IMPORTANCE OF CYTOMEGALOVIRUS INFECTION IN BREAST CANCER

Afsar Rahbar, PhD, Senior researcher
Karolinska Institutet, Stockholm, Sweden

CYTOMEGALOVIRUS (CMV)

- Infects 50-90% of the world´s population
- Establishes latency and persistence
  - Adapted to persist in the immunocompetent host
  - Evolutionary pressure to develop mechanisms that affect cell functions and the immune system
- 252 genes; encodes over 750 proteins
  - Only 50 are essential for virus replication

ACTIVE CMV INFECTION IN MALIGNANCIES

- 99-100% of malignant glioblastoma
- 100% of neuroblastoma
- 92% of medulloblastoma
- >90% of colon cancer
- >90% of prostate cancer
- >90% of breast cancer
- >90% of rhabdomyosarcoma
- >90% of epidermoid cancer

- Not found in ALL (Acute Lymphoblastic Leukemia), AML (Acute myeloid leukemia)

- Present in 96-98% of lymphnode and brain metastases of colon and breast cancer

- Elevation in serum CMV-IgG antibody levels has been reported to precede the development of breast cancer in some women.

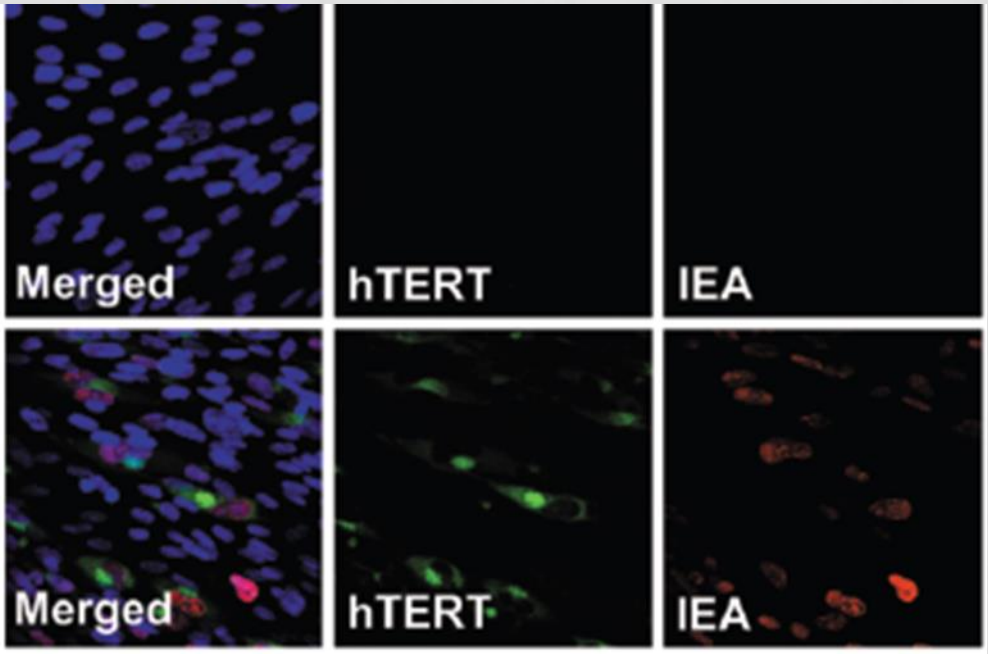
CMV INFLUENCES THE REGULATION OF VARIOUS CELLULAR PROCESSES “CMV ONCOMODULATION”:

- Inhibits cellular differentiation (of neuronal stem cells, induces stemness)
- CMV IE proteins are transcription factors that control cellular gene expression
- 16 CMV microRNA can control cellular gene expression
- Proliferation / cell cycle control (p53, Rb, p21, cyclins, PTEN, telomerase activity, Connexin 43)
- Affects intracellular signaling pathways; PI3K, AKT, mTOR, β-cathenin, GSK-3b, STAT3P
- Chromosomal instability and mutations
- Regulates epigenetic functions; CMV affects DNMTs and induce hypomethylation
- Angiogenesis (induces VEGF production, thrombospondin)
- Migration
- Immune evasion mechanisms
- Induced inflammation (cyclooxygenase-2;Cox-2 and5-lipoxygenase;5-LO)
- Inhibits apoptosis

CMV CAN BE ONCOGENIC

- CMV-IE72 induces significantly high telomerase activity through direct interaction with the hTERT promoter

- Induction of telomerase activity is a key event in cancer development and a common phenomenon of oncogenic viruses



CMV induces hTERT expression

Stråat et al JNCI 2009; April:101;488-97

CMV US28 HAS ONCOGENIC PRPOPERTIES

- **CMV-US28** is a constitutively active chemokine receptor

  - Induces VEGF production through induction of COX-2 and IL-6.

  - Induces STAT-3 phosphorylation leading to enhanced cellular proliferation.

