Revisión Presentaciones Orales

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Sevilla

Felicitaciones a ambos

Asociación entre pérdida de PTEN, supervivencia y respuesta en cáncer de próstata resistente a la castración (CPRC) tratado con abiraterona

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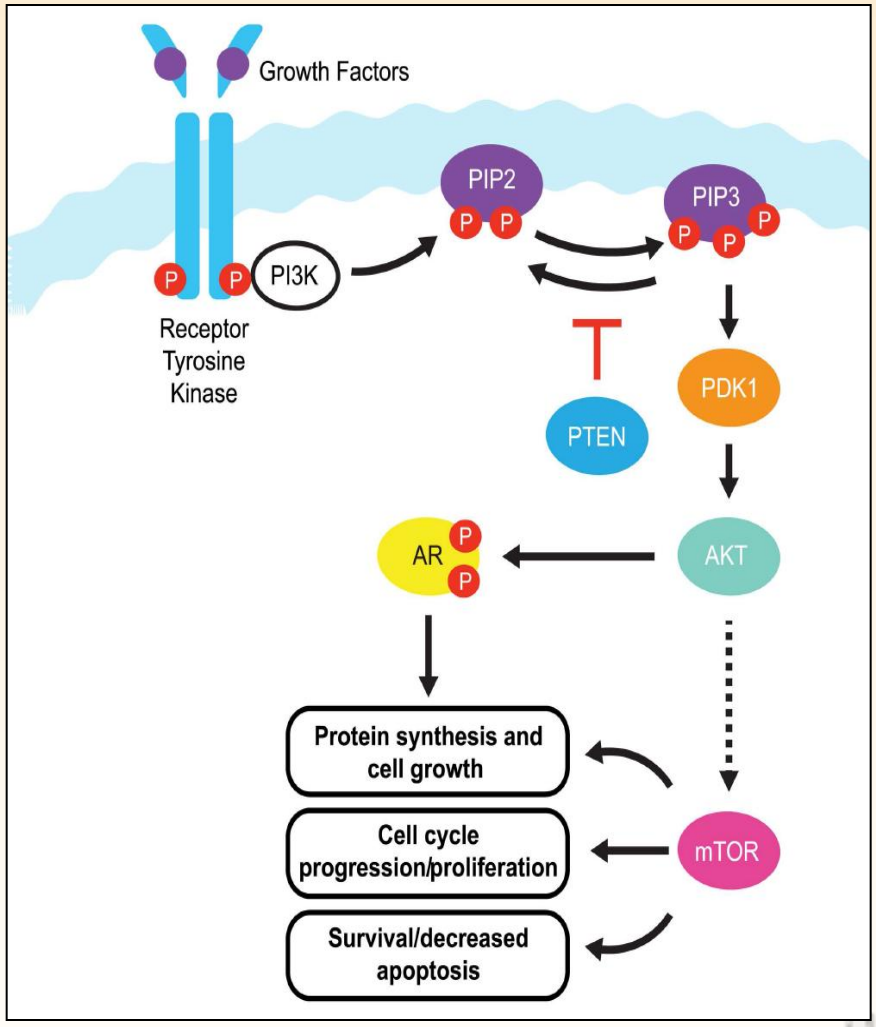
Check List

- ❑ Pregunta científica del estudio es correcta?
- ❑ La ejecución es la adecuada?
- ❑ Son los resultados relevantes científicamente?
- ❑ Tiene aplicabilidad

Pregunta Científica

- "Existe **asociación** entre **la perdida de PTEN** y parámetros como **supervivencia** y **respuesta** en pacientes con **mCRPC** tratados con acetato de abiraterona"

