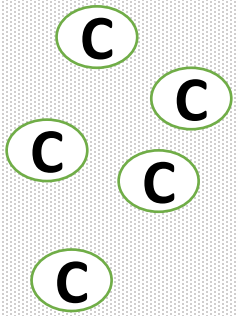
IHC → ↑ tissue VEGF --→ ↑ MVD

↑ MVD → ? Predictor of Avastin response

No 16966 -- Phase III study → ↑ Density of CD31

↑ Response to Bev

Tissue Expression of VEGF-R



Low VEGF R1 — ↑ OS after Bev

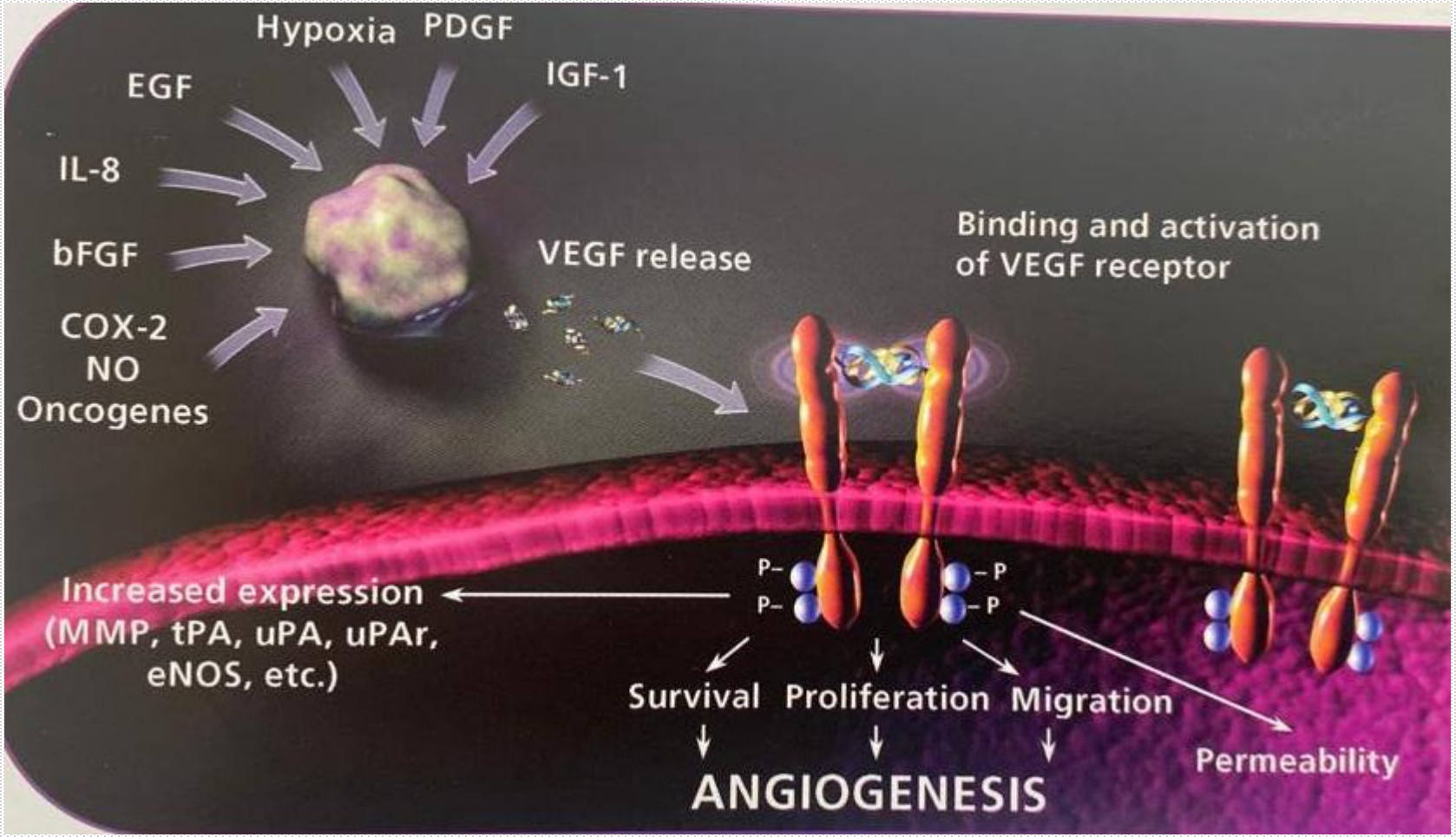
Two trials

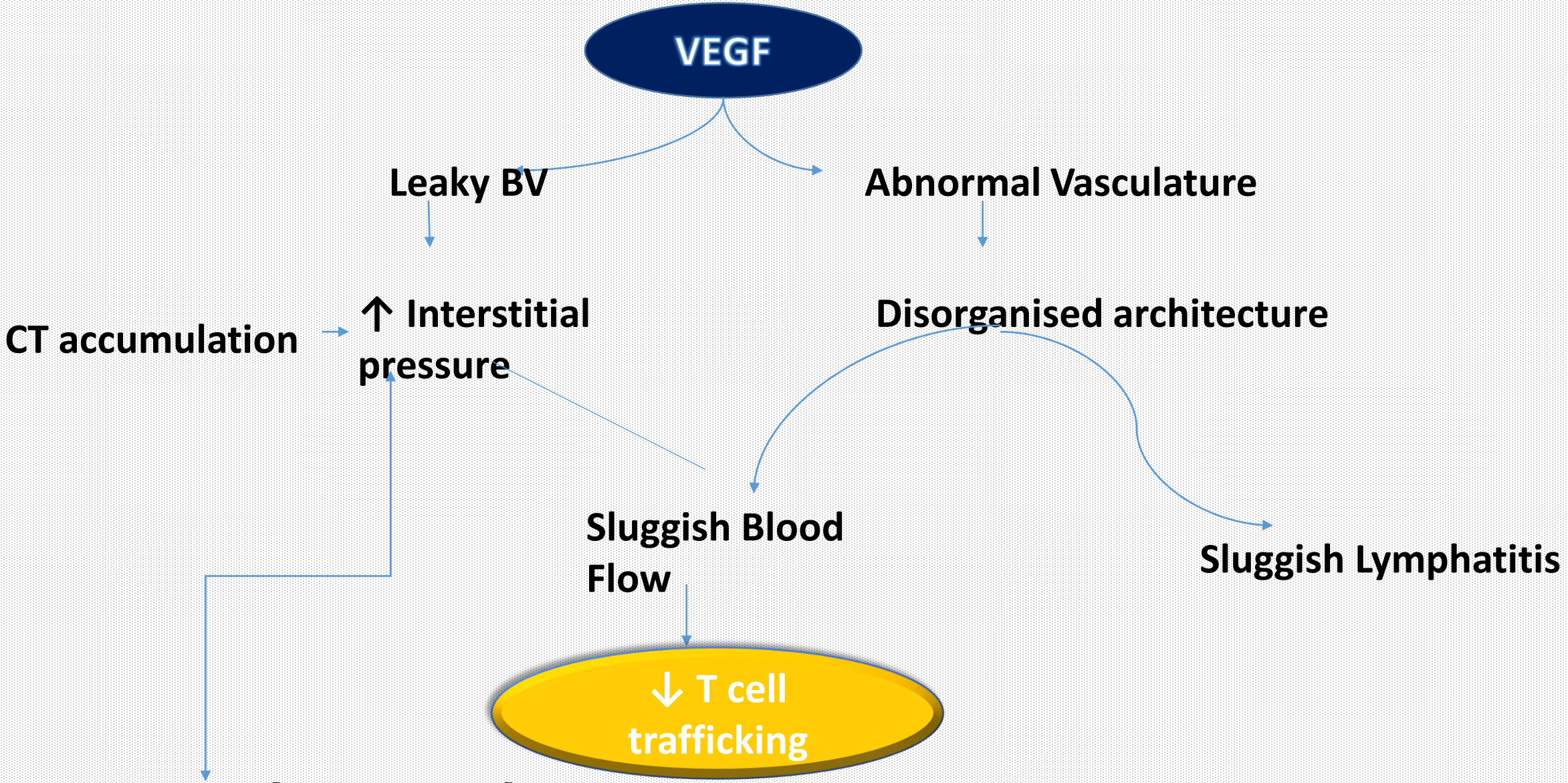
- AGITG MAX – MCRC trial → ↑OS
- AVAGAST -------- ↑ PFS

Oncogenes ↑ VEGF Expression in tumor tissue

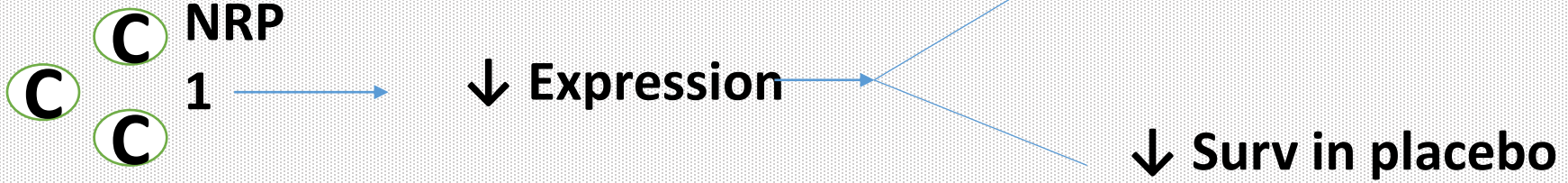
- **P53**
- **P16**
- **VHL**
- **PTEN**
- **srC**
- **C-myc**
- **bCr – Abl**
- **EGFR**
- **Her-2**
- **RAS**

Even in normoxic conditions tumor -- ↑ VEGF


Hypoxia
PDGF
EGF
IGF-1
IL-8
bFGF
COX-2
NO
Oncogenes
VEGF release
Binding and activation
of VEGF receptor
P–
P–
– P
– P
Increased expression
(MMP, tPA, uPA, uPAr,
eNOS, etc.)
Survival
Proliferation
Migration
Permeability
ANGIOGENESIS


VEGF
Leaky BV
Abnormal Vasculature
CT accumulation
↑ Interstitial pressure
Disorganised architecture
Sluggish Blood Flow
Sluggish Lymphatitis
↓ T cell trafficking
Normal tissue → 3 mm Hg -→ + 3 mm Hg
Cancer → + 60 mm Hg