  - Promotes tumor formation in vivo in transgenic mice (through inhibition GSK-3β,accumulation of β-catenin)

Maussang D. et.al. PNAS 2006;103:13068-13073

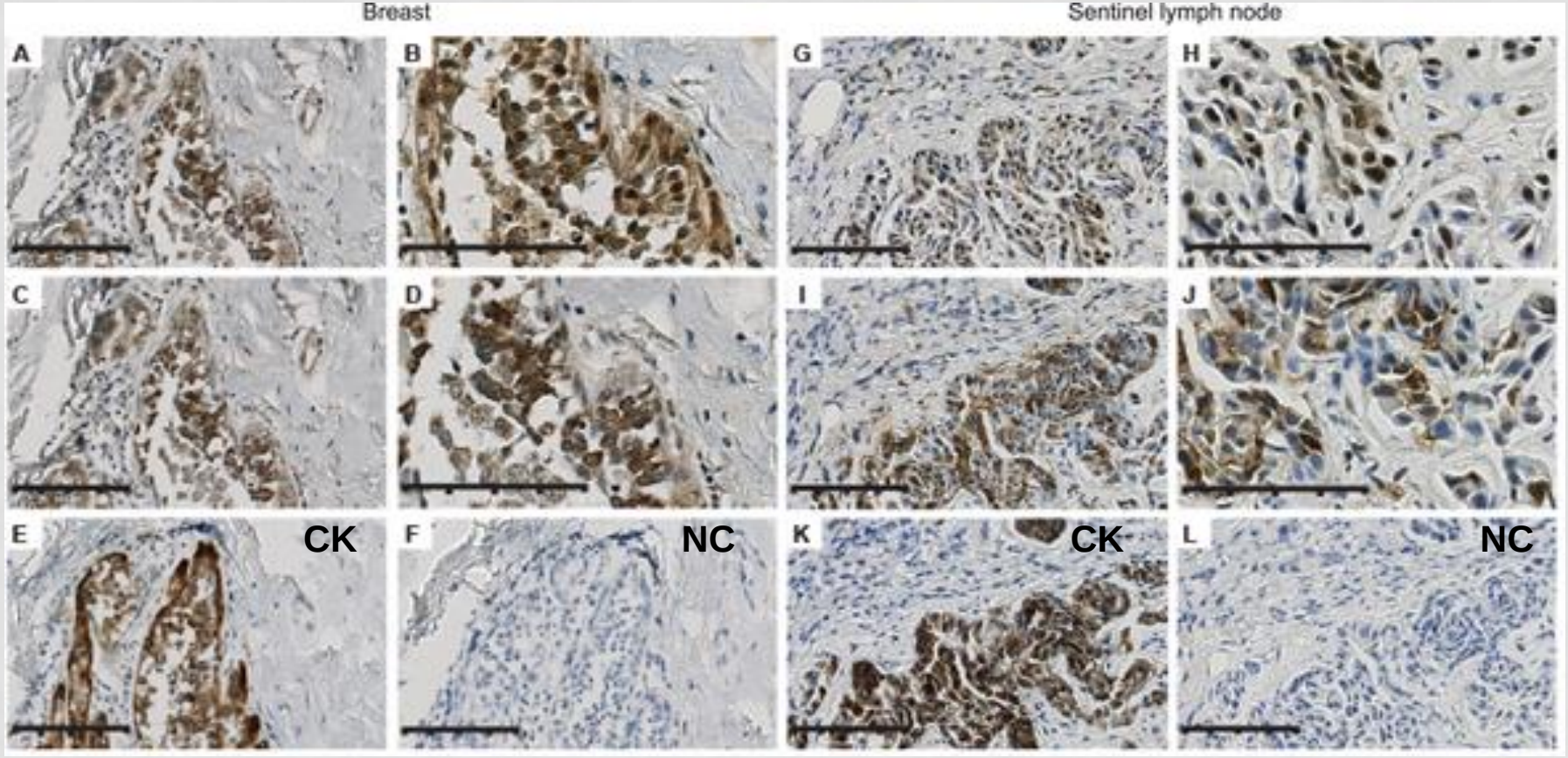
DOES CMV PLAY AN IMPORTANT ROLE IN BREAST CANCER?

MAJOR SIGNALING PATHWAYS TARGETED BY CMV AND ACTIVATED IN BREAST CANCER

Signaling pathways altered upon HCMV infection	Effector viral protein
JAK-STAT3	US28, IE1
PI3K-AKT	IE1, IE2
MAPK-ERK	gB
Wnt/beta-catenin	Not known

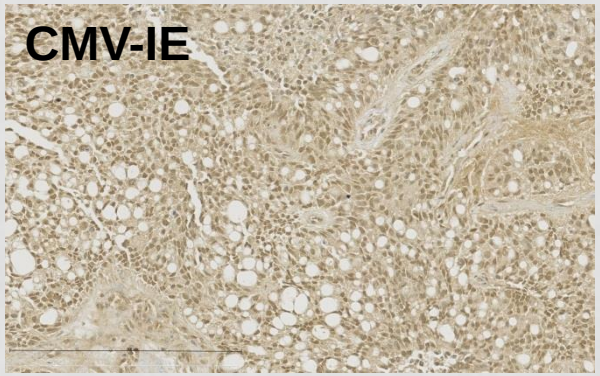
SlingerE. , et al. SciSignal (2010). ReitsmaJM,et al. J Virol (2013).LiuCY, et al.BreastCancerRes (2013). YuY,et al. J Virol (2002). SauraC,et al. Clin CancerRes (2014). SmithMS, et al. J LeukocBiol (2004). SerraV,et al. Clin CancerRes (2012). BoyleKA, et al. MolCellBiol (1999). JohnsonRA,et al. J Virol (1998). ReevesMB,et al. ProcNatlAcadSciUSA (2012). WilhelmSM,et al. CancerRes (2004). RinehartJ, et al.ClinOncol (2004). AngelovaM,et al.PLoSPathog (2012). BaoR, et al.PLoS One (2012).

