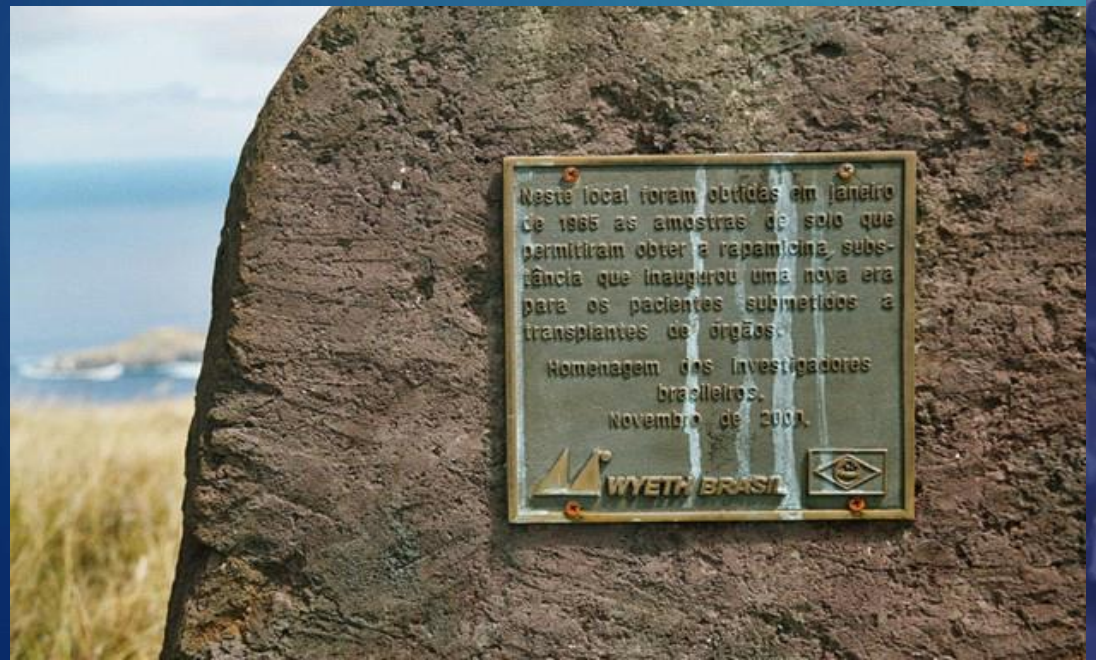
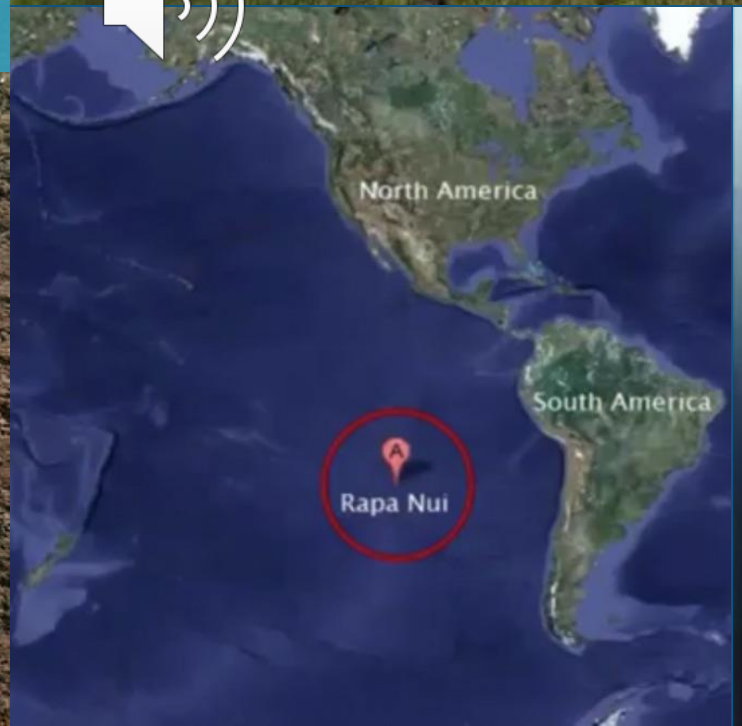
Anti- tumor Properties of

mTOR: Mechanistic Target of Rapamycin

Dr.Abedi Azar.S
Professor of nephrology
TUMC

- Triene macrolide antibiotic from S. hygroscopicus in a soil sample from Easter Island (Rapa Nui) in 1975
- – Originally developed as antifungal agent
- – Sirolimus (Rapamune.) approved by FDA in 1999 as
- immunosuppressant used to prevent rejection in organ transplant





Clinical Significance

mTOR Inhibition

Antifungal

Clinical Significance

mTOR Inhibition

Antifungal

Immunosuppresant

Clinical Significance

mTOR Inhibition

Antifungal

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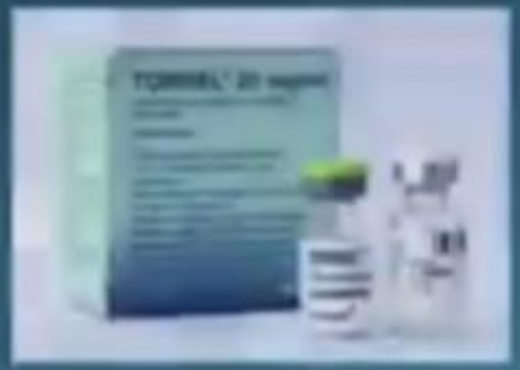
Anti-cancerous



Antifungal

Imm

Growth factors
Insulin/ IGF
Nutrient status
Amino acids
Energy
Hypoxia
RTK
IRS1
PI3K
Class IA PI3K
Class III PI3K
PIP3
PTEN
PDK1
Akt
T308
S473
Beclin1
MAP4K3
LKB1
REDD1
AMPK
TSC1/2
Rheb
mTOR
mLST8
mSIN1
Rictor
Raptor
mTORC2
PKCα, cytoskeletal organization
mTORC1
rapamycin
Torisel
RAD001
AP23573
FKBP-12
S6K1
4E-BP1
HIF-1α
VHL
Protein translation
Ribosome biogenesis
Autophagy
Hypoxic adaptation
Mutated and/or amplified in tumor
Known tumor suppressors
PTEN–Cowden's disease
LKB1–Peutz-Jeghers syndrome
TSC1/2–Tuberous sclerosis
VHL–von Hippel-Lindau disease