Tissue Expression of NRP1

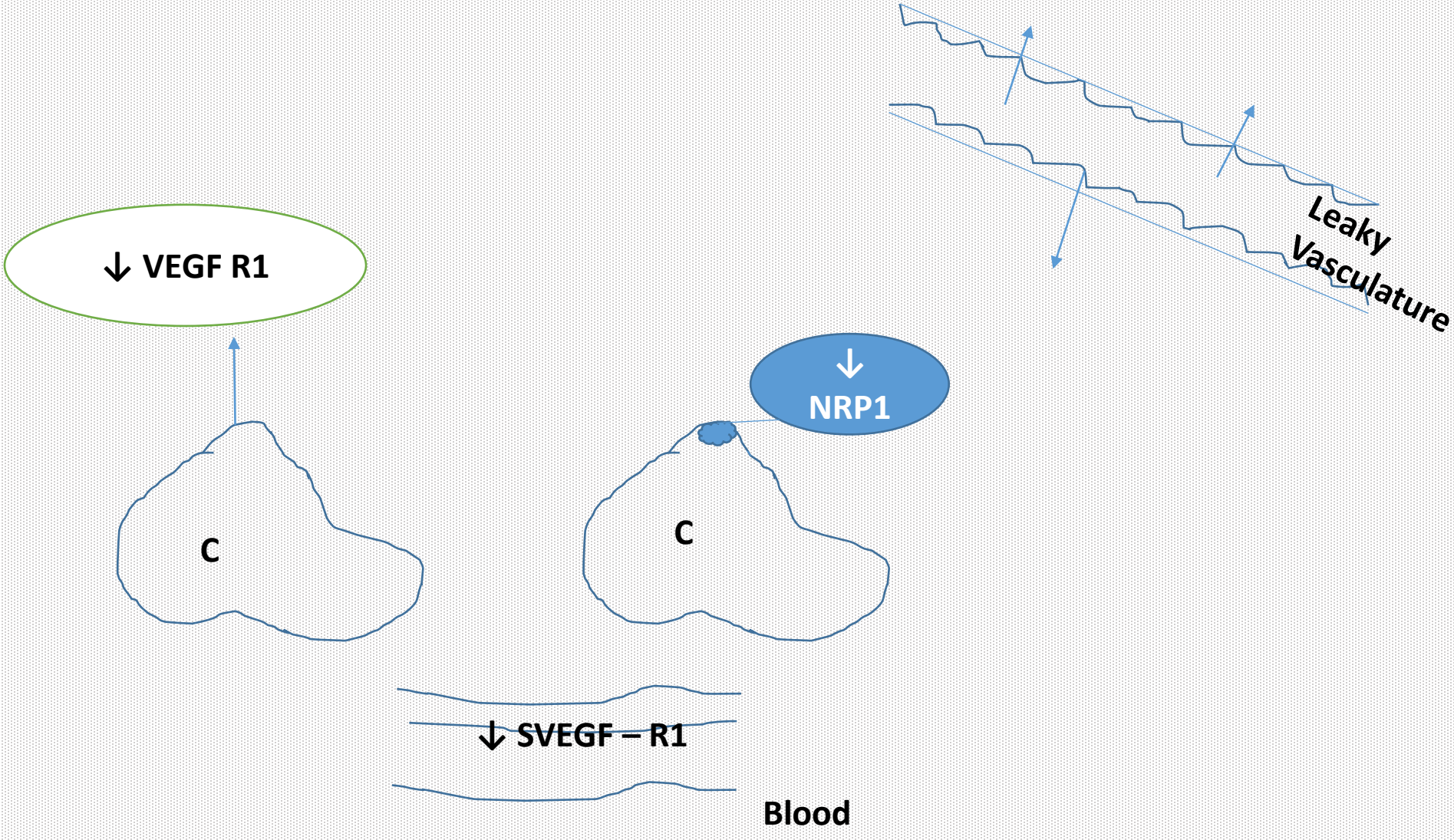


HR = 0.75

Breast
Colon
Lung

Low NRP1 expression is a good, consistent predictive factor

Response to Avastin - Factors



DCE-MR1

Dynamic – Contrast enhanced MRI

↓

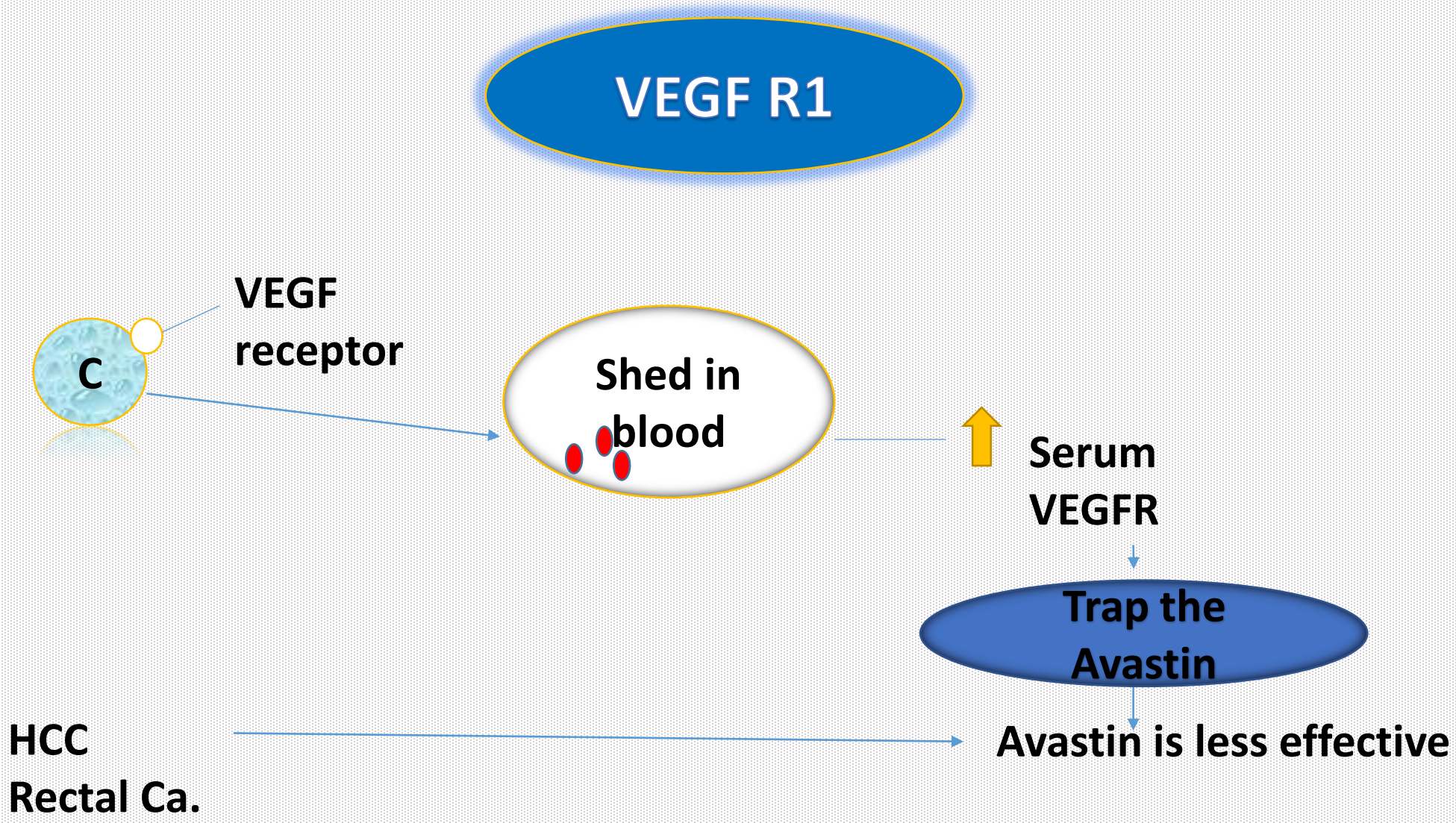
Monitors change in – vascular structure function

↓

Change in tumor blood vol
tumor blood flow

↓

? Predict response to Avastin early

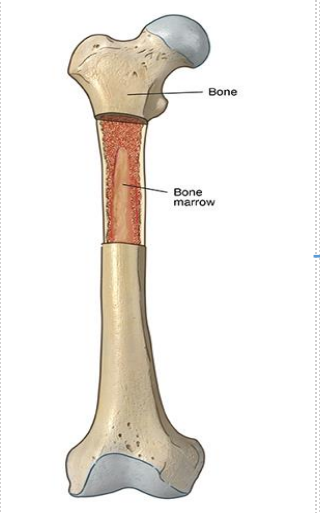

VEGF R1
VEGF receptor
C
Shed in blood
Serum VEGFR
Trap the Avastin
HCC
Rectal Ca.
Avastin is less effective

Circulating ECs

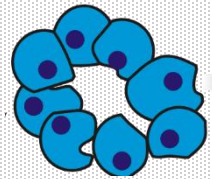
Blood

Circulating Endothelial cells

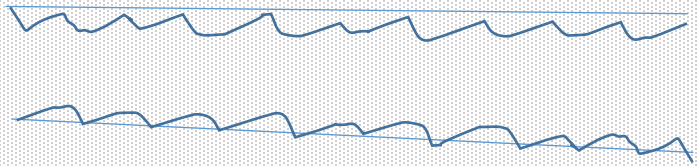
Circulating Endothelial Progenitors



Progenitor cells



Tumor Integration



B V Formation

↑ VEGF - A

↑ CEP

Poor Prognosis

Partly predictive of response to Avastin

Why dose of Avastin varies

Lung	Bev	15mg/Kg
Ovary	Bev	7.5 mg/kg 15 mg/kg
Colon	Bev	7.5 mg /kg
GBM	Bev	10 mg/ kg
RCC	Bev	10mg/ kg
HCC	Bev	10mg /kg

Dose decided by → Stage
- **→ Type of Cancer**
- **→ VEGF Levels**
- **→ Response**
- **→ PFS**
- **→ Accompanying Chemo**
- **→ Accompany I/o**

Avastin

- Within 24 hours → ↓ Blood flow in tumor
- Endothelial cells → undergo apoptosis

- MVD → ↓ by > 50% in some cases

- Later → Avastin normalizes the blood vessels

↓

↓ Hypoxia / Acidosis -- > ↓ RT Resistance
↓ Interstitial pressure → Better CT Penetration

In a study 1 done → ↓ Interstitial pressure by 70%

→ O2 tension -- ↑ by 50%

AVFO 780 trial

	Low Dose Bev 5mg / kg	High Dose Bev 10mg / Kg	5 FU
RR	40%	34%	17%
PFS	9 mo	7.2 mo	5.2 mo
OS	21 mo	16 mo	14 mo

Antiangiogenic Combinations

Lung Ca	CT + Bev Erlotinib + Bev CT + Bev + I/o
Colon	CT + Bev Bev alone TKIs
Renal	TKI + I/o Bev + I/o
Liver	Lenvatinib + I/o Avastin + I/o Ramicizumab + I/o
GBM	TEM + BEV Trinotecan + Bev

Avastin

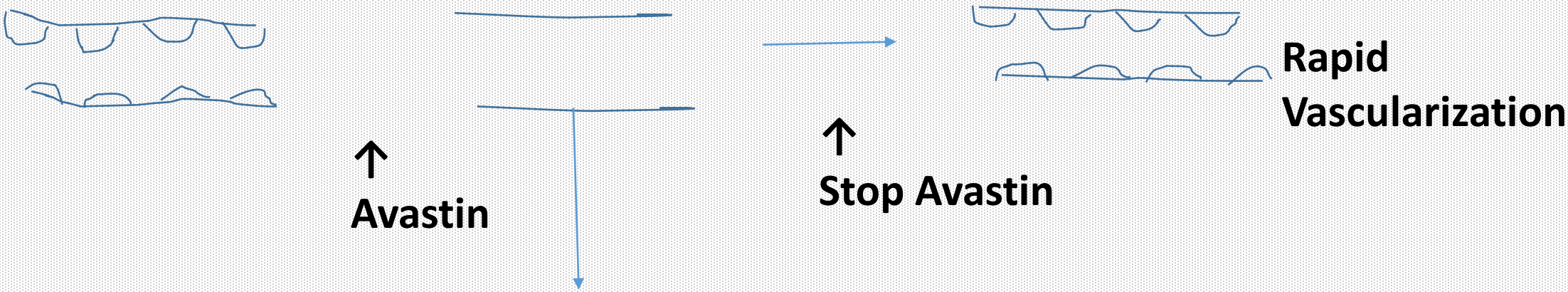
Sudden stoppage of Avastin

↓

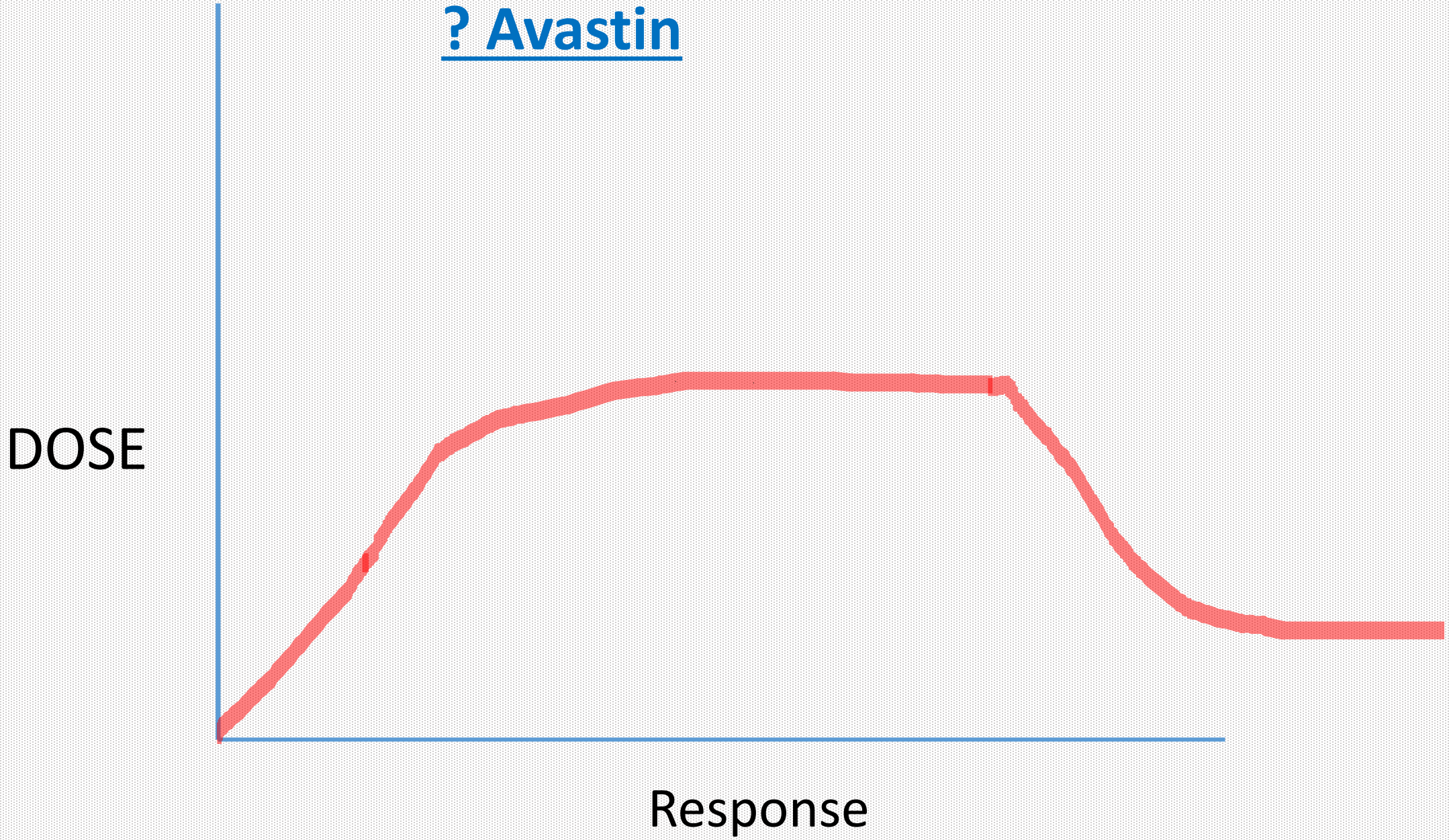
2-3 weeks Vessels grow back

↓

It is a fast track growth (Rebound effect)



