

4.BÖLÜM

MELANOSİTİK LEZYONLARA MOLEKÜLER BAKIŞ

Pınar ERGEN³

GİRİŞ

Melanositler en çok deride bulunmakta ve cilt pigmentasyonunda ve güneşten korunmada kritik rol oynamaktadır. İç organlarda da fonksiyonu tam olarak anlaşılammakla birlikte melanositler mevcuttur ve melanositik tümörlere öncülük ederler.⁽¹⁾ Etyolojisinde erken çocukluk çağında izlenen ultraviyole (UV) radyasyon maruziyeti önemli yer tutmaktadır. Ancak hiç UV radyasyona maruz kalmayan lokalizasyonlarda da melanom gelişebilmektedir. Melanom erken evrede tespit edildiğinde basit rezeksiyon ile kolayca tedavi edilebilir ve tipik olarak iyi prognoz ile ilişkilidir.⁽²⁾ Ancak metastatik tümör, geleneksel kemoterapi ve radyoterapiye son derece dirençlidir.⁽³⁾

Melanomların üç major kategorisi başlangıçta radial büyüme fazının (RBF) varlığına ya da yokluğuna göre kategorilendirilmiştir.⁽⁴⁾ RBF mevcut ise yüzeysel yayılan malign melanom (Pagetoid melanom) (YYM), lentigo malign melanom (LMM) iken, nodüler melanom (NM) sadece vertikal büyüme fazına (VBF) sahiptir.⁽⁵⁾ Bastian ve ark. UV radyasyon, orjin aldığı hücre (ya da doku) ve karakteristik tekrarlayan genomik değişikliklerin rolüne dayanarak melanositik lezyonlar için yeni bir sınıflandırma önermiştir.⁽⁶⁾

UV radyasyon maruziyeti olan melanomlar aralıklı (düşük) kümülatif güneş hasarı (KGH) ve kronik (yüksek) KGH olarak iki gruba ayrılmıştır. Düşük KGH grubundaki melanom tipleri: YYM ve NM'nin bazı alt tipleridir. Yüksek KGH melanom grubundakiler ise LMM ve NM'nin birkaç alt tipidir.⁽⁵⁾

Mevcut moleküler yönelimli sınıflandırma şeması, histolojik kriterlerin ve tedavi yaklaşımlarının iyileştirilmesine yönelik ilk adımı oluşturabilir.⁽⁶⁾ (Şekil 1 ve 2)

Melanomagenез birçok moleküler yolak ile gerçekleşebilmektedir. Bu genetik değişikliklere neden olan mutasyon mekanizmalarındaki çeşitlilik melanom tipine bağlıdır.

