

Bölüm 22

ESMO 2018'DE ÖNE ÇIKAN 5 ÇALIŞMANIN ANALİZİ

Lokman KORAL¹

GİRİŞ

2000'li yılların başına kadar tedavilerin temelini kemoterapi oluşturuyordu. Aynı dönemlerde malign melanom ve renal hücreli karsinomda kullanılan interferon ve interlökin-2 immunoterapinin ilk uygulamaları olarak kabul edilebilir. Daha sonra monoklonal antikorların ve tirozin kinazların yeni oyuncular olarak sahne alması ile gerek adjuvan hem metastatik hastalıkta daha uzun sağkalımları konuşabilir hale geldik. İçinde olduğumuz dekat ise immunoterapinin monoterapi olarak yakın zamanlarda da kombine tedavilerle ön plana çıktığı dönem oldu. Burada metastatik baş-boyun kanseri, triple negatif meme kanseri, metastatik kolorektal karsinom, metastatik renal hücreli karsinom ve over kanserinde ESMO 2018'de sunulan 5 çalışma ile birlikte geçmişten günümüze bazı çalışmaların değerlendirilmesi yapılmıştır.

METASTATİK BAŞ-BOYUN KANSERİ

Rekürren veya metastatik skuamöz hücreli baş-boyun tümörlerinde, platin rezistan hastalarda son 10 yıla damgasını vuran EXTREME çalışmasında hiç tedavi almamış hastalar ; Platin, 5-Fluorourasil ve setuksimab kombinasyonu (EXTREME kolu) ile platin, 5-Fluorourasil ve plasebo kombinasyonu olarak karşılaştırılmış. Medyan genel sağkalım setuksimab alan hastalar lehine 10.1 & 7.4 ay saptanmış. Medyan progresyonsuz sağkalım 3.3 ay & 5.6 ay setuksimab kolu lehineydi ($p<0.001$) ve hastalık kontrol oranı %81'e karşılık %60 ile setuksimablı kombinasyon lehineydi. Her iki grup arasında yan etkiler açısından belirgin fark saptanmadı. Bu çalışma sonuçlarından sonra kemoterapi + setuksimab rekürren metastatik başboyun tümörlerinde ilk sıra tedavide kategori 1 düzeyinde önerildi. Epidermal Growth Faktör Reseptör (EGFR) ekspresyon düzeyi hastaların %80'den fazlasında %40 ve üzerinde saptandı. Tedavi yanıtlarında EGFR %'sine göre fark saptanmadı (Vermoken JB & ark, 2008). Aynı periyodda yayınlanan

¹ Dr öğr. üyesi Lokman KORAL, Çanakkale Onsekiz Mart Üniversitesi Tıbbi Onkoloji Bilim Dalı, lokmankoral@hotmail.com

≥ %25 üzerindeydi. Evre ≥ 3 ve üzeri yan etki oluparib kolunda %21.5 anemi, %8.5 nötropeni, %3.8 bitkinlik ve %3.1 diyare olarak görüldü, plasebo kolunda ise evre ≥ 3 ve üzeri yan etki olarak %4.6 oranında nötropeni ve %1.5 oranında da bitkinlik ve anemi görüldü. Sonuç olarak BRCA mutant ileri over kanseri hastalarında PFS'yi eşi görülmemiş bir şekilde artırdı, oluparib genel olarak iyi tolere edildi. (Moore K & ark, 2018). Olaparib, BRCA mutant ileri over kanser hastalarında standart platin bazlı kemoterapiyi takiben kılavuzda platin sensitif tedavide idame tedavisi olarak bevasizumab, niraparib, oluparib ve rucaparib önerilirken bu çalışma ile oluparibin idame tedavideki öneri düzeyi olarak bir adım öne çıkması söz konusu olabilir. (NCCN Version 2.2018)