PI3K-AKT-mTOR



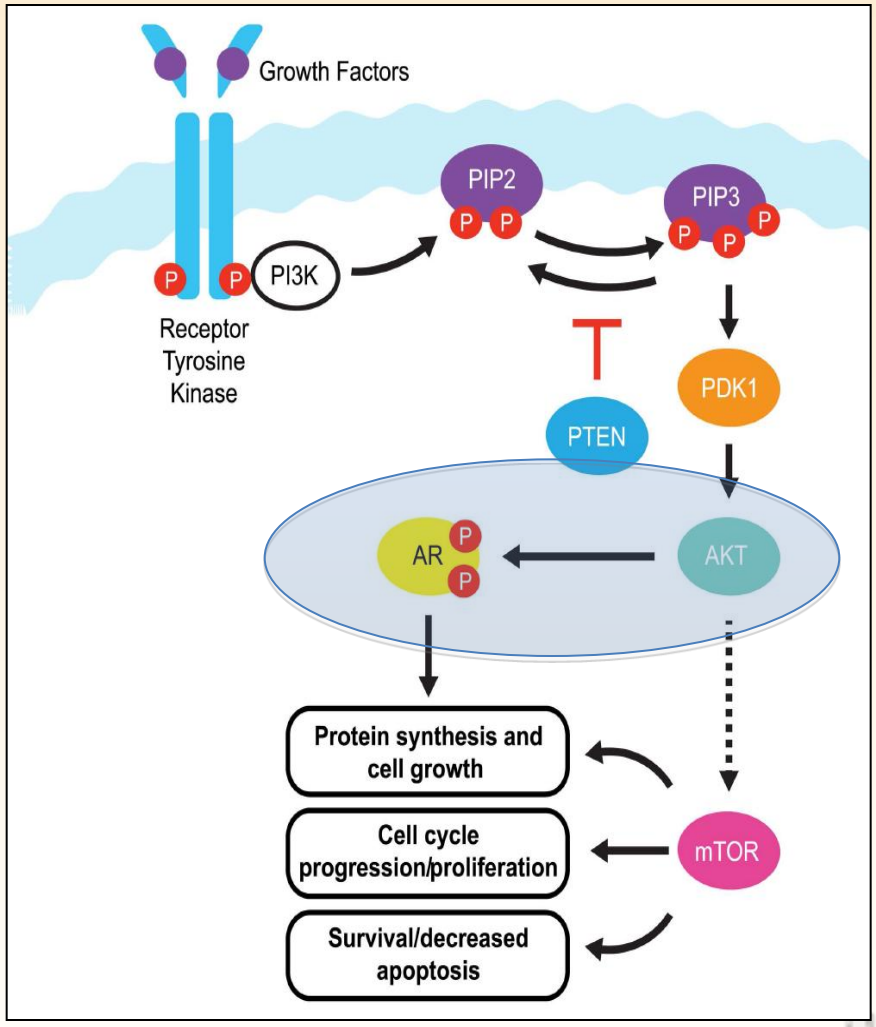
One pathway with a prominent role in prostate cancer is the **phosphatidylinositide 3-kinases (PI3K) signaling pathway**

Current estimates suggest that this signaling pathway is **up-regulated** in 30–50% of prostate cancers

FeldmanBJ,FeldmanD.The development of androgen-independent Prostate cancer. *NatRevCancer* (2001) **1**:34–45

DeVelasco MA,Uemura H.Pre- clinical remodeling of human prostate cancer through the PTEN/AKT pathway. *Adv Urol* (2012) **2012**:419348