? Avastin



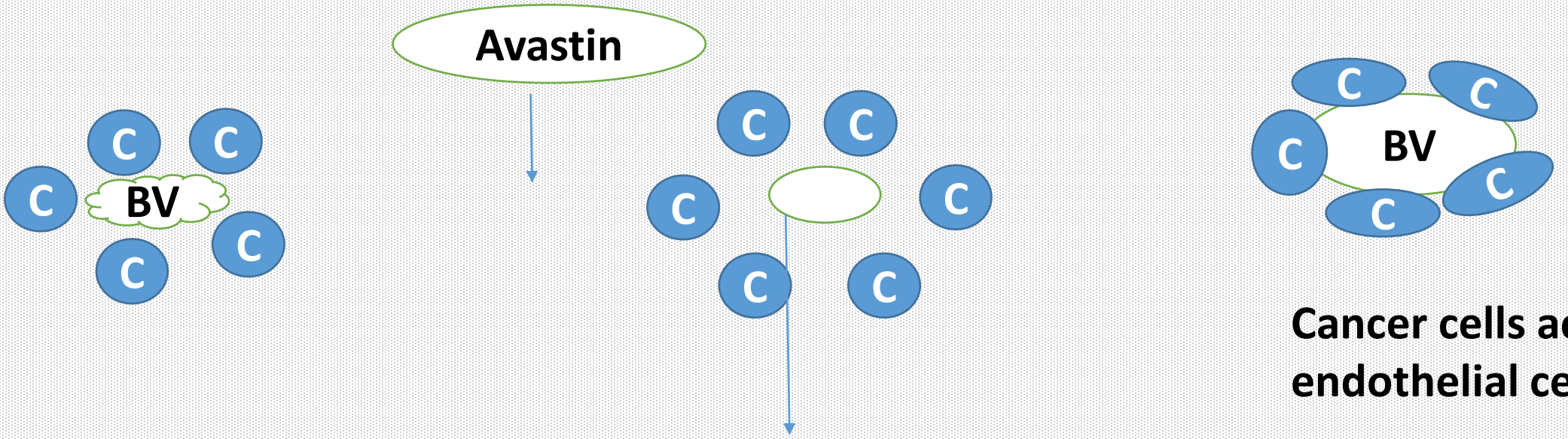
Vascular Co-option

Cancer cells start regrouping around existing mature B.V.

Avastin →

resistance mechanism
Instead of B.V going to tumor, tumor cells go to B.V

Vascular Mimicry



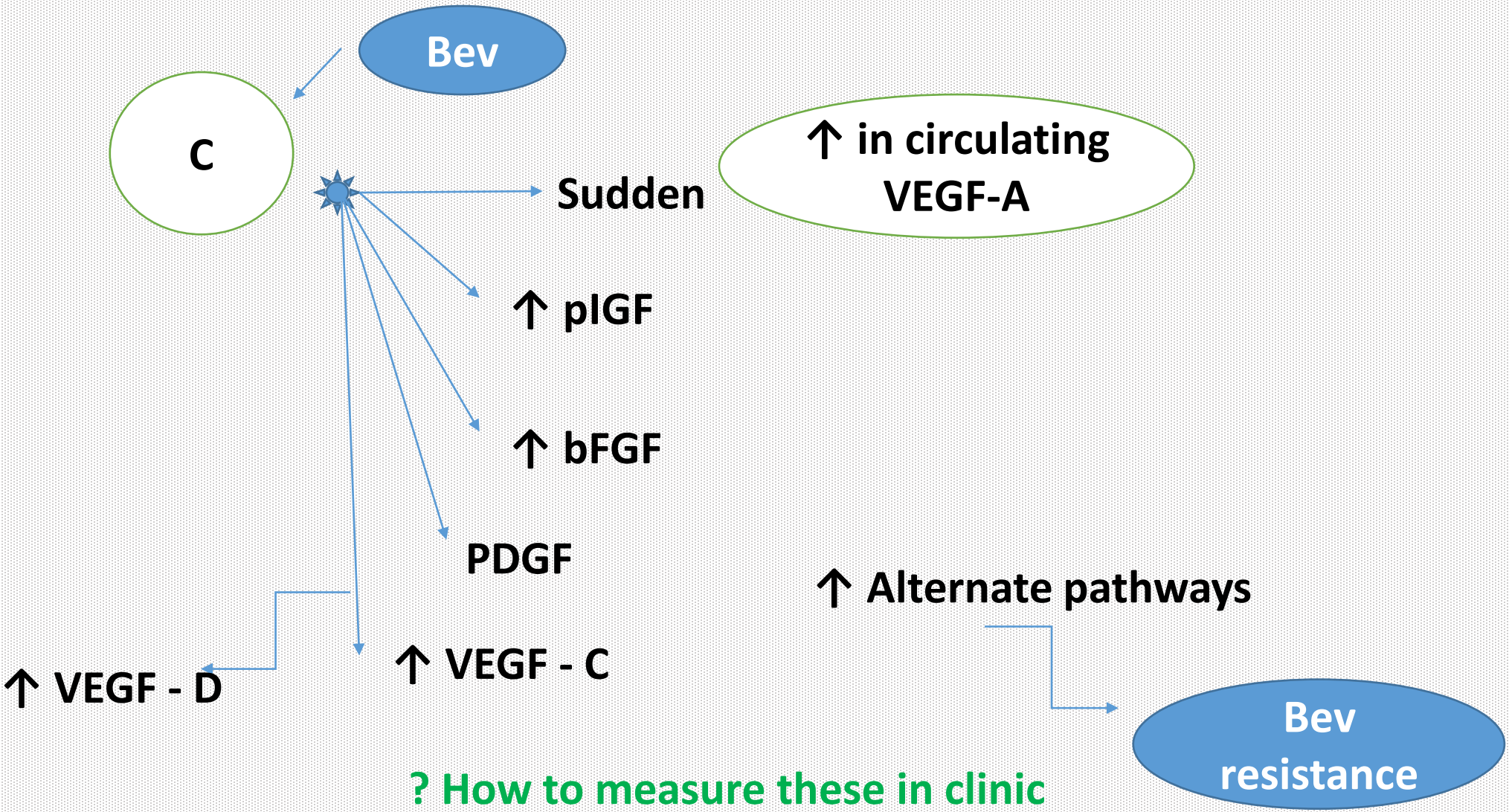
Cancer cells act like endothelial cells

Ghost Membrane

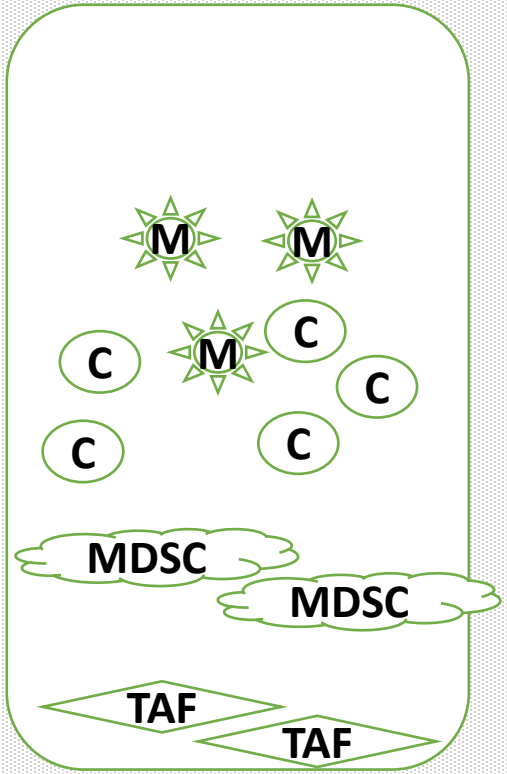
Very commonly seen in GBM after Avastin therapy

It is a resistance mechanism

Therapy Changes



Avastin Resistance – Mechanisms



Non leaky vessel

Pericyte covered

↑ VEGF R1

↑ NRP1

3

↑ Alternative proangiogenics

4

↑ FGF
↑EGFR
↑bFGF

↑ P1GF
↑ PDGF
↑ VEGF – C
VEGF - D

How to measure efficacy

1)MRI Changes

2)Resp Rate

3)PFS

Chemo Vs Bev -→? How to diff

I/O Vs Bev → ? How to Diff

Controversial

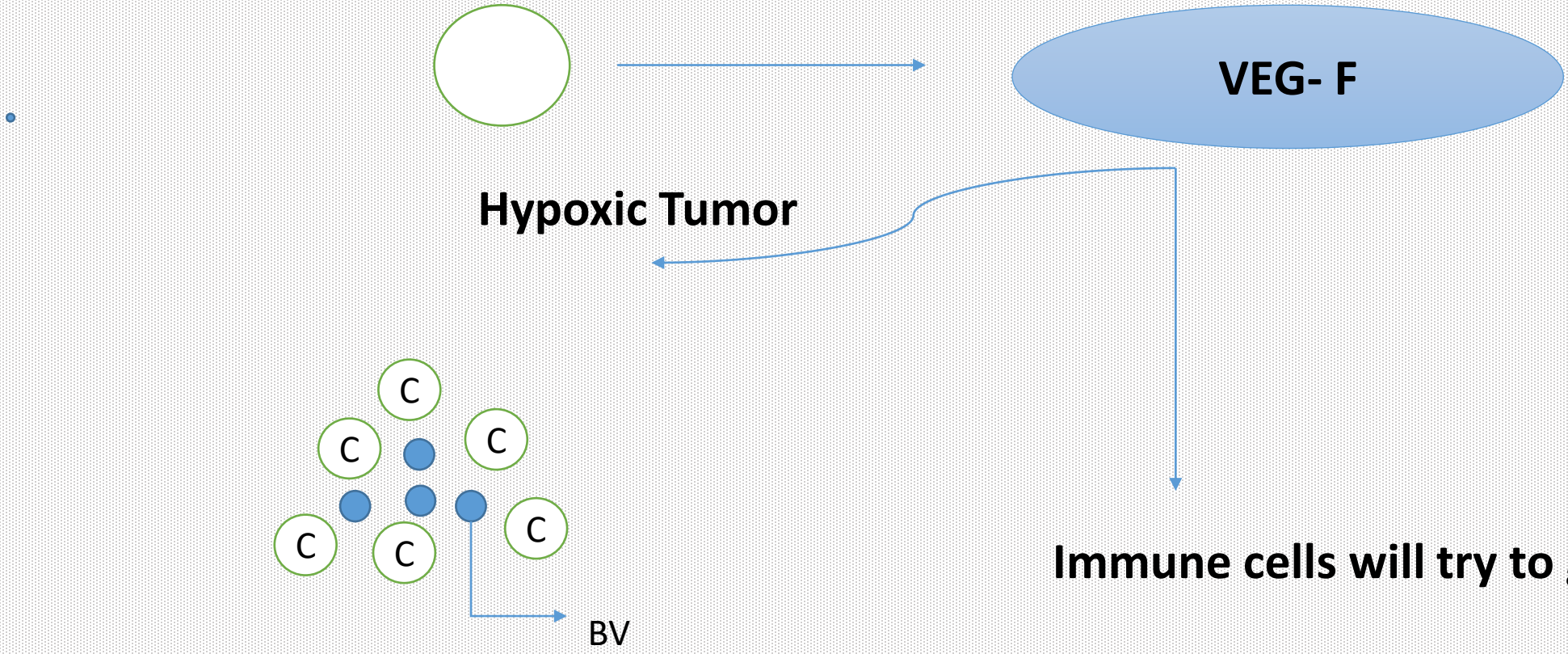
- **Use as monotherapy - less useful**
- **CT + I/o + Bev – may be best**
- **CT + Bev**