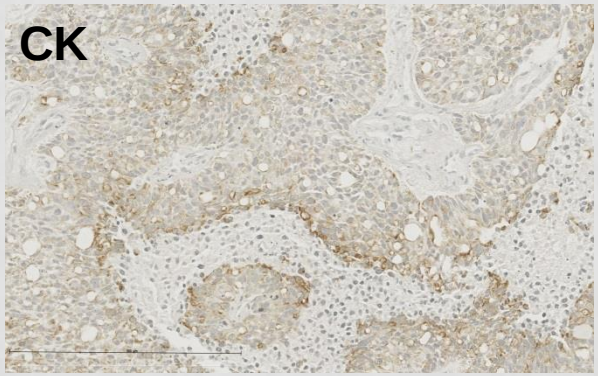
HIGH PREVALENCE OF CMV INFECTION IN BREAST CANCER AND METASTATIC SENTINEL LYMPH NODES

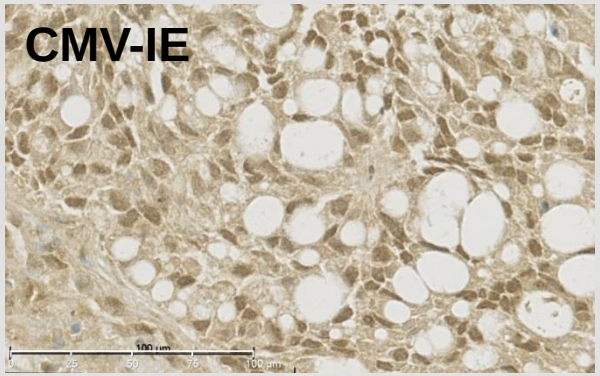


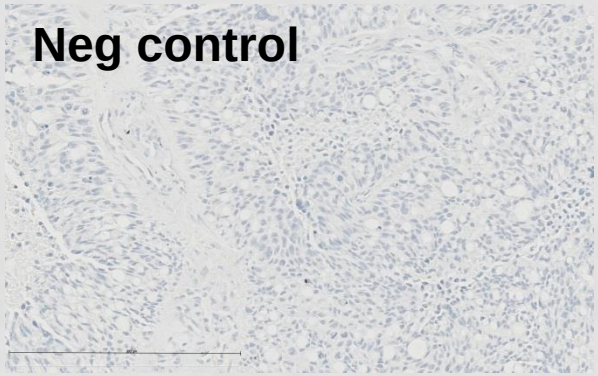
Taher C,. PLoS ONE 8(2): e56795.