PI3K-AKT-mTOR



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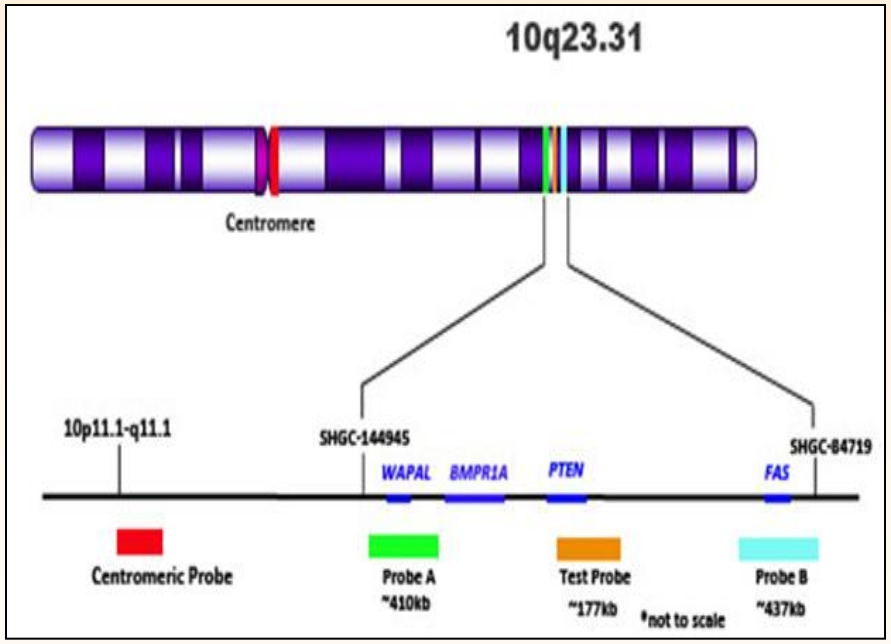
PTEN

It is a **negative regulator** of the **PIK3/Akt** survival pathway and is **the most frequently deleted tumor suppressor gene in prostate cancer**



PTEN is a **tumor suppressor gene** located at 10q23

This region is known to exhibit **high rates of loss of heterozygosity** in a variety of human malignancies, including **prostate cancer**

Kwabi-Addo B,Giri D,Schmid tK, et al.Haploinsufficiency of the PTEN tumor suppressor gene promotes prostate cancer progression. *ProcNatlAcadSciUSA* (2001) **98**:11563–8

PTEN

- Early reports on the *PTEN* gene focused on DNA **point mutations** that led to inactivation of PTEN protein function

- The ***PTEN* gene** may also be inactivated by **epigenetic events** such as promoter methylation

- Relatively **large deletions** and **genomic rearrangements** affecting *PTEN* are most prevalent in prostate cancer

Dong JT. Prevalent mutations in Prostate cancer. *J Cell Biochem* (2006) **97**:433–47.

Check List

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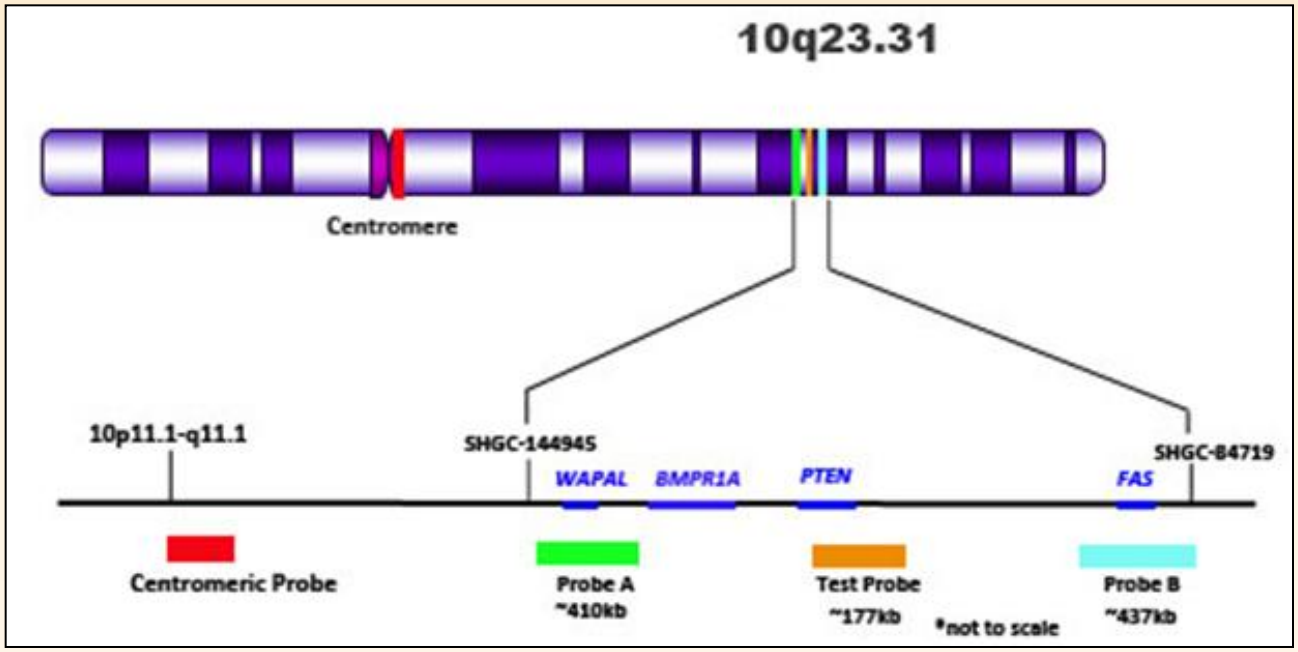
How should PTEN status be determined?