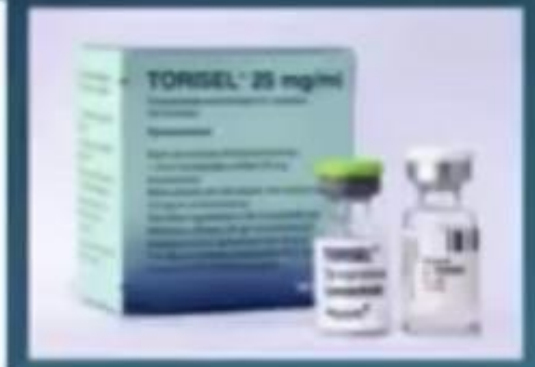
Clinical Significance

mTOR Inhibition

Antifungal

Immunosuppresant

Anti-cancerous



Neuronal Health

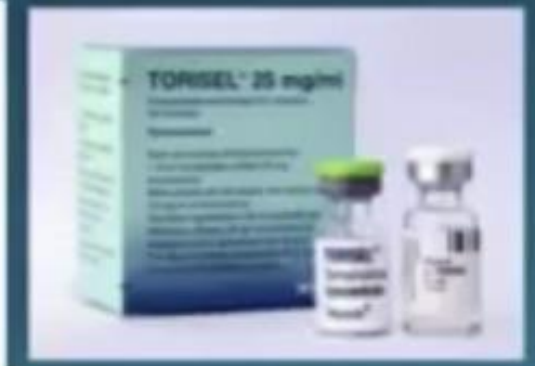
Clinical Significance

mTOR Inhibition

- **Antifungal**

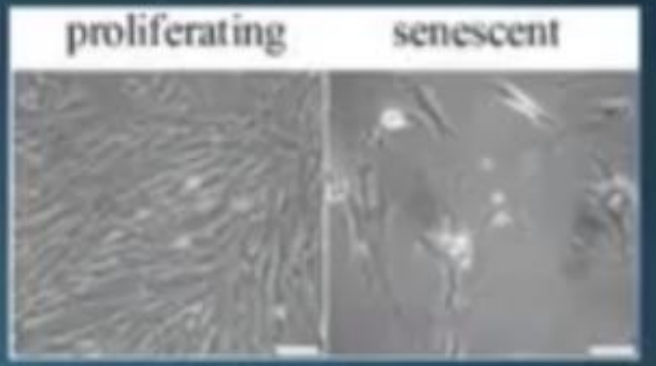
- **Immunosuppresant**

- **Anti-cancerous**

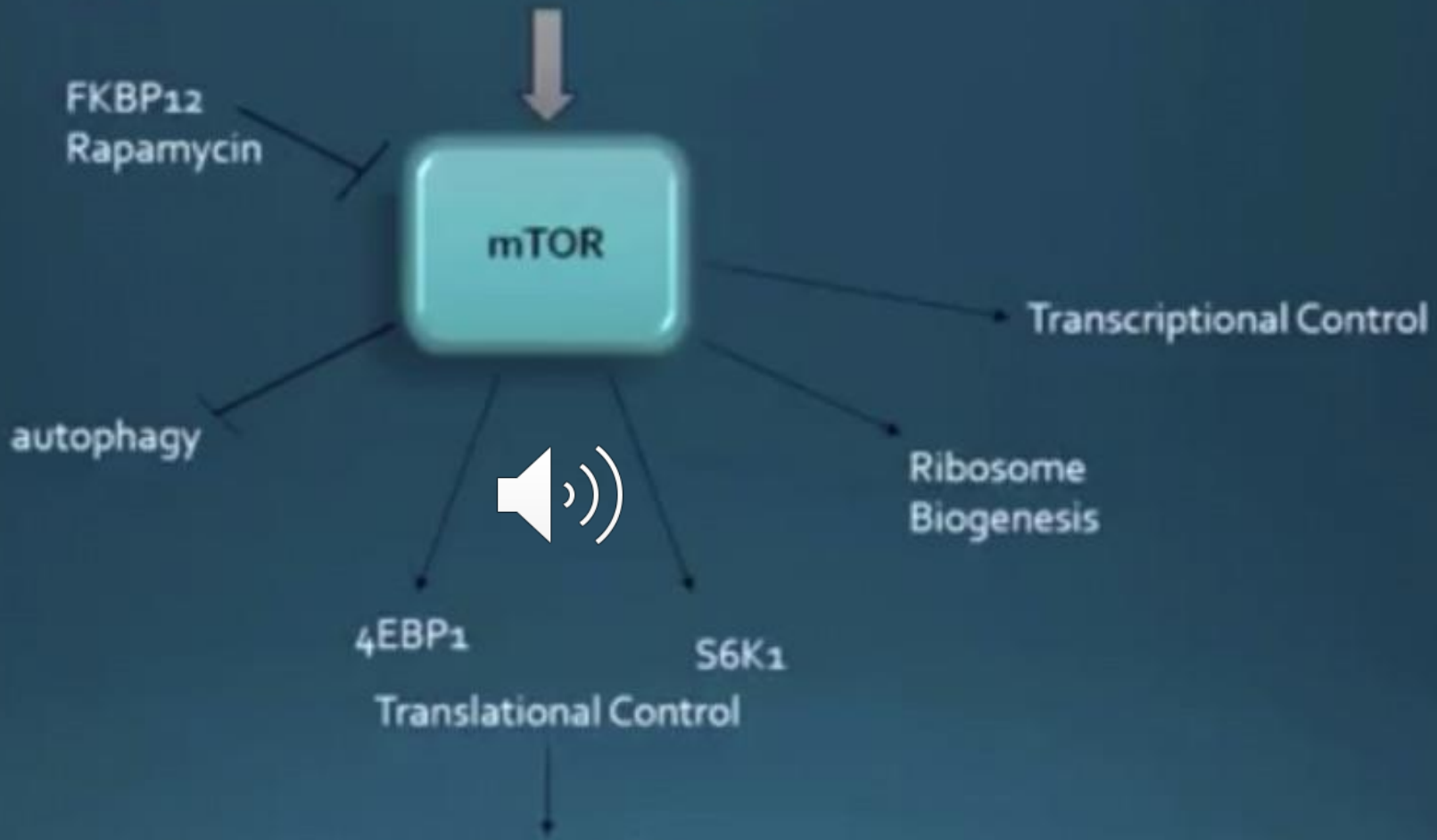


- **Neuronal Health**

- **Anti-aging**



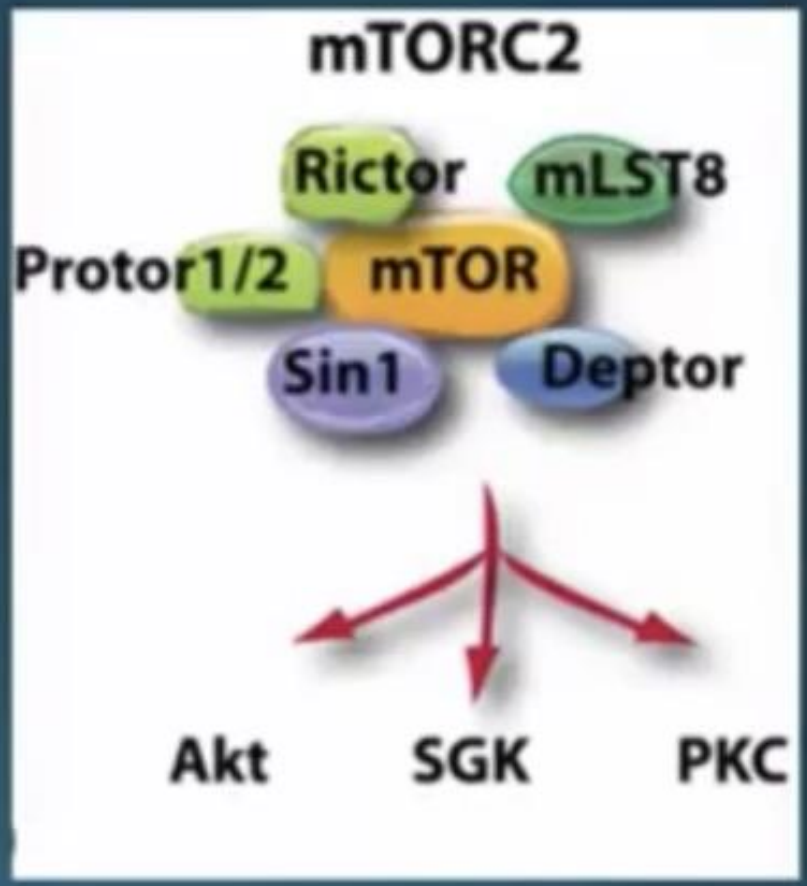
Energy, nutrients, O2, growth factors



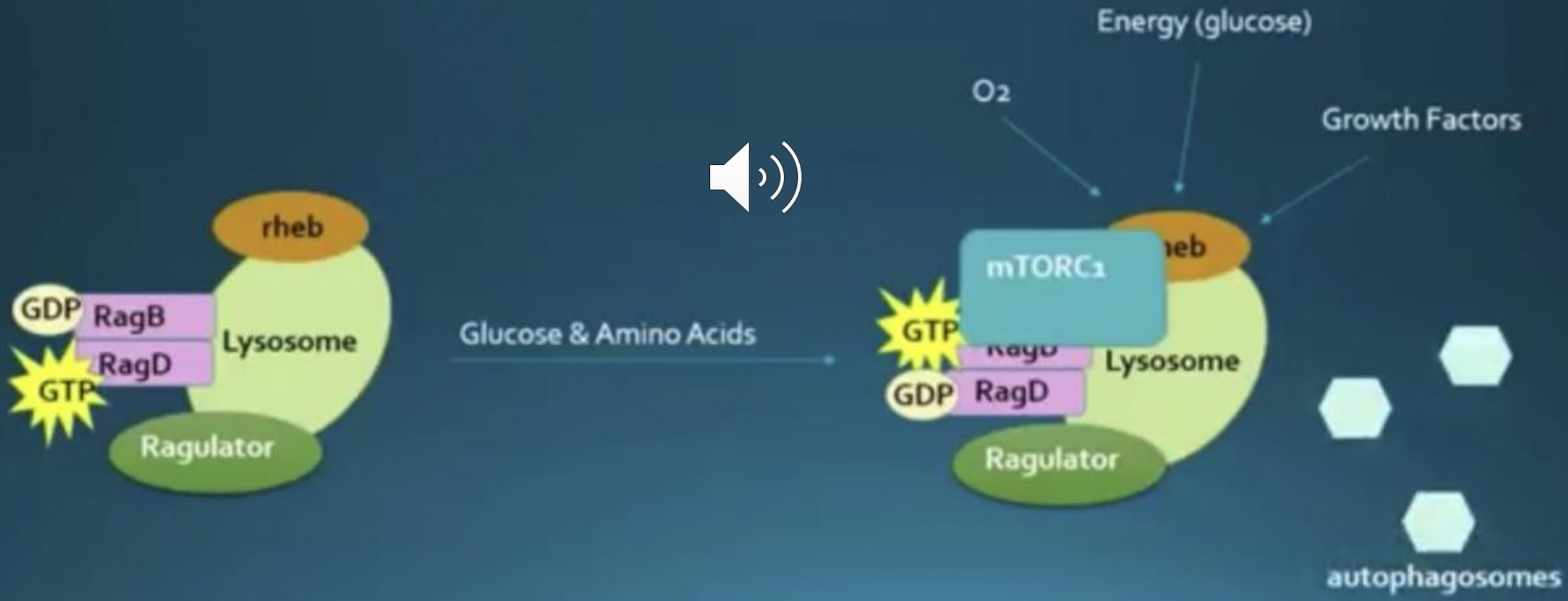
Growth

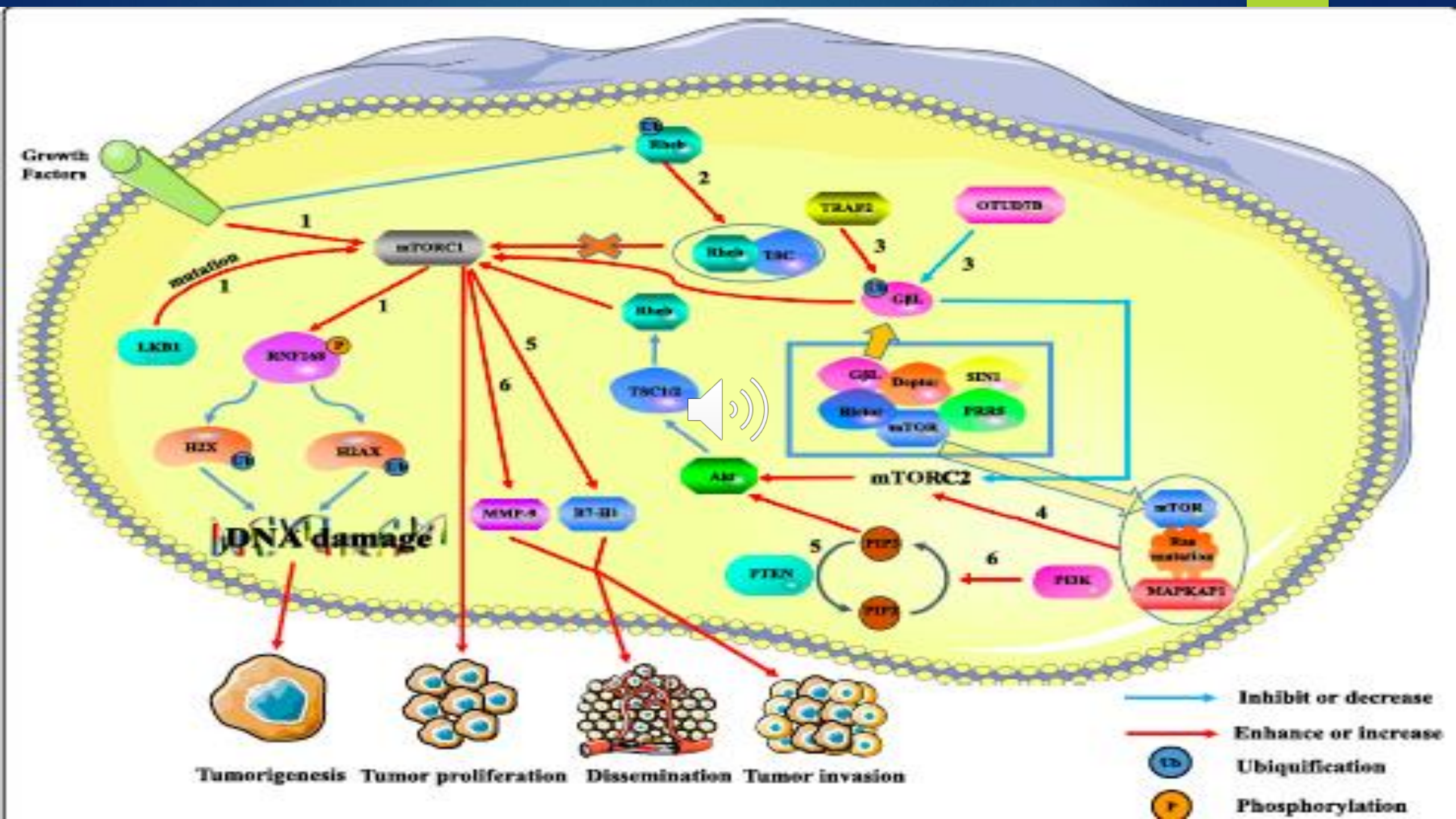
Anabolism vs Catabolism

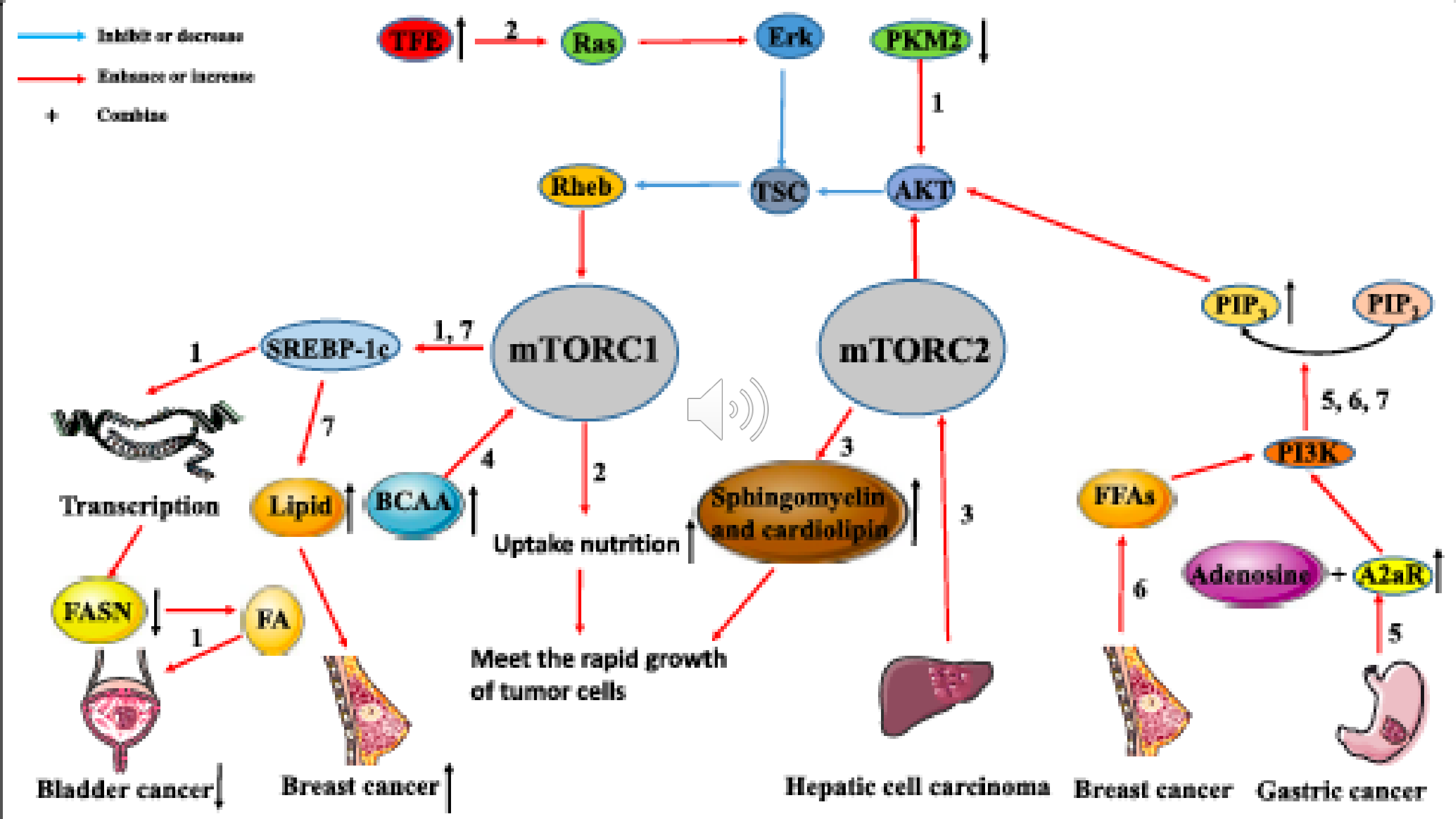

mTORC1
Raptor
mLST
mTOR
PRAS40
Deptor
S6Ks
4EBPs
others
(ULK1, etc.)


mTORC2
Rictor
mLST8
Protor1/2
mTOR
Sin1
Deptor
Akt
SGK
PKC

mTORC1 Activation




Growth Factors
Rheb
2
TRAF2
OTUD7B
1
mTORC1
Rheb
TSC
3
3
mutation
1
GβL
1
Rheb
LKB1
RNF168
5
6
TSC1/2
GβL
Deptor
SIN1
Rictor
PRR5
mTOR
H2X
RIAX
Akt
mTORC2
4
MMP-9
MT-MI
mTOR
Ras mutation
DNX damage
PIP3
5
6
PTEN
PDK
MAPKAP1
PIP2
Tumorigenesis
Tumor proliferation
Dissemination
Tumor invasion
Inhibit or decrease
Enhance or increase
Ubiquification
Phosphorylation


Inhibit or decrease
Enhance or increase
Combine
TFE
2
Ras
Erk
PKM2
1
Rheb
TSC
AKT
mTORC1
mTORC2
PIP3
PIP2
1, 7
1
SREBP-1c
5, 6, 7
PI3K
7
Transcription
Lipid
BCAA
4
2
3
Sphingomyelin and cardiolipin
3
FFAs
6
Adenosine
A2aR
5
FASN
1
FA
Uptake nutrition
Meet the rapid growth of tumor cells
Bladder cancer
Breast cancer
Hepatic cell carcinoma
Breast cancer
Gastric cancer

Zou et al. Cell Biosci (2020) 10:31
https://doi.org/10.1186/s13578-020-00396-1

Cell & Bioscience

REVIEW Open Access

mTOR signaling pathway and mTOR inhibitors in cancer: progress and challenges