³ Uzman Doktor, Selahaddin Eyyubi Devlet Hastanesi, pinar3133@gmail.com

KAYNAKLAR

1. Shain AH, Bastian BC. From melanocytes to melanomas. *Nat Rev Cancer*. 2016 Jun;16(6):345-58. doi: 10.1038/nrc.2016.37.
2. Tarhini AA, Lorigan P, Leachman S. Operable Melanoma: Screening, Prognostication, and Adjuvant and Neoadjuvant Therapy. *Am Soc Clin Oncol Educ Book*. 2017;37:651-660. doi: 10.14694/EDBK_174930.
3. Wu S, Singh RK. Resistance to chemotherapy and molecularly targeted therapies: rationale for combination therapy in malignant melanoma. *Curr Mol Med*. 2011 Oct;11(7):553-63. Review. PubMed PMID: 21707515
4. Clark WH Jr, From L, Bernardino EA et al. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. *Cancer Res*. 1969 Mar;29(3):705-27
5. Elder DE, Massi D, Richardson AS (2018). WHO classification of skin tumours 4th edition. International Agency for Research on Cancer (IARC) 69372 Lyon Cedex 08, France
6. Bastian BC. The molecular pathology of melanoma: an integrated taxonomy of melanocytic neoplasia. *Annu Rev Pathol* 2014;9:239-71.
7. Cancer Genome Atlas Network. Genomic Classification of Cutaneous Melanoma. *Cell*. 161(7):1681-96. doi: 10.1016/j.cell.2015.05.044.
8. Calonje E, Brenn T, Lazar A (2012). *McKee's Pathology of the Skin*. 4th Edition. Printed in China
9. Pasini, L. Molecular Pathways in Melanomagenesis. *Oncogenomics*, 2019:623–642. doi:10.1016/b978-0-12-811785-9.00044-2
10. Hodis E, Watson I, Kryukov G et al. A landscape of driver mutations in melanoma. *Cell* 150:251–263. <https://doi.org/10.1016/j.cell.2012.06.024>
11. Ji Z, Flaherty KT, Tsao H. Targeting the RAS pathway in melanoma. *Trends Mol Med*. 2012 Jan;18(1):27-35. doi: 10.1016/j.molmed.2011.08.001.
12. Curtin J, Fridlyand J, Kageshita T et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med* 2005;353:2135–2147. <https://doi.org/10.1056/NEJMoa050092>
13. Dietrich P, Kuphal S, Spruss T et al. Wild-type KRAS is a novel therapeutic target for melanoma contributing to primary and acquired resistance to BRAF inhibition. *Oncogene*. 2018 Feb 15;37(7):897-911. doi: 10.1038/onc.2017.391.
14. Gajewski TE, Salama AK, Niedzwiecki D et al; Cancer and Leukemia Group B. Phase II study of the farnesyltransferase inhibitor R115777 in advanced melanoma (CALGB 500104). *J Transl Med*. 2012 Dec 10;10:246. doi: 10.1186/1479-5876-10-246.
15. Ali L, Helm T, Cheney R et al. Correlating array comparative genomic hybridization findings with histology and outcome in spitzoid melanocytic neoplasms. *Int J Clin Exp Pathol*. 2010 Jun 28;3(6):593-9. PubMed PMID: 20661407
16. Hussein MR, Wood GS. Molecular aspects of melanocytic dysplastic nevi. *J Mol Diagn*. 2002 May;4(2):71-80. doi: 10.1016/S1525-1578(10)60684-8
17. Abildgaard C, Guldberg P. Molecular drivers of cellular metabolic reprogramming in melanoma. *Trends Mol Med*. 2015 Mar;21(3):164-71. doi: 10.1016/j.molmed.2014.12.007.
18. Wan PT, Garnett MJ, Roe SM, et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. *Cell*; 2004; 116:855-67. DOI: 10.1016/s0092-8674(04)00215-6

19. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature*; 2002; 417:949-54. DOI: 10.1038/nature00766
20. Kumar R, Angelini S, Snellman E, et al. BRAF mutations are common somatic events in melanocytic nevi. *J Invest Dermatol*; 2004; 122:342-8 DOI: 10.1046/j.0022-202X.2004.22225.x
21. Grossmann, A. H., Grossmann, K. F., Wallander, M. L., Molecular testing in malignant melanoma. *Diagn Cytopathol* 2012;40(6):503-10 <http://doi.org/10.1002/dc.22810>
22. Yu H, Lee H, Herrmann A, Buettner R, et al. Revisiting STAT3 signalling in cancer: new and unexpected biological functions. *Nat Rev Cancer*. 2014 Nov;14(11):736-46. doi: 10.1038/nrc3818.
23. Nazarian R, Shi H, Wang Q, et al. Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. *Nature*. 2010 Dec 16;468(7326):973-7. doi: 10.1038/nature09626.
24. Cheng L, Lopez-Beltran A, Massari F et al. Molecular testing for BRAF mutations to inform melanoma treatment decisions: a move toward precision medicine. *Mod Pathol*. 2018 Jan;31(1):24-38. doi: 10.1038/modpathol.2017.104
25. Huang FW, Hodis E, Xu MJ, et al. Highly recurrent TERT promoter mutations in human melanoma. *Science*; 2013;339:957-9. DOI: 10.1126/science.1229259
26. Shain AH, Garrido M, Botton T et al. Exome sequencing of desmoplastic melanoma identifies recurrent NFKBIE promoter mutations and diverse activating mutations in the MAPK pathway. *Nat Genet* 2015; 47:1194–1199. <https://doi.org/10.1038/ng.3382>
27. Horn S, Figl A, Rachakonda PS, et al. TERT promoter mutations in familial and sporadic melanoma. *Science*; 2013; 339:959-61 doi: 10.1126/science.1230062
28. Aguisa-Touré AH, Li G. Genetic alterations of PTEN in human melanoma. *Cell Mol Life Sci*. 2012 May;69(9):1475-91. doi: 10.1007/s00018-011-0878-0.
29. Hollander MC, Blumenthal GM, Dennis PA. PTEN loss in the continuum of common cancers, rare syndromes and mouse models. *Nat Rev Cancer*. 2011 Apr;11(4):289-301. doi: 10.1038/nrc3037.
30. Omholt K, Kröckel D, Ringborg U, et al. Mutations of PIK3CA are rare in cutaneous melanoma. *Melanoma Res* 2006;16:197-200. DOI: 10.1097/01.cmr.0000200488.77970.e3
31. Deng W, Gopal YN, Scott A et al. Role and therapeutic potential of PI3K-mTOR signaling in de novo resistance to BRAF inhibition. *Pigment Cell Melanoma Res*. 2012 Mar;25(2):248-58. doi: 10.1111/j.1755-148X.2011.00950.x.
32. Bastian BC. Understanding the progression of melanocytic neoplasia using genomic analysis: from fields to cancer. *Oncogene* 2003;22:3081-6 DOI: 10.1038/sj.onc.1206463
33. Stahl JM, Cheung M, Sharma A, et al. Loss of PTEN promotes tumor development in malignant melanoma. *Cancer Res* 2003;63:2881-90.
34. Mirmohammadsadegh A, Marini A, Nambiar S, et al. Epigenetic silencing of the PTEN gene in melanoma. *Cancer Res* 2006;66:6546-52. DOI: 10.1158/0008-5472.CAN-06-0384
35. Jonsson A, Tuominen R, Grafström E, et al. High frequency of p16(INK4A) promoter methylation in NRAS-mutated cutaneous melanoma. *J Invest Dermatol*. 2010 Dec;130(12):2809-17. doi: 10.1038/jid.2010.216.
36. Chin L, Pomerantz J, Polsky D, Jacobson M, Cohen C, Cordon-Cardo C, Horner JW 2nd, DePinho RA. Cooperative effects of INK4a and ras in melanoma susceptibility in vivo. *Genes Dev*. 1997 Nov 1;11(21):2822-34. DOI: 10.1101/gad.11.21.2822