HIGH PREVALENCE OF CMV-IE IN BRAIN METATESIS FROM PATIENTS WITH BREAST CANCER

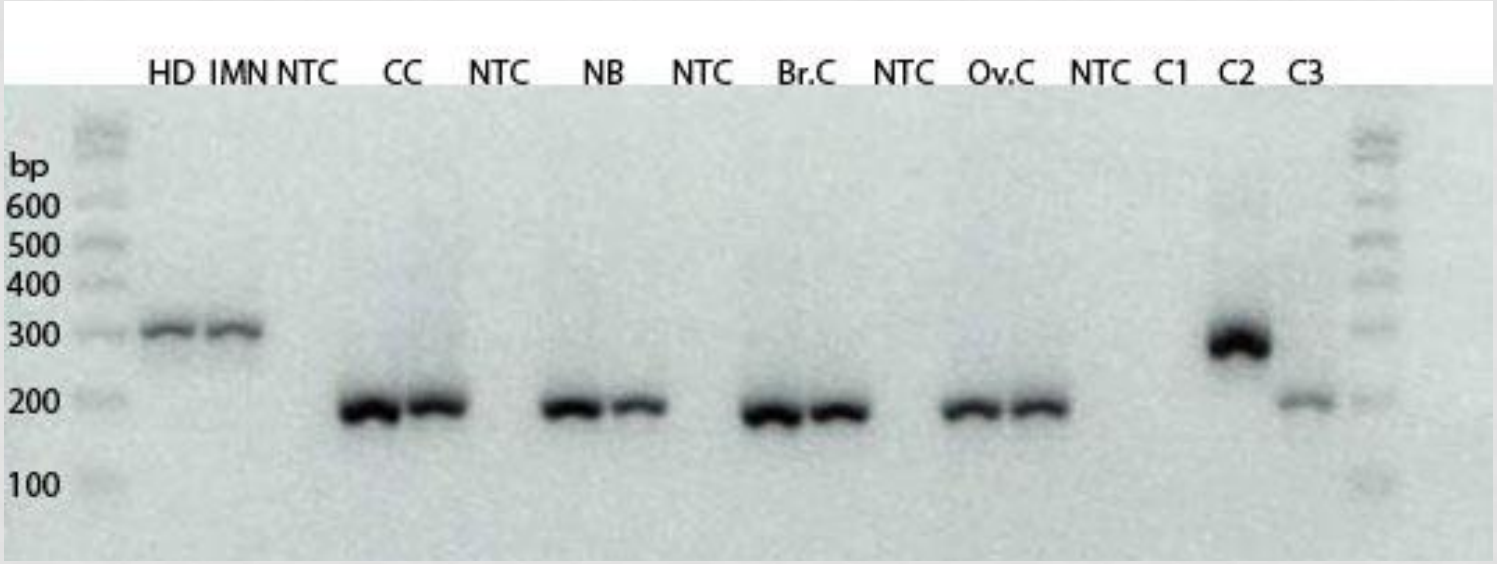








A CMV VARIANT WITH A DELETION IN A CMV GENE IS THE MOST PREVALENT CMV STRAIN IN CANCER OF DIFFERENT ORIGIN

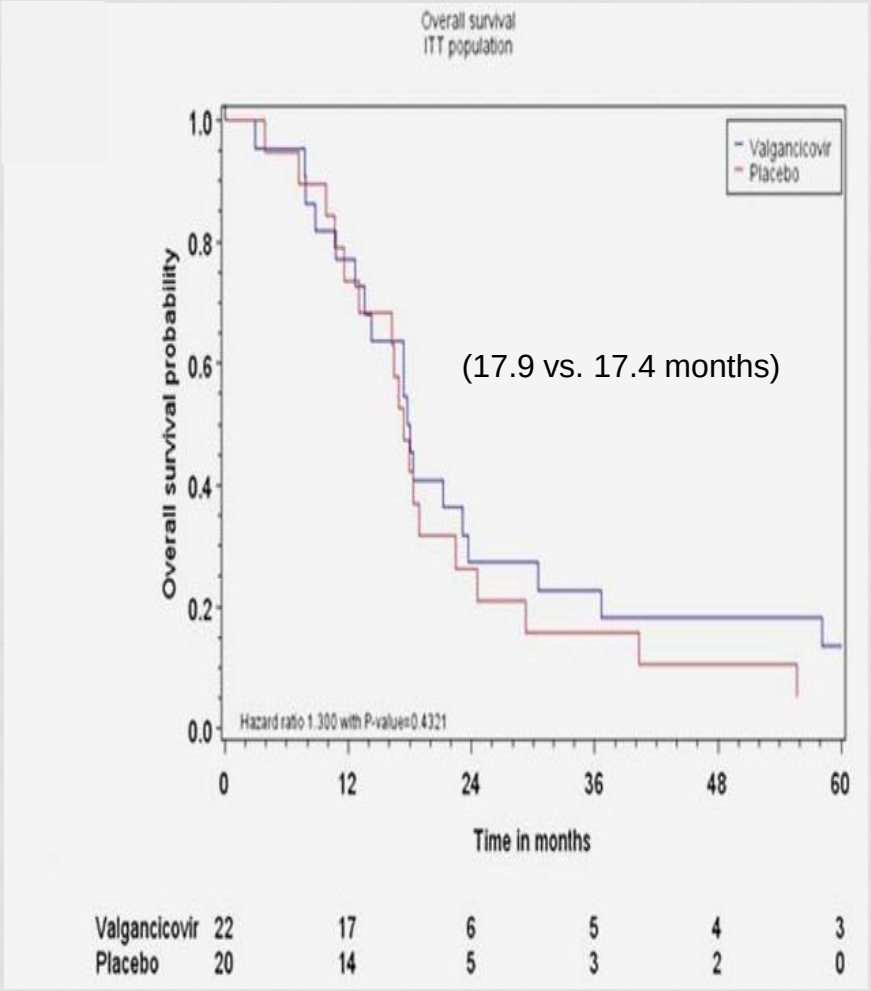


HD Healthy donor, IMN infectious mono nucleosis, CC colon cancer, NTC non template control, NB neuroblastoma, BrC breast cancer, Ov.C overian cancer,
C1 control 1 non-infected fibroblast, C2 DNA from infected fibroblast, C3 cDNA from infected fibroblast