KAYNAKLAR

- Aghajanian C & ark, (2012). OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol.* 2012 Jun 10;30(17):2039-45. doi: 10.1200/JCO.2012.42.0505. Epub 2012 Apr 23.
- Ang KK & ark, (2010). Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. *N Engl J Med* 2010;363:24-35.
- Burger RA & ark, (2011). Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011;365(26):2473-83.
- Burstein MD & ark, (2015). Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. *Clin Cancer Res.* 2015 Apr 1;21(7):1688-98. doi: 10.1158/1078-0432.CCR-14-0432. Epub 2014 Sep 10
- Burtneß B & ark, (2018). KEYNOTE-048: Phase 3 Study of First-Line Pembrolizumab for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC). *ESMO Congress, 19-23 October 2018 Munich, Germany. ABRSTRACT LBA8_PR.* *Annals of Oncology, Volume 29 Supplement 8 October 2018*
- Chan S & ark, (2009). Phase III study of gemcitabine plus docetaxel compared with capecitabine plus docetaxel for anthracycline-pretreated patients with metastatic breast cancer. *J Clin Oncol.* 2009 Apr 10;27(11):1753-60. doi: 10.1200/JCO.2007.15.8485. Epub 2009 Mar 9.
- Clark JI & ark, (2017). Impact of sequencing targeted therapies with high-dose interleukin2 immunotherapy: An Analysis of outcome and survival of patients with metastatic renal cell carcinoma from an on-going observational IL-2 Clinical Trial: PROC-LAISM *Clin Genitourin Cancer* 2017;15(1):31-41.
- Collignon J & ark, (2016). Triple-negative breast cancer: treatment challenges and solutions. *Breast Cancer (Dove Med Press).* 2016 May 20;8:93-107. doi: 10.2147/BCTT.S69488. eCollection 2016.
- Deeks ED, (2015). Olaparib: first global approval. *Drugs.* 2015 Feb;75(2):231-40. doi: 10.1007/s40265-015-0345-6.
- Delaloge S & ark, (2016). Paclitaxel plus bevacizumab or paclitaxel as first-line treatment for HER2-negative metastatic breast cancer in a multicenter national observational study. *Ann Oncol.* 2016 Sep;27(9):1725-32. doi: 10.1093/annonc/mdw260. Epub

- 2016 Jul 19.
- Du Bois A & ark, (2010). Phase III trial of carboplatin plus paclitaxel with or without gemcitabine in first-line treatment of epithelial ovarian cancer. *J Clin Oncol*. 2010 Sep 20;28(27):4162-9. doi: 10.1200/JCO.2009.27.4696. Epub 2010 Aug 23.
- Escudier B & ark, (2007). Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007;370(9605):2103-11
- ESMO (2016). ESMO Consensus Guidelines for the Management of Patients with Metastatic Colorectal Cancer. (21.01.2019 tarihinde <https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Management-of-Patients-with-Metastatic-Colorectal-Cancer> adresinden ulaşılmıştır)
- Ferris RL & ark, (2016). Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med* 2016;375:1856-67. doi:10.1056/NEJMoa1602252
- Gampenrieder, Rinnerthaler, & Greil, (2017). SABCS 2016: systemic therapy for metastatic breast cancer. *Memo*. 2017;10(2):86-89. doi: 10.1007/s12254-017-0326-4. Epub 2017 Apr 4
- Gonzalez-Martin A, (2005). Treatment of recurrent disease: randomized trials of monotherapy versus combination chemotherapy. *Int J Gynecol Cancer*. 2005 Nov-Dec;15 Suppl 3:241-6. doi: 10.1111/j.1525-1438.2005.00436.x
- Guigay J & ark, (2011). Cetuximab, docetaxel, and cisplatin (TPEX) as first-line treatment in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Final results of phase II trial GORTEC 2008-03. ASCO annual meeting, JUNE 3-7, 2011, Chicago, USA. (abstract:5567)
- Hudes G, & ark, (2007). Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;356(22):2271-81
- Jordan RC & ark, (2012). Validation of methods for oropharyngeal cancer HPV status determination in US cooperative group trials. *Am J Surg Pathol* 2012; 36: 945-54.
- Khosravi-Shahi, Cabezón-Gutiérrez & Custodio-Cabello, (2016). Metastatic triple negative breast cancer: Optimizing treatment options, new and emerging targeted therapies. *Asia Pac J Clin Oncol*. 2018 Feb;14(1):32-39. doi: 10.1111/ajco.12748. Epub 2017 Aug 16
- Kim H & ark, (1994). Clinical and pathological characteristics of sporadic colorectal carcinomas with DNA replication errors in microsatellite sequences. *Am J Pathol*. 1994 Jul;145(1):148-56.
- Koopman M & ark, (2009). Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. *Br J Cancer*. 2009 Jan 27;100(2):266-73. doi: 10.1038/sj.bjc.6604867.
- Le DT & ark, (2015). PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med*. 2015 Jun 25;372(26):2509-20. doi: 10.1056/NEJMoa1500596. Epub 2015 May 30.
- Ledermann J & ark, (2014). Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol* 2014; 15: 852–61
- Lehmann BD & ark, (2011). Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest*. 2011 Jul;121(7):2750-67. doi: 10.1172/JCI45014.
- Lenz JH-J & ark, (2018). Durable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC). ESMO Congress, 19-23 October 2018 Munich, Germany. ABSTRACT LBA18_R, *Annals of Onco-*