37. Shain AH, Yeh I, Kovalyshyn I et al. The Genetic Evolution of Melanoma from Precursor Lesions. *N Engl J Med.* 2015 Nov 12;373(20):1926-36. doi: 10.1056/NEJMoa1502583.
38. Houben R, Hesbacher S, Schmid CP, et al. High-level expression of wild-type p53 in melanoma cells is frequently associated with inactivity in p53 reporter gene assays. *PLoS One.* 2011;6(7):e22096. doi: 10.1371/journal.pone.0022096.
39. Fu M, Wang C, Li Z, Sakamaki T, Pestell RG. Minireview: Cyclin D1: normal and abnormal functions. *Endocrinology.* 2004 Dec;145(12):5439-47. DOI: 10.1210/en.2004-0959
40. Vízkeleti L, Ecsedi S, Rákossy Z, Orosz A, Lázár V, Emri G, Koroknai V, Kiss T, Ádány R, Balázs M. The role of CCND1 alterations during the progression of cutaneous malignant melanoma. *Tumour Biol.* 2012 Dec;33(6):2189-99. doi: 10.1007/s13277-012-0480-6.
41. Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. *J Clin Oncol.* 2006 Sep 10;24(26):4340-6. DOI: 10.1200/JCO.2006.06.2984
42. Feng X, Degese MS, Iglesias-Bartolome R et al. Hippo-independent activation of YAP by the GNAQ uveal melanoma oncogene through a trio-regulated rho GTPase signaling circuitry. *Cancer Cell.* 2014 Jun 16;25(6):831-45. doi: 10.1016/j.ccr.2014.04.016.
43. Yu F-XX, Luo J, Mo J-SS et al. Mutant Gq/11 promote uveal melanoma tumorigenesis by activating YAP. *Cancer Cell.* 2014 Jun 16;25(6):822-30. doi: 10.1016/j.ccr.2014.04.017.
44. Raamsdonk C, Bezrookove V, Green G et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. *Nature.* 2009 Jan 29;457(7229):599-602. doi: 10.1038/nature07586.
45. Raamsdonk C, Griewank K, Crosby M et al. Mutations in GNA11 in uveal melanoma. *N Engl J Med* 2010; 363:2191–2199. <https://doi.org/10.1056/NEJMoa1000584>
46. Johansson P, Aoude LG, Wadt K et al. Deep sequencing of uveal melanoma identifies a recurrent mutation in PLCB4. *Oncotarget.* 2016 Jan 26;7(4):4624-31. doi: 10.18632/oncotarget.6614.
47. Moore AR, Ceraudo E, Sher JJ et al. Recurrent activating mutations of G-protein-coupled receptor CYSLTR2 in uveal melanoma. *Nat Genet.* 2016 Jun;48(6):675-80. doi: 10.1038/ng.3549.
48. Van Raamsdonk CD, Bezrookove V, Green G et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. *Nature.* 2009 Jan 29;457(7229):599-602. doi:10.1038/nature07586.
49. Yilmaz I, Gamsizkan M, Sari SO et al. Molecular alterations in malignant blue nevi and related blue lesions. *Virchows Arch.* 2015 Dec;467(6):723-732. DOI: 10.1007/s00428-015-1851-3
50. Whittaker SR, Theurillat JP, Van Allen E, et al. A genome-scale RNA interference screen implicates NF1 loss in resistance to RAF inhibition. *Cancer Discov.* 2013 Mar;3(3):350-62. doi: 10.1158/2159-8290.CD-12-0470.
51. Machida YJ, Machida Y, Vashisht AA et al. The deubiquitinating enzyme BAP1 regulates cell growth via interaction with HCF-1. *J Biol Chem.* 2009 Dec 4;284(49):34179-88. doi: 10.1074/jbc.M109.046755.
52. Wiesner, T, Obenauf, A. C., Murali, R., et al. Germline mutations in BAP1 predispose to melanocytic tumors. *Nat Genet.* 2011 Aug 28;43(10):1018-21. doi: 10.1038/ng.910.