- Fluorescence in *situ hy*bridization(**FISH)** analyses provided robust evaluation of the genomic status of PTEN and became gold standard

- Studies **initially** used a two-color (FISH) assay for **PT*EN co*py number detection** in formalin fixed paraffin embedded tissue preparations

- Yet, variability was 20-60%

FISH



The PTEN probe consists of four colors: red, orange, green, aqua

The red fluor localizes to the centromere of chromosome 10, while **the orange fluor is specific for the gene of interest (PTEN)**.
The green fluor localizes to the WAPAL gene and is centromeric to PTEN, while the aqua fluor localizes to the FAS gene and is telomeric to PTEN.

- More recently, **a four-color FISH assay** containing **two additional control probes** flanking the *PTEN* locus with a lower false-positive rate was reported

Yoshimoto et al. PTEN genomic deletions that characterize aggressive prostate cance originate close to segmental duplications *GenesChromosomesCancer* (2012) **51**:149–60.

PTEN Staining

Human Pathology (2014) **45**, 522–532

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Optimal protocol for PTEN immunostaining; role of analytical and preanalytical variables in PTEN staining in normal and neoplastic endometrial, breast, and prostatic tissues☆,☆☆

Did Lorente et al used the proper method for evaluating PTEN Status?
I am not 100% sure

Check List

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- ☐ La ejecución es la adecuada? **NOT SURE**
- ☐ Son los resultados relevantes científicamente?

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- **Son los resultados relevantes científicamente?**

Scientific Relevance

- The **importance of *PTEN* genomic status** for PC **prognosis** is **compelling**

Combined with the detection of **other critical genomic biomarkers for prostate cancer** such as ***ERG***, ***androgen receptor***, and ***MYC***, the evaluation of *PTEN* genomic status has proven to be invaluable for patient stratification and management.

Do we have any information about ERG, AR or MYC in Lorente's work?

Check List

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- ❑ **Son los resultados relevantes científicamente?☑**
- ❑ **Aplicabilidad de los resultados**

Aplicable?

- To me these results are considered only hypothesis generating and need further refinement

Check List

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- ❑ La ejecución es la adecuada? NOT SURE
- ❑ Son los resultados relevantes científicamente? ☑
- ❑ **Aplicabilidad de los resultados? NOT SURE**

Conclusions

- 1.-The effort of Lorente et al should be acknowledged and the group congratulated
- 2.-It adds to the value of PTEN as a relevant biomarker in PC [prognostic/predictive?]
- 3. However some methodological issues are considered
  - Method of PTEN evaluation
  - Validity of hh sensitive determinations
- 4. Still non aplicable to routine inical practice

Análisis actualizado de UROTELIAL HER 2: estudio fase II, multicéntrico, de cisplatino, gemcitabina y trastuzumab en el tratamiento de 1ª línea de carcinoma urotelial de células transicionales avanzado con sobreexpresión de Her2.