Zhilin Zou[1,2,3†], Tao Tao[4†], Hongmei Li[3*] and Xiao Zhu[1,2*]

Table 1 Summary of the research phase of the mTOR inhibitors

mTOR inhibitors	Applied tumor	Phase	References
Everolimus	RCC	FDA approved	–
Temsirolimus	Advanced RCC	FDA approved	–
ICSN3250	Colon cancer cell	Pre-clinical studies	Nguyen et al. [53]
LY3023414	Solid tumor or lymphoma	Phase I clinical trial	Bendell et al. [54]
OSU-53	Thyroid cancer cell	Pre-clinical studies	Plews et al. [55]
AZD8055	OCCC cell	Pre-clinical studies	Caumanns et al. [59]
Everolimus	Aggressive and RAIR thyroid cancer	Phase II clinical trial	Hanna et al. [60]
Rapamycin	Pancreatic cancer	Pre-clinical studies	Morran et al. [61]
Temsirolimus	PCNSL	Phase II clinical trial	Korfel et al. [62]

RCC renal cell carcinoma, *OCCC* ovarian clear cell carcinoma, *RAIR* radioactive iodine-refractory, *PCNSL* primary central nervous system lymphoma, *FDA* Food and Drug Administration

- The incidence of post-transplant malignancies is increased 2- to 4-fold compared to the general population and tumors often show a more aggressive phenotype under immunosuppression.
- Certain skin tumors are amongst those with the steepest increase

under immunosuppression.

- tumor incidence seems particularly high for infectionrelated

tumors, i.e. lymphomas, cancers of anus, vulva, Kaposi

- infection- unrelated tumors is also increased but to a lesser extent while some other tumors, i.e. breast, prostate etc. do not show an increased incidence

- it has been known for a long time that immunosuppressive therapy itself poses a risk for the development of certain tumors .Ensuing experimental work could confirm this finding especially for Azathioprine and CNIs .

- CsA is classified as carcinogenic by the InternationalAgency for Research on Cancer.