53. Wiesner T, Murali R, Fried I et al. A distinct subset of atypical Spitz tumors is characterized by BRAF mutation and loss of BAP1 expression. *Am J Surg Pathol.* 2012 Jun;36(6):818-30. doi: 10.1097/PAS.0b013e3182498be5.
54. Harbour JW, Onken MD, Roberson ED et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. *Science.* 2010 Dec 3;330(6009):1410-3. doi: 10.1126/science.1194472.
55. Lang UE, Yeh I, McCalmont TH. Molecular Melanoma Diagnosis Update: Gene Fusion, Genomic Hybridization, and Massively Parallel Short-Read Sequencing. *Clin Lab Med.* 2017 Sep;37(3):473-484. doi: 10.1016/j.cll.2017.06.002.
56. Hodis E, Garraway LA1. (2017) *Molecular Genetics of Melanocytic Neoplasia.* Springer reference, Live Melanoma
57. Bevona C, Goggins W, Quinn T et al. Cutaneous melanomas associated with nevi. *Arch Dermatol* 2003;139:1620–1624; discussion 1624. [https://doi.org/ 10.1001/archderm.139.12.1620](https://doi.org/10.1001/archderm.139.12.1620)
58. Shitara D, Nascimento MM, Puig S et al. Nevus-associated melanomas: clinicopathologic features. *Am J Clin Pathol.* 2014 Oct;142(4):485-91. doi: 10.1309/AJCP4L5CJ-GKTJVDD.
59. Pollock PM, Harper UL, Hansen KS et al. High frequency of BRAF mutations in nevi. *Nat Genet* 2003;33:19–20. <https://doi.org/10.1038/ng1054>
60. Krauthammer M, Kong Y, Ha B et al. Exome sequencing identifies recurrent somatic RAC1 mutations in melanoma. *Nat Genet.* 2012 Sep;44(9):1006-14. doi: 10.1038/ng.2359.
61. Wiesner T, He J, Yelensky R et al. Kinase fusions are frequent in Spitz tumours and spitzoid melanomas. *Nat Commun.* 2014;5:3116. doi: 10.1038/ncomms4116.
62. Yeh I, Botton T, Talevich E et al. Activating MET kinase rearrangements in melanoma and Spitz tumours. *Nat Commun.* 2015 May 27;6:7174. doi: 10.1038/ncomms8174.
63. Bastian BC, LeBoit PE, Pinkel D. Mutations and copy number increase of HRAS in Spitz nevi with distinctive histopathological features. *Am J Pathol.* 2000 Sep;157(3):967-72. DOI: 10.1016/S0002-9440(10)64609-3
64. Yeh I, Tee MK, Botton T et al. NTRK3 kinase fusions in Spitz tumours. *J Pathol.* 2016 Nov;240(3):282-290. doi: 10.1002/path.4775
65. Kiuru M, Jungbluth A, Kutzner H et al. Spitz Tumors: Comparison of Histological Features in Relationship to Immunohistochemical Staining for ALK and NTRK1. *Int J Surg Pathol.* 2016 May;24(3):200-6. doi: 10.1177/1066896916630375.
66. Dimonitsas E, Liakea A, Sakellariou S et al. An update on molecular alterations in melanocytic tumors with emphasis on Spitzoid lesions. *Ann Transl Med.* 2018 Jun;6(12):249. doi: 10.21037/atm.2018.05.23.
67. Gerami P, Pouryazdanparast P, Vemula S, et al. Molecular analysis of a case of nevus of ota showing progressive evolution to melanoma with intermediate stages resembling cellular blue nevus. *Am J Dermatopathol.* 2010 May;32(3):301-5. doi: 10.1097/DAD.0b013e3181b96db7.
68. Maldonado JL, Fridlyand J, Patel H et al. Determinants of BRAF mutations in primary melanomas. *J Natl Cancer Inst.* 2003 Dec 17;95(24):1878-90. DOI: 10.1093/jnci/djg123
69. Glatz-Krieger K, Pache M, Tapia C et al. Anatomic site-specific patterns of gene copy number gains in skin, mucosal, and uveal melanomas detected by fluorescence in