or

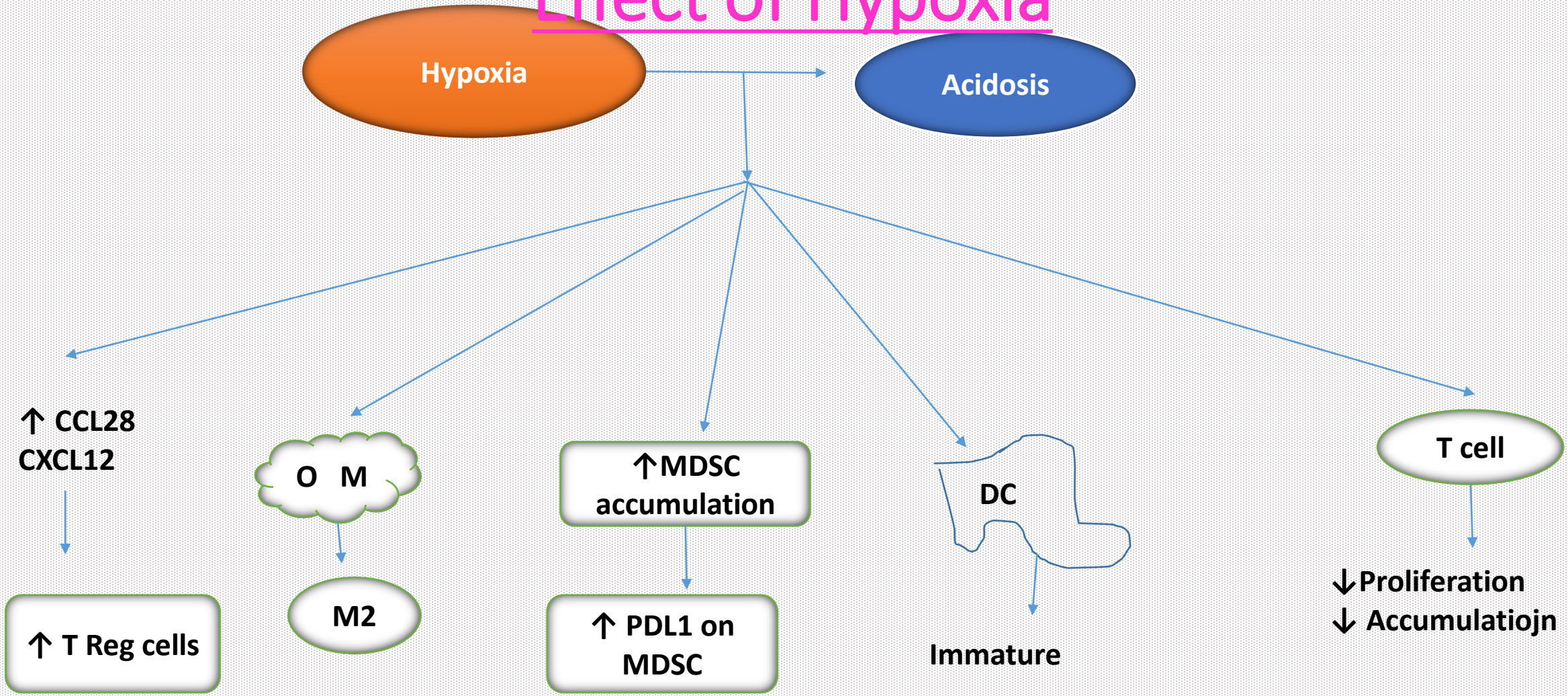
I/O + Bev

Anti Angio + Anti Angio → Not proven

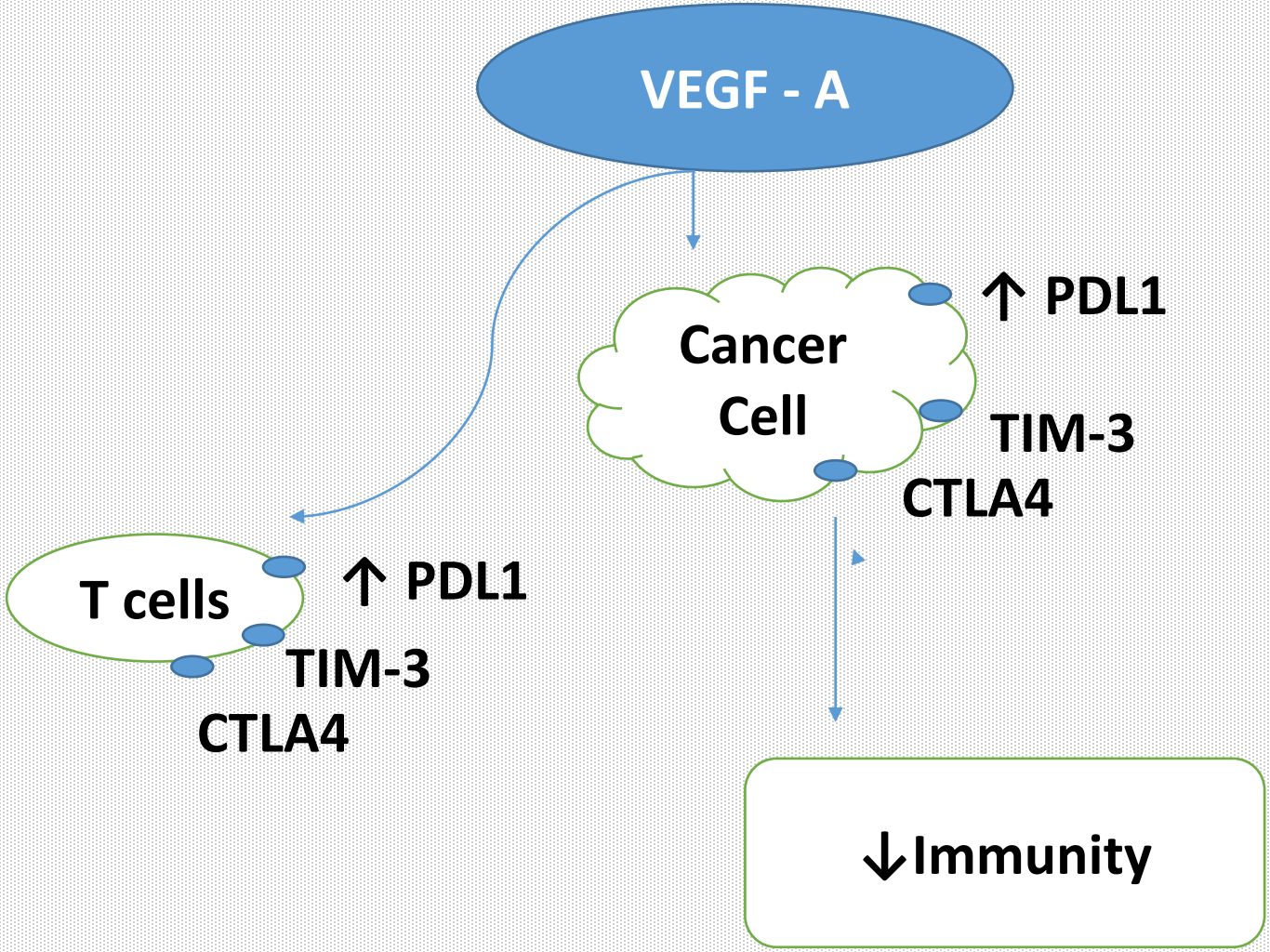
Intermediate efficacy


VEG- F
Hypoxic Tumor
C
C
C
C
C
C
BV
Immune cells will try to get in

Effect of Hypoxia

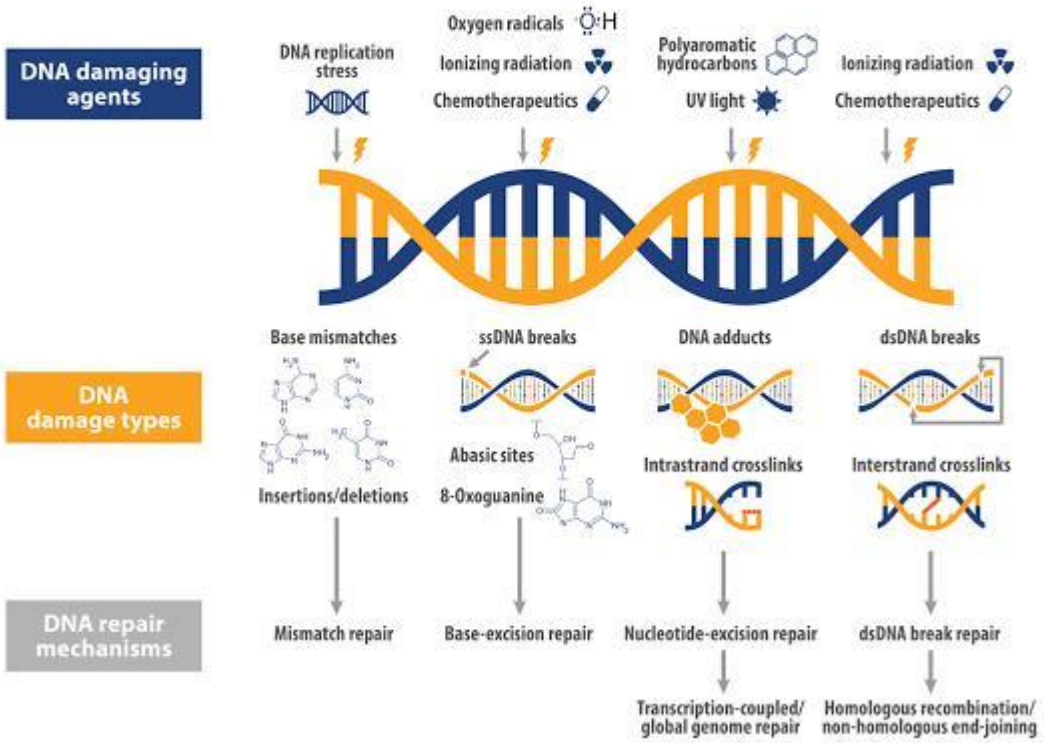


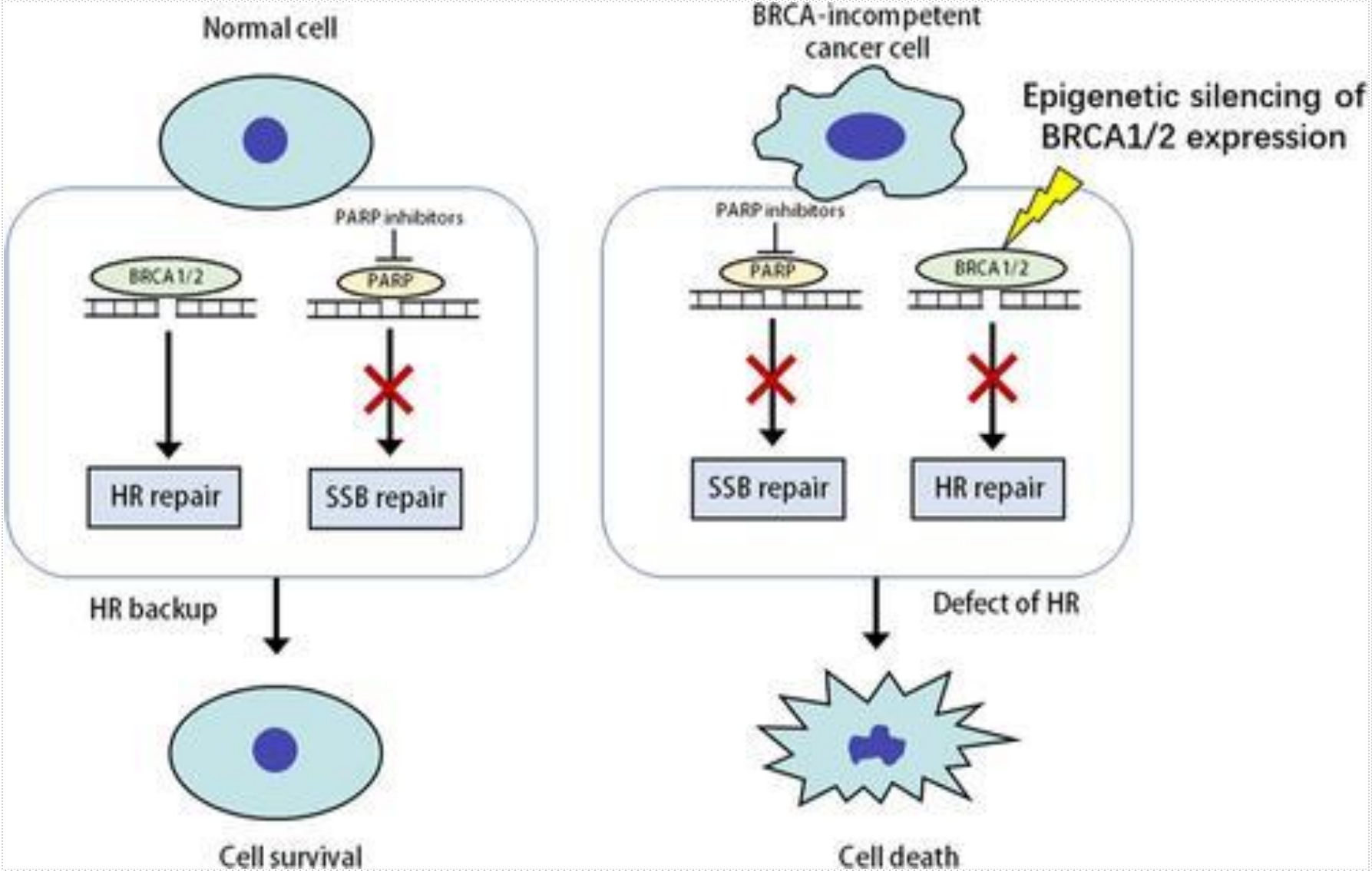
Direct effect on cancer cells and T Cells