RESEARCH ARTICLE

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Sebastian Wolf[1,2☯], Verena S. Hoffmann[3,4☯], Antje Habicht[5], Teresa Kauke[1], Julian Bucher[1], Markus Schoenberg[1], Jens Werner[1], Markus Guba[1], Joachim Andrassy[1]*

PLOS ONE | https://doi.org/10.1371/journal.pone.0194975 April 16, 2018

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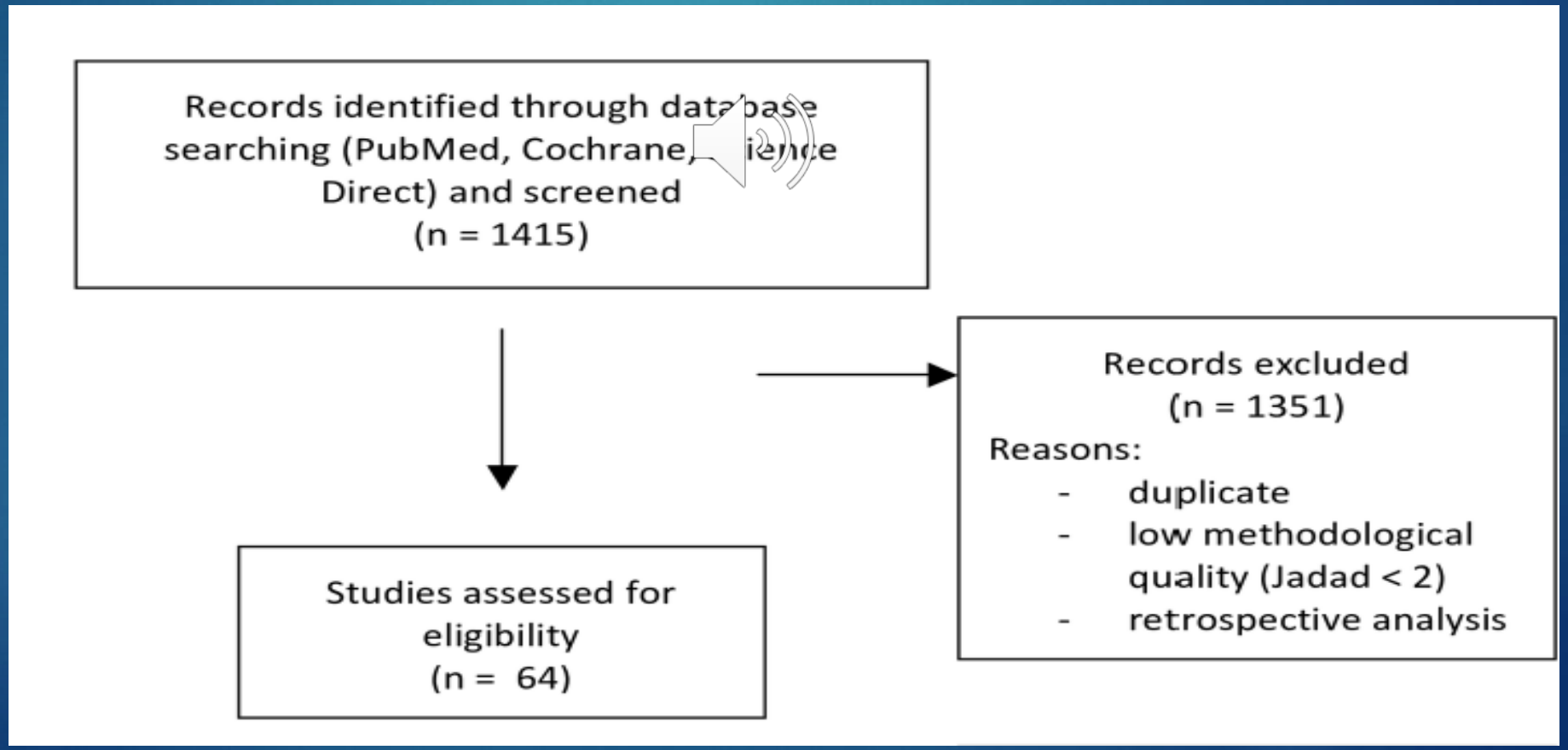

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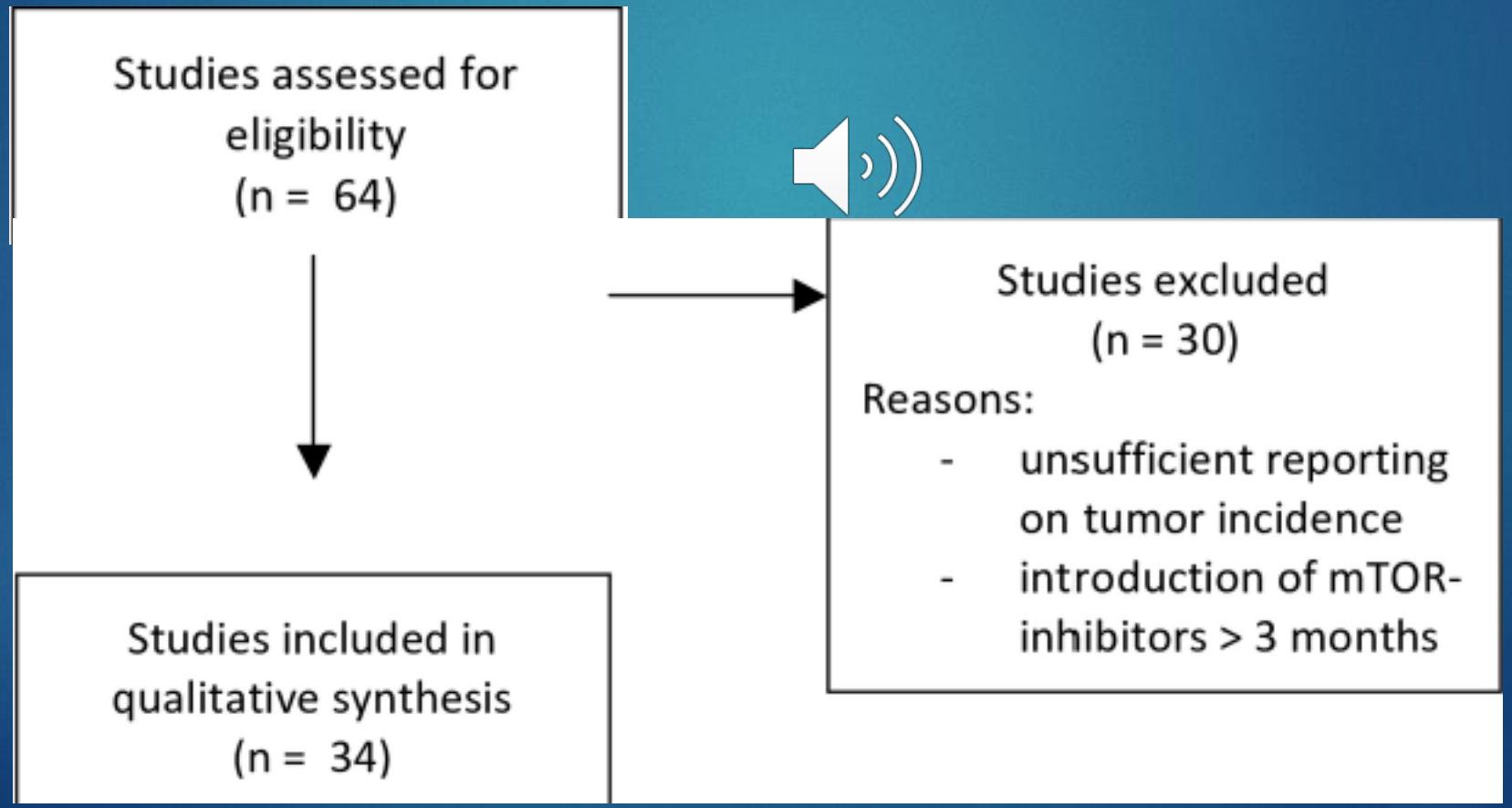

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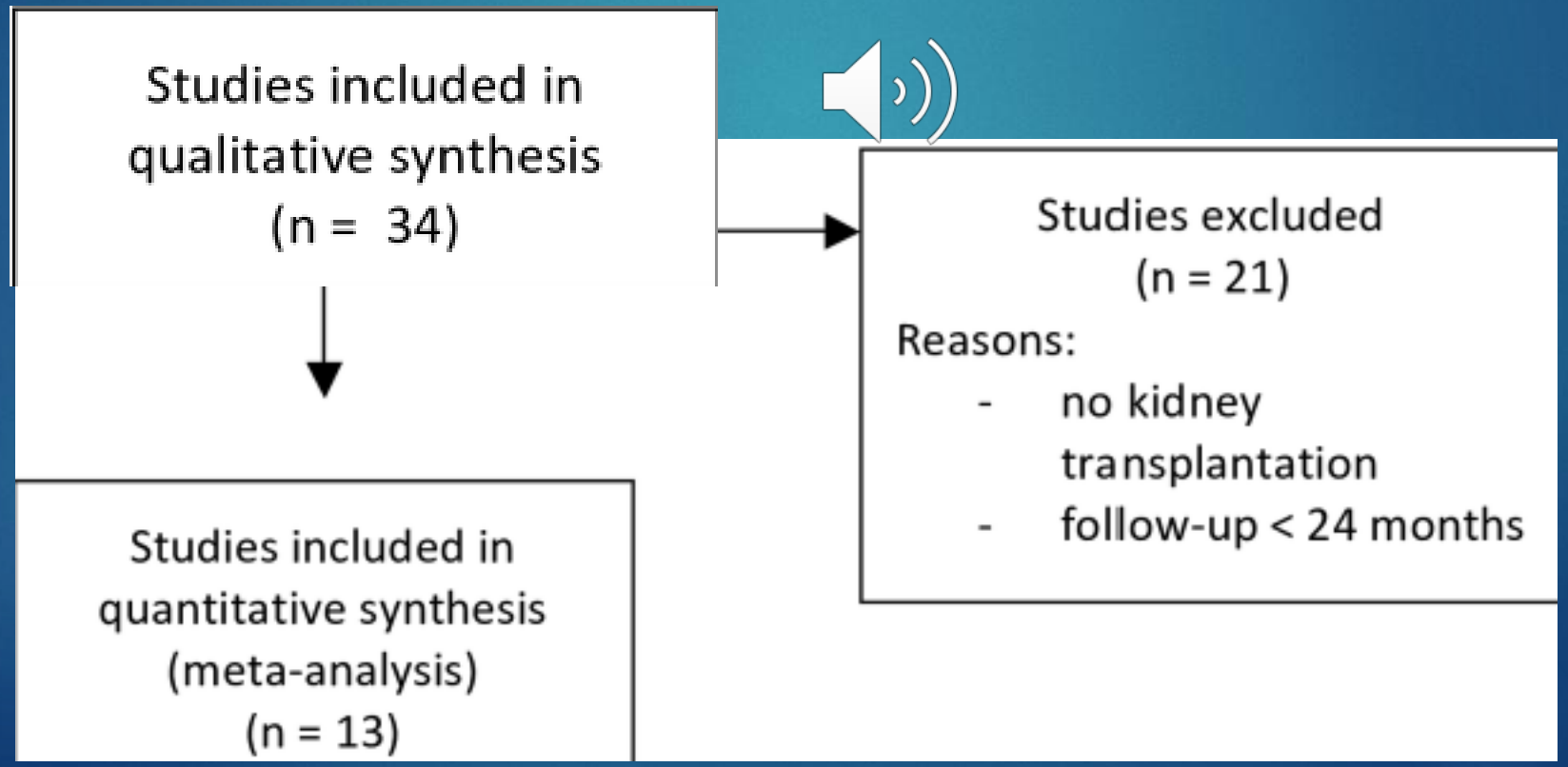