- logy, Volume 29, Issue suppl_8, 1 October 2018, mdy424.019, <https://doi.org/10.1093/annonc/mdy424.019>
- Litton JK & ark, (2018). Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N Engl J Med*. 2018 Aug 23;379(8):753-763. doi: 10.1056/NEJMoa1802905. Epub 2018 Aug 15.
- Mirza MR & ark, (2016). Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med* 2016;375(22):2154-64.
- Mittendorf EA & ark, (2014). PD-L1 expression in triple-negative breast cancer. *Cancer Immunol Res*. 2014 Apr;2(4):361-70. doi: 10.1158/2326-6066.CIR-13-0127. Epub 2014 Jan 10.
- Moore K & ark, (2018). Maintenance olaparib following platinum-based chemotherapy in newly diagnosed patients (pts) with advanced ovarian cancer (OC) and a BRCA1/2 mutation (BRCAm): Phase III SOLO1 trial. ESMO Congress, 19-23 October 2018 Munich, Germany. ABSTRACT LBA7_PR, *Annals of Oncology*, Volume 29, Issue suppl_8, 1 October 2018, mdy424.041, <https://doi.org/10.1093/annonc/mdy424.041>
- Motzer RJ & ark, (2007). Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356(2):115-24.
- Motzer RJ & ark, (2015). Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med* 2015;373:1803-13.
- Motzer RJ & ark, (2018). Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2018 Apr 5;378(14):1277-1290
- Motzer RJ & ark, (2018). JAVELIN renal 101: A randomized, phase III study of avelumab + axitinib vs sunitinib as first-line treatment of advanced renal cell carcinoma (aRCC). ESMO Congress, 19-23 October 2018 Munich, Germany. ABSTRACT LBA6_PR, *Annals of Oncology*, Volume 29, Issue suppl_8, 1 October 2018, mdy424.036, <https://doi.org/10.1093/annonc/mdy424.036>
- National Comprehensive Cancer Network, Breast cancer Version 3.2018 October 25 2018. (21.01.2019 tarihinde https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf adresinden ulaşılmıştır.)
- National Comprehensive Cancer Network, Colon cancer Version 4.2018 October 19, 2018. (21.01.2019 tarihinde https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf adresinden ulaşılmıştır)
- National Comprehensive Cancer Network, head and neck Version 2.2018-june 20, 2018. (19.01.2019 tarihinde https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf adresinden ulaşılmıştır)
- Overman MJ & ark, (2016). Nivolumab ± ipilimumab treatment (Tx) efficacy, safety, and biomarkers in patients (Pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): results from the CheckMate-142 study. ESMO Congress, 7-11 October 2016, Copenhagen, Denmark. *Annals of Oncology*, Volume 27, Issue suppl_6, 1 October 2016, 479P, <https://doi.org/10.1093/annonc/mdw370.27>
- Overman MJ & ark, (2017). Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017 Sep;18(9):1182-1191. doi: 10.1016/S1470-2045(17)30422-9. Epub 2017 Jul 19.
- Parmer MK & ark, (2003). Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the