Gema Bruixola[1], Enrique Gallardo[2], Monsterrat Domenech[3], Aranzazu González del Alba[4], Jose Luís Pérez Gracia[5], Oscar Juan[6] , Luis Antonio Fernández[7], Gaspar Reynés[1]

1) Servicio de Oncología Médica. Hospital Universitari i Politècnic La Fe. Valencia.
2) Servicio de Oncología Médica. Hospital Parc Taulí. Sabadell.
3) Servicio de Oncología Médica. Hospital Althaia. Manresa.
4) Servicio de Oncología Médica. Hospital Son Espases. Palma de Mallorca.
5) Servicio de Oncología Médica. Clinica Universitaria de Navarra. Pamplona.
6) Servicio de Oncología Médica. Hospital Arnau de Vilanova. Valencia
7) Servicio de Oncología Médica. Consorci Sanitari de Terrassa. Terrassa.

- Excellent presentation
- Great effort/Great challenge
- A small phase II study is always a methodological challenge

Check List

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- ❑ Es la población del estudio representativa?
- ❑ Es la ejecución correcta?
- ❑ Son los resultados relevantes?

Pregunta Científica

- Añade Herceptin beneficio al tratamiento convencional con cisplatino y gemcitabina en pacientes con cáncer urotelial avanzado tratados en primera línea?

Excitement in 2005

Study finds Herceptin may have role in bladder cancer treatment

--added 5/16/05

Ann Arbor - A targeted drug shown to improve the outcome of certain breast cancer patients may be of use in the treatment of advanced cases of bladder cancer, according to new research led by the University of Michigan Comprehensive Cancer Center.

Researchers investigated the role of the protein HER2 – which has been associated with more aggressive breast cancers – in bladder cancer that has metastasized, or spread to other parts of the body. More than half of bladder cancer patients in this study had high levels of the HER2 protein. Recently reported research found the targeted drug Herceptin given along with chemotherapy to women with HER2-positive breast cancer cut the risk of recurrence in half. Here, researchers found Herceptin may also play a role in treating HER2-postive bladder cancer.

Maha Hussain, M.D.

"The model for Herceptin is breast cancer. While we are still in the beginning, I think this trial provides an approach for metastatic bladder cancer that has not been previously explored. This opens up the possibility of targeted therapies for bladder cancer," says Maha Hussain, M.D., professor of internal medicine and urology at the U-M Medical School. Hussain will present the findings Saturday, May 14, at the American Society of Clinical Oncology annual meeting in Orlando, Fla.

This multicenter trial is one of the first efforts in which researchers have looked at using targeted therapy in bladder cancer based on the presence of the specific target. Targeted therapies such as Herceptin, which are designed to seek out specific molecules known to play a role in cancer development or growth, tend to be less toxic for patients because they do not harm normal cells, unlike traditional chemotherapy drugs.

HER2 & Urothelial Cancer

- **Her-2/neu expression** in urothelial cancers (UCs) is **variable**, ranging from **8.5% to 81%**.

- Some reported a **correlation** between **Her-2/neu overexpression** with **a more aggressive clinical course.**

Wester K, Sjostrom A, de la Torre M, et al:HER-2: A possible target for therapy of metastatic urinary bladder carcinoma. Acta Oncol 41:282-288,
2002Lipponen P, Eskelinen M, Syrjanen S, et al:Use of immunohistochemically demonstrated c-erb B-2 oncoprotein expression as a prognostic factor in transitional cell carcinoma of the urinary bladder. Eur Urol 20:238-242, 1991

Trastuzumab & Bladder Cancer

VOLUME 25 · NUMBER 16 · JUNE 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Trastuzumab, Paclitaxel, Carboplatin, and Gemcitabine in Advanced Human Epidermal Growth Factor Receptor-2/*neu*–Positive Urothelial Carcinoma: Results of a Multicenter Phase II National Cancer Institute Trial

Maha H.A. Hussain, Gary R. MacVicar, Daniel P. Petrylak, Rodney L. Dunn, Ulka Vaishampayan, Primo N. Lara Jr, Gurkamal S. Chatta, David M. Nanus, L. Michael Glode, Donald L. Trump, Helen Chen, and David C. Smith