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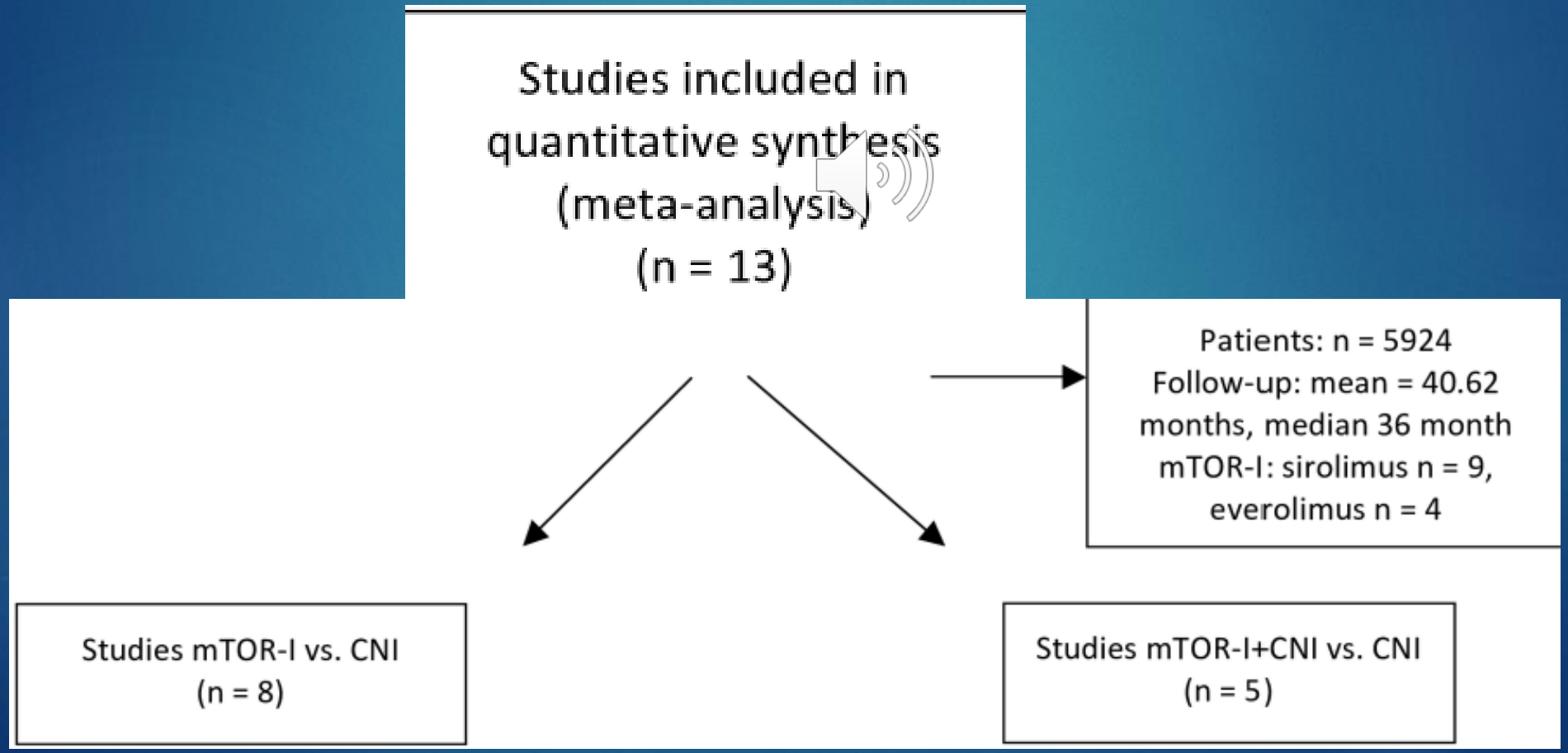
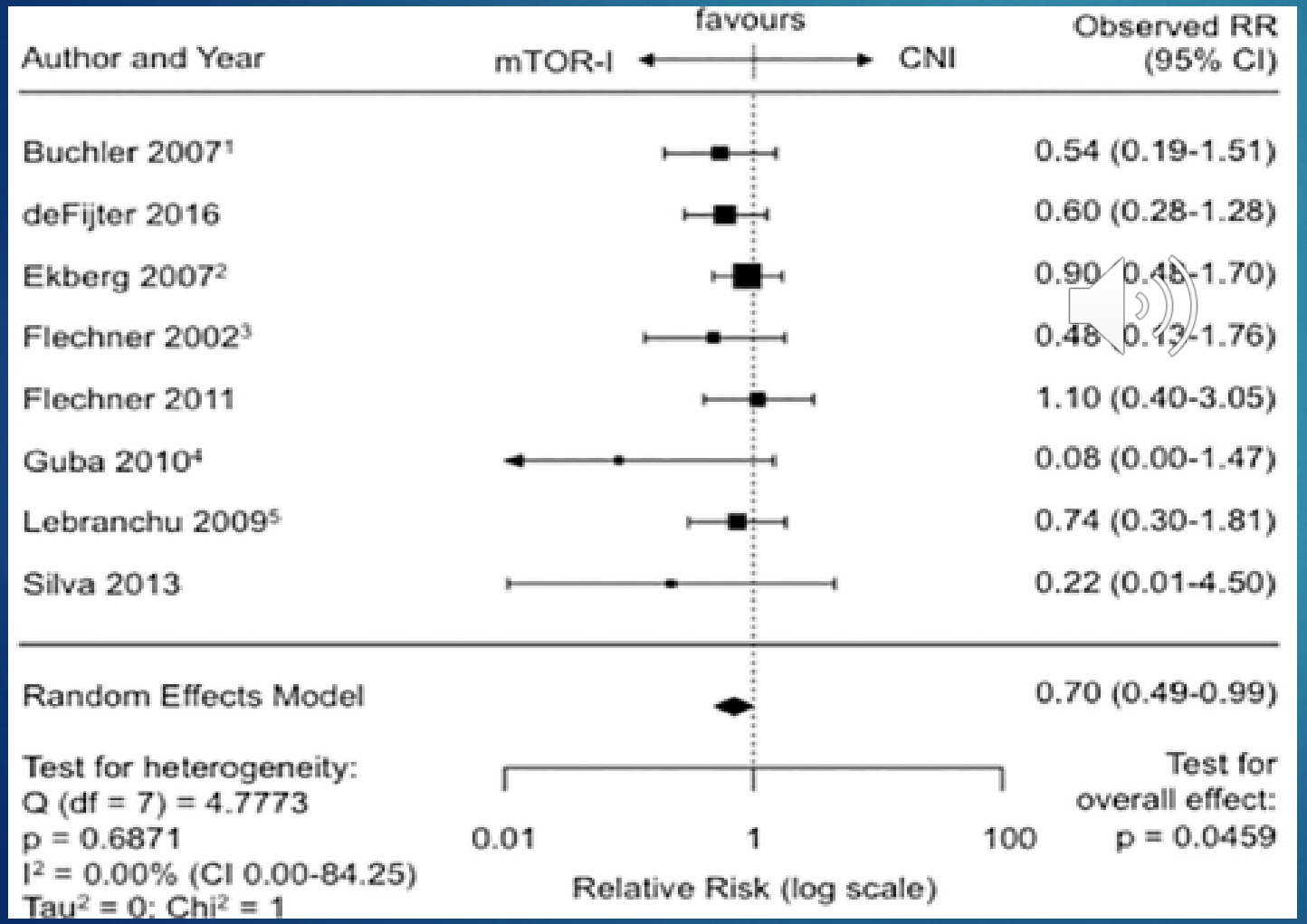


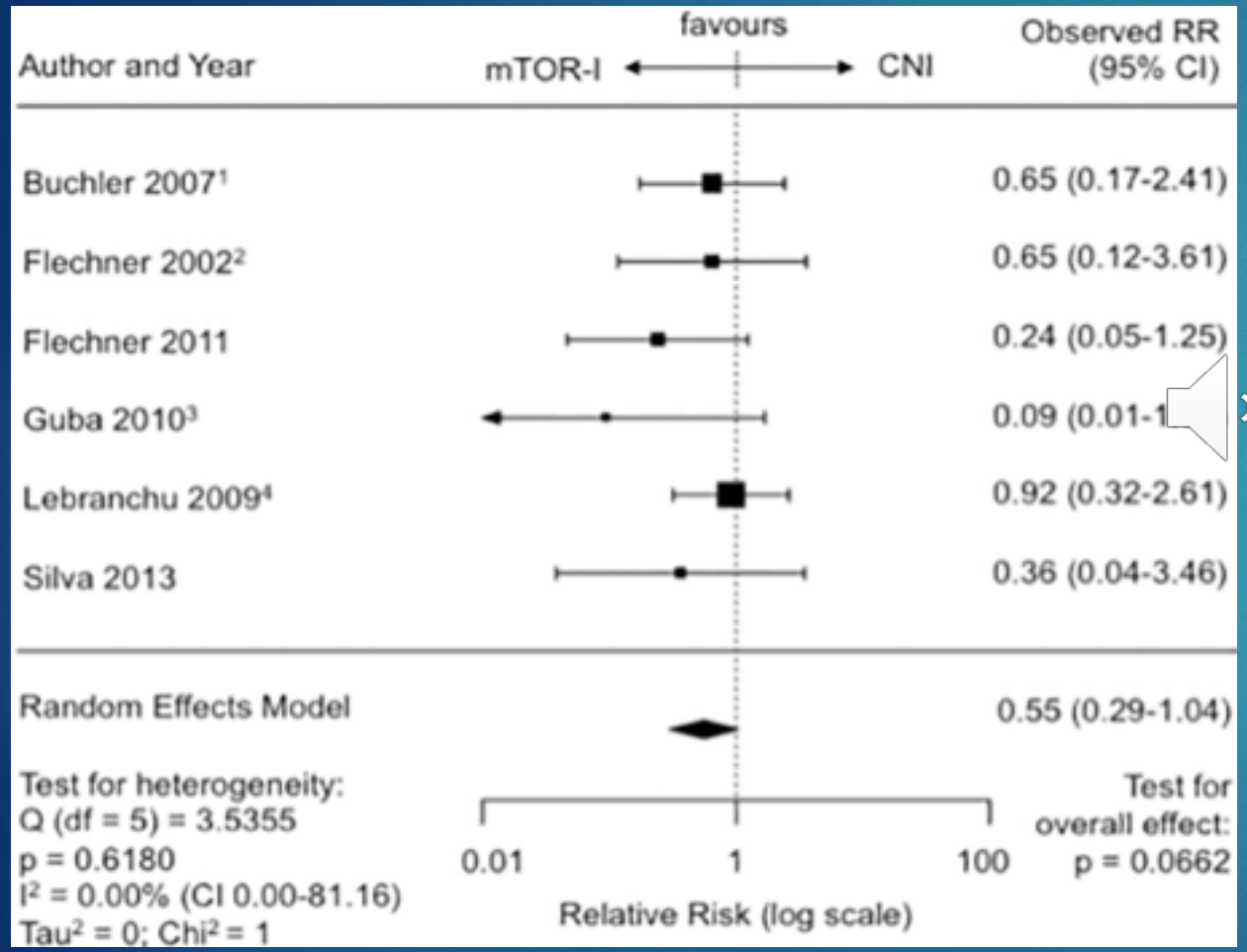
The relative risk of the occurrence of malignancies