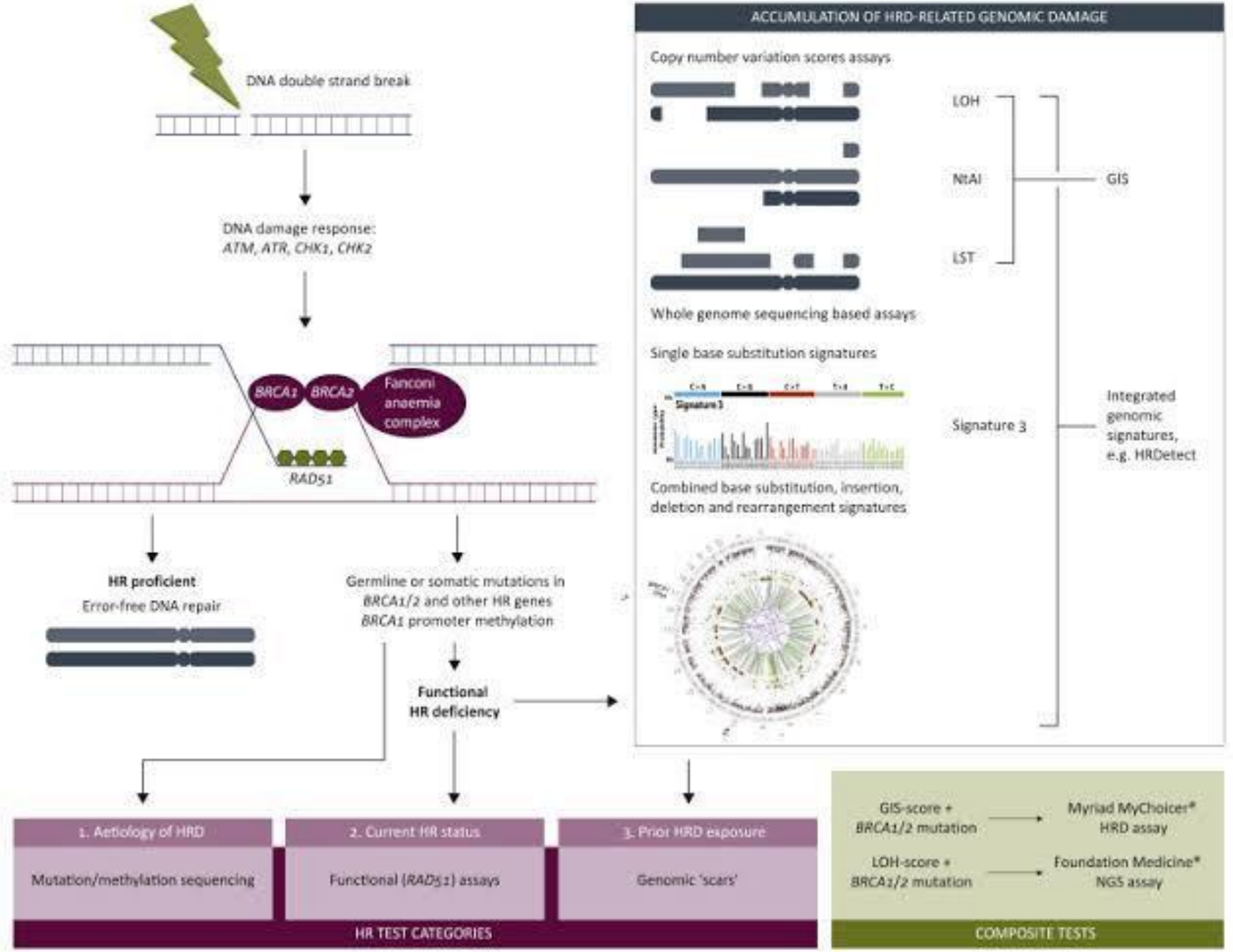


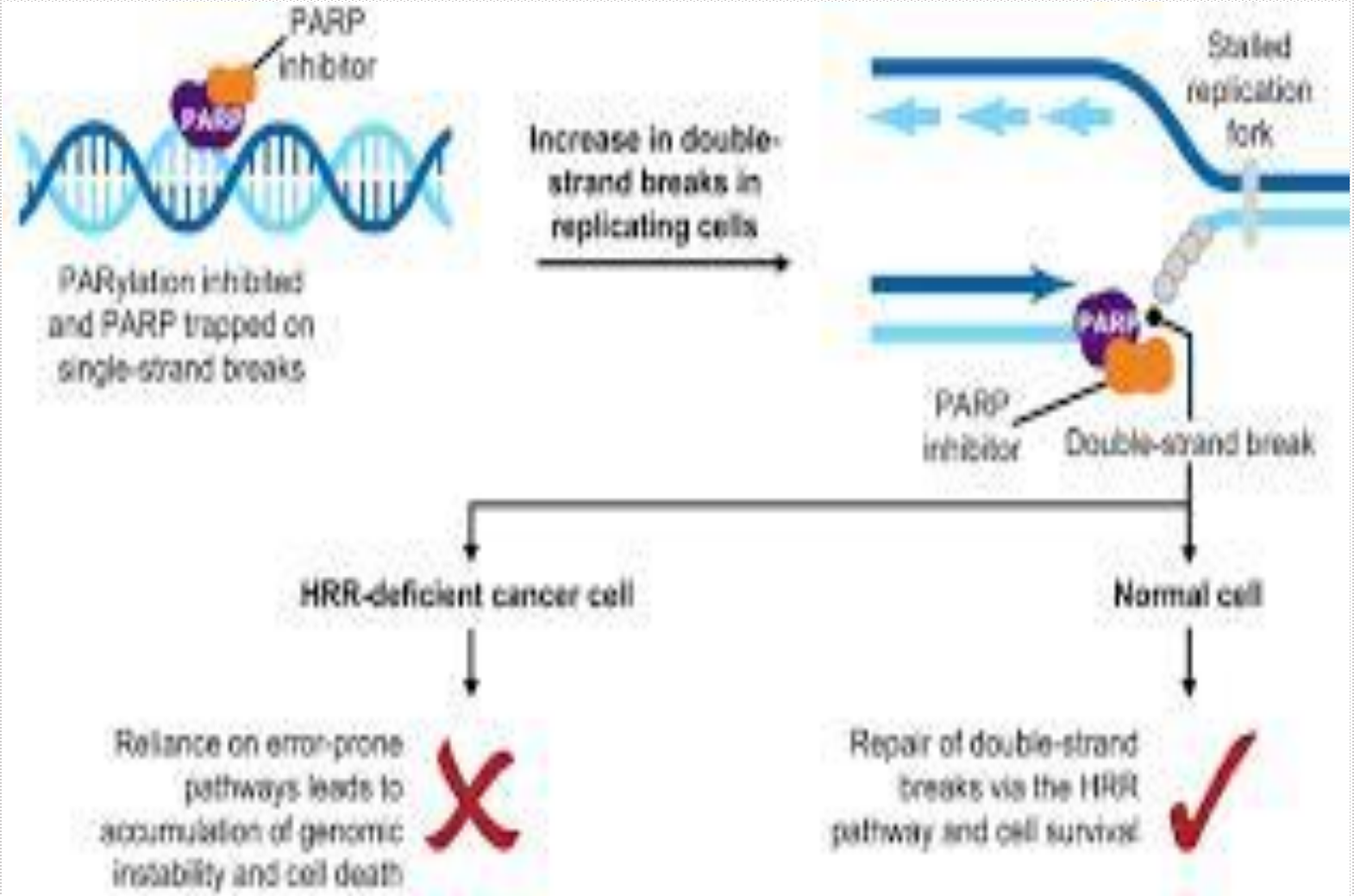
DNA Repair Mechanisms

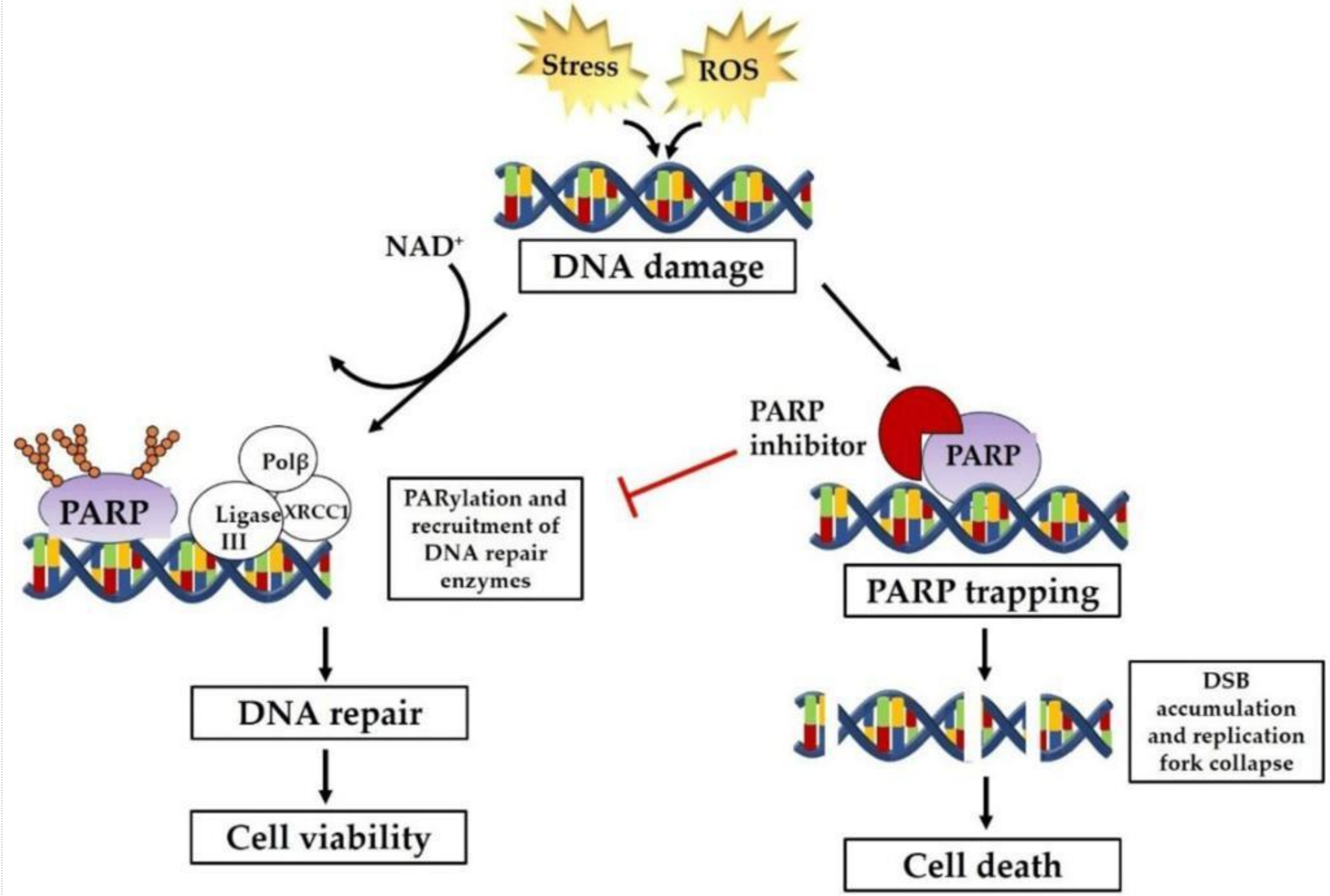
CrownBio
CONNECTING SCIENCE TO PATIENTS

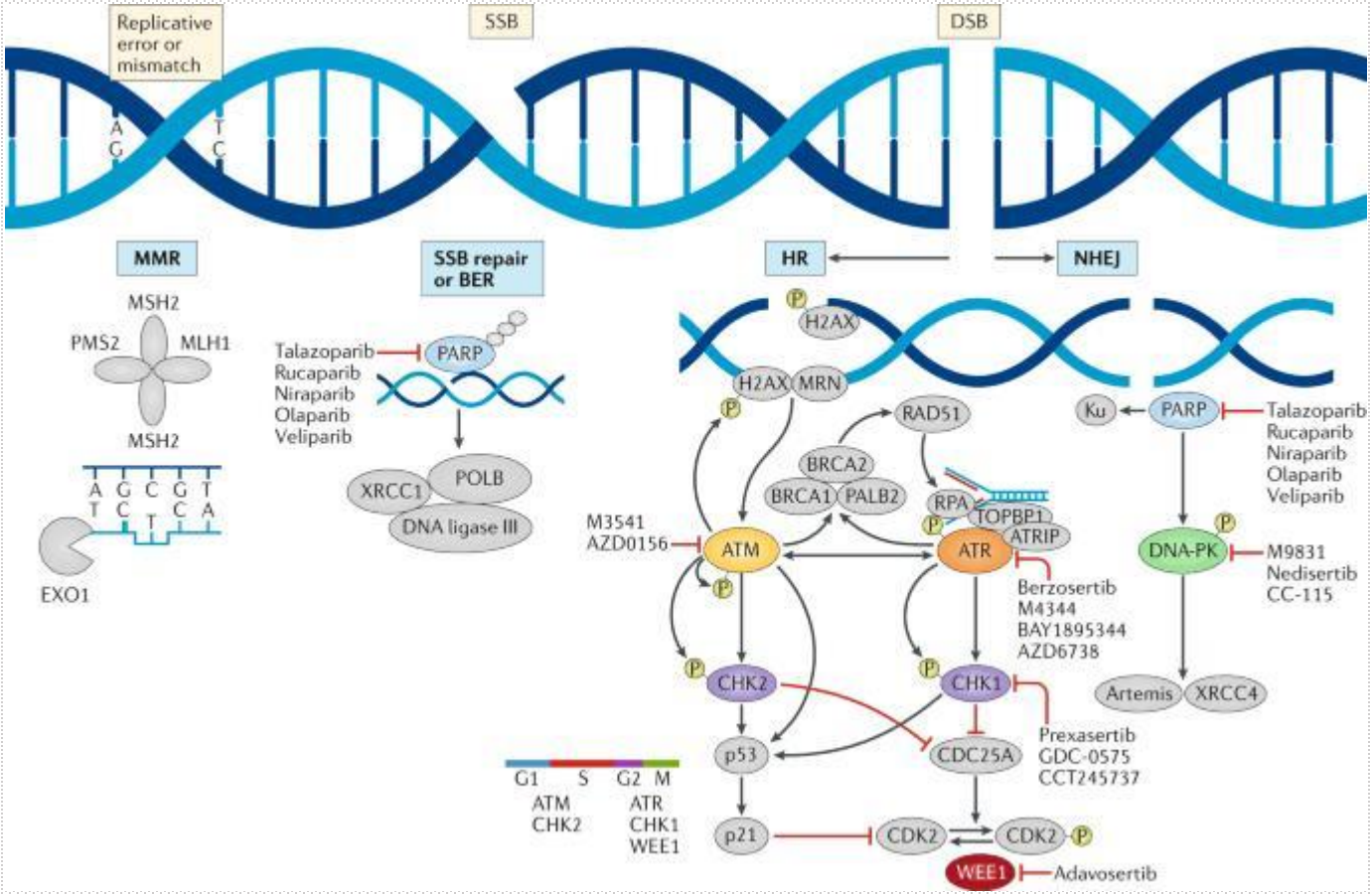



Normal cell
PARP inhibitors
BRCA1/2
PARP
HR repair
SSB repair
HR backup
Cell survival
BRCA-incompetent cancer cell
Epigenetic silencing of BRCA1/2 expression
PARP inhibitors
PARP
BRCA1/2
SSB repair
HR repair
Defect of HR
Cell death


DNA double strand break
DNA damage response:
ATM, ATR, CHK1, CHK2
BRCA1
BRCA2
Fanconi anaemia complex
RAD51
HR proficient
Error-free DNA repair
Germline or somatic mutations in
BRCA1/2 and other HR genes
BRCA1 promoter methylation
Functional HR deficiency
ACCUMULATION OF HRD-RELATED GENOMIC DAMAGE
Copy number variation scores assays
LOH
NtAI
LST
GIS
Whole genome sequencing based assays
Single base substitution signatures
Signature 3
Integrated genomic signatures, e.g. HRDetect
Combined base substitution, insertion, deletion and rearrangement signatures
1. Aetiology of HRD
Mutation/methylation sequencing
2. Current HR status
Functional (RAD51) assays
3. Prior HRD exposure
Genomic 'scars'
HR TEST CATEGORIES
GIS-score + BRCA1/2 mutation
Myriad MyChoice® HRD assay
LOH-score + BRCA1/2 mutation
Foundation Medicine® NGS assay
COMPOSITE TESTS


PARP inhibitor
PARP
PARylation inhibited and PARP trapped on single-strand breaks
Increase in double-strand breaks in replicating cells
Stalled replication fork
PARP