Results

Fifty-seven (52.3%) of 109 registered patients were Her-2/*neu* positive, and 48.6% were positive by IHC. Her-2/neu–positive patients had more metastatic sites and visceral metastasis than did Her-2/*neu* negative patients. Forty-four of 57 Her-2/neu–positive patients were treated with TPCG. The median number of cycles was six (range, 1 to 12 cycles). The most common grade 3/4 toxicity was myelosuppression. Grade 3 sensory neuropathy occurred in 14% of patients, and 22.7% experienced grade 1 to 3 cardiac toxicity (grade 3, n = 2: one left ventricular dysfunction, one tachycardia). There were two therapy-related deaths. Thirty-one (70%) of 44 patients responded (five complete and 26 partial), and 25 (57%) of 44 were confirmed responses. Median time to progression and survival were 9.3 and 14.1 months, respectively.

Conclusion

Check List

- ❑ **Pregunta científica del estudio es correcta?☑**
- ❑Es la población del estudio representativa?
- ❑Es la ejecución correcta?
- ❑Son los resultados relevantes?

Study Population

- Small n [19 patients]
- 84% ECOG 0-1
- 3 patients G1 tumors ?
- Not entirely clear what % had visceral metastases? should by high in HER2+?
- Data should be presented according to Bajorin classification
- ?Selected Population? Too good candidates?

Check List

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  PROBABLY NOT
- ❑ Es la ejecución correcta?
- ❑ Son los resultados relevantes?

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  PROBABLY NOT
- Es la ejecución correcta?
- Son los resultados relevantes?

Methods

- Overall yes, but ….
- Median number of cycles below the anticipated # (4,5 Vs 6 planned)
- About a third of patients didn't receive the planned treatment
- Lack of detail in Stats. [Simon's design]
- Lack of info about the rationale for this chemo schema?

Check List

- ❑ Pregunta científica del estudio es correcta? ☑
- ❑ Es la población del estudio representativa? PROBABLY NOT
- ❑ **Es la ejecución correcta? PERHAPS IMPROVABLE**
- ❑ Son los resultados relevantes?

Check List

- ❑ Pregunta científica del estudio es correcta? ☑
- ❑ Es la población del estudio representativa? PROBABLY NOT
- ❑ Es la ejecución correcta? SO SO
- ❑ Son los resultados relevantes?

Results

- They could be relevant but…
- There are a few unusual things

  [The Phase II syndrome?]

  – White cell tox is replicable
  – Much lower toxicity than reported in the original study in red cell/platelets (Von der Maase)
    - 3%G3-4 anemia Vs 27% !!
    - 36% G3-4 Thrombocitopenia Vs 57%
    - ?Wrong data collection/ excellent patients or low dose intensity?

Results

- There is an unusual high response rate and OS:
  - 82, 4 % ORR [35% CR!!]
    - Were these responses confirmed?
  - How do you justify these huge differences?
  - Is Herceptin such a good drug to create these differences?
    - The original CDDP-GEM: 49% RR
    - Carbo-Taxol-Gem-Hercept: 44% RR (8% CR) [70%not conf]
    - Was response assesment central or by investigator?
    - OS 14 mos for CDDP-GEM Vs 54 mos!!! (33 is mOS for patients with zero Bajorin criteria)

Results

- Long survivors
  - Why that threshold ?
  - Patients with favorable features
    - Local Advanced Vs Metastatic
    - ECOG
    - Low incidence of Visceral Disease
  - What treatments did they receive after progressing?
- Open question: Role of herceptin maintenance?

Check List

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- ❑ Es la población del estudio representativa? PROBABLY NOT
- ❑ Es la ejecución correcta? SO SO
- ❑ Son los resultados relevantes? SON SORPRENDENTES

Conclusion

- 1. Every Urothelial study deserves all the congratulations [very difficult studies to run]
- 2. Perhaps the bias of a small phase II Study could be interfering with the final results of the trial and overestimating them
- 3. Those results are somehow discordant with previous data in the literature deserve to be revised and confirm……who knows, may be your combo is so good…. Or may be not

- ….When data in any study are so good….try to replicate them in another set of patient before you make any conclusions

- Any plans to pursue a bigger study ?