- situ hybridization. *Virchows Arch.* 2006 Sep;449(3):328-33. Epub 2006 Mar 8. doi: 10.1007/s00428-006-0167-8
70. Whiteman DC, Watt P, Purdie DM et al. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J Natl Cancer Inst.* 2003 Jun 4;95(11):806-12. DOI: 10.1093/jnci/95.11.806
 71. Lachiewicz AM, Berwick M, Wiggins CL et al. Epidemiologic support for melanoma heterogeneity using the surveillance, epidemiology, and end results program. *J Invest Dermatol.* 2008 May;128(5):1340-2. doi: 10.1038/jid.2008.18.
 72. Wiesner T, Kiuru M, Scott SN et al. NF1 Mutations Are Common in Desmoplastic Melanoma. *Am J Surg Pathol.* 2015 Oct;39(10):1357-62. doi: 10.1097/PAS.0000000000000451.
 73. De Vazquez V, Vicente A, Carloni A et al. Molecular profiling, including TERT promoter mutations, of acral lentiginous melanomas. *Melanoma Res.* 2016 Apr;26(2):93-9. doi: 10.1097/CMR.0000000000000222.
 74. Curtin J, Fridlyand J, Kageshita T et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med.* 2005 Nov 17;353(20):2135-47. DOI: 10.1056/NEJMoa050092
 75. Furney SJ, Turajlic S, Stamp G et al. Genome sequencing of mucosal melanomas reveals that they are driven by distinct mechanisms from cutaneous melanoma. *J Pathol.* 2013 Jul;230(3):261-9. doi: 10.1002/path.4204.
 76. Hodis E, Watson I, Kryukov G et al. A landscape of driver mutations in melanoma. *Cell* 2012;150:251–263. doi: 10.1016/j.cell.2012.06.024
 77. Woodman SE, Davies MA. Targeting KIT in melanoma: a paradigm of molecular medicine and targeted therapeutics. *Biochem Pharmacol.* 2010;1;80(5):568-74. doi: 10.1016/j.bcp.2010.04.032.
 78. Dumaz N, Jouenne F, Delyon J. Atypical BRAF and NRAS Mutations in Mucosal Melanoma. *Cancers (Basel).* 2019;11(8). pii: E1133. doi: 10.3390/cancers11081133.
 79. Rivolta C, Royer-Bertrand B, Rimoldi D et al. UV light signature in conjunctival melanoma; not only skin should be protected from solar radiation. *J Hum Genet* 2015;61:361–362. <https://doi.org/10.1038/jhg.2015.152>
 80. Griewank KG, Westekemper H, Murali R et al. Conjunctival melanomas harbor BRAF and NRAS mutations and copy number changes similar to cutaneous and mucosal melanomas. *Clin Cancer Res* 2013; 19:3143–3152. <https://doi.org/10.1158/1078-0432.CCR-13-0163>
 81. Koopmans A, Ober K, Dubbink H et al; Rotterdam Ocular Melanoma Study Group. Prevalence and implications of TERT promoter mutation in uveal and conjunctival melanoma and in benign and premalignant conjunctival melanocytic lesions. *Invest Ophthalmol Vis Sci.* 2014 Aug 26;55(9):6024-30. doi: 10.1167/iovs.14-14901.
 82. Charbel C, Fontaine R, Malouf G et al. NRAS mutation is the sole recurrent somatic mutation in large congenital melanocytic nevi. *J Invest Dermatol* 2013;134:1067–1074. doi: 10.1038/jid.2013.429
 83. Fan Y, Lee S, Wu G. Telomerase Expression by Aberrant Methylation of the TERT Promoter in Melanoma Arising in Giant Congenital Nevi. *J Invest Dermatol.* 2016 Jan;136(1):339-342. doi: 10.1038/JID.2015.374.
 84. Bastian BC, Xiong J, Frieden IJ et al. Genetic changes in neoplasms arising in congenital melanocytic nevi: differences between nodular proliferations and melanomas. *Am J Pathol.* 2002 Oct;161(4):1163-9. DOI: 10.1016/S0002-9440(10)64393-3

85. Tse JY, Walls BE, Pomerantz H et al. Melanoma arising in a nevus of Ito: novel genetic mutations and a review of the literature on cutaneous malignant transformation of dermal melanocytosis. *J Cutan Pathol.* 2016 Jan;43(1):57-63. doi: 10.1111/cup.12568.
86. Dai J, Tetzlaff MT, Schuchter LM et al.. Histopathologic and mutational analysis of a case of blue nevus-like melanoma. *J Cutan Pathol.* 2016 Sep;43(9):776-80. doi: 10.1111/cup.12731.
87. Yeh I, Mully T, Wiesner T et al. Ambiguous melanocytic tumors with loss of 3p21. *Am J Surg Pathol.* 2014 Aug;38(8):1088-95. doi: 10.1097/PAS.0000000000000209.
88. Chattopadhyay C, Kim DW, Gombos DS et al. Uveal melanoma: From diagnosis to treatment and the science in between. *Cancer.* 2016 Aug 1;122(15):2299-312. doi: 10.1002/cncr.29727.
89. Horsman DE, White VA. Cytogenetic analysis of uveal melanoma. Consistent occurrence of monosomy 3 and trisomy 8q. *Cancer.* 1993 Feb 1;71(3):811-9. DOI: 10.1002/1097-0142(19930201)71:3<811::aid-cncr2820710325>3.0.co;2-f
90. Harbour JW, Roberson ED, Anbunathan H et al. Recurrent mutations at codon 625 of the splicing factor SF3B1 in uveal melanoma. *Nat Genet.* 2013 Feb;45(2):133-5. doi: 10.1038/ng.2523.
91. Martin M, Maßhöfer L, Temming P et al. Exome sequencing identifies recurrent somatic mutations in EIF1AX and SF3B1 in uveal melanoma with disomy 3. *Nat Genet.* 2013 Aug;45(8):933-6. doi: 10.1038/ng.26