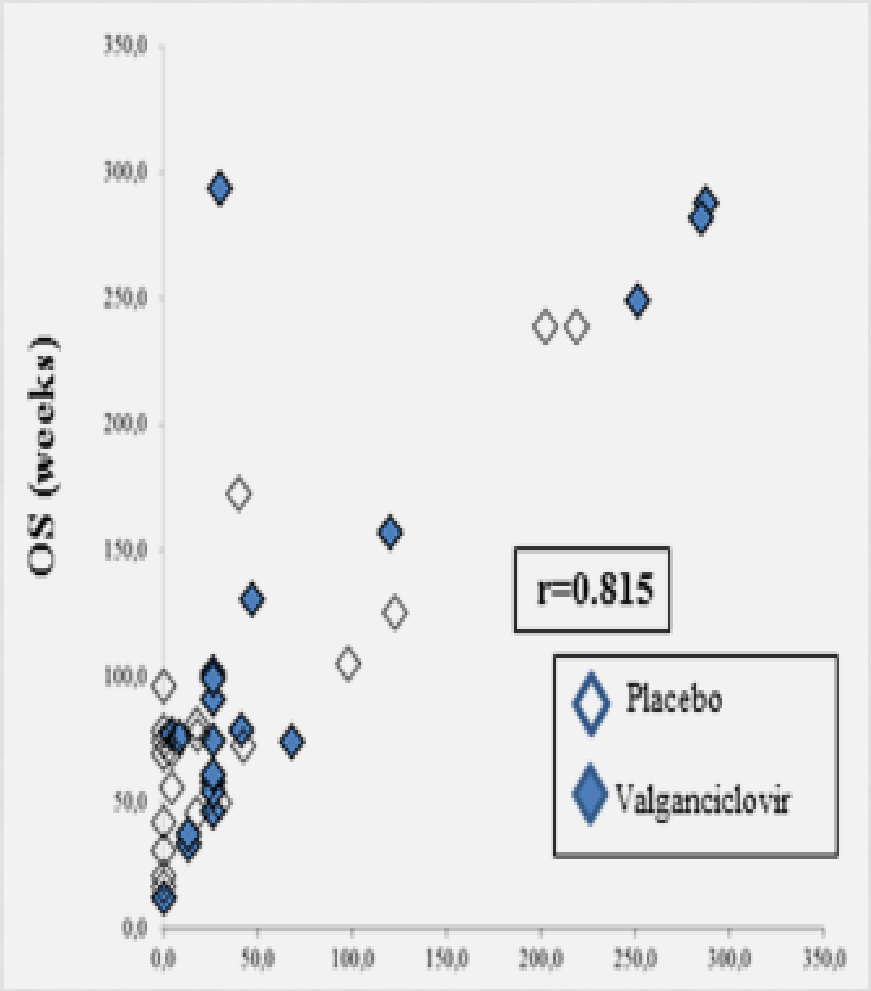
EFFICACY AND SAFETY OF VALCYTE® AS AN ADD-ON THERAPY IN PATIENTS WITH MALIGNANT GLIOBLASTOMA AND CYTOMEGALOVIRUS (CMV) INFECTION (VIGAS STUDY)

International Journal of Cancer
Volume 133, Issue 5, pages 1204-1213, 13 MAR 2013