all studies on long term tumor incidence (n = 13, SIR = 9, ERL = 4),

the risk of posttransplant malignancy was significantly reduced under mTOR-I treatment

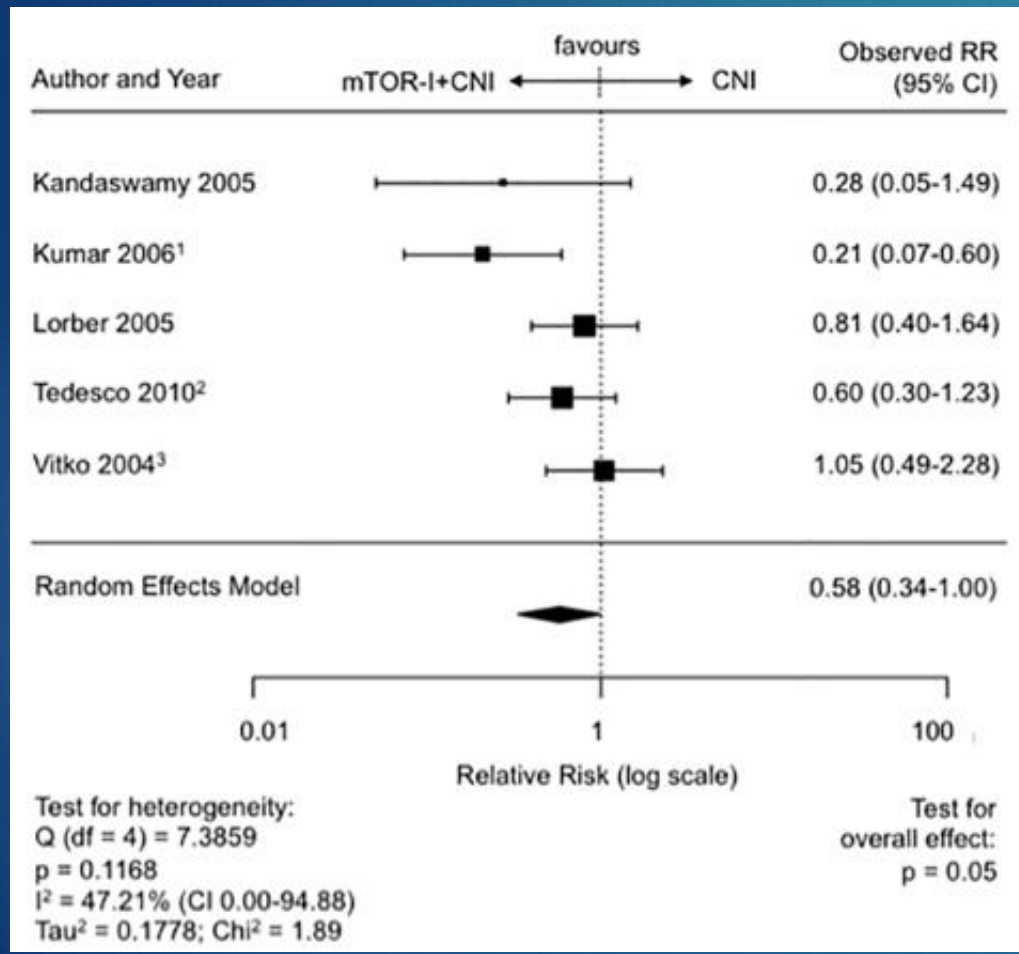
The relative risk of the occurrence of malignancies excluding NMSC's

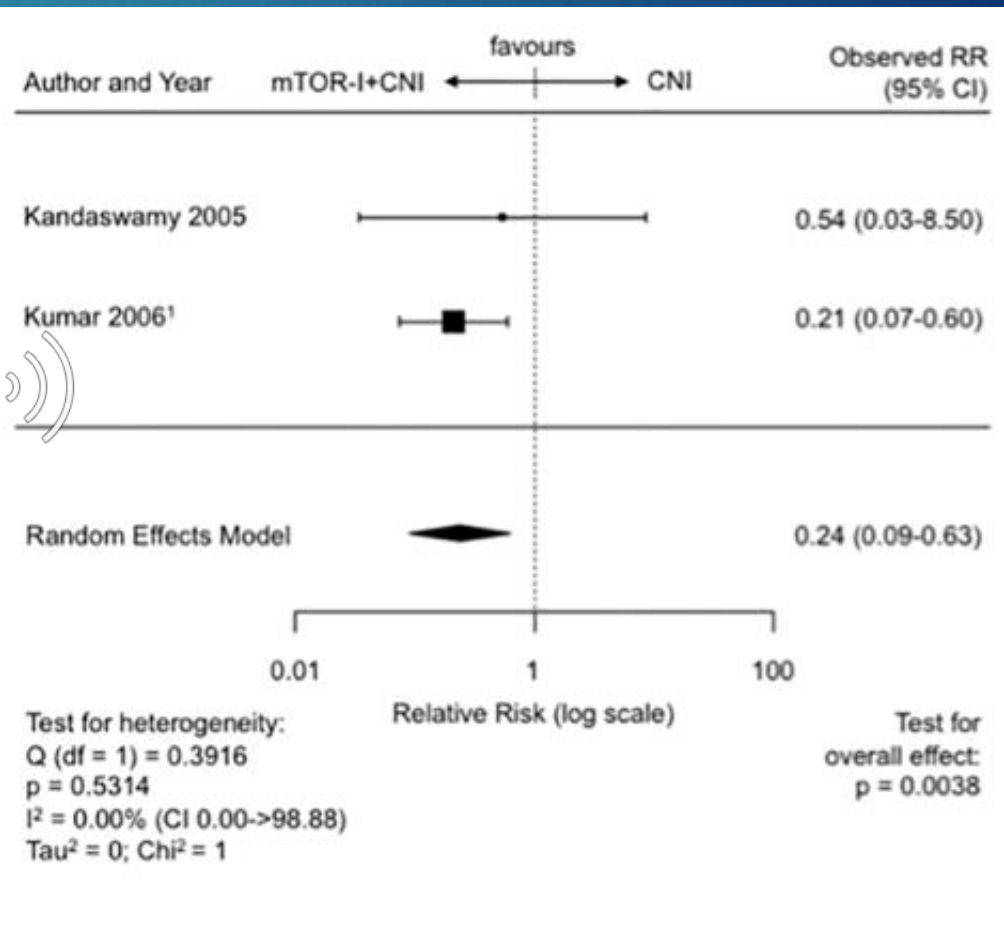


When NMSCs were excluded 8 RCTs could still be included in the statistical analysis. Here, the relative risk was also significantly reduced under mTOR-Is (RR 0.43, CI 0.24±0.77, p = 0.0046

PLOS ONE | https://doi.org/10.1371/journal.pone.0194975 April 16, 2018

Malignancies on mTOR-I+CNI vs. CNI treatment post transplantation





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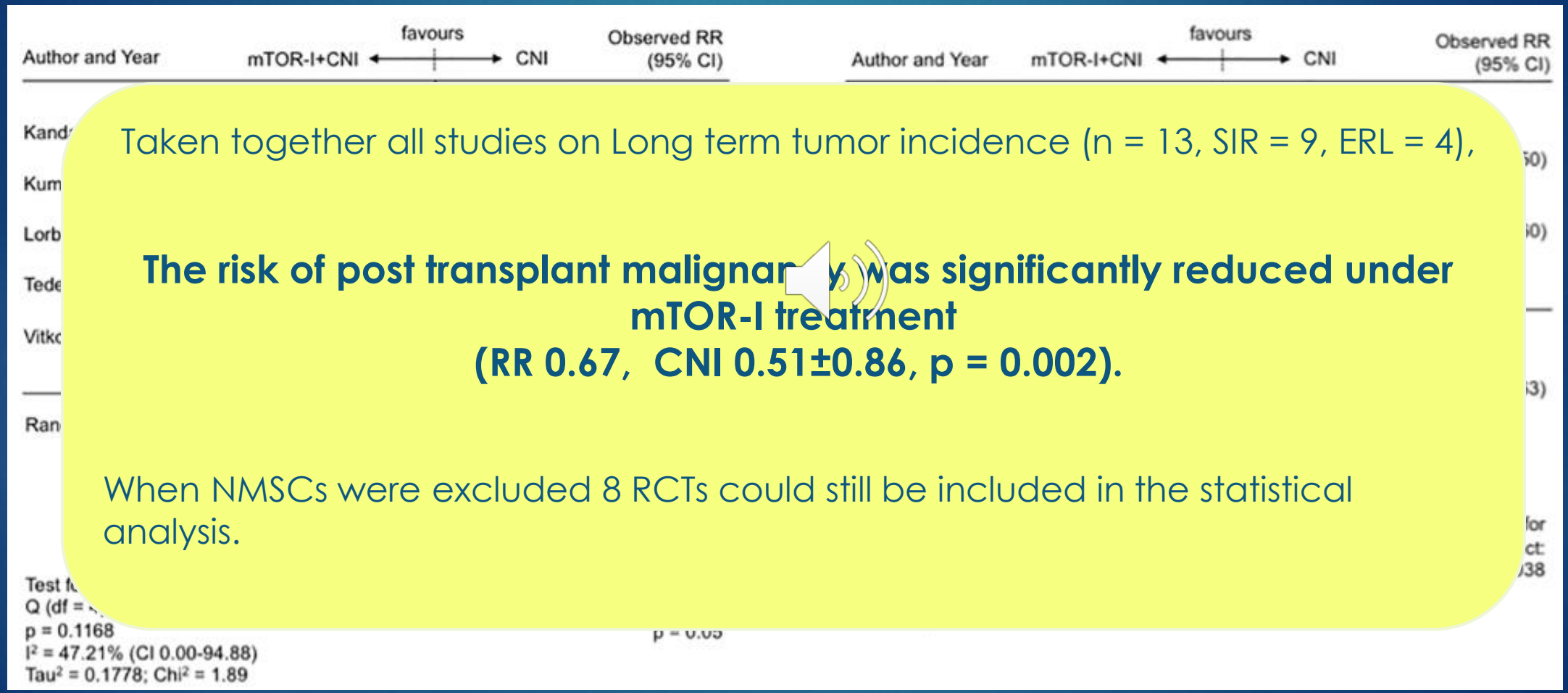