PARP inhibitor
Double-strand break
HRR-deficient cancer cell
Normal cell
Reliance on error-prone pathways leads to accumulation of genomic instability and cell death
Repair of double-strand breaks via the HRR pathway and cell survival


Stress
ROS
DNA damage
NAD+
PARP
Polβ
Ligase III
XRCC1
PARylation and recruitment of DNA repair enzymes
DNA repair
Cell viability
PARP inhibitor
PARP
PARP trapping
DSB accumulation and replication fork collapse
Cell death


Replicative error or mismatch
SSB
DSB
MMR
SSB repair or BER
HR
NHEJ
MSH2
PMS2
MLH1
MSH2
EXO1
Talazoparib
Rucaparib
Niraparib
Olaparib
Veliparib
PARP
XRCC1
POLB
DNA ligase III
H2AX
MRN
RAD51
BRCA2
BRCA1
PALB2
RPA
TOPBP1
ATRIP
M3541
AZD0156
ATM
ATR
Berzosertib
M4344
BAY1895344
AZD6738
CHK2
CHK1
Prexasertib
GDC-0575
CCT245737
p53
CDC25A
G1 S G2 M
ATM CHK2
ATR CHK1 WEE1
p21
CDK2
CDK2
WEE1
Adavosertib
Ku
PARP
Talazoparib
Rucaparib
Niraparib
Olaparib
Veliparib
DNA-PK
M9831
Nedisertib
CC-115
Artemis
XRCC4

PARP – I Predictive Markers Ovarian Ca

Necessity

- **Only 22 % --- BRCA mut**
- **Only 50 % --- HRD**

Metanalysis of Ovarian Ca – PARP I use

PFS Benefit

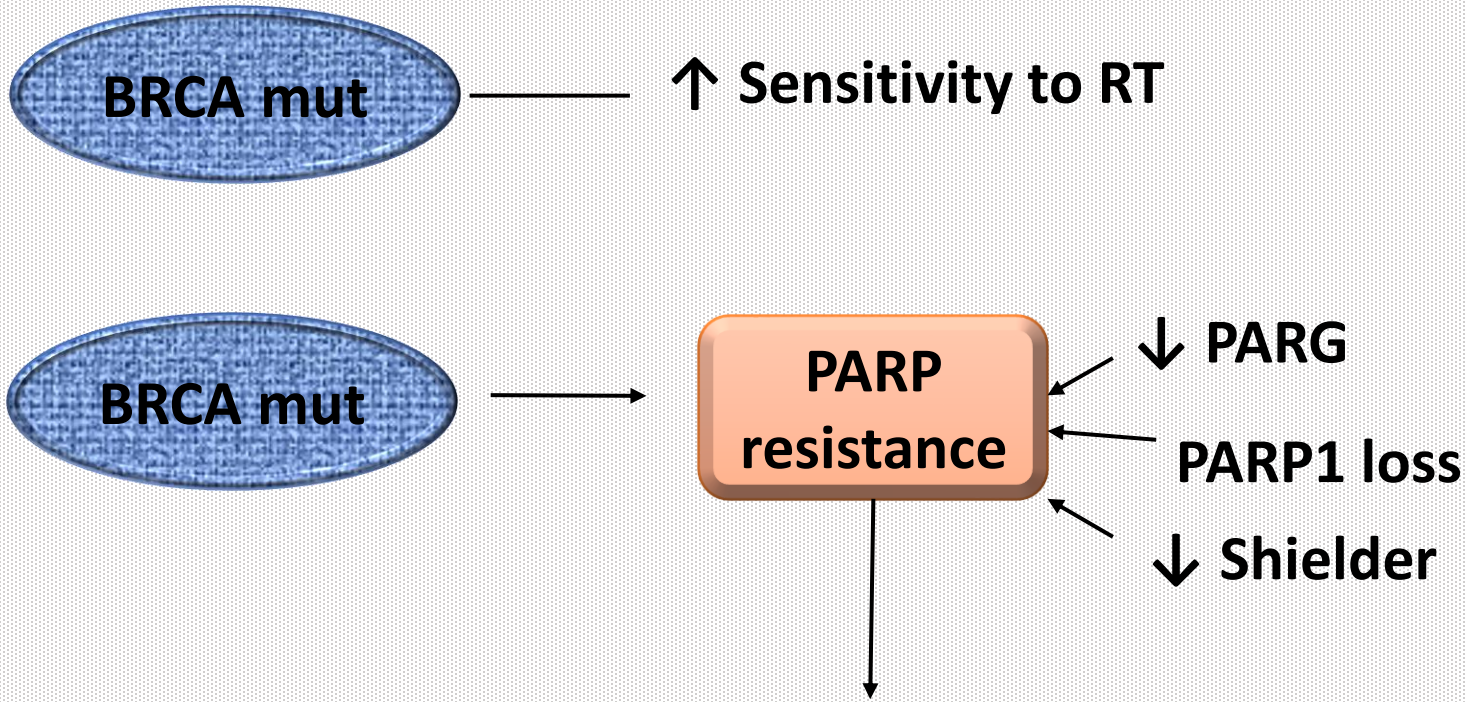
- **BRCA – mut → HR ---0.30**
- **BRCA – WT → HR = 0.60**

PFS Benefit

- **HRD ⊕ → HR-------0.40**
- **HRD θ → HR -------0.74**

But all ovarian ca – Benefit to some extent

PARP I + RT



RT – Good option in PARP – I Resistant Cancers

PARP-I

+ I/O

BRCA - mut

↑ Mutations

↓

↑ Neo antigens

↑Recognition by APC[3]

↑ Recruitment of CD8 †

↑ Efficacy of Combination

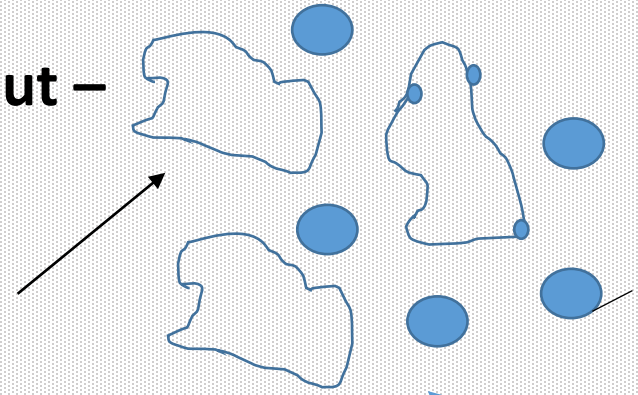
PARP-I

+ I/O

PARP I

↑ PDL 1

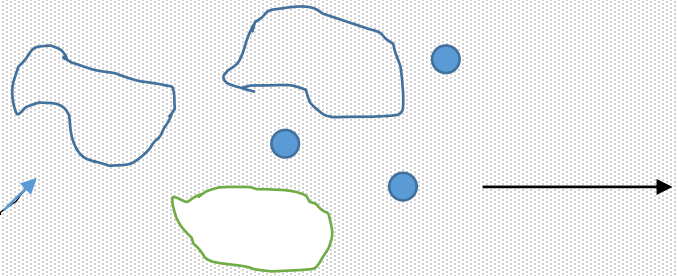
BRCA- mut –
↑
PARP - I



↑CGAS –STING Signalling

↑ CD8 L

BRCA -mut



↑ Disruption of Chromatin Boundaries

↑ Immunity

↑ RNAs

PARP-I

+ I/O

Several Combinations

Mostly Ovarian Ca

- Engoy –OV 46
- Denovo Phase III

Durvatumab + (Plat + Pacli) + Bev

Maintanance

Durvalumab + Bev

Durvalumab + Bev + Olaparib

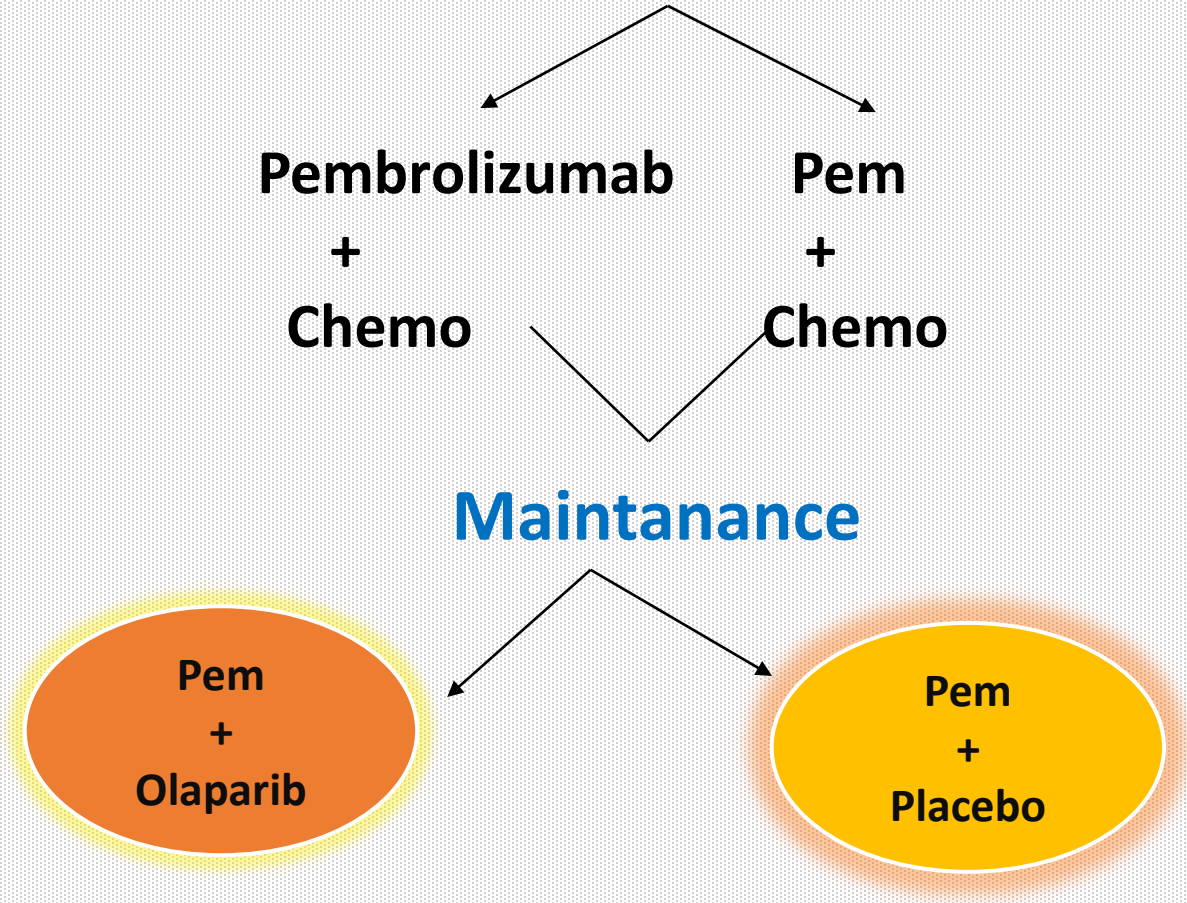
PARP-I

+ I/O

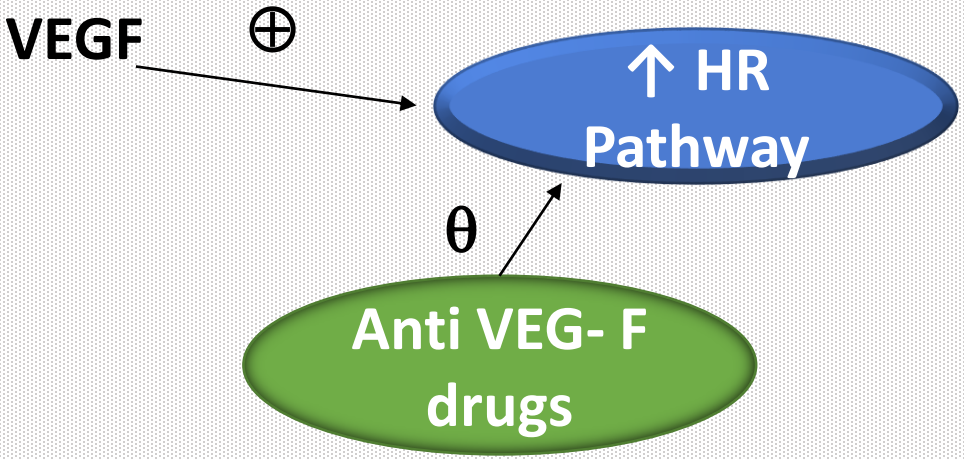
Key Lynk – 001

Phase III

BRCA -WT



PARP-I
+ Antiangio drugs



Ovarian Ca

Olaparib / Niraparib + Bev

↓

↑ PFS both new & recurrent Ovarian Ca

Both HRD / HRP Pts

PARP –I

+

Cell cycle check point signal blockers

- ATR inhibitors
- Ex : Cancer ↓ARIDIA
- WEE1 inhibitor (Adavosertib)

  Can reverse resistance to PARP I

  Now trials with olaparib + Adavorsertib
- Mek/ MAP/ ERK path Blocker

  Selumetinib

  Olaparib + Selumetinib
- P13k → AKT →M- TOR path way

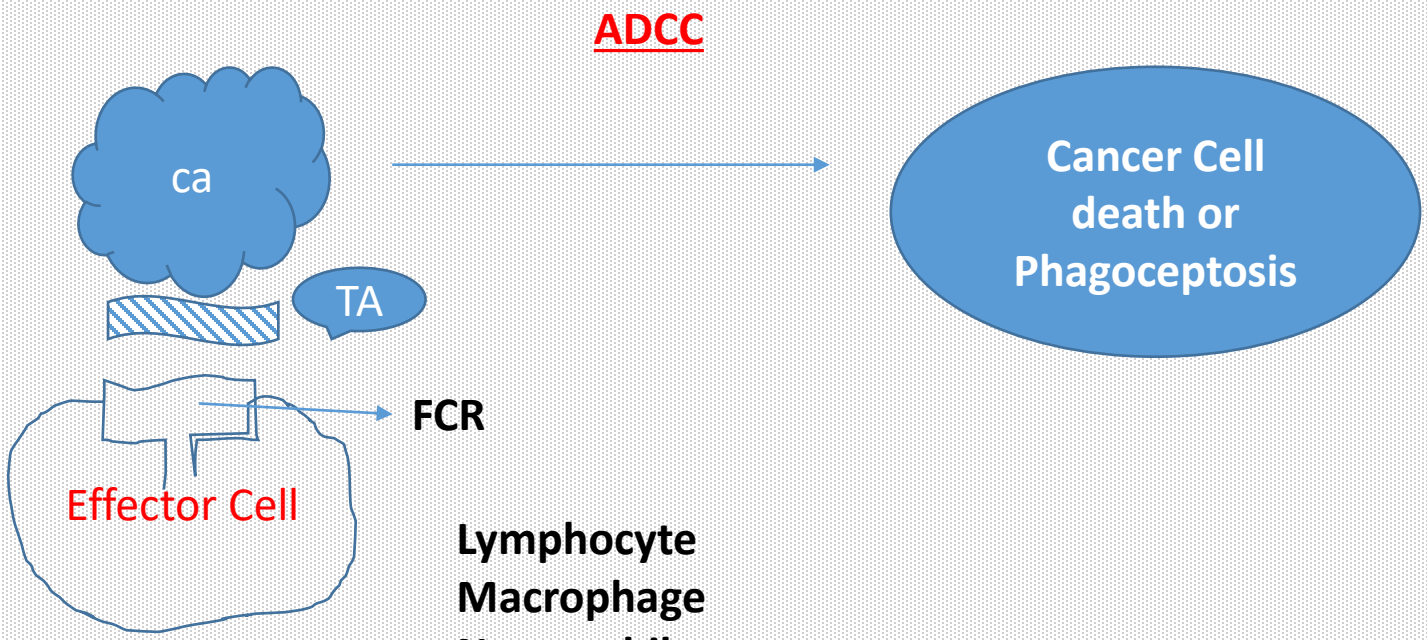
  - Alpalerib -- > p13k
  - Capivasertib – AKT
- POL Q inhibitors – Ex --Novobiocin

Resistance

% TIL

Prognostic & predictive factor for chemo & Herceptin in Neoadjuvant setting

Predicts ↑ PCR



Lymphocyte
Macrophage
Neutrophil
NK cell

Her-2 --- ⊕ / ⊕⊕

More biologically similar to
Her -2 +++
Than to Her-2 - 0

Present with

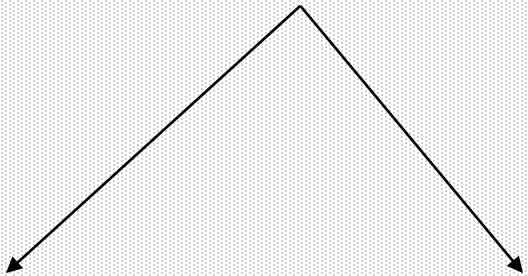
Larger tumors
↑ Grade
↑ Ki – 67%
↑ N Status

DFS – Closer to Her -2 +++

Low Her-2 Breast Ca
Failure of Herceptin

NSABP – B47 STUDY

N = 3270 **Adjuvant low Her-2 BC**

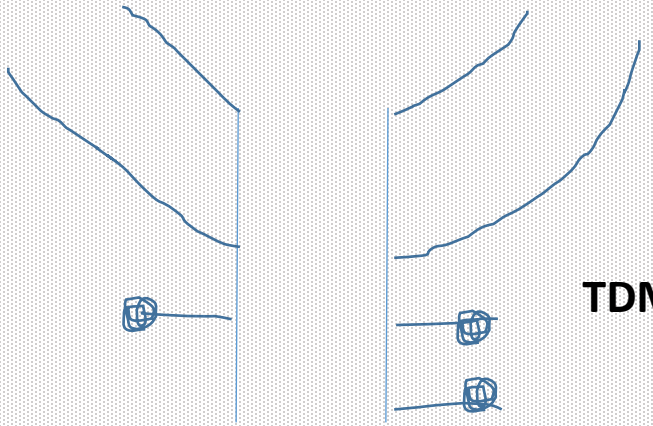


CT + Herceptin **CT**

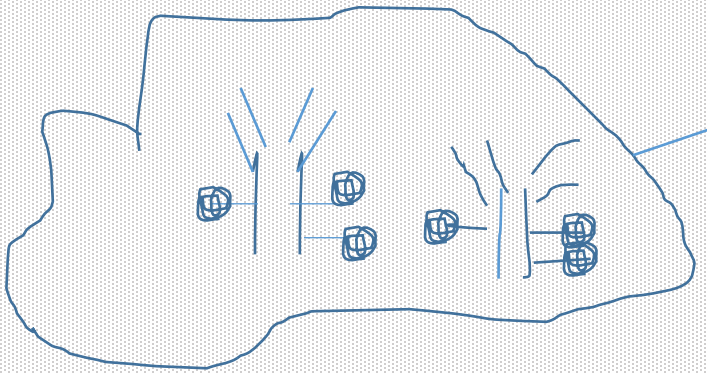
DFS – HR = 0.98

Even Her-2 ++ **pts also did not benefit**

Low Her-2
TDM_1



TDM1 (Tubulotoxin)



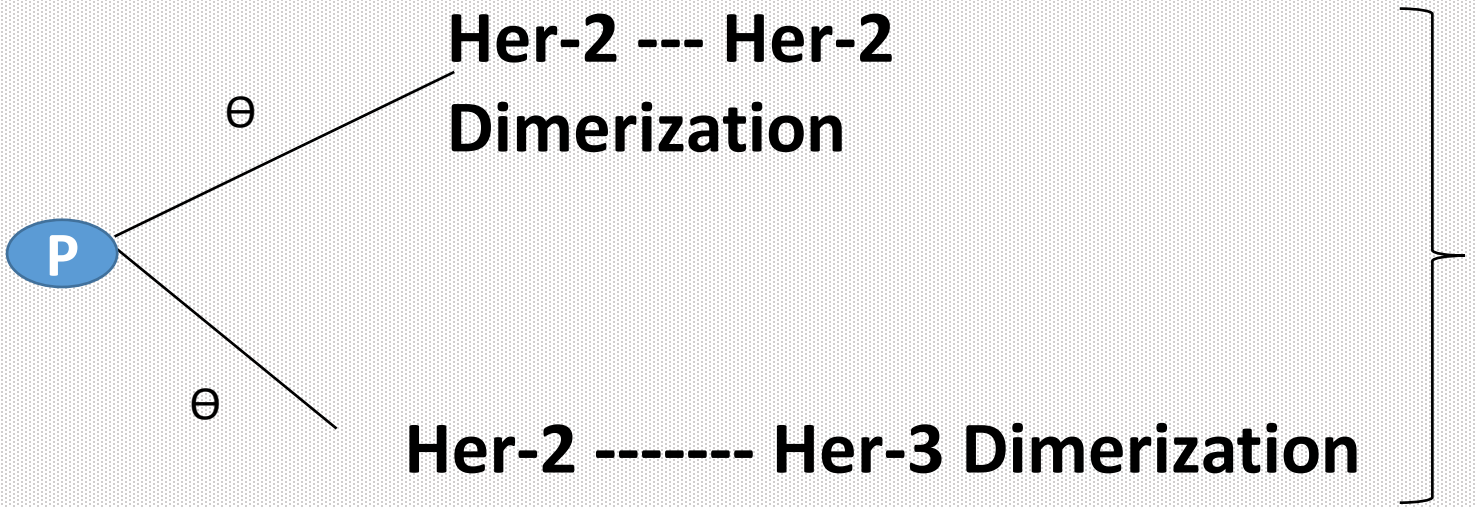
Not Permeable
Less TDM1 molecule/ Herceptin

↓

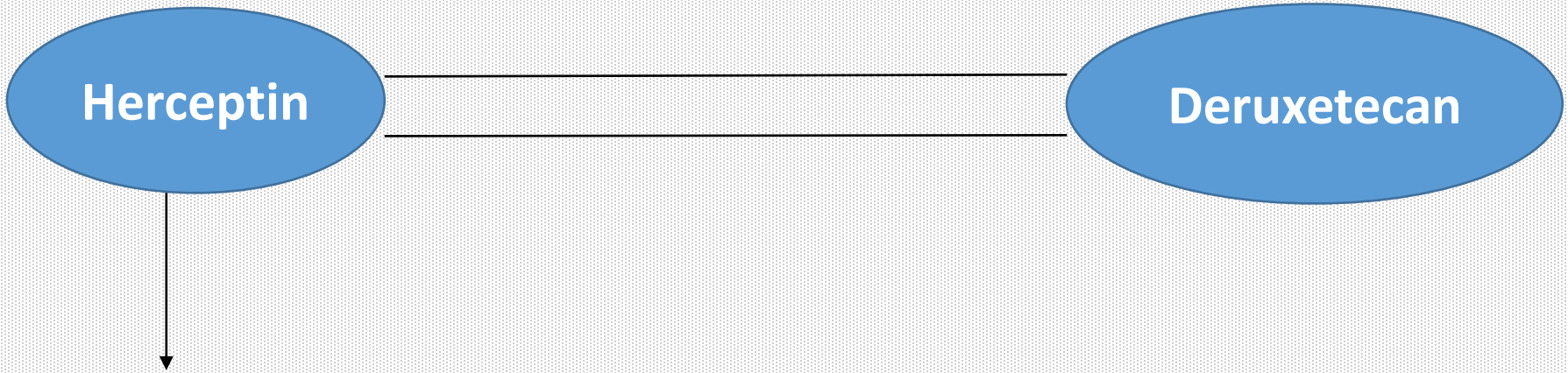
Less payload
No bystander kill effect less immunomodulation
So Her-2 +++ cells are killed
Her-2 + / ++ / 0 cells are spared

Low Her-2 BC Pertuzumab Phase II Study

Negative results



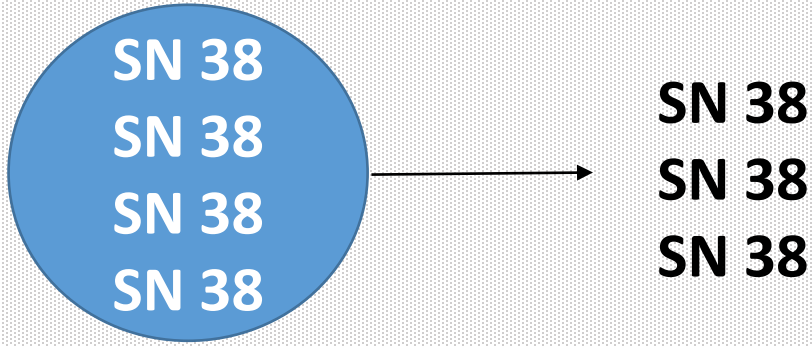
Low Her-2 BC
Transtuzumab – Deruxtecan (T- Dxd)



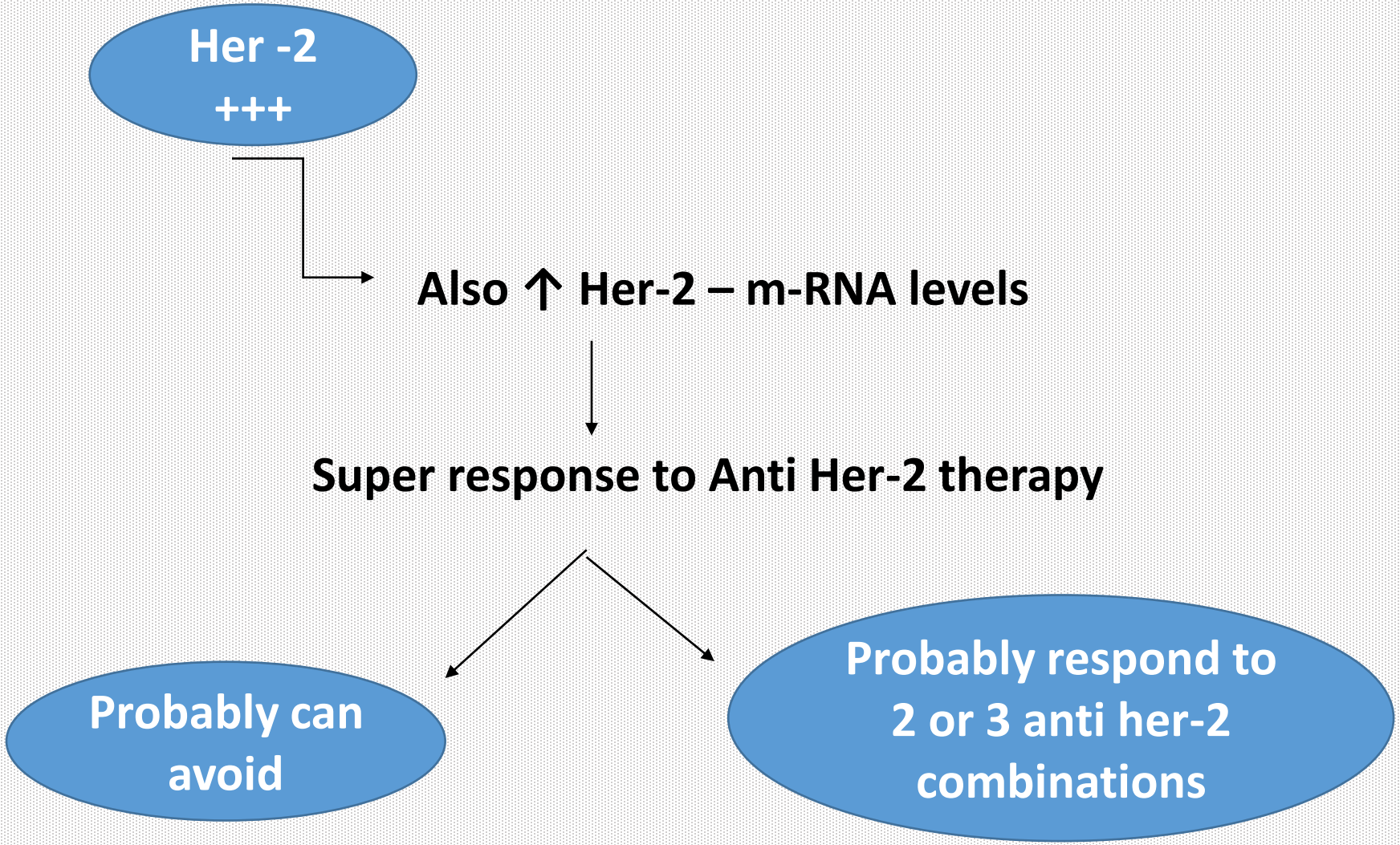
Antibody
Topoisomerase I

inhibitor

Linker → Cleavable



Transcriptomic analysis
Concept of Her-2 enriched in Breast Ca Pts



Concept of Circ – Her-2

30% TNBCs

No Her- 2 amplification

↓

Circ – Her-2 was ⊕

which is pre translational Her-2 gene splice

↓

↑ Her-2 activity ----- > ↑ Dimerization of Her-1 & Her – III

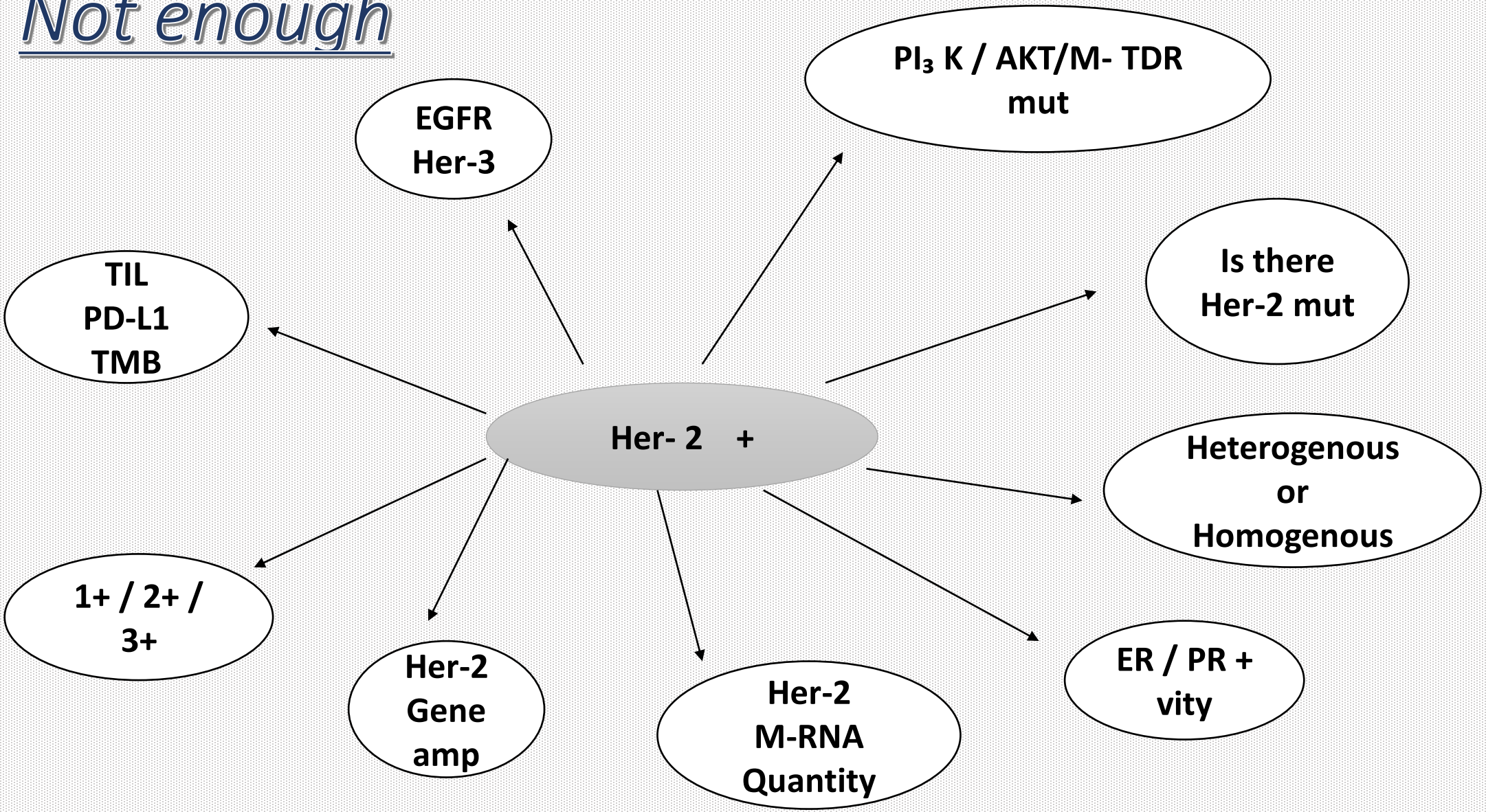
↓

Poor Prognosis

↓

Pertuzumab is effective

Her-2 ⊕
Not enough




THANK YOU!