VIGAS CLINICAL STUDY

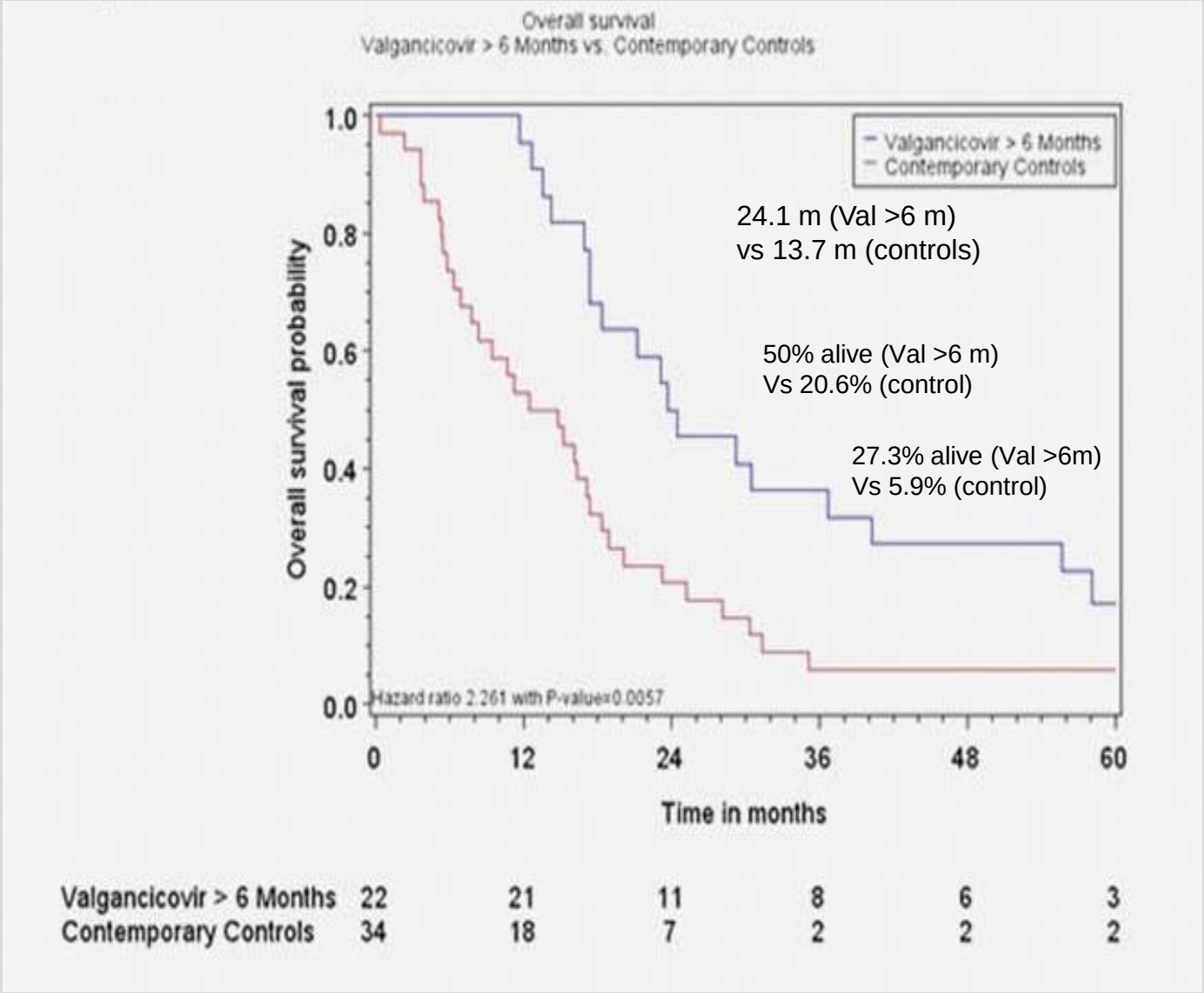


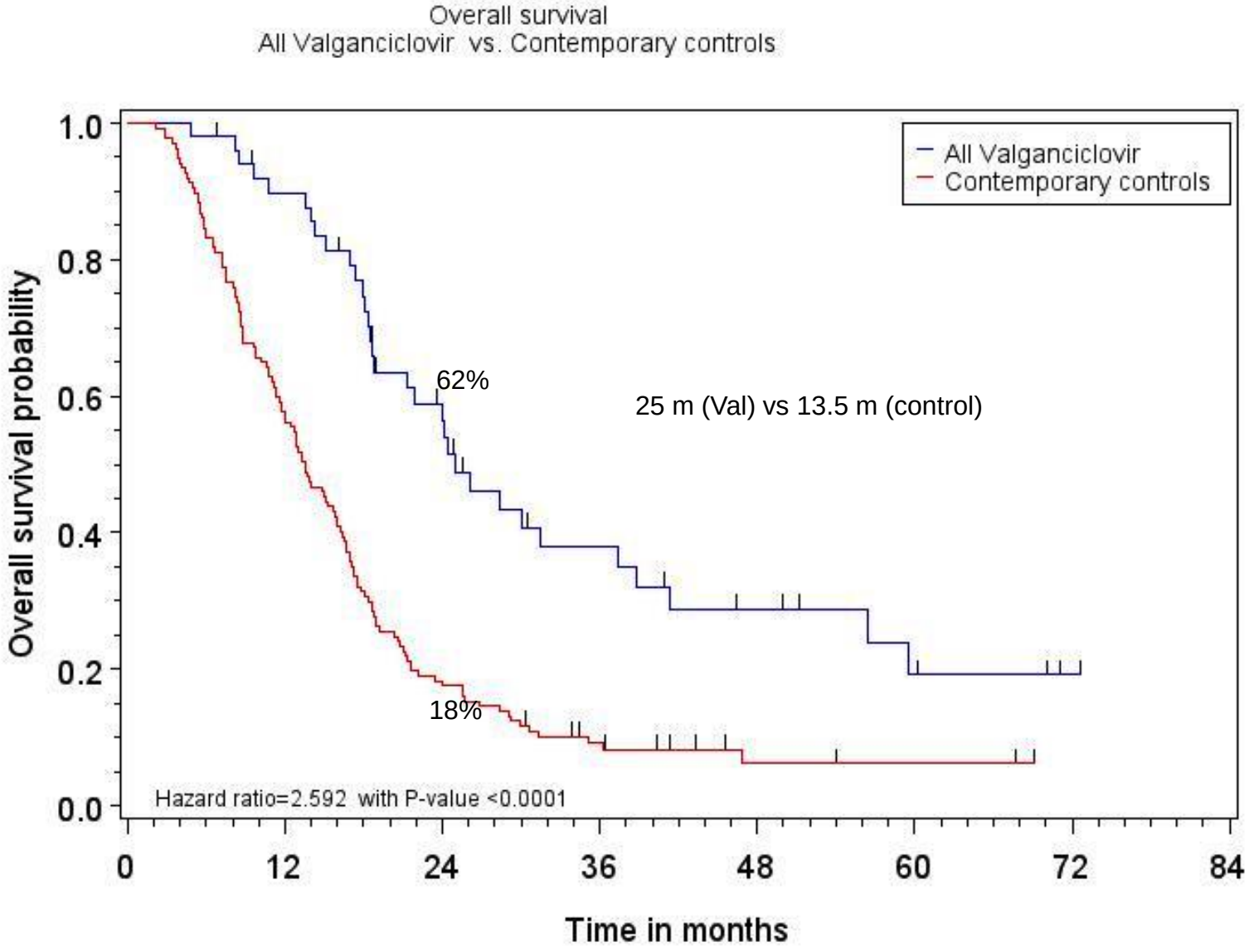
(17.9 vs. 17.4 months)



Survival of GBM patients correlate with duration of Valcyte treatment.

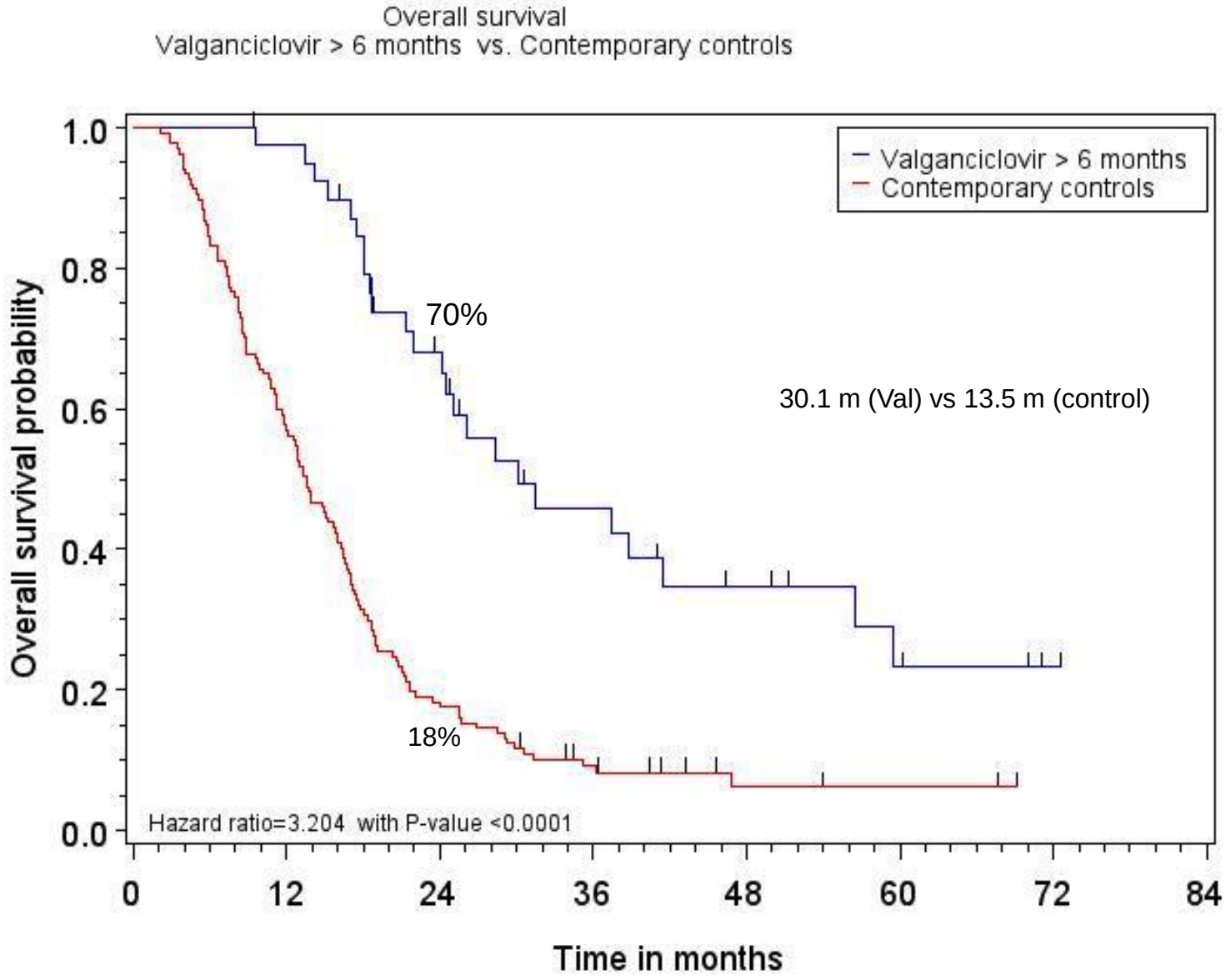
LONGER OVERALL SURVIVAL IN GBM PATIENTS RECEIVING VALGANCICLOVIR FOR AT LEAST 6 MONTHS