Taken together all studies on Long term tumor incidence (n = 13, SIR = 9, ERL = 4),

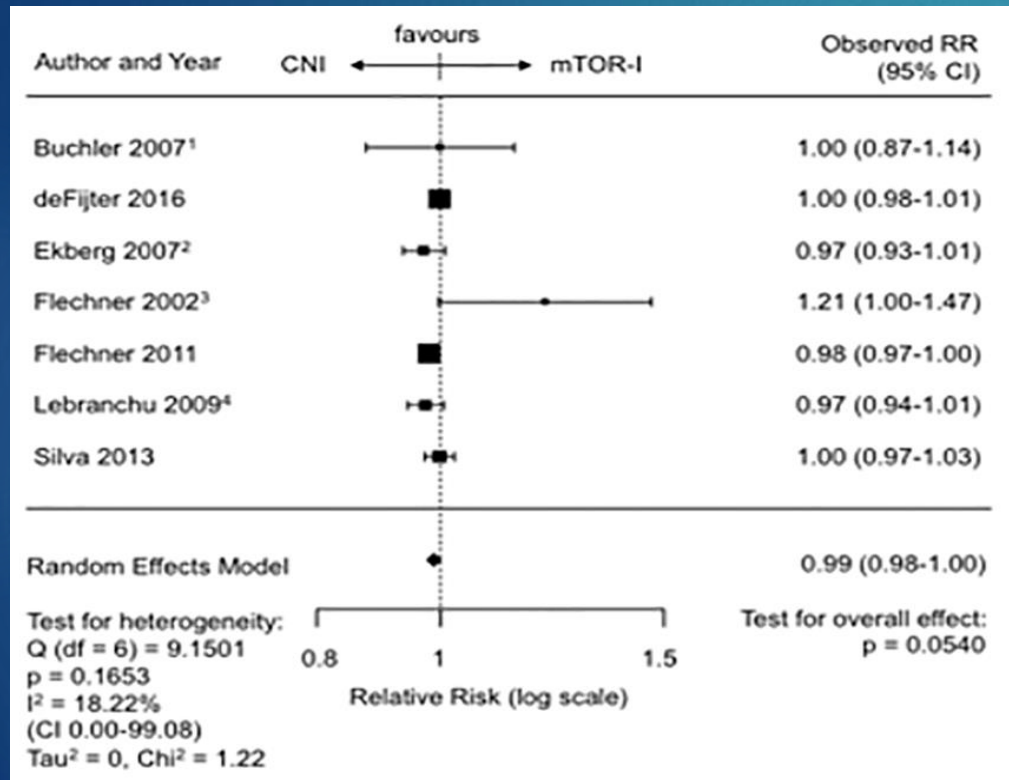
The risk of post transplant malignancy was significantly reduced under mTOR-I treatment (RR 0.67, CNI 0.51±0.86, p = 0.002).

When NMSCs were excluded 8 RCTs could still be included in the statistical analysis.

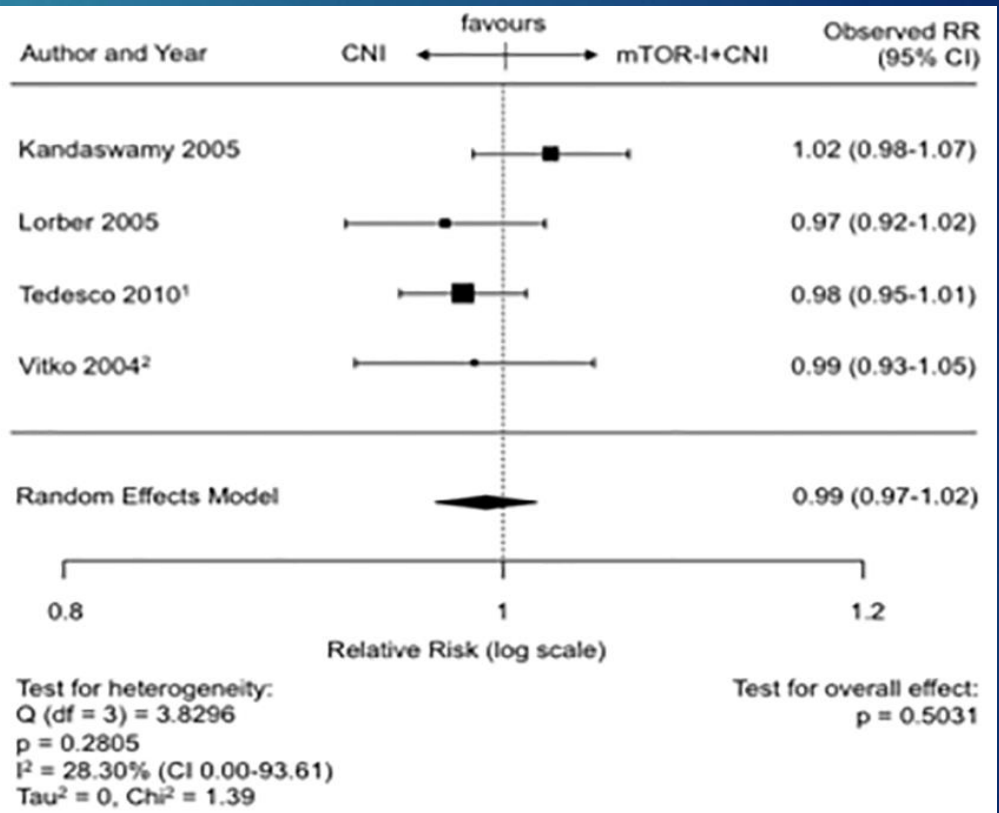
PLOS ONE | https://doi.org/10.1371/journal.pone.0194975 April 16, 2018

Graft survival (censored for death)(mTOR-I vs. CNI (monotherapy or combined with CNI)

graft survival censored for death on mTOR-I vs. CNI



graft survival censored for death on mTOR-I+CNI vs. CNI



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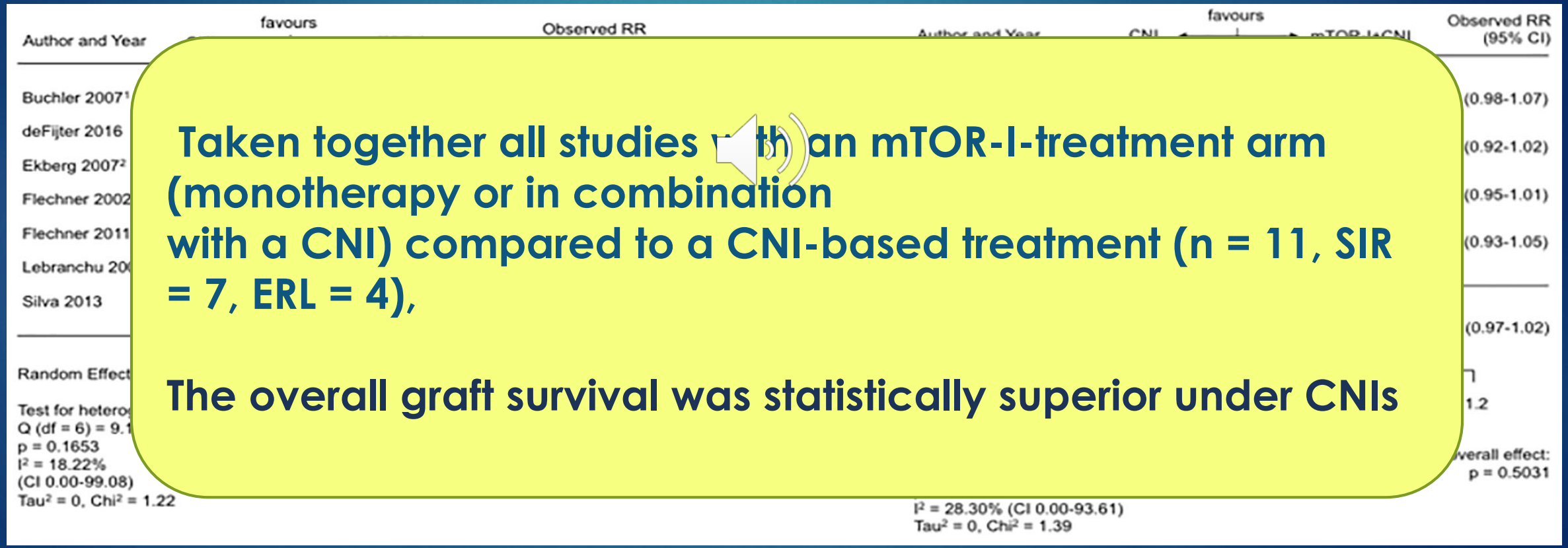
Graft survival (censored for death)(mTOR-I vs. CNI (monotherapy or combined with CNI)