- ICON4/AGO-OVAR-2.2 trial. *Lancet*. 2003 Jun 21;361(9375):2099-106.
- Perren TJ & ark, (2011). A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011;365(26):2484-96.
- Pujade-Lauraine E & ark, (2014). Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial *J Clin Oncol* 2014;32(13):1302-8.
- Pujade-Lauraine E & ark, (2017). Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial
- Robson M & ark, (2017). Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med*. 2017 Aug 10;377(6):523-533. doi: 10.1056/NEJMoa1706450. Epub 2017 Jun 4.
- Rugo HS & ark, (2009). xabepilone plus capecitabine vs capecitabine in patients with triple negative tumors: a pooled analysis of patients from two large phase III clinical studies. DOI: 10.1158/0008-5472.SABCS-3057 Published January 2009
- Schmid P & ark, (2018). IMpassion130: Results from a global, randomised, double-blind, phase 3 study of atezolizumab (atezo) + nab-paclitaxel (nab-P) vs placebo + nab-P in treatment-naïve, locally advanced or metastatic triple-negative breast cancer. ESMO Congress, 19-23 October 2018 Munich, Germany. *Annals of Oncology*, ABSTRACT LBA1_PR, Volume 29 Supplement 8 October 2018,
- Sini V & ark, (2016). Bevacizumab as first-line treatment in HER2-negative advanced breast cancer: pros and cons. *Tumori*. 2016 Oct 13;102(5):472-480. doi: 10.5301/tj.5000555. Epub 2016 Aug 23.
- Swisher EM & ark, (2017). Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial
- Twelves C & ark, (2016). Subgroup Analyses from a Phase 3, Open-Label, Randomized Study of Eribulin Mesylate Versus Capecitabine in Pretreated Patients with Advanced or Metastatic Breast Cancer. *Breast Cancer (Auckl)*. 2016 Jun 28;10:77-84. doi: 10.4137/BCBCR.S39615. eCollection 2016
- Varga A & ark, (2015). Antitumor activity and safety of pembrolizumab in patients (pts) with PD-L1 positive advanced ovarian cancer: Interim results from a phase Ib study. *Journal of Clinical Oncology* 33, no. 15_suppl (May 2015) 5510-5510.
- Varga A & ark, (2017). Pembrolizumab in patients (pts) with PD-L1-positive (PD-L1+) advanced ovarian cancer: Updated analysis of KEYNOTE-028 *Journal of Clinical Oncology* 35, no. 15_suppl (May 2017) 5513-5513)
- Venderbosch S & ark, (2014). Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. *Clin Cancer Res*. 2014 Oct 15;20(20):5322-30. doi: 10.1158/1078-0432.CCR-14-0332. Epub 2014 Aug 19.
- Vermoken JB & ark, (2008). Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer. *N Engl J Med* 2008;359:1116-27
- Vermoken JB & ark, (2013). Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial. *Lancet Oncol* 2013; 14: 697-710.
- Zeichner, Terawaki & Gogineni, (2016). A Review of Systemic Treatment in Metastatic Triple-Negative Breast Cancer. *Breast Cancer (Auckl)*. 2016 Mar 22;10:25-36. doi: 10.4137/BCBCR.S32783. eCollection 2016.