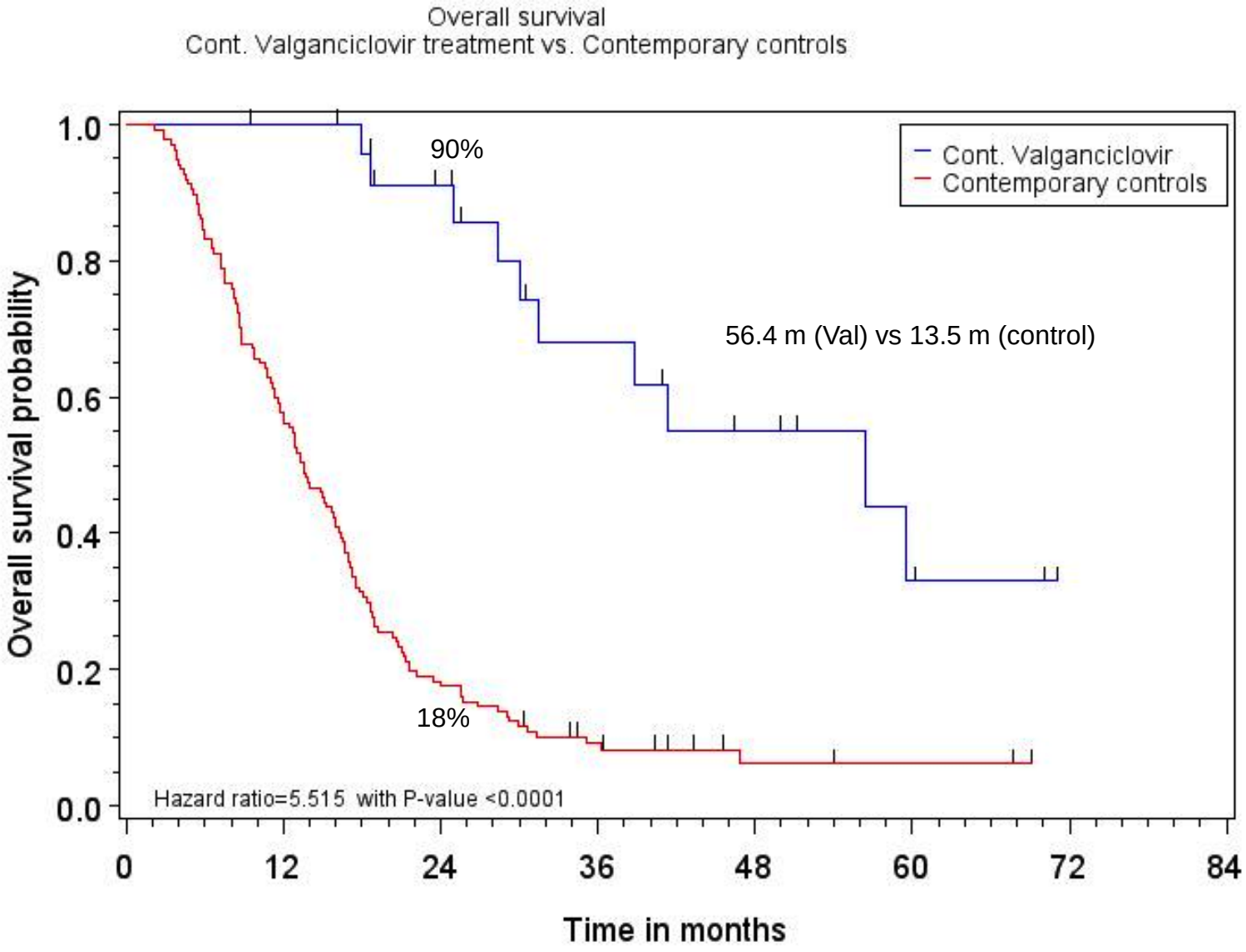
All Valganciclovir	50	43	24	13	8	4	1	0
Contemporary controls	137	79	25	10	3	2	0	0

N Engl J Med; 369:985-986September 5, 2013



Valganciclovir > 6 months	40	38	23	13	8	4	1	0
Contemporary controls	137	79	25	10	3	2	0	0

N Engl J Med; 369:985-986September 5, 2013



Cont. Valganciclovir	25	24	18	11	7	3	0	0
Contemporary controls	137	79	25	10	3	2	0	0

N Engl J Med; 369:985-986September 5, 2013

CONCLUSIONS

- CMV infection is highly prevalent in breast cancer, sentinel lymph nodes and in brain metastasis from breast cancer.
- Our observations raise the question whether CMV is just an “epiphenomenon” or crucial player in the progression of cancer needs further investigations.
- Future studies in larger cohort are needed to further evaluate CMV as prognostic marker for breast cancer and its metastasis, to assess the possible role of CMV in metastasis formation, and to determine whether CMV targeted therapies have a place in the treatment of brain metastasis.

ACKNOWLEDGEMENTS

Roche

BILTEMA FOUNDATION

nxt2b

Tore Nilsons Stiftelse för medicinsk forskning

RATOS

Torsten Söderbergs Stiftelse

JOCHNICK FOUNDATION
STICHTING AF JOCHNICK FOUNDATION

Karolinska Institutet

STEN A OLSSONS STIFTELSE FÖR FORSKNING OCH KULTUR

Cancerfonden

Svenska Läkaresällskapet

Centre for molecular medicin(CMM),
Unit for Microbial Pathogens,
Karolinska Institutet,
Karolinska University Hospital, Stockholm, Sweden

Magnus Bergvalls Stiftelse

Lindhés Advokatbyrå AB

SVENSKA SÄLLSKAPET FÖR MEDICINSK FORSKNING

Familjen Erling-Perssons Stiftelse

INGABRITT OCH ARNE LUNDBERGS FORSKNINGSSTIFTELSE

JANE AND DAN OLSSON FOUNDATIONS