graft survival censored for death on mTOR-I vs. CNI

graft survival censored for death on mTOR-I+CNI vs. CNI



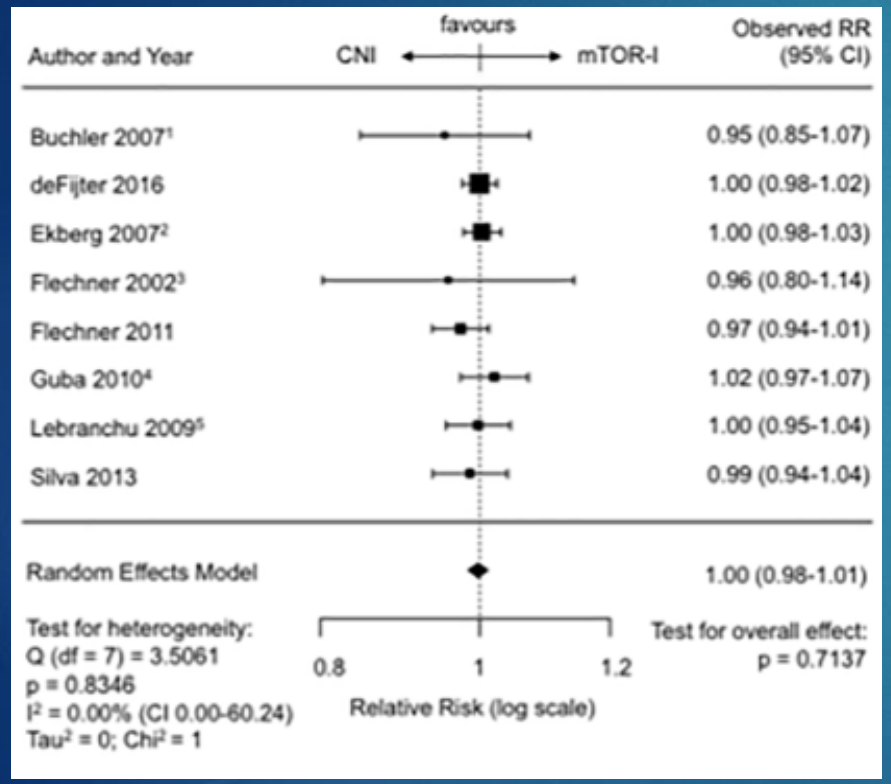
Taken together all studies with an mTOR-I-treatment arm (monotherapy or in combination with a CNI) compared to a CNI-based treatment (n = 11, SIR = 7, ERL = 4),

The overall graft survival was statistically superior under CNIs

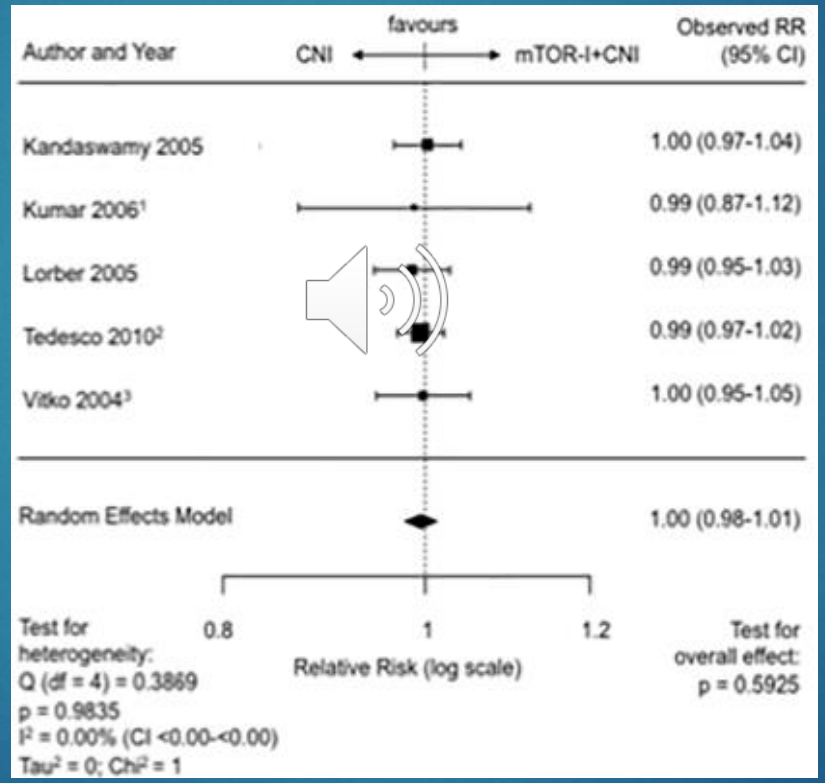
PLOS ONE | https://doi.org/10.1371/journal.pone.0194975 April 16, 2018

Patient survival post transplantation

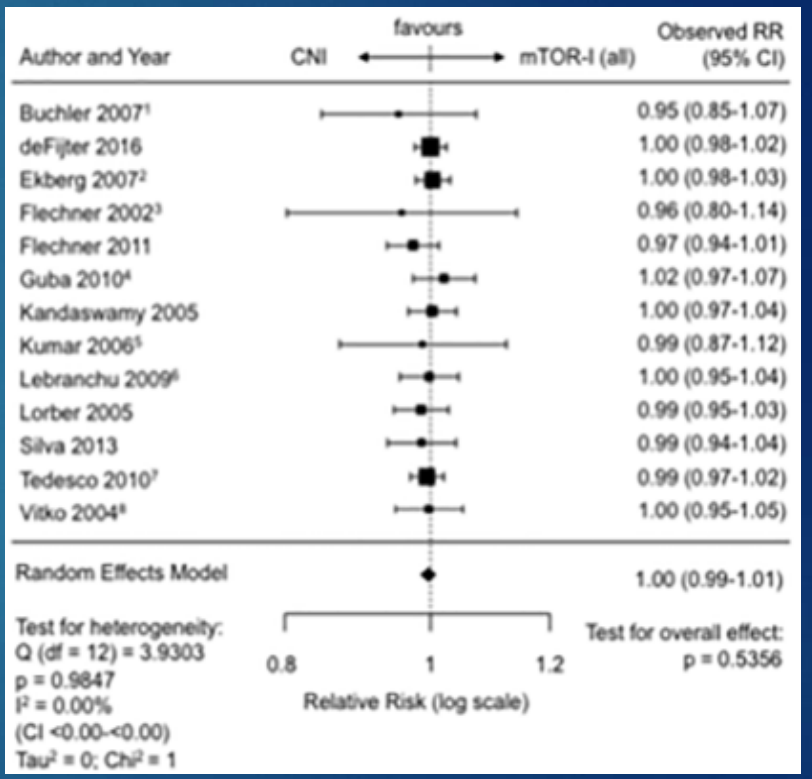
mTOR-I vs. CNI



mTOR-I + CNI vs. CNI



mTOR-I vs. CNI (monotherapy or combined with CNI

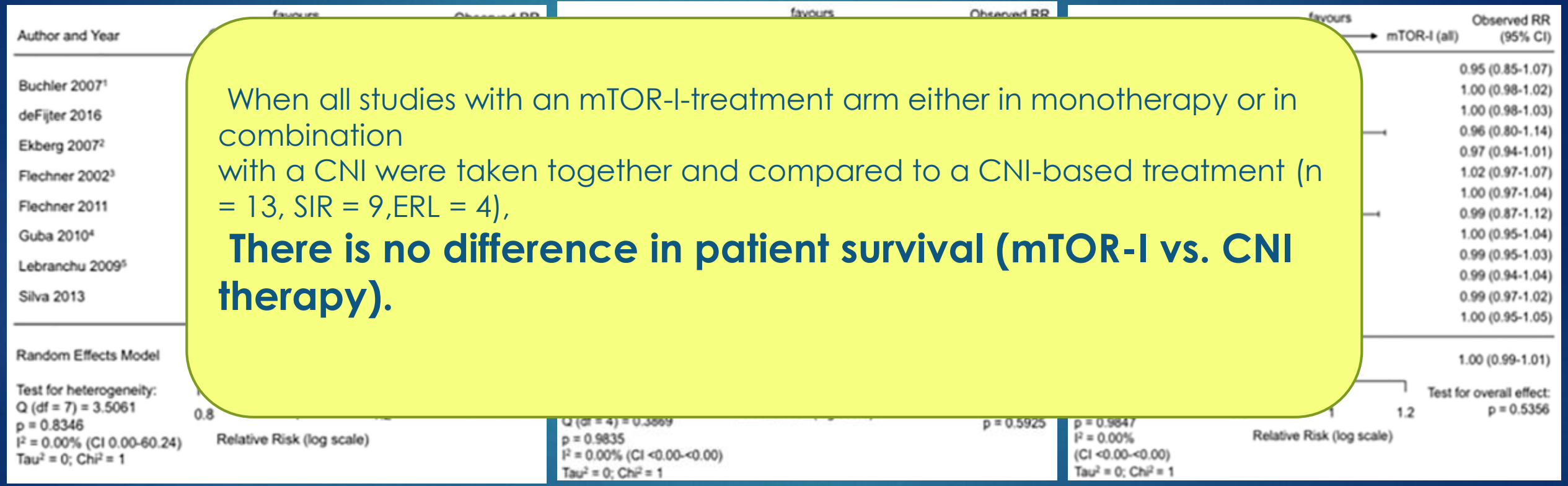


Patient survival post transplantation

mTOR-I vs. CNI

mTOR-I + CNI vs. CNI

mTOR-I vs. CNI (monotherapy or combined with CNI



When all studies with an mTOR-I-treatment arm either in monotherapy or in combination
with a CNI were taken together and compared to a CNI-based treatment (n = 13, SIR = 9,ERL = 4),

There is no difference in patient survival (mTOR-I vs. CNI therapy).

In conclusion

- The mTOR signaling pathway is closely related to tumors, and it is closely related to its cell growth, metabolism, apoptosis and autophagy

Increasing investigations of mTOR signaling in cancer cells has provided the platforms towards novel therapeutic strategies that will safely and effectively eradicate cancers.

In conclusion

- Early initiation or conversion to mTORI-I within 3 months of kidney transplantation may reduce the future risk of cancer, when compared with patients remaining on CNI-based regimens.
- The primary effect is against NMSC, but there also exists a significant effect against other tumors.
- The predominant part of the anti-tumor effect remains present even when administered in combination with a CNI.
- There is no increased mortality nor graft loss under currently used mTOR-